1. TITLE PAGE

An Extension Study to Assess the Safety and Efficacy of Intermittent Bilateral Intraputamenal Glial Cell Line-Derived Neurotrophic Factor (GDNF) Infusions Administered via Convection-Enhanced Delivery (CED) in Subjects with Parkinson's Disease

Study No.	2797
EudraCT No:	2013-001881-40
Development Phase:	II
Investigational Medicinal Product:	Glial cell line-derived neurotrophic factor (GDNF)
Indication:	Parkinson's disease
Study Design:	Open-label, uncontrolled extension of study 2553; single-center
Principal Investigator:	Dr Alan Whone Consultant Senior Lecturer in Movement Disorders, University of Bristol Honorary Consultant Neurologist, Southmead Hospital Movement Disorder Service, Bristol Brain Centre Southmead Hospital, North Bristol NHS Trust Bristol BS10 5NB, United Kingdom
Study Neurosurgeon:	Professor Steven Gill Consultant Neurosurgeon Department of Neurosurgery Southmead Hospital, North Bristol NHS Trust Bristol BS10 5NB, United Kingdom
Sponsor:	North Bristol NHS Trust
Sponsor signatory:	Professor David Wynick
Initiation Date (first subject, informed consent)**:**	08 Oct 2013
Completion Date (last subject, last visit)**:**	15 Feb 2017
Date of Report:	18 Oct 2017

The study was conducted according to the protocol and in compliance with Good Clinical Practice (GCP), including the archiving of essential documents, and other applicable regulatory requirements.

2.   SYNOPSIS

Study No.: 2797

Title: An extension study to assess the safety and efficacy of intermittent bilateral intraputamenal glial cell line-derived neurotrophic factor (GDNF) infusions administered via convection-enhanced delivery (CED) in subjects with Parkinson's disease

Principal investigator: Dr Alan Whone   **Study neurosurgeon:** Professor Steven Gill

Study center:
Oct 2013 – May 2014: Department of Neurology, Frenchay Hospital, North Bristol NHS Trust, Bristol BS16 1LE, United Kingdom
Jun 2014 – Feb 2017: Department of Neurology, Movement Disorder Service, Bristol Brain Centre, Southmead Hospital, North Bristol NHS Trust, Bristol BS10 5NB, United Kingdom (study site moved location in May-June 2014)

Publication:
The study results had not been published at the time of preparation of this report.

Study period: From 15 Oct 2013 to 15 Feb 2017

Development phase: Phase II

Objectives:

Primary
- To compare the effects of intermittent bilateral intraputamenal GDNF infusions on OFF state motor function after 18 months of study treatment with the effects after 9 months of treatment in subjects who completed study 2553.

Secondary
- To compare the effects of intermittent bilateral intraputamenal GDNF infusions on ON state motor function, motor complications, and ON and OFF state activities of daily living (ADL) after 18 months of treatment with the effects after 9 months of treatment in subjects who completed study 2553.
- To assess the safety of intermittent bilateral intraputamenal GDNF infusions at 18 months in subjects who received GDNF or placebo for 9 months in study 2553.

Other
- To explore the effects of intermittent bilateral intraputamenal GDNF infusions on other motor and non-motor functions, quality of life assessments and imaging endpoints at 18 months in subjects who completed study 2553.
- To compare the results for various motor outcomes between the subjects who started GDNF early (i.e. were randomized to GDNF in study 2553) and those who started GDNF late (i.e. were randomized to placebo in study 2553).

- Pilot and Supplemental Extensions: To generate long-term safety data and provide continued access to GDNF until the end of December 2016 when the results of study 2553 are expected, which will inform interested parties with potential future studies.

Methodology: This was a single-center, open-label, uncontrolled trial of intraputamenal infusion of GDNF via CED. Following the final study visit at Week 40 in the parent study 2553, study completers who gave informed consent for study 2797 returned within 1 week to receive their first infusion of open-label GDNF. Initially, study treatment was given at 4-weekly intervals for 9 months (40 weeks; 10 infusions total; the "Initial Extension"). Subsequently, the study protocol was extended twice to permit continuation of open-label GDNF and collection of further safety data: "Pilot Extension" for 80 weeks (Pilot Stage subjects only) and "Supplemental Extension" until the end of December 2016 (Pilot Stage subjects completing Week 2-80 of the Pilot Extension and Primary Stage subjects completing Week e40 of the Initial Extension). At the end of the Initial Extension, subjects who had received GDNF in study 2553 had been treated with GDNF for a total of 18 months, while those who had received placebo in study 2553 had been treated with GDNF for a total of 9 months. Individual treatment codes in study 2553 were not disclosed to subjects or raters before database lock in study 2797.

Number of subjects (planned and analyzed):

Planned: All subjects who completed study 2553 (41) and gave informed consent for study 2797 (41).

		GDNF/GDNF[a]	Placebo/GDNF[a]	Total
Analyzed	ITT Primary Population	17	18	35
	ITT Overall Population	21	20	41
	Safety Overall Population	21	20	41

ITT: Intention-to-treat

[a] Subjects included in the GDNF/GDNF treatment group were those that received randomized double-blind GDNF in study 2553, followed by open-label GDNF in study 2797. Subjects included in the placebo/GDNF treatment group were those that received randomized double-blind placebo in study 2553, followed by open-label GDNF in study 2797.

Diagnosis and main criteria for inclusion: Subjects with idiopathic Parkinson's disease (PD) with motor fluctuations who completed study 2553 and gave informed consent for study 2797. Exclusion criteria were early discontinuation of treatment in study 2553; significant protocol deviation in study 2553; presence of clinically significant depression; Montreal Cognitive Assessment (MoCA) score < 24 at final assessment in study 2553; and any new medical condition which might impair outcome measure assessments or safety measures including ability to undergo magnetic resonance imaging (MRI) scanning.

Test product, dose and mode of administration, batch number(s):
Recombinant-methionyl human glial cell line-derived neurotrophic factor (GDNF).

Study medication	GDNF (0.20 µg/µL in artificial cerebrospinal fluid [aCSF])
Infusion volume per treatment	300 µL GDNF plus 100 µL aCSF line flush per catheter, 600 µL GDNF plus 200 µL aCSF per putamen, 1200 µL GDNF plus 400 µL aCSF overall
Route	Intraputamenal infusion using a CED system with 2 indwelling catheters per putamen
Frequency	Every 4 weeks
Total dose every 4 weeks	60 µg per catheter, 120 µg per putamen, 240 µg overall
Total number of treatments	Initial Extension: 10 Pilot Extension: 19 Supplemental Extension: up to 13 until December 2016
Total duration of treatment	Initial Extension: 40 weeks Pilot Extension: 80 weeks Supplemental Extension: up to 52 weeks until December 2016

GDNF: Batches P03113 and P07012
Artificial cerebrospinal fluid (aCSF): Batches P03716 and P06513

Reference therapy, dose and mode of administration, batch number(s):
Not applicable

Criteria for evaluation:

Primary endpoint
- Percentage change from baseline (Week 0) to Week 80/e40 in the practically defined OFF state Unified Parkinson's Disease Rating Scale (UPDRS) motor score (part III).

Secondary endpoints
- Change from baseline to Week 80/e40 in OFF state UPDRS motor score (part III).
- Change and percentage change from baseline to Week 80/e40 in:
  - UPDRS motor score (part III) in the ON state (following a levodopa challenge).
  - UPDRS ADL score (part II) in the OFF state and in the ON state.
  - UPDRS total score (sum of motor + ADL scores) in the OFF state and in the ON state.
- Change from baseline to Week 40/e0 for the GDNF/GDNF group compared to change from baseline to Week 80/e40 for the placebo/GDNF group in:
  - OFF state UPDRS motor score (part III).
  - OFF state UPDRS ADL score (part II).
  - OFF state UPDRS total score (sum of motor + ADL scores).
- Change from baseline to Week 80/e40 for the GDNF/GDNF group compared to change from baseline to Week 40/e0 for the placebo/GDNF group in:
  - OFF state UPDRS motor score (part III).
  - OFF state UPDRS ADL score (part II).
  - OFF state UPDRS total score (sum of motor + ADL scores).

- Change from baseline to Week 80/e40 in PD diary ratings:
  - Total OFF time per day.
  - Total good-quality ON time per day (ON without dyskinesias or ON with non- troublesome dyskinesias).
  - ON time per day with troublesome dyskinesias.
- Treatment response based on the following criteria:
  - Decrease from baseline to Week 80/e40 by ≥10 points in OFF state UPDRS motor score (part III).
  - Increase from baseline to Week 80/e40 by ≥1 hour in total good-quality ON time per day (ON without dyskinesias or ON with non-troublesome dyskinesias).
  - Both of the above criteria, i.e. decrease from baseline to Week 80/e40 by ≥10 points in OFF state UPDRS motor score (part III) and increase from baseline to Week 80/e40 by ≥1 hour in total good-quality ON time per day (ON without dyskinesias or ON with non-troublesome dyskinesias).

Supplementary efficacy endpoints
- Change from baseline to Week 80/e40 in supplementary motor, non-motor, medication, and quality of life endpoints, including the following
  - Timed walking test (OFF and ON state).
  - Timed tapping test (OFF and ON state).
  - Non-Motor Symptom Assessment Scale for PD (NMSS).
  - Parkinson's Disease Questionnaire-39 (PDQ-39).
  - EuroQOL 5-Dimensional Scale (EQ-5D).
  - Simplified Nutritional Appetite Questionnaire (SNAQ).
  - Total daily dose of levodopa and total daily levodopa equivalent dose.

Imaging endpoints
- Change from baseline to Week 80/e40 in volume of distribution of infusate as determined by contrast-enhanced T1-weighted MRI.
- Change from baseline to Week 80/e40 in volume of interest (VOI) coverage and total putamenal coverage as determined by contrast-enhanced T1-weighted MRI.
- Correlation between primary study endpoint and VOI coverage and total putamenal coverage at baseline as determined by contrast-enhanced T1-weighted MRI.
- Correlation between primary study endpoint and change from baseline to Week 40/e0 in ^{18}F-DOPA uptake as determined by positron emission tomography (PET) scan.
- Correlation between baseline OFF state UPDRS motor score (part III) and baseline ^{18}F-DOPA uptake as determined by PET scan.
- Correlation between baseline OFF state UPDRS ADL score (part II) and baseline ^{18}F-DOPA uptake as determined by PET scan.
- Correlation between Week 40/e0 OFF state UPDRS motor score (part III) and Week 40/e0 ^{18}F-DOPA uptake as determined by PET scan.
- Correlation between Week 40/e0 OFF state UPDRS ADL score (part II) and Week 40/e0 ^{18}F-DOPA uptake as determined by PET scan.
- Correlation between Week 80/e40 OFF state UPDRS motor score (part III) and Week 40/e0 ^{18}F-DOPA uptake as determined by PET scan.

- Correlation between Week 80/e40 OFF state UPDRS ADL score (part II) and Week 40/e0 ^{18}F-DOPA uptake as determined by PET scan.

Safety endpoints

- Frequency of treatment-emergent adverse events (TEAEs; all TEAEs and TEAEs related to study drug) during the study period.
- Frequency of device-related TEAEs during the study period.
- Frequency of dyskinesias, falls, adverse changes in mood, and impulsivity reported as TEAEs during the study period (AEs of special interest, AESIs).
- Adverse changes in MRI findings as captured by AE reporting.
- Results of routine laboratory blood tests (hematology, serum chemistry) and urinalysis performed during the study period.
- Frequency of subjects with anti-GDNF serum antibodies during the study period.
- Change from baseline in the Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease (QUIP) as assessed during the study period.
- Change from baseline in the MoCA as assessed during the study period.
- Change from baseline in the Mattis Dementia Rating Scale (MDRS) as assessed during the study period.

Statistical methods: The primary efficacy analysis compared the percentage change from baseline (Week 0 in study 2553) to Week 80/e40 in the practically defined OFF state UPDRS motor score (part III) between treatment groups for the ITT Primary Population using a mixed-effect model with repeated measures (MMRM), with baseline score as a covariate, treatment group and visit and treatment group*visit as fixed effects, and subject within treatment group as a random effect. As a sensitivity analysis, the primary efficacy analysis was repeated for the ITT Overall Population.

An MMRM adjusted for the baseline value of the respective assessment was also used to analyze further UPDRS scores, PD diary data, timed walking and timed tapping test results, and NMSS scores between treatment groups. For OFF state UPDRS scores, it was further used to compare change to Week 80/e40 in one group with change to Week 40/e0 in the other group. Treatment response was compared between treatment groups using Fisher's exact test. Analyses of PDQ-39, EQ-5D, SNAQ, total daily levodopa dose, and total daily levodopa equivalent dose and analyses of MRI imaging endpoints were performed to compare treatment groups using an analysis of covariance model adjusted for the baseline value of the respective assessment. Non-parametric Spearman rank correlation analyses were used to test for potential correlations between clinical endpoints (OFF state UPDRS motor score [part III] and OFF state UPDRS ADL score [part II]) and imaging data (MRI and PET).

Descriptive statistics were presented for all endpoints by treatment group (exception: PET data from study 2553 used in correlation analyses). All hypothesis tests were run with 2-sided alpha = 0.05. No multiplicity adjustments were done. All inferential analyses were for exploratory purposes only.

Safety data were analyzed descriptively by treatment group (and overall, where appropriate). No statistical testing was performed.

Summary and conclusions:

Study subjects

All 41 subjects who completed study 2553 were enrolled in the extension study. All 41 subjects received open-label study treatment and completed the Initial Extension. Five of the 6 Pilot Stage subjects were subsequently enrolled and treated in the Pilot Extension. Twenty-three subjects (2 Pilot Stage subjects, 21 Primary Stage subjects) were enrolled and treated in the Supplemental Extension by the end of December 2016. The maximum duration of involvement in study 2797 was approximately 34 months.

In the ITT Primary Population, 18 of the 35 subjects were male and 17 were female. Thirty-four subjects were white and 1 was Asian. The mean age at time of informed consent for study 2553 was 56.4 years (range: 41-72 years), with 6 subjects aged ≥65 years. The mean duration since onset of PD symptoms was 10.9 years (range: 5-26 years), and the mean duration since PD diagnosis was 8.3 years (range: 2-19 years). All subjects presented at a Hoehn and Yahr stage of 2-3 in the OFF state and with an OFF state UPDRS motor score (part III) of 26-45 at screening. With the exception of small imbalances in sex distribution, proportions of subjects with Hoehn and Yahr stage 2 and 2.5 in the OFF state, and total daily levodopa dose, there were no notable differences in demographic and PD characteristics between the treatment groups. Demographic and PD characteristics for the ITT Overall Population including all 41 subjects were very similar to those for the ITT Primary Population.

Efficacy results

No statistically significant difference could be demonstrated between the treatment groups in the prespecified primary efficacy analysis of percentage change from baseline to Week 80/e40 in OFF state UPDRS motor score in the ITT Primary Population. The MMRM showed a small mean treatment difference in favor of placebo/GDNF that was not statistically significant (LS mean difference: 6.0%, 95% confidence interval [CI]: -8.6, 20.7, p=0.4078). The findings of the sensitivity analysis of the primary efficacy endpoint in the ITT Overall Population at Week 80/e40 were similar (LS mean difference: 0.4%, 95% CI: -13.9, 14.6, p=0.9587).

Analyses of the secondary and supplementary efficacy endpoints at Week 80/e40 also showed no statistically significant treatment differences, except for total daily levodopa equivalent dose which remained mostly unchanged in the GDNF/GDNF group (increase of 59 mg) but increased notably in the placebo/GDNF group (increase of 289 mg; p=0.0156).

The lack of statistically significant treatment differences in most clinical endpoints at Week 80/e40 was expected in view of the results of study 2553 and given that all placebo subjects received GDNF in their second 9-month treatment period. However, detailed analyses of the nature and direction of the efficacy results in both treatment groups revealed consistent findings in favor of GDNF treatment in this study.

Both treatment groups showed moderate to large clinically important mean improvements in OFF state UPDRS scores between baseline and Week 80/e40 (motor score: -9.6 points in the GDNF/GDNF group vs. -9.0 points in the placebo/GDNF group; ADL score: -6.9

vs. -4.6 points). The change in OFF state UPDRS motor score put subjects close to the lower end of the range of OFF state UPDRS motor scores permitted at entry to study 2553 (25-45). Moreover, it is in contrast to the predicted disease progression reflected by a 2.4-point worsening of OFF state UPDRS motor score over 80 weeks for a modelled control based on data from the Parkinson's Progression Markers Initiative database.
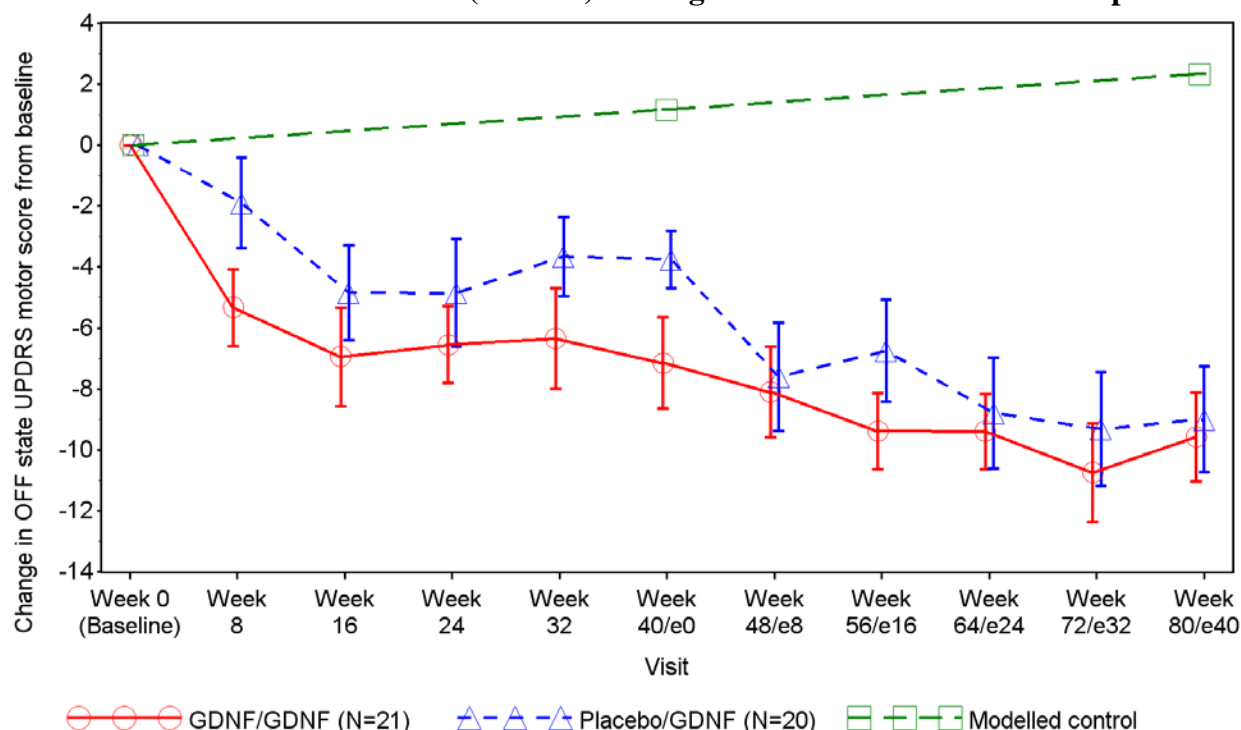
OFF State UPDRS Scores (Mean [SD]): Change Over Time - ITT Overall Population

| UPDRS score	GDNF/GDNF (N=21[a])			Placebo/GDNF (N=20)			LS mean difference vs placebo (95% CI); p-value[b]
	Week 0 (baseline)	Week 80/e40	Change from baseline	Week 0 (baseline)	Week 80/e40	Change from baseline	
Motor (part III)	36.0 (11.73)	26.4 (11.33)	-9.6 (6.70)	32.2 (8.29)	23.2 (8.99)	-9.0 (7.75)	-0.0 (-4.4, 4.4); 0.9929
ADL (part II)	18.5 (6.38)	11.7 (4.89)	-6.9 (5.46)	16.9 (5.82)	12.3 (6.60)	-4.6 (4.71)	-1.7 (-4.6, 1.2); 0.2455
Total (part II+III)	55.0 (16.70)	37.9 (14.89)	-17.1 (8.64)	49.1 (10.95)	35.5 (13.04)	-13.6 (9.97)	-2.6 (-8.3, 3.2); 0.3689

[a] N=20 for analyses of ADL and total scores.
[b] MMRM with baseline UPDRS score as a covariate, treatment group and visit and treatment group*visit as fixed effects, and subject within treatment group as a random effect

OFF State UPDRS Motor Score (Part III): Change Over Time - ITT Overall Population

Note: Data points represent means, and error bars represent standard errors. Modelled control based on data from the Parkinson's Progression Markers Initiative database.

OFF State UPDRS ADL Score (Part II): Change Over Time - ITT Overall Population
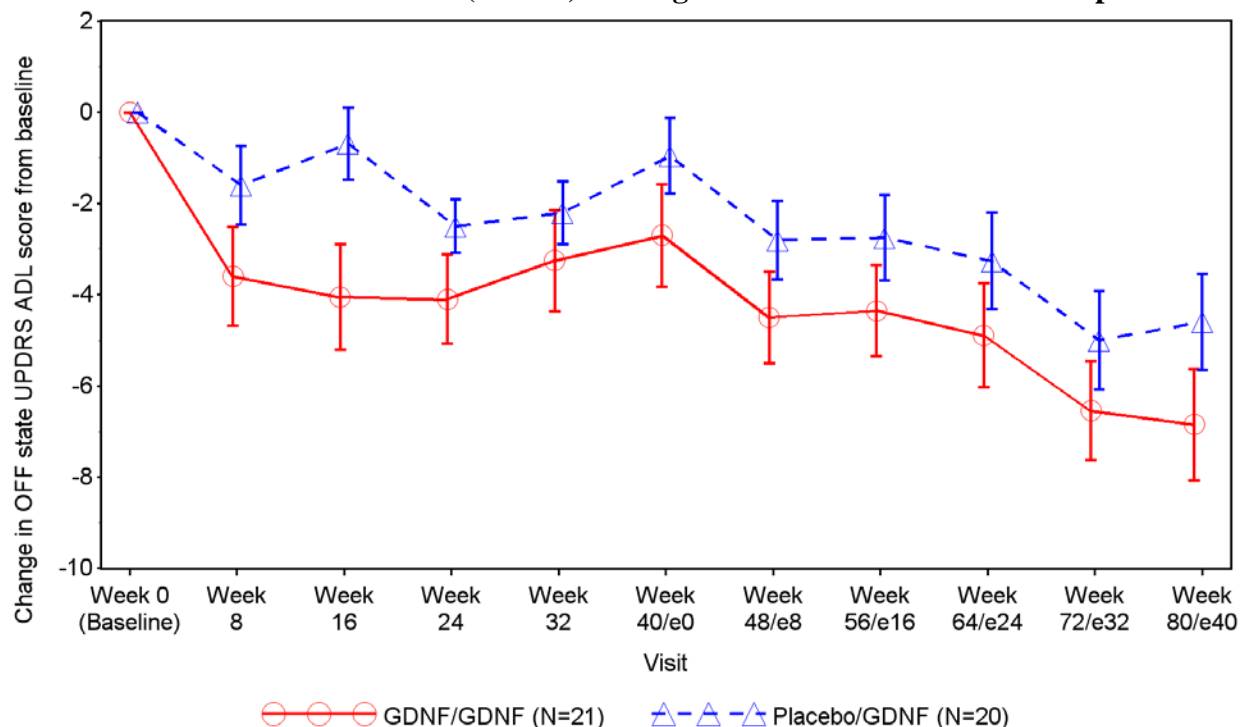
Note: Data points represent means, and error bars represent standard errors.

The mean OFF state UPDRS improvements from baseline to Week 80/e40 in the GDNF/GDNF group were significantly larger than the corresponding mean changes to Week 40/e0 in the placebo/GDNF group (motor score: -9.6 vs. -3.8 points, p=0.0108; ADL score: -6.9 vs. -1.0 points, p=0.0003).

OFF State UPDRS Scores (Mean [SD]): Change from Baseline to Week 80/e40 for the GDNF/GDNF Group Compared to Change from Baseline to Week 40/e0 for the Placebo/GDNF Group, MMRM - ITT Overall Population

UPDRS score	GDNF/GDNF (N=21[a])			Placebo/GDNF (N=20)			LS mean difference vs placebo (95% CI); p-value[b]
	Week 0 (baseline)	Week 80/e40	Change from baseline	Week 0 (baseline)	Week 40/e0	Change from baseline	
Motor (part III)	36.0 (11.73)	26.4 (11.33)	-9.6 (6.70)	32.2 (8.29)	28.5 (9.29)	-3.8 (4.20)	-5.3 (-9.3, -1.3); 0.0108
ADL (part II)	18.5 (6.38)	11.7 (4.89)	-6.9 (5.46)	16.9 (5.82)	15.9 (5.34)	-1.0 (3.71)	-5.3 (-8.1, -2.5); 0.0003
Total (part II+III)	55.0 (16.70)	37.9 (14.89)	-17.1 (8.64)	49.1 (10.95)	44.4 (12.40)	-4.7 (5.27)	-11.5 (-16.9, -6.1); <0.0001

[a] N=20 for analyses of ADL and total scores.
[b] MMRM with baseline UPDRS score as a covariate, treatment group and visit and treatment group*visit as fixed effects, and subject within treatment group as a random effect

Improvements in all PD motor fluctuation diary ratings were reported by subjects in both treatment groups between baseline and Week 80/e40, with a decrease in mean total OFF time per day (GDNF/GDNF: -1.47 hours, placebo/GDNF: -0.82 hours), an increase in total good-quality ON time (GDNF/GDNF: 1.64 hours, placebo/GDNF: 0.54 hours), and a small decrease in ON time per day with troublesome dyskinesias (GDNF/GDNF: -0.23 hours, placebo/GDNF: -0.11 hours).

PD Motor Fluctuation Diary Ratings (Hours; Mean [SD]): Change from Baseline to Week 80/e40, MMRM - ITT Overall Population

Variable	GDNF/GDNF (N=21[a])			Placebo/GDNF (N=20[a])			LS mean difference vs placebo (95% CI); p-value[b]
	Week 0 (baseline)	Week 80/e40	Change from baseline	Week 0 (baseline)	Week 80/e40	Change from baseline	
Total OFF time per day	6.11 (1.689)	4.54 (1.770)	-1.47 (1.388)	4.83 (2.243)	3.97 (2.124)	-0.82 (2.768)	-0.159 (-1.403, 1.085); 0.7975
Total good-quality ON time per day	10.19 (1.996)	11.80 (2.202)	1.64 (1.487)	12.48 (2.609)	13.09 (3.085)	0.54 (3.034)	0.571 (-0.965, 2.107); 0.4573
ON time per day with troublesome dyskinesias	0.56 (1.202)	0.36 (1.041)	-0.23 (0.814)	0.47 (0.977)	0.35 (0.737)	-0.11 (1.189)	-0.066 (-0.585, 0.454); 0.7997

[a]   N=20 at Week 80/e40 in GDNF/GDNF group, N=19 at Week 0 in placebo/GDNF group

[b]   MMRM with baseline variable as a covariate, treatment group and visit and treatment group*visit as fixed effects, and subject within treatment group as a random effect

Note: Total good-quality ON time per day is defined as the sum of ON time per day without dyskinesias and ON time per day with non-troublesome dyskinesias.

At Week 80/e40, the number of strong OFF state UPDRS motor score responders (decrease of ≥10 points) in the placebo/GDNF group was the same (9) as in the GDNF/GDNF group at Week 40/e0, thus independently replicating the latter result. In the GDNF/GDNF group, the number of strong responders increased further from 9 subjects at Week 40/e0 to 11 subjects at Week 80/e40. Fifteen subjects in the GDNF/GDNF group and 9 subjects in the placebo/GDNF group had an improvement of ≥1 hour in good-quality ON time between baseline and Week 80/e40.

Eleven (52.4%) GDNF/GDNF subjects showed large clinically important improvements (≥10 points) in OFF state UPDRS motor score from baseline to Week 80/e40, 5 (23.8%) showed moderate improvements (5-9 points), and 3 (14.3%) showed small improvements (1-4 points).

In a post hoc analysis, mean integrated overall response (IOR) scores differed substantially between the treatment groups during the entire 80-week period, favoring GDNF/GDNF at each time point. At Week 40/e0, the treatment difference in the IOR was highly statistically significant in favor of GDNF/GDNF, with virtually no effect in the placebo/GDNF group (-23.98 vs. -1.36, p=0.0032). Subsequently, there was continued improvement up to Week 80/e40 (-40.28 vs. -24.02, p=0.1201). The effect size in the first 40 weeks of GDNF treatment was the same in both groups, confirming the findings for strong UPDRS motor score responders. All subjects in the GDNF/GDNF group were responding to treatment in one or more components of the IOR at Week 80/e40. In a number of analyses of robustness modifying the PD diary

component of the IOR and its weight, the score was found to be remarkably stable, and adjusting for baseline did not impact the conclusions or improve the model fit.

Integrated Overall Response Score Over Time - ITT Overall Population
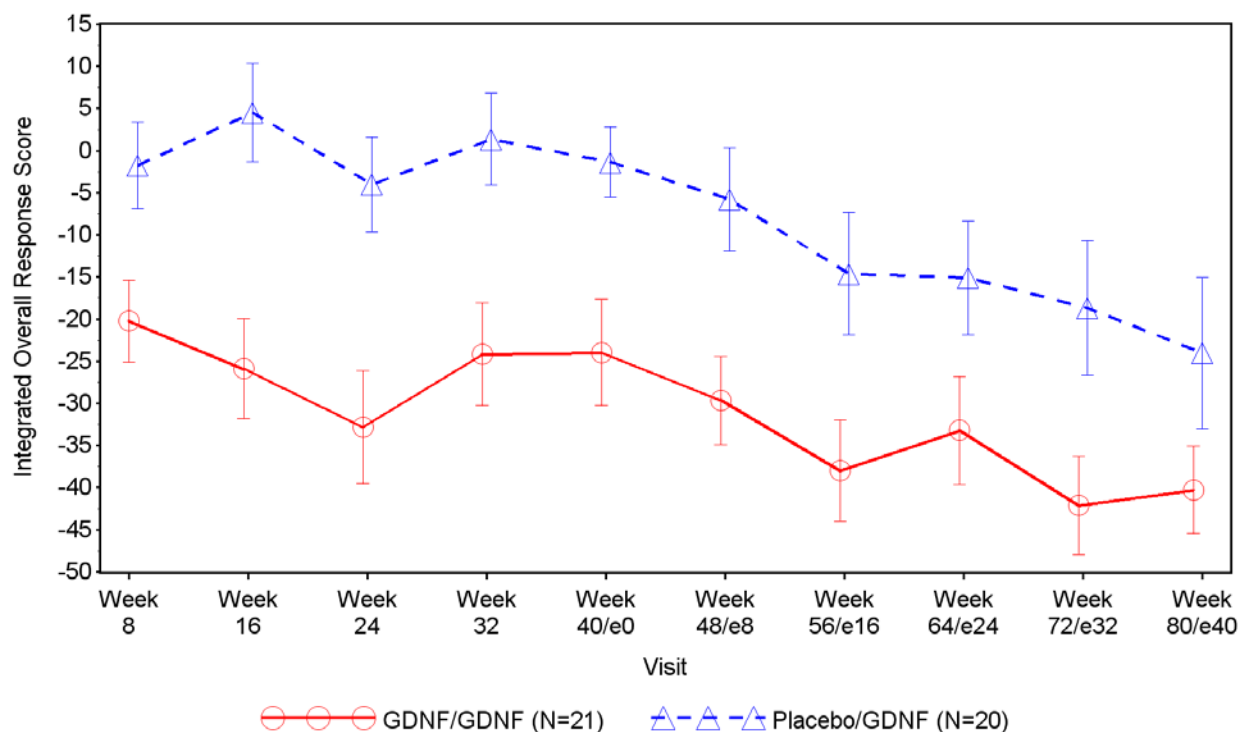
Note: Data points represent means, and error bars represent standard errors. The IOR score is calculated as (1 × change in OFF state motor score) + (2 × change in OFF state ADL score) – (10 × change in total good-quality ON time per day). A decrease in IOR score represents an improvement.

Imaging results

During the course of the extension study, volume of distribution of infusate, VOI coverage, and total putamenal coverage showed only small changes in both treatment groups. Treatment differences for change from baseline to Week 80/e40 were not statistically significant. ^{18}F-DOPA uptake was not re-assessed at Week 80/e40.

Correlation analyses did not reveal any relationship between the primary study endpoint and VOI coverage or total putamenal coverage at baseline, or between the primary study endpoint and change from baseline to Week 40 in ^{18}F-DOPA uptake, except for a trend for the expected negative correlation (i.e., greater increase in ^{18}F-DOPA uptake correlated with greater decrease in OFF state UPDRS motor score) in the dorsal central/posterior putamen in the GDNF/GDNF group in the ITT Overall Population (correlation coefficient: -0.371, p=0.0904).

Safety results

Compliance with the visit schedule was very good. In the Initial Extension, 401 (97.8%) of 410 GDNF infusions scheduled were administered, and mean total exposure to GDNF was 2.347 mg. Overall, during the course of all extension parts of study 2797, a total of 609 infusions

of study medication were administered, 305 to the 21 subjects in the GDNF/GDNF group and 304 to the 20 subjects in the placebo/GDNF group. The number of infusions given per subject ranged from 5 to 36 (GDNF/GDNF: 5 to 31, placebo/GDNF: 10 to 36). Mean total exposure to GDNF in the study was 3.565 mg. Interruption or early termination of infusion due to occlusion of one or more catheters occurred predominantly in Pilot Stage subjects and was probably caused by septum debris resulting from long-term repeated septum penetration. To address the problem, changes to the septum manufacturing process were made early in the Primary Stage.

TEAEs were reported for all 41 subjects. In the Initial Extension, the pattern of TEAEs observed was consistent with the GDNF group in study 2553 and previous clinical studies testing continuous intraputamenal administration of GDNF in subjects with PD. Nine of the 10 most frequently reported TEAEs in the Initial Extension (dyskinesia, Lhermitte's sign, nasopharyngitis, paresthesia, fall, ON and OFF phenomenon, freezing phenomenon, application site infection, and headache) were also amongst the 10 most frequently reported TEAEs in the GDNF group in study 2553. Dystonia (9 [22.0%] subjects) was the only frequently reported TEAE that occurred at a markedly lower frequency in the GDNF group in study 2553 (1 [4.8%] subject). The individual frequencies of the 9 matching frequently reported TEAEs, their overall frequency range (22.0-41.5% in the Initial Extension vs. 19.0-42.9% in study 2553), and the range of ratios of event reports relative to the number of reporting subjects (approximately 1.1-2.3 vs. 1.1-2.1) were similar in both studies.

The treatment groups were generally comparable with regard to the frequencies of individual TEAEs in the Initial Extension. There were only few individual TEAEs with a difference in frequency of at least 3 subjects between the treatment groups, and no pattern could be discerned in the distribution of these TEAEs by treatment group.

The profile of the most frequent individual TEAEs that occurred in the entire extension study (TEAEs experienced by at least 3 subjects of a treatment group) was very similar to that for the Initial Extension.

In the entire extension study, 22 (53.7%) subjects experienced TEAEs rated as severe, 11 (26.8%) subjects experienced TEAEs rated with a maximum severity of moderate, and 8 (19.5%) subjects experienced TEAEs rated with a maximum severity of mild. The high frequency of severe TEAEs was attributable largely to severe musculoskeletal and connective tissue disorders (10 [24.4%] subjects) and severe nervous system disorders (8 [19.5%] subjects). The only severe TEAEs reported for 3 or more subjects overall were back pain (4 subjects), muscle spasms (3 subjects), and dystonia (3 subjects). Dystonia was the only severe TEAE with a notable difference between the treatment groups (3 subjects in the GDNF/GDNF group, 0 subjects in the placebo/GDNF group). These events are commonly reported by PD patients.

Study medication-related TEAEs were reported for 34 (82.9%) subjects in the entire extension study. By far the most common types of study medication-related TEAE were disorders of the nervous system (30 [73.2%] subjects), followed by psychiatric disorders (11 [26.8%] subjects). With the exception of muscle spasms, all individual study medication-related TEAEs reported for at least 3 subjects overall were classified in the "Nervous system disorders" system organ class. Lhermitte's sign, paresthesia, headache, Parkinson's disease, and head discomfort were

reported more frequently in the GDNF/GDNF group than in the placebo/GDNF group (difference of ≥3 subjects between treatment groups).

Device-related TEAEs were reported for 19 (46.3%) subjects in the entire extension study. All device-related TEAEs reported by 3 or more subjects overall were related to the application site (port), and there were no TEAEs related the intracerebral parts of the drug delivery system. No notable differences were observed between the treatment groups with respect to the individual device-related TEAEs.

No subjects died. Serious TEAEs were reported for 8 (19.5%) subjects during the Initial Extension and 5 (19.2%) subjects in the Pilot or Supplemental Extensions. Overall, in the entire extension study, a total of 18 serious TEAEs were reported for 10 (24.4%) subjects. Nine of the 18 serious TEAEs were complications associated with the device, application site, or surgical procedures that were considered by the investigator as device-related and not related to the study medication; all of these device-related TEAEs occurred in 3 Pilot Stage subjects. The other 9 serious TEAEs (in 7 Primary Stage subjects) were not device complications, and none of them were considered by the investigator as related to study medication or to the device. Two subjects had to discontinue study medication after explantation of their device (or parts thereof) approximately halfway through the Pilot Extension, subsequent to device-related or application site infections.

Treatment-emergent AESIs (dyskinesias, falls, adverse changes in mood, impulsivity) were reported for 33 (80.5%) subjects in the entire extension study. The frequencies of the individual AESIs were generally well balanced between the treatment groups, except for falls which occurred more frequently in the placebo/GDNF group (10 subjects) than in the GDNF/GDNF group (6 subjects).

Clinically relevant changes in clinical laboratory parameters, vital signs, weight, electrocardiogram, or assessments of cognitive and neurological status were observed only sporadically during the study, and there was no treatment-related pattern discernible. No anti-GDNF binding serum antibodies were identified at any time point during the study.

Conclusions

The lack of statistically significant treatment differences in most clinical endpoints at Week 80/e40 was expected in view of the results of the parent study and given that all placebo subjects received GDNF in their second 9-month treatment period. However, both treatment groups showed moderate to large clinically important mean improvements in OFF state UPDRS motor and ADL scores and improvements in all PD motor fluctuation diary ratings. In addition, while acknowledging the limitations of the open-label study design, results for analyses of OFF state UPDRS motor and ADL scores, treatment responders, and IOR scores support the conclusion that the benefits observed in the GDNF/GDNF group were the result of a true drug effect.

GDNF was well tolerated and safe in the PD population investigated. The pattern of TEAEs observed in the Initial Extension was consistent with the GDNF group in study 2553 and

previous clinical studies testing continuous intraputamenal administration of GDNF in subjects with PD.

In conclusion, the findings of this study suggest that GDNF given via intermittent bilateral intraputamenal CED continues to hold promise as a neurorestorative and neuroprotective treatment for PD and warrants further investigation leveraging key learnings from the current program.

Date of the report: 18 Oct 2017

3.   **TABLE OF CONTENTS**

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

4.   LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

aCSF	Artificial cerebrospinal fluid
ADL	Activities of daily living
AE	Adverse event
AESI	Adverse event of special interest
ANCOVA	Analysis of covariance
BDI	Beck Depression Inventory
BP	Blood pressure
CED	Convection-enhanced delivery
CI	Confidence interval
COMT	Catechol-O-methyl transferase
CRF	Case report form
CSF	Cerebrospinal fluid
DMC	Data monitoring committee
DOPA	Dihydroxyphenylalanine
ECG	Electrocardiogram
EQ-5D	EuroQOL 5-Dimensional Scale
FLAIR	Fluid-attenuated inversion recovery
FrSBe	Frontal Systems Behavioural Scale
GCP	Good Clinical Practice
GDNF	Glial cell line-derived neurotrophic factor
ICH	International Conference on Harmonisation
IOR	Integrated overall response
ITT	Intention-to-treat
LOCF	Last observation carried forward
MAO-B	Monoamine oxidase B
MDRS	Mattis Dementia Rating Scale
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare Products Regulatory Agency
MMRM	Mixed-effect model with repeated measures

MoCA	Montreal Cognitive Assessment
MRI	Magnetic resonance imaging
NMSS	Non-Motor Symptom Scale
PD	Parkinson's disease
PDQ-39	Parkinson's Disease Questionnaire-39
PET	Positron emission tomography
PT	Preferred term
QUIP	Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease
r-metHuGDNF	Recombinant-methionyl human glial cell line-derived neurotrophic factor
ROI	Region of interest
RT	Deary-Liewald Reaction Time
SAP	Statistical analysis plan
SD	Standard deviation
SNAQ	Simplified Nutritional Appetite Questionnaire
SOC	System organ class
TEAE	Treatment-emergent adverse event
UPDRS	Unified Parkinson's Disease Rating Scale
UPSIT	University of Pennsylvania Smell Identification Test
VOI	Volume of interest
WHO DDE	World Health Organization Drug Dictionary Enhanced

NOMENCLATURE NOTES

The chemical name of the active investigational medicinal product given in this study is recombinant-methionyl human glial cell line-derived neurotrophic factor (r-metHuGDNF). The international non-proprietary name for r-metHuGDNF is liatermin. Throughout this document, r-metHuGDNF is referred to as GDNF, unless differentiation from native human GDNF is needed.

The term "contrast-enhanced T1-weighted MRI" denotes T1-weighted MRI performed following a gadolinium contrast-enhanced test infusion.

5. ETHICS

5.1 Independent Ethics Committee or Institutional Review Board

The protocol and protocol amendments 1 to 4 were reviewed and approved by the study center's responsible ethics committee (NRES Committee South West - Central Bristol, Bristol Research Ethics Committee Centre, Level 3, Block B, Whitefriars, Lewin's Mead, Bristol BS1 2NT, United Kingdom; Chair: Dr Pamela Cairns) and by the Medicines and Healthcare Products Regulatory Agency (MHRA) of the United Kingdom before the start of the study and before implementation of the amendments respectively.

5.2 Ethical Conduct of the Study

The conduct of this clinical study met all local legal and regulatory requirements. The study was conducted in accordance with the protocol and with the ethical principles that have their origin in the Declaration of Helsinki and the International Conference on Harmonisation (ICH) guideline E6: Good Clinical Practice (GCP).

5.3 Subject Information and Consent

Informed consent of subjects was obtained before any study-specific procedures and assessments were performed, i.e. before Week e0 procedures for this study were performed. Week 40 procedures for study 2553 could be used as screening for this study and could be performed before consent for the extension study was obtained.

The experimental nature of the study; the implications and constraints of the protocol; the known side effects of the study treatment; and any risks involved in taking part were explained to each potential subject by the principal investigator or a designee. The explanations were given both verbally and in writing using the subject information ("patient information sheet") and informed consent form.

The information about the study was provided to the potential subjects at the Week 36 visit or earlier in study 2553, so as to allow the subjects ample time to consider the information and the opportunity to question the principal investigator or designee, their general practitioner, or other independent parties to decide whether to participate in the study. Subjects were assured of the right to withdraw from the study at any time without prejudice to future care and with no obligation to give the reason for withdrawal.

The informed consent form was then signed and dated by the subject and by the person who presented and obtained the informed consent. A copy of the signed informed consent form was given to the subject. The original signed form was retained at the study center, and a copy was filed in the medical notes.

Subjects who enrolled in the Pilot and Supplemental Extensions were required to sign and date an additional informed consent form prior to initiation of any Pilot or Supplemental Extension procedures.

Both the subject information and the informed consent form were amended as appropriate during the study to always allow for provision of the most up-to-date information on the study. All amendments were approved by the ethics committee prior to implementation. For details, refer to Section 9.9.2.

For <u>surgical interventions</u> required to treat issues related to the drug delivery system, a separate consent was presented by the study neurosurgeon or designee, to ensure that subjects were fully informed and had the opportunity to ask questions regarding risks specific to the neurosurgical procedure.

For the most recent versions of the subject information and informed consent documents, see Section 17.1.3 Patient information sheet, Consent form, and Surgery informed consent document.

6.   INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

The study was an investigator-initiated single-center study sponsored by North Bristol NHS Trust, Bristol, United Kingdom.

The principal investigator was Dr Alan Whone, Consultant Senior Lecturer in Movement Disorders, University of Bristol, and Honorary Consultant Neurologist, Movement Disorder Service, Bristol Brain Centre, Southmead Hospital, North Bristol NHS Trust, Bristol BS10 5NB, United Kingdom.

The study neurosurgeon was Professor Steven Gill, Consultant Neurosurgeon, Department of Neurosurgery, Southmead Hospital, North Bristol NHS Trust, Bristol BS10 5NB, United Kingdom.

From October 2013 to May 2014, the study was performed at the Department of Neurology, Frenchay Hospital, Bristol BS16 1LE, United Kingdom. Due to reorganization of hospital services within North Bristol NHS Trust, the hospital moved in May-June 2014 to a new location, Southmead Hospital, Bristol BS10 5NB, United Kingdom. Therefore, from June 2014 to the end of the study in February 2017, the study was performed at Southmead Hospital.

Figure 1 shows the roles and responsibilities of the Trial Steering Committee, study team/on-site trial team, Sponsor, drug manufacturer, and device contract manufacturer (subcontracted by North Bristol NHS Trust). See also Section 17.1.4, List of important contributors to the study and List of Trial Steering Committee members.

The study was monitored by the independent data monitoring committee (DMC) established by the Sponsor for study 2553, using the original charter. The DMC could recommend termination of the trial at any point for safety reasons. See also Section 17.1.8, DMC charter.

Figure 1   Roles and Responsibilities in the Study

Steering Committee - - - - - - - - - - - - - - - -   **Study Team**

Strategic decision making body

- Oversee and advise on study/program goals, design, timing and conduct
- Approve study protocols and amendments and recommend approval to sponsor
- Manage and resolve major operational, scientific/medical and technical issues

Operational decision making body

- Manage day to day activities and ensure regular flow of communication
- Review (need for) protocol amendments and study tools
- Monitor study progress and compliance
- Identify and evaluate issues and recommend solutions to steering committee

Sponsor (NBT) / R&I

- Provide contractual framework
- Provide indemnification
- Ensure access to necessary facilities and equipment for study conduct
- Maintain/update budget and provide to grantor
- Hire on-site trial team resources
- Monitor on regular schedule
- Ensure proper SAE reporting
- Review and sign DSURs
- Approve protocol and amendments
- Provide device design specifications to contract manufacturer

Parkinson's UK

- Provide primary funding for study conduct

MedGenesis

- Manufacture and provide study drug
- Provide supportive funding for study conduct
- Prepare protocols / amendments
- Prepare DSURs
- Provide trial management support and GCP guidance; lead Study Team calls
- Provide guidance for monitoring team
- Oversee MHRA submissions on behalf of sponsor (via Granzer)
- Interface and contract with PRA for:
  - Co-monitoring
  - Data management
  - Preparation of statistical analysis plan
  - Statistical analysis
- Prepare study reports

Renishaw

- Contract manufacture and provide delivery device, administration kits, planning software and surgical tooling according to sponsor specifications
- Provide technical support during surgeries and infusions
- Support surgical planning and MRI evaluation

On-site Trial Team

- Sign off on protocols and amendments (PI)
- Develop patient information sheet and amendments
- Prepare submissions to ethics committee
- Recruit eligible subjects and make medical decisions (PI)
- Treat subjects according to protocol and ensure compliance with GCP
- Manage all study logistics/interfaces and subject flow including liaison with and scheduling for:
  - Hospital pharmacy
  - Surgeons for replacement surgeries and follow up
  - Outcome assessments
  - MRI scans
- Report SAEs
- Document study findings and maintain study files
- Provide documentation required to support financial management of trial
- Identify and communicate resource needs
- Report to DMC on regular basis

Table 1 lists other organizations that performed activities during the study or in connection with the analysis and reporting of the study findings. For a list of the full addresses of these organizations, see Section 17.1.4, List of other organizations performing activities in the study.

Table 1   Other Organizations Performing Activities in the Study

Organization	Activity
Catalent Pharma Solutions, Bathgate, United Kingdom	Clinical supplies and packaging
Chris Priestley Ltd, High Wycombe, United Kingdom	Medical writing support (clinical study report)
Eurofins Pharma Bioanalysis Services UK Limited, Abingdon, United Kingdom	Analysis of anti-GDNF antibodies in serum
Granzer Regulatory Consulting & Services, Munich, Germany	Regulatory consulting and submissions
Insite Quality Assurance, Inc., Sammamish, WA, USA	Unblinded pharmacy monitoring
MedGenesis Therapeutix Inc., Victoria, BC, Canada	Project management, medical oversight, protocol writing, clinical study report writing, regulatory submission oversight
PRA Health Sciences, Inc., Raleigh, NC, USA	Co-monitoring, data management, statistical analysis (statistical analysis plan and analysis of final study data)
Renishaw plc, Wotton-under-Edge, United Kingdom	Contract manufacturer of device, volumetric analysis of MRI scans, provision of surgical planning software, surgical assistance
Sartorius Stedim BioOutsource Limited, Glasgow, United Kingdom	Analysis of plasma GDNF concentrations

7. INTRODUCTION

7.1 Parkinson's Disease

Parkinson's disease (PD) is the second most common neurodegenerative disorder with an estimated overall prevalence of 0.3% in industrialized countries [1]. The 4 cardinal features of PD are resting tremor, slowed movement (bradykinesia), rigidity, and postural instability. Of note, it is estimated that by the time patients develop symptoms, they have lost approximately 50% of their nigral dopamine neurons and approximately 80% of striatal dopamine content [2].

Current therapeutic options for PD are limited to purely symptomatic treatments, and levodopa remains the most effective medication available [3, 4]. Despite treatment, PD relentlessly progresses and, with time, patients develop both treatment resistance and motor and non-motor complications of dopaminergic therapy [5]. Motor complications include wearing-off (gradual and predictable decline in the duration of response to a dose of levodopa), ON and OFF phenomena (fluctuations in motor performance that are not clearly related to levodopa dosing), and dyskinesias (involuntary movements) that can occur when levodopa concentrations reach their maximum (peak-dose dyskinesias) or when the levels are rising or falling (diphasic dyskinesias) [6].

While modifications of medical therapy can improve these symptoms in some patients for a time, no medical therapy exists which is capable of providing prolonged and stable dopaminergic responsiveness. This has led to an increasing use of surgical therapies for medically refractory cases, most importantly deep brain stimulation (DBS). DBS has been shown to provide major benefit to OFF period signs and symptoms with as much as a 50% reduction in OFF period motor scores and activity of daily living scores as measured by the Unified Parkinson's Disease Rating Scale (UPDRS) [5]. While it may permit a decrease in PD medication intake, this treatment does not substantially improve the patient's ON period function, nor does it reverse the progression of the disease [5].

There remains, therefore, a substantial need both for therapies that delay the progression of the disease and for therapies that restore and maintain consistent motor function and symptom control.

7.2 GDNF History

GDNF is a neurotrophic factor with potent effects on diverse nerve cell lines including dopaminergic, serotonergic, noradrenergic, and cholinergic neurones [7, 8]. It has been shown to have both neurorestorative and neuroprotective actions in primate models of PD when administered intracerebrally, as protein infusion and through gene therapy by viral vectors [9, 10, 11, 12, 13].

The development of GDNF has taken place in 2 stages. The first stage, performed by Amgen, Inc., included 3 clinical studies in PD testing continuous intraputamenal infusion of GDNF via indwelling microinfusion pumps implanted in the abdominal wall. The first was an open-label,

investigator-initiated Phase I study in 5 subjects with PD that showed substantial improvements in motor function at 6 months and 1 year [14]. This, together with another similarly successful Phase I study in 10 subjects [15, 16], led to a placebo-controlled Phase II study in 34 subjects that showed a modest improvement in ^{18}F-DOPA uptake in the caudal putamen of subjects treated with GDNF but did not achieve the expected improvement in motor outcome at 6 months [17, 18].

The adverse event (AE) profile of GDNF in these studies was quite favorable, dominated by mild to moderate sensory disturbances (paresthesias, Lhermitte's sign), headache, insomnia, falls, and constipation. As a potential concern, more than half of the subjects treated with GDNF developed binding antibodies to the protein, including 5 subjects with neutralizing antibodies. However, all of the affected subjects remained asymptomatic [19]. In parallel, intraputamenal GDNF was found to induce unexpected cerebellar toxicity in a small number of rhesus monkeys receiving very high doses (2,800 µg per 4 weeks) over 6 months [20].

While seemingly unrelated, the observed triad of questionable efficacy, immunogenicity, and cerebellar toxicity suggested an unfavorable benefit-to-risk ratio for GDNF. This led to a temporary halt of the program, initiated by Amgen, in 2004. Since then, problems pertaining to drug delivery have been identified as an important factor [21, 22, 23], if not the root cause, underlying all 3 issues. Most importantly, it was shown that the continuous low-rate infusion schemes (≤0.1 µL/min) employed in the initial intraputamenal studies led to drug distribution via diffusion and produced only minimal parenchymal coverage with unpredictable and highly variable tissue concentrations of GDNF [21]. Convection-enhanced delivery (CED), introduced to overcome the limitations of diffusion-based delivery [24], requires high maintenance flow rates (≥0.5 µL/min) [25, 26]. In turn, long-term use of CED-enabling flow rates requires intermittent dosing regimens to avoid substantial drug distribution beyond the desired target volume ("flooding") and leakage into white matter and/or the cerebrospinal fluid (CSF) compartment [27]. This, together with recent reports on extended pharmacokinetics and pharmacodynamics of GDNF in putamen [28, 29], was the rationale to switch to a novel intermittent CED paradigm at the second stage of the GDNF development program that was initiated by MedGenesis Therapeutix, Inc. in 2010.

The toxicity of intermittent GDNF administration via CED was evaluated in 20 rhesus monkeys in a 40-week placebo-controlled study with a 12-week recovery period. GDNF was delivered at the same concentration that previously induced cerebellar lesions when infused continuously (0.67 µg/µL). The total GDNF dose given every 4 weeks was 87.1 µg. There were no GDNF-related findings in the study, with the exception of anti-GDNF antibody formation and GDNF immunostaining in the brain of GDNF-treated animals, which were both expected [30]. Therefore, the tested dose was determined to be the no observed adverse effect level. When scaled to adjust for volume differences between rhesus monkey and Parkinsonian human brain [31], this dose corresponds to a scaled human equivalent dose of 1,307 µg every 4 weeks.

In parallel, a placebo-controlled, randomized, double-blind Phase II trial was performed in 41 subjects with PD to assess the safety and efficacy of intermittent bilateral intraputamenal GDNF infusions administered via CED (study 2553). Subjects were treated every 4 weeks for a

total of 40 weeks. GDNF was delivered at a concentration of 0.2 µg/µL. The total GDNF dose given every 4 weeks was 240 µg.

In this double-blind study, GDNF did not show a statistically significant greater effect than placebo on the primary endpoint (percentage change from baseline to Week 40 in OFF state UPDRS motor score [part III]) or any of the secondary efficacy endpoints [32]. However, virtually all efficacy endpoints showed numerical treatment differences in favor of GDNF, and a post hoc responder analysis showed a statistically highly significant difference in favor of GDNF for absolute response (decrease of ≥10 points in OFF state UPDRS motor score [part III]). In addition, GDNF induced a strong and statistically highly significant increase in putamenal ^{18}F-DOPA uptake.

GDNF appeared to be well tolerated and safe in the study. Overall, the pattern of treatment-emergent AEs (TEAEs) was consistent with the initial clinical studies testing continuous intraputamenal administration of GDNF in subjects with PD. However, no anti-GDNF binding serum antibodies were identified at any time point during the study. The safety risks of the study procedure were reflective of the development stage of the device and considered acceptable.

The present study was an open-label extension of study 2553.

8. STUDY OBJECTIVES

8.1 Primary Objective

To compare the effects of intermittent bilateral intraputamenal GDNF infusions on OFF state motor function after 18 months of study treatment with the effects after 9 months of treatment in subjects who completed study 2553.

8.2 Secondary Objectives

To compare the effects of intermittent bilateral intraputamenal GDNF infusions on ON state motor function, motor complications, and ON and OFF state activities of daily living (ADL) after 18 months of treatment with the effects after 9 months of treatment in subjects who completed study 2553.

To assess the safety of intermittent bilateral intraputamenal GDNF infusions at 18 months in subjects who received GDNF or placebo for 9 months in study 2553.

8.3 Other Objectives

To explore the effects of intermittent bilateral intraputamenal GDNF infusions on other motor and non-motor functions, quality of life assessments and imaging endpoints at 18 months in subjects who completed study 2553.

To compare the results for various motor outcomes between the subjects who started GDNF early (i.e. were randomized to GDNF in study 2553) and those who started GDNF late (i.e. were randomized to placebo in study 2553).

Pilot and Supplemental Extensions: To generate long-term safety data and provide continued access to GDNF until the end of December 2016 when the results of study 2553 are expected, which will inform interested parties with potential future studies (*objective added by amendments 2 and 4*).

9. INVESTIGATIONAL PLAN

The clinical study protocol and amendments are given in Section 17.1.1. The changes introduced by the amendments are summarized in Section 9.9.1.

The sample blank case report forms (CRFs) are provided in Section 17.1.2.

9.1 Overall Study Design

This was a Phase II, single-center, open-label, uncontrolled trial of intermittent bilateral intraputamenal GDNF infusions administered via CED in subjects with idiopathic PD who had completed the parent study 2553.

Following the final study visit at Week 40 in study 2553, study completers who gave informed consent for study 2797 returned within 1 week to receive their first infusion of open-label GDNF. Initially, study treatment was given at 4-weekly intervals for 9 months (40 weeks; 10 infusions total; the "Initial Extension"). Subsequently, the study protocol was extended twice to permit continuation of open-label GDNF and collection of further safety data:

- Pilot Stage subjects who completed the Initial Extension were eligible for up to an additional 80 weeks of treatment with GDNF (the "Pilot Extension"; *added by amendment 2*).

- Pilot Stage subjects completing Week e2-80 of the Pilot Extension and Primary Stage subjects completing Week e40 of the Initial Extension were eligible to enroll in a further extension (the "Supplemental Extension"; *added by amendment 4*) and continue to receive GDNF until the end of December 2016.

At the end of the first 9 months of open-label study treatment, subjects who had received GDNF in study 2553 had been treated with GDNF for a total of 18 months, while those who received placebo in study 2553 had been treated with GDNF for a total of 9 months.

Figure 2 presents an overview of the study. A total of 42 subjects were to be enrolled.

The primary endpoint of the study was the percentage change from baseline to Week 80/e40 in the practically defined OFF state UPDRS motor score (part III). The primary analysis was an intention-to-treat (ITT) analysis of the primary endpoint in the Primary Stage subjects, comparing the effect of study treatment after 18 months with that after 9 months.

Figure 2   Overview of the Study
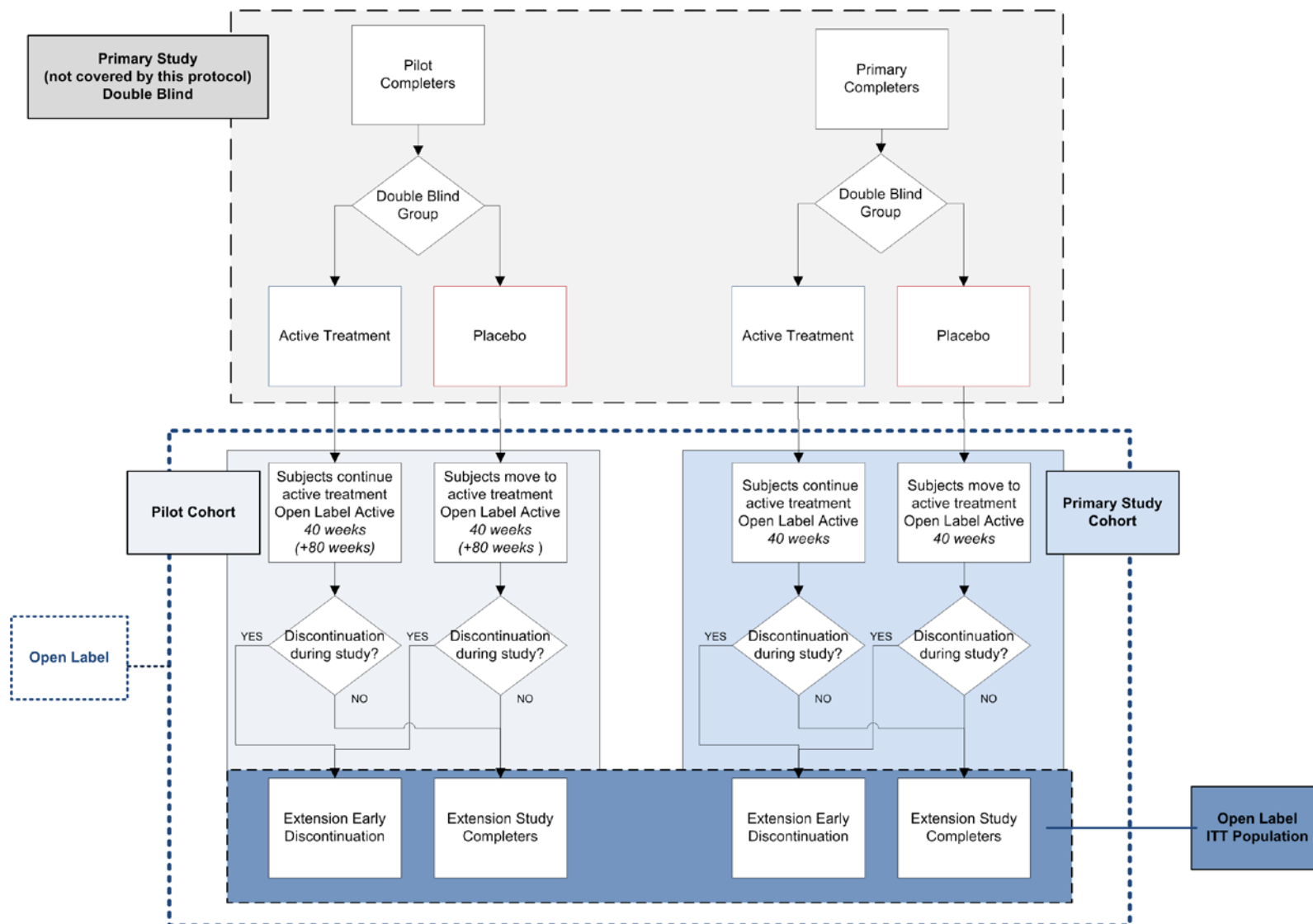
Note: The schema does not include the Supplemental Extension part of the study.

9.1.1 Post-Study Access to Treatment

During the informed consent process, subjects were advised that continued availability of GDNF beyond the end of the study could not be guaranteed even if the study outcome was positive and/or the individual subject derived benefit from being treated with GDNF during the study.

9.2 Discussion of Study Design

This study was an open-label uncontrolled extension of the Phase II randomized, double-blind, placebo-controlled study 2553 which assessed the safety and efficacy of GDNF infusions administered via CED in subjects with PD.

The extension study included subjects who completed study 2553. All subjects received GDNF using the same treatment protocol as used in study 2553.

The study was initially designed to assess the long-term safety and efficacy of GDNF when given up to 18 months in total, using similar endpoints to those used in study 2553. In addition, the study aimed to provide initial insight as to whether the effect on motor and other outcomes is improved with a longer duration of treatment (18 months versus 9 months). The additional parts of the study (Pilot Extension, Supplemental Extension) obtained further long-term safety data and provided continued access to GDNF until the end of December 2016 when the results of study 2553 were expected.

Acknowledging the obvious limitations of the open-label study design, to reduce any potential for bias, individual treatment codes from the parent study were not disclosed to subjects until database lock for study 2797, unless required for specific safety reasons. In addition, every effort was made to avoid unblinding of the blinded UPDRS raters before database lock for study 2797.

9.3 Selection of Study Population

The study was performed in subjects with idiopathic PD with motor fluctuations who completed study 2553.

9.3.1 Inclusion Criteria

In order to qualify for entry into the study, subjects had to meet all of the following criteria (as specified in the protocol and amendments):

1. Enrolled and completed treatment in the Pilot or Primary Stages of study 2553.

2. Females of childbearing potential must have a negative pregnancy test at study entry and be willing to use an approved (by the principal investigator or designee) form of contraception until the end of the study.

3. Males with female partners of childbearing potential must be willing to use condoms for contraception until the end of the study.

4. Provision of informed consent.

9.3.2 Exclusion Criteria

Subjects who met any of the following criteria (as specified in the protocol and amendments) were not eligible for inclusion in the study:

1. Discontinued treatment early in study 2553.

2. Had any significant (in the opinion of the principal investigator or designee) protocol deviation in study 2553; this included receipt of any disallowed anti-parkinsonian treatment or any investigational treatment.

3. Presence of clinically significant (in the opinion of the principal investigator) depression.

4. Montreal Cognitive Assessment (MoCA) score <24 at the final assessment in study 2553.

5. Any new medical condition which might impair outcome measure assessments or safety measures including ability to undergo magnetic resonance imaging (MRI) scanning.

9.3.3 Removal of Subjects from Therapy or Assessment

Subjects could withdraw from the study at any time. In addition, the principal investigator could discontinue a subject from the study at any time if considered necessary for any reason, including:

- Pregnancy.
- Ineligibility (either arising during the study or retrospectively, not having been identified at screening).
- Significant protocol deviation.
- Significant non-compliance with treatment regimen or study requirements.
- An AE which required discontinuation of the study medication or resulted in inability to continue to comply with study procedures.
- Disease progression which required discontinuation of the study medication or resulted in inability to continue to comply with study procedures.
- Consent withdrawn.
- Lost to follow-up.

Subjects who discontinued the study early were encouraged to observe the visit schedule for study assessments, at a minimum the final visit, unless they withdrew consent to do so.

The reason for withdrawal was to be recorded in the CRF. If the subject was withdrawn due to an AE, the subject was to be followed up until the AE had resolved or stabilized.

9.4 Convection-Enhanced Drug Delivery System

9.4.1 Composition of Drug Delivery System

In this study, the study treatment was administered intraputamenally using a customized in-house system for CED comprising 4 microcatheters, 4 catheter guide tubes, and a skull-mounted transcutaneous drug delivery port. The microcatheters were connected under the scalp to separate in-line bacterial filters and further to the drug delivery port. Figure 3 shows the drug delivery system used in the study, including the implanted components and the drug administration set.

The drug delivery system was surgically implanted in study 2553. Surgical interventions could be performed in the current study to treat relevant device-related issues, including device occlusion or severe device infection.

Figure 3   Drug Delivery System Used in the Study

Implanted catheters with in-line bacteria and particle filters

Transcutaneous port with mounted 4-line drug application set with in-line bacteria, air and particle filters
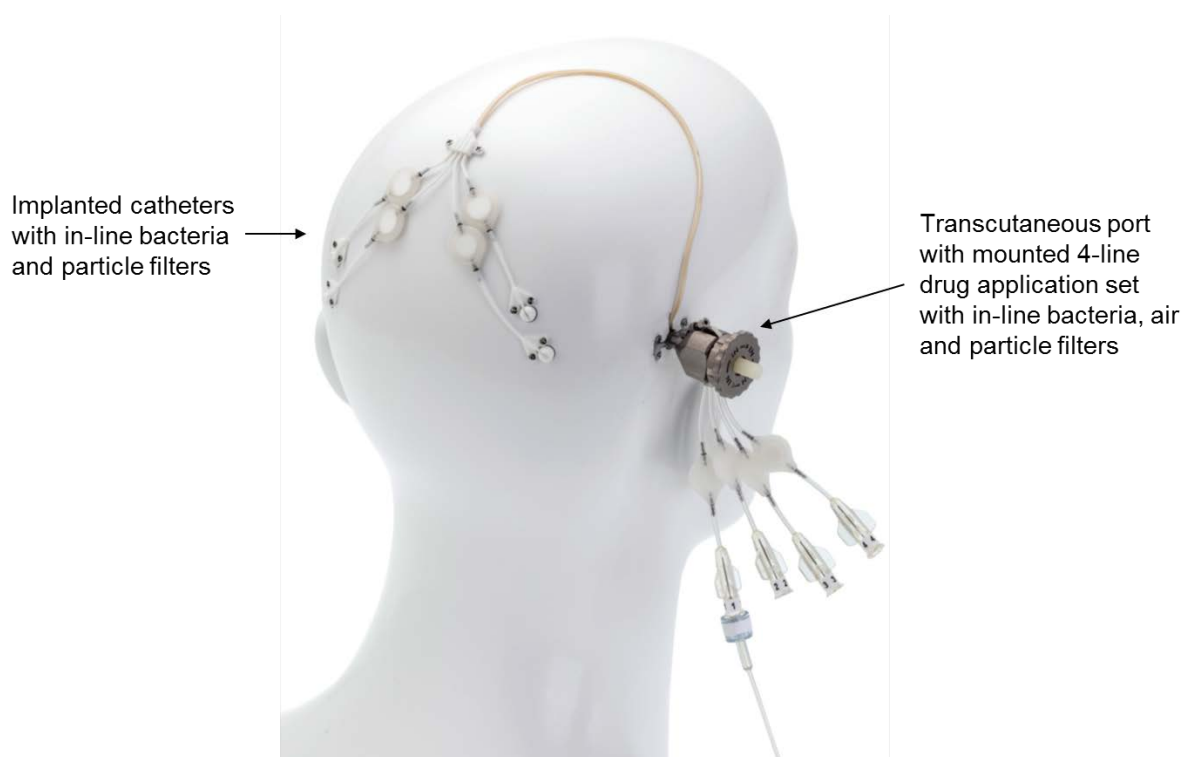
9.4.2 Preparation of Drug Administration System

The drug administration system comprised 4 programmable Perfusor® Space syringe infusion pumps (B Braun), four 5-mL Plastipak syringes (Becton Dickinson), 4 sealed extension lines with male Luer attachments (each containing a septum) at one end ("septum Luer lines"), 4 double-sided syringe connectors with female Luer attachments (each holding an internal needle), 4 lengths of sealed drug administration tubing with male Luer attachments (each

containing a septum) at both ends ("fixed-volume extension sets"), and a 4-channelled drug administration set. The latter comprised 4 needles mounted in a hub, each connected to independent bacteria and bubble filters and thence to short lengths of tubing, each with a female Luer attachment holding an internal needle. In addition, 3 syringe connectors with female Luer attachments at both ends and holding an internal needle at one end were used by the study site pharmacist preparing the study drug to fill the sealed extension lines and sealed drug administration lines. The "assembled and primed" administration set components are shown in Figure 4.

Figure 4   "Assembled and Primed" Administration Set Components
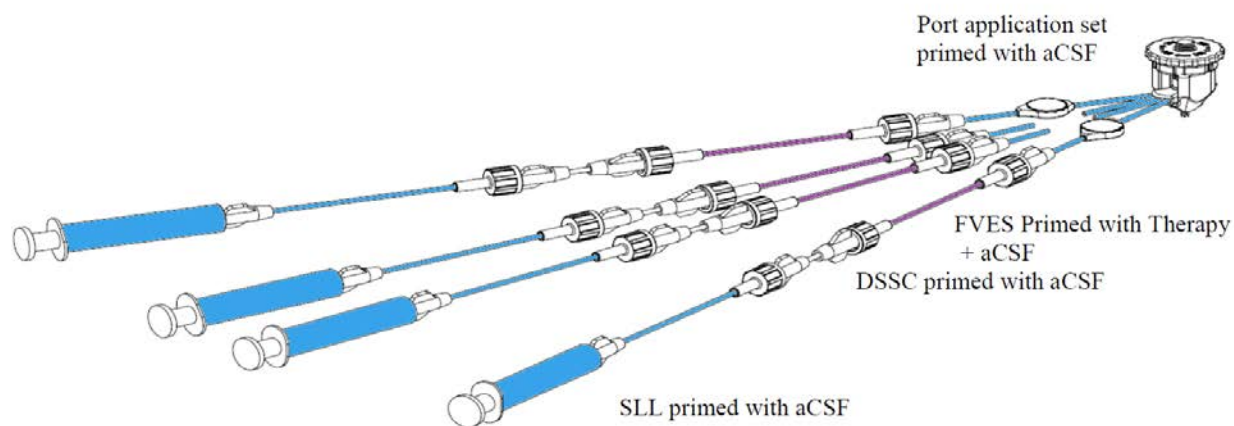
Note: Only 2 in-line filters are shown in the figure.
DSSC = Double-sided syringe connector; FVES = Fixed-volume extension set; SLL = Septum Luer line

Prior to study drug administration, the pharmacist filled the 4 lengths of drug administration tubing with an appropriate dose of GDNF (using 2 syringe connectors, one at each end of the sealed tubing), and labeled each line appropriately. The pharmacist also filled 4 syringes with artificial CSF (aCSF), connected them to the open ends of the extension lines, and filled the extension lines (using a single syringe connector at the opposite end to evacuate air). All syringe connectors were disconnected and discarded once all lines had been filled. The filling of devices took place up to 48 hours before a planned study drug infusion.

For the infusion, each syringe/sealed extension line assembly was connected to a double-sided syringe connector, then to a drug administration line, and then to one of the 4 channels of the drug administration set which prior to this had been flushed with aCSF.

Prior to connection of the drug administration set to the port, the health professional cleaned the port and the immediate surrounds with an aseptic technique. The cylindrical needle hub of the drug administration set was positioned over the port and locked to the port using a socket screw key. The 4 needles were lowered through the port septum by use of a hand-tightened nut and thence individually guided into their separate channels that conducted the drug to identifiable catheters.

Once the connection had been secured, study medication was administered as detailed in Section 9.5.1. On completion of the infusion, the administration set was disconnected from the port by unscrewing both the nut and the socket screw.

9.5 Treatments

9.5.1 Treatments Administered

The study treatment was GDNF.

9.5.1.1 Treatment Protocol

Table 2 summarizes the treatment protocol used for administration of GDNF.

Table 2 Treatment Protocol for GDNF

Study medication	GDNF (0.20 µg/µL in aCSF)
Infusion volume per treatment	300 µL GDNF plus 100 µL aCSF line flush per catheter, 600 µL GDNF plus 200 µL aCSF per putamen, 1200 µL GDNF plus 400 µL aCSF overall
Route	Intraputamenal infusion using a CED system with 2 indwelling catheters per putamen
Frequency	Every 4 weeks
Total dose every 4 weeks	60 µg per catheter, 120 µg per putamen, 240 µg overall
Total number of treatments	Initial Extension: 10 Pilot Extension: 19 Supplemental Extension: up to 13 until December 2016
Total duration of treatment	Initial Extension: 40 weeks Pilot Extension: 80 weeks Supplemental Extension: up to 52 weeks until December 2016
Scheme type	Linear ramping scheme
Infusion rate	Up-titrated from 0 µL/min to 3-5 µL/min (0.18-0.30 mL/hour) over 30 to 40 minutes
Total infusion time	Approximately 90-150 minutes

At each treatment visit, a drug administration set was prepared and connected with the transcutaneous port using a standard aseptic technique, as described in Section 9.4.2. Study drug was administered intraputamenally using preprogrammed infusion algorithms. For any given subject, the timing of administration during the day was kept approximately the same.

The infusions were delivered by trained personnel. During infusion, subjects remained semi-recumbent in a reclining chair.

An aCSF line flush was given after each infusion to clear the dead space of the implanted system.

9.5.1.2   Test Infusion

A test infusion of gadolinium-containing diluent (aCSF) was administered at Weeks e2-0 and e2-80 in the Pilot Extension (Pilot Stage subjects; *amendments 2 and 3*) and at Week 80/e40 (Primary Stage subjects; *amendment 3*).

The test infusions were freshly prepared on site prior to use according to the same procedure as for study medication. Four lengths of drug administration tubing (each holding 300 µL) were filled with aCSF containing 2 mM gadopentetate dimeglumine (1:250 dilution of gadopentetate dimeglumine in aCSF). The drug administration lines were then connected as specified in Section 9.4.2, and the infusate was delivered according to the infusion protocol described in Section 9.5.1.1.

9.5.2   Identity of Investigational Product(s)

9.5.2.1   GDNF

The investigational product GDNF was recombinant-methionyl human glial cell line-derived neurotrophic factor (r-metHuGDNF). The international non-proprietary name for r-metHuGDNF is liatermin. Throughout this document, r-metHuGDNF is referred to as GDNF, unless differentiation from native human GDNF is needed.

The GDNF drug product was a concentrate for dilution which was formulated at a concentration of 10 mg/mL in a buffer of 10 mM sodium citrate and 150 mM sodium chloride at pH 5.0. The final product was filled into 2 mL Type 1 glass vials. Each vial contained 0.5 ± 0.1 mL of sterile formulated bulk GDNF.

GDNF drug substance was prepared on behalf of MedGenesis Therapeutix, Inc., by Lonza Ltd, Visp, Switzerland. GDNF drug product was manufactured at Aptuit Ltd (now Albany Molecular Research Inc.), Glasgow, United Kingdom. Two drug product batches were used in the study: P03113 and P07012.

GDNF supplies were stored at the study site pharmacy in secure, limited-access, and temperature-controlled conditions ($-20 \pm 5°C$).

Prior to use, the GDNF vials were allowed to thaw (<30 minutes), and then the study site pharmacist prepared the study samples of GDNF solution in the required final concentration by addition of the requisite amounts of GDNF to an aCSF vial. The final concentration of GDNF used was 0.2 µg/µL. Drug preparation guidelines were provided in a separate pharmacy manual (Section 17.1.1, Pharmacy manual).

9.5.2.2   Artificial Cerebrospinal Fluid (aCSF)

Artificial CSF (aCSF) was supplied in 20 mL glass vials (19.6 mL per vial).

The aCSF was manufactured on behalf of MedGenesis Therapeutix, Inc. at Aptuit Ltd (now Albany Molecular Research Inc.), Glasgow, United Kingdom. Two aCSF batches were used in the study: P03716 and P06513.

Supplies of aCSF were stored at the study site pharmacy in secure, limited-access, and temperature-controlled conditions (15 – 25°C).

Commercial gadopentetate dimeglumine (Magnevist® Injection, Bayer HealthCare) was used at a 2 mM concentration in aCSF for test infusions at Week e40 (Primary Stage subjects only) and at Weeks e2-0 and e2-80 in the Pilot Extension (Pilot Stage subjects only).

9.5.2.3 Clinical Supplies and Packaging

Clinical supplies were packaged and provided directly to the study site pharmacy on behalf of MedGenesis Therapeutix, Inc., by Catalent Pharma Solutions, Bathgate, West Lothian, United Kingdom.

9.5.3 Method of Assigning Subjects to Treatment Groups

All subjects enrolled in the extension study received GDNF as open-label study treatment.

Subjects were identified on the CRF for the extension study using the subject number assigned at the start of study 2553, together with the subject's initials.

In the statistical analysis, findings are organized by "treatment group" reflecting a combination of the randomized treatment received in the parent study 2553 and the GDNF received in the extension study (GDNF/GDNF and placebo/GDNF, see Section 9.8.1.1).

9.5.4 Blinding

The extension study was an open-label study. However, subjects remained blinded to the study treatment they had received during study 2553 until database lock for study 2797. In addition, every effort was made to avoid unblinding of the blinded UPDRS raters until database lock for study 2797.

9.5.5 Prior and Concomitant Therapy

Every effort was to be made not to increase a subject's medication for PD during the study, but medication could be increased if required to maintain the subject's well being. The dose of a subject's PD medication could be decreased at the discretion of the principal investigator to manage PD drug-related side effects. No PD medications were permitted after 6:00 PM on the night before study visits with PD assessments, and no long-acting PD medications were permitted on the day before study visits with PD assessments.

Non-PD medications could be altered at any time at the discretion of the principal investigator. The principal investigator could, at any time in the study, prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care.

All over-the-counter or prescription medications, vitamins, and herbal supplements taken during the study were to be recorded in the CRF, together with the indications for which they were given.

9.5.6   Treatment Compliance

All treatments were administered by the principal investigator or designee. Administration records were kept on site, and administration information, including time and date of infusion, infusion rate and duration, and the reasons for any interruptions of the infusion or for any missed or omitted infusions were recorded in the CRF.

All supplies of study medication were accounted for in accordance with GCP.

Both GDNF and aCSF were stored at the study site pharmacy under secure, limited-access, and temperature-controlled conditions.

The study site pharmacist maintained accurate records of the disposition of all study medication supplies received and dispensed during the study, including the amounts and dates clinical drug supplies were dispensed to the principal investigator or designee for any given subject. If issues with the clinical drug supply were observed, the pharmacist notified MedGenesis immediately so that the situation could be investigated and appropriate corrective action could be taken as needed. The study monitors periodically checked the supplies of study medication held by the pharmacist to verify accountability of all medication used and to confirm that temperature logs demonstrated proper storage of study medication. Copies of the study medication accountability records were provided by the pharmacist for inclusion in the trial master file after database lock.

Any used or partially used vials of study medication were destroyed in the pharmacy at the end of the preparation session in accordance with the Sponsor's standard procedure for waste control. Infusion supplies (extension sets, administration sets, syringes, etc) were generally sent to the pharmacy for disposal at the conclusion of each subject infusion. If technical issues were observed during an infusion and could not be fully resolved on site, infusion supplies were collected by the manufacturing subcontractor Renishaw for further investigation.

9.6   Study Procedures, Assessments, and Endpoints

9.6.1   Schedule of Procedures and Assessments

Subjects enrolled in the extension study 2797 immediately upon completion of study 2553 provided they met the eligibility criteria and gave informed consent.

The extension study was performed in 3 parts: the Initial Extension, the Pilot Extension, and the Supplemental Extension. Visit numbers for each part started from zero and were prefixed in the protocol with an "e" in the Initial Extension (e.g. "Week e0"), an "e2-" in the Pilot Extension (e.g. "Week e2-0"), and an "e3-" in the Supplemental Extension (e.g. "Week e3-0") to differentiate them from the visit numbering in study 2553. However, wherever possible and suitable in this report, the designation of the visits in the Initial Extension has been modified from the protocol by adding the consecutive week number from the parent study 2553 baseline to facilitate the interpretation of the analyses (e.g. Week 40/e0, Week 44/e4, Week 48/e8, etc).

9.6.1.1   Initial Extension

The schedule for the study procedures and assessments in the Initial Extension is shown in Table 3. The table includes all modifications introduced by protocol amendments. The most important modifications are summarized in Section 9.9.1. For full details of modifications introduced by amendments, see Section 17.1.1.

Procedures and assessments performed at Week 40 of study 2553 were used as Week e0 assessments for the Initial Extension in study 2797.

The Initial Extension included 11 scheduled visits (Week e0 and 10 further visits at 4-weekly intervals until Week 80/e40). Visits were performed on an outpatient basis or on an in-patient basis if it was felt likely that the subject required nursing help to manage overnight without PD medication. If necessary, visits could take place over more than 1 day, for example when infusion of study medication was planned for early morning, preventing pre-treatment assessments from being done the same day.

Open-label GDNF was administered at Week e0 and all subsequent visits except Week 80/e40. The treatment protocol followed was the same as for the parent study 2553. All infusions of study drug and aCSF were followed by clinical assessment of safety, including direct questioning regarding impulsivity, mood, falls, and freezing. In addition, vital signs were measured before, during, and after the infusion, and a brief neurological screen (Glasgow Coma Scale) was done before infusion, 30 minutes into the infusion, and after completion of the infusion at all visits.

Subjects remained at the facility for safety observation for at least 2 to 4 hours after completing study drug administration at Week e0 and for at least 1 to 2 hours after completing study drug administration at all subsequent visits.

Every 8 weeks (Weeks 48/e8, 56/e16, 64/e24, 72/e32, and 80/e40), PD assessments (UPDRS, timed walking test, timed tapping test) were performed before the administration of the study

drug (or aCSF at Week 80/e40). The assessments were performed first in the OFF state (except UPDRS parts I and IV) and then in the ON state after levodopa challenge (same levodopa dose regimen as used in parent study 2553). In addition, the Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease (QUIP) was assessed in the ON state. No PD medications were permitted after 6:00 PM on the night before the assessments, and no long-acting PD medications were permitted on the day before the assessments. No high-protein foods were to be eaten on the morning of the assessments. The subject performed 3-day diary recordings in the week before each 8-weekly PD assessment visit for collection and review at the respective visits. Non-Motor Symptom Scale (NMSS) was assessed at Weeks 52/e12, 64/e24, and 80/e40. Deary-Liewald Reaction Time (RT), Montreal Cognitive Assessment (MoCA), and Mattis Dementia Rating Scale (MDRS) were assessed at Weeks 56/e16 and 80/e40. Weight and height were recorded every 8 weeks. The port site status, AEs, concomitant medications, and vital signs were recorded at all visits.

Blood and urine sampling was done for routine laboratory tests (hematology, serum chemistry, urinalysis, pregnancy test) at Weeks 44/e4, 56/e16, 68/e28, and 80/e40. At the same visits, blood sampling was also done for determination of anti-GDNF serum antibodies and plasma GDNF concentrations. Analysis of the samples for anti-GDNF serum antibodies and plasma GDNF concentrations was completed after the end of the study.

Week 80/e40 was the final visit and marked the completion of the Initial Extension for the subject. A full safety and efficacy assessment was performed at this visit, including all tests and assessments shown in Table 3.

At Week 80/e40, Primary Stage subjects received a gadolinium contrast-containing test infusion of aCSF (using the infusion algorithm for study medication detailed in Section 9.5.1.1) and underwent T1-weighted, T2-weighted, and fluid-attenuated inversion recovery (FLAIR) MRI scans (*added by amendment 3*). The test infusion was to be given at any time within a 2-week window around Week 80/e40, but preferably 1 week before Week 80/e40 if possible.

The Week e0 visit was to take place within 1 week of completion of all study measures from the Week 40 visit in study 2553 so as to keep the interval between the last treatment in the parent study (Week 36) and the first treatment in the extension study to a maximum of 5 weeks. All subsequent visits in the Initial Extension were to be performed within ± 3 days of the scheduled date. If necessary, a treatment could be given a maximum of + 7 days from the scheduled date; if the treatment could not be given within + 7 days, it was to be considered missed and the treatments resumed with the following scheduled date (*clarified by amendment 4*).

Table 3 Schedule of Study Procedures and Assessments: Initial Extension

Procedure/Assessment	Week in Initial Extension										
	40/e0 [A]	44/e4	48/e8 [B]	52/e12	56/e16 [B]	60/e20	64/e24 [B]	68/e28	72/e32 [B]	76/e36	80/e40 [B]
Informed consent [C]	(X)										
MRI [D]											X
Vital signs [E]	X	X	X	X	X	X	X	X	X	X	X
Weight and height	(X)		X		X		X		X		X
Physical examination [F]											X
Port review	X	X	X	X	X	X	X	X	X	X	X
ECG											X
Laboratory tests [G]		X			X			X			X
Anti-GDNF serum antibodies and plasma GDNF concentrations		X			X			X			X
UPDRS part II and part III in OFF state	(X)		X		X		X		X		X
Timed walking test in OFF state	(X)		X		X		X		X		X
Timed tapping test in OFF state	(X)		X		X		X		X		X
Levodopa challenge	(X)		X		X		X		X		X
UPDRS in ON state	(X)		X		X		X		X		X
Timed walking test in ON state	(X)		X		X		X		X		X
Timed tapping test in ON state	(X)		X		X		X		X		X
NMSS				X			X				X
PDQ-39, EQ-5D, SNAQ											X
MoCA, MDRS					X						X
Stroop test, FrSBe, verbal fluency, UPSIT, BDI											X
QUIP	(X)		X		X		X		X		X
RT					X						X
Collect PD fluctuation diaries	(X)		X		X		X		X		X
Dispense PD fluctuation diaries		X		X		X		X		X	
Infusion of study drug	X	X	X	X	X	X	X	X	X	X	
Glasgow Coma Scale [H]	X	X	X	X	X	X	X	X	X	X	X
Adverse events [I]	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications [J]	X	X	X	X	X	X	X	X	X	X	X

Table 3   **Schedule of Study Procedures and Assessments: Initial Extension:**
                     Explanation of footnote symbols

A   Assessments in parentheses were done at the Week 40 visit in study 2553 or earlier (informed consent). With the exception of informed consent, no procedures were required specifically for the extension study; however, procedures scheduled for Week 40 in study 2553 were to be performed in accordance with that protocol.

B   At Weeks 48/e8, 56/e16, 64/e24 and 72/e32, no PD medications were to be taken after 6:00 PM on the night before the assessments, and no long-acting PD medications were to be taken on the day before the assessments. Subjects were to refrain from eating any high-protein foods on the morning of the assessments.

C   Informed consent was to be obtained before any extension study-specific procedures or assessments were performed.

D   T1-weighted, T2-weighted, and FLAIR MRI scans were to be completed in Primary Stage subjects within 2 hours of a gadolinium contrast-containing test infusion at Week 80/e40 (±1 week). If possible, the test infusion and MRI were to be done 1 week before the visit.

E   For times of assessment of vital signs, see Section 9.6.4.6.

F   Brief physical examination, targeted, at the investigator's discretion, to identify changes from baseline.

G   Hematology, serum chemistry, urinalysis, pregnancy test. For individual tests see Section 9.6.4.3.

H   Performed before infusion, 30 minutes into the infusion, and after completion of the infusion.

I   All AEs occurring during the study until 28 days after the last dose of GDNF were to be recorded on the AE pages of the CRF. The subject was directly questioned at each infusion visit about impulsivity, mood, falls, and freezing for recording in case notes.

J   All over-the-counter or prescription medications, vitamins, and herbal supplements taken from study entry until Week 80/e40 or early discontinuation were to be recorded in the CRF with the indications for administration.

Abbreviations used in the table

AE: Adverse event; BDI: Beck Depression Inventory; CRF: Case report form; ECG: Electrocardiogram; EQ-5D: EuroQOL 5-Dimensional Scale; FLAIR: Fluid-attenuated inversion recovery; FrSBe: Frontal Systems Behavioural Scale; GDNF: Glial cell line-derived neurotrophic factor; MDRS: Mattis Dementia Rating Scale; MoCA: Montreal Cognitive Assessment; MRI: Magnetic resonance imaging; NMSS: Non-Motor Symptom Scale; PD: Parkinson's disease; PDQ-39: Parkinson's Disease Questionnaire-39; QUIP: Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease; RT: Deary-Liewald Reaction Time; SNAQ: Simplified Nutritional Appetite Questionnaire; UPDRS: Unified Parkinson's Disease Rating Scale; UPSIT: University of Pennsylvania Smell Identification Test.

9.6.1.2   Pilot Extension and Supplemental Extension

Pilot Stage subjects who completed the Initial Extension (Week 80/e40) were eligible for up to an additional 80 weeks of treatment with GDNF (the "Pilot Extension"; *added by amendment 2*).

Pilot Stage subjects completing Week e2-80 of the Pilot Extension and Primary Stage subjects completing Week 80/e40 of the Initial Extension were eligible to enroll in a further extension (the "Supplemental Extension"; *added by amendment 4*) and continue to receive GDNF until the end of December 2016. Only subjects who could have at least one visit by the end of December 2016 were enrolled in the Supplemental Extension.

Subjects who enrolled in the Pilot and Supplemental Extensions were required to sign and date an additional informed consent form prior to initiation of any Pilot or Supplemental Extension procedures. Procedures and assessments performed at Week 80/e40 in the Initial Extension were used as Week e2-0 assessments for the Pilot Extension (Pilot Stage subjects). For the Supplemental Extension, procedures and assessments performed at Week e2-80 (Pilot Stage subjects) or Week 80/e40 (Primary Stage subjects) served as Week e3-0 assessments.

Open-label GDNF was administered in both extensions at 4-weekly intervals according to the same treatment protocol as used in the parent study 2553 and the Initial Extension. In the Pilot Extension, GDNF was given at all visits from Week e2-4 to Week e2-76. At Weeks e2-0 and e2-80 in the Pilot Extension, subjects received a gadolinium contrast-containing test infusion of aCSF, followed by T1-weighted, T2-weighted, and FLAIR MRI scans. In the Supplemental Extension, open-label GDNF was given at all visits. No MRI scanning was done in the Supplemental Extension.

The schedules for the study procedures and assessments in each extension are shown in Table 4 (Pilot Extension) and Table 5 (Supplemental Extension). The tables include all modifications introduced by protocol amendments. The most important modifications are summarized in Section 9.9.1. For full details of modifications introduced by amendments, see Section 17.1.1.

The overall approach to study procedures and assessments for these extensions was similar to the Initial Extension. PD assessments were performed less frequently, and some assessments of efficacy, quality of life, and cognitive measures performed in the Initial Extension were not continued in the Pilot Extension and/or Supplemental Extension.

Table 4   Schedule of Study Procedures and Assessments: Pilot Extension

Procedure/Assessment	Week in Pilot Extension																				
	e2-0[A]	e2-4	e2-8	e2-12	e2-16[B]	e2-20	e2-24	e2-28	e2-32[B]	e2-36	e2-40	e2-44	e2-48	e2-52	e2-56[B]	e2-60	e2-64	e2-68	e2-72	e2-76	e2-80[B]
Informed consent[C]	(X)																				
MRI[D]	X																				X
Vital signs[E]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight and height							X							X							X
Physical examination[F]																					X
Port review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECG																					X
Laboratory tests[G]																					X
Anti-GDNF serum antibodies and plasma GDNF concentrations							X						X						X		
UPDRS part II and part III in OFF state	(X)				X				X						X						X
Timed walking test in OFF state	(X)				X				X						X						X
Timed tapping test in OFF state	(X)				X				X						X						X
Levodopa challenge	(X)				X				X						X						X
UPDRS in ON state	(X)				X				X						X						X
Timed walking test in ON state	(X)				X				X						X						X
Timed tapping test in ON state	(X)				X				X						X						X
NMSS	(X)										X										X
MoCA, MDRS	(X)																				X
QUIP	(X)				X				X				X				X				X
UPSIT, BDI	(X)																				X
Collect PD diaries	(X)				X				X						X						X
Dispense PD diaries				X			X						X						X		
Infusion of study drug		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Glasgow Coma Scale[H]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events[I]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concom. medications[J]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

**Table 4   Schedule of Study Procedures and Assessments: Pilot Extension:
                 Explanation of footnote symbols**

A   The Week e2-0 visit was to take place at the same time as (or within 1 week of) Week 80/e40. Assessments in parentheses were done at Week 80/e40 or earlier (informed consent). The safety assessments and outcome measures taken at Week 80/e40 served as the baseline for this part of the study and were not repeated at Week e2-0.

B   At Weeks e2-16, e2-32, e2-56, and e2-80, no PD medications were to be taken after 6:00 PM on the night before the assessments, and no long-acting PD medications were to be taken on the day before the assessments. Subjects were to refrain from eating any high-protein foods on the morning of the assessments.

C   Informed consent was to be obtained before any extension study-specific procedures or assessments were performed.

D   T1-weighted, T2-weighted, and FLAIR MRI were to be completed within 2 hours of a gadolinium contrast-containing test infusion at Weeks e2-0 and e2-80 (±1 week). At the Week e2-80 visit, the test infusion and MRI were to be done 1 week before the visit, if possible.

E   For times of assessment of vital signs, see Section 9.6.4.6.

F   Brief physical examination, targeted, at the Investigator's discretion, to identify changes from baseline.

G   Hematology, serum chemistry, urinalysis, pregnancy test. For individual tests see Section 9.6.4.3.

H   Performed before infusion, 30 minutes into the infusion, and after completion of the infusion.

I   All AEs occurring during the study until 28 days after the last dose of GDNF were to be recorded on the AE pages of the CRF. The subject was directly questioned at each infusion visit about impulsivity, mood, falls, and freezing for recording in case notes.

J   All over-the-counter or prescription medications, vitamins, and herbal supplements taken from study entry until Week e2-80 or early discontinuation were to be recorded in the CRF with the indications for administration.

Abbreviations used in the table

AE: Adverse event; BDI: Beck Depression Inventory; CRF: Case report form; ECG: Electrocardiogram; FLAIR: Fluid-attenuated inversion recovery; GDNF: Glial cell line-derived neurotrophic factor; MDRS: Mattis Dementia Rating Scale; MoCA: Montreal Cognitive Assessment; MRI: Magnetic resonance imaging; NMSS: Non-Motor Symptom Scale; PD: Parkinson's disease; QUIP: Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease; UPDRS: Unified Parkinson's Disease Rating Scale; UPSIT: University of Pennsylvania Smell Identification Test.

Table 5   Schedule of Study Procedures and Assessments: Supplemental Extension

Procedure/Assessment	Week in Supplemental Extension													
	e3-0 [A]	e3-4	e3-8	e3-12	e3-16 [B]	e3-20	e3-24	e3-28	e3-32 [B]	e3-36	e3-40	e3-44	e3-48 [C]	Last Study Visit Additional procedures/ assessments [C]
Informed consent [D]	(X)													
Vital signs [E]	X	X	X	X	X	X	X	X	X	X	X	X	X	
Port review	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory tests [F]														X
Anti-GDNF serum antibodies and plasma GDNF concentrations														X
UPDRS part II and part III in OFF state	(X)				X				X					
Timed walking test in OFF state	(X)				X				X					
Timed tapping test in OFF state	(X)				X				X					
Levodopa challenge	(X)				X				X					
UPDRS in on state	(X)				X				X					
Timed walking test in ON state	(X)				X				X					
Timed tapping test in ON state	(X)				X				X					
MoCA, MDRS														X
BDI	(X)													X
QUIP	(X)				X				X					X
Collect PD fluctuation diaries	(X)				X				X					
Dispense PD fluctuation diaries				X				X						
Infusion of study drug	X	X	X	X	X	X	X	X	X	X	X	X	X	
Glasgow Coma Scale [G]	X	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse events [H]	X	X	X	X	X	X	X	X	X	X	X	X	X	
Concomitant medications [I]	X	X	X	X	X	X	X	X	X	X	X	X	X	

**Table 5   Schedule of Study Procedures and Assessments: Supplemental Extension:
              Explanation of footnote symbols**

A   The Week e3-0 visit was to take place approximately 1-2 weeks after Week 80/e40 (Primary Stage subjects) or Week e2-80 (Pilot Stage subjects). Assessments in parentheses were done at Week 80/e40 (Primary Stage subjects) or Week e2-80 (Pilot Stage subjects) or earlier (informed consent). The safety assessments and outcome measures taken at Week 80/e40 or Week e2-80 (whichever was applicable) served as the baseline for this part of the study and were not repeated at Week e3-0.

B   At Weeks e3-16 and e3-32, no PD medications were to be taken after 6:00 PM on the night before the assessments, and no long-acting PD medications were to be taken on the day before the assessments. Subjects were to refrain from eating any high-protein foods on the morning of the assessments.

C   At the last study visit (Week e3-48 or earlier), the subject was to undergo all procedures and assessments scheduled for the respective visit reached by the subject as per the visit schedule. In addition, regardless of the assessments scheduled for the respective visit, MoCA, MDRS, QUIP, and BDI assessments were to be performed and samples obtained for laboratory tests and determination of anti-GDNF serum antibodies and plasma GDNF concentrations. The same approach to final assessments was to be taken, if possible, for any subjects who discontinued the Supplemental Extension early.

D   Informed consent was to be obtained before any extension study-specific procedures or assessments were performed.

E   For times of assessment of vital signs, see Section 9.6.4.6.

F   Hematology, serum chemistry, urinalysis, pregnancy test. For individual tests see Section 9.6.4.3.

G   Performed before infusion, 30 minutes into the infusion, and after completion of the infusion.

H   All AEs occurring during the study until 28 days after the last dose of GDNF were to be recorded on the AE pages of the CRF. The subject was directly questioned at each infusion visit about impulsivity, mood, falls, and freezing for recording in case notes.

I   All over-the-counter or prescription medications, vitamins, and herbal supplements taken from study entry until last study visit were to be recorded in the CRF with the indications for administration.

Abbreviations used in the table

AE: Adverse event; BDI: Beck Depression Inventory; CRF: Case report form; GDNF: Glial cell line-derived neurotrophic factor; MDRS: Mattis Dementia Rating Scale; MoCA: Montreal Cognitive Assessment; PD: Parkinson's disease; QUIP: Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease; UPDRS: Unified Parkinson's Disease Rating Scale.

9.6.2   Efficacy Assessments and Endpoints

9.6.2.1   Efficacy Endpoints

The **primary endpoint** of the study was:

- Percentage change from baseline (Week 0) to Week 80/e40 in the practically defined OFF state UPDRS motor score (part III).

Secondary endpoints were:

- Change from baseline to Week 80/e40 in OFF state UPDRS motor score (part III).

- Change and percentage change from baseline to Week 80/e40 in:

    - UPDRS motor score (part III) in the ON state (following a levodopa challenge).

    - UPDRS ADL score (part II) in the OFF state and in the ON state.

    - UPDRS total score (sum of motor + ADL scores) in the OFF state and in the ON state.

- Change from baseline to Week 40/e0 for the GDNF/GDNF group compared to change from baseline to Week 80/e40 for the placebo/GDNF group in:

    - OFF state UPDRS motor score (part III).

    - OFF state UPDRS ADL score (part II).

    - OFF state UPDRS total score (sum of motor + ADL scores).

- Change from baseline to Week 80/e40 for the GDNF/GDNF group compared to change from baseline to Week 40/e0 for the placebo/GDNF group in:

    - OFF state UPDRS motor score (part III).

    - OFF state UPDRS ADL score (part II).

    - OFF state UPDRS total score (sum of motor + ADL scores).

- Change from baseline to Week 80/e40 in PD diary ratings:

    - Total OFF time per day.

    - Total good-quality ON time per day (ON without dyskinesias or ON with non- troublesome dyskinesias).

    - ON time per day with troublesome dyskinesias.

- Treatment response based on the following criteria:

    - Decrease from baseline to Week 80/e40 by ≥10 points in OFF state UPDRS motor score (part III).

    - Increase from baseline to Week 80/e40 by ≥1 hour in total good-quality ON time per day (ON without dyskinesias or ON with non-troublesome dyskinesias).

- Both of the above criteria, i.e. decrease from baseline to Week 80/e40 by ≥10 points in OFF state UPDRS motor score (part III) and increase from baseline to Week 80/e40 by ≥1 hour in total good-quality ON time per day (ON without dyskinesias or ON with non-troublesome dyskinesias).

Supplementary efficacy endpoints were:

- Change from baseline to Week 80/e40 in supplementary motor, non-motor, medication, and quality of life endpoints, including the following

  - Timed walking test (OFF and ON state).

  - Timed tapping test (OFF and ON state).

  - Non-Motor Symptom Assessment Scale for PD (NMSS).

  - Parkinson's Disease Questionnaire-39 (PDQ-39).

  - EuroQOL 5-Dimensional Scale (EQ-5D).

  - Simplified Nutritional Appetite Questionnaire (SNAQ).

  - Total daily dose of levodopa and total daily levodopa equivalent dose.

The secondary and supplementary endpoints listed above reflect changes made during preparation of the statistical analysis plan (SAP; for further details see Section 9.8.1).

Methods of data collection and assessment for efficacy endpoints are summarized in the following sections.

9.6.2.2   Unified Parkinson's Disease Rating Scale (UPDRS)

The UPDRS was developed as an outcome measure for rating PD in clinical trials. It has 4 parts: mentation, behavior and mood (part I), ADL (part II), motor examination (part III), and complications of therapy (part IV). Except for the motor examination which is performed at the assessment, all sections of the UPDRS rate the subject based on his/her state in the week preceding the assessment. Higher scores represent worse functioning. For the full text of the rating scale, see Appendix F of the protocol in Section 17.1.1, Protocol appendices.

In this study, UPDRS motor (part III) and ADL (part II) ratings were performed by trained raters who were blinded to all other aspects of the subject's condition. The motor UPDRS was performed with the subject in a practically defined OFF state (at least 12 hours since last PD medication) and in the ON state after levodopa challenge. Every effort was made to avoid unblinding of the raters until database lock for study 2797.

ON and OFF UPDRS ratings were done at Weeks 48/e8, 56/e16, 64/e24, 72/e32, and 80/e40 in the Initial Extension, at Weeks e2-16, e2-32, e2-56, and e2-80 in the Pilot Extension, and at Weeks e3-16 and e3-32 in the Supplemental Extension. UPDRS parts I and IV were assessed only in the ON state.

9.6.2.3   PD Fluctuation Diaries

Motor fluctuations in this study were quantified using subject-completed diaries [33]. For 3 consecutive predetermined days prior to the relevant study assessments (not including the day immediately prior to the assessment, as the subject was asked to withhold PD medication on that day), subjects recorded their state for every half-hour time period. Categories for rating were: ON with no dyskinesias, ON with non-troublesome dyskinesias, ON with troublesome dyskinesias, OFF, and asleep. Caregivers were permitted to assist with the physical completion of the diary, but the decision regarding the subject's state was to be made by the subject alone. For details of the diary, see Appendix G of the protocol in Section 17.1.1, Protocol appendices.

During the parent study, subjects were trained on the completion of the diary and had to demonstrate their ability to accurately determine their state by comparing their own assessments to those of a qualified staff member over a 2-4 hour period, demonstrating at least a 75% concordance in the ON/OFF rating.

Diaries were collected at Weeks 48/e8, 56/e16, 64/e24, 72/e32, and 80/e40 in the Initial Extension, at Weeks e2-16, e2-32, e2-56, and e2-80 in the Pilot Extension, and at Weeks e3-16 and e3-32 in the Supplemental Extension. Diaries were to be reviewed by the coordinator each time they were returned, and retraining was to be offered if errors in completion were noted. Diaries were dispensed at the visit prior to their collection.

9.6.2.4   Timed Walking Test

During the timed walking test, the subject had to walk as fast as possible 7 meters back and forth including turning. The time to perform this test was recorded. The test was performed twice in the practically defined OFF state and twice in the ON state after levodopa challenge.

The test was done at Weeks 48/e8, 56/e16, 64/e24, 72/e32, and 80/e40 in the Initial Extension, at Weeks e2-16, e2-32, e2-56, and e2-80 in the Pilot Extension, and at Weeks e3-16 and e3-32 in the Supplemental Extension.

9.6.2.5   Timed Tapping Test

During the timed tapping test, the subject was instructed to alternate tapping the index finger for 20 seconds between 2 points spaced 30 cm apart. The number of taps completed on each side was recorded. The test was performed twice for each hand in the practically defined OFF state and twice for each hand in the ON state after levodopa challenge.

The test was done at Weeks 48/e8, 56/e16, 64/e24, 72/e32, and 80/e40 in the Initial Extension, at Weeks e2-16, e2-32, e2-56, and e2-80 in the Pilot Extension, and at Weeks e3-16 and e3-32 in the Supplemental Extension.

9.6.2.6   Non-Motor Symptom Scale (NMSS)

The NMSS is an interview-based scale used to rate non-motor symptoms commonly occurring in PD (developed by the International Parkinson's Disease Non-Motor Group). The 30-item scale

rates symptoms which occurred in the preceding month in 9 domains: cardiovascular including falls, sleep/fatigue, mood/cognition, perceptual problems/hallucinations, attention/memory, gastrointestinal tract, urinary, sexual function, and miscellaneous. Each item is rated from 0 (none) to 3 (severe) for severity and from 1 (rarely) to 4 (very frequent) for frequency. The score for each item is the product of the severity rating multiplied by the frequency. The maximum score for an individual item is 12. The higher the score, the worse the subject's condition. Individual item scores in each domain are summed to give the domain score, and the domains are summed to give the total score. The maximum NMSS total score is 360. For details of the scale, see Appendix H of the protocol in Section 17.1.1, Protocol appendices.

The NMSS takes 20-30 minutes. It was completed by the principal investigator or designee while the subject was in the ON state.

This scale was administered at Weeks 52/e12, 64/e24, and 80/e40 in the Initial Extension and at Weeks e2-40 and e2-80 in the Pilot Extension, but was not administered in the Supplemental Extension.

9.6.2.7 Parkinson's Disease Questionnaire-39 (PDQ-39) and EuroQOL EQ-5D

The PDQ-39 is a self-administered 39-item PD-specific quality of life tool that rates symptoms that occurred in the preceding month in 8 dimensions: mobility, ADL, emotional well being, stigma, social support, cognitions, communication, and bodily discomfort [34]. Each item is rated from 0 (never) to 4 (always) for frequency. Each dimension is calculated as a scale from 0 to 100 considering the number of questions in that dimension. The total score, or single index, is the average of all 8 dimension scores. The higher the score, the worse the subject's condition.

The EQ-5D is a subject self-report measure of quality of life consisting of a questionnaire and a visual analog scale [35]. The questionnaire comprises 5 questions on mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, with 3 possible answers for each item (1=no problem, 2=moderate problem, 3=severe problem). The visual analog scale serves as an indicator of general health status; the scale ranges from 0 to 100, where 0 indicates worst health and 100 indicates best health.

The scales take approximately 20 minutes for the subject to complete. For details of the assessments, see Appendix I (PDQ-39) and Appendix J (EQ-5D) of the protocol in Section 17.1.1, Protocol appendices.

The PDQ-39 and EQ-5D were completed at Week 80/e40 in the Initial Extension, but were not completed in the Pilot Extension or the Supplemental Extension. The scales were completed while the subject was in the ON state during the visit. The subject was permitted to receive assistance with the physical completion of the scales, but the subject alone had to determine the answer provided.

9.6.2.8 Simplified Nutritional Appetite Questionnaire (SNAQ)

The SNAQ is a self-administered 4-question instrument with total scores ranging from 4 to 20 (4=poor appetite, 20=good appetite). Posterior lateral putamen dopamine appears to be critical

for eating, and restoration may induce improved appetite as a signal of efficacy [36]. Loss of appetite and weight loss were to be recorded as AEs if reported at study visits, but applying this brief measure allows demonstration of improvement. The SNAQ was to be completed regardless of ON/OFF state.

The SNAQ was completed at Week 80/e40 in the Initial Extension, but was not completed in the Pilot Extension or the Supplemental Extension.

9.6.3   Imaging Assessments and Endpoints

9.6.3.1   Imaging Endpoints

The imaging endpoints were as follows (*defined in the SAP*):

- Change from baseline to Week 80/e40 in volume of distribution of infusate as determined by contrast-enhanced T1-weighted MRI.

- Change from baseline to Week 80/e40 in volume of interest (VOI) coverage and total putamenal coverage as determined by contrast-enhanced T1-weighted MRI.

- Correlation between primary study endpoint and VOI coverage and total putamenal coverage at baseline as determined by contrast-enhanced T1-weighted MRI.

- Correlation between primary study endpoint and change from baseline to Week 40/e0 in ^{18}F-DOPA uptake as determined by positron emission tomography (PET) scan.

- Correlation between baseline OFF state UPDRS motor score (part III) and baseline ^{18}F-DOPA uptake as determined by PET scan.

- Correlation between baseline OFF state UPDRS ADL score (part II) and baseline ^{18}F-DOPA uptake as determined by PET scan.

- Correlation between Week 40/e0 OFF state UPDRS motor score (part III) and Week 40/e0 ^{18}F-DOPA uptake as determined by PET scan.

- Correlation between Week 40/e0 OFF state UPDRS ADL score (part II) and Week 40/e0 ^{18}F-DOPA uptake as determined by PET scan.

- Correlation between Week 80/e40 OFF state UPDRS motor score (part III) and Week 40/e0 ^{18}F-DOPA uptake as determined by PET scan.

- Correlation between Week 80/e40 OFF state UPDRS ADL score (part II) and Week 40/e0 ^{18}F-DOPA uptake as determined by PET scan.

9.6.3.2   Magnetic Resonance Imaging (MRI)

The original study protocol planned that volume of distribution of infusate was to be determined by T2-weighted and FLAIR MRI in all subjects at Week 56/e16 and Week 76/e36. Scans were to be completed within 2 hours after infusion of diluent. Additional scans were to be performed at the discretion of the principal investigator.

During the study, the MRI schedule was modified by amendments 2, 3, and 4 based on the experience gained during study 2553. As a result, MRIs were performed in the extension study as follows:

- In the **Initial Extension**, volume of distribution of infusate was determined in Pilot Stage subjects by T2-weighted and FLAIR MRI at Week 56/e16 and Week 76/e36 according to the original schedule. In Primary Stage subjects, T1-weighted, T2-weighted, and FLAIR MRI were completed within 2 hours of a gadolinium contrast-containing test infusion at Week 80/e40 (±1 week); if possible, the test infusion and MRI were to be done 1 week before the visit. No interim MRIs were to be done in Primary Stage subjects unless clinically indicated.

- In the **Pilot Extension**, volume of distribution of infusate was determined by T1-weighted, T2-weighted, and FLAIR MRI within 2 hours of a gadolinium contrast-containing test infusion at Week e2-0 and e2-80 (±1 week); if possible, the test infusion and MRI at Week e2-80 were to be done 1 week before the visit.

In the **Supplemental Extension**, MRI scans were not a required study procedure.

MRI scans were done at the study site (Department of Radiology). Volumetric MRI analyses were performed by Renishaw. Pre-infusion images were subtracted from post-infusion images, with windowing aimed to maximize the contrast resulting from the infusion. Profiles were drawn around the area of contrast distribution on sequential axial slices. The actual volumes of distribution of infusate were then calculated using a semi-automated function of the surgical planning software. Based on the results of study 2553, it was expected that the analysis technique overestimated the true volume of distribution of GDNF.

All data were reviewed by the principal investigator or a medically qualified designee before the results were entered into the database.

9.6.4 Safety Assessments and Endpoints

9.6.4.1 Safety Endpoints

The safety endpoints were as follows:

- Frequency of TEAEs (all TEAEs and TEAEs related to study drug) during the study period.

- Frequency of device-related TEAEs during the study period.

- Frequency of dyskinesias, falls, adverse changes in mood, and impulsivity reported as TEAEs during the study period (AEs of special interest, AESIs).

- Adverse changes in MRI findings as captured by AE reporting.

- Results of routine laboratory blood tests (hematology, serum chemistry) and urinalysis performed during the study period.

- Frequency of subjects with anti-GDNF serum antibodies during the study period.

- Change from baseline in the Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease (QUIP) as assessed during the study period.

- Change from baseline in the MoCA as assessed during the study period.

- Change from baseline in the MDRS as assessed during the study period.

Other safety data analyzed or listed were exposure to study medication, plasma GDNF concentrations, physical examination, frequency of port symptoms, vital signs, weight and height, electrocardiogram (ECG), Glasgow Coma Scale, Stroop test, Frontal Systems Behavioural Scale (FrSBe), RT, verbal fluency assessment, Beck Depression Inventory (BDI) and University of Pennsylvania Smell Identification Test (UPSIT).

Methods of data collection and assessment for safety endpoints and other safety data are summarized in the following sections.

9.6.4.2   Adverse Events

9.6.4.2.1   Definitions

An **adverse event (AE)** or adverse experience was defined as any untoward medical occurrence in a subject or clinical investigation participant administered a medicinal product, which did not necessarily have a causal relationship with this treatment (the study medication). An AE could therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of the study medication, whether or not considered related to the study medication.

A **serious AE** was defined as any untoward medical occurrence that at any dose:

- Resulted in death.

- Was life-threatening, i.e. an event in which the participant was at risk of death at the time of the event, but not an event which hypothetically might have caused death if it had been more severe.

- Required inpatient hospitalization or prolongation of existing hospitalization.

- Resulted in persistent or significant disability/incapacity.

- Was a congenital anomaly/birth defect.

- Other important medical events: Other events which did not result in death, were not life-threatening, or did not require hospitalization could be considered a serious AE when, based upon appropriate medical judgement, the event might jeopardize the subject and require medical or surgical intervention to prevent one of the outcomes listed above.

9.6.4.2.2   Causality of Adverse Events to Study Medication and Device

The relationship of each AE to the study medication was determined by a medically qualified individual according to the following definitions:

- **Related:** The AE followed a reasonable temporal sequence from study medication administration. It could not reasonably be attributed to any other cause.

- **Not related:** The AE was probably produced by the participant's clinical state or by other modes of therapy administered to the participant.

Although this was a drug-only study, the relationship to the device was also assessed. "Device-related" included related to the device itself, related to the surgical procedure, or related to the test infusion.

9.6.4.2.3 Documentation of Adverse Events

All AEs occurring during the study until 28 days after the last dose of GDNF were recorded on the AE pages of the CRF (*documentation period clarified by amendment 4*).

The following information was recorded for each AE on the CRF: description, date and time of onset, date and time of end, occurrence during infusion (yes or no), severity (mild, moderate, severe), assessment of relatedness to study medication or device (related or not related), seriousness (yes or no), action taken, and outcome (recovered/resolved, not recovered/not resolved, recovered/resolved with sequelae, fatal). Action taken was specified as one or more of the following: current infusion interrupted and restarted; current infusion terminated; infusion protocol modified; infusion schedule suspended and resumed; treatment stopped permanently; surgical revision/replacement of extracerebral device parts (port, filters, tubing); surgical repositioning/replacement of intracerebral device parts (guide tube, catheter); other. Follow-up information was provided as necessary.

AEs considered related to the study medication or to the device as judged by the principal investigator or a medically qualified designee were followed up until resolution or the event was considered stable. All related AEs that resulted in a participant's withdrawal from the study or were present at the end of the study were followed up until a satisfactory resolution occurred.

Any pregnancy occurring during the clinical study and the outcome of the pregnancy was to be recorded and followed up for any congenital abnormality or birth defect.

9.6.4.3 Clinical Laboratory Evaluation

The following laboratory tests were performed at Weeks 44/e4, 56/e16, 68/e28, and 80/e40 in the Initial Extension, at Week e2-80 in the Pilot Extension, and at the last study visit in the Supplemental Extension:

- **Hematology:** Hematocrit, hemoglobin, mean cellular hemoglobin, mean cellular hemoglobin concentration, mean cellular volume, platelet count, red blood cell count, white blood cell count, and differential count (basophils, eosinophils, lymphocytes, monocytes, and neutrophils).

- **Serum chemistry:** Albumin, alkaline phosphatase, alanine transaminase, creatinine, estimated glomerular filtration rate, glucose, potassium, sodium, total bilirubin, and urea.

- **Urinalysis:** Color, appearance, pH, glucose, ketones, nitrite, and microscopy (microscopy required only if indicated to follow up abnormal findings).

- **Pregnancy test:** For all women of childbearing potential. Women not of childbearing potential were defined as those who were surgically sterile or were >45 years of age and without menses for ≥2 years.

Analyses were performed at the study site's in-house laboratories (Departments of Clinical Biochemistry and Haematology). Available accreditation certificates are provided in Section 17.1.9.

9.6.4.4   Anti-GDNF Antibodies in Serum

Blood samples were taken at Weeks 44/e4, 56/e16, 68/e28, and 80/e40 in the Initial Extension, at Week e2-24, e2-48, and e2-72 in the Pilot Extension, and at the last study visit in the Supplemental Extension for determination of anti-GDNF antibodies in serum.

At each sampling time, 2 mL of blood were collected in an appropriately sized clot tube that did not contain any anticoagulant. The sample was allowed to stand until fully clotted, centrifuged at 2400 rpm for 15 minutes at room temperature, and the serum was transferred to a cryo-vial. Sample processing was performed at the study site's in-house laboratory (Department of Neuropathology).

The serum samples were stored at -70°C at North Bristol NHS Trust until shipment to the testing laboratory (Eurofins Pharma Bioanalysis Services UK Limited, Abingdon, United Kingdom) for analysis after all subjects had completed the study. The samples were analyzed using validated cell-based bioassays (for validation reports see Section 17.1.12, Anti-GDNF binding antibodies and Anti-GDNF neutralizing antibodies).

9.6.4.5   Plasma GDNF Concentrations

Blood samples were taken at Weeks 44/e4, 56/e16, 68/e28, and 80/e40 in the Initial Extension, at Week e2-24, e2-48, and e2-72 in the Pilot Extension, and at the last study visit in the Supplemental Extension for determination of plasma GDNF concentrations.

At each sampling time, 2 mL of blood were collected in an appropriately sized EDTA tube. The sample was centrifuged at 2400 rpm for 15 minutes at room temperature, and the plasma was transferred to a cryo-vial. Sample processing was performed at the study site's in-house laboratory (Department of Neuropathology).

The plasma samples were stored at -70°C at North Bristol NHS Trust until shipment to the testing laboratory (Sartorius Stedim BioOutsource Ltd, Glasgow, United Kingdom) for analysis after all subjects had completed the study. The samples were analyzed using a validated enzyme-linked immunosorbent assay (for validation report see Section 17.1.12, Plasma GDNF concentration assay).

9.6.4.6   Vital Signs

Vital signs were determined at all visits during the study.

At each visit, seated systolic and diastolic blood pressure (BP), pulse, respiration rate, and temperature were assessed before treatment after the subject had been sitting quietly for at least 5 minutes; standing systolic and diastolic BP and pulse were assessed after the subject had been standing for 3 minutes. During administration of study drug, seated systolic and diastolic BP, pulse, and respiration rate were assessed every 30 minutes (every 15 minutes at Week e0), and both seated and standing systolic and diastolic BP and pulse were assessed within 30 minutes after the end of the infusion. The same measurements of vital signs were also performed before, during, and after administration of diluent at test infusion visits.

9.6.4.7   Weight and Height

Weight and height were determined at Weeks 48/e8, 56/e16, 64/e24, 72/e32, and 80/e40 in the Initial Extension and at Weeks e2-24, e2-56, and e2-80 in the Pilot Extension. These parameters were not determined in the Supplemental Extension.

9.6.4.8   Physical Examination

Physical examination (brief, targeted, at the investigator's discretion, to identify changes from baseline) was performed at Week 80/e40 in the Initial Extension and at Week e2-80 in the Pilot Extension. No physical examination was required in the Supplemental Extension. The port site was inspected at each visit.

9.6.4.9   12-Lead Electrocardiogram (ECG)

A standard 12-lead ECG was recorded at Week 80/e40 in the Initial Extension and at Week e2-80 in the Pilot Extension, including at least the following ECG parameters: heart rate, PR, QT, QRS, and corrected QT (QTc) intervals. In addition, the ECG was assessed by the principal investigator or designee as normal, abnormal but not clinically significant, or abnormal and clinically significant. Details of any abnormality were to be specified on the CRF.

9.6.4.10   Glasgow Coma Scale

A brief neurological screen (Glasgow Coma Scale) was performed before infusion, 30 minutes into the infusion, and after completion of all infusions (diluent or study medication).

9.6.4.11   Other Safety Assessments

9.6.4.11.1   Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease (QUIP)

The QUIP was developed to assess the occurrence of impulsive and compulsive disorders in PD [37]. It is a subject self-administered or informant-completed scale which includes 13 questions covering symptoms related to the 4 commonest impulse control disorders in PD (gambling, sex,

buying, and eating) as well as other behaviors and problematic use of medication. The QUIP-Current-Full, version 1.0, was used in the study (for questionnaire, see Appendix E of study protocol in Section 17.1.1, Protocol appendices).

The QUIP was completed by the subject while in the ON state at Weeks 48/e8, 56/e16, 64/e24, 72/e32, and 80/e40 in the Initial Extension, at Weeks e2-16, e2-32, e2-48, e2-64, and e2-80 in the Pilot Extension, and at Weeks e3-16, e3-32, and the last visit in the Supplemental Extension. Where possible, at these visits in the Initial Extension, a spouse or partner was also requested to complete the assessments.

9.6.4.11.2   Montreal Cognitive Assessment (MoCA)

The MoCA is a rater-administered cognitive screening tool which assesses both cortical and subcortical function [38, 39]. It has 8 components: visuospatial/executive, naming, memory, attention, language, abstraction, delayed recall, and orientation. The total score ranges from 0 to 30, with lower scores representing poorer cognitive function. A total score of 26 or above is considered normal. The test takes approximately 30 minutes to administer. Version 7.1 of the test was used in the study (for test form, see Appendix C of study protocol in Section 17.1.1, Protocol appendices).

The test was performed while the subject was in the ON state at Weeks 56/e16 and 80/e40 in the Initial Extension, at Week e2-80 in the Pilot Extension (*added by amendment 4*), and at the last visit in the Supplemental Extension.

The scale was completed by the trained site personnel. Subjects had to score a minimum of 24 on the MoCA at the final assessment in study 2553 to be eligible for the extension study.

Learning effects are always of high importance in investigations such as this. Therefore different variations of MoCA Version 7.1 were used to minimize the impact of learning.

9.6.4.11.3   Mattis Dementia Rating Scale (MDRS)

The MDRS is a rater-administered global scale of cognition that is sensitive to the frontal/subcortical deficits that are common in PD [40, 41]. It includes 5 subscales: attention, initiation/perseveration, construction, conceptualization, and memory. Scores range from 0 to 144, with higher scores representing better cognitive function. In PD, scores <123 are associated with some degree of dementia. The age- and education-corrected Mayo Older Adults Normative Studies scaled score (AEMSS) total score ranges from 0 to 20, with higher scores representing better cognitive function. The MDRS can be analyzed using total scores or using individual subscale scores. The scale takes 30–45 minutes to complete. Version 2 of the scale was used in the study.

The MDRS was administered by a trained rater with the subject in the ON state at Weeks 56/e16 and 80/e40 in the Initial Extension, at Week e2-80 in the Pilot Extension (*added by amendment 4*), and at the last visit in the Supplemental Extension.

9.6.4.11.4   Stroop Test

The Stroop test is a global scale of reaction time including 4 conditions: color naming, word reading, inhibition, and inhibition/switching [42]. Total time to complete the test in each condition can range from 0 to 999 seconds, with lower time representing better reaction time.

The test was administered with the subject in the ON state at Week 80/e40 in the Initial Extension, but was not administered in the Pilot Extension or the Supplemental Extension.

9.6.4.11.5   Frontal Systems Behavioural Scale (FrSBe)

The FrSBe is a scale that assesses behavior related to frontal systems damage including 3 subscales: apathy, disinhibition, and executive dysfunction [43]. Higher subscale scores indicate greater pathology.

The FrSBe was completed by the subject, in the ON state, at Week 80/e40 in the Initial Extension, but was not completed in the Pilot Extension or the Supplemental Extension.

9.6.4.11.6   Deary-Liewald Reaction Time (RT)

The Deary-Liewald RT is a computerized measure of simple and four-choice reaction time that has been validated in longitudinal studies and is suitable for older individuals [44].

The RT was performed, in the ON state, at Weeks 56/e16 and 80/e40 in the Initial Extension, but was not performed in the Pilot Extension or the Supplemental Extension.

9.6.4.11.7   Verbal Fluency Assessment

The verbal fluency assessment is a test of verbal functioning in 2 categories: phonemic and semantic [40]. Scores (number of correct words in one minute) range from 0 to 200, with a higher score representing better verbal functioning.

The verbal fluency assessment was performed by a trained rater at Week 80/e40 in the Initial Extension, but was not performed in the Pilot Extension or the Supplemental Extension.

9.6.4.11.8   Beck Depression Inventory (BDI)

The BDI is a depression scale that is commonly used both in clinical trials and in clinical practice. It has been recommended by the Movement Disorder Society as an outcome measure to rate the severity of depression in PD [45]. The BDI is a 21-question subject self-report scale with each item being rated on a scale of 0 to 3. Scores range from 0 to 63, with higher scores representing worse depression. The version used in the study was BDI-II (for questionnaire, see Appendix D of study protocol in Section 17.1.1, Protocol appendices).

The BDI was completed by the subject in the ON state at Week 80/e40 in the Initial Extension, at Week e2-80 in the Pilot Extension, and at the last visit in the Supplemental Extension.

9.6.4.11.9   University of Pennsylvania Smell Identification Test (UPSIT)

The UPSIT is a self-administered test which can be used to identify and quantitate olfactory dysfunction in PD. The number of correct responses out of 40 total items constitutes a subject's score. Lower scores represent greater olfactory dysfunction.

The test was completed regardless of ON/OFF state at Week 80/e40 in the Initial Extension and at Week e2-80 in the Pilot Extension, but was not completed in the Supplemental Extension.

9.6.5   Other Assessments

Not applicable.

9.6.6   Appropriateness of Measurements

The efficacy assessments performed in this study are generally recognized as reliable, accurate, and relevant for PD patients. The primary and secondary efficacy endpoints investigated were chosen in accordance with the recommendations of the Core Assessment Program for Interventional Surgeries for Parkinson's Disease (CAPSIT-PD) [40] and, as such, are the typical methods of assessment of efficacy in PD surgical trials.

The primary and secondary endpoints of the study are also consistent with the "Guideline on Clinical Investigation of Medicinal Products in the Treatment of Parkinson's Disease" issued by the European Medicines Agency [46]. The primary endpoint of the study was the percentage change from baseline to Week 80/e40 in the practically defined OFF state UPDRS motor score (part III). The UPDRS III is referenced by the guideline as an accepted and validated scale for the assessment of motor function in PD that facilitates the comparison between studies. In addition, consistent with the guideline, the study evaluated the effect of treatment on a number of other motor and non-motor outcomes including the UPDRS motor score (part III) in the ON state, UPDRS ADL score (part II), PD diary ratings, timed motor tests, medication equivalents, cognitive assessments, and quality of life. While the additional motor outcomes were primarily assessed to provide for consistency testing of the primary motor results, the non-motor assessments were included mostly on an exploratory basis.

In order to further corroborate the results and, in particular, to support the disease-modifying quality of the treatment, the relationship between clinical presentation (UPDRS motor score [part III] and ADL score [part II]) and ^{18}F-DOPA uptake as determined by PET scan was assessed both cross-sectionally (at baseline and at Week 40) and longitudinally (^{18}F-DOPA uptake at Week 40 vs clinical outcome at Week 80/e40). Such assessments are recommended by the European guideline in order to evaluate whether both are causally associated and to assess the potential predictive value of a biomarker for clinical outcome.

Safety assessments such as the MDRS and verbal fluency were performed as recommended in CAPSIT [40]. The MoCA, an additional cognitive safety test performed in this study, was designed specifically for the PD population and is the scale currently recommended for cognitive screening in PD clinical trials [39]. The assessment of depression (BDI) was chosen from scales recommended for this purpose in PD clinical trials [45]. The potential for the development of

impulse disorders was monitored with the QUIP, a scale specifically developed for this purpose [37]. Additional cognitive measures were added as exploratory measures.

Other safety assessments, including physical examinations, vital signs, clinical laboratory tests, ECGs, and AEs, were standard evaluations in accordance with GCP to ensure the safety of research subjects.

9.7   Data Quality Assurance

The study was performed according to North Bristol NHS Trust standard operating procedures.

All study site personnel provided their curriculum vitae to confirm their qualifications and completed North Bristol NHS Trust on-line GCP training prior to study start and then at regular intervals in accordance with Sponsor requirements. Additional in-person GCP training was provided in September 2014, and again in February 2015, for personnel who subsequently joined the team.

UPDRS motor (part III) and ADL (part II) scores were assessed by raters who were blinded to all other aspects of the subject's condition. Four blinded raters performed the UPDRS part III during the trial. Wherever possible, the same rater that had performed the baseline and other assessments in study 2553 also performed the assessments in study 2797.

All raters had successfully completed the UPDRS training program run by the Movement Disorder Society. In addition, the raters provided hands-on training for each other. To ensure standardization and to verify rater performance, the principal investigator and the lead study nurse watched a sampling of videos of each rater performing the UPDRS and independently confirmed their scoring.

Regular study monitoring was performed by the Sponsor monitors and clinical research associates from PRA Health Sciences according to ICH GCP and the monitoring plan. The monitors verified that the study was conducted and data were generated, documented, and reported in compliance with the protocol, GCP, and applicable regulatory requirements. All study data were recorded in the subject CRFs. The CRF data were compared to source documentation by the study monitors, according to the CRF Completion Guidelines. Any deviations were noted on protocol deviation forms as well as in CRF log pages. The study monitors remained blinded to the treatment allocation of subjects.

All study data on CRFs were processed by a data management group from PRA Health Sciences according to PRA standard operating procedures. Data edit checks were performed as detailed in the data management plan. Data queries were issued to the clinical site in order to resolve any discrepancies found during the discrepancy management process, and data were updated accordingly. The subjects were identified only by a study-specific subject number and/or code in any database.

Concomitant medications were coded to preferred names using the World Health Organization Drug Dictionary Enhanced (WHO DDE, 2016Mar01). AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA version 19.0).

GDNF

A pharmacy manual provided instructions for the proper storage, handling, preparation, and accountability of study drug, including both the aCSF and GDNF (Section 17.1.1, Pharmacy manual). The pharmacy was monitored to verify that the pharmacy aspects of the study were conducted according to the pharmacy manual and in compliance with GCP and applicable regulatory requirements.

9.8 Statistical Methods and Determination of Sample Size

9.8.1 Statistical and Analytical Plans

The statistical analyses described in the following sections were detailed in the final SAP version 2.0 dated 10 Apr 2017.

During the preparation of the SAP for the parent study 2553, it was recognized that the wording of certain study endpoints was less clear than anticipated. In addition, a number of endpoints were added in order to provide for a more comprehensive analysis of the study data. The endpoints in study 2797 were refined in a similar manner to achieve consistency between the protocols and to improve the preciseness of the definitions. For OFF state UPDRS scores, comparisons of change from baseline to Week 80/e40 in one group with change to Week 40/e0 in the other group were added as secondary endpoints. Furthermore, treatment response was added as a secondary endpoint pursuant to the post hoc analysis of study 2553. Due to the open, uncontrolled design of the extension study, these changes were implemented in the SAP without amending the protocol itself. No change was made to the primary efficacy endpoint for the extension study. The SAP was finalized and approved prior to database lock (13 Apr 2017).

The following sections give an overview of the SAP analyses. For full details, see Section 17.1.8, SAP.

Post hoc analyses performed after the final study results became available are summarized briefly in Section 9.9.4.

9.8.1.1 General Aspects

All analyses were performed using SAS® version 9.4.

Summary tables were organized by treatment group. The names of the treatment groups reflected the randomized treatment (GDNF or placebo) received in study 2553 followed by the non-randomized GDNF treatment received in study 2797. Subjects included in the GDNF/GDNF treatment group were those that received randomized double-blind GDNF in study 2553, followed by open-label GDNF in study 2797. Subjects included in the placebo/GDNF treatment group were those that received randomized double-blind placebo in study 2553, followed by open-label GDNF in study 2797.

Summary tables and listings for efficacy and imaging analyses included baseline and Week 40 data from study 2553. Summary tables and listings for safety analyses that used Week 0 from study 2553 as the baseline value included both baseline and Week 40 data from study 2553. With the exception of demographic data and PD history at screening in study 2553, no other data from

the parent study were included in summary tables or listings. Important CRF data were included in data listings, sorted by treatment group, subject, and by visit within subject.

Unless otherwise noted, categorical data were presented using counts and percentages, with the number of subjects in the analysis population by treatment group as the denominator for percentages. Continuous data, unless otherwise noted, were summarized using the number of observations (n), mean, standard deviation (SD), median, minimum, and maximum.

Any hypothesis testing was performed with a 2-sided alternative at the level of $\alpha = 0.05$. No adjustments for multiplicity were made. All inferential analyses were for exploratory purposes only.

9.8.1.2 Analysis Populations

The following analysis populations were defined:

- The ITT Primary Population included all enrolled Primary Stage subjects. This population was used for analyses of the primary efficacy endpoint, some secondary efficacy endpoints, and all imaging endpoints. It was also used for tabulation of subject disposition and summaries of demographic and baseline characteristics from study 2553. Subjects were counted according to their randomized treatment group in study 2553.

- The ITT Overall Population included all enrolled Pilot Stage subjects and all enrolled Primary Stage subjects. This population was used for analyses of all efficacy endpoints and some correlation imaging endpoints, for tabulation of subject disposition, and for summaries of demographic and baseline characteristics from study 2553. Subjects were counted according to their randomized treatment group in study 2553.

- The Safety Overall Population included all enrolled Pilot Stage subjects who received at least one dose of open-label study medication in study 2797 plus all enrolled Primary Stage subjects who received at least one dose of open-label study medication in study 2797. This population was used for all safety analyses. Subjects were counted according to the treatment actually received in study 2553.

9.8.1.3 Subject Disposition

Subject disposition was summarized for all subjects enrolled and treated in each part of the extension study (Initial Extension, Pilot Extension, Supplemental Extension), including numbers of subjects in each analysis population for the Initial Extension. The number and percentage of subjects who completed the Week 80/e40 visit was summarized for the ITT Primary Population and ITT Overall Population by treatment group and overall, together with a breakdown of primary reasons for early termination for subjects who withdrew from the study prematurely during the Initial Extension.

9.8.1.4 Protocol Deviations

Although no Per-Protocol Population was defined for this extension study, protocol deviations recorded on the protocol deviation form were categorized for summarization, applying controlled

terminology. They were also classified as major or minor, based on whether they might potentially impact the outcome of the study. Prior to database lock, the database entries for protocol deviations were reviewed by an adjudication team for consistency of the categorizations and classifications. Final determination of the classifications (major or minor) was made by the Sponsor. For full details, see Section 17.1.8, SAP.

The number and percentage of subjects in the ITT Overall Population with protocol deviations was summarized by treatment group and overall by deviation category (major and minor deviations) and deviation name (only major deviations).

9.8.1.5 Demographics and Baseline Characteristics

Demographic characteristics and PD history from study 2553 were tabulated by treatment group and overall for the ITT Primary Population and the ITT Overall Population.

9.8.1.6 Concomitant Medications

Medications received concomitantly with open-label study medication in any extension part of study 2797 were categorized by ATC class and preferred name according to WHO DDE and summarized by treatment group and overall for the ITT Primary Population. Separate tables were provided for concomitant PD medications and other concomitant medications.

9.8.1.7 Surgery and Test Infusions

Catheter trajectory data and catheter positioning accuracy data from repositioning surgery were listed by study stage, treatment group, and subject.

Data for all test infusions, including repeat or unscheduled test infusions, were listed by study stage, treatment group, and subject.

9.8.1.8 Analyses of Efficacy

Except where specified, efficacy analyses assessed change from the baseline value of study 2553 to Week 80/e40 (last scheduled visit in the Initial Extension of study 2797). In the subsections below, "baseline" denotes baseline in study 2553. Efficacy data collected during the Pilot Extension and Supplemental Extension were included in the subject listings.

Depending on the individual endpoint, efficacy analyses were performed for both the ITT Primary Population and the ITT Overall Population, or for the ITT Overall Population alone. The primary analysis was the analysis of the primary efficacy endpoint in the ITT Primary Population.

9.8.1.8.1   Analyses of Primary Efficacy Endpoint

Primary Analysis

The percentage change from baseline to Week 80/e40 in the practically defined OFF state UPDRS motor score (part III) was compared between treatment groups for the ITT Primary Population using a mixed-effect model with repeated measures (MMRM). Baseline UPDRS score was a covariate, treatment group and visit and treatment group*visit were fixed effects, and subject within treatment group was a random effect. The covariance matrix was unstructured. The analyses included all scheduled postbaseline data from study 2553 in the model, but data from interim visits in study 2553 were not summarized in tables or listed.

Summary statistics for the treatment comparison were least squares means with 95% confidence intervals (CIs) per treatment group, difference between least squares means (GDNF – placebo) with 95% CIs, and the corresponding p-value.

The GDNF/GDNF treatment group was to be judged superior compared with placebo/GDNF if there was sufficient statistical evidence to reject the following null hypothesis in the direction favorable to GDNF/GDNF:

H_0: No significant difference in the percentage change from baseline to Week 80/e40 in the OFF state UPDRS motor score (part III) between GDNF/GDNF and placebo/GDNF.

and accept the alternative hypothesis:

H_a: A significantly greater percentage decrease (lower UPDRS is better) in the change from baseline to Week 80/e40 in the OFF state UPDRS motor score (part III) for GDNF/GDNF relative to placebo/GDNF.

It was also possible that a significantly greater percentage decrease for placebo/GDNF as compared with GDNF/GDNF would be found, in which case placebo/GDNF was to be judged superior to GDNF/GDNF (i.e. the test was 2-sided).

An exploratory model was developed to describe the disease progression in PD as a function of time using Parkinson's Progression Markers Initiative data [47]. Baseline severity was a significant covariate in the model showing a decrease in the rate of disease progression as baseline severity increases. The population estimate of disease progression was similar to previously reported values. Using a baseline OFF state UPDRS motor score (part III) of 35, disease progression was predicted to occur at a modest annual rate of 1.56 points (4.5%) per year, translating to an increase of the baseline score by 1.2 points (3.4%) at 40 weeks and 2.4 points (6.9%) at 80 weeks. This modelled control was included in the graphs of OFF state UPDRS motor score (part III).

Sensitivity Analysis

The primary efficacy analysis was repeated for the ITT Overall Population as a sensitivity analysis.

9.8.1.8.2 Analyses of Secondary Efficacy Endpoints

Analyses of secondary efficacy endpoints were performed using the ITT Primary Population and/or ITT Overall Population in a manner similar to the analyses of the primary endpoint.

<u>Analyses of UPDRS Scores</u>

Change and Percentage Change in UPDRS scores from Baseline to Week 80/e40
Further analyses of change and percentage change in UPDRS scores from baseline to Week 80/e40 were performed for the following secondary endpoints using an MMRM in the same manner as for the primary efficacy endpoint:

- Change from baseline to Week 80/e40 in OFF state UPDRS motor score (part III).

- Change and percentage change from baseline to Week 80/e40 in:

  - UPDRS motor score (part III) in the ON state (following a levodopa challenge).

  - UPDRS ADL score (part II) in the OFF state and ON state.

  - UPDRS total score (sum of motor + ADL scores) in the OFF state and in the ON state.

The analyses of each endpoint in the OFF state were performed for both the ITT Primary Population and the ITT Overall Population, while the analyses of the endpoints in the ON state were performed only for the ITT Overall Population.

Change in UPDRS Scores from Baseline to Week 40/e0 for the GDNF/GDNF Group Compared to Change from Baseline to Week 80/e40 for the Placebo/GDNF Group
Change from baseline to Week 40/e0 for the GDNF/GDNF group was compared to change from baseline to Week 80/e40 for the placebo/GDNF group for OFF state UPDRS motor score (part III), OFF state UPDRS ADL score (part II), and OFF state UPDRS total score (sum of motor + ADL scores) for the ITT Overall Population using an MMRM in the same manner as for the primary efficacy endpoint. This analysis served to compare the effects of the first 40 weeks of treatment with GDNF in both groups.

Change in UPDRS Scores from Baseline to Week 80/e40 for the GDNF/GDNF Group Compared to Change from Baseline to Week 40/e0 for the Placebo/GDNF Group
Change from baseline to Week 80/e40 for the GDNF/GDNF group was compared to change from baseline to Week 40/e0 for the placebo/GDNF group for OFF state UPDRS motor score (part III), OFF state UPDRS ADL score (part II), and OFF state UPDRS total score (sum of motor + ADL scores) for the ITT Overall Population using an MMRM in the same manner as for the primary efficacy endpoint. This analysis served to compare the effects of treatment with GDNF over 80 weeks with the longest period of treatment with placebo alone (40 weeks) as the best available internal control.

<u>Analyses of PD Diary Ratings</u>

Change from baseline to Week 80/e40 in PD motor fluctuation diary ratings (total OFF time per day; total good-quality ON time per day; ON time per day with troublesome dyskinesias) was

compared between treatment groups for the ITT Primary Population and ITT Overall Population using an MMRM in the same manner as for the primary efficacy endpoint.

Analyses of Treatment Response

Treatment response at Week 80/e40 was compared between treatment groups for the ITT Overall Population based on the following criteria:

- Decrease from baseline to Week 80/e40 by ≥10 points in OFF state UPDRS motor score (part III).

- Increase from baseline to Week 80/e40 by ≥1 hour in total good-quality ON time per day (ON without dyskinesias or ON with non-troublesome dyskinesias).

- Both of the above criteria, i.e. decrease from baseline to Week 80/e40 by ≥10 points in OFF state UPDRS motor score (part III) and increase from baseline to Week 80/e40 by ≥1 hour in total good-quality ON time per day (ON without dyskinesias or ON with non-troublesome dyskinesias).

Treatment response at Week 40/e0 was analyzed using the same criteria. The UPDRS motor score criterion of a decrease of ≥10 points ("strong responder") was based on the estimates of moderate and large clinically important differences as published by Shulman et al [48].

Response rates were displayed by visit for Week 40/e0 and Week 80/e40 and compared between treatment groups using Fisher's exact test. In addition, UPDRS response (≥10 points in OFF state UPDRS motor score [part III]) was summarized using a shift table comparing numbers of responders/nonresponders per treatment group between the two time points. Frequency distribution plots were provided to display the number of subjects for any given change by treatment group.

9.8.1.8.3   Analyses of Supplementary Efficacy Endpoints

All analyses of supplementary efficacy endpoints were done for the ITT Overall Population.

For the timed walking test (OFF state and ON state), timed tapping test (OFF state and ON state), and NMSS, the change from baseline to Week 80/e40 was compared between treatment groups using an MMRM in the same manner as for the primary efficacy endpoint.

Change from baseline to Week 80/e40 in PDQ-39 data was analyzed using an analysis of covariance (ANCOVA) model adjusted for baseline PDQ-39 score. EQ-5D questionnaire data were reported using frequency counts and percentages for baseline, Week 40/e0, and Week 80/e40. Analysis of change from baseline to Week 80/e40 in EQ-5D visual analog scale data was performed using an ANCOVA model adjusted for baseline EQ-5D visual analog scale score. Change from baseline to Week 80/e40 in SNAQ data was analyzed using an ANCOVA model adjusted for baseline SNAQ score.

For total daily levodopa dose and total daily levodopa equivalent dose, the change from baseline to Week 80/e40 was analyzed using an ANCOVA model adjusted for baseline total daily

levodopa dose and total daily levodopa equivalent dose, respectively. Conversion factors for the calculation of levodopa and levodopa equivalent doses are listed in the SAP (see Section 17.1.8, SAP).

9.8.1.9   Analyses of Imaging Endpoints

The analyses of imaging endpoints were performed for the ITT Primary Population and/or ITT Overall Population as specified below. All MRI analyses and correlation analyses including MRI data were restricted to the ITT Primary Population since, in Pilot Stage subjects, only T2-weighted MRI scans were taken at baseline. For comparisons of postbaseline values to baseline values, baseline was defined as the baseline value from study 2553.

9.8.1.9.1   MRI Analyses

Change from baseline to Week 80/e40 in volume of distribution of infusate as determined by "contrast-enhanced T1-weighted MRI" (i.e. T1-weighted MRI following administration of contrast-enhanced test infusion) was compared between treatment groups in the ITT Primary Population using an ANCOVA model adjusted for baseline volume of distribution.

Change from baseline to Week 40 in VOI coverage (percentage of total VOI covered by infusate) and total putamenal coverage (percentage of total putamenal volume covered by infusate) as determined by contrast-enhanced T1-weighted MRI was analyzed in the same manner, adjusting the ANCOVA for the respective baseline coverage value in each case.

9.8.1.9.2   Correlation Analyses

Non-parametric Spearman rank correlation analyses were performed to explore the following relationships:

- Correlation between primary study endpoint and VOI coverage and total putamenal coverage at baseline as determined by contrast-enhanced T1-weighted MRI (ITT Primary Population).

- Correlation between primary study endpoint and change from baseline to Week 40/e0 in ^{18}F-DOPA uptake as determined by PET scan (ITT Primary Population and ITT Overall Population).

- Correlation between baseline OFF state UPDRS motor score (part III) and baseline ^{18}F-DOPA uptake as determined by PET scan (ITT Overall Population).

- Correlation between baseline OFF state UPDRS ADL score (part II) and baseline ^{18}F-DOPA uptake as determined by PET scan (ITT Overall Population).

- Correlation between Week 40/e0 OFF state UPDRS motor score (part III) and Week 40/e0 ^{18}F-DOPA uptake as determined by PET scan (ITT Overall Population).

- Correlation between Week 40/e0 OFF state UPDRS ADL score (part II) and Week 40/e0 ^{18}F-DOPA uptake as determined by PET scan (ITT Overall Population).

- Correlation between Week 80/e40 OFF state UPDRS motor score (part III) and Week 40/e0 ^{18}F-DOPA uptake as determined by PET scan (ITT Overall Population).

- Correlation between Week 80/e40 OFF state UPDRS ADL score (part II) and Week 40/e0 ^{18}F-DOPA uptake as determined by PET scan (ITT Overall Population).

Correlations were calculated separately for each treatment group.

9.8.1.10   Analyses of Safety

Unless otherwise specified, safety analyses assessed the safety findings obtained in the extension study 2797 for the Safety Overall Population. Data collected at Week 40 in study 2553 were used as the baseline, where a baseline value was not obtained at Week e0 of the extension study. No imputation was performed for missing safety data other than questionnaire data.

9.8.1.10.1   Study Medication Exposure

Open-label study medication exposure data were analyzed descriptively, giving summary statistics for number of infusions received, total GDNF exposure in mg, and details of duration of infusion (minutes) and any infusion interruptions/early terminations per study medication visit in the extension study.

9.8.1.10.2   Adverse Events

Due to the temporal proximity of the start of study 2797 to the end of study 2553, all AEs reported during study 2797 were considered treatment-emergent AEs (TEAEs), regardless of whether their onset was before, on, or after the date of the first dose of open-label study medication. TEAEs that were present or ongoing at the beginning of study 2797 (date of consent or date of last visit in study 2553, if consent was obtained earlier) were considered pre-existing, if the event term, severity, and date and time of onset in study 2797 were identical to the corresponding information given for the TEAE in study 2553. If any of these conditions was not met, the TEAE was considered new or worsening. Only new or worsening TEAEs were tabulated in this CSR. Pre-existing TEAEs were listed. Unless otherwise specified, in the text below and in the summary tables, the term "TEAE" denotes "new or worsening TEAE".

Analyses of TEAEs included TEAE data from all extension parts of study 2797 (Initial Extension, Pilot Extension, Supplemental Extension). Findings were tabulated by treatment group and overall. The following summaries were prepared:

- Overall summary of TEAEs.

- TEAEs by MedDRA system organ class (SOC) and preferred term (PT).

- TEAEs experienced by at least 3 subjects in any treatment group by PT (number of subjects and number of events).

- TEAEs by MedDRA SOC, PT, and maximum severity.

- Serious TEAEs by MedDRA SOC and PT.

- Study medication-related TEAEs by MedDRA SOC and PT.

- Serious study medication-related TEAEs by MedDRA SOC and PT.

- Device-related TEAEs by MedDRA SOC and PT.

- Serious device-related TEAEs by MedDRA SOC and PT.

Overall summaries of TEAEs, TEAEs experienced by at least 3 subjects in any treatment group by PT, and serious TEAEs by MedDRA SOC and PT were also reported separately for the Initial Extension and the Pilot and Supplemental Extensions.

Treatment-emergent AEs of special interest (AESIs) were analyzed by category (dyskinesias; falls; adverse changes in mood; impulsivity) and PT. For MedDRA PTs that were predefined for each category prior to database lock see Section 17.1.8, SAP.

Adverse changes in MRI findings were defined in the SAP as any AE coded as the MedDRA PT term "Nuclear magnetic resonance imaging brain abnormal" (MedDRA higher level term "Central nervous system imaging procedures").

9.8.1.10.3   Clinical Laboratory Evaluation

Postbaseline hematology and serum chemistry results rated clinically significant by the investigator were summarized with the direction of significance indicated (high or low). Urinalysis parameters were listed.

9.8.1.10.4   Anti-GDNF Antibodies in Serum

Anti-GDNF serum antibody data were summarized by treatment group as the number and percentage of subjects in each category (positive, negative, not done, or missing) by visit for screening from study 2553 (baseline); Weeks 40/e0, 44/e4, 56/e16, 68/e28, and 80/e40; e2-24, e2-48, and e2-72; and the last study visit in the Supplemental Extension. Summary data were also provided for subjects who were positive at any postbaseline visit in study 2553 or study 2797 and those who were positive at more than one postbaseline visit in study 2553 or study 2797. If a subject had a repeat sample, then the worse result was used in the analysis. A positive result was considered worse than a negative result.

9.8.1.10.5   Plasma GDNF Concentrations

Plasma GDNF concentrations were summarized by treatment group for screening from study 2553 (baseline); Weeks 40/e0, 44/e4, 56/e16, 68/e28, and 80/e40; e2-24, e2-48, and e2-72; and the last study visit in the Supplemental Extension. Values below the limit of quantitation were not included in summary statistics. If a subject had a repeat sample, then the higher result was used in the analysis.

9.8.1.10.6   Vital Signs

For vital signs, frequency tabulations were prepared which displayed the number and percentage of subjects per treatment group with clinically relevant abnormalities for vital signs during or after infusion at test infusion visits and study medication infusion visits in the Initial Extension. For criteria for clinically relevant postbaseline abnormalities, see Section 17.1.8, SAP.

9.8.1.10.7   Weight

Body weight data were listed by study stage, treatment group, and subject.

9.8.1.10.8   Physical Examination

Physical examination data were listed by study stage, treatment group, subject, and body system. Port symptoms were listed by study stage, treatment group, and subject.

9.8.1.10.9   Electrocardiogram

Summary statistics were prepared for change in quantitative ECG parameters from screening in study 2553 (baseline) to Week 40/e0 and Week 80/e40 per treatment group. In addition, the ECG data were analyzed by treatment group with respect to the number and percentage of subjects with normal and abnormal ECG results at Week 80/e40 (overall and those judged clinically significant by the investigator) and the number and percentage of subjects with Week 80/e40 QTc abnormalities assessed as clinically relevant (overall and per category, see Section 17.1.8, SAP).

9.8.1.10.10   Glasgow Coma Scale

The Glasgow Coma Scale data were summarized as a frequency tabulation displaying the number and percentage of subjects per treatment group with a total Glasgow Coma Scale score of 15 or less than 15 at any time during or after infusion at test infusion visits and study medication infusion visits in the Initial Extension.

9.8.1.10.11   Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease

QUIP data were summarized for both subject and informant parameters using a shift table comparing postbaseline to baseline (Week 40/e0) values by treatment group and responder.

9.8.1.10.12   Other Safety Assessments

Data for MoCA, MDRS, Stroop test, FrSBe, Deary-Liewald four-choice RT, verbal fluency assessment, BDI, and UPSIT were summarized by treatment group as summary statistics for change from baseline in study 2553 to all assessment times in study 2797.

9.8.1.11   Data Handling Aspects

9.8.1.11.1   Definition of Baseline

In efficacy and imaging analyses, for comparisons of postbaseline values to baseline values, the baseline value was defined as the baseline value from study 2553.

In analyses of laboratory data, Glasgow Coma Scale, and QUIP, the baseline value was defined as the value collected at Week 40/e0. If data were collected at both Week 40 from study 2553 and Week e0, then the latter value was used as the baseline value.

For comparisons of vital sign values during or after infusion with pre-infusion values, the baseline was the pre-infusion value.

For all other safety analyses, the baseline value was defined as the baseline value from study 2553.

9.8.1.11.2   Visit Windows

The visit windows in Table 6 were applied for analyses of the Initial Extension of study 2797 in conjunction with data from study 2553. The visit schedules were distinguished using either database visit labels for Pilot Stage subjects or study day for Primary Stage subjects for study 2553 visits. The visit schedules were distinguished using study day for all subjects for study 2797 visits.

The Week 40 and Week 80/e40 visit windows were wider than for other visits since the number and duration of assessments required special arrangements in some cases in order to minimize subject burden. As a consequence, the adjacent windows (Week 36 and Week 76/e36) were smaller.

Other than the Week 40/e0/early termination and Week 80/e40/early termination visits, postbaseline unscheduled visit values were not windowed and were excluded from tabulations by visit. All unscheduled visit values were included in data listings.

Table 6   Visit Windows for Analyses

Visit	Nominal study day	Study day range Prior to study 2553 amendment 3	Study day range After study 2553 amendment 3	Study day range for study 2797
Week 0	0	-6-7	-13-14	
Week 2	14	8-21		
Week 4	28	22-35	15-42	
Week 6	42	36-49		
Week 8	56	50-63	43-70	
Week 10	70	64-77		
Week 12	84	78-91	71-98	
Week 14	98	92-105		
Week 16	112	106-119	99-126	
Week 18	126	120-133		
Week 20	140	134-147	127-154	
Week 22	154	148-161		
Week 24	168	162-175	155-182	
Week 26	182	176-189		
Week 28	196	190-203	183-210	
Week 30	210	204-217		
Week 32	224	218-231	211-238	
Week 34	238	232-245		
Week 36	252	246-259	239-259	
Week 38	266	260-273		
Week 40	280	274-287	260-304	
Week e0	1			-13-14
Week 44/e4	29			15-42
Week 48/e8	57			43-70
Week 52/e12	85			71-98
Week 56/e16	113			99-126
Week 60/e20	141			127-154
Week 64/e24	169			155-182
Week 68/e28	197			183-210
Week 72/e32	225			211-238
Week 76/e36	252			239-259
Week 80/e40	281			260-304

GDNF   Clinical Study Report
                                                                            Study No. 2797

9.8.1.11.3   Missing Data

Missing or partial dates for AEs, concomitant medications, dosing records, Week 40/e0/early termination, and Week 80/e40/early termination visits were imputed as described in the SAP (Section 17.1.8, SAP).

For primary and secondary efficacy endpoints, missing data were not imputed. Handling of missing and duplicate PD motor fluctuation diary ratings and missing data for supplementary efficacy endpoints is described in the respective parts of the SAP.

For imaging endpoints, missing postbaseline PET scan data were imputed using last observation carried forward (LOCF). No other missing imaging data were imputed.

No imputation was performed for missing safety data other than questionnaire data. Details of the approach to handling of missing data for questionnaires are given in the SAP.

9.8.1.11.4   Special Arrangements for Subject 45

Special arrangements were made for subject 45 who was involved in a car accident and had a conus injury during study 2553 that was unrelated to study treatment or device (Section 17.1.8, File note concerning subject 45). As a result of this, items 27, 28, 29 and 30 of the UPDRS score could not be completed beyond Week 8 in study 2553. Item 22, although recorded, was considered to be confounded. Therefore, for this subject, these 5 items were excluded from all calculations of the UPDRS motor score (part III) used in the efficacy analyses, and a truncated score including all other items of part III was used instead. UPDRS parts I, II, and IV were collected as far as possible, but the data were not included in any efficacy analyses because they were considered to be confounded due to the injury. The timed walking test could not be done after Week 8 in study 2553 and was therefore excluded from efficacy analyses. PDQ-39 (items 14 to 39), EQ-5D, and NMSS were recorded but were considered to be confounded due to the injury and were therefore excluded from efficacy analyses.

9.8.1.12   Interim Analyses and Data Monitoring

No formal interim analyses were planned or performed.

The study was monitored by an independent DMC established by the Sponsor (see Section 6; see also Section 17.1.8, DMC charter and DMC minutes, 1st meeting, 2nd meeting, 3rd meeting, and 4th meeting).

9.8.2   Determination of Sample Size

This was an open-label extension study which planned to enroll up to 42 subjects. No power calculations were performed. The study was open to all subjects who completed study 2553 without significant toxicity or other exclusion.

9.9   Changes in the Conduct of the Study or Planned Analyses

9.9.1   Protocol Amendments

The original protocol (version 1.0) was dated 18 Jun 2013. There were 4 protocol amendments (3 major, 1 minor). Table 7 summarizes the version numbers and dates of the protocol and amendments, together with the dates of approval by the MHRA, the ethics committee, and the Sponsor.

Table 7   Overview of Versions and Dates of Approval for Protocol and Amendments

Protocol		Amendment		Approval		
Version	Date	Version	Date	MHRA	Ethics committee	Sponsor
1.0	18 Jun 13	–	–	-	29 Jul 13	01 Oct 13
1.1 (minor)	02 Sep 13	1	02 Sep 13	16 Sep 13	Not required	Not required
1.2	30 Jun 14	2	30 Jun 14	05 Aug 14	21 Oct 14	28 Oct 14
1.3	19 Sep 14	3	19 Sep 14	13 Nov 14	12 Aug 15	19 Oct 15
1.4	16 Dec 15	4	16 Dec 15	15 Jan 16	18 Jan 16	01 Feb 16

Sponsor approvals mark the effective date of the respective document.

The substantial delay between the finalization of protocol amendment 1.3 and MHRA approval in mid- to late 2014 and the ethics committee and Sponsor approvals in August 2015 was due to site staff workload. However, all approvals were received prior to the first Primary Stage subject's Week 80/e40 gadolinium contrast-containing test infusion of aCSF.

A summary of the most important changes introduced by each amendment is given below. For full details, see Section 17.1.1.

9.9.1.1   Amendment 1, dated 02 Sep 2013

This amendment revised protocol section 7.9 (Reporting Procedures for Serious Adverse Events) to harmonize the initial reporting period for serious AEs with current effective regulations stipulating that all serious AEs had to be reported to North Bristol NHS Trust Research and Innovation within 24 hours (instead of 1 working day) of discovery or notification of the event.

9.9.1.2   Amendment 2, dated 30 Jun 2014

This amendment added further extension study visits for Pilot Stage subjects (Pilot Extension), corrected minor protocol inconsistencies, provided the new addresses for the Sponsor, principal investigator, and study neurosurgeon, and removed the Cattell Culture Fair Intelligence Test as an outcome measure.

The Pilot Stage subjects from study 2553 began treatment substantially before those from the main study cohort (Primary Stage). The Pilot Extension comprised an additional 80 weeks of treatment and was designed to generate long-term safety data and ensure ongoing access to

GDNF for the Pilot Stage subjects until results of study 2553 become available. At the beginning of the Pilot Extension (Week e2-0), Pilot Stage subjects were to receive an infusion of aCSF containing gadolinium contrast to allow for volumetric catheter performance by means of T1-weighted MRI scans in addition to T2-weighted and FLAIR MRI scans.

9.9.1.3   Amendment 3, dated 19 Sep 2014

This amendment modified the MRI schedule to reflect changes introduced by amendments in study 2553. A gadolinium contrast-containing test infusion of aCSF, followed both by contrast-enhanced T1-weighted MRI and by T2-weighted and FLAIR MRI scans, was added at Week 80/e40 in the extension study (Primary Stage subjects only) and at Weeks e2-0 and e2-80 in the Pilot Extension. GDNF was not to be delivered at any of these visits. A 2-week window around the Week 80/e40 and Week e2-80 visits was allowed for the test infusions, in order to minimize the burden on subjects at these busy visits while keeping a 3- to 5-week window from the preceding infusion of GDNF at Week 76/e36 and Week e2-76, respectively. Interim MRI scans were no longer to be done during the study unless clinically indicated.

9.9.1.4   Amendment 4, dated 16 Dec 2015

This amendment added further extension study visits to facilitate continuation of the study until anticipated completion at the end of December 2016. The amendment also provided a number of clarifications and refinements that were considered mostly administrative in nature or evolved during the preparation of protocol amendment 7 of study 2553. The most important changes were:

- **Supplemental Extension**: Further extension study visits were added to generate long-term safety data and to facilitate continuation of the study until the end of December 2016 when the results of study 2553 were expected. The protocol was modified accordingly.

- **Disclosure of treatment codes in parent study**. Where applicable, the protocol text was modified to clarify that individual treatment codes from the parent study 2553 would not be disclosed to subjects until database lock for study 2797, unless required for specific safety reasons. In addition, additional text was inserted to indicate that every effort would be made to avoid unblinding of the blinded UPDRS raters until database lock for study 2797.

- **Timing of test infusion relative to visits:** For the test infusions to be administered at Week 80/e40 and Week e2-80, the protocol was modified to clarify that the test infusion followed by T1-weighted, T2-weighted, and FLAIR MRI scans should take place preferably 1 week before the study visit, if possible.

- **Protocol section 5.6.1 (Treatments):** In order to avoid infusion intervals of <3 weeks, the protocol text was modified to clarify that, if necessary, a treatment could be given a maximum of + 7 days from the scheduled date; if the treatment could not be given within + 7 days, it was to be considered missed and the treatments resumed with the following scheduled date.

- **MoCA and MDRS:** The protocol was modified to indicate that the MoCA and MDRS were also to be performed at Week e2-80 at the end of the Pilot Extension.

- **AE documentation:** The protocol was revised to eliminate inconsistencies with respect to the required approach to documentation of AEs. All AEs occurring during the study until 28 days after the last dose of GDNF were to be recorded on the AE pages of the CRF. In addition, the protocol was revised to correctly reflect the information documented in the CRF for each AE.

9.9.2 Changes to Subject Information and Consent Documents

Both the patient information sheet and the informed consent form were amended as appropriate to reflect changes introduced by the protocol amendments. All amendments were approved by the ethics committee prior to implementation. The most recent versions of the consent documents are given in Section 17.1.3.

9.9.3 Changes to Database and Analyses after Database Lock

Subsequent to database lock (13 Apr 2017), 2 missing AEs and a number of minor data errors were discovered during preparation of the clinical study report. The database was therefore unlocked on 14 Jun 2017 to permit data corrections to be made (Section 17.1.8, Unlocking plan). The database was relocked on 25 Jul 2017.

In addition, the following additional issues were identified and addressed during preparation of the clinical study report:

- The imputation method used for the timed walking test and timed tapping test was corrected to use the worst result from the respective study (2553 or 2797) rather than the worst result across both studies (Tables 16.2.4.1 and 16.2.4.2).

- The analyses of change in total daily levodopa dose and total daily levodopa equivalent dose did not use the correct baseline as specified in the SAP ("baseline value from study 2553"). This was corrected (Tables 16.2.4.7 and 16.2.4.8).

- Comparison of SAP v2.0 with v1.0 revealed that, due to human error, SAP Sections 9.8.2.3 to 9.8.2.8 were updated incorrectly before finalization of SAP v2.0, with the result that some intended changes were not implemented and other unintentional changes were introduced. The changes mainly concerned the subject groups and parameters for which scatterplots were to be produced. Details of the discrepancies identified between SAP v1.0 and v2.0 were documented in a note to file (Section 17.1.8, SAP note to file 17 Jul 2017) and accompanying change log (Section 17.1.8, SAP change log 17 Jul 2017). Three new scatterplots were generated to provide correlation analyses that had been inadvertently omitted (Figures 16.5.5.16, 16.5.5.17, and 16.5.5.18).

- Minor discrepancies between the following tables of most frequent TEAEs were corrected: Table 16.4.2.3.1, title changed from "overall" to "in any treatment group" (as per SAP); Tables 16.4.2.3.2 and 16.4.2.3.3, analysis approach changed from "overall" to "in any treatment group" to be consistent with Table 16.4.2.3.1.

9.9.4   Post Hoc Analyses

After the final study results became available, additional, post hoc analyses were performed to help provide a better understanding of the study results and to aid in drawing conclusions. Due to the exploratory nature of these analyses, no post hoc SAP was prepared. All post hoc analyses were done using the ITT Overall Population.

9.9.4.1   Efficacy Analyses

9.9.4.1.1   Integrated Overall Response (IOR) Score

During review of the study results, it was noted that individual subjects were not always all concordant with respect to the change observed in OFF state UPDRS motor score (part III), OFF state UPDRS ADL score (part II), and total good-quality ON time per day. Therefore, an integrated approach was used to assess clinical change as a combined endpoint including all 3 measures. This endpoint was defined as the "integrated overall response (IOR) score".

Since the 3 individual measures differ substantially in terms of their nominal weights, they were normalized for inclusion in the IOR endpoint. On the basis of the predefined thresholds for "strong response" in OFF state motor score (≥10 points) and total good-quality ON time per day (≥1 hour; see Section 9.6.2.1 and Section 9.8.1.8.2), correction factors of 1 and -10, respectively, were used for these endpoints. Based on the ratio of the maximum possible values for motor and ADL scores (108 vs. 52), the correction factor for change in OFF state ADL score was set to 2.

With these correction factors, and considering the different directions of improvement in motor and ADL scores (-) vs. good-quality ON time (+), the IOR score was calculated as follows:

IOR score =   (1 × change in OFF state motor score) + (2 × change in OFF state ADL score) - (10 × change in total good-quality ON time per day)

Analyses of the IOR were performed using the ITT Overall Population in a manner similar to the analyses of the primary endpoint. However, since the IOR is a change score that is not calculated at baseline, the original MMRM did not include baseline IOR as a covariate. A decrease in IOR score represents an improvement.

Further post hoc analyses were performed to investigate the robustness of the threshold and correction factor used for the good-quality ON time component when calculating the IOR score. While the basis for the relative weights of motor and ADL scores is robust in the light of published literature [48, 49], the basis for using a 1-hour threshold for change in good-quality ON time is possibly less robust, since a 1-hour gain may be considered a minimal or minimal to moderate clinically important difference rather than a substantial clinical difference [49]. The original IOR analyses were therefore repeated using different thresholds for good-quality ON time, i.e. 1.25 and 1.67 hours, translating to correction factors of 8 and 6 in the calculation formula.

As a further alternative, the IOR analyses were performed using change in total OFF time per day instead of good-quality ON time, where the same 1-hour threshold translates into a bigger

percentage change from baseline (16.4% for OFF time versus 8.8% for good-quality ON time, based on the data for study 2797). These modified IOR analyses were performed using 1.0, 1.25, and 1.67 hours as the threshold, translating to correction factors of 10, 8, and 6 in the calculation formula. Since decrease is the direction of interest for OFF time, the result for this parameter was added, not subtracted, in the calculations.

Finally, additional analyses were performed with the IOR score using change in total good-quality ON time per day with the 1.67-hour threshold as the PD diary component. The objective of these additional analyses was to investigate the impact of adjusting for baseline by including the sum of the underlying scores at baseline (weighted the same as in the IOR score) as a covariate in the MMRM, and to replicate the analysis for strong treatment response in OFF state motor score (Section 9.8.1.8.2) using IOR score as the endpoint and 30 (3 × 10) points as the cut-off for strong response.

10. STUDY SUBJECTS

10.1 Disposition of Subjects

The extension study 2797 was conducted at a single center in the United Kingdom.

All 41 subjects who completed study 2553 were enrolled in the extension study. All 41 subjects received open-label study treatment and completed the Initial Extension (Table 8 and Table 16.1.1.2.2).

Five of the 6 Pilot Stage subjects were subsequently enrolled and treated in the Pilot Extension (Table 16.1.1.1). One Pilot Stage subject did not proceed to the Pilot Extension because his catheters were found to be occluded at the Week 76/e36 infusion (subject 01, GDNF/GDNF). One Pilot Stage subject discontinued treatment due to catheter occlusion during the Pilot Extension but still returned for further visits until the end of the study (subject 03, placebo/GDNF). Two Pilot Stage subjects had to discontinue study medication during the Pilot Extension after explantation of their device (or parts thereof) subsequent to a device-related infection (subject 04, GDNF/GDNF) or an application site infection (subject 05, GDNF/GDNF; for subject narratives see Section 16.6). Subject 04 still returned for further visits until the end of the study, subject 05 terminated the study early.

Twenty-three subjects (2 Pilot Stage subjects, 21 Primary Stage subjects) were enrolled and treated in the Supplemental Extension; 2 other Pilot Stage subjects were also enrolled but not treated and only followed clinically (subject 04, GDNF/GDNF and subject 03, placebo/GDNF; Table 16.1.1.1 and Listing 17.2.1.1).

Fourteen Primary Stage subjects were not enrolled in the Supplemental Extension because they completed the Initial Extension too late to have at least one study visit by the end of December 2016 as required by the protocol (Listing 17.2.1.1).

The maximum duration of involvement in study 2797 was approximately 34 months (Listing 17.2.1.1 and Listing 17.2.4.1.2).

Study completion status by subject is given in Listing 17.2.1.1.

Table 8   Numbers of Subjects Enrolled and Treated in Each Extension Part

	GDNF/GDNF	Placebo/GDNF	Total
Initial Extension (Pilot Stage + Primary Stage subjects)			
Enrolled	21	20	41
Treated	21	20	41
Pilot Extension (Pilot Stage subjects)			
Enrolled	3	2	5
Treated	3	2	5
Supplemental Extension (Pilot Stage + Primary Stage subjects)			
Enrolled	12	13	25
Treated	11	12	23

Source: Table 16.1.1.1

10.2   Protocol Deviations

Major protocol deviations were identified for 2 subjects in the ITT Overall Population (Table 9):

- Subject 42 (GDNF/GDNF) missed a total of 5 study medication infusions (Weeks 44/e4, 52/e12, 60/e20, 68/e28, and 76/e36). The subject missed every second infusion based on personal preference (Listings 17.2.1.2.1 and 17.2.1.2.2).

- Subject 45 (GDNF/GDNF) had 2 major protocol deviations: 2 study medication infusions missed (Weeks 52/e12 and 60/e20) and full UPDRS not completed at Week 80/e40 (Listings 17.2.1.2.1 and 17.2.1.2.2).

Table 9   Major Protocol Deviations - ITT Overall Population

Category Deviation	GDNF/GDNF (N=21) n (%)	Placebo/GDNF (N=20) n (%)	Total (N=41) n (%)
Subjects with at least one major protocol deviation	2 (9.5)	0	2 (4.9)
Outcome assessment	1 (4.8)	0	1 (2.4)
Full UPDRS not completed at Week 40	1 (4.8)	0	1 (2.4)
Study medication (including overdose)	2 (9.5)	0	2 (4.9)
More than one infusion of study medication missed in Initial Extension	2 (9.5)	0	2 (4.9)

Source: Table 16.1.2, Listing 17.2.1.2.2

Minor protocol deviations were identified for 40 of the 41 subjects in the ITT Overall Population (Table 10). The most common types of minor deviation were related to the study schedule/visit windows and the performance of outcome assessments. The overall frequency of such minor protocol deviations was comparable in both treatment groups.

Minor protocol deviations related to study medication were due to missing more than one study medication infusion in the Initial Extension (GDNF/GDNF subjects 42 and 45, see also above; the second missed infusion was counted as a major protocol deviation, other missed infusions as minor protocol deviations); missing a single study medication infusion in the Initial Extension (2 GDNF/GDNF subjects); and missing one or more study medication infusions in the Pilot Extension or Supplemental Extension (2 GDNF/GDNF subjects and 2 placebo/GDNF subjects). One subject in the GDNF/GDNF group had a minor protocol deviation related to use of long-acting PD medication at the wrong time. Two GDNF/GDNF subjects were initially given a wrong version of the patient information sheet, and 1 GDNF/GDNF subject left the site early after completing a study medication infusion.

For protocol deviations by subject see Listing 17.2.1.2.1 (major deviations) and Listing 17.2.1.2.2 (minor deviations).

Table 10   Minor Protocol Deviations - ITT Overall Population

Category	GDNF/GDNF (N=21) n (%)	Placebo/GDNF (N=20) n (%)	Total (N=41) n (%)
Subjects with at least one minor protocol deviation	21 (100)	19 (95.0)	40 (97.6)
Study schedule/visit window	21 (100)	19 (95.0)	40 (97.6)
Outcome assessment	16 (76.2)	14 (70.0)	30 (73.2)
Study medication (including overdose)	6 (28.6)	2 (10.0)	8 (19.5)
Non-study medication	1 (4.8)	0	1 (2.4)
Other	3 (14.3)	0	3 (7.3)

Note: For each category, subjects are included only once, even if they experienced multiple events in that category.
Source: Table 16.1.2

10.3   Data Sets Analyzed

In accordance with the analysis population definitions (see Section 9.8.1.2), all enrolled subjects were included in the ITT populations (Table 11).

All enrolled subjects received at least one dose of study medication and were included in the Safety Overall Population.

The subjects included in each population are presented in Listing 17.2.1.3.

Table 11   Numbers of Subjects in Analysis Populations

Population	GDNF/GDNF	Placebo/GDNF	Total
ITT Primary Population	17	18	35
ITT Overall Population	21	20	41
Safety Overall Population	21	20	41

Source: Table 16.1.1.1

10.4   Demographic and Other Baseline Characteristics

10.4.1   Demographic Characteristics

Demographic characteristics were documented at the start of the parent study 2553; with the exception of weight, these data were not collected again at the start of the extension study. The demographic characteristics of the ITT Primary Population from study 2553 are presented in Table 12 for information purposes. With the exception of a small imbalance in sex distribution, there were no clinically meaningful differences in demographic characteristics between the treatment groups at the start of study 2553.

Demographic characteristics for the ITT Overall Population were very similar to those for the ITT Primary Population (Table 16.1.3.2).

For demographic characteristics from study 2553 by subject see Listing 17.2.1.4.1.

Table 12   Demographic Characteristics from Study 2553 - ITT Primary Population

Variable	GDNF/GDNF (N=17)	Placebo/GDNF (N=18)	Total (N=35)
Sex, n (%)			
Female	10 (58.8)	7 (38.9)	17 (48.6)
Male	7 (41.2)	11 (61.1)	18 (51.4)
Race, n (%)			
White	17 (100)	17 (94.4)	34 (97.1)
Asian	0	1 (5.6)	1 (2.9)
Ethnicity, n (%)			
Hispanic or Latino	0	0	0
Not Hispanic or Latino	17 (100)	18 (100)	35 (100)
Age (years)			
n	17	18	35
Mean (SD)	57.7 (8.24)	55.1 (7.52)	56.4 (7.87)
Median (Min, Max)	57.0 (45, 72)	55.0 (41, 67)	55.0 (41, 72)
Age group, n (%)			
<65 years	13 (76.5)	16 (88.9)	29 (82.9)
≥65 years	4 (23.5)	2 (11.1)	6 (17.1)
Weight at baseline (kg)			
n	17	18	35
Mean (SD)	78.01 (15.139)	80.02 (22.293)	79.05 (18.905)
Median (Min, Max)	77.00 (49.3, 111.3)	74.55 (43.0, 124.0)	74.70 (43.0, 124.0)
Body mass index at baseline (kg/m^2)			
n	17	18	35
Mean (SD)	26.755 (4.192)	26.895 (5.847)	26.827 (5.037)
Median (Min, Max)	26.110 (19.65, 33.98)	27.540 (17.57, 39.31)	26.927 (17.57, 39.31)
NART error score (points)			
n	17	18	35
Mean (SD)	11.8 (5.36)	13.3 (6.91)	12.6 (6.16)
Median (Min, Max)	12.0 (4, 21)	12.0 (4, 32)	12.0 (4, 32)

Note: National Adult Reading Test (NART) error score is the number of words pronounced incorrectly out of 50 total words.

Source: Table 16.1.3.1

10.4.2   Parkinson's Disease History

PD characteristics were documented at screening in study 2553; these data were not collected again at the start of the extension study. The PD characteristics of the ITT Primary Population from study 2553 are presented in Table 13 for information purposes. With the exception of a slight difference in the proportions of subjects with Hoehn and Yahr stage 2 and 2.5 in the OFF state at screening, no notable differences were observed between the treatment groups in the PD characteristics.

Table 13   Parkinson's Disease Characteristics at Screening in Study 2553 - ITT Primary Population

Variable	GDNF/GDNF (N=17)	Placebo/GDNF (N=18)	Total (N=35)
Duration since first PD symptom (years)			
n	17	18	35
Mean (SD)	10.8 (4.97)	10.9 (5.78)	10.9 (5.32)
Median (Min, Max)	10.0 (5, 21)	8.5 (5, 26)	9.0 (5, 26)
Duration since PD diagnosis (years)			
n	17	18	35
Mean (SD)	8.6 (4.33)	7.9 (3.69)	8.3 (3.97)
Median (Min, Max)	8.0 (3, 19)	8.5 (2, 17)	8.0 (2, 19)
Hoehn and Yahr stage in OFF state, n (%)			
Stage 2	8 (47.1)	5 (27.8)	13 (37.1)
Stage 2.5	4 (23.5)	8 (44.4)	12 (34.3)
Stage 3	5 (29.4)	5 (27.8)	10 (28.6)
OFF state UPDRS motor score (part III)			
n	17	18	35
Mean (SD)	37.1 (7.20)	35.8 (6.14)	36.4 (6.60)
Median (Min, Max)	40.0 (26, 45)	35.5 (27, 45)	37.0 (26, 45)
ON state UPDRS motor score (part III)			
n	17	18	35
Mean (SD)	16.9 (5.17)	16.9 (4.52)	16.9 (4.77)
Median (Min, Max)	16.0 (9, 26)	15.5 (10, 26)	16.0 (9, 26)
Responsiveness to levodopa[a] (%)			
n	17	18	35
Mean (SD)	54.24 (9.351)	52.80 (9.434)	53.50 (9.283)
Median (Min, Max)	55.00 (40.0, 67.0)	52.00 (40.6, 72.9)	54.00 (40.0, 72.9)
OFF time per day (hours)			
n	17	18	35
Mean (SD)	6.26 (2.217)	6.07 (2.076)	6.17 (2.116)
Median (Min, Max)	6.80 (2.8, 9.3)	5.75 (3.2, 9.5)	6.00 (2.8, 9.5)

[a]   Percentage improvement in UPDRS motor score (part III) following a levodopa challenge

Source: Table 16.1.4.1

At screening in study 2553, 34 of the 35 subjects in the ITT Primary Population were receiving levodopa preparations and 30 subjects were receiving a dopamine agonist (Table 14). The mean total daily levodopa dose was 609 mg, and the mean total daily levodopa equivalent dose was 972 mg.

The frequencies of PD medications at screening in study 2553 were similar in both treatment groups, except that slightly fewer GDNF/GDNF subjects than placebo/GDNF subjects were receiving monoamine oxidase B (MAO-B) inhibitors and "Other" PD medications. The mean total daily levodopa dose was higher in the GDNF/GDNF group than in the placebo/GDNF group, while there was no appreciable difference between the treatment groups in the mean total daily levodopa equivalent dose.

PD characteristics and medications for the ITT Overall Population were very similar to those for the ITT Primary Population (Table 16.1.4.2).

For PD history at screening in study 2553 by subject see Listing 17.2.1.4.2.

Table 14   Parkinson's Disease Medication at Screening in Study 2553 - ITT Primary Population

Variable	GDNF/GDNF (N=17)	Placebo/GDNF (N=18)	Total (N=35)
PD medications, n (%)			
Levodopa preparations	16 (94.1)	18 (100)	34 (97.1)
Dopamine agonists	14 (82.4)	16 (88.9)	30 (85.7)
COMT inhibitors	7 (41.2)	9 (50.0)	16 (45.7)
MAO-B inhibitors	6 (35.3)	10 (55.6)	16 (45.7)
Other	3 (17.6)	6 (33.3)	9 (25.7)
Total daily levodopa dose (mg)			
n	16	18	34
Mean (SD)	662.23 (345.258)	562.07 (272.303)	609.21 (308.150)
Median (Min, Max)	598.50 (300.0, 1596.0)	566.00 (100.0, 1000.0)	598.50 (100.0, 1596.0)
Total daily levodopa equivalent dose (mg)			
n	17	18	35
Mean (SD)	981.60 (384.827)	963.45 (355.535)	972.26 (364.661)
Median (Min, Max)	915.00 (300.0, 1890.0)	967.90 (299.5, 1656.0)	930.00 (299.5, 1890.0)

Source: Table 16.1.4.1

10.4.3 Other Medical History

Details of other medical history were documented at screening in study 2553; these data were not collected again at the start of the extension study.

10.4.4 Prior Medications

Details of prior medication were documented at screening in study 2553; these data were not collected again at the start of the extension study.

10.4.5 Concomitant Medications

For the purpose of the analysis, concomitant medications were defined as any medications ongoing at the start of open-label study medication dosing or with a start date on or after the date of the first dose of open-label study medication.

10.4.5.1 Concomitant Parkinson's Disease Medications

Concomitant PD medications were reported for all 35 subjects in the ITT Primary Population (Table 15). All subjects received a concomitant levodopa preparation, and 28 subjects also received a concomitant dopamine agonist, without notable differences between the treatment groups with regard to the individual preparations taken. MAO-B inhibitors were taken by a higher proportion of placebo/GDNF subjects (15 subjects, 83.3%) than GDNF/GDNF subjects (9 subjects, 52.9%). Catechol-O-methyl transferase (COMT) inhibitors (as mono- or combination products) were taken by 7 (41.2%) subjects in the GDNF/GDNF group and by 11 (61.1%) subjects in the placebo/GDNF group.

For all concomitant medications by subject see Listing 17.2.1.5.

Table 15   Concomitant Parkinson's Disease Medications - ITT Primary Population

Category Preferred name	GDNF/GDNF (N=17) n (%)	Placebo/GDNF (N=18) n (%)	Total (N=35) n (%)
Subjects with at least one concomitant PD medication	17 (100)	18 (100)	35 (100)
DOPA and DOPA derivatives	17 (100)	18 (100)	35 (100)
Ledopsan	5 (29.4)	6 (33.3)	11 (31.4)
Madopar	9 (52.9)	9 (50.0)	18 (51.4)
Sastravi	0	1 (5.6)	1 (2.9)
Sinemet	11 (64.7)	10 (55.6)	21 (60.0)
Stalevo /01631201/	7 (41.2)	7 (38.9)	14 (40.0)
Dopamine agonists	13 (76.5)	15 (83.3)	28 (80.0)
Pramipexole	5 (29.4)	6 (33.3)	11 (31.4)
Pramipexole dihydrochloride	3 (17.6)	1 (5.6)	4 (11.4)
Ropinirole	3 (17.6)	6 (33.3)	9 (25.7)
Ropinirole hydrochloride	2 (11.8)	2 (11.1)	4 (11.4)
Rotigotine	0	1 (5.6)	1 (2.9)
COMT inhibitors	0	3 (16.7)	3 (8.6)
Entacapone	0	3 (16.7)	3 (8.6)
MAO-B inhibitors	9 (52.9)	15 (83.3)	24 (68.6)
Rasagiline	8 (47.1)	12 (66.7)	20 (57.1)
Selegiline	2 (11.8)	3 (16.7)	5 (14.3)
Other	7 (41.2)	9 (50.0)	16 (45.7)
Amantadine	7 (41.2)	8 (44.4)	15 (42.9)
Propranolol	0	1 (5.6)	1 (2.9)
Rivastigmine	0	1 (5.6)	1 (2.9)

Note: Concomitant medications are any medications ongoing at the start of open-label study medication dosing or with a start date on or after the date of the first dose of open-label study medication. Medications are coded using WHO Drug Dictionary Enhanced version 2016Mar01. For each preferred name, subjects are included only once.

Source: Table 16.1.5.1, Listing 17.2.1.5

10.4.5.2 Other Concomitant Medications

Other concomitant medications were reported for all 35 subjects in the ITT Primary Population (Table 16). Most of the medications were reported for only 1-3 subjects overall. Individual concomitant medications reported for more than 3 subjects overall included analgesics (ibuprofen, paracetamol, Panadeine Co), atorvastatin, drugs for constipation (Movicol, Senna alexandrina), flucloxacillin, influenza vaccine, psycholeptics (diazepam, melatonin, zopiclone), and sodium chloride. With the exception of a slightly higher number of subjects receiving flucloxacillin in the GDNF/GDNF group, no notable differences were detected between the treatment groups with respect to such medication.

For all concomitant medications by subject see Listing 17.2.1.5.

Table 16   Other Concomitant Medications: Preferred Names Reported for More Than 3 Subjects Overall - ITT Primary Population

Preferred name	GDNF/GDNF (N=17) n (%)	Placebo/GDNF (N=18) n (%)	Total (N=35) n (%)
Subjects with at least one other concomitant medication	17 (100)	18 (100)	35 (100)
Paracetamol	11 (64.7)	13 (72.2)	24 (68.6)
Flucloxacillin	8 (47.1)	3 (16.7)	11 (31.4)
Ibuprofen	4 (23.5)	6 (33.3)	10 (28.6)
Melatonin	2 (11.8)	5 (27.8)	7 (20.0)
Diazepam	3 (17.6)	3 (16.7)	6 (17.1)
Movicol /08437601/	4 (23.5)	2 (11.1)	6 (17.1)
Senna alexandrina	2 (11.8)	3 (16.7)	5 (14.3)
Atorvastatin	2 (11.8)	2 (11.1)	4 (11.4)
Influenza vaccine	1 (5.9)	3 (16.7)	4 (11.4)
Panadeine Co	1 (5.9)	3 (16.7)	4 (11.4)
Sodium chloride	1 (5.9)	3 (16.7)	4 (11.4)
Zopiclone	2 (11.8)	2 (11.1)	4 (11.4)

Note: Concomitant medications are any medications ongoing at the start of open-label study medication dosing or with a start date on or after the date of the first dose of open-label study medication. Medications are coded using WHO Drug Dictionary Enhanced version 2016Mar01. For each preferred name, subjects are included only once.
Source: Table 16.1.5.2

10.4.6   Surgery and Test Infusions

10.4.6.1   Catheter Trajectories and Positioning Accuracy

Two Pilot Stage subjects (04 and 05, both GDNF/GDNF) underwent repositioning surgery immediately prior to entry into the Pilot Extension (Listing 17.2.1.7). Posterior-anterior horizontal trajectories were used in both subjects, although only documented in the CRF for subject 04 (Listing 17.2.1.6). Catheter positioning was rated as satisfactory in both cases (Listing 17.2.1.7).

10.4.6.2   Contrast-Enhanced Test Infusions with T1-Weighted MRI

Contrast-enhanced test infusions followed by T1-weighted MRI were used to monitor catheter performance.

Five of 6 Pilot Stage subjects received a contrast-enhanced test infusion with T1-weighted MRI at the start of the Pilot Extension (Week e2-0). Unlike Primary Stage subjects who underwent repeat monitoring of catheter performance via T1-weighted MRI both at the beginning and at the end of study 2553, Pilot Stage subjects did not receive any contrast-enhanced test infusions for the monitoring of catheter performance in study 2553.

Three of the 6 Pilot Stage subjects also received a contrast-enhanced test infusion with T1-weighted MRI at the end of the Pilot Extension (Week e2-80).

All 35 Primary Stage subjects received a contrast-enhanced test infusion with T1-weighted MRI at the end of the Initial Extension (Week 80/e40).

Test infusion data are presented by subject and visit in Listing 17.2.1.8. Information on test infusion catheter interruptions and early terminations is provided in Listing 17.2.1.9.

10.5   Measurements of Treatment Compliance

The study medication was administered by the investigator or designee. Administration records were kept on site, and administration information, including date and time of infusion, infusion rate and duration, and the reasons for any interruptions of the infusion or for any missed or omitted infusions were recorded in the CRF.

In the Initial Extension, only 9 of the 410 study medication infusions scheduled were missed (Listing 17.2.4.1.2). For information on study medication exposure, see Section 13.1.

11. EFFICACY EVALUATION

11.1 Analyses of Primary Efficacy Endpoint

11.1.1 Primary Efficacy Analysis

The primary efficacy analysis was the comparison of percentage change from baseline to Week 80/e40 in the practically defined OFF state UPDRS motor score (part III) between treatment groups for the ITT Primary Population using a mixed-effect model with repeated measures (MMRM).

The percentage change in OFF state UPDRS motor score over time from baseline to Week 80/e40 is shown graphically in Figure 5. The results of the primary analysis are presented in Table 17.

Figure 5   OFF State UPDRS Motor Score (Part III): Percentage Change Over Time - ITT Primary Population
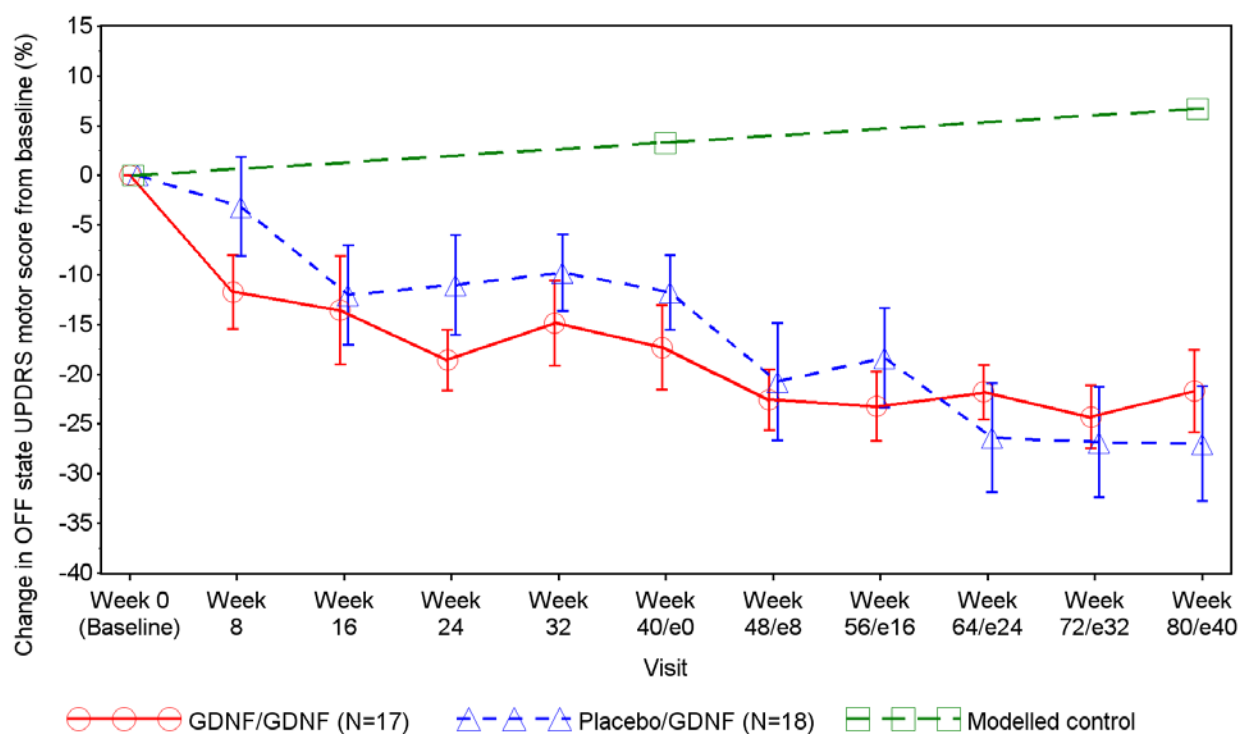
Note: Data points represent means, and error bars represent standard errors. For subject 45 (GDNF/GDNF), items 22, 27, 28, 29, and 30 are excluded from the score. Modelled control based on data from the Parkinson's Progression Markers Initiative database [47].
Source: Figure 16.5.1.1.1

Table 17   **Primary Efficacy Analysis - OFF State UPDRS Motor Score (Part III): Percentage Change from Baseline to Week 80/e40, MMRM - ITT Primary Population**

Visit Statistic	GDNF/GDNF (N=17)		Placebo/GDNF (N=18)	
	Value	Percentage change from baseline	Value	Percentage change from baseline
Week 0 (baseline)				
n	17		18	
Mean (SD)	35.3 (9.38)		32.2 (8.73)	
Median (Min, Max)	35.0 (19, 53)		33.0 (16, 45)	
Week 40/e0				
n	17	17	18	18
Mean (SD)	29.1 (10.29)	-17.3 (17.60)	28.8 (9.75)	-11.8 (15.76)
Median (Min, Max)	27.0 (15, 58)	-21.1 (-41, 23)	30.5 (11, 44)	-13.8 (-43, 21)
Week 80/e40				
n	17	17	18	18
Mean (SD)	27.1 (7.46)	-21.7 (17.11)	23.3 (9.34)	-27.0 (24.57)
Median (Min, Max)	28.0 (15, 39)	-23.1 (-50, 13)	23.5 (8, 39)	-27.0 (-67, 29)
Treatment comparison[a]				
LS mean difference vs placebo		6.0		
(95% CI)		(-8.6, 20.7)		
p-value		0.4078		

[a]   MMRM with baseline UPDRS score as a covariate, treatment group and visit and treatment group*visit as fixed effects, and subject within treatment group as a random effect

Note: Lower scores represent better functioning. For subject 45 (GDNF/GDNF), items 22, 27, 28, 29, and 30 are excluded from the score.

Source: Table 16.2.1.1

Baseline mean OFF state UPDRS motor score was slightly higher in the GDNF/GDNF group than in the placebo/GDNF group (35.3 vs. 32.2).

Between baseline and Week 40 (parent study 2553), the mean OFF state UPDRS motor score decreased in both treatment groups, with a greater mean percentage decrease in the GDNF/GDNF group (-17.3%) than in the placebo/GDNF group (-11.8%).

A further decrease was observed in each treatment group in the subsequent 40 weeks of study treatment (Initial Extension part of extension study 2797). As expected based on the Week 40 results (study 2553), the percentage decrease in mean OFF state UPDRS motor score during the Initial Extension was greater in the placebo/GDNF group than in the GDNF/GDNF group, since subjects who received placebo in the parent study were switched to GDNF at the start of the extension study and neurorestoration is likely to have a sigmoidal time-effect curve, with the steeper part in the earlier phases of treatment. Overall, between baseline and Week 80/e40, mean OFF state UPDRS motor score decreased by 21.7% in the GDNF/GDNF group and 27.0% in the placebo/GDNF group, in contrast to the predicted disease progression reflected by a

6.9%-increase in OFF state UPDRS motor score over 80 weeks for a modelled control (Figure 5; for details of model see Section 9.8.1.8.1). In the primary analysis for the extension study, the MMRM showed a small mean treatment difference in favor of placebo/GDNF that was not statistically significant (LS mean difference: 6.0%, 95% CI: -8.6, 20.7, p=0.4078).

In the Supplemental Extension, UPDRS assessments were performed at wider intervals of 16 weeks. Only a very small number of subjects had assessments at Week e3-16 (11 subjects: 5 GDNF/GDNF, 6 placebo/GDNF) and Week e3-32 (8: 4 GDNF/GDNF, 4 placebo/GDNF; Listing 17.2.2.1). Therefore no meaningful evaluation of this data is possible.

Individual subject scores for OFF state UPDRS motor score over time are displayed in Figure 16.5.3.

For OFF state and ON state UPDRS scores by subject see Listing 17.2.2.1.

11.1.2   Sensitivity Analysis

The findings of the sensitivity analysis of the primary efficacy endpoint in the ITT Overall Population were similar to the findings of the primary analysis (Figure 6, Table 18). At Week 80/e40, almost no treatment difference was detected between the treatment groups in the MMRM (LS mean difference: 0.4%, 95% CI: -13.9, 14.6, p=0.9587).

Figure 6   OFF State UPDRS Motor Score (Part III): Percentage Change Over Time - ITT Overall Population
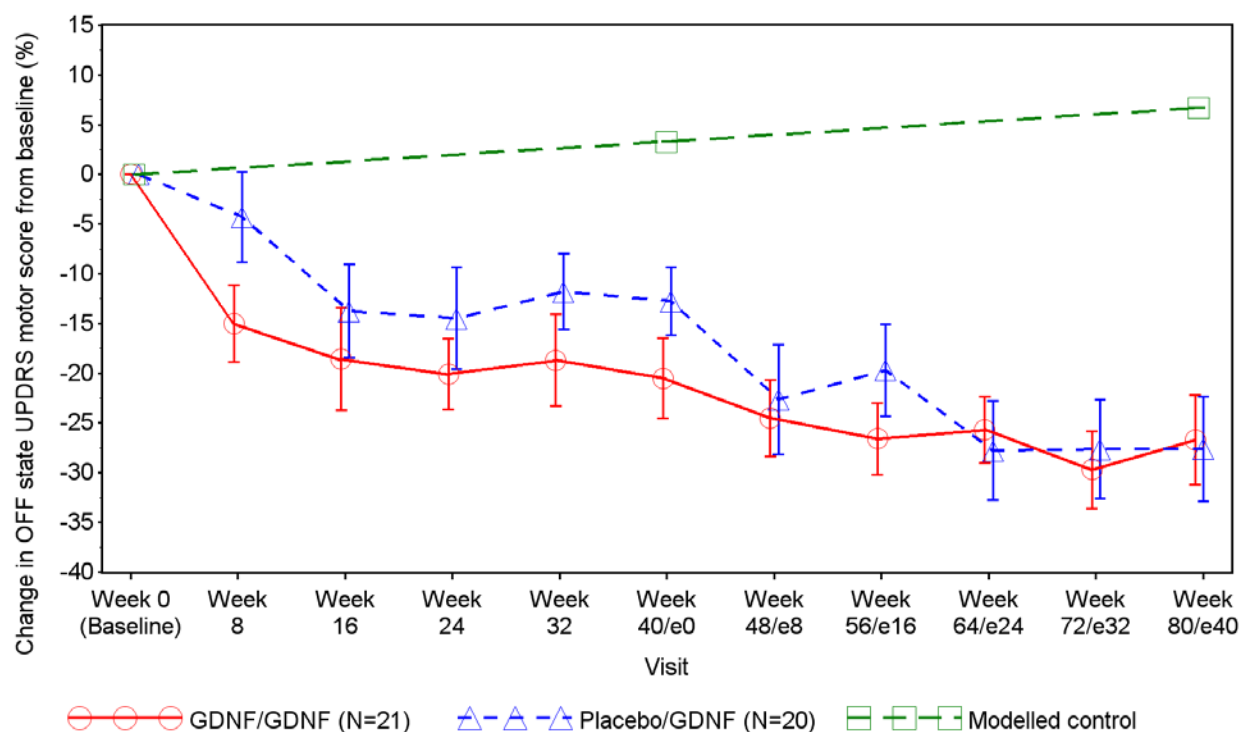
Note: Data points represent means, and error bars represent standard errors. For subject 45 (GDNF/GDNF), items 22, 27, 28, 29, and 30 are excluded from the score. Modelled control based on data from the Parkinson's Progression Markers Initiative database [47].
Source: Figure 16.5.1.1.2

Table 18   Sensitivity Analysis - OFF State UPDRS Motor Score (Part III): Percentage Change from Baseline to Week 80/e40, MMRM - ITT Overall Population

Visit Statistic	GDNF/GDNF (N=21)		Placebo/GDNF (N=20)	
	Value	**Percentage change from baseline**	**Value**	**Percentage change from baseline**
Week 0 (baseline)				
n	21		20	
Mean (SD)	36.0 (11.73)		32.2 (8.29)	
Median (Min, Max)	34.0 (19, 70)		33.0 (16, 45)	
Week 40/e0				
n	21	21	20	20
Mean (SD)	28.8 (12.53)	-20.5 (18.60)	28.5 (9.29)	-12.7 (15.21)
Median (Min, Max)	27.0 (14, 60)	-21.1 (-53, 23)	28.5 (11, 44)	-14.1 (-43, 21)
Week 80/e40				
n	21	21	20	20
Mean (SD)	26.4 (11.33)	-26.7 (20.67)	23.2 (8.99)	-27.6 (23.55)
Median (Min, Max)	26.0 (9, 58)	-23.3 (-70, 13)	23.5 (8, 39)	-27.0 (-67, 29)
Treatment comparison[a]				
LS mean difference vs placebo		0.4		
(95% CI)		(-13.9, 14.6)		
p-value		0.9587		

[a]   MMRM with baseline UPDRS score as a covariate, treatment group and visit and treatment group*visit as fixed effects, and subject within treatment group as a random effect

Note: Lower scores represent better functioning. For subject 45 (GDNF/GDNF), items 22, 27, 28, 29, and 30 are excluded from the score.

Source: Table 16.2.1.2

11.2   Analyses of Secondary Efficacy Endpoints

11.2.1   Analyses of UPDRS Scores

11.2.1.1   Change and Percentage Change in UPDRS scores from Baseline to Week 80/e40

In addition to the primary analysis, changes in UPDRS motor, ADL, and total scores from baseline to Week 80/e40 were analyzed comprehensively as secondary endpoints. The analyses were performed both for OFF state data and for ON state data, and both change and percentage change from baseline were evaluated (for analytical details see Section 9.8.1.8.2).

OFF State

Analyses of change in OFF state UPDRS motor score and change and percentage change in OFF state UPDRS ADL and total scores from baseline to Week 80/e40 showed similar mean improvements in both treatment groups and both analysis populations (ITT Primary and ITT Overall). Both treatment groups showed moderate to large clinically important mean improvements [48, 49] in OFF state UPDRS scores between baseline and Week 80/e40 (motor score: -9.6 points in the GDNF/GDNF group vs. -9.0 points in the placebo/GDNF group; ADL score: -6.9 vs. -4.6 points; ITT Overall Population). The MMRM of change from baseline to Week 80/e40 showed small mean treatment differences that were mostly in favor of the GDNF/GDNF treatment group; as expected based on the Week 40 results (study 2553), none of the treatment differences were statistically significant. However, the change in OFF state UPDRS motor score put subjects close to the lower end of the range of OFF state UPDRS motor scores permitted at entry to study 2553 (25-45). Moreover, it is in contrast to the predicted disease progression reflected by a 2.4-point worsening of OFF state UPDRS motor score over 80 weeks for a modelled control based on data from the Parkinson's Progression Markers Initiative database [47].

Findings for change from baseline in each score are summarized in Table 19 and presented graphically in Figure 7 (ITT Overall Population) and Figure 16.5.1.2.1 (ITT Primary Population) for motor score; Figure 8 (ITT Overall Population) and Figure 16.5.1.4.1 (ITT Primary Population) for ADL score; and Figure 16.5.1.6.1 (ITT Primary Population) and Figure 16.5.1.6.2 (ITT Overall Population) for total score.

For findings for percentage change from baseline see Tables 16.2.1.1 and 16.2.1.2 (motor score); Tables 16.2.2.2.1 and 16.2.2.2.2 (ADL score); and Tables 16.2.2.4.1 and 16.2.2.4.2 (total score).

**Table 19   OFF State UPDRS Scores (Mean [SD]): Change Over Time - ITT Primary and Overall Populations**

UPDRS score	GDNF/GDNF (N=17[a] for ITT Primary Population, N=21[a] for ITT Overall Population)			Placebo/GDNF (N=18 for ITT Primary Population, N=20 for ITT Overall Population)			Least squares mean difference versus placebo (95% CI); p-value[b]
	Week 0 (baseline)	Week 80/e40	Change from baseline	Week 0 (baseline)	Week 80/e40	Change from baseline	
ITT PRIMARY							
Motor (part III)	35.3 (9.38)	27.1 (7.46)	-8.2 (6.45)	32.2 (8.73)	23.3 (9.34)	-8.8 (8.13)	1.4 (-3.3, 6.0); 0.5564
ADL (part II)	18.4 (6.27)	11.4 (4.95)	-6.9 (5.92)	16.9 (6.10)	11.9 (6.77)	-5.0 (4.75)	-1.4 (-4.8, 1.9); 0.3892
Total (part II+III)	54.3 (13.80)	38.4 (10.98)	-15.8 (9.14)	49.1 (11.57)	35.3 (13.77)	-13.8 (10.51)	-0.9 (-7.4, 5.6); 0.7746
ITT OVERALL							
Motor (part III)	36.0 (11.73)	26.4 (11.33)	-9.6 (6.70)	32.2 (8.29)	23.2 (8.99)	-9.0 (7.75)	-0.0 (-4.4, 4.4); 0.9929
ADL (part II)	18.5 (6.38)	11.7 (4.89)	-6.9 (5.46)	16.9 (5.82)	12.3 (6.60)	-4.6 (4.71)	-1.7 (-4.6, 1.2); 0.2455
Total (part II+III)	55.0 (16.70)	37.9 (14.89)	-17.1 (8.64)	49.1 (10.95)	35.5 (13.04)	-13.6 (9.97)	-2.6 (-8.3, 3.2); 0.3689

[a] For subject 45 (GDNF/GDNF), items 22, 27, 28, 29, and 30 are excluded from the motor (part III) score. The subject's data are excluded completely from analysis of the ADL (part II) and total scores. For analyses of ADL and total scores, the number of subjects for the GDNF/GDNF group is therefore N=16 instead of N=17 in the ITT Primary Population and N=20 instead of N=21 in the ITT Overall Population.

[b] MMRM with baseline UPDRS score as a covariate, treatment group and visit and treatment group*visit as fixed effects, and subject within treatment group as a random effect

Note: Lower scores represent better functioning.

Source: Tables 16.2.1.1, 16.2.1.2, 16.2.2.2.1, 16.2.2.2.2, 16.2.2.4.1, and 16.2.2.4.2

**Figure 7   OFF State UPDRS Motor Score (Part III): Change Over Time - ITT Overall
                Population**
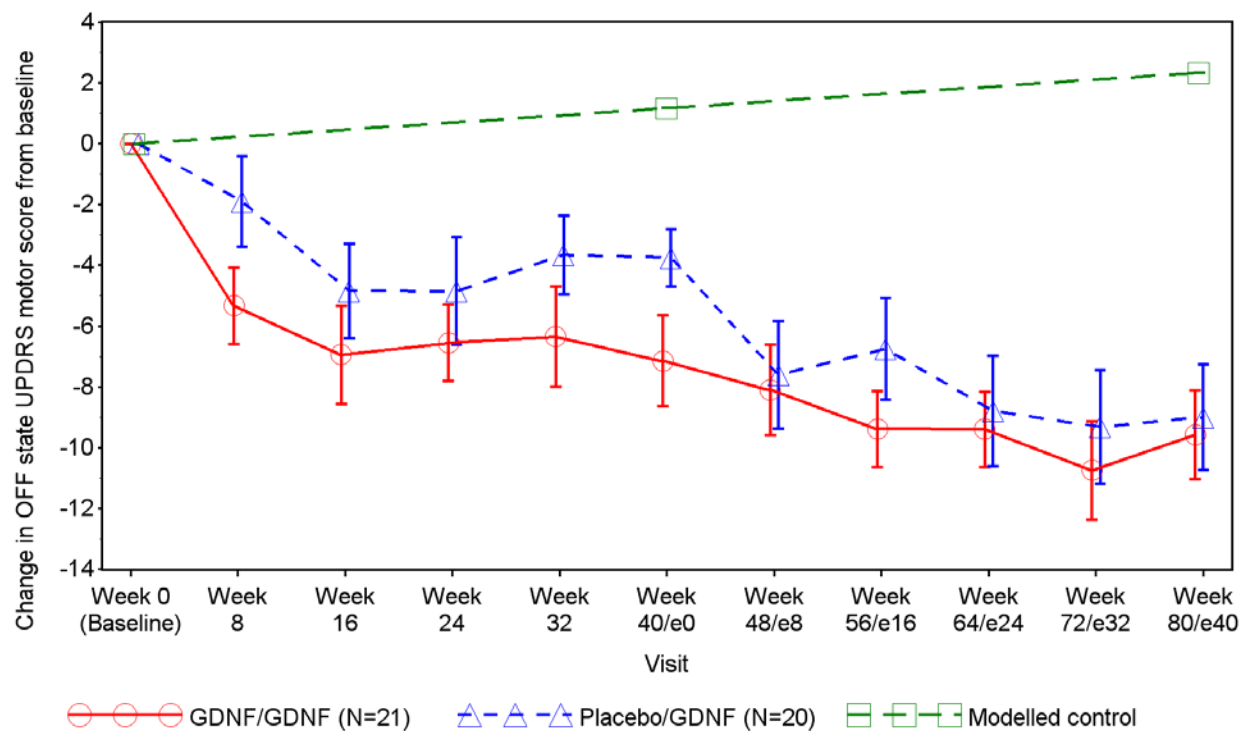
Note: Data points represent means, and error bars represent standard errors. For subject 45
(GDNF/GDNF), items 22, 27, 28, 29, and 30 are excluded from the score. Modelled control based on data
from the Parkinson's Progression Markers Initiative database [47].
Source: Figure 16.5.1.2.2

Figure 8   **OFF State UPDRS ADL Score (Part II): Change Over Time - ITT Overall Population**
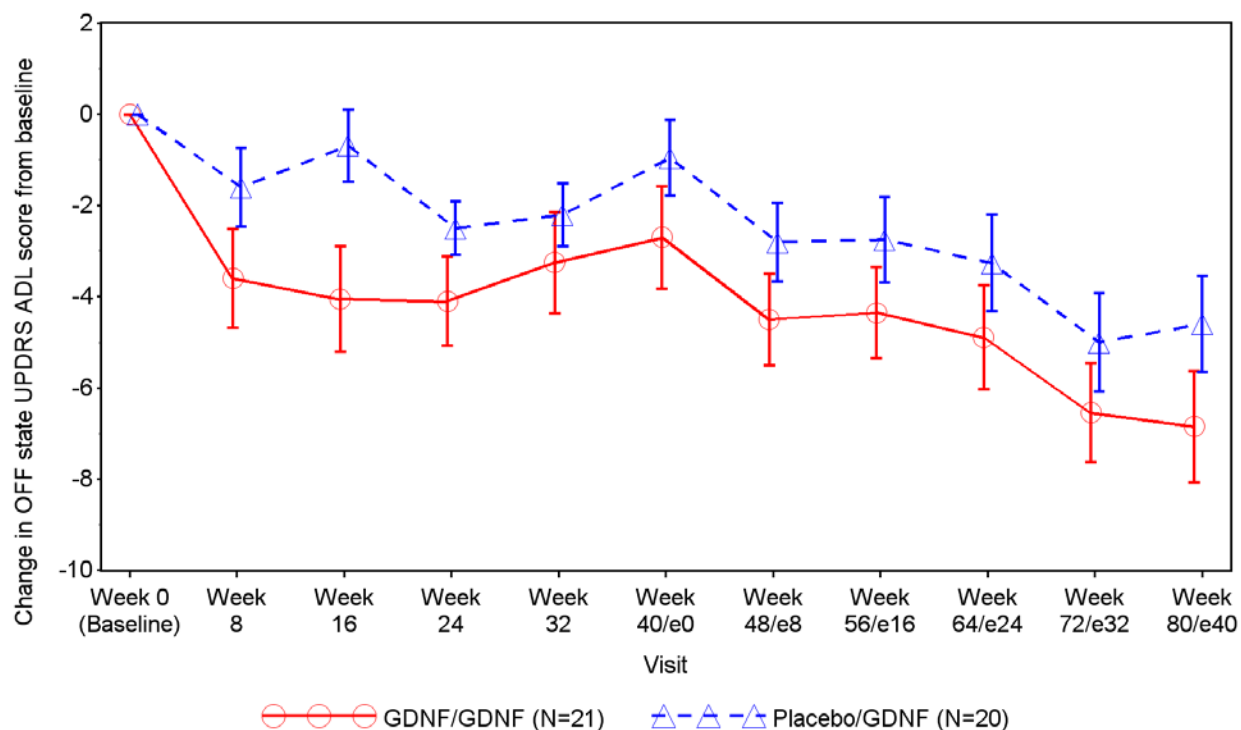
Note: Data points represent means, and error bars represent standard errors. Data for subject 45 (GDNF/GDNF) are excluded from analysis.
Source: Figure 16.5.1.4.2

ON State

Analyses of change and percentage change in ON state UPDRS motor, ADL, and total scores from baseline to Week 80/e40 showed similar mean decreases in both treatment groups. The MMRM of change from baseline to Week 80/e40 showed small mean treatment differences that were mostly in favor of the GDNF/GDNF treatment group; however, none of the treatment differences were statistically significant. The analyses were performed only for the ITT Overall Population.

For findings see Table 16.2.2.1 and Figure 16.5.1.3 (motor score); Table 16.2.2.3 and Figure 16.5.1.5 (ADL score); and Table 16.2.2.5 and Figure 16.5.1.7 (total score).

11.2.1.2   OFF State UPDRS Scores: Change from Baseline to Week 40/e0 for the GDNF/GDNF Group Compared to Change from Baseline to Week 80/e40 for the Placebo/GDNF Group

Comparison of the effects of the first 40 weeks of treatment with GDNF on change in OFF state UPDRS scores in the two treatment groups showed slightly greater effects of GDNF in the group of subjects treated with placebo in study 2553 followed by GDNF in the extension study (Table 20). The MMRM of change from baseline showed small mean treatment differences that were in favor of the placebo/GDNF treatment group in the ITT Overall Population; for the ADL and total scores, the results approached statistical significance. This may in part be due to differences in the use of levodopa medication which was notably increased in the placebo/GDNF group compared to the GDNF/GDNF group (see Section 11.3.7).

Table 20   **OFF State UPDRS Scores (Mean [SD]): Change from Baseline to Week 40/e0 for the GDNF/GDNF Group Compared to Change from Baseline to Week 80/e40 for the Placebo/GDNF Group, MMRM - ITT Overall Population**

UPDRS score	GDNF/GDNF (N=21[a])			Placebo/GDNF (N=20)			Least squares mean difference versus placebo (95% CI); p-value[b]
	Week 0 (baseline)	Week 40/e0	Change from baseline	Week 0 (baseline)	Week 80/e40	Change from baseline	
Motor (part III)	36.0 (11.73)	28.8 (12.53)	-7.1 (6.83)	32.2 (8.29)	23.2 (8.99)	-9.0 (7.75)	2.4 (-1.6, 6.4); 0.2368
ADL (part II)	18.5 (6.38)	15.8 (7.32)	-2.7 (5.04)	16.9 (5.82)	12.3 (6.60)	-4.6 (4.71)	2.5 (-0.3, 5.3); 0.0852
Total (part II+III)	55.0 (16.70)	45.2 (18.38)	-9.8 (9.82)	49.1 (10.95)	35.5 (13.04)	-13.6 (9.97)	4.7 (-0.7, 10.1); 0.0867

[a]   For subject 45 (GDNF/GDNF), items 22, 27, 28, 29, and 30 are excluded from the motor (part III) score. The subject's data are excluded completely from analysis of the ADL (part II) and total scores. For analyses of ADL and total scores, the number of subjects for the GDNF/GDNF group is therefore N=20 instead of N=21 in the ITT Overall Population.

[b]   MMRM with baseline UPDRS score as a covariate, treatment group and visit and treatment group*visit as fixed effects, and subject within treatment group as a random effect

Note: Lower scores represent better functioning.

Source: Tables 16.2.2.6.1, 16.2.2.6.2, and 16.2.2.6.3

11.2.1.3   OFF State UPDRS Scores: Change from Baseline to Week 80/e40 for the GDNF/GDNF Group Compared to Change from Baseline to Week 40/e0 for the Placebo/GDNF Group

Comparison of the effects of treatment with GDNF over 80 weeks with the longest period of treatment with placebo alone (40 weeks) as the best available internal control showed a greater effect of GDNF compared to placebo on change in OFF state UPDRS scores (Table 21). The MMRM of change from baseline showed highly statistically significant mean treatment differences in favor of the GDNF/GDNF treatment group for all three UPDRS scores analyzed in the ITT Overall Population.

Table 21   OFF State UPDRS Scores (Mean [SD]): Change from Baseline to Week 80/e40 for the GDNF/GDNF Group Compared to Change from Baseline to Week 40/e0 for the Placebo/GDNF Group, MMRM - ITT Overall Population

UPDRS score	GDNF/GDNF (N=21[a])			Placebo/GDNF (N=20)			Least squares mean difference versus placebo (95% CI); p-value[b]
	Week 0 (baseline)	Week 80/e40	Change from baseline	Week 0 (baseline)	Week 40/e0	Change from baseline	
Motor (part III)	36.0 (11.73)	26.4 (11.33)	-9.6 (6.70)	32.2 (8.29)	28.5 (9.29)	-3.8 (4.20)	-5.3 (-9.3, -1.3); 0.0108
ADL (part II)	18.5 (6.38)	11.7 (4.89)	-6.9 (5.46)	16.9 (5.82)	15.9 (5.34)	-1.0 (3.71)	-5.3 (-8.1, -2.5); 0.0003
Total (part II+III)	55.0 (16.70)	37.9 (14.89)	-17.1 (8.64)	49.1 (10.95)	44.4 (12.40)	-4.7 (5.27)	-11.5 (-16.9, -6.1); <0.0001

[a]   For subject 45 (GDNF/GDNF), items 22, 27, 28, 29, and 30 are excluded from the motor (part III) score. The subject's data are excluded completely from analysis of the ADL (part II) and total scores. For analyses of ADL and total scores, the number of subjects for the GDNF/GDNF group is therefore N=20 instead of N=21 in the ITT Overall Population.

[b]   MMRM with baseline UPDRS score as a covariate, treatment group and visit and treatment group*visit as fixed effects, and subject within treatment group as a random effect

Note: Lower scores represent better functioning.

Source: Tables 16.2.2.7.1, 16.2.2.7.2, and 16.2.2.7.3

11.2.2   Analyses of PD Diary Ratings

Findings for the ITT Overall Population were consistent with those for the ITT Primary Population (Table 22 and Tables 16.2.3.1 and 16.2.3.2). Results reported in this section are for the larger ITT Overall Population.

For PD motor fluctuation diary ratings by subject see Listing 17.2.2.2.

11.2.2.1   Total OFF Time per Day

Mean total OFF time per day at baseline was noticeably longer in the GDNF group (6.11 hours) than in the placebo group (4.83 hours; Table 22).

Between baseline and Week 40/e0, mean total OFF time per day decreased in the GDNF/GDNF group (-0.99 hours) but increased in the placebo/GDNF group (0.50 hours; Table 16.2.3.2).

By Week 80/e40, mean total OFF time per day had decreased in both treatment groups relative to baseline (-1.47 hours in the GDNF/GDNF group, -0.82 hours in the placebo/GDNF group). The MMRM showed a small treatment difference in favor of GDNF/GDNF that was not statistically significant (LS mean difference: -0.159 hours, 95% CI: -1.403, 1.085, p=0.7975; Table 22).

Change in total OFF time per day over time is displayed graphically for the ITT Primary Population in Figure 16.5.2.1 and for the ITT Overall Population in Figure 16.5.2.2.

Table 22 **PD Motor Fluctuation Diary Ratings (Hours; Mean [SD]): Change from Baseline to Week 80/e40, MMRM - ITT Primary and Overall Populations**

Population/ Variable	GDNF/GDNF (N=17[a] for ITT Primary Population, N=21[a] for ITT Overall Population)			Placebo/GDNF (N=18 for ITT Primary Population, N=20[b] for ITT Overall Population)			Least squares mean difference versus placebo (95% CI); p-value[c]
	Week 0 (baseline)	Week 80/e40	Change from baseline	Week 0 (baseline)	Week 80/e40	Change from baseline	
ITT PRIMARY							
Total OFF time per day	6.11 (1.819)	4.53 (1.888)	-1.46 (1.101)	4.76 (2.284)	3.88 (2.161)	-0.88 (2.838)	-0.064 (-1.420, 1.292); 0.9243
Total good-quality ON time per day	10.33 (2.112)	12.00 (2.282)	1.70 (1.630)	12.50 (2.683)	13.15 (3.201)	0.65 (3.086)	0.468 (-1.240, 2.176); 0.5818
ON time per day with troublesome dyskinesias	0.48 (1.065)	0.33 (1.095)	-0.17 (0.809)	0.50 (0.998)	0.39 (0.769)	-0.11 (1.223)	-0.034 (-0.636, 0.568); 0.9113
ITT OVERALL							
Total OFF time per day	6.11 (1.689)	4.54 (1.770)	-1.47 (1.388)	4.83 (2.243)	3.97 (2.124)	-0.82 (2.768)	-0.159 (-1.403, 1.085); 0.7975
Total good-quality ON time per day	10.19 (1.996)	11.80 (2.202)	1.64 (1.487)	12.48 (2.609)	13.09 (3.085)	0.54 (3.034)	0.571 (-0.965, 2.107); 0.4573
ON time per day with troublesome dyskinesias	0.56 (1.202)	0.36 (1.041)	-0.23 (0.814)	0.47 (0.977)	0.35 (0.737)	-0.11 (1.189)	-0.066 (-0.585, 0.454); 0.7997

[a] At Week 80/e40, N=16 in the ITT Primary Population and N=20 in the ITT Overall Population

[b] At Week 0, N=19 in the ITT Overall Population

[c] MMRM with baseline variable as a covariate, treatment group and visit and treatment group*visit as fixed effects, and subject within treatment group as a random effect

Note: Total good-quality ON time per day is defined as the sum of ON time per day without dyskinesias and ON time per day with non-troublesome dyskinesias.

Source: Tables 16.2.3.1 and 16.2.3.2

11.2.2.2   Total Good-Quality ON Time per Day

Mean total good-quality ON time per day at baseline was noticeably shorter in the GDNF/GDNF group (10.19 hours) than in the placebo/GDNF group (12.48 hours; Table 22).

Between baseline and Week 40/e0, mean total good-quality ON time per day increased in the GDNF/GDNF group (1.18 hours) but decreased in the placebo/GDNF group (-0.46 hours; Table 16.2.3.2).

By Week 80/e40, mean total good-quality ON time per day had increased in both treatment groups relative to baseline (1.64 hours in the GDNF/GDNF group, 0.54 hours in the placebo/GDNF group). The MMRM showed a mean treatment difference in favor of GDNF/GDNF that was not statistically significant (LS mean difference: 0.571 hours, 95% CI: -0.965, 2.107, p=0.4573; Table 22).

Analyses of the components of good-quality ON time per day showed similar increases in ON time per day without dyskinesias accompanied by small decreases in ON time per day with non-troublesome dyskinesias in both groups by Week 80/e40 (Table 16.2.3.2).

Change in total good-quality ON time per day over time is displayed graphically for the ITT Primary Population in Figure 16.5.2.3 and for the ITT Overall Population in Figure 16.5.2.4.

11.2.2.3   ON Time per Day With Troublesome Dyskinesias

Baseline mean values for ON time per day with troublesome dyskinesias were comparably low in both treatment groups (GDNF/GDNF 0.56 hours, placebo/GDNF 0.47 hours; Table 22).

Between baseline and Week 40/e0, mean ON time per day with troublesome dyskinesias decreased slightly in both treatment groups (GDNF/GDNF -0.17 hours, placebo/GDNF -0.10 hours; Table 16.2.3.2).

By Week 80/e40, mean ON time per day with troublesome dyskinesias had decreased slightly further in the GDNF/GDNF group (-0.23 hours) and remained effectively unchanged in the placebo/GDNF group (-0.11 hours). The MMRM showed essentially no treatment difference between the treatment groups (LS mean difference: -0.066 hours, 95% CI: -0.585, 0.454, p=0.7997; Table 22).

11.2.3   Treatment Responder Analyses

Analyses were performed only for the ITT Overall Population.

Significantly more subjects in the GDNF/GDNF group had a decrease of ≥10 points ("strong responders") in OFF state UPDRS motor score from baseline to Week 40/e0 (9 GDNF/GDNF subjects vs. 0 placebo/GDNF subjects, p=0.0013; Table 23). By Week 80/e40, the number of strong responders in the GDNF/GDNF group had increased from 9 to 11, and the number of strong responders in the placebo/GDNF group was 9, i.e. the same as was found in the

GDNF/GDNF group at Week 40/e0 (treatment difference: p=0.7579). In the GDNF/GDNF group, 7 of the 9 subjects who were strong responders at Week 40/e0 were still strong responders at Week 80/e40, and 4 subjects who were not strong responders at Week 40/e0 had become strong responders at Week 80/e40 (Table 16.2.3.3.2).

Frequency distributions of change in OFF state UPDRS motor score are depicted in Figure 9 (Week 40/e0) and Figure 10 (Week 80/e40). Eleven (52.4%) GDNF/GDNF subjects showed large clinically important improvements (≥10 points) in OFF state UPDRS motor score from baseline to Week 80/e40, 5 (23.8%) showed moderate improvements (5-9 points), and 3 (14.3%) showed small improvements (1-4 points). Two (9.5%) GDNF/GDNF subjects were nonresponders (increase of 3 points in OFF state UPDRS motor score from baseline to Week 80/e40).

The results for improvement from baseline to Week 40/e0 in good-quality ON time by ≥1 hour also showed a trend in favor of the GDNF/GDNF group (9 GDNF/GDNF subjects vs. 3 placebo/GDNF subjects, p=0.0750). By Week 80/e40, the numbers of subjects with ≥1 hour gain had increased to 15 and 9 respectively (treatment difference: p=0.1053; Table 23).

Analysis using the combination of both responder definitions showed a small difference between the treatment groups at Week 40/e0 (4 GDNF/GDNF subjects vs. 0 placebo/GDNF subjects, p=0.1060) and no treatment difference at Week 80/e40 (7 GDNF/GDNF subjects vs. 6 placebo/GDNF subjects, p>0.9999; Table 23).

For treatment response data by subject see Listing 17.2.2.3.

Table 23   Treatment Response at Week 40/e0 and Week 80/e40 - ITT Overall Population

Response definition Time point	GDNF/GDNF (N=21)	Placebo/GDNF (N=20)	Treatment comparison
	n (%) responders	n (%) responders	p-value[a]
OFF state UPDRS motor score (part III) decrease of ≥10 points from baseline			
Week 40/e0	9 (42.9)	0	0.0013
Week 80/e40	11 (52.4)	9 (45.0)	0.7579
Total good-quality ON time per day increase of ≥1 hour from baseline			
Week 40/e0	9 (42.9)	3 (15.0)	0.0750
Week 80/e40	15 (71.4)	9 (45.0)	0.1053
OFF state UPDRS motor score (part III) decrease of ≥10 points from baseline AND total good-quality ON time per day increase of ≥1 hour from baseline			
Week 40/e0	4 (19.0)	0	0.1060
Week 80/e40	7 (33.3)	6 (30.0)	>0.9999

[a]   Between-treatment comparison of proportions of responders using Fisher's exact test.
Source: Table 16.2.3.3.1

Figure 9 **OFF State UPDRS Motor Score (Part III): Frequency Distribution of Change at Week 40/e0 - ITT Overall Population**
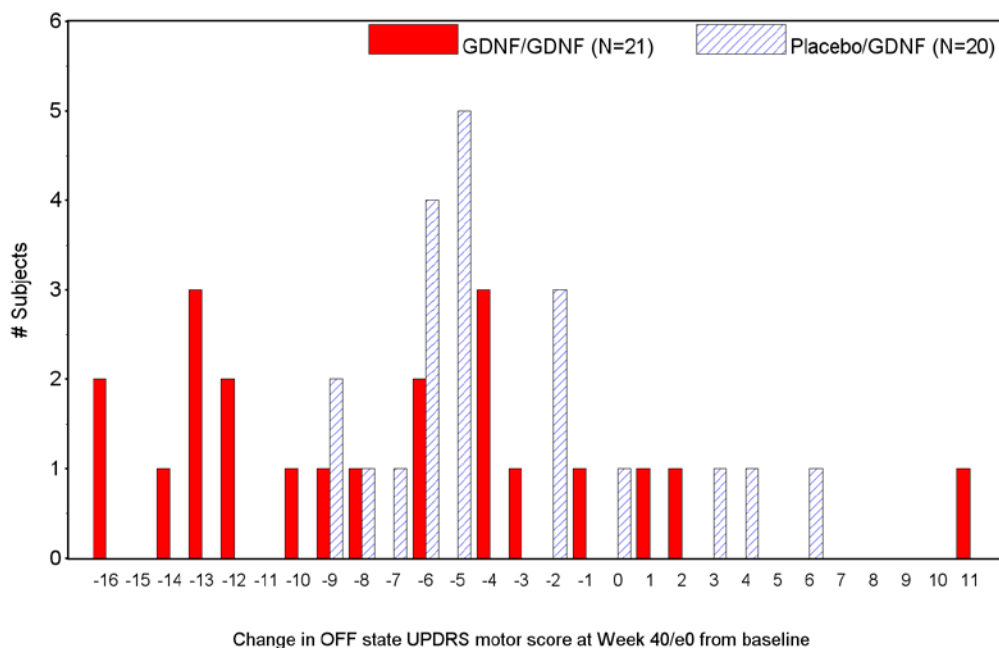
Note: For subject 45 (GDNF/GDNF), items 22, 27, 28, 29 and 30 are excluded from the score.
Source: Figure 16.5.4.1

Figure 10 **OFF State UPDRS Motor Score (Part III): Frequency Distribution of Change at Week 80/e40 - ITT Overall Population**
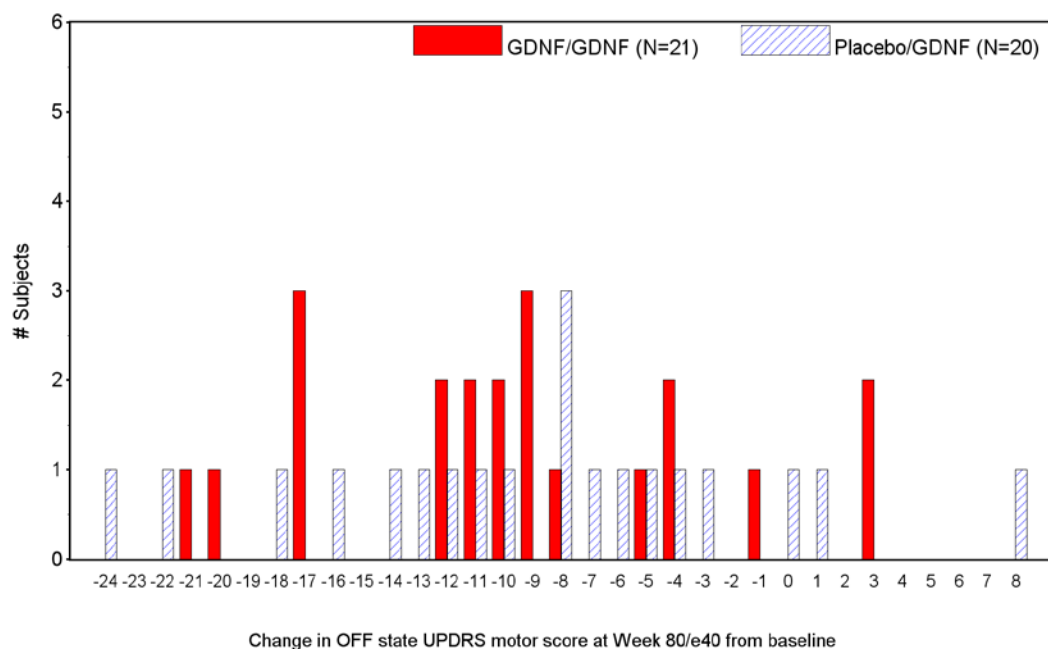
Note: For subject 45 (GDNF/GDNF), items 22, 27, 28, 29 and 30 are excluded from the score.
Source: Figure 16.5.4.2

11.3   Analyses of Supplementary Efficacy Endpoints

Analyses of supplementary endpoints were performed only for the ITT Overall Population (for
analytical details see Section 9.8.1.8.3).

11.3.1   Timed Walking Test

Mean timed walking test time in the OFF state at baseline was markedly longer in the
GDNF/GDNF group (45.25 seconds) than in the placebo/GDNF group (17.58 seconds;
Table 24), predominantly due to 3 subjects with very long times (203 seconds in subject 29,
195.5 seconds in subject 38, 129.5 seconds in subject 58; Listing 17.2.2.4.1).

At Week 40/e0, the difference between the treatment groups in mean timed walking test time in
the OFF state was smaller (GDNF/GDNF 21.71 seconds, placebo/GDNF 16.28 seconds;
Table 16.2.4.1), mostly due to a larger mean decrease in the GDNF/GDNF group (-20.03
vs. -4.53 seconds).

At Week 80/e40, mean timed walking test time in the OFF state was slightly longer than at
Week 40/e0 in the GDNF/GDNF group (27.63 seconds, mean change -13.18 seconds), while it
appeared to be slightly shorter in the placebo/GDNF group (11.68 seconds), although the mean
change was similar to Week 40/e0 (-4.33 seconds). The MMRM showed a small mean treatment
difference in favor of placebo/GDNF that was not statistically significant (LS mean difference:
5.01 seconds, 95% CI: -20.47, 30.49, p=0.6987).

Mean timed walking test time in the ON state was comparable in both treatment groups at
baseline (GDNF/GDNF 10.95 seconds, placebo/GDNF 10.43 seconds) and remained mostly
unchanged during the study (Week 80/e40: GDNF/GDNF -0.58 seconds,
placebo/GDNF -0.66 seconds; Table 24 and Table 16.2.4.1).

For OFF state and ON state timed walking test data by subject see Listing 17.2.2.4.1.

Table 24   Timed Walking Test (Seconds): Change from Baseline to Week 80/e40, MMRM - ITT Overall Population

State Statistic	GDNF/GDNF (N=21)			Placebo/GDNF (N=20)			Least squares mean difference versus placebo (95% CI); p-value[a]
	Week 0 (baseline)	Week 80/e40	Change from baseline	Week 0 (baseline)	Week 80/e40	Change from baseline	
OFF state							
n	20	19	19	19	19	18	
Mean (SD)	45.25 (59.933)	27.63 (52.003)	-13.18 (72.569)	17.58 (10.812)	11.68 (2.916)	-4.33 (6.403)	5.01 (-20.47, 30.49); 0.6987
ON state							
n	20	20	20	20	19	19	
Mean (SD)	10.95 (2.620)	10.38 (1.798)	-0.58 (1.801)	10.43 (1.935)	9.76 (1.584)	-0.66 (1.375)	0.27 (-0.49, 1.04); 0.4694

[a] MMRM with baseline time as a covariate, treatment group and visit and treatment group*visit as fixed effects, and subject within treatment group as a random effect

Note: Shorter times represent better function. Data for subject 45 (GDNF/GDNF) are excluded from analysis.

Source: Table 16.2.4.1

11.3.2   Timed Tapping Test

Baseline mean values for the timed tapping test in the OFF state were comparable in both treatment groups (GDNF/GDNF: 43.11 taps, placebo/GDNF: 42.38 taps; Table 25).

Between baseline and Week 40/e0, the mean number of taps in the OFF state increased in both treatment groups (GDNF/GDNF: 11.68 taps, placebo/GDNF: 10.81 taps; Table 16.2.4.2).

By Week 80/e40, the mean number of taps in the OFF state had increased further in both treatment groups relative to baseline (20.65 taps in the GDNF/GDNF group, 16.75 taps in the placebo/GDNF group). The MMRM showed a small mean treatment difference in favor of GDNF/GDNF that was not statistically significant (LS mean difference: 3.86 taps, 95% CI: -5.10, 12.82, p=0.3889).

Findings of the analysis of the timed tapping test in the ON state were very similar to those for the OFF state analysis, except that the baseline ON state values were greater while the increases observed in each treatment group were slightly smaller (Table 25 and Table 16.2.4.2).

For OFF state and ON state timed tapping test data by subject see Listing 17.2.2.4.2.

Table 25 **Timed Tapping Test (Number of Taps): Change from Baseline to Week 80/e40, MMRM - ITT Overall Population**

State Statistic	GDNF/GDNF (N=21)			Placebo/GDNF (N=20)			Least squares mean difference versus placebo (95% CI); p-value[a]
	Week 0 (baseline)	Week 80/e40	Change from baseline	Week 0 (baseline)	Week 80/e40	Change from baseline	
OFF state							
n	21	21	21	20	20	20	
Mean (SD)	43.11 (15.010)	63.76 (22.566)	20.65 (15.379)	42.38 (9.437)	59.13 (17.799)	16.75 (12.912)	3.86 (-5.10, 12.82); 0.3889
ON state							
n	21	21	21	20	19	19	
Mean (SD)	64.20 (17.643)	79.89 (22.665)	15.69 (13.556)	61.00 (17.388)	73.55 (19.171)	12.72 (9.988)	3.38 (-4.20, 10.96); 0.3728

[a] MMRM with baseline number of taps as a covariate, treatment group and visit and treatment group*visit as fixed effects, and subject within treatment group as a random effect

Note: More taps represent better function.

Source: Table 16.2.4.2

11.3.3 NMSS

Baseline (screening) mean values for NMSS total score were similar in both treatment groups (GDNF/GDNF 40.4, placebo/GDNF 36.9; Table 26).

Between baseline and Week 40/e0, the mean NMSS total score decreased in both treatment groups, with a slightly greater decrease in the GDNF/GDNF group (-14.7) than in the placebo/GDNF group (-7.8; Table 16.2.4.3).

By Week 80/e40, the mean NMSS total score had decreased in both treatment groups relative to baseline, although the decrease in the GDNF/GDNF group was slightly smaller than that observed at Week 40/e0 (-12.5 in GDNF/GDNF group, -10.3 in placebo/GDNF group). The MMRM showed essentially no treatment difference between the treatment groups (LS mean difference: -0.1, 95% CI: -10.8, 10.6, p=0.9833).

Changes from baseline to Week 80/e40 in the 9 individual NMSS domains were small, with no relevant differences between the treatment groups (Table 16.2.4.3).

For NMSS scores by subject see Listing 17.2.2.5.

Table 26   NMSS Total Score: Change from Baseline to Week 80/e40, MMRM - ITT Overall Population

Statistic	GDNF/GDNF (N=21)			Placebo/GDNF (N=20)			Least squares mean difference versus placebo (95% CI); p-value[a]
	Screening (baseline)	Week 80/e40	Change from baseline	Screening (baseline)	Week 80/e40	Change from baseline	
n	20	20	20	20	20	20	-0.1 (-10.8, 10.6); 0.9833
Mean (SD)	40.4 (22.54)	27.9 (20.00)	-12.5 (21.71)	36.9 (29.83)	26.7 (22.24)	-10.3 (19.32)	

[a]   MMRM with baseline score as a covariate, treatment group and visit and treatment group*visit as fixed effects, and subject within treatment group as a random effect

Note: The higher the score, the worse the subject's condition. The maximum NMSS total score is 360. Data for subject 45 (GDNF/GDNF) are excluded from analysis.

Source: Table 16.2.4.3

11.3.4 PDQ-39

The baseline (screening) mean value for the PDQ-39 single index (total) score was slightly lower in the GDNF/GDNF group than in the placebo/GDNF group (25.487 vs. 28.414; Table 27).

Between baseline and Week 40/e0, the mean PDQ-39 single index (total) score remained almost unchanged in the GDNF/GDNF group and decreased in the placebo/GDNF group (-1.094 vs. -5.880; Table 16.2.4.4).

At Week 80/e40, the changes in mean PDQ-39 single index (total) score from baseline were similar to those observed at Week 40/e0 (-0.422 vs. -6.602). The mean treatment difference was in favor of placebo/GDNF but was not statistically significant (4.962, 95% CI: -2.943, 12.866, p=0.2114).

Findings for the 8 individual PDQ-39 dimensions were similar to the findings for the total score (Table 16.2.4.4).

For PDQ-39 scores by subject see Listing 17.2.2.6.

Table 27   **PDQ-39 Single Index (Total) Score: Change from Baseline to Week 80/e40, ANCOVA - ITT Overall Population**

Statistic	GDNF/GDNF (N=21)			Placebo/GDNF (N=20)			Mean difference versus placebo (95% CI); p-value[a]
	Screening (baseline)	Week 80/e40	Change from baseline	Screening (baseline)	Week 80/e40	Change from baseline	
n	20	20	20	20	20	20	
Mean (SD)	25.487 (13.066)	25.065 (16.323)	-0.422 (15.343)	28.414 (15.665)	21.812 (12.986)	-6.602 (11.394)	4.962 (-2.943, 12.866); 0.2114

a   ANCOVA with baseline score as a covariate and treatment group as a factor

Note: The higher the score, the worse the subject's condition. PDQ-39 total scores range from 0 to 100 (0 = no problem, 100 = problem as worse as possible). Data for subject 45 (GDNF/GDNF) are excluded from analysis.

Source: Table 16.2.4.4

11.3.5   EQ-5D

For nearly all subjects in both treatment groups, the responses to the EQ-5D questionnaire were "no problem" or "moderate" (Table 16.2.4.5.1) at all assessments, i.e. baseline (screening), Week 40/e0, and Week 80/e40. A notable difference between the treatment groups was detected only for the "pain/discomfort" item: between baseline and Week 40/e0, no change in answers to this item was observed for the GDNF/GDNF group, but 5 subjects in the placebo/GDNF group reported a shift from "no problem" to "moderate". At Week 80/e40, this difference was no longer discernible.

The findings for the EQ-5D visual analog scale in the ITT Overall Population indicated a small improvement in both treatment groups by Week 80/e40, with a minimally greater change in the placebo/GDNF group (mean difference between treatments: -2.88, 95% CI: -10.10, 4.33, p=0.4230; Table 16.2.4.5.2).

For EQ-5D scores by subject see Listing 17.2.2.7.

11.3.6   SNAQ

Baseline (screening) mean scores for the SNAQ were the same in both treatment groups (GDNF/GDNF 15.8, placebo/GDNF 15.8; Table 16.2.4.6).

Mean change in the SNAQ score between baseline, Week 40/e0, and Week 80/e40 was small in both groups. No significant treatment difference was detected at Week 80/e40 (mean difference between treatments: -0.9, 95% CI: -1.9, 0.2, p=0.1166).

For SNAQ scores by subject see Listing 17.2.2.8.

11.3.7   Use of Levodopa Medication

At Week 0 (baseline), the mean total daily levodopa dose was higher in the GDNF/GDNF group (639 mg) than in the placebo/GDNF group (561 mg; Table 28).

By Week 40/e0, the mean total daily levodopa dose had fallen minimally in the GDNF/GDNF group (-10 mg) but had increased notably in the placebo/GDNF group (49 mg; Table 16.2.4.7).

By Week 80/e40, the mean total daily levodopa dose had increased in both treatment groups relative to baseline, with a smaller increase in the GDNF/GDNF group (36 mg) than in the placebo/GDNF group (160 mg). The mean treatment difference of -121.12 mg approached statistical significance (95% CI: -255.98, 13.74, p=0.0769).

Analysis of the total daily levodopa equivalent dose revealed a similar trend by Week 80/e40 (increase of 59 mg in GDNF/GDNF group and increase of 289 mg in placebo/GDNF group; Table 28 and Table 16.2.4.8). The resulting mean treatment difference of -232.66 mg in favor of the GDNF/GDNF group was statistically significant (95% CI: -418.65, -46.67, p=0.0156).

For levodopa and levodopa equivalent medication actual total daily doses by subject see Listing 17.2.2.9.1. For effective levodopa and levodopa equivalent medication total daily doses by subject see Listing 17.2.2.9.2.

Table 28   Total Daily Levodopa Dose (mg) and Total Daily Levodopa Equivalent Dose (mg): Change from Baseline to Week 80/e40, ANCOVA - ITT Overall Population

Variable Statistic	GDNF/GDNF (N=21)			Placebo/GDNF (N=20)			Mean difference versus placebo (95% CI); p-value[a]
	Week 0 (baseline)	Week 80/e40	Change from baseline	Week 0 (baseline)	Week 80/e40	Change from baseline	
Total daily levodopa dose							
n	21	21	21	20	20	20	
Mean (SD)	638.95 (305.969)	674.82 (309.695)	35.87 (186.313)	560.80 (283.570)	721.00 (390.982)	160.20 (230.317)	-121.12 (-255.98, 13.74); 0.0769
Total daily levodopa equivalent dose							
n	21	21	21	20	20	20	
Mean (SD)	1011.26 (340.357)	1070.63 (395.559)	59.37 (193.563)	953.67 (383.393)	1242.68 (552.209)	289.01 (364.820)	-232.66 (-418.65, -46.67); 0.0156

[a]   ANCOVA with baseline levodopa dose or baseline levodopa equivalent dose as a covariate and treatment group as a factor
Source: Tables 16.2.4.7 and 16.2.4.8

11.4   Post Hoc Efficacy Analyses

Findings of post hoc efficacy analyses are presented in Section 17.1.13.

11.4.1   Integrated Overall Response Score

Mean IOR scores differed substantially between the treatment groups during the entire 80-week period, favoring GDNF/GDNF at each time point (Figure 11).

Figure 11   Integrated Overall Response Score Over Time - ITT Overall Population
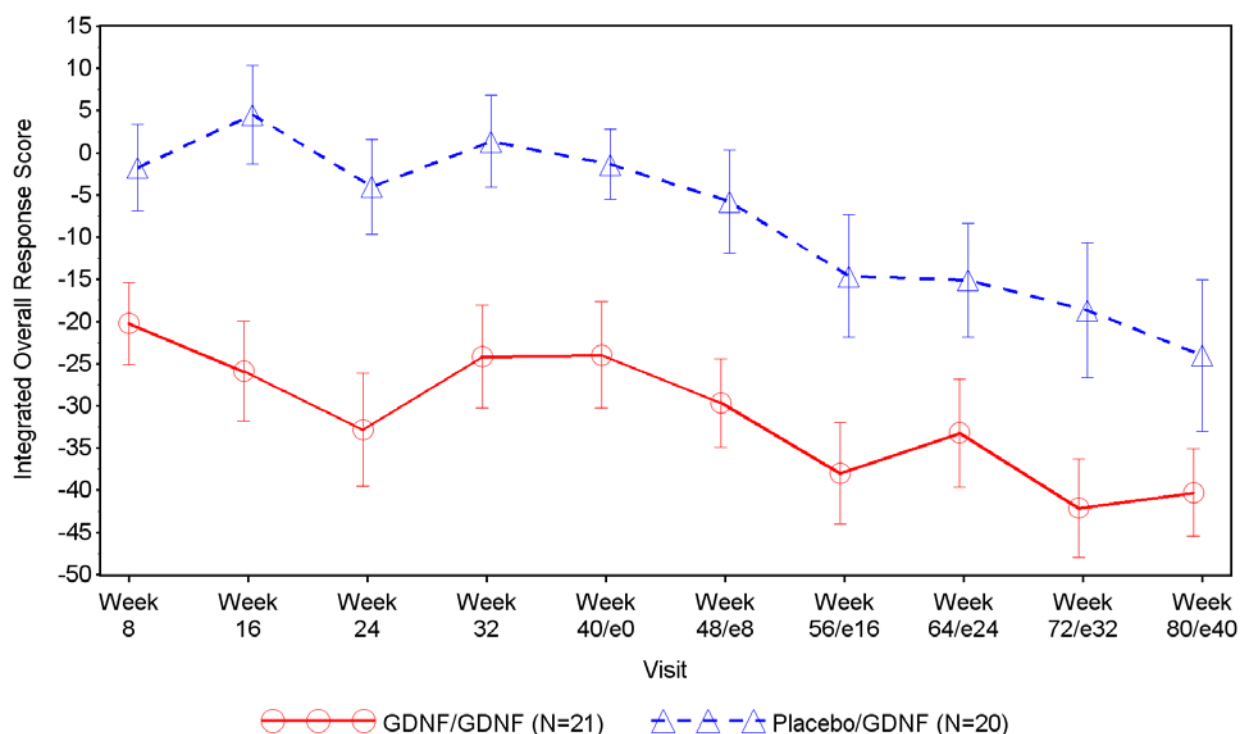
Note: Data points represent means, and error bars represent standard errors. The IOR score is calculated as (1 × change in OFF state motor score) + (2 × change in OFF state ADL score) – (10 × change in total good-quality ON time per day). Data for subject 45 (GDNF/GDNF) are excluded from analysis. A decrease in IOR score represents an improvement.
Source: Section 17.1.13, Figure 16.5.6.1

At Week 40/e0, the mean IOR score was -23.98 in the GDNF/GDNF group and -1.36 in the placebo/GDNF group (Table 29). The MMRM showed a highly statistically significant treatment difference in favor of GDNF/GDNF (LS mean difference: -23.537, 95% CI: -38.647, -8.428, p=0.0032).

By Week 80/e40, the mean IOR score had further decreased to -40.28 in the GDNF/GDNF group and -24.02 in the placebo/GDNF group. The effect size in the first 40 weeks of GDNF treatment was the same in both treatment groups, while it was notably smaller in the second 40 weeks in the GDNF/GDNF group. Therefore, while the MMRM still showed a treatment difference in

favor of GDNF/GDNF at Week 80/e40, the difference was no longer statistically significant (LS mean difference: -16.257, 95% CI: -36.958, 4.443, p=0.1201).

As an additional observation, the IOR score at Week 80/e40 in the GDNF/GDNF group ranged from -10.0 to -99.2, indicating that all subjects in this group were responding to treatment in one or more components of the IOR.

Table 29   Integrated Overall Response Score, MMRM - ITT Overall Population

Visit Statistic	GDNF/GDNF (N=21)	Placebo/GDNF (N=20)
	Change from baseline	Change from baseline
Week 40/e0		
n	18	18
Mean (SD)	-23.98 (26.756)	-1.36 (17.730)
Median (Min, Max)	-19.33 (-64.0, 53.2)	-2.67 (-38.0, 30.3)
Treatment comparison[a]		
LS mean difference vs placebo	-23.537	
(95% CI)	(-38.647, -8.428)	
p-value	0.0032	
Week 80/e40		
n	20	19
Mean (SD)	-40.28 (23.154)	-24.02 (39.048)
Median (Min, Max)	-32.17 (-99.2, -10.0)	-24.00 (-85.7, 50.3)
Treatment comparison[a]		
LS mean difference vs placebo	-16.257	
(95% CI)	(-36.958, 4.443)	
p-value	0.1201	

[a]   MMRM with treatment group and visit and treatment group*visit as fixed effects, and subject within treatment group as a random effect

Note: The IOR score is calculated as (1 × change in OFF state motor score) + (2 × change in OFF state ADL score) – (10 × change in total good-quality ON time per day). Data for subject 45 (GDNF/GDNF) are excluded from analysis. A decrease in IOR score represents an improvement.

Source: Section 17.1.13, Table 16.2.5

Results of the post hoc analyses of robustness of the IOR score are summarized in Table 30, in comparison to the results of the original IOR analysis using change in total good-quality ON time per day as the PD diary component with a 1-hour threshold. The data show that the IOR score is remarkably stable over the entire range of threshold values tested and is not materially affected by replacing total good-quality ON time per day with total OFF time per day as the PD diary component.

Table 30   Integrated Overall Response Score, Summary of Robustness Analyses - ITT Overall Population

	Good-quality ON time			OFF time		
	1-hour threshold	1.25-hour threshold	1.67-hour threshold	1-hour threshold	1.25-hour threshold	1.67-hour threshold
Week 40 mean IOR score						
GDNF/GDNF (n=18)	-23.98	-21.63	-19.28	-22.08	-20.11	-18.14
Placebo/GDNF (n=18)	-1.36	-2.28	-3.19	-0.94	-1.94	-2.94
Treatment comparison[a], p-value	0.0032	0.0034	0.0041	0.0113	0.0119	0.0130
Week 80 mean IOR score						
GDNF/GDNF (n=20)	-40.28	-37.00	-33.73	-38.65	-35.70	-32.75
Placebo/GDNF (n=19)	-24.02	-22.93	-21.84	-26.82	-25.18	-23.53
Treatment comparison[a], p-value	0.1201	0.1196	0.1214	0.1949	0.1829	0.1722

[a]   MMRM with treatment group and visit and treatment group*visit as fixed effects, and subject within treatment group as a random effect

Source: Section 17.1.13, Tables 16.2.5, 16.2.7.1, 16.2.7.2, 16.2.7.3, 16.2.7.4, and 16.2.7.5

Findings of the baseline-adjusted post hoc analysis using change in total good-quality ON time per day with the 1.67-hour threshold as the PD diary component are summarized in Table 31. Compared to the corresponding unadjusted analysis (Table 16.2.7.2), there was only a small reduction in the LS mean differences between the treatment groups at Week 40/e0 and Week 80/e40, along with a small increase in the associated p-values. These results indicate that adjusting for baseline does not impact the conclusions from the unadjusted model or improve the model fit.

Table 31 **Integrated Overall Response Score with a 1.67-Hour Threshold for Total Good-Quality ON Time including the Sum of the Baseline Scores as a Covariate, MMRM - ITT Overall Population**

Visit Statistic	GDNF/GDNF (N=21)	Placebo/GDNF (N=20)
	Change from baseline	Change from baseline
Week 40/e0		
n	18	18
Mean (SD)	-19.28 (20.761)	-3.19 (11.694)
Median (Min, Max)	-18.00 (-49.0, 39.5)	-3.50 (-28.0, 14.0)
Treatment comparison[a]		
LS mean difference vs placebo	-15.821	
(95% CI)	(-28.206, -3.436)	
p-value	0.0138	
Week 80/e40		
n	20	19
Mean (SD)	-33.73 (18.350)	-21.84 (27.747)
Median (Min, Max)	-27.50 (-75.5, -10.0)	-22.00 (-69.0, 35.0)
Treatment comparison[a]		
LS mean difference vs placebo	-10.613	
(95% CI)	(-26.148, 4.922)	
p-value	0.1748	

[a] MMRM with baseline IOR score as a covariate, treatment group and visit and treatment group*visit as fixed effects, and subject within treatment group as a random effect

Note: The IOR score is calculated as (1 × change in OFF state motor score) + (2 × change in OFF state ADL score) – (6 × change in total good-quality ON time per day). Data for subject 45 (GDNF/GDNF) are excluded from analysis. A decrease in IOR score represents an improvement.

Source: Section 17.1.13, Table 16.2.8

The results of the post hoc treatment responder analysis using change in total good-quality ON time per day with the 1.67-hour threshold as the PD diary component corroborated the results obtained for the OFF state UPDRS motor score (see Section 11.2.3). Despite the stringent cut-off, 7 GDNF/GDNF subjects had an IOR score of at least -30 points at Week 40/e0, whereas no strong responders were observed in the placebo/GDNF group at this time (p=0.0076; Table 16.2.9.1). By Week 80/e40, the number of strong responders had increased to 9 in the GDNF/GDNF group and to 8 in the placebo/GDNF group, confirming that the treatment response in the first 40 weeks on GDNF was similar in both treatment groups. Frequency distributions of the IOR score are depicted in Figure 16.5.6.4 (Week 40/e0) and Figure 16.5.6.5 (Week 80/e40).

There was some fluctuation in the treatment response between Week 40/e0 and Week 80/e40 in the GDNF/GDNF group, with 4 subjects switching from "yes" to "no" and 5 subjects from "no" to "yes" (Table 16.2.9.2). However, at Week 80/e40, all GDNF/GDNF subjects showed at least a modest response as indicated by an IOR score of at least -10 points, and 12 (66.7%) of 18 GDNF/GDNF subjects with an IOR score at Week 40/e0 showed a stronger response than at Week 40/e0 (Figure 12). Similarly, in the placebo/GDNF group, 13 (72.2%) of 18 subjects with

an IOR score at Week 40/e0 showed a stronger treatment response at Week 80/e40 than at Week 40/e0 (Figure 12).

Figure 12   Integrated Overall Response Score with a 1.67-Hour Threshold for Good-Quality ON Time: Subject Response - ITT Overall Population
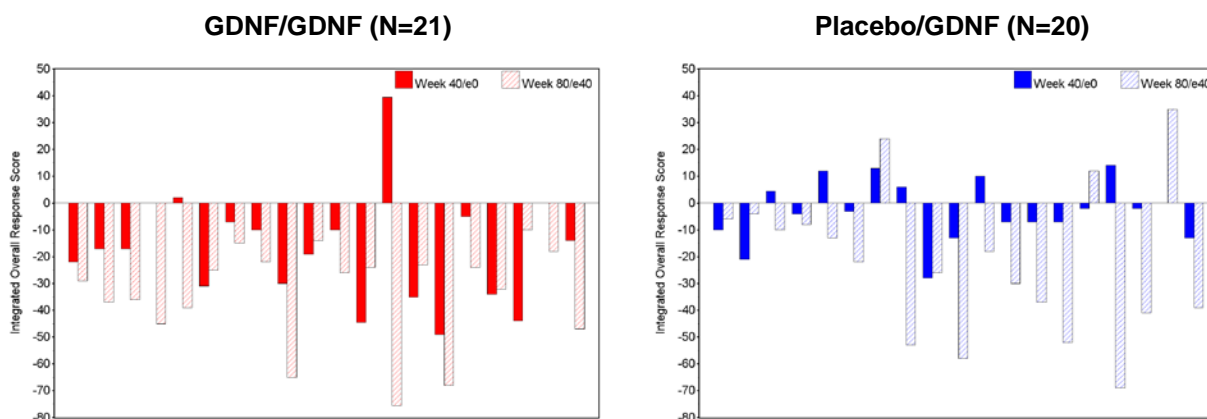
Note: The IOR score is calculated as (1 × change in OFF state motor score) + (2 × change in OFF state ADL score) – (6 × change in total good-quality ON time per day). Data for subject 45 (GDNF/GDNF) are excluded from analysis. A decrease in IOR score represents an improvement.
Source: Section 17.1.13, Figure 16.5.6.6

11.5   Drug Dose, Drug Concentration, and Relationships to Response

Exposure data are described in Section 13.1. Concentration data for GDNF in plasma are presented in Section 13.6. Local tissue concentrations of GDNF in VOI, total putamen or brain could not be measured for obvious reasons. However, under the conditions of CED, it is assumed that drug concentrations in the extracellular space covered by the volume of distribution at the end of the infusion are comparable to drug concentrations in the infusate. Therefore, in this study, volumetric coverage of the target structures (VOI and total putamen) was used as a surrogate for dose in the analysis of relationships between dose and response on the basis of selected clinical outcome variables and putamenal ^{18}F-DOPA uptake. The results of these analyses are presented in Section 12.2.

11.6   Drug-Drug and Drug-Disease Interactions

No formal drug-drug or drug-disease interaction analyses were performed.

11.7   Efficacy Conclusions

No statistically significant difference could be demonstrated between the treatment groups in the prespecified primary efficacy analysis of percentage change from baseline to Week 80/e40 in OFF state UPDRS motor score in the ITT Primary Population. The MMRM showed a small mean treatment difference in favor of placebo/GDNF that was not statistically significant (LS mean difference: 6.0%, 95% CI: -8.6, 20.7, p=0.4078). The findings of the sensitivity

analysis of the primary efficacy endpoint in the ITT Overall Population at Week 80/e40 were
similar (LS mean difference: 0.4%, 95% CI: -13.9, 14.6, p=0.9587).

Analyses of the secondary and supplementary efficacy endpoints at Week 80/e40 also showed no
statistically significant treatment differences, except for total daily levodopa equivalent dose
which remained mostly unchanged in the GDNF/GDNF group (increase of 59 mg) but increased
notably in the placebo/GDNF group (increase of 289 mg; p=0.0156).

The lack of statistically significant treatment differences in most clinical endpoints at
Week 80/e40 was expected in view of the results of study 2553 and given that all placebo
subjects received GDNF in their second 9-month treatment period. However, detailed analyses of
the nature and direction of the efficacy results in both treatment groups revealed consistent
findings in favor of GDNF treatment in this study:

- Both treatment groups showed moderate to large clinically important mean improvements
  [48, 49] in OFF state UPDRS scores between baseline and Week 80/e40 (motor
  score: -9.6 points in the GDNF/GDNF group vs. -9.0 points in the placebo/GDNF group;
  ADL score: -6.9 vs. -4.6 points). The change in OFF state UPDRS motor score put subjects
  close to the lower end of the range of OFF state UPDRS motor scores permitted at entry to
  study 2553 (25-45). Moreover, it is in contrast to the predicted disease progression reflected
  by a 2.4-point worsening of OFF state UPDRS motor score over 80 weeks for a modelled
  control based on data from the Parkinson's Progression Markers Initiative database [47].

- The mean OFF state UPDRS improvements from baseline to Week 80/e40 in the
  GDNF/GDNF group were significantly larger than the corresponding mean changes to
  Week 40/e0 in the placebo/GDNF group as the best available internal control (motor
  score: -9.6 vs. -3.8 points, p=0.0108; ADL score: -6.9 vs. -1.0 points, p=0.0003).

- Improvements in all PD motor fluctuation diary ratings were reported by subjects in both
  treatment groups between baseline and Week 80/e40, with a decrease in mean total OFF time
  per day (GDNF/GDNF: -1.47 hours, placebo/GDNF: -0.82 hours), an increase in total
  good-quality ON time (GDNF/GDNF: 1.64 hours, placebo/GDNF: 0.54 hours), and a small
  decrease in ON time per day with troublesome dyskinesias (GDNF/GDNF: -0.23 hours,
  placebo/GDNF: -0.11 hours).

- At Week 80/e40, the number of strong OFF state UPDRS motor score responders (decrease
  of ≥10 points) in the placebo/GDNF group was the same (9) as in the GDNF/GDNF group at
  Week 40/e0, thus independently replicating the latter result. In the GDNF/GDNF group, the
  number of strong responders increased further from 9 subjects at Week 40/e0 to 11 subjects
  at Week 80/e40. Fifteen subjects in the GDNF/GDNF group and 9 subjects in the
  placebo/GDNF group had an improvement of ≥1 hour in good-quality ON time between
  baseline and Week 80/e40.

- Eleven (52.4%) GDNF/GDNF subjects showed large clinically important improvements
  (≥10 points) in OFF state UPDRS motor score from baseline to Week 80/e40, 5 (23.8%)
  showed moderate improvements (5-9 points), and 3 (14.3%) showed small improvements
  (1-4 points).

- In a post hoc analysis, mean IOR scores differed substantially between the treatment groups during the entire 80-week period, favoring GDNF/GDNF at each time point. At Week 40/e0, the treatment difference in the IOR was highly statistically significant in favor of GDNF/GDNF, with virtually no effect in the placebo/GDNF group (-23.98 vs. -1.36, p=0.0032). Subsequently, there was continued improvement up to Week 80/e40 (-40.28 vs. -24.02, p=0.1201). The effect size in the first 40 weeks of GDNF treatment was the same in both groups, confirming the findings for strong UPDRS motor score responders. All subjects in the GDNF/GDNF group were responding to treatment in one or more components of the IOR at Week 80/e40. In a number of analyses of robustness modifying the PD diary component of the IOR and its weight, the score was found to be remarkably stable, and adjusting for baseline did not impact the conclusions or improve the model fit.

Overall, therefore, the study findings suggest that GDNF had beneficial effects in subjects with idiopathic PD treated for up to 80 weeks.

12.   IMAGING EVALUATION

12.1   Magnetic Resonance Imaging Analyses

Only contrast-enhanced T1-weighted MRI scans were used for volumetric imaging evaluations, limiting the analyses to the ITT Primary Population.

12.1.1   Volume of Distribution of Infusate

Mean volumes of distribution at baseline (healing phase) in study 2553 ranged between 4.57 mL and 4.91 mL per hemisphere in both treatment groups (Table 16.3.1).

Between baseline and Week 40/e0, mean volumes of distribution increased in both treatment groups, resulting in a narrow range of mean values between 6.44 mL and 6.71 mL per hemisphere at Week 40/e0.

At Week 80/e40, mean volumes of distribution were similar to those observed at Week 40/e0 in the GDNF/GDNF group (left 6.42 mL, right 6.30 mL). In the placebo/GDNF group, they had increased slightly in the left hemisphere (to 7.19 mL) and decreased slightly in the right hemisphere (to 6.25 mL). The treatment differences were not statistically significant.

For volumes of distribution by subject see Listing 17.2.3.1.

12.1.2   Volume of Interest Coverage

Mean VOI coverage at baseline (healing phase) in study 2553 was substantially higher than the protocol-specified minimum coverage of 40%. Mean values were 74.2% (left putamen) and 70.6% (right putamen) in the GDNF/GDNF group, and 67.2% (left putamen) and 67.1% (right putamen) in the placebo/GDNF group (Table 16.3.2.1).

Between baseline and Week 40/e0, mean VOI coverage increased slightly in both treatment groups. Mean values at Week 40/e0 were 78.5% (left putamen) and 78.4% (right putamen) in the GDNF/GDNF group, and 68.7% (left putamen) and 71.0% (right putamen) in the placebo/GDNF group.

During the course of the extension study, VOI coverage decreased again slightly in the GDNF/GDNF group and on the right side in the placebo/GDNF group, while it further increased slightly on the left side in the placebo/GDNF group. At Week 80/e0, mean values were 71.9% (left putamen) and 70.0% (right putamen) in the GDNF/GDNF group, and 74.3% (left putamen) and 67.9% (right putamen) in the placebo/GDNF group. Differences in change in VOI coverage from baseline to Week 80/e40 between the treatment groups were small and not statistically significant.

VOI coverage at Week 80/e40 was found to be below the 40% threshold on one side in 5 subjects (GDNF/GDNF 3, placebo/GDNF 2) and on both sides in 1 subject (GDNF/GDNF; Listing 17.2.3.1). Only in the case of the latter subject was the average of both sides also found

to be below the 40% threshold (subject 42, 29.0%). All cases of unilateral decrease were presumably caused by a decrease from Week 40/e0 in the volume of distribution in the same hemisphere. In the case of bilateral decrease, the volume of distribution had in fact increased from Week 40/e0 on both sides. Therefore, in this case, the low VOI coverage at Week 80/e40 was most likely due to a change in the shape or position of the volume of distribution relative to VOI itself.

For VOI coverage by subject see Listing 17.2.3.1.

12.1.3 Total Putamenal Coverage

Mean total putamenal coverage at baseline (randomization) in study 2553 was 55.0% (left putamen) and 50.7% (right putamen) in the GDNF/GDNF group, and 50.3% (left putamen) and 50.2% (right putamen) in the placebo/GDNF group (Table 16.3.2.2). Hence, there was substantial coverage of putamenal regions beyond VOI.

Between baseline and Week 40/e0, mean total putamenal coverage showed only small changes. Mean values at Week 40/e0 were 54.8% (left putamen) and 53.4% (right putamen) in the GDNF/GDNF group, and 47.7% (left putamen) and 48.1% (right putamen) in the placebo/GDNF group.

During the course of the extension study, total putamenal coverage was largely maintained in both treatment groups. At Week 80/e0, mean values were 57.2% (left putamen) and 48.5% (right putamen) in the GDNF/GDNF group, and 54.2% (left putamen) and 51.1% (right putamen) in the placebo/GDNF group. Differences in change in total putamenal coverage from baseline to Week 80/e40 between the treatment groups were small and not statistically significant.

Three subjects were found to have total putamenal coverage slightly below 20% on one side at Week 80/e40 (GDNF/GDNF 2, placebo/GDNF 1). In one of these cases, the average of both sides was also found to be below 20% (subject 49 [GDNF/GDNF], 19.3%). All 3 cases were presumably caused by a decrease from Week 40/e0 in the volume of distribution in the same hemisphere.

For total putamenal coverage by subject see Listing 17.2.3.1.

12.2 Correlation Analyses

12.2.1 Correlation Analyses Between Primary Endpoint and MRI Endpoints

Non-parametric Spearman rank correlation analyses were performed to explore the relationship between the primary study endpoint (percentage change from baseline to Week 80/e40 in OFF state UPDRS motor score) and VOI coverage or total putamenal coverage at baseline in the ITT Primary Population. Coverage data from both putamina were combined in the analyses.

The analyses did not reach the level of statistical significance in either treatment group, and no relationship between clinical outcome and coverage at baseline was detected (Table 16.3.3.1). Scatterplots of each analysis are provided in Figures 16.5.5.1 and 16.5.5.2.

12.2.2   Correlation Analyses Between Primary Endpoint and PET Endpoints

Non-parametric Spearman rank correlation analyses were performed to explore the relationship between the primary study endpoint (percentage change from baseline to Week 80/e40 in OFF state UPDRS motor score) and change from baseline to Week 40/e0 in ^{18}F-DOPA uptake in both the ITT Primary Population and the ITT Overall Population. Each PET region of interest (ROI) was analyzed separately, but ^{18}F-DOPA uptake rate constant (K_{occ})values from the same ROI in both hemispheres were combined in the analyses.

None of the analyses reached the level of statistical significance in either treatment group (Tables 16.3.3.2 and 16.3.3.3), and no relationship between the primary endpoint at Week 80/e40 and change from baseline to Week 40/e0 in ^{18}F-DOPA uptake was detected, except for a trend for the expected negative correlation (i.e., greater increase in ^{18}F-DOPA uptake correlated with greater decrease in OFF state UPDRS motor score) in the dorsal central/posterior putamen in the GDNF/GDNF group in the ITT Overall Population (correlation coefficient: -0.371, p=0.0904). Scatterplots of the analysis are provided in Figure 16.5.5.3 for the ITT Primary Population and in Figure 16.5.5.18 for the ITT Overall Population.

Additional non-parametric Spearman rank correlation analyses were performed to explore the relationship between OFF state UPDRS scores (motor score, ADL score) and ^{18}F-DOPA uptake in the dorsal central/posterior and dorsal anterior ROIs as determined by PET scan at specific study time points (baseline vs. baseline, Week 40/e0 vs. Week 40/e0, and Week 80/e40 vs. Week 40/e0) in the ITT Overall Population. The findings are presented in Figures 16.5.5.4 to 16.5.5.17.

The relationship between ^{18}F-DOPA uptake in the dorsal central/posterior putamen and OFF state UPDRS motor and ADL scores at baseline was directionally consistent with published correlations [50]; in a combined analysis of both treatment groups, the relationship between baseline ^{18}F-DOPA uptake and baseline ADL score was statistically significant (correlation coefficient: -0.370, p=0.0167; Figure 16.5.5.17). At Week 40/e0, the slope of the correlation curves in the GDNF/GDNF group flattened, while it became steeper again when comparing the ^{18}F-DOPA uptake at Week 40/e0 with Week 80/e40 UPDRS scores. In the latter comparison, the strength of the relationship with OFF state motor score was similar to the above reported correlation for changes to these time points (correlation coefficient: -0.356, p=0.1054; Figure 16.5.5.12), and the relationship with OFF state ADL score became significant (correlation coefficient: -0.467, p=0.0324; Figure 16.5.5.14). No consistent pattern was noticeable in the placebo/GDNF group.

12.3   Imaging Conclusions

During the course of the extension study, volume of distribution of infusate, VOI coverage, and total putamenal coverage showed only small changes in both treatment groups. Treatment differences for change from baseline to Week 80/e40 were not statistically significant. ^{18}F-DOPA uptake was not re-assessed at Week 80/e40.

Correlation analyses did not reveal any relationship between the primary study endpoint and VOI coverage or total putamenal coverage at baseline, or between the primary study endpoint and change from baseline to Week 40 in ^{18}F-DOPA uptake, except for a trend for the expected negative correlation in the dorsal central/posterior putamen in the GDNF/GDNF group in the ITT Overall Population (correlation coefficient: -0.371, p=0.0904).

13.   SAFETY EVALUATION

All analyses were performed for the Safety Overall Population.

13.1   Extent of Exposure

13.1.1   Overall Exposure

Overall, during the course of all extension parts of study 2797, a total of 609 infusions of study medication were administered, 305 to the 21 subjects in the GDNF/GDNF group and 304 to the 20 subjects in the placebo/GDNF group (Table 32). The number of infusions given per subject ranged from 5 to 36 (GDNF/GDNF: 5 to 31, placebo/GDNF: 10 to 36; Table 16.4.1.1). Mean total exposure to GDNF was 3.565 mg (median 3.120 mg). Exposure in the individual extension parts is summarized in Table 32 and discussed in the following sections.

Table 32   Exposure to Study Medication - Overview - Safety Overall Population

	GDNF/GDNF (N=21)	Placebo/GDNF (N=20)	Total (N=41)
Number of subjects treated			
Initial Extension	21	20	41
Pilot Extension	3	2	5
Supplemental Extension	11	12	23
Number of infusions of study medication given			
Initial Extension	201	200	401
Pilot Extension	36	34	70
Supplemental Extension	68	70	138
TOTAL	**305**	**304**	**609**

Source: Table 16.4.1.1 and Listing 17.2.4.1.2

13.1.2   Exposure in Initial Extension

All but 4 study subjects received all 10 protocol-specified infusions of study medication in the Initial Extension (Listing 17.2.4.1.2). The mean number of infusions of study medication was 9.8 (9.6 in the GDNF/GDNF group and 10.0 in the placebo/GDNF group; Table 33). Seventeen of the 21 subjects in the GDNF/GDNF group received 10 infusions, 2 received 9 infusions (subjects 49 and 57), 1 received 8 infusions (subject 45), and 1 received 5 infusions (subject 42; Listing 17.2.4.1.2; see also Section 10.2). All 20 subjects in the placebo/GDNF group received 10 infusions. Hence, 401 (97.8%) of 410 infusions scheduled for the Initial Extension were administered. Mean total exposure to GDNF in the Initial Extension was 2.347 mg (median 2.4 mg).

Table 33 **Exposure to Study Medication - Initial Extension - Safety Overall Population**

Variable	GDNF/GDNF (N=21)	Placebo/GDNF (N=20)	Total (N=41)
Number of infusions of study medication			
n	21	20	41
Mean (SD)	9.6 (1.16)	10.0 (0.00)	9.8 (0.85)
Median (Min, Max)	10.0 (5, 10)	10.0 (10, 10)	10.0 (5, 10)
Total GDNF exposure (mg)[a]			
n	21	20	41
Mean (SD)	2.297 (0.280)	2.400 (0.000)	2.347 (0.204)
Median (Min, Max)	2.400 (1.20, 2.40)	2.400 (2.40, 2.40)	2.400 (1.20, 2.40)

[a]   Total exposure in mg assumes the entire infusion was completed at each administration.
Source: Table 16.4.1.1

The mean duration of infusion of study medication (including potential interruption times) at the individual visits in the Initial Extension ranged from 114.2 to 127.0 minutes for all subjects, with a trend to shorter mean duration over time (Table 16.4.1.2). Median duration of infusion of study medication was 102.0 minutes at all visits. Only small differences were observed between the treatment groups in the duration of infusion of study medication.

Interruption or early termination of infusion (affecting one or more catheters) occurred in the case of 48 infusions of study medication during the Initial Extension (30 infusions in the GDNF/GDNF group, 18 infusions in the placebo/GDNF group; Listing 17.2.4.1.3). Thirty of the 48 cases occurred in subjects who had been in the Pilot Stage in study 2553 (23 infusions in 4 GDNF/GDNF subjects, 7 infusions in 2 placebo/GDNF subjects); hence, 30 (50.0%) of 60 infusions given to Pilot Stage subjects were interrupted or terminated early (Listings 17.2.4.1.2 and 17.2.4.1.3). In contrast, only 18 (5.3%) of 341 infusions given to subjects who had been in the Primary Stage of study 2553 were interrupted or terminated early (7 infusions in 5 GDNF/GDNF subjects, 11 infusions in 7 placebo/GDNF subjects; Listings 17.2.4.1.2 and 17.2.4.1.3).

In nearly all cases, the reason for interruption or early termination was high pump pressure resulting from occlusion. This, in turn, was probably caused by septum debris which gradually collected at the bottom of the ports as a result of long-term repeated septum penetration. The marked difference in frequency of occurrence between Pilot Stage subjects and Primary Stage subjects is reflective of changes to the septum manufacturing process made early in the Primary Stage to address the problem.

13.1.3   Exposure in Pilot Extension and Supplemental Extension

After completion of the Initial Extension, 5 of the 6 Pilot Stage subjects received infusions of study medication in the Pilot Extension (Table 16.4.1.1). A total of 70 infusions of study medication were given in the Pilot Extension (range: 8 to 19 infusions per subject; Listing 17.2.4.1.2). Fifty-three (75.7%) infusions were interrupted or terminated early due to high pump pressure resulting from occlusion probably caused by septum debris (Listing 17.2.4.1.3). One further infusion was interrupted due to the presence of large bubbles in

the external infusion lines. Despite these technical problems, infusions were continued beyond the end of the Pilot Extension in 2 subjects (subject 07, GDNF/GDNF and subject 06, placebo/GDNF).

Twenty-three subjects received infusions of study medication in the Supplemental Extension, including 2 Pilot Stage subjects who completed the Pilot Extension and 21 Primary Stage subjects who completed the Initial Extension (Tables 16.1.1.1 and 16.4.1.1). A total of 138 infusions of study medication were given in the Supplemental Extension (range: 2 to 12 infusions per subject; Listing 17.2.4.1.2). Twenty-seven (19.6%) infusions were interrupted or terminated early, including 9 infusions in the 2 Pilot Stage subjects (Listing 17.2.4.1.3).

13.2   Adverse Events

All AEs reported during study 2797 were considered TEAEs. TEAEs that were present or ongoing at the beginning of study 2797 were considered pre-existing, if the event term, severity, and date and time of onset in study 2797 were identical to the corresponding information given for the TEAE in study 2553. If any of these conditions was not met, the TEAE was considered new or worsening. Only new or worsening TEAEs were tabulated in this CSR. Pre-existing TEAEs were listed. Unless otherwise specified, in the text below and in the summary tables, the term "TEAE" denotes "new or worsening TEAE".

In the text and tables of this section, the findings for TEAEs are presented as the number and percentage of subjects with each AE unless otherwise specified. In the tables of most frequent AEs given in this section, data-driven cut-offs have been chosen to facilitate tabular presentation, e.g. all PTs occurring in at least 3 subjects of a treatment group. All SOCs and PTs have nevertheless been evaluated for safety signals and any relevant findings are reported in the text.

Since all subjects received GDNF in the study, the results are discussed primarily on the basis of the overall extension study population rather than the treatment groups. The overall frequencies of TEAEs, most frequent individual TEAEs, and serious TEAEs are discussed both for the Initial Extension and for the entire extension study. Additional analyses of individual TEAEs by maximum severity, relationship to study medication, relationship to device, and category of special interest (AESIs) are described only on the basis of the frequency data for the entire extension study.

13.2.1   Brief Summary of Adverse Events

TEAEs were reported for all 41 subjects in the Initial Extension (Table 34). Severe TEAEs were reported for 18 (43.9%) subjects, but serious TEAEs occurred in only 8 (19.5%) subjects. None of the TEAEs led to permanent discontinuation of study medication. None of the subjects died (Listings 17.2.1.1 and 17.2.4.2).

Study medication-related TEAEs occurred in 34 (82.9%) subjects, but none of the study medication-related TEAEs were reported as serious. Device-related TEAEs were reported for 19 (46.3%) subjects, but were reported as serious in only 3 (7.3%) subjects.

The frequency of subjects with serious TEAEs was higher in the GDNF/GDNF group (7 [33.3%] subjects) than in the placebo/GDNF group (1 [5.0%] subject). A relevant part of the difference was caused by 3 (14.3%) subjects in the GDNF/GDNF group whose serious TEAEs were all device-related; all 3 subjects were Pilot Stage subjects (Listing 17.2.4.2). No serious device-related TEAEs were reported for the placebo/GDNF group.

Table 34   Overall Summary of AEs in the Initial Extension - Safety Overall Population

AE category	GDNF/GDNF (N=21) n (%)	Placebo/GDNF (N=20) n (%)	Total (N=41) n (%)
Any TEAE	21 (100)	20 (100)	41 (100)
Any severe TEAE	9 (42.9)	9 (45.0)	18 (43.9)
Any serious TEAE	7 (33.3)	1 (5.0)	8 (19.5)
Any TEAE leading to permanent discontinuation of study medication	0	0	0
Any study medication-related TEAE	16 (76.2)	18 (90.0)	34 (82.9)
Any serious study medication-related TEAE	0	0	0
Any device-related TEAE	9 (42.9)	10 (50.0)	19 (46.3)
Any serious device-related TEAE	3 (14.3)	0	3 (7.3)

Note: For each category, subjects are included only once, even if they experienced multiple events in that category. All AEs reported during the study period were considered TEAEs. TEAEs present or ongoing at the beginning of study 2797 were considered pre-existing, if the event term, severity, and date and time of onset in study 2797 were identical to the corresponding information given for the TEAE in study 2553. If any of these conditions was not met, the TEAE was considered new or worsening. Only new or worsening TEAEs are summarized.
Source: Table 16.4.2.1.2

For the Pilot and Supplemental Extensions, lower frequencies of subjects with severe TEAEs (26.9%), study medication-related TEAEs (34.6%), and device-related TEAEs (30.8%) than in the Initial Extension were observed (Table 16.4.2.1.3). However, these findings should be interpreted with caution, given the lower total number of 26 subjects who received study medication in the Pilot and/or Supplemental Extensions and the variable length of subject participation in these further extension parts.

For the entire extension study (including all extension parts), the frequencies of subjects in the different TEAE categories were broadly comparable to the frequencies for the Initial Extension (Table 35).

Table 35   Overall Summary of AEs in the Entire Extension Study - Safety Overall Population

AE category	GDNF/GDNF (N=21) n (%)	Placebo/GDNF (N=20) n (%)	Total (N=41) n (%)
Any TEAE	21 (100)	20 (100)	41 (100)
Any severe TEAE	10 (47.6)	12 (60.0)	22 (53.7)
Any serious TEAE	7 (33.3)	3 (15.0)	10 (24.4)
Any TEAE leading to permanent discontinuation of study medication	2 (9.5) [a]	0	2 (4.9) [a]
Any study medication-related TEAE	16 (76.2)	18 (90.0)	34 (82.9)
Any serious study medication-related TEAE	0	0	0
Any device-related TEAE	9 (42.9)	10 (50.0)	19 (46.3)
Any serious device-related TEAE	3 (14.3)	0	3 (7.3)

Note: For each category, subjects are included only once, even if they experienced multiple events in that category. All AEs reported during the study period were considered TEAEs. TEAEs present or ongoing at the beginning of study 2797 were considered pre-existing, if the event term, severity, and date and time of onset in study 2797 were identical to the corresponding information given for the TEAE in study 2553. If any of these conditions was not met, the TEAE was considered new or worsening. Only new or worsening TEAEs are summarized.

[a]   These 2 subjects had to discontinue study medication after explantation of their device (or parts thereof) in the Pilot Extension, subsequent to a device-related infection (see Section 13.3.3.1).

Source: Table 16.4.2.1.1

13.2.2   Analysis of Adverse Events

Frequency tables of TEAEs are provided in Table 16.4.2.1.1 to Table 16.4.2.10.

All TEAEs reported in the extension study are presented by study stage, treatment group, and subject number in Listing 17.2.4.2.

13.2.2.1   All Treatment-Emergent Adverse Events

TEAEs were reported for all 41 subjects in the extension study. Table 36 gives a summary of the frequencies of the SOCs most frequently affected (SOCs with at least 6 subjects per treatment group). The treatment groups were generally comparable with regard to the frequencies of TEAEs per SOC. The only SOCs with a higher frequency of subjects in the GDNF/GDNF group (difference of ≥3 subjects between treatment groups) were respiratory, thoracic and mediastinal disorders (8 GDNF/GDNF subjects, 4 placebo/GDNF subjects) and vascular disorders (6 GDNF/GDNF subjects, 1 placebo/GDNF subject).

Table 36   TEAEs - Most Frequent SOCs (at Least 6 Subjects Per Treatment Group) - Safety Overall Population

MedDRA system organ class	GDNF/GDNF (N=21) n (%)	Placebo/GDNF (N=20) n (%)	Total (N=41) n (%)
Subjects with at least one TEAE	21 (100)	20 (100)	41 (100)
Nervous system disorders	18 (85.7)	16 (80.0)	34 (82.9)
Infections and infestations	18 (85.7)	15 (75.0)	33 (80.5)
Musculoskeletal and connective tissue disorders	15 (71.4)	13 (65.0)	28 (68.3)
Psychiatric disorders	15 (71.4)	13 (65.0)	28 (68.3)
General disorders and administration site conditions	14 (66.7)	13 (65.0)	27 (65.9)
Injury, poisoning and procedural complications	13 (61.9)	14 (70.0)	27 (65.9)
Gastrointestinal disorders	10 (47.6)	9 (45.0)	19 (46.3)
Respiratory, thoracic and mediastinal disorders	8 (38.1)	4 (20.0)	12 (29.3)
Skin and subcutaneous tissue disorders	6 (28.6)	6 (30.0)	12 (29.3)
Eye disorders	6 (28.6)	4 (20.0)	10 (24.4)
Vascular disorders	6 (28.6)	1 (5.0)	7 (17.1)

Source: Table 16.4.2.2

TEAEs in the Initial Extension

Table 37 summarizes the most frequent individual TEAEs (PTs) that occurred in the Initial Extension (TEAEs experienced by at least 3 subjects of a treatment group). The pattern of TEAEs observed was consistent with the GDNF group in study 2553 and previous clinical studies testing continuous intraputamenal administration of GDNF in subjects with PD [Section 4.1 in reference 51]. Nine of the 10 most frequently reported TEAEs in the Initial Extension (dyskinesia, Lhermitte's sign, nasopharyngitis, paresthesia, fall, ON and OFF phenomenon, freezing phenomenon, application site infection, and headache) were also amongst the 10 most frequently reported TEAEs in the GDNF group in study 2553 [Table 16.4.2.3.2 in reference 32]. Dystonia (9 [22.0%] subjects) was the only frequently reported TEAE that occurred at a markedly lower frequency in the GDNF group in study 2553 (1 [4.8%] subject). The individual frequencies of the 9 matching frequently reported TEAEs, their overall frequency range (22.0-41.5% in the Initial Extension vs. 19.0-42.9% in study 2553), and the range of ratios of event reports relative to the number of reporting subjects (approximately 1.1-2.3 vs. 1.1-2.1) were similar in both studies (Table 16.4.2.3.2).

The treatment groups were generally comparable with regard to the frequencies of individual TEAEs in the Initial Extension. Individual TEAEs with a difference in frequency of at least 3 subjects between the treatment groups were Lhermitte's sign (GDNF/GDNF 9, placebo/GDNF 4), ON and OFF phenomenon (GDNF/GDNF 4, placebo/GDNF 7), freezing phenomenon (GDNF/GDNF 7 subjects, placebo/GDNF 3 subjects), muscle spasms (GDNF/GDNF 2, placebo/GDNF 6), pain in extremity (GDNF/GDNF 5, placebo/GDNF 2), abdominal pain upper (GDNF/GDNF 3, placebo/GDNF 0), anemia (GDNF/GDNF 3, placebo/GDNF 0), dysphagia

(GDNF/GDNF 0, placebo/GDNF 3), and head discomfort (GDNF/GDNF 3, placebo/GDNF 0). No pattern could be discerned in the distribution of these TEAEs by treatment group.

Table 37   TEAEs Experienced by at Least 3 Subjects of A Treatment Group in the Initial Extension - Safety Overall Population

MedDRA preferred term	GDNF/GDNF (N=21) n (%)	Placebo/GDNF (N=20) n (%)	Total (N=41) n (%)
Subjects with at least one TEAE	21 (100)	20 (100)	41 (100)
Dyskinesia	8 (38.1)	9 (45.0)	17 (41.5)
Lhermitte's sign	9 (42.9)	4 (20.0)	13 (31.7)
Nasopharyngitis	7 (33.3)	6 (30.0)	13 (31.7)
Paraesthesia	6 (28.6)	7 (35.0)	13 (31.7)
Fall	5 (23.8)	7 (35.0)	12 (29.3)
On and off phenomenon	4 (19.0)	7 (35.0)	11 (26.8)
Freezing phenomenon	7 (33.3)	3 (15.0)	10 (24.4)
Application site infection	5 (23.8)	4 (20.0)	9 (22.0)
Dystonia	5 (23.8)	4 (20.0)	9 (22.0)
Headache	4 (19.0)	5 (25.0)	9 (22.0)
Back pain	3 (14.3)	5 (25.0)	8 (19.5)
Muscle spasms	2 (9.5)	6 (30.0)	8 (19.5)
Contusion	4 (19.0)	3 (15.0)	7 (17.1)
Pain in extremity	5 (23.8)	2 (10.0)	7 (17.1)
Urinary tract infection	3 (14.3)	4 (20.0)	7 (17.1)
Application site erythema	2 (9.5)	4 (20.0)	6 (14.6)
Dizziness	3 (14.3)	3 (15.0)	6 (14.6)
Joint injury	4 (19.0)	2 (10.0)	6 (14.6)
Nausea	4 (19.0)	2 (10.0)	6 (14.6)
Constipation	2 (9.5)	3 (15.0)	5 (12.2)
Drug effect decreased	2 (9.5)	3 (15.0)	5 (12.2)
Abnormal dreams	3 (14.3)	1 (5.0)	4 (9.8)
Application site inflammation	3 (14.3)	1 (5.0)	4 (9.8)
Application site reaction	3 (14.3)	1 (5.0)	4 (9.8)
Cough	3 (14.3)	1 (5.0)	4 (9.8)
Diarrhoea	3 (14.3)	1 (5.0)	4 (9.8)
Insomnia	1 (4.8)	3 (15.0)	4 (9.8)
Abdominal pain upper	3 (14.3)	0	3 (7.3)
Anaemia	3 (14.3)	0	3 (7.3)
Dysphagia	0	3 (15.0)	3 (7.3)
Head discomfort	3 (14.3)	0	3 (7.3)

Source: Tables 16.4.2.1.2 and 16.4.2.3.2

TEAEs in the Entire Extension Study

The profile of the most frequent individual TEAEs that occurred in the entire extension study (TEAEs experienced by at least 3 subjects of a treatment group) was very similar to that for the Initial Extension (Table 38). Individual TEAEs with a difference in frequency of at least 3 subjects between the treatment groups were fall (GDNF/GDNF 6 subjects, placebo/GDNF 10 subjects), Lhermitte's sign (GDNF/GDNF 9, placebo/GDNF 4), freezing phenomenon (GDNF/GDNF 8 subjects, placebo/GDNF 3 subjects), muscle spasms (GDNF/GDNF 4, placebo/GDNF 7), pain in extremity (GDNF/GDNF 6, placebo/GDNF 2), nausea (GDNF/GDNF 5, placebo/GDNF 2), Parkinson's disease (GDNF/GDNF 5, placebo/GDNF 1), cough (GDNF/GDNF 4, placebo/GDNF 1), anemia (GDNF/GDNF 4, placebo/GDNF 0), abdominal pain upper (GDNF/GDNF 3, placebo/GDNF 0), and limb discomfort (GDNF/GDNF 3, placebo/GDNF 0).

In the Pilot and/or Supplemental Extensions, few TEAEs were reported by at least 3 subjects of a treatment group (Table 16.4.2.3.3). Five of the 7 most frequently reported TEAEs in the Pilot and Supplemental Extensions were amongst the 10 most frequently reported TEAEs in the Initial Extension (fall, ON and OFF phenomenon, dyskinesia, application site infection, headache). The only other most frequently reported TEAEs were Parkinson's disease and depressed mood, both of which were reported by few subjects only (Parkinson's disease: GDNF/GDNF 3, placebo/GDNF 0; depressed mood: GDNF/GDNF 3, placebo/GDNF 1).

Table 38   **TEAEs Experienced by at Least 3 Subjects of A Treatment Group in the Entire Extension Study - Safety Overall Population**

MedDRA preferred term	GDNF/GDNF (N=21) n (%)	Placebo/GDNF (N=20) n (%)	Total (N=41) n (%)
Subjects with at least one TEAE	21 (100)	20 (100)	41 (100)
Dyskinesia	10 (47.6)	9 (45.0)	19 (46.3)
Nasopharyngitis	9 (42.9)	8 (40.0)	17 (41.5)
Fall	6 (28.6)	10 (50.0)	16 (39.0)
ON and OFF phenomenon	7 (33.3)	7 (35.0)	14 (34.1)
Lhermitte's sign	9 (42.9)	4 (20.0)	13 (31.7)
Paraesthesia	6 (28.6)	7 (35.0)	13 (31.7)
Dystonia	6 (28.6)	5 (25.0)	11 (26.8)
Freezing phenomenon	8 (38.1)	3 (15.0)	11 (26.8)
Headache	6 (28.6)	5 (25.0)	11 (26.8)
Muscle spasms	4 (19.0)	7 (35.0)	11 (26.8)
Application site infection	6 (28.6)	4 (20.0)	10 (24.4)
Back pain	5 (23.8)	5 (25.0)	10 (24.4)
Contusion	5 (23.8)	4 (20.0)	9 (22.0)
Pain in extremity	6 (28.6)	2 (10.0)	8 (19.5)
Urinary tract infection	4 (19.0)	4 (20.0)	8 (19.5)
Application site erythema	3 (14.3)	4 (20.0)	7 (17.1)
Depressed mood	4 (19.0)	3 (15.0)	7 (17.1)
Nausea	5 (23.8)	2 (10.0)	7 (17.1)
Dizziness	3 (14.3)	3 (15.0)	6 (14.6)
Joint injury	4 (19.0)	2 (10.0)	6 (14.6)
Parkinson's disease	5 (23.8)	1 (5.0)	6 (14.6)
Application site swelling	3 (14.3)	2 (10.0)	5 (12.2)
Arthralgia	2 (9.5)	3 (15.0)	5 (12.2)
Constipation	2 (9.5)	3 (15.0)	5 (12.2)
Cough	4 (19.0)	1 (5.0)	5 (12.2)
Diarrhoea	3 (14.3)	2 (10.0)	5 (12.2)
Drug effect decreased	2 (9.5)	3 (15.0)	5 (12.2)
Fatigue	3 (14.3)	2 (10.0)	5 (12.2)
Insomnia	2 (9.5)	3 (15.0)	5 (12.2)
Rapid eye movement sleep behaviour disorder	2 (9.5)	3 (15.0)	5 (12.2)
Abnormal dreams	3 (14.3)	1 (5.0)	4 (9.8)
Anaemia	4 (19.0)	0	4 (9.8)
Application site inflammation	3 (14.3)	1 (5.0)	4 (9.8)
Application site reaction	3 (14.3)	1 (5.0)	4 (9.8)
Drug ineffective	3 (14.3)	1 (5.0)	4 (9.8)
Dysphagia	1 (4.8)	3 (15.0)	4 (9.8)
Head discomfort	3 (14.3)	1 (5.0)	4 (9.8)
Musculoskeletal pain	3 (14.3)	1 (5.0)	4 (9.8)
Abdominal pain upper	3 (14.3)	0	3 (7.3)
Limb discomfort	3 (14.3)	0	3 (7.3)

Source: Tables 16.4.2.1.1 and 16.4.2.3.1

13.2.2.2   Treatment-Emergent Adverse Events by Maximum Severity

In the entire extension study, 22 (53.7%) subjects experienced TEAEs rated as severe,
11 (26.8%) subjects experienced TEAEs rated with a maximum severity of moderate, and
8 (19.5%) subjects experienced TEAEs rated with a maximum severity of mild (Table 16.4.2.4).

The high frequency of severe TEAEs was attributable largely to severe musculoskeletal and
connective tissue disorders (10 [24.4%] subjects) and severe nervous system disorders
(8 [19.5%] subjects). Table 39 shows the frequency of all severe TEAEs reported in these SOCs.
The only severe TEAEs reported for 3 or more subjects overall were back pain (4 subjects),
muscle spasms (3 subjects), and dystonia (3 subjects). Dystonia was the only severe TEAE with
a notable difference between the treatment groups (3 subjects in the GDNF/GDNF group,
0 subjects in the placebo/GDNF group). These events are commonly reported by PD patients.

For all other SOCs, the overall number of subjects with severe TEAEs was 4 or lower, and no
individual TEAEs rated as severe were reported by more than 2 subjects overall.

**Table 39   Severe TEAEs in the SOCs "Nervous System Disorders" and
               "Musculoskeletal and Connective Tissue Disorders" in the Entire Extension
               Study - Safety Overall Population**

MedDRA system organ class Preferred term	GDNF/GDNF (N=21) n (%)	Placebo/GDNF (N=20) n (%)	Total (N=41) n (%)
Subjects with at least one severe TEAE	10 (47.6)	12 (60.0)	22 (53.7)
Musculoskeletal and connective tissue disorders	5 (23.8)	5 (25.0)	10 (24.4)
Arthralgia	0	1 (5.0)	1 (2.4)
Back pain	2 (9.5)	2 (10.0)	4 (9.8)
Foot deformity	1 (4.8)	0	1 (2.4)
Limb discomfort	1 (4.8)	0	1 (2.4)
Mobility decreased	0	1 (5.0)	1 (2.4)
Muscle spasms	2 (9.5)	1 (5.0)	3 (7.3)
Muscular weakness	1 (4.8)	0	1 (2.4)
Pain in extremity	1 (4.8)	0	1 (2.4)
Nervous system disorders	4 (19.0)	4 (20.0)	8 (19.5)
Balance disorder	1 (4.8)	0	1 (2.4)
Bradykinesia	1 (4.8)	0	1 (2.4)
Coordination abnormal	0	1 (5.0)	1 (2.4)
Dyskinesia	1 (4.8)	1 (5.0)	2 (4.9)
Dystonia	3 (14.3)	0	3 (7.3)
Freezing phenomenon	1 (4.8)	0	1 (2.4)
Headache	0	1 (5.0)	1 (2.4)
ON and OFF phenomenon	2 (9.5)	0	2 (4.9)
Sciatica	0	1 (5.0)	1 (2.4)

Source: Table 16.4.2.4

13.2.2.3   Study Medication-Related Treatment-Emergent Adverse Events

Study medication-related TEAEs were reported for 34 (82.9%) subjects in the entire extension study (Table 40). By far the most common types of study medication-related TEAE were disorders of the nervous system (30 [73.2%] subjects), followed by psychiatric disorders (11 [26.8%] subjects; Table 16.4.2.6). With the exception of muscle spasms ("Musculoskeletal and connective tissue disorders" SOC), all individual study medication-related TEAEs reported for at least 3 subjects overall were classified in the "Nervous system disorders" SOC. Lhermitte's sign, paresthesia, headache, Parkinson's disease, and head discomfort were reported more frequently in the GDNF/GDNF group than in the placebo/GDNF group (difference of ≥3 subjects between treatment groups).

Table 40   Study Medication-Related TEAEs Experienced by at Least 3 Subjects Overall in the Entire Extension Study - Safety Overall Population

MedDRA preferred term	GDNF/GDNF (N=21) n (%)	Placebo/GDNF (N=20) n (%)	Total (N=41) n (%)
Subjects with at least one study medication-related TEAE	16 (76.2)	18 (90.0)	34 (82.9)
Dyskinesia	7 (33.3)	9 (45.0)	16 (39.0)
Lhermitte's sign	9 (42.9)	4 (20.0)	13 (31.7)
Paraesthesia	6 (28.6)	2 (10.0)	8 (19.5)
Headache	5 (23.8)	1 (5.0)	6 (14.6)
Parkinson's disease	4 (19.0)	1 (5.0)	5 (12.2)
Freezing phenomenon	2 (9.5)	2 (10.0)	4 (9.8)
Muscle spasms	1 (4.8)	2 (10.0)	3 (7.3)
Head discomfort	3 (14.3)	0	3 (7.3)

Source: Table 16.4.2.6

13.2.2.4   Device-Related Treatment-Emergent Adverse Events

Device-related TEAEs were reported for 19 (46.3%) subjects in the entire extension study (Table 41). All device-related TEAEs reported by 3 or more subjects overall were related to the application site (port), and there were no TEAEs related to the intracerebral parts of the drug delivery system. No notable differences were observed between the treatment groups with respect to the individual device-related TEAEs.

Table 41   Device-Related TEAEs Experienced by at Least 3 Subjects Overall in the Entire Extension Study - Safety Overall Population

MedDRA preferred term	GDNF/GDNF (N=21) n (%)	Placebo/GDNF (N=20) n (%)	Total (N=41) n (%)
Subjects with at least one device-related TEAE	9 (42.9)	10 (50.0)	19 (46.3)
Application site infection	6 (28.6)	4 (20.0)	10 (24.4)
Application site erythema	3 (14.3)	4 (20.0)	7 (17.1)
Application site swelling	3 (14.3)	2 (10.0)	5 (12.2)
Application site inflammation	3 (14.3)	1 (5.0)	4 (9.8)
Application site reaction	3 (14.3)	1 (5.0)	4 (9.8)
Application site haemorrhage	1 (4.8)	2 (10.0)	3 (7.3)
Application site pain	2 (9.5)	1 (5.0)	3 (7.3)

Source: Table 16.4.2.8

13.3   Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

13.3.1   Deaths

No subjects died during the study (Listing 17.2.1.1 and Listing 17.2.4.2).

13.3.2   Serious Adverse Events

Overall, in the entire extension study, 18 individual serious TEAEs were reported for 10 (24.4%) subjects, including 9 events in 8 (19.5%) subjects in the Initial Extension and 9 events in 5 (19.2%) subjects in the Pilot and Supplemental Extensions (Table 42 and Tables 16.4.2.5.1 to 16.4.2.5.3). The frequency of subjects with serious TEAEs was higher in the GDNF/GDNF group (7 [33.3%] subjects) than in the placebo/GDNF group (3 [15.0%] subjects). In addition, more individual serious TEAEs were reported for subjects in the GDNF/GDNF group than for subjects in the placebo/GDNF group. Review of the individual serious TEAEs showed that these findings were attributable principally to early experience with and hence longer usage of the study device in Pilot Stage subjects:

- Half (9) of the serious TEAEs occurred in 3 GDNF/GDNF subjects originally enrolled in the Pilot Stage of study 2553. All of these serious TEAEs were complications associated with the device, application site, or surgical procedures that were therefore considered by the investigator as device-related and not related to the study medication.

- Subjects originally enrolled in the Primary Stage of study 2553 had a lower frequency of serious TEAEs in the extension study. The 9 serious TEAEs reported for the Primary Stage subjects were not device complications, and none of them were considered by the investigator as related to study medication or to the device.

Full subject narratives for all serious TEAEs are provided in Section 16.6.

Table 42   Serious TEAEs by Subject - Safety Overall Population

Subj. No.	Treatment group	MedDRA preferred term	Extension part	Study med.-related?	Device-related?
PILOT STAGE					
04	GDNF/GDNF	Device occlusion	Initial	No	Yes
		Procedural complication	Pilot [a]	No	Yes
		Application site hypertrophy	Pilot	No	Yes
		Device related infection	Pilot [b]	No	Yes
		Psychosis postoperative	Pilot	No	Yes
05	GDNF/GDNF	Device occlusion	Initial	No	Yes
		Application site infection	Pilot [c]	No	Yes
		Application site infection	Pilot [d]	No	Yes
07	GDNF/GDNF	Application site inflammation	Initial	No	Yes
PRIMARY STAGE					
13	GDNF/GDNF	Muscle rupture	Initial	No	No
22	Placebo/GDNF	Dehydration	Supplemental	No	No
23	GDNF/GDNF	Menorrhagia	Initial	No	No
		Post procedural infection	Initial	No	No
24	Placebo/GDNF	Appendicitis	Supplemental	No	No
39	Placebo/GDNF	Osteoarthritis	Initial	No	No
45	GDNF/GDNF	Confusional state	Initial	No	No
47	GDNF/GDNF	Depression	Initial	No	No
		Paranoia	Supplemental	No	No

[a]   During replacement surgery between Initial Extension and Pilot Extension.
[b]   AE leading to port explantation 8 days after Week e2-36.
[c]   AE leading to port explantation 2 days after Week e2-32.
[d]   AE leading to removal of remaining device parts approximately 4.5 months after port explantation.
Source: Listing 17.2.4.2 and Section 16.6 Subject Narratives

13.3.3   Other Significant Adverse Events

13.3.3.1   Treatment-Emergent Adverse Events Leading to Permanent Discontinuation of Study Medication

No subjects discontinued study medication due to a TEAE in the Initial Extension (Table 16.1.1.2.2). Two subjects had to discontinue study medication during the Pilot Extension after explantation of their device (or parts thereof) subsequent to a device-related infection (subject 04, GDNF/GDNF, 8 days after the Week e2-36 visit) or an application site infection (subject 05, GDNF/GDNF, 2 days after the Week e2-32 visit; for subject narratives see Section 16.6).

13.3.3.2   Adverse Events of Special Interest

Treatment-emergent AESIs were reported for 33 (80.5%) subjects in the entire extension study (Table 43). The frequencies of the individual AESIs were generally well balanced between the treatment groups, except for falls which occurred more frequently in the placebo/GDNF group than in the GDNF/GDNF group.

For AESIs by subject see Listing 17.2.4.3.1 (dyskinesias), Listing 17.2.4.3.2 (falls), Listing 17.2.4.3.3 (adverse changes in mood), and Listing 17.2.4.3.4 (impulsivity).

Table 43   Treatment-emergent AEs of Special Interest - Safety Overall Population

AESI category MedDRA preferred term	GDNF/GDNF (N=21) n (%)	Placebo/GDNF (N=20) n (%)	Total (N=41) n (%)
Subjects with at least one treatment-emergent AESI	16 (76.2)	17 (85.0)	33 (80.5)
Dyskinesias	13 (61.9)	11 (55.0)	24 (58.5)
Blepharospasm	0	2 (10.0)	2 (4.9)
Dyskinesia	10 (47.6)	9 (45.0)	19 (46.3)
Dystonia	6 (28.6)	5 (25.0)	11 (26.8)
Excessive eye blinking	1 (4.8)	0	1 (2.4)
Falls	6 (28.6)	10 (50.0)	16 (39.0)
Fall	6 (28.6)	10 (50.0)	16 (39.0)
Adverse changes in mood	8 (38.1)	7 (35.0)	15 (36.6)
Affective disorder	1 (4.8)	0	1 (2.4)
Agitation	0	1 (5.0)	1 (2.4)
Anxiety	2 (9.5)	2 (10.0)	4 (9.8)
Crying	0	1 (5.0)	1 (2.4)
Depressed mood	4 (19.0)	3 (15.0)	7 (17.1)
Depression	1 (4.8)	0	1 (2.4)
Feeling of despair	1 (4.8)	0	1 (2.4)
Hypomania	0	1 (5.0)	1 (2.4)
Irritability	0	1 (5.0)	1 (2.4)
Tearfulness	0	1 (5.0)	1 (2.4)
Impulsivity	4 (19.0)	2 (10.0)	6 (14.6)
Compulsive shopping	0	1 (5.0)	1 (2.4)
Dopamine dysregulation syndrome	0	1 (5.0)	1 (2.4)
Hypersexuality	0	1 (5.0)	1 (2.4)
Impulsive behaviour	1 (4.8)	0	1 (2.4)
Libido increased	2 (9.5)	0	2 (4.9)
Obsessive-compulsive disorder	2 (9.5)	1 (5.0)	3 (7.3)

Source: Table 16.4.2.10

13.4   Clinical Laboratory Evaluation

13.4.1   Hematology

Clinically significant postbaseline results for hematology parameters were reported by the investigator for 2 GDNF/GDNF subjects and 1 placebo/GDNF subject during the extension study (Table 16.4.3.1 and Listing 17.2.4.5):

- Subject 03 (placebo/GDNF) had clinically significant postbaseline values of low erythrocytes, hemoglobin, and hematocrit and high neutrophils at Week 68/e28. The subject had mild oropharyngeal pain (sore throat) reported as an AE at this time (Listing 17.2.4.2).

- Subject 04 (GDNF/GDNF) had clinically significant postbaseline values of low hemoglobin at Week 68/e28 and low hemoglobin and low hematocrit at the last visit in the Supplemental Extension. Mild anemia was reported as an AE at both time points (Listing 17.2.4.2). Hemoglobin, hematocrit, and erythrocyte values for the subject were below the normal range sporadically throughout the extension study. The subject was placed on iron supplements during the study (Listing 17.2.1.5).

- Subject 38 (GDNF/GDNF) had a clinically significant postbaseline value of low hemoglobin at Week 80/e40. The subject had low hemoglobin, hematocrit, and erythrocyte values at various time points during the extension study. Mild anemia was reported as an AE for the subject during the extension study (Listing 17.2.4.2).

For hematology data by subject see Listing 17.2.4.5.

13.4.2   Serum Chemistry

Clinically significant postbaseline results for serum chemistry parameters were reported by the investigator for 1 GDNF/GDNF subject and 2 placebo/GDNF subjects during the extension study (Table 16.4.3.2 and Listing 17.2.4.6):

- Subject 44 (placebo/GDNF) had a clinically significant postbaseline value of low albumin at Week 80/e40. The subject's albumin value was below the lower limit of the normal range at all measuring times during the extension study.

- Subject 57 (GDNF/GDNF) had a clinically significant postbaseline value of high glucose at Week 80/e40. Glucose was also high at Week 40/e0 but was within the normal range at other measuring times during the extension study.

- Subject 59 (placebo/GDNF) had clinically significant postbaseline values of borderline-high creatinine, high urea, and low glomerular filtration rate at Week 68/e28. Mild renal impairment was diagnosed and reported as an AE at this visit (Listing 17.2.4.2).

For serum chemistry data by subject see Listing 17.2.4.6.

13.4.3   Urinalysis

Postbaseline urinalysis findings rated by the investigator as clinically significant were reported in the following isolated cases (Listing 17.2.4.7):

- Subject 09 (placebo/GDNF): positive nitrite at Week 80/e40 and abnormal microscopy findings at Week 44/e4 and Week 80/e40.

- Subject 12 (GDNF/GDNF): abnormal microscopy findings at Week 44/e4.

- Subject 23 (GDNF/GDNF): abnormal microscopy findings at last visit in Supplemental Extension.

- Subject 45 (GDNF/GDNF): abnormal microscopy findings at Week 68/e28.

- Subject 60 (placebo/GDNF): abnormal microscopy findings at Week 80/e40.

13.5   Anti-GDNF Antibodies in Serum

Assays for anti-GDNF binding antibodies in serum were performed for the samples of all subjects at all scheduled time points except for the following 4 cases where the sample was lost: subject 07, GDNF/GDNF: Week 80/e40; subject 15, placebo/GDNF: Week 68/e28; subject 36, placebo/GDNF: Week 80/e40; subject 42, GDNF/GDNF: Week 44/e4 (Listing 17.2.4.8).
Note: The missing sample for subject 42 is not included as "missing" in the descriptive analysis of the antibody data (Table 16.4.4.1) because the date of sampling was missing in this case (Listing 17.2.4.8). In addition, the sample for subject 04 at Week 68/e28 was taken outside of the visit window. The test result was negative but was not included in the descriptive analysis of the antibody data.

No anti-GDNF binding serum antibodies were identified in any of the 192 samples assayed for the extension study (Table 16.4.4.1 and Listing 17.2.4.8). Therefore, testing for anti-GDNF neutralizing antibodies was not performed (Table 16.4.4.2).

For anti-GDNF serum antibody data by subject see Listing 17.2.4.8. The bioanalytical data report is provided in Section 17.1.12.

13.6   Plasma GDNF Concentrations

Plasma GDNF concentrations above the limit of quantification (0.19 ng/mL) were found for only 3 subjects (Table 16.4.5 and Listing 17.2.4.9):

- Subject 07 (GDNF/GDNF) had very low quantifiable concentrations at most time points during the extension study (range: 1.269-1.800 ng/mL).

- Subject 24 (placebo/GDNF) had a single very low quantifiable concentration at the last visit in the Supplemental Extension (0.276 ng/mL).

- Subject 61 (placebo/GDNF) had very low quantifiable concentrations at baseline (screening, 0.290 ng/mL) and Week 40/e0 (0.447 ng/mL) and higher concentrations at Weeks 56/e16, 68/e28, and 80/e40 (range: 7.183-7.857 ng/mL).

For plasma GDNF concentration data by subject see Listing 17.2.4.9. The bioanalytical data report is provided in Section 17.1.12.

13.7   Vital Signs, Physical Findings, and Other Observations Related to Safety

13.7.1   Vital Signs

Vital signs were monitored before, during, and after each test infusion and each infusion of study medication in the extension study.

As expected with intensified monitoring in this kind of population, clinically relevant increases and/or decreases in sitting and standing BP were observed frequently during the study. Summary statistics were only provided for the Initial Extension, where the numbers of subjects with changes were similar in both treatment groups, except that clinically relevant increases in sitting systolic BP occurred in fewer subjects in the GDNF/GDNF group than in the placebo/GDNF group (5 vs. 10 subjects) and clinically relevant increases in standing diastolic BP occurred in more subjects in the GDNF/GDNF group than in the placebo/GDNF group (11 vs. 6 subjects; Table 44). No trend or pattern in the occurrence of such findings over time was detected. No notable differences were observed between the treatment groups with regard to the frequency of subjects with clinically relevant postbaseline abnormalities for pulse or respiration. No clinically relevant postbaseline abnormalities were detected for temperature.

For vital sign data from infusions with a clinically relevant abnormal result see Listing 17.2.4.11.

Table 44 **Vital Signs: Frequency of Clinically Relevant Postbaseline Abnormalities at any Visit in the Initial Extension - Safety Overall Population**

Parameter and criterion	GDNF/GDNF (N=21) n (%)	Placebo/GDNF (N=20) n (%)
SYSTOLIC BP		
Sitting systolic BP < 90 mmHg or a decrease from pre-dose of ≥ 30 mmHg	13 (61.9)	12 (60.0)
Sitting systolic BP ≥ 180 mmHg or an increase from pre-dose of ≥ 30 mmHg	5 (23.8)	10 (50.0)
Standing systolic BP < 90 mmHg or a decrease from pre-dose of ≥ 30 mmHg	6 (28.6)	4 (20.0)
Standing systolic BP ≥ 180 mmHg or an increase from pre-dose of ≥ 30 mmHg	6 (28.6)	7 (35.0)
DIASTOLIC BP		
Sitting diastolic BP < 50 mmHg or a decrease from pre-dose of ≥ 20 mmHg	17 (81.0)	17 (85.0)
Sitting diastolic BP ≥ 105 mmHg or an increase from pre-dose of ≥ 20 mmHg	12 (57.1)	12 (60.0)
Standing diastolic BP < 50 mmHg or a decrease from pre-dose of ≥ 20 mmHg	6 (28.6)	4 (20.0)
Standing diastolic BP ≥ 105 mmHg or an increase from pre-dose of ≥ 20 mmHg	11 (52.4)	6 (30.0)
PULSE		
Sitting pulse < 50 bpm	2 (9.5)	5 (25.0)
Sitting pulse ≥ 120 bpm or an increase from pre-dose of > 20 bpm	4 (19.0)	1 (5.0)
Standing pulse < 50 bpm	1 (4.8)	2 (10.0)
Standing pulse ≥ 120 bpm or an increase from pre-dose of > 20 bpm	4 (19.0)	2 (10.0)
RESPIRATION		
Respiration < 12 or > 20 breaths/min	2 (9.5)	2 (10.0)

Note: For the comparisons of values during or after infusion with pre-infusion values, the baseline is the pre-infusion value.
Source: Table 16.4.6

13.7.2 Weight

Review of the individual weight data showed no notable trends in weight over time in any subject, with the exception of subject 11 (placebo/GDNF) whose weight increased from 104.5 kg at baseline (Week e0) to 118.8 kg at Week e3-24 (a period of approximately 15 months). Only one other subject (24, placebo/GDNF) had a change of more than 10 kg in weight from baseline at one visit during the extension study (Week e0, 96.2 kg; Week 76/e36, 85.6 kg).

For weight data by subject see Listing 17.2.4.12.

13.7.3   Physical Examination

Physical examination data are listed by study stage, treatment group, subject, and body system in Listing 17.2.4.10. New abnormal findings at physical examination were to be reported as AEs.

The condition of the port site was also checked during physical examination. Eight subjects (5 in the GDNF/GDNF group, 3 in the placebo/GDNF group) had a finding of overt infection reported on the Port Symptoms page of the CRF at one or more study visits (Listing 17.2.4.4). With the exception of the overt infection in placebo/GDNF subject 26 at Week e3-12, all the findings of overt infection reported on the Port Symptoms page were also reported as AEs of "application site infection" with a start date on or before the date of the visit at which the overt infections were reported as port symptoms. In 1 case (subject 05, GDNF/GDNF), the infection was reported as a serious AE because the infection persisted and, in order to avoid spread of infection, the port was removed by day-case surgery (for subject narrative see Section 16.6). All other cases of overt infection reported as an AE of application site infection were classified as nonserious.

In addition to overt infection, occurrences of redness with slight or moderate swelling were observed at one or several visits in 17 subjects (7 in the GDNF/GDNF group, 10 in the placebo/GDNF group).

13.7.4   Electrocardiogram

No relevant differences were observed between the treatment groups for median change in quantitative ECG parameters from baseline (screening in study 2553) to Week 40/e0 and Week 80/e40 (Table 16.4.7.1). A difference between the treatment groups with respect to PR interval was due to an uncorrected data error in GDNF/GDNF subject 47 whose PR interval was entered as 706 ms at Week 40/e0. The subject had a PR interval of 156 ms at baseline and 160 ms at Week 80/e40, without notable change in any other ECG parameter; these findings make it extremely unlikely that the PR interval at Week 40/e0 could indeed have been 706 ms (Listing 17.2.4.13).

Overall ECG impression at Week 80/e40 was normal for 34 subjects (16 GDNF/GDNF, 18 placebo/GDNF; Table 45). An abnormal Week 80/e40 result was reported for 7 subjects (5 GDNF/GDNF, 2 placebo/GDNF), but none of the abnormal Week 80/e40 results were rated by the investigator as clinically significant.

Clinically relevant abnormal Week 80/e40 QTc interval values were identified for 5 subjects (3 GDNF/GDNF, 2 placebo/GDNF; Table 45 and Listing 17.2.4.13).

- Subject 19 (GDNF/GDNF) had a Week 80/e40 QTc interval of 460 ms, i.e. marginally above the criterion of >450 ms; the subject's baseline QTc interval was 434 ms, although the subject did have a QTc interval of 465 ms at the first screening visit measurement.

- Subject 45 (GDNF/GDNF) and subjects 09 and 22 (placebo/GDNF) had an increase of >30 ms in QTc interval from baseline to Week 80/e40; the maximum increase up to

Week 80/e40 in these 3 cases was 38 ms. In the case of subjects 45 and 09, the QTc interval was already increased by >30 ms from baseline to Week 40/e0.

- Subject 23 (GDNF/GDNF) had an increase of >60 ms in QTc interval from baseline to Week 80/e40; the subject's QTc interval was 342 ms at baseline, 383 ms at Week 40/e0 (>30 ms increase in QTc interval), and 431 ms at Week 80/e40. The subject did not have any medical history documented at screening in study 2553 or AEs reported during study 2553 or study 2797 which might explain or appeared to be related to this increase (Listing 17.2.4.2; Listings 17.2.1.6 and 17.2.4.2 in reference [32]).

Two other subjects (both GDNF/GDNF) had a QTc interval >450 ms at a postbaseline time point other than Week 80/e40 but not at Week 80/e40 (Listing 17.2.4.13):

- Subject 04 (GDNF/GDNF) had a QTc interval of 454 ms at Week e2-80. Previously, the subject's QTc interval was 416 ms at baseline, 442 ms at Week 40/e0, and 419 ms at Week 80/e40.

- Subject 66 (GDNF/GDNF) had a QTc interval of 453 ms at Week 40/e0, but previous and subsequent values were lower than 450 ms (baseline: 429 ms, Week 80/e40: 427 ms).

For ECG data by subject see Listing 17.2.4.13 (continuous parameters) and Listing 17.2.4.14 (overall impression).

Table 45   Electrocardiogram: Overall Impression and Frequency of Clinically Relevant Abnormal Week 80/e40 QTc Interval Results - Safety Overall Population

Assessment and criterion	GDNF/GDNF (N=21) n (%)	Placebo/GDNF (N=20) n (%)
OVERALL IMPRESSION		
Normal Week 80/e40 result	16 (76.2)	18 (90.0)
Any abnormal Week 80/e40 result	5 (23.8)	2 (10.0)
Any clinically significant abnormal Week 80/e40 result	0	0
CLINICALLY RELEVANT ABNORMAL WEEK 80/e40 QTc INTERVAL RESULTS	3 (14.3)	2 (10.0)
> 450 ms	1 (4.8)	0
> 500 ms	0	0
Change from baseline > 30 ms	1 (4.8)	2 (10.0)
Change from baseline > 60 ms	1 (4.8)	0

Note: Overall ECG impression was rated by the investigator as abnormal and clinically significant on the CRF based on medical judgment. Hodges QT correction formula was used.
Source: Table 16.4.7.2

13.7.5 Glasgow Coma Scale

A Glasgow Coma Scale score less than 15 was reported for 2 subjects, each at a single visit (Table 16.4.8 and Listing 17.2.4.15):

- Subject 03 (placebo/GDNF group) had a Glasgow Coma Scale score of 14, 30 minutes after start of the infusion at Week e0. The subject's pre-infusion and post-infusion scores at this visit were 15.

- Subject 45 (GDNF/GDNF) had a Glasgow Coma Scale score of 14 at the assessments before infusion, 30 minutes after start of infusion, and after the infusion at Week 56/e16.

13.7.6 Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease

The findings of the analysis of the QUIP completed by the subjects show no patterns or trends with regard to impulse control disorders, other behaviors, or medication use (Table 16.4.9.1). No clear differences were observed between the treatment groups. Results of informant-completed QUIP data are difficult to interpret because only a small number of informants completed the questionnaire.

For QUIP items answered with "yes" see Listing 17.2.4.16.

13.7.7 Montreal Cognitive Assessment

The treatment groups were comparable with regard to mean MoCA total scores at baseline (pre-test infusion in study 2553; Table 46). Only small changes in mean MoCA total score were observed up to Week 80/e40, with no notable differences between the treatment groups. Mean values for MoCA total score remained almost unchanged for subjects assessed at the last study visit in the Supplemental Extension (Table 16.4.9.2).

For MoCA total score data by subject see Listing 17.2.4.17.

Table 46   Montreal Cognitive Assessment (MoCA): Change in Total Score from Baseline to Week 80/e40 - Safety Overall Population

Visit Statistic	GDNF/GDNF (N=21)		Placebo/GDNF (N=20)	
	Value	Change from baseline	Value	Change from baseline
Pre-test infusion (baseline)				
n	21		20	
Mean (SD)	27.6 (1.72)		27.9 (1.77)	
Median (Min, Max)	28.0 (24, 30)		28.5 (25, 30)	
Week 40/e0				
n	21	21	20	20
Mean (SD)	28.1 (1.81)	0.5 (2.34)	27.6 (2.14)	-0.3 (1.87)
Median (Min, Max)	28.0 (25, 30)	0.0 (-5, 4)	28.0 (24, 30)	0.0 (-4, 5)
Week 80/e40				
n	21	21	20	20
Mean (SD)	28.0 (2.44)	0.4 (2.42)	27.8 (2.21)	-0.1 (1.80)
Median (Min, Max)	29.0 (20, 30)	1.0 (-8, 4)	28.5 (22, 30)	0.0 (-3, 4)

Note: The MoCA is a rater-administered cognitive screening tool with 8 components. The total score ranges from 0 to 30, with lower scores representing poorer cognitive function. A total score of 26 or above is considered normal.
Source: Table 16.4.9.2

13.7.8   Mattis Dementia Rating Scale

The treatment groups were comparable with regard to MDRS AEMSS total scores at baseline (screening in study 2553; Table 47). Only small changes in mean MDRS AEMSS total score were observed up to Week 80/e40, with no notable differences between the treatment groups. Mean values for MDRS AEMSS total score remained almost unchanged for subjects assessed at the last study visit in the Supplemental Extension (Table 16.4.9.3).

For MDRS AEMSS total score data by subject see Listing 17.2.4.18.

Table 47 **Mattis Dementia Rating Scale (MDRS): Change in AEMSS Total Score from Baseline to Week 80/e40 - Safety Overall Population**

Visit Statistic	GDNF/GDNF (N=21)		Placebo/GDNF (N=20)	
	Value	Change from baseline	Value	Change from baseline
Screening (baseline)				
n	21		20	
Mean (SD)	11.7 (1.68)		11.9 (1.89)	
Median (Min, Max)	12.0 (9, 15)		12.0 (9, 15)	
Week 40/e0				
n	21	21	20	20
Mean (SD)	12.0 (2.82)	0.3 (2.56)	12.6 (2.61)	0.7 (2.66)
Median (Min, Max)	13.0 (4, 15)	0.0 (-5, 4)	14.0 (8, 16)	0.0 (-4, 5)
Week 80/e40				
n	21	21	20	20
Mean (SD)	13.0 (2.13)	1.2 (1.84)	12.7 (2.01)	0.8 (2.20)
Median (Min, Max)	14.0 (8, 16)	1.0 (-2, 5)	12.5 (9, 16)	0.0 (-3, 6)

Note: The MDRS is a rater-administered global scale of cognition including 5 subscales. The AEMSS total score ranges from 0 to 20, with higher scores representing better cognitive function.
Source: Table 16.4.9.3

13.7.9 Stroop Test

The treatment groups were comparable with regard to Stroop test times at baseline (screening in study 2553), Week 40/e0, and Week 80/e40, with very small changes from baseline (Table 16.4.9.4).

For Stroop test data by subject see Listing 17.2.4.19.

13.7.10 Frontal Systems Behavioural Scale

The treatment groups were comparable with regard to FrSBe scores at baseline (screening "after", study 2553), Week 40/e0, and Week 80/e40 (Table 16.4.9.5). Changes from baseline in FrSBe scores were small. Pilot Stage subjects did not complete the FrSBe at baseline and Week 40/e0.

For FrSBe data by subject see Listing 17.2.4.20.

13.7.11 Deary-Liewald Four-Choice Reaction Time

No notable effects on Deary-Liewald four-choice RT were observed in either treatment group (Table 16.4.9.6). The Deary-Liewald four-choice RT was not performed for Pilot Stage subjects.

For Deary-Liewald four-choice RT data by subject see Listing 17.2.4.21.

13.7.12 Verbal Fluency Assessment

The treatment groups were comparable with regard to verbal fluency assessment at baseline (screening in study 2553), Week 40/e0, and Week 80/e40, and no notable trend in change from baseline was observed in either treatment group (Table 16.4.9.7). The verbal fluency assessment was not performed for Pilot Stage subjects at baseline and Week 40/e0.

For verbal fluency assessment data by subject see Listing 17.2.4.22.

13.7.13 Beck Depression Inventory

At baseline (screening in study 2553), mean BDI total score was slightly higher in the GDNF/GDNF group than the placebo/GDNF group (Table 16.4.9.8). Small improvements in mean BDI total score were observed in both treatment groups at Week 40/e0 and Week 80/e40 and in the GDNF/GDNF group at the last visit in the Supplemental Extension.

For BDI data by subject see Listing 17.2.4.23.

13.7.14 University of Pennsylvania Smell Identification Test

At baseline (screening in study 2553), the mean UPSIT score (number of correct responses) was slightly lower in the GDNF/GDNF group than the placebo/GDNF group (Table 16.4.9.9). Small decreases in the mean UPSIT score were observed in both treatment groups at Week 40/e0 and in the placebo/GDNF group at Week 80/e40 relative to baseline. In the GDNF/GDNF group, mean UPSIT score at Week 80/e40 was slightly higher than at baseline.

For UPSIT data by subject see Listing 17.2.4.24.

13.8 Safety Conclusions

Compliance with the visit schedule was very good. In the Initial Extension, 401 (97.8%) of 410 GDNF infusions scheduled were administered, and mean total exposure to GDNF was 2.347 mg. Overall, during the course of all extension parts of study 2797, a total of 609 infusions of study medication were administered, 305 to the 21 subjects in the GDNF/GDNF group and 304 to the 20 subjects in the placebo/GDNF group. The number of infusions given per subject ranged from 5 to 36 (GDNF/GDNF: 5 to 31, placebo/GDNF: 10 to 36). Mean total exposure to GDNF in the study was 3.565 mg. Interruption or early termination of infusion due to occlusion of one or more catheters occurred predominantly in Pilot Stage subjects and was probably caused by septum debris resulting from long-term repeated septum penetration. To address the problem, changes to the septum manufacturing process were made early in the Primary Stage.

TEAEs were reported for all 41 subjects. In the Initial Extension, the pattern of TEAEs observed was consistent with the GDNF group in study 2553 and previous clinical studies testing continuous intraputamenal administration of GDNF in subjects with PD. Nine of the 10 most frequently reported TEAEs in the Initial Extension (dyskinesia, Lhermitte's sign, nasopharyngitis, paresthesia, fall, ON and OFF phenomenon, freezing phenomenon, application site infection, and headache) were also amongst the 10 most frequently reported TEAEs in the

GDNF group in study 2553. Dystonia (9 [22.0%] subjects) was the only frequently reported TEAE that occurred at a markedly lower frequency in the GDNF group in study 2553 (1 [4.8%] subject). The individual frequencies of the 9 matching frequently reported TEAEs, their overall frequency range (22.0-41.5% in the Initial Extension vs. 19.0-42.9% in study 2553), and the range of ratios of event reports relative to the number of reporting subjects (approximately 1.1-2.3 vs. 1.1-2.1) were similar in both studies.

The treatment groups were generally comparable with regard to the frequencies of individual TEAEs in the Initial Extension. There were only few individual TEAEs with a difference in frequency of at least 3 subjects between the treatment groups, and no pattern could be discerned in the distribution of these TEAEs by treatment group.

The profile of the most frequent individual TEAEs that occurred in the entire extension study (TEAEs experienced by at least 3 subjects of a treatment group) was very similar to that for the Initial Extension.

In the entire extension study, 22 (53.7%) subjects experienced TEAEs rated as severe, 11 (26.8%) subjects experienced TEAEs rated with a maximum severity of moderate, and 8 (19.5%) subjects experienced TEAEs rated with a maximum severity of mild. The high frequency of severe TEAEs was attributable largely to severe musculoskeletal and connective tissue disorders (10 [24.4%] subjects) and severe nervous system disorders (8 [19.5%] subjects). The only severe TEAEs reported for 3 or more subjects overall were back pain (4 subjects), muscle spasms (3 subjects), and dystonia (3 subjects). Dystonia was the only severe TEAE with a notable difference between the treatment groups (3 subjects in the GDNF/GDNF group, 0 subjects in the placebo/GDNF group). These events are commonly reported by PD patients.

Study medication-related TEAEs were reported for 34 (82.9%) subjects in the entire extension study. By far the most common types of study medication-related TEAE were disorders of the nervous system (30 [73.2%] subjects), followed by psychiatric disorders (11 [26.8%] subjects). With the exception of muscle spasms, all individual study medication-related TEAEs reported for at least 3 subjects overall were classified in the "Nervous system disorders" SOC. Lhermitte's sign, paresthesia, headache, Parkinson's disease, and head discomfort were reported more frequently in the GDNF/GDNF group than in the placebo/GDNF group (difference of ≥3 subjects between treatment groups).

Device-related TEAEs were reported for 19 (46.3%) subjects in the entire extension study. All device-related TEAEs reported by 3 or more subjects overall were related to the application site (port), and there were no TEAEs related the intracerebral parts of the drug delivery system. No notable differences were observed between the treatment groups with respect to the individual device-related TEAEs.

No subjects died. Serious TEAEs were reported for 8 (19.5%) subjects during the Initial Extension and 5 (19.2%) subjects in the Pilot or Supplemental Extensions. Overall, in the entire extension study, a total of 18 serious TEAEs were reported for 10 (24.4%) subjects. Nine of the 18 serious TEAEs were complications associated with the device, application site, or surgical procedures that were considered by the investigator as device-related and not related to the study

medication; all of these device-related TEAEs occurred in 3 Pilot Stage subjects. The other 9 serious TEAEs (in 7 Primary Stage subjects) were not device complications, and none of them were considered by the investigator as related to study medication or to the device. Two subjects had to discontinue study medication after explantation of their device (or parts thereof) approximately halfway through the Pilot Extension, subsequent to device-related or application site infections.

Treatment-emergent AESIs (dyskinesias, falls, adverse changes in mood, impulsivity) were reported for 33 (80.5%) subjects in the entire extension study. The frequencies of the individual AESIs were generally well balanced between the treatment groups, except for falls which occurred more frequently in the placebo/GDNF group (10 subjects) than in the GDNF/GDNF group (6 subjects).

Clinically relevant changes in clinical laboratory parameters, vital signs, weight, ECG, or assessments of cognitive and neurological status were observed only sporadically during the study, and there was no treatment-related pattern discernible. No anti-GDNF binding serum antibodies were identified at any time point during the study.

14.   DISCUSSION AND OVERALL CONCLUSIONS

Analyses of the primary, secondary, and supplementary efficacy endpoints at Week 80/e40 showed no statistically significant differences between the treatment groups, except for total daily levodopa equivalent dose which remained mostly unchanged in the GDNF/GDNF group (change of 59 mg) but increased notably in the placebo/GDNF group (change of 289 mg; p=0.0156) in the ITT Overall Population.

The lack of statistically significant treatment differences in most clinical endpoints at Week 80/e40 was expected in view of the results of the parent study and given that all placebo subjects received GDNF in their second 9-month treatment period. However, both treatment groups showed moderate to large clinically important mean improvements [48, 49] in OFF state UPDRS scores between baseline and Week 80/e40 (motor score: -9.6 points in the GDNF/GDNF group vs. -9.0 points in the placebo/GDNF group; ADL score: -6.9 vs. -4.6 points). The change in OFF state UPDRS motor score put subjects close to the lower end of the range of OFF state UPDRS motor scores permitted at entry to study 2553 (25-45). Moreover, it is in contrast to the predicted disease progression reflected by a 2.4-point worsening of OFF state UPDRS motor score over 80 weeks for a modelled control based on data from the Parkinson's Progression Markers Initiative database [47]. The UPDRS improvements were accompanied by improvements in all PD motor fluctuation diary ratings; in particular, there was a notable gain in total good-quality ON time per day of 1.64 hours in the GDNF/GDNF group and 0.54 hours in the placebo/GDNF group.

Acknowledging the limitations of the open-label study design, there were several findings that support the conclusion that the benefits observed in the GDNF/GDNF group were the result of a true drug effect. First, when comparing the results for the OFF state UPDRS motor and ADL scores in the GDNF/GDNF group at Week 80/e40 with those in the placebo/GDNF group at Week 40/e0 as the best available internal control, the differences were highly statistically significant in favor of GDNF/GDNF (motor score: -9.6 vs. -3.8 points, p=0.0108; ADL score: -6.9 vs. -1.0 points, p=0.0003). Second, the number of strong OFF state UPDRS motor score responders (decrease of ≥10 points) in the placebo/GDNF group at Week 80/e40 was the same (9) as in the GDNF/GDNF group at Week 40/e0, thus independently replicating the latter result. Third, in a post hoc analysis, mean IOR scores differed substantially between the treatment groups during the entire 80-week period, favoring GDNF/GDNF at each time point. At Week 40/e0, the treatment difference in the IOR was highly statistically significant in favor of GDNF/GDNF, with virtually no effect in the placebo/GDNF group (-23.98 vs. -1.36, p=0.0032). Subsequently, there was continued improvement up to Week 80/e40 (-40.28 vs. -24.02, p=0.1201). In addition, the effect size in the first 40 weeks of GDNF treatment was the same in both groups, confirming the findings for strong OFF state UPDRS motor score responders. In a number of analyses of robustness modifying the PD diary component of the IOR and its weight, the score was found to be remarkably stable, and adjusting for baseline did not impact the conclusions or improve the model fit.

When reviewing the results of the parent study, it was hypothesized that clinical effects may be lagging behind biological changes during disease reversion (neurorestoration), similar to the

sequence observed during disease progression [52, 53]. The extension study results potentially suggest that, indeed, it may require more than 9 months of treatment for neural network improvements to translate into clinical benefit. While functional changes resulting from restoring the dopaminergic phenotype of affected dysfunctional neurons may be recognized early [54], it seems likely that there may be delays between structural changes including terminal-sprouting, synapse-formation and circuit-reestablishment, and subsequent functional improvement in cerebral function. The time course of the improvements observed in the study would be consistent with this proposed sequence. In contrast, it would not be easily compatible with the anticipated pattern of a placebo response that shows greatest benefit during the initial treatment phase and plateaus or deteriorates thereafter.

The pattern of TEAEs observed in the Initial Extension was consistent with the GDNF group in study 2553 and previous clinical studies testing continuous intraputamenal administration of GDNF in subjects with PD. Nine of the 10 most frequently reported TEAEs in the Initial Extension (dyskinesia, Lhermitte's sign, nasopharyngitis, paresthesia, fall, ON and OFF phenomenon, freezing phenomenon, application site infection, and headache) were also amongst the 10 most frequently reported TEAEs in the GDNF group in study 2553. Dystonia (9 [22.0%] subjects) was the only frequently reported TEAE that occurred at a markedly lower frequency in the GDNF group in study 2553 (1 [4.8%] subject). The individual frequencies of the 9 matching frequently reported TEAEs, their overall frequency range (22.0-41.5% in the Initial Extension vs. 19.0-42.9% in study 2553), and the range of ratios of event reports relative to the number of reporting subjects (approximately 1.1-2.3 vs. 1.1-2.1) were similar in both studies.

As a notable difference, the frequency of severe TEAEs in the entire extension study was higher than in the GDNF group in study 2553 (22 [53.7%] subjects as compared to 5 [23.8%] subjects). The high frequency of severe TEAEs was attributable largely to severe musculoskeletal and connective tissue disorders (10 [24.4%] subjects) and severe nervous system disorders (8 [19.5%] subjects). The only severe TEAEs reported for 3 or more subjects overall were back pain (4 subjects), muscle spasms (3 subjects), and dystonia (3 subjects), and dystonia was the only severe TEAE with a notable difference between the treatment groups (3 subjects in the GDNF/GDNF group, 0 subjects in the placebo/GDNF group). These events are commonly reported by PD patients. No notable difference was observed between the extension study and the GDNF group in study 2553 for study medication-related TEAEs (34 [82.9%] subjects as compared to 19 [90.5%] subjects).

Device-related TEAEs were reported for 19 (46.3%) subjects in the entire extension study. All device-related TEAEs reported by 3 or more subjects overall were related to the application site (port), and there were no TEAEs related the intracerebral parts of the drug delivery system. The frequency of device-related TEAEs was unchanged from study 2553, although the device was used for significantly longer than the originally assumed lifetime of approximately one year.

No subjects died. A total of 18 serious TEAEs were reported for 10 (24.4%) subjects. Nine of the 18 serious TEAEs were complications associated with the device, application site, or surgical procedures that were considered by the investigator as device-related and not related to the study medication; all of these device-related TEAEs occurred in 3 Pilot Stage subjects. The other 9 serious TEAEs (in 7 Primary Stage subjects) were not device complications, and none of them

were considered by the investigator as related to study medication or to the device. Two subjects had to discontinue study medication after explantation of their device (or parts thereof) approximately halfway through the Pilot Extension, subsequent to device-related or application site infections.

Clinically relevant changes in clinical laboratory parameters, vital signs, weight, ECG, or assessments of cognitive and neurological status were observed only sporadically during the study, and there was no treatment-related pattern discernible.

Consistent with study 2553, no anti-GDNF binding serum antibodies were identified at any time point during the study. This is in contrast to previous studies testing continuous intraputamenal delivery, where more than half of the subjects treated with GDNF developed an asymptomatic immune response with binding anti-drug antibodies, including 5 subjects with neutralizing antibodies [19, Section 4.1 in reference 51]. Absence of immunogenicity was expected, as the implanted transcutaneous port provides for noninvasive repeat access and therefore avoids systemic exposure to drug. In contrast, the invasive refill process required for the implanted infusion pumps was a consistent source of systemic exposure to GDNF in the earlier studies.

In conjunction with the safety observations, the study confirmed the feasibility of using intermittent intraputamenal CED for long-term administration of GDNF as introduced in study 2553. This was demonstrated on the basis of preserved volume coverage on MRI at Week 80/e40 (mean VOI coverage: 67.9% to 74.3%; mean total putamenal coverage: 48.5% to 57.2%), the large overall number of study drug infusions handled by a single study site (609 in the extension study, in addition to 417 in study 2553), and the observed high compliance rate of 97.8% in the Initial Extension. Catheter occlusions due to suspected septum debris were observed predominantly in Pilot Stage subjects. To address the problem, changes to the septum manufacturing process were made early in the Primary Stage.

In conclusion, the findings of this study suggest that GDNF given via intermittent bilateral intraputamenal CED continues to hold promise as a neurorestorative and neuroprotective treatment for PD and warrants further investigation leveraging key learnings from the current program.

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16. **TABLES, FIGURES AND GRAPHS REFERRED TO BUT NOT INCLUDED IN THE TEXT**

Table of Contents

Table of Contents

Table of Contents

Table of Contents

Table 16.1.1.1 Subject Populations - All Enrolled Subjects

Population	GDNF/GDNF	Placebo/GDNF	Total
INITIAL EXTENSION			
Pilot Stage			
Subjects enrolled [n]	4	2	6
Subjects treated [n]	4	2	6
Primary Stage			
Subjects enrolled (ITT Primary Population) [n]	17	18	35
Subjects treated [n]	17	18	35
Overall (Pilot + Primary Stage)			
Subjects enrolled (ITT Overall Population) [n]	21	20	41
Subjects treated (Safety Overall Population) [n]	21	20	41
PILOT EXTENSION (Pilot Stage subjects only)			
Subjects enrolled [n]	3	2	5
Subjects treated [n]	3	2	5
SUPPLEMENTAL EXTENSION			
Pilot Stage			
Subjects enrolled [n]	2	2	4
Subjects treated [n]	1	1	2
Primary Stage			
Subjects enrolled [n]	10	11	21
Subjects treated [n]	10	11	21
Overall (Pilot + Primary Stage)			
Subjects enrolled [n]	12	13	25
Subjects treated [n]	11	12	23

Source: Listing 17.2.1.3, 17.2.4.1.2, Dataset: ADSL, Program: t_pop.sas, Output: t_16-1-1-1-pop.rtf, Generated on: 28JUL2017 05:53
Page 1 of 1

Table 16.1.1.2.1 Subject Disposition - ITT Primary Population

Variable	GDNF/GDNF (N=17) n (%)	Placebo/GDNF (N=18) n (%)	Total (N=35) n (%)
Completed Initial Extension	17 (100)	18 (100)	35 (100)
Discontinued study during Initial Extension (primary reason for early termination)	0	0	0
Death	0	0	0
Adverse event(s)	0	0	0
Withdrawal by subject	0	0	0
Protocol violation(s)	0	0	0
Lost to follow-up	0	0	0
Physician decision	0	0	0
Other	0	0	0
Missing	0	0	0

Note: Reasons for discontinuation are based on the End of Study CRF page.
Source: Listing 17.2.1.1, Dataset: ADSL, Program: t_disp.sas, Output: t_16-1-1-2-1-disp.rtf, Generated on: 28JUL2017 05:53
Page 1 of 1

Table 16.1.1.2.2 Subject Disposition - ITT Overall Population

Variable	GDNF/GDNF (N=21) n (%)	Placebo/GDNF (N=20) n (%)	Total (N=41) n (%)
Completed Initial Extension	21 (100)	20 (100)	41 (100)
Discontinued study during Initial Extension (primary reason for early termination)	0	0	0
Death	0	0	0
Adverse event(s)	0	0	0
Withdrawal by subject	0	0	0
Protocol violation(s)	0	0	0
Lost to follow-up	0	0	0
Physician decision	0	0	0
Other	0	0	0
Missing	0	0	0

Note: Reasons for discontinuation are based on the End of Study CRF page.
Source: Listing 17.2.1.1, Dataset: ADSL, Program: t_disp.sas, Output: t_16-1-1-2-2-disp.rtf, Generated on: 28JUL2017 05:53
Page 1 of 1

Table 16.1.2 Protocol Deviations - ITT Overall Population

Category Deviation (brief description)	GDNF/GDNF (N=21) n (%)	Placebo/GDNF (N=20) n (%)	Total (N=41) n (%)
Subjects with at least one major protocol deviation	2 (9.5)	0	2 (4.9)
OUTCOME ASSESSMENT	1 (4.8)	0	1 (2.4)
AT E40 VISIT UPDRS Q27, 28, 29, 30 NOT DONE	1 (4.8)	0	1 (2.4)
STUDY MEDICATION (INCLUDING OVERDOSE)	2 (9.5)	0	2 (4.9)
E20 INFUSION MISSED	1 (4.8)	0	1 (2.4)
SUBJECT MISSED WEEK E12 INFUSION	1 (4.8)	0	1 (2.4)
Subjects with at least one minor protocol deviation	21 (100)	19 (95.0)	40 (97.6)
NON-STUDY MEDICATION	1 (4.8)	0	1 (2.4)
OTHER	3 (14.3)	0	3 (7.3)
OUTCOME ASSESSMENT	16 (76.2)	14 (70.0)	30 (73.2)
STUDY MEDICATION (INCLUDING OVERDOSE)	6 (28.6)	2 (10.0)	8 (19.5)
STUDY SCHEDULE/VISIT WINDOW	21 (100)	19 (95.0)	40 (97.6)

Note: For each category and deviation, subjects are included only once, even if they experienced multiple events in that category or deviation. If a subject
    missed more than one study drug infusion during the Initial Extension, the second missed infusion is classified as major.
Source: Listing 17.2.1.2.1, 17.2.1.2.2, Dataset: ADPDV, Program: t_pdev.sas, Output: t_16-1-2-pdev.rtf, Generated on: 28JUL2017 05:53
Page 1 of 1

Table 16.1.3.1 Demographic Characteristics from Study 2553 - ITT Primary Population

Variable	GDNF/GDNF (N=17)	Placebo/GDNF (N=18)	Total (N=35)
Age (years)			
n	17	18	35
Mean (SD)	57.7 (8.24)	55.1 (7.52)	56.4 (7.87)
Median	57.0	55.0	55.0
Min, Max	45, 72	41, 67	41, 72
Age group [n (%)]			
< 65 years	13 (76.5)	16 (88.9)	29 (82.9)
≥ 65 years	4 (23.5)	2 (11.1)	6 (17.1)
Sex [n (%)]			
Female	10 (58.8)	7 (38.9)	17 (48.6)
Male	7 (41.2)	11 (61.1)	18 (51.4)
Race [n (%)]			
White	17 (100)	17 (94.4)	34 (97.1)
Black	0	0	0
Asian	0	1 (5.6)	1 (2.9)
Native Hawaiian or other Pacific Islander	0	0	0
American Indian or Alaska Native	0	0	0
Other	0	0	0
Ethnicity [n (%)]			
Hispanic or Latino	0	0	0
Not Hispanic or Latino	17 (100)	18 (100)	35 (100)

[a] NART error score is the number of words pronounced incorrectly out of 50 total words.
Source: Listing 17.2.1.4.1, Dataset: ADSL, Program: t_demog.sas, Output: t_16-1-3-1-demog.rtf, Generated on: 28JUL2017 05:53
Page 1 of 2

Table 16.1.3.1 Demographic Characteristics from Study 2553 - ITT Primary Population

Variable	GDNF/GDNF (N=17)	Placebo/GDNF (N=18)	Total (N=35)
Weight at baseline (kg)			
n	17	18	35
Mean (SD)	78.01 (15.139)	80.02 (22.293)	79.05 (18.905)
Median	77.00	74.55	74.70
Min, Max	49.3, 111.3	43.0, 124.0	43.0, 124.0
Height at baseline (m)			
n	17	18	35
Mean (SD)	1.704 (0.080)	1.716 (0.104)	1.710 (0.092)
Median	1.702	1.722	1.705
Min, Max	1.58, 1.87	1.56, 1.92	1.56, 1.92
BMI at baseline (kg/m^2)			
n	17	18	35
Mean (SD)	26.755 (4.192)	26.895 (5.847)	26.827 (5.037)
Median	26.110	27.540	26.927
Min, Max	19.65, 33.98	17.57, 39.31	17.57, 39.31
NART error score (points)[a]			
n	17	18	35
Mean (SD)	11.8 (5.36)	13.3 (6.91)	12.6 (6.16)
Median	12.0	12.0	12.0
Min, Max	4, 21	4, 32	4, 32

[a] NART error score is the number of words pronounced incorrectly out of 50 total words.
Source: Listing 17.2.1.4.1, Dataset: ADSL, Program: t_demog.sas, Output: t_16-1-3-1-demog.rtf, Generated on: 28JUL2017 05:53

Table 16.1.3.2 Demographic Characteristics from Study 2553 - ITT Overall Population

Variable	GDNF/GDNF (N=21)	Placebo/GDNF (N=20)	Total (N=41)
Age (years)			
n	21	20	41
Mean (SD)	55.9 (8.75)	54.3 (7.60)	55.1 (8.15)
Median	54.0	54.5	54.0
Min, Max	41, 72	41, 67	41, 72
Age group [n (%)]			
< 65 years	17 (81.0)	18 (90.0)	35 (85.4)
≥ 65 years	4 (19.0)	2 (10.0)	6 (14.6)
Sex [n (%)]			
Female	12 (57.1)	7 (35.0)	19 (46.3)
Male	9 (42.9)	13 (65.0)	22 (53.7)
Race [n (%)]			
White	21 (100)	19 (95.0)	40 (97.6)
Black	0	0	0
Asian	0	1 (5.0)	1 (2.4)
Native Hawaiian or other Pacific Islander	0	0	0
American Indian or Alaska Native	0	0	0
Other	0	0	0
Ethnicity [n (%)]			
Hispanic or Latino	0	0	0
Not Hispanic or Latino	21 (100)	20 (100)	41 (100)

[a] NART error score is the number of words pronounced incorrectly out of 50 total words.
Source: Listing 17.2.1.4.1, Dataset: ADSL, Program: t_demog.sas, Output: t_16-1-3-2-demog.rtf, Generated on: 28JUL2017 05:53
Page 1 of 2

Table 16.1.3.2 Demographic Characteristics from Study 2553 - ITT Overall Population

Variable	GDNF/GDNF (N=21)	Placebo/GDNF (N=20)	Total (N=41)
Weight at baseline (kg)			
n	21	20	41
Mean (SD)	76.15 (14.201)	79.34 (21.216)	77.70 (17.811)
Median	72.90	74.55	74.40
Min, Max	49.3, 111.3	43.0, 124.0	43.0, 124.0
Height at baseline (m)			
n	21	20	41
Mean (SD)	1.707 (0.080)	1.714 (0.099)	1.710 (0.089)
Median	1.705	1.713	1.710
Min, Max	1.58, 1.87	1.56, 1.92	1.56, 1.92
BMI at baseline (kg/m^2)			
n	21	20	41
Mean (SD)	26.096 (4.220)	26.758 (5.550)	26.419 (4.863)
Median	25.763	27.088	26.110
Min, Max	19.65, 33.98	17.57, 39.31	17.57, 39.31
NART error score (points)[a]			
n	17	18	35
Mean (SD)	11.8 (5.36)	13.3 (6.91)	12.6 (6.16)
Median	12.0	12.0	12.0
Min, Max	4, 21	4, 32	4, 32

[a] NART error score is the number of words pronounced incorrectly out of 50 total words.
Source: Listing 17.2.1.4.1, Dataset: ADSL, Program: t_demog.sas, Output: t_16-1-3-2-demog.rtf, Generated on: 28JUL2017 05:53
Page 2 of 2

Table 16.1.4.1 Parkinson's Disease History at Screening from Study 2553 - ITT Primary Population

Variable	GDNF/GDNF (N=17)	Placebo/GDNF (N=18)	Total (N=35)
Duration since first PD symptom (years)			
n	17	18	35
Mean (SD)	10.8 (4.97)	10.9 (5.78)	10.9 (5.32)
Median	10.0	8.5	9.0
Min, Max	5, 21	5, 26	5, 26
Duration since PD diagnosis (years)			
n	17	18	35
Mean (SD)	8.6 (4.33)	7.9 (3.69)	8.3 (3.97)
Median	8.0	8.5	8.0
Min, Max	3, 19	2, 17	2, 19
Hoehn and Yahr stage in OFF state [n (%)]			
Stage 0: No signs of disease	0	0	0
Stage 1: Unilateral symptoms only	0	0	0
Stage 1.5: Unilateral and axial involvement	0	0	0
Stage 2: Bilateral symptoms; no impairment of balance	8 (47.1)	5 (27.8)	13 (37.1)
Stage 2.5: Mild bilateral disease with recovery on pull test	4 (23.5)	8 (44.4)	12 (34.3)
Stage 3: Balance impairment; mild to moderate disease; physically independent	5 (29.4)	5 (27.8)	10 (28.6)
OFF state UPDRS motor score (part III)			
n	17	18	35
Mean (SD)	37.1 (7.20)	35.8 (6.14)	36.4 (6.60)
Median	40.0	35.5	37.0
Min, Max	26, 45	27, 45	26, 45

[a] Percentage change in UPDRS motor score (part III) following a levodopa challenge.
Source: Listing 17.2.1.4.2, Dataset: ADSL, Program: t_pdhis.sas, Output: t_16-1-4-1-pdhis.rtf, Generated on: 28JUL2017 05:53

Table 16.1.4.1 Parkinson's Disease History at Screening from Study 2553 - ITT Primary Population

Variable	GDNF/GDNF (N=17)	Placebo/GDNF (N=18)	Total (N=35)
ON state UPDRS motor score (part III)			
n	17	18	35
Mean (SD)	16.9 (5.17)	16.9 (4.52)	16.9 (4.77)
Median	16.0	15.5	16.0
Min, Max	9, 26	10, 26	9, 26
Total daily levodopa dose (mg)			
n	16	18	34
Mean (SD)	662.23 (345.258)	562.07 (272.303)	609.21 (308.150)
Median	598.50	566.00	598.50
Min, Max	300.0, 1596.0	100.0, 1000.0	100.0, 1596.0
Total daily levodopa equivalent dose (mg)			
n	17	18	35
Mean (SD)	981.60 (384.827)	963.45 (355.535)	972.26 (364.661)
Median	915.00	967.90	930.00
Min, Max	300.0, 1890.0	299.5, 1656.0	299.5, 1890.0
PD medications [n (%)]			
Levodopa Preparations	16 (94.1)	18 (100)	34 (97.1)
Dopamine Agonists	14 (82.4)	16 (88.9)	30 (85.7)
COMT Inhibitors	7 (41.2)	9 (50.0)	16 (45.7)
MAO-B Inhibitors	6 (35.3)	10 (55.6)	16 (45.7)
Other	3 (17.6)	6 (33.3)	9 (25.7)

[a] Percentage change in UPDRS motor score (part III) following a levodopa challenge.
Source: Listing 17.2.1.4.2, Dataset: ADSL, Program: t_pdhis.sas, Output: t_16-1-4-1-pdhis.rtf, Generated on: 28JUL2017 05:53
Page 2 of 3

Table 16.1.4.1 Parkinson's Disease History at Screening from Study 2553 - ITT Primary Population

Variable	GDNF/GDNF (N=17)	Placebo/GDNF (N=18)	Total (N=35)
Responsiveness to levodopa[a] (%)			
n	17	18	35
Mean (SD)	54.24 (9.351)	52.80 (9.434)	53.50 (9.283)
Median	55.00	52.00	54.00
Min, Max	40.0, 67.0	40.6, 72.9	40.0, 72.9
OFF time per day (hours)			
n	17	18	35
Mean (SD)	6.26 (2.217)	6.07 (2.076)	6.17 (2.116)
Median	6.80	5.75	6.00
Min, Max	2.8, 9.3	3.2, 9.5	2.8, 9.5

[a] Percentage change in UPDRS motor score (part III) following a levodopa challenge.
Source: Listing 17.2.1.4.2, Dataset: ADSL, Program: t_pdhis.sas, Output: t_16-1-4-1-pdhis.rtf, Generated on: 28JUL2017 05:53
Page 3 of 3

Table 16.1.4.2 Parkinson's Disease History at Screening from Study 2553 - ITT Overall Population

Variable	GDNF/GDNF (N=21)	Placebo/GDNF (N=20)	Total (N=41)
Duration since first PD symptom (years)			
n	21	20	41
Mean (SD)	10.6 (5.01)	10.6 (5.54)	10.6 (5.21)
Median	9.0	8.0	9.0
Min, Max	5, 21	5, 26	5, 26
Duration since PD diagnosis (years)			
n	21	20	41
Mean (SD)	8.6 (4.39)	7.9 (3.50)	8.2 (3.95)
Median	8.0	8.0	8.0
Min, Max	3, 19	2, 17	2, 19
Hoehn and Yahr stage in OFF state [n (%)]			
Stage 0: No signs of disease	0	0	0
Stage 1: Unilateral symptoms only	0	0	0
Stage 1.5: Unilateral and axial involvement	0	0	0
Stage 2: Bilateral symptoms; no impairment of balance	11 (52.4)	5 (25.0)	16 (39.0)
Stage 2.5: Mild bilateral disease with recovery on pull test	4 (19.0)	9 (45.0)	13 (31.7)
Stage 3: Balance impairment; mild to moderate disease; physically independent	6 (28.6)	6 (30.0)	12 (29.3)
OFF state UPDRS motor score (part III)			
n	21	20	41
Mean (SD)	36.0 (7.72)	36.3 (6.16)	36.1 (6.92)
Median	37.0	36.0	37.0
Min, Max	26, 45	27, 45	26, 45

[a] Percentage change in UPDRS motor score (part III) following a levodopa challenge.
Source: Listing 17.2.1.4.2, Dataset: ADSL, Program: t_pdhis.sas, Output: t_16-1-4-2-pdhis.rtf, Generated on: 28JUL2017 05:53
Page 1 of 3

Table 16.1.4.2 Parkinson's Disease History at Screening from Study 2553 - ITT Overall Population

Variable	GDNF/GDNF (N=21)	Placebo/GDNF (N=20)	Total (N=41)
ON state UPDRS motor score (part III)			
n	21	20	41
Mean (SD)	15.7 (5.79)	16.6 (4.55)	16.1 (5.18)
Median	15.0	15.5	15.0
Min, Max	5, 26	10, 26	5, 26
Total daily levodopa dose (mg)			
n	20	20	40
Mean (SD)	630.51 (313.796)	554.96 (258.842)	592.74 (286.488)
Median	524.50	532.00	528.50
Min, Max	300.0, 1596.0	100.0, 1000.0	100.0, 1596.0
Total daily levodopa equivalent dose (mg)			
n	21	20	41
Mean (SD)	981.36 (346.559)	940.83 (349.081)	961.59 (344.027)
Median	916.00	948.00	930.00
Min, Max	300.0, 1890.0	299.5, 1656.0	299.5, 1890.0
PD medications [n (%)]			
Levodopa Preparations	20 (95.2)	20 (100)	40 (97.6)
Dopamine Agonists	18 (85.7)	17 (85.0)	35 (85.4)
COMT Inhibitors	10 (47.6)	11 (55.0)	21 (51.2)
MAO-B Inhibitors	10 (47.6)	11 (55.0)	21 (51.2)
Other	5 (23.8)	6 (30.0)	11 (26.8)

[a] Percentage change in UPDRS motor score (part III) following a levodopa challenge.
Source: Listing 17.2.1.4.2, Dataset: ADSL, Program: t_pdhis.sas, Output: t_16-1-4-2-pdhis.rtf, Generated on: 28JUL2017 05:53
Page 2 of 3

Table 16.1.4.2 Parkinson's Disease History at Screening from Study 2553 - ITT Overall Population

Variable	GDNF/GDNF (N=21)	Placebo/GDNF (N=20)	Total (N=41)
Responsiveness to levodopa[a] (%)			
n	21	20	41
Mean (SD)	56.86 (11.303)	54.17 (9.977)	55.55 (10.630)
Median	56.00	54.50	56.00
Min, Max	40.0, 81.0	40.6, 72.9	40.0, 81.0
OFF time per day (hours)			
n	21	20	41
Mean (SD)	6.25 (2.031)	5.96 (2.034)	6.11 (2.013)
Median	6.20	5.75	6.00
Min, Max	2.8, 9.3	3.2, 9.5	2.8, 9.5

[a] Percentage change in UPDRS motor score (part III) following a levodopa challenge.
Source: Listing 17.2.1.4.2, Dataset: ADSL, Program: t_pdhis.sas, Output: t_16-1-4-2-pdhis.rtf, Generated on: 28JUL2017 05:53
Page 3 of 3

Table 16.1.5.1 Concomitant Parkinson's Disease Medications by WHO Drug Dictionary ATC Class and Preferred Name - ITT Primary Population

ATC Class Preferred Name	GDNF/GDNF (N=17) n (%)	Placebo/GDNF (N=18) n (%)	Total (N=35) n (%)
Subjects with at least one concomitant PD medication	17 (100)	18 (100)	35 (100)
ADAMANTANE DERIVATIVES	7 (41.2)	8 (44.4)	15 (42.9)
AMANTADINE	7 (41.2)	8 (44.4)	15 (42.9)
ANTICHOLINESTERASES	0	1 (5.6)	1 (2.9)
RIVASTIGMINE	0	1 (5.6)	1 (2.9)
BETA BLOCKING AGENTS, NON-SELECTIVE	0	1 (5.6)	1 (2.9)
PROPRANOLOL	0	1 (5.6)	1 (2.9)
DIRECT ACTING ANTIVIRALS	7 (41.2)	8 (44.4)	15 (42.9)
AMANTADINE	7 (41.2)	8 (44.4)	15 (42.9)
DOPA AND DOPA DERIVATIVES	17 (100)	18 (100)	35 (100)
CARBIDOPA MONOHYDRATE W/ENTACAPONE/LEVODOPA	0	1 (5.6)	1 (2.9)
LEDOPSAN	5 (29.4)	6 (33.3)	11 (31.4)
MADOPAR	9 (52.9)	9 (50.0)	18 (51.4)
SINEMET	11 (64.7)	10 (55.6)	21 (60.0)
STALEVO /01631201/	7 (41.2)	7 (38.9)	14 (40.0)
DOPAMINE AGONISTS	13 (76.5)	15 (83.3)	28 (80.0)
PRAMIPEXOLE	5 (29.4)	6 (33.3)	11 (31.4)
PRAMIPEXOLE DIHYDROCHLORIDE	3 (17.6)	1 (5.6)	4 (11.4)
ROPINIROLE	3 (17.6)	6 (33.3)	9 (25.7)
ROPINIROLE HYDROCHLORIDE	2 (11.8)	2 (11.1)	4 (11.4)

Note: Concomitant medications are defined as any medications ongoing at the start of open-label study medication dosing or with a start date on or after
    the first open-label study medication dose date. Medications are coded using WHO Drug Dictionary Enhanced version 2016Mar01. For each ATC
    class and preferred name, subjects are included only once.
Source: Listing 17.2.1.5, Dataset: ADCM, Program: t_med.sas, Output: t_16-1-5-1-med.rtf, Generated on: 28JUL2017 05:53
Page 1 of 2

Table 16.1.5.1 Concomitant Parkinson's Disease Medications by WHO Drug Dictionary ATC Class and Preferred Name - ITT Primary Population

ATC Class Preferred Name	GDNF/GDNF (N=17) n (%)	Placebo/GDNF (N=18) n (%)	Total (N=35) n (%)
DOPAMINE AGONISTS			
ROTIGOTINE	0	1 (5.6)	1 (2.9)
MONOAMINE OXIDASE B INHIBITORS	9 (52.9)	15 (83.3)	24 (68.6)
RASAGILINE	8 (47.1)	12 (66.7)	20 (57.1)
SELEGILINE	2 (11.8)	3 (16.7)	5 (14.3)
OTHER ANTIMIGRAINE PREPARATIONS	0	1 (5.6)	1 (2.9)
PROPRANOLOL	0	1 (5.6)	1 (2.9)
OTHER DOPAMINERGIC AGENTS	0	3 (16.7)	3 (8.6)
ENTACAPONE	0	3 (16.7)	3 (8.6)

Note: Concomitant medications are defined as any medications ongoing at the start of open-label study medication dosing or with a start date on or after the first open-label study medication dose date. Medications are coded using WHO Drug Dictionary Enhanced version 2016Mar01. For each ATC class and preferred name, subjects are included only once.
Source: Listing 17.2.1.5, Dataset: ADCM, Program: t_med.sas, Output: t_16-1-5-1-med.rtf, Generated on: 28JUL2017 05:53
Page 2 of 2

Table 16.1.5.2 Other Concomitant Medications by WHO Drug Dictionary ATC Class and Preferred Name - ITT Primary Population

ATC Class Preferred Name	GDNF/GDNF (N=17) n (%)	Placebo/GDNF (N=18) n (%)	Total (N=35) n (%)
Subjects with at least one other concomitant medication	17 (100)	18 (100)	35 (100)
AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM	1 (5.9)	0	1 (2.9)
LOSARTAN	1 (5.9)	0	1 (2.9)
ALL OTHER NON-THERAPEUTIC PRODUCTS	0	1 (5.6)	1 (2.9)
PROPANOL	0	1 (5.6)	1 (2.9)
ALL OTHER THERAPEUTIC PRODUCTS	1 (5.9)	1 (5.6)	2 (5.7)
CALCIUM CARBONATE	0	1 (5.6)	1 (2.9)
HYDROXOCOBALAMIN	1 (5.9)	0	1 (2.9)
ANALGESICS	11 (64.7)	15 (83.3)	26 (74.3)
ACETYLSALICYLIC ACID	2 (11.8)	1 (5.6)	3 (8.6)
CODEINE	0	2 (11.1)	2 (5.7)
CODEINE PHOSPHATE	1 (5.9)	0	1 (2.9)
FENTANYL	1 (5.9)	1 (5.6)	2 (5.7)
GABAPENTIN	1 (5.9)	1 (5.6)	2 (5.7)
MORPHINE	1 (5.9)	0	1 (2.9)
MORPHINE SULFATE PENTAHYDRATE	1 (5.9)	1 (5.6)	2 (5.7)
OXYCODONE	0	1 (5.6)	1 (2.9)
PANADEINE CO	1 (5.9)	3 (16.7)	4 (11.4)

Note: Concomitant medications are defined as any medications ongoing at the start of open-label study medication dosing or with a start date on or after the first open-label study medication dose date. Medications are coded using WHO Drug Dictionary Enhanced version 2016Mar01. For each ATC class and preferred name, subjects are included only once.
Source: Listing 17.2.1.5, Dataset: ADCM, Program: t_med.sas, Output: t_16-1-5-2-med.rtf, Generated on: 28JUL2017 05:53
Page 1 of 22

Table 16.1.5.2 Other Concomitant Medications by WHO Drug Dictionary ATC Class and Preferred Name - ITT Primary Population

ATC Class Preferred Name	GDNF/GDNF (N=17) n (%)	Placebo/GDNF (N=18) n (%)	Total (N=35) n (%)
ANALGESICS			
PARACETAMOL	11 (64.7)	13 (72.2)	24 (68.6)
PETHIDINE	0	1 (5.6)	1 (2.9)
PREGABALIN	0	1 (5.6)	1 (2.9)
SUMATRIPTAN	0	1 (5.6)	1 (2.9)
TRAMADOL	0	1 (5.6)	1 (2.9)
ANESTHETICS	1 (5.9)	1 (5.6)	2 (5.7)
FENTANYL	1 (5.9)	1 (5.6)	2 (5.7)
LEVOBUPIVACAINE	1 (5.9)	0	1 (2.9)
PROPOFOL	1 (5.9)	0	1 (2.9)
ANTI-ACNE PREPARATIONS	3 (17.6)	3 (16.7)	6 (17.1)
CHLORAMPHENICOL	1 (5.9)	2 (11.1)	3 (8.6)
DEXAMETHASONE	1 (5.9)	0	1 (2.9)
DOXYCYCLINE	1 (5.9)	0	1 (2.9)
ERYTHROMYCIN	0	1 (5.6)	1 (2.9)
NICOTINAMIDE	0	1 (5.6)	1 (2.9)
RETINOL	1 (5.9)	0	1 (2.9)
ANTIANEMIC PREPARATIONS	2 (11.8)	1 (5.6)	3 (8.6)
FERROUS FUMARATE	0	1 (5.6)	1 (2.9)

Note: Concomitant medications are defined as any medications ongoing at the start of open-label study medication dosing or with a start date on or after the first open-label study medication dose date. Medications are coded using WHO Drug Dictionary Enhanced version 2016Mar01. For each ATC class and preferred name, subjects are included only once.
Source: Listing 17.2.1.5, Dataset: ADCM, Program: t_med.sas, Output: t_16-1-5-2-med.rtf, Generated on: 28JUL2017 05:53
Page 2 of 22

Table 16.1.5.2 Other Concomitant Medications by WHO Drug Dictionary ATC Class and Preferred Name - ITT Primary Population

ATC Class Preferred Name	GDNF/GDNF (N=17) n (%)	Placebo/GDNF (N=18) n (%)	Total (N=35) n (%)
ANTIANEMIC PREPARATIONS			
FERROUS SULFATE	1 (5.9)	0	1 (2.9)
HYDROXOCOBALAMIN	1 (5.9)	0	1 (2.9)
ANTIBACTERIALS FOR SYSTEMIC USE	11 (64.7)	8 (44.4)	19 (54.3)
AMOXICILLIN	2 (11.8)	1 (5.6)	3 (8.6)
AMOXICILLIN W/CLAVULANATE POTASSIUM	1 (5.9)	0	1 (2.9)
AUGMENTIN /00756801/	1 (5.9)	0	1 (2.9)
CEFALEXIN	1 (5.9)	0	1 (2.9)
CEFUROXIME	0	1 (5.6)	1 (2.9)
CHLORAMPHENICOL	1 (5.9)	2 (11.1)	3 (8.6)
CLARITHROMYCIN	0	2 (11.1)	2 (5.7)
DOXYCYCLINE	1 (5.9)	0	1 (2.9)
ERYTHROMYCIN	0	1 (5.6)	1 (2.9)
FLUCLOXACILLIN	8 (47.1)	3 (16.7)	11 (31.4)
FUSIDIC ACID	2 (11.8)	1 (5.6)	3 (8.6)
GENTAMICIN	1 (5.9)	0	1 (2.9)
LYMECYCLINE	0	1 (5.6)	1 (2.9)
METRONIDAZOLE	1 (5.9)	0	1 (2.9)
NITROFURANTOIN	2 (11.8)	1 (5.6)	3 (8.6)

Note: Concomitant medications are defined as any medications ongoing at the start of open-label study medication dosing or with a start date on or after the first open-label study medication dose date. Medications are coded using WHO Drug Dictionary Enhanced version 2016Mar01. For each ATC class and preferred name, subjects are included only once.
Source: Listing 17.2.1.5, Dataset: ADCM, Program: t_med.sas, Output: t_16-1-5-2-med.rtf, Generated on: 28JUL2017 05:53
Page 3 of 22

Table 16.1.5.2 Other Concomitant Medications by WHO Drug Dictionary ATC Class and Preferred Name - ITT Primary Population

ATC Class Preferred Name	GDNF/GDNF (N=17) n (%)	Placebo/GDNF (N=18) n (%)	Total (N=35) n (%)
ANTIBACTERIALS FOR SYSTEMIC USE			
TEICOPLANIN	1 (5.9)	1 (5.6)	2 (5.7)
TRIMETHOPRIM	1 (5.9)	2 (11.1)	3 (8.6)
ANTIBIOTICS AND CHEMOTHERAPEUTICS FOR DERMATOLOGICAL USE	7 (41.2)	4 (22.2)	11 (31.4)
ACICLOVIR	1 (5.9)	0	1 (2.9)
ANTIBIOTICS FOR TOPICAL USE	1 (5.9)	0	1 (2.9)
CHLORAMPHENICOL	1 (5.9)	2 (11.1)	3 (8.6)
CLARITHROMYCIN	0	2 (11.1)	2 (5.7)
DOXYCYCLINE	1 (5.9)	0	1 (2.9)
ERYTHROMYCIN	0	1 (5.6)	1 (2.9)
FUSIDIC ACID	2 (11.8)	1 (5.6)	3 (8.6)
GENTAMICIN	1 (5.9)	0	1 (2.9)
METRONIDAZOLE	1 (5.9)	0	1 (2.9)
MUPIROCIN	3 (17.6)	0	3 (8.6)
NASEPTIN	1 (5.9)	0	1 (2.9)
ANTIDIARRHEALS, INTESTINAL ANTIINFLAMMATORY/ANTIINFECTIVE AGENTS	2 (11.8)	3 (16.7)	5 (14.3)
BISMUTH SUBSALICYLATE	0	1 (5.6)	1 (2.9)
HYDROCORTISONE	2 (11.8)	0	2 (5.7)
LOPERAMIDE	0	1 (5.6)	1 (2.9)

Note: Concomitant medications are defined as any medications ongoing at the start of open-label study medication dosing or with a start date on or after the first open-label study medication dose date. Medications are coded using WHO Drug Dictionary Enhanced version 2016Mar01. For each ATC class and preferred name, subjects are included only once.
Source: Listing 17.2.1.5, Dataset: ADCM, Program: t_med.sas, Output: t_16-1-5-2-med.rtf, Generated on: 28JUL2017 05:53
Page 4 of 22

Table 16.1.5.2 Other Concomitant Medications by WHO Drug Dictionary ATC Class and Preferred Name - ITT Primary Population

ATC Class Preferred Name	GDNF/GDNF (N=17) n (%)	Placebo/GDNF (N=18) n (%)	Total (N=35) n (%)
ANTIDIARRHEALS, INTESTINAL ANTIINFLAMMATORY/ANTIINFECTIVE AGENTS			
SULFASALAZINE	0	1 (5.6)	1 (2.9)
ANTIEMETICS AND ANTINAUSEANTS	2 (11.8)	1 (5.6)	3 (8.6)
HYOSCINE	1 (5.9)	0	1 (2.9)
ONDANSETRON	1 (5.9)	1 (5.6)	2 (5.7)
ANTIEPILEPTICS	4 (23.5)	7 (38.9)	11 (31.4)
CLONAZEPAM	0	2 (11.1)	2 (5.7)
DIAZEPAM	3 (17.6)	3 (16.7)	6 (17.1)
GABAPENTIN	1 (5.9)	1 (5.6)	2 (5.7)
LORAZEPAM	1 (5.9)	0	1 (2.9)
PREGABALIN	0	1 (5.6)	1 (2.9)
ANTIFUNGALS FOR DERMATOLOGICAL USE	3 (17.6)	0	3 (8.6)
CLOTRIMAZOLE	1 (5.9)	0	1 (2.9)
DAKTACORT	1 (5.9)	0	1 (2.9)
FLUCONAZOLE	1 (5.9)	0	1 (2.9)
KETOCONAZOLE	2 (11.8)	0	2 (5.7)
ANTIHEMORRHAGICS	0	1 (5.6)	1 (2.9)
TRANEXAMIC ACID	0	1 (5.6)	1 (2.9)

Note: Concomitant medications are defined as any medications ongoing at the start of open-label study medication dosing or with a start date on or after the first open-label study medication dose date. Medications are coded using WHO Drug Dictionary Enhanced version 2016Mar01. For each ATC class and preferred name, subjects are included only once.
Source: Listing 17.2.1.5, Dataset: ADCM, Program: t_med.sas, Output: t_16-1-5-2-med.rtf, Generated on: 28JUL2017 05:53
Page 5 of 22

Table 16.1.5.2 Other Concomitant Medications by WHO Drug Dictionary ATC Class and Preferred Name - ITT Primary Population

ATC Class Preferred Name	GDNF/GDNF (N=17) n (%)	Placebo/GDNF (N=18) n (%)	Total (N=35) n (%)
ANTIHISTAMINES FOR SYSTEMIC USE	3 (17.6)	2 (11.1)	5 (14.3)
CETIRIZINE	1 (5.9)	0	1 (2.9)
CHLORPHENAMINE	1 (5.9)	0	1 (2.9)
CHLORPHENAMINE MALEATE	0	1 (5.6)	1 (2.9)
FEXOFENADINE	1 (5.9)	0	1 (2.9)
LORATADINE	1 (5.9)	1 (5.6)	2 (5.7)
ANTIHYPERTENSIVES	2 (11.8)	2 (11.1)	4 (11.4)
SILDENAFIL	2 (11.8)	0	2 (5.7)
TADALAFIL	0	2 (11.1)	2 (5.7)
ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS	6 (35.3)	9 (50.0)	15 (42.9)
CURCUMA LONGA RHIZOME	0	1 (5.6)	1 (2.9)
DICLOFENAC SODIUM	0	1 (5.6)	1 (2.9)
IBUPROFEN	4 (23.5)	6 (33.3)	10 (28.6)
NAPROXEN	2 (11.8)	1 (5.6)	3 (8.6)
PARECOXIB SODIUM	1 (5.9)	0	1 (2.9)
SULFASALAZINE	0	1 (5.6)	1 (2.9)
ANTIMYCOTICS FOR SYSTEMIC USE	3 (17.6)	0	3 (8.6)
FLUCONAZOLE	1 (5.9)	0	1 (2.9)

Note: Concomitant medications are defined as any medications ongoing at the start of open-label study medication dosing or with a start date on or after the first open-label study medication dose date. Medications are coded using WHO Drug Dictionary Enhanced version 2016Mar01. For each ATC class and preferred name, subjects are included only once.
Source: Listing 17.2.1.5, Dataset: ADCM, Program: t_med.sas, Output: t_16-1-5-2-med.rtf, Generated on: 28JUL2017 05:53
Page 6 of 22

Table 16.1.5.2 Other Concomitant Medications by WHO Drug Dictionary ATC Class and Preferred Name - ITT Primary Population

ATC Class Preferred Name	GDNF/GDNF (N=17) n (%)	Placebo/GDNF (N=18) n (%)	Total (N=35) n (%)
ANTIMYCOTICS FOR SYSTEMIC USE			
KETOCONAZOLE	2 (11.8)	0	2 (5.7)
ANTINEOPLASTIC AGENTS	0	3 (16.7)	3 (8.6)
CLARITHROMYCIN	0	2 (11.1)	2 (5.7)
FLUOROURACIL	0	1 (5.6)	1 (2.9)
ANTIPROTOZOALS	3 (17.6)	0	3 (8.6)
CLOTRIMAZOLE	1 (5.9)	0	1 (2.9)
METRONIDAZOLE	1 (5.9)	0	1 (2.9)
QUININE	1 (5.9)	0	1 (2.9)
ANTIPRURITICS, INCL. ANTIHISTAMINES, ANESTHETICS, ETC.	2 (11.8)	0	2 (5.7)
ANTIHISTAMINES FOR TOPICAL USE	1 (5.9)	0	1 (2.9)
CROTAMITON	1 (5.9)	0	1 (2.9)
ANTISEPTICS AND DISINFECTANTS	2 (11.8)	2 (11.1)	4 (11.4)
POVIDONE-IODINE	2 (11.8)	1 (5.6)	3 (8.6)
PROPANOL	0	1 (5.6)	1 (2.9)
ANTITHROMBOTIC AGENTS	3 (17.6)	2 (11.1)	5 (14.3)
ACETYLSALICYLIC ACID	2 (11.8)	1 (5.6)	3 (8.6)
DALTEPARIN SODIUM	1 (5.9)	0	1 (2.9)
ENOXAPARIN SODIUM	0	1 (5.6)	1 (2.9)

Note: Concomitant medications are defined as any medications ongoing at the start of open-label study medication dosing or with a start date on or after the first open-label study medication dose date. Medications are coded using WHO Drug Dictionary Enhanced version 2016Mar01. For each ATC class and preferred name, subjects are included only once.
Source: Listing 17.2.1.5, Dataset: ADCM, Program: t_med.sas, Output: t_16-1-5-2-med.rtf, Generated on: 28JUL2017 05:53
Page 7 of 22

Table 16.1.5.2 Other Concomitant Medications by WHO Drug Dictionary ATC Class and Preferred Name - ITT Primary Population

ATC Class Preferred Name	GDNF/GDNF (N=17) n (%)	Placebo/GDNF (N=18) n (%)	Total (N=35) n (%)
ANTITHROMBOTIC AGENTS			
RIVAROXABAN	1 (5.9)	0	1 (2.9)
ANTIVIRALS FOR SYSTEMIC USE	1 (5.9)	0	1 (2.9)
ACICLOVIR	1 (5.9)	0	1 (2.9)
BETA BLOCKING AGENTS	1 (5.9)	1 (5.6)	2 (5.7)
BISOPROLOL	1 (5.9)	1 (5.6)	2 (5.7)
BILE AND LIVER THERAPY	0	1 (5.6)	1 (2.9)
CURCUMA LONGA RHIZOME	0	1 (5.6)	1 (2.9)
BLOOD SUBSTITUTES AND PERFUSION SOLUTIONS	1 (5.9)	3 (16.7)	4 (11.4)
FLEBOBAG RING LACT	0	1 (5.6)	1 (2.9)
RINGER-LACTATE	1 (5.9)	0	1 (2.9)
SODIUM CHLORIDE	1 (5.9)	3 (16.7)	4 (11.4)
CALCIUM CHANNEL BLOCKERS	1 (5.9)	1 (5.6)	2 (5.7)
FELODIPINE	0	1 (5.6)	1 (2.9)
LACIDIPINE	1 (5.9)	0	1 (2.9)
CARDIAC THERAPY	6 (35.3)	7 (38.9)	13 (37.1)
AMIODARONE	1 (5.9)	0	1 (2.9)
ATROPINE	0	1 (5.6)	1 (2.9)
DIGOXIN	1 (5.9)	0	1 (2.9)

Note: Concomitant medications are defined as any medications ongoing at the start of open-label study medication dosing or with a start date on or after the first open-label study medication dose date. Medications are coded using WHO Drug Dictionary Enhanced version 2016Mar01. For each ATC class and preferred name, subjects are included only once.
Source: Listing 17.2.1.5, Dataset: ADCM, Program: t_med.sas, Output: t_16-1-5-2-med.rtf, Generated on: 28JUL2017 05:53
Page 8 of 22

Table 16.1.5.2 Other Concomitant Medications by WHO Drug Dictionary ATC Class and Preferred Name - ITT Primary Population

ATC Class Preferred Name	GDNF/GDNF (N=17) n (%)	Placebo/GDNF (N=18) n (%)	Total (N=35) n (%)
CARDIAC THERAPY			
IBUPROFEN	4 (23.5)	6 (33.3)	10 (28.6)
METARAMINOL	0	1 (5.6)	1 (2.9)
NICOTINAMIDE	0	1 (5.6)	1 (2.9)
UBIDECARENONE	1 (5.9)	1 (5.6)	2 (5.7)
CORTICOSTEROIDS FOR SYSTEMIC USE	6 (35.3)	0	6 (17.1)
CORTISONE	1 (5.9)	0	1 (2.9)
DEXAMETHASONE	1 (5.9)	0	1 (2.9)
FLUDROCORTISONE	1 (5.9)	0	1 (2.9)
HYDROCORTISONE	2 (11.8)	0	2 (5.7)
KETOCONAZOLE	2 (11.8)	0	2 (5.7)
CORTICOSTEROIDS, DERMATOLOGICAL PREPARATIONS	5 (29.4)	1 (5.6)	6 (17.1)
DEXAMETHASONE	1 (5.9)	0	1 (2.9)
FLUTICASONE	1 (5.9)	0	1 (2.9)
FUCICORT	1 (5.9)	0	1 (2.9)
FUCIDIN-HYDROCORTISON	1 (5.9)	0	1 (2.9)
HYDROCORTISONE	2 (11.8)	0	2 (5.7)
MOMETASONE FUROATE	2 (11.8)	0	2 (5.7)
OTOMIZE	0	1 (5.6)	1 (2.9)

Note: Concomitant medications are defined as any medications ongoing at the start of open-label study medication dosing or with a start date on or after the first open-label study medication dose date. Medications are coded using WHO Drug Dictionary Enhanced version 2016Mar01. For each ATC class and preferred name, subjects are included only once.
Source: Listing 17.2.1.5, Dataset: ADCM, Program: t_med.sas, Output: t_16-1-5-2-med.rtf, Generated on: 28JUL2017 05:53
Page 9 of 22

Table 16.1.5.2 Other Concomitant Medications by WHO Drug Dictionary ATC Class and Preferred Name - ITT Primary Population

ATC Class Preferred Name	GDNF/GDNF (N=17) n (%)	Placebo/GDNF (N=18) n (%)	Total (N=35) n (%)
COUGH AND COLD PREPARATIONS	1 (5.9)	2 (11.1)	3 (8.6)
CODEINE	0	2 (11.1)	2 (5.7)
CODEINE PHOSPHATE	1 (5.9)	0	1 (2.9)
QUININE	1 (5.9)	0	1 (2.9)
DIURETICS	1 (5.9)	0	1 (2.9)
FUROSEMIDE	1 (5.9)	0	1 (2.9)
DRUGS FOR ACID RELATED DISORDERS	4 (23.5)	3 (16.7)	7 (20.0)
BISMUTH SUBSALICYLATE	0	1 (5.6)	1 (2.9)
CALCIUM CARBONATE	0	1 (5.6)	1 (2.9)
GAVISCON ADVANCE	0	1 (5.6)	1 (2.9)
LANSOPRAZOLE	1 (5.9)	0	1 (2.9)
OMEPRAZOLE	2 (11.8)	1 (5.6)	3 (8.6)
RANITIDINE	1 (5.9)	0	1 (2.9)
RANITIDINE HYDROCHLORIDE	0	1 (5.6)	1 (2.9)
DRUGS FOR CONSTIPATION	6 (35.3)	8 (44.4)	14 (40.0)
BISACODYL	0	2 (11.1)	2 (5.7)
CITRAMAG /01815501/	0	1 (5.6)	1 (2.9)
DOCUSATE	0	1 (5.6)	1 (2.9)

Note: Concomitant medications are defined as any medications ongoing at the start of open-label study medication dosing or with a start date on or after the first open-label study medication dose date. Medications are coded using WHO Drug Dictionary Enhanced version 2016Mar01. For each ATC class and preferred name, subjects are included only once.
Source: Listing 17.2.1.5, Dataset: ADCM, Program: t_med.sas, Output: t_16-1-5-2-med.rtf, Generated on: 28JUL2017 05:53
Page 10 of 22

Table 16.1.5.2 Other Concomitant Medications by WHO Drug Dictionary ATC Class and Preferred Name - ITT Primary Population

ATC Class Preferred Name	GDNF/GDNF (N=17) n (%)	Placebo/GDNF (N=18) n (%)	Total (N=35) n (%)
DRUGS FOR CONSTIPATION			
DOCUSATE SODIUM	0	1 (5.6)	1 (2.9)
ELECTROLYTES NOS W/MACROGOL 3350	1 (5.9)	0	1 (2.9)
MEROKEN NEW	0	1 (5.6)	1 (2.9)
MOVICOL /01749801/	0	1 (5.6)	1 (2.9)
MOVICOL /08437601/	4 (23.5)	2 (11.1)	6 (17.1)
MOVIPREP /06224801/	0	1 (5.6)	1 (2.9)
PICOLAX /06440801/	0	1 (5.6)	1 (2.9)
SENNA ALEXANDRINA	2 (11.8)	3 (16.7)	5 (14.3)
SODIUM CHLORIDE	1 (5.9)	3 (16.7)	4 (11.4)
SODIUM PICOSULFATE	1 (5.9)	0	1 (2.9)
DRUGS FOR FUNCTIONAL GASTROINTESTINAL DISORDERS	4 (23.5)	2 (11.1)	6 (17.1)
ATROPINE	0	1 (5.6)	1 (2.9)
CURCUMA LONGA RHIZOME	0	1 (5.6)	1 (2.9)
DOMPERIDONE	1 (5.9)	0	1 (2.9)
HYOSCINE	1 (5.9)	0	1 (2.9)
MEBEVERINE	0	1 (5.6)	1 (2.9)
TROSPIUM	1 (5.9)	0	1 (2.9)
TROSPIUM CHLORIDE	1 (5.9)	0	1 (2.9)

Note: Concomitant medications are defined as any medications ongoing at the start of open-label study medication dosing or with a start date on or after the first open-label study medication dose date. Medications are coded using WHO Drug Dictionary Enhanced version 2016Mar01. For each ATC class and preferred name, subjects are included only once.
Source: Listing 17.2.1.5, Dataset: ADCM, Program: t_med.sas, Output: t_16-1-5-2-med.rtf, Generated on: 28JUL2017 05:53

Table 16.1.5.2 Other Concomitant Medications by WHO Drug Dictionary ATC Class and Preferred Name - ITT Primary Population

ATC Class Preferred Name	GDNF/GDNF (N=17) n (%)	Placebo/GDNF (N=18) n (%)	Total (N=35) n (%)
DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES	3 (17.6)	0	3 (8.6)
FLUTICASONE	1 (5.9)	0	1 (2.9)
MOMETASONE FUROATE	2 (11.8)	0	2 (5.7)
DRUGS FOR TREATMENT OF BONE DISEASES	0	1 (5.6)	1 (2.9)
ALENDRONIC ACID	0	1 (5.6)	1 (2.9)
ECTOPARASITICIDES, INCL. SCABICIDES, INSECTICIDES AND REPELLENTS	2 (11.8)	3 (16.7)	5 (14.3)
CROTAMITON	1 (5.9)	0	1 (2.9)
SODIUM CHLORIDE	1 (5.9)	3 (16.7)	4 (11.4)
EMOLLIENTS AND PROTECTIVES	1 (5.9)	0	1 (2.9)
AVENA SATIVA FLUID EXTRACT	1 (5.9)	0	1 (2.9)
DERMOL /01330701/	1 (5.9)	0	1 (2.9)
ENDOCRINE THERAPY	0	1 (5.6)	1 (2.9)
ESTRADIOL	0	1 (5.6)	1 (2.9)
GENERAL NUTRIENTS	2 (11.8)	1 (5.6)	3 (8.6)
CAFFEINE W/CARBOHYDRATES NOS/CHOLIN/08302001/	0	1 (5.6)	1 (2.9)
CARBOHYDRATES NOS W/FATS NOS/MINERA/07459701/	1 (5.9)	0	1 (2.9)
FISH OIL	1 (5.9)	0	1 (2.9)

Note: Concomitant medications are defined as any medications ongoing at the start of open-label study medication dosing or with a start date on or after the first open-label study medication dose date. Medications are coded using WHO Drug Dictionary Enhanced version 2016Mar01. For each ATC class and preferred name, subjects are included only once.
Source: Listing 17.2.1.5, Dataset: ADCM, Program: t_med.sas, Output: t_16-1-5-2-med.rtf, Generated on: 28JUL2017 05:53
Page 12 of 22

Table 16.1.5.2 Other Concomitant Medications by WHO Drug Dictionary ATC Class and Preferred Name - ITT Primary Population

ATC Class Preferred Name	GDNF/GDNF (N=17) n (%)	Placebo/GDNF (N=18) n (%)	Total (N=35) n (%)
GYNECOLOGICAL ANTIINFECTIVES AND ANTISEPTICS	6 (35.3)	3 (16.7)	9 (25.7)
ASCORBIC ACID	1 (5.9)	0	1 (2.9)
CHLORAMPHENICOL	1 (5.9)	2 (11.1)	3 (8.6)
CLOTRIMAZOLE	1 (5.9)	0	1 (2.9)
FLUCONAZOLE	1 (5.9)	0	1 (2.9)
KETOCONAZOLE	2 (11.8)	0	2 (5.7)
METRONIDAZOLE	1 (5.9)	0	1 (2.9)
POVIDONE-IODINE	2 (11.8)	1 (5.6)	3 (8.6)
HOMEOPATHIC PREPARATION	3 (17.6)	1 (5.6)	4 (11.4)
ASCORBIC ACID	1 (5.9)	0	1 (2.9)
CORTISONE	1 (5.9)	0	1 (2.9)
GINKGO BILOBA	0	1 (5.6)	1 (2.9)
UBIDECARENONE	1 (5.9)	1 (5.6)	2 (5.7)
LIPID MODIFYING AGENTS	4 (23.5)	4 (22.2)	8 (22.9)
ATORVASTATIN	2 (11.8)	2 (11.1)	4 (11.4)
FISH OIL	1 (5.9)	0	1 (2.9)
ROSUVASTATIN	1 (5.9)	0	1 (2.9)
SIMVASTATIN	0	2 (11.1)	2 (5.7)

Note: Concomitant medications are defined as any medications ongoing at the start of open-label study medication dosing or with a start date on or after the first open-label study medication dose date. Medications are coded using WHO Drug Dictionary Enhanced version 2016Mar01. For each ATC class and preferred name, subjects are included only once.
Source: Listing 17.2.1.5, Dataset: ADCM, Program: t_med.sas, Output: t_16-1-5-2-med.rtf, Generated on: 28JUL2017 05:53
Page 13 of 22

Table 16.1.5.2 Other Concomitant Medications by WHO Drug Dictionary ATC Class and Preferred Name - ITT Primary Population

ATC Class Preferred Name	GDNF/GDNF (N=17) n (%)	Placebo/GDNF (N=18) n (%)	Total (N=35) n (%)
MEDICATED DRESSINGS	5 (29.4)	4 (22.2)	9 (25.7)
FUSIDIC ACID	2 (11.8)	1 (5.6)	3 (8.6)
POVIDONE-IODINE	2 (11.8)	1 (5.6)	3 (8.6)
SODIUM CHLORIDE	1 (5.9)	3 (16.7)	4 (11.4)
MINERAL SUPPLEMENTS	1 (5.9)	4 (22.2)	5 (14.3)
CALCIUM CARBONATE	0	1 (5.6)	1 (2.9)
CALTRO	1 (5.9)	0	1 (2.9)
LEKOVIT CA	0	2 (11.1)	2 (5.7)
SODIUM CHLORIDE	1 (5.9)	3 (16.7)	4 (11.4)
MUSCLE RELAXANTS	1 (5.9)	0	1 (2.9)
BACLOFEN	1 (5.9)	0	1 (2.9)
BOTULINUM TOXIN TYPE A	1 (5.9)	0	1 (2.9)
NASAL PREPARATIONS	6 (35.3)	4 (22.2)	10 (28.6)
DEXAMETHASONE	1 (5.9)	0	1 (2.9)
DUONASE /06209401/	1 (5.9)	0	1 (2.9)
FLUTICASONE	1 (5.9)	0	1 (2.9)
HYALURONATE SODIUM	1 (5.9)	0	1 (2.9)
MOMETASONE FUROATE	2 (11.8)	0	2 (5.7)

Note: Concomitant medications are defined as any medications ongoing at the start of open-label study medication dosing or with a start date on or after the first open-label study medication dose date. Medications are coded using WHO Drug Dictionary Enhanced version 2016Mar01. For each ATC class and preferred name, subjects are included only once.
Source: Listing 17.2.1.5, Dataset: ADCM, Program: t_med.sas, Output: t_16-1-5-2-med.rtf, Generated on: 28JUL2017 05:53

Table 16.1.5.2 Other Concomitant Medications by WHO Drug Dictionary ATC Class and Preferred Name - ITT Primary Population

ATC Class Preferred Name	GDNF/GDNF (N=17) n (%)	Placebo/GDNF (N=18) n (%)	Total (N=35) n (%)
NASAL PREPARATIONS			
MUPIROCIN	3 (17.6)	0	3 (8.6)
PSEUDOEPHEDRINE	0	1 (5.6)	1 (2.9)
RETINOL	1 (5.9)	0	1 (2.9)
SODIUM CHLORIDE	1 (5.9)	3 (16.7)	4 (11.4)
OPHTHALMOLOGICAL AND OTOLOGICAL PREPARATIONS	2 (11.8)	3 (16.7)	5 (14.3)
CHLORAMPHENICOL	1 (5.9)	2 (11.1)	3 (8.6)
DEXAMETHASONE	1 (5.9)	0	1 (2.9)
GENTAMICIN	1 (5.9)	0	1 (2.9)
OTOMIZE	0	1 (5.6)	1 (2.9)
OPHTHALMOLOGICALS	8 (47.1)	8 (44.4)	16 (45.7)
ACICLOVIR	1 (5.9)	0	1 (2.9)
ASCORBIC ACID	1 (5.9)	0	1 (2.9)
ATROPINE	0	1 (5.6)	1 (2.9)
CARBOMER	1 (5.9)	1 (5.6)	2 (5.7)
CEFUROXIME	0	1 (5.6)	1 (2.9)
CHLORAMPHENICOL	1 (5.9)	2 (11.1)	3 (8.6)
CLOTRIMAZOLE	1 (5.9)	0	1 (2.9)
CORTISONE	1 (5.9)	0	1 (2.9)

Note: Concomitant medications are defined as any medications ongoing at the start of open-label study medication dosing or with a start date on or after the first open-label study medication dose date. Medications are coded using WHO Drug Dictionary Enhanced version 2016Mar01. For each ATC class and preferred name, subjects are included only once.
Source: Listing 17.2.1.5, Dataset: ADCM, Program: t_med.sas, Output: t_16-1-5-2-med.rtf, Generated on: 28JUL2017 05:53
Page 15 of 22

Table 16.1.5.2 Other Concomitant Medications by WHO Drug Dictionary ATC Class and Preferred Name - ITT Primary Population

ATC Class Preferred Name	GDNF/GDNF (N=17) n (%)	Placebo/GDNF (N=18) n (%)	Total (N=35) n (%)
OPHTHALMOLOGICALS			
DEXAMETHASONE	1 (5.9)	0	1 (2.9)
DICLOFENAC SODIUM	0	1 (5.6)	1 (2.9)
ERYTHROMYCIN	0	1 (5.6)	1 (2.9)
FLUCONAZOLE	1 (5.9)	0	1 (2.9)
FUSIDIC ACID	2 (11.8)	1 (5.6)	3 (8.6)
GENTAMICIN	1 (5.9)	0	1 (2.9)
HYALURONATE SODIUM	1 (5.9)	0	1 (2.9)
HYDROCORTISONE	2 (11.8)	0	2 (5.7)
HYOSCINE	1 (5.9)	0	1 (2.9)
NAPROXEN	2 (11.8)	1 (5.6)	3 (8.6)
OTOMIZE	0	1 (5.6)	1 (2.9)
POVIDONE-IODINE	2 (11.8)	1 (5.6)	3 (8.6)
RETINOL	1 (5.9)	0	1 (2.9)
OTHER ALIMENTARY TRACT AND METABOLISM PRODUCTS	2 (11.8)	1 (5.6)	3 (8.6)
CARBOHYDRATES NOS W/FATS NOS/MINERA/07459701/	1 (5.9)	0	1 (2.9)
UBIDECARENONE	1 (5.9)	1 (5.6)	2 (5.7)
OTHER DERMATOLOGICAL PREPARATIONS	7 (41.2)	3 (16.7)	10 (28.6)
ASCORBIC ACID	1 (5.9)	0	1 (2.9)

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Source: Listing 17.2.1.5, Dataset: ADCM, Program: t_med.sas, Output: t_16-1-5-2-med.rtf, Generated on: 28JUL2017 05:53
Page 16 of 22

Table 16.1.5.2 Other Concomitant Medications by WHO Drug Dictionary ATC Class and Preferred Name - ITT Primary Population

ATC Class Preferred Name	GDNF/GDNF (N=17) n (%)	Placebo/GDNF (N=18) n (%)	Total (N=35) n (%)
OTHER DERMATOLOGICAL PREPARATIONS			
DICLOFENAC SODIUM	0	1 (5.6)	1 (2.9)
ESTRADIOL	0	1 (5.6)	1 (2.9)
HYALURONATE SODIUM	1 (5.9)	0	1 (2.9)
POVIDONE-IODINE	2 (11.8)	1 (5.6)	3 (8.6)
SILDENAFIL	2 (11.8)	0	2 (5.7)
UBIDECARENONE	1 (5.9)	1 (5.6)	2 (5.7)
OTHER DRUGS FOR DISORDERS OF THE MUSCULO-SKELETAL SYSTEM	2 (11.8)	0	2 (5.7)
HYALURONATE SODIUM	1 (5.9)	0	1 (2.9)
QUININE	1 (5.9)	0	1 (2.9)
OTHER GYNECOLOGICALS	6 (35.3)	7 (38.9)	13 (37.1)
CARBOMER	1 (5.9)	1 (5.6)	2 (5.7)
IBUPROFEN	4 (23.5)	6 (33.3)	10 (28.6)
NAPROXEN	2 (11.8)	1 (5.6)	3 (8.6)
OTHER NERVOUS SYSTEM DRUGS	0	1 (5.6)	1 (2.9)
GINKGO BILOBA	0	1 (5.6)	1 (2.9)
OTOLOGICALS	4 (23.5)	4 (22.2)	8 (22.9)
CHLORAMPHENICOL	1 (5.9)	2 (11.1)	3 (8.6)
CLOTRIMAZOLE	1 (5.9)	0	1 (2.9)

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Source: Listing 17.2.1.5, Dataset: ADCM, Program: t_med.sas, Output: t_16-1-5-2-med.rtf, Generated on: 28JUL2017 05:53
Page 17 of 22

Table 16.1.5.2 Other Concomitant Medications by WHO Drug Dictionary ATC Class and Preferred Name - ITT Primary Population

ATC Class Preferred Name	GDNF/GDNF (N=17) n (%)	Placebo/GDNF (N=18) n (%)	Total (N=35) n (%)
OTOLOGICALS			
DEXAMETHASONE	1 (5.9)	0	1 (2.9)
DOCUSATE	0	1 (5.6)	1 (2.9)
DOCUSATE SODIUM	0	1 (5.6)	1 (2.9)
GENTAMICIN	1 (5.9)	0	1 (2.9)
HYDROCORTISONE	2 (11.8)	0	2 (5.7)
OTOMIZE	0	1 (5.6)	1 (2.9)
PERIPHERAL VASODILATORS	0	1 (5.6)	1 (2.9)
GINKGO BILOBA	0	1 (5.6)	1 (2.9)
PREPARATIONS FOR TREATMENT OF WOUNDS AND ULCERS	4 (23.5)	3 (16.7)	7 (20.0)
COD-LIVER OIL	2 (11.8)	1 (5.6)	3 (8.6)
HYALURONATE SODIUM	1 (5.9)	0	1 (2.9)
SODIUM CHLORIDE	1 (5.9)	3 (16.7)	4 (11.4)
PSYCHOANALEPTICS	5 (29.4)	4 (22.2)	9 (25.7)
AMITRIPTYLINE	0	1 (5.6)	1 (2.9)
CITALOPRAM	1 (5.9)	2 (11.1)	3 (8.6)
GINKGO BILOBA	0	1 (5.6)	1 (2.9)
MIRTAZAPINE	1 (5.9)	0	1 (2.9)
NORTRIPTYLINE	0	1 (5.6)	1 (2.9)

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Source: Listing 17.2.1.5, Dataset: ADCM, Program: t_med.sas, Output: t_16-1-5-2-med.rtf, Generated on: 28JUL2017 05:53
Page 18 of 22

Table 16.1.5.2 Other Concomitant Medications by WHO Drug Dictionary ATC Class and Preferred Name - ITT Primary Population

ATC Class Preferred Name	GDNF/GDNF (N=17) n (%)	Placebo/GDNF (N=18) n (%)	Total (N=35) n (%)
PSYCHOANALEPTICS			
PAROXETINE	1 (5.9)	0	1 (2.9)
RIVASTIGMINE	1 (5.9)	0	1 (2.9)
SERTRALINE	1 (5.9)	0	1 (2.9)
PSYCHOLEPTICS	6 (35.3)	9 (50.0)	15 (42.9)
CLONAZEPAM	0	2 (11.1)	2 (5.7)
DIAZEPAM	3 (17.6)	3 (16.7)	6 (17.1)
HYOSCINE	1 (5.9)	0	1 (2.9)
LORAZEPAM	1 (5.9)	0	1 (2.9)
MELATONIN	2 (11.8)	5 (27.8)	7 (20.0)
MIDAZOLAM	0	1 (5.6)	1 (2.9)
PREGABALIN	0	1 (5.6)	1 (2.9)
QUETIAPINE	1 (5.9)	0	1 (2.9)
ZOPICLONE	2 (11.8)	2 (11.1)	4 (11.4)
SEX HORMONES AND MODULATORS OF THE GENITAL SYSTEM	0	2 (11.1)	2 (5.7)
ESTRADIOL	0	1 (5.6)	1 (2.9)
TESTOSTERONE UNDECANOATE	0	1 (5.6)	1 (2.9)
STOMATOLOGICAL PREPARATIONS	8 (47.1)	7 (38.9)	15 (42.9)
ACETYLSALICYLIC ACID	2 (11.8)	1 (5.6)	3 (8.6)

Note: Concomitant medications are defined as any medications ongoing at the start of open-label study medication dosing or with a start date on or after the first open-label study medication dose date. Medications are coded using WHO Drug Dictionary Enhanced version 2016Mar01. For each ATC class and preferred name, subjects are included only once.
Source: Listing 17.2.1.5, Dataset: ADCM, Program: t_med.sas, Output: t_16-1-5-2-med.rtf, Generated on: 28JUL2017 05:53
Page 19 of 22

Table 16.1.5.2 Other Concomitant Medications by WHO Drug Dictionary ATC Class and Preferred Name - ITT Primary Population

ATC Class Preferred Name	GDNF/GDNF (N=17) n (%)	Placebo/GDNF (N=18) n (%)	Total (N=35) n (%)
STOMATOLOGICAL PREPARATIONS			
CARBOMER	1 (5.9)	1 (5.6)	2 (5.7)
CHLORAMPHENICOL	1 (5.9)	2 (11.1)	3 (8.6)
CLOTRIMAZOLE	1 (5.9)	0	1 (2.9)
DEXAMETHASONE	1 (5.9)	0	1 (2.9)
DOXYCYCLINE	1 (5.9)	0	1 (2.9)
HYALURONATE SODIUM	1 (5.9)	0	1 (2.9)
HYDROCORTISONE	2 (11.8)	0	2 (5.7)
METRONIDAZOLE	1 (5.9)	0	1 (2.9)
NAPROXEN	2 (11.8)	1 (5.6)	3 (8.6)
POVIDONE-IODINE	2 (11.8)	1 (5.6)	3 (8.6)
SODIUM CHLORIDE	1 (5.9)	3 (16.7)	4 (11.4)
TRANEXAMIC ACID	0	1 (5.6)	1 (2.9)
THROAT PREPARATIONS	6 (35.3)	7 (38.9)	13 (37.1)
IBUPROFEN	4 (23.5)	6 (33.3)	10 (28.6)
POVIDONE-IODINE	2 (11.8)	1 (5.6)	3 (8.6)
THYROID THERAPY	3 (17.6)	0	3 (8.6)
LEVOTHYROXINE	3 (17.6)	0	3 (8.6)

Note: Concomitant medications are defined as any medications ongoing at the start of open-label study medication dosing or with a start date on or after the first open-label study medication dose date. Medications are coded using WHO Drug Dictionary Enhanced version 2016Mar01. For each ATC class and preferred name, subjects are included only once.
Source: Listing 17.2.1.5, Dataset: ADCM, Program: t_med.sas, Output: t_16-1-5-2-med.rtf, Generated on: 28JUL2017 05:53
Page 20 of 22

Table 16.1.5.2 Other Concomitant Medications by WHO Drug Dictionary ATC Class and Preferred Name - ITT Primary Population

ATC Class Preferred Name	GDNF/GDNF (N=17) n (%)	Placebo/GDNF (N=18) n (%)	Total (N=35) n (%)
TONICS	0	1 (5.6)	1 (2.9)
CURCUMA LONGA RHIZOME	0	1 (5.6)	1 (2.9)
TOPICAL PRODUCTS FOR JOINT AND MUSCULAR PAIN	7 (41.2)	8 (44.4)	15 (42.9)
ACETYLSALICYLIC ACID	2 (11.8)	1 (5.6)	3 (8.6)
DICLOFENAC SODIUM	0	1 (5.6)	1 (2.9)
IBUPROFEN	4 (23.5)	6 (33.3)	10 (28.6)
NAPROXEN	2 (11.8)	1 (5.6)	3 (8.6)
UNSPECIFIED HERBAL AND TRADITIONAL MEDICINE	3 (17.6)	4 (22.2)	7 (20.0)
AVENA SATIVA FLUID EXTRACT	1 (5.9)	0	1 (2.9)
CURCUMA LONGA RHIZOME	0	1 (5.6)	1 (2.9)
GINKGO BILOBA	0	1 (5.6)	1 (2.9)
SENNA ALEXANDRINA	2 (11.8)	3 (16.7)	5 (14.3)
UROLOGICALS	7 (41.2)	3 (16.7)	10 (28.6)
HYALURONATE SODIUM	1 (5.9)	0	1 (2.9)
MIRABEGRON	1 (5.9)	0	1 (2.9)
SILDENAFIL	2 (11.8)	0	2 (5.7)
SOLIFENACIN	1 (5.9)	0	1 (2.9)
TADALAFIL	0	2 (11.1)	2 (5.7)

Note: Concomitant medications are defined as any medications ongoing at the start of open-label study medication dosing or with a start date on or after the first open-label study medication dose date. Medications are coded using WHO Drug Dictionary Enhanced version 2016Mar01. For each ATC class and preferred name, subjects are included only once.
Source: Listing 17.2.1.5, Dataset: ADCM, Program: t_med.sas, Output: t_16-1-5-2-med.rtf, Generated on: 28JUL2017 05:53

Table 16.1.5.2 Other Concomitant Medications by WHO Drug Dictionary ATC Class and Preferred Name - ITT Primary Population

ATC Class Preferred Name	GDNF/GDNF (N=17) n (%)	Placebo/GDNF (N=18) n (%)	Total (N=35) n (%)
UROLOGICALS			
TAMSULOSIN	0	1 (5.6)	1 (2.9)
TROSPIUM	1 (5.9)	0	1 (2.9)
TROSPIUM CHLORIDE	1 (5.9)	0	1 (2.9)
VACCINES	1 (5.9)	4 (22.2)	5 (14.3)
DITEMER	0	1 (5.6)	1 (2.9)
INFLUENZA VACCINE	1 (5.9)	3 (16.7)	4 (11.4)
TYPHOID VACCINE	0	1 (5.6)	1 (2.9)
YELLOW FEVER VACCINE	0	1 (5.6)	1 (2.9)
VASOPROTECTIVES	3 (17.6)	0	3 (8.6)
DEXAMETHASONE	1 (5.9)	0	1 (2.9)
HYDROCORTISONE	2 (11.8)	0	2 (5.7)
VITAMINS	4 (23.5)	3 (16.7)	7 (20.0)
ASCORBIC ACID	1 (5.9)	0	1 (2.9)
COD-LIVER OIL	2 (11.8)	1 (5.6)	3 (8.6)
COLECALCIFEROL	0	2 (11.1)	2 (5.7)
MULTIVITAMINS	2 (11.8)	0	2 (5.7)
NICOTINAMIDE	0	1 (5.6)	1 (2.9)
RETINOL	1 (5.9)	0	1 (2.9)

Note: Concomitant medications are defined as any medications ongoing at the start of open-label study medication dosing or with a start date on or after the first open-label study medication dose date. Medications are coded using WHO Drug Dictionary Enhanced version 2016Mar01. For each ATC class and preferred name, subjects are included only once.
Source: Listing 17.2.1.5, Dataset: ADCM, Program: t_med.sas, Output: t_16-1-5-2-med.rtf, Generated on: 28JUL2017 05:53
Page 22 of 22

Table 16.2.1.1 OFF State UPDRS Motor Score (Part III): Change and Percentage Change from Baseline to Week 80/e40 – MMRM, ITT Primary Population

Visit Statistic	GDNF/GDNF (N=17)			Placebo/GDNF (N=18)		
	Value	Change From Baseline	Percentage Change From Baseline	Value	Change From Baseline	Percentage Change From Baseline
Week 0 (Baseline)						
n	17			18		
Mean (SD)	35.3 (9.38)			32.2 (8.73)		
Median	35.0			33.0		
Min, Max	19, 53			16, 45		
Week 40/e0						
n	17	17	17	18	18	18
Mean (SD)	29.1 (10.29)	-6.2 (7.05)	-17.3 (17.60)	28.8 (9.75)	-3.4 (4.27)	-11.8 (15.76)
Median	27.0	-6.0	-21.1	30.5	-5.0	-13.8
Min, Max	15, 58	-16, 11	-41, 23	11, 44	-9, 6	-43, 21
Week 80/e40						
n	17	17	17	18	18	18
Mean (SD)	27.1 (7.46)	-8.2 (6.45)	-21.7 (17.11)	23.3 (9.34)	-8.8 (8.13)	-27.0 (24.57)
Median	28.0	-9.0	-23.1	23.5	-8.0	-27.0
Min, Max	15, 39	-20, 3	-50, 13	8, 39	-24, 8	-67, 29
Least squares mean[a] (95% CI)		-7.8 (-11.2, -4.5)	-21.3 (-31.8, -10.9)		-9.2 (-12.4, -6.0)	-27.4 (-37.5, -17.2)
Least squares mean difference versus placebo[a] (95% CI)		1.4 (-3.3, 6.0)	6.0 (-8.6, 20.7)			
p-value[a]		0.5564	0.4078			

[a] Estimates are from a mixed-effect model with repeated measures (MMRM) with baseline UPDRS score as a covariate, treatment group and visit and treatment group*visit as fixed effects, and subject within treatment group as a random effect.

Note: Lower scores represent better functioning. End of study visit data are included in the appropriate visit week. For subject 45, items 22, 27, 28, 29 and 30 are excluded from the score.

Source: Listing 17.2.2.1, Dataset: ADQUPDRS, Program: t_updrs_mmrm.sas, Output: t_16-2-1-1-updrs.rtf, Generated on: 28JUL2017 05:54

Page 1 of 1

Table 16.2.1.2 OFF State UPDRS Motor Score (Part III): Change and Percentage Change from Baseline to Week 80/e40 – MMRM, ITT Overall Population

Visit Statistic	GDNF/GDNF (N=21)			Placebo/GDNF (N=20)		
	Value	Change From Baseline	Percentage Change From Baseline	Value	Change From Baseline	Percentage Change From Baseline
Week 0 (Baseline)						
n	21			20		
Mean (SD)	36.0 (11.73)			32.2 (8.29)		
Median	34.0			33.0		
Min, Max	19, 70			16, 45		
Week 40/e0						
n	21	21	21	20	20	20
Mean (SD)	28.8 (12.53)	-7.1 (6.83)	-20.5 (18.60)	28.5 (9.29)	-3.8 (4.20)	-12.7 (15.21)
Median	27.0	-8.0	-21.1	28.5	-5.0	-14.1
Min, Max	14, 60	-16, 11	-53, 23	11, 44	-9, 6	-43, 21
Week 80/e40						
n	21	21	21	20	20	20
Mean (SD)	26.4 (11.33)	-9.6 (6.70)	-26.7 (20.67)	23.2 (8.99)	-9.0 (7.75)	-27.6 (23.55)
Median	26.0	-10.0	-23.3	23.5	-8.0	-27.0
Min, Max	9, 58	-21, 3	-70, 13	8, 39	-24, 8	-67, 29
Least squares mean[a] (95% CI)		-9.3 (-12.4, -6.3)	-27.0 (-36.8, -17.1)		-9.3 (-12.4, -6.2)	-27.3 (-37.5, -17.2)
Least squares mean difference versus placebo[a] (95% CI)		-0.0 (-4.4, 4.4)	0.4 (-13.9, 14.6)			
p-value[a]		0.9929	0.9587			

[a] Estimates are from a mixed-effect model with repeated measures (MMRM) with baseline UPDRS score as a covariate, treatment group and visit and treatment group*visit as fixed effects, and subject within treatment group as a random effect.

Note: Lower scores represent better functioning. End of study visit data are included in the appropriate visit week. For subject 45, items 22, 27, 28, 29 and 30 are excluded from the score.

Source: Listing 17.2.2.1, Dataset: ADQUPDRS, Program: t_updrs_mmrm.sas, Output: t_16-2-1-2-updrs.rtf, Generated on: 28JUL2017 05:54

Page 1 of 1

Table 16.2.2.1 ON State UPDRS Motor Score (Part III): Change and Percentage Change from Baseline to Week 80/e40 – MMRM, ITT Overall Population

Visit Statistic	GDNF/GDNF (N=21)			Placebo/GDNF (N=20)		
	Value	Change From Baseline	Percentage Change From Baseline	Value	Change From Baseline	Percentage Change From Baseline
Week 0 (Baseline)						
n	21			20		
Mean (SD)	16.3 (5.58)			16.3 (7.18)		
Median	17.0			14.5		
Min, Max	7, 27			6, 34		
Week 40/e0						
n	21	21	21	20	20	20
Mean (SD)	15.0 (6.84)	-1.4 (5.29)	-8.2 (32.36)	17.2 (8.20)	0.9 (3.30)	6.1 (22.26)
Median	15.0	-2.0	-13.6	16.0	0.5	2.3
Min, Max	4, 32	-12, 15	-56, 88	5, 39	-6, 6	-29, 42
Week 80/e40						
n	21	21	21	19	19	19
Mean (SD)	15.0 (5.97)	-1.4 (4.77)	-7.0 (32.30)	14.8 (6.01)	-1.6 (4.07)	-5.1 (22.71)
Median	15.0	-2.0	-11.8	14.0	-1.0	-4.8
Min, Max	3, 25	-10, 8	-70, 64	6, 26	-9, 6	-43, 43
Least squares mean[a] (95% CI)		-1.4 (-3.3, 0.5)	-7.0 (-19.4, 5.4)		-1.2 (-3.2, 0.7)	-3.2 (-16.2, 9.7)
Least squares mean difference versus placebo[a] (95% CI)		-0.2 (-2.9, 2.6)	-3.7 (-21.7, 14.2)			
p-value[a]		0.9101	0.6743			

[a] Estimates are from a mixed-effect model with repeated measures (MMRM) with baseline UPDRS score as a covariate, treatment group and visit and treatment group*visit as fixed effects, and subject within treatment group as a random effect.

Note: Lower scores represent better functioning. End of study visit data are included in the appropriate visit week. For subject 45, items 22, 27, 28, 29 and 30 are excluded from the score.

Source: Listing 17.2.2.1, Dataset: ADQUPDRS, Program: t_updrs_mmrm.sas, Output: t_16-2-2-1-updrs.rtf, Generated on: 28JUL2017 05:54

Page 1 of 1

Table 16.2.2.2.1 OFF State UPDRS ADL Score (Part II): Change and Percentage Change from Baseline to Week 80/e40 – MMRM, ITT Primary Population

Visit Statistic	GDNF/GDNF (N=17)			Placebo/GDNF (N=18)		
	Value	Change From Baseline	Percentage Change From Baseline	Value	Change From Baseline	Percentage Change From Baseline
Week 0 (Baseline)						
n	16			18		
Mean (SD)	18.4 (6.27)			16.9 (6.10)		
Median	18.5			17.5		
Min, Max	6, 28			8, 27		
Week 40/e0						
n	16	16	16	18	18	18
Mean (SD)	16.0 (7.02)	-2.4 (5.35)	-12.2 (26.92)	16.2 (5.45)	-0.7 (3.83)	-1.0 (26.63)
Median	16.0	-3.0	-17.9	16.0	-0.5	-1.9
Min, Max	4, 32	-13, 6	-59, 35	4, 26	-8, 5	-50, 50
Week 80/e40						
n	16	16	16	18	18	18
Mean (SD)	11.4 (4.95)	-6.9 (5.92)	-34.6 (24.35)	11.9 (6.77)	-5.0 (4.75)	-30.5 (26.27)
Median	12.0	-5.5	-25.9	11.5	-4.5	-28.6
Min, Max	3, 20	-19, 0	-86, 0	3, 29	-15, 2	-70, 15
Least squares mean[a] (95% CI)		-6.7 (-9.1, -4.2)	-33.6 (-46.7, -20.5)		-5.2 (-7.5, -2.9)	-31.3 (-43.7, -18.9)
Least squares mean difference versus placebo[a] (95% CI)		-1.4 (-4.8, 1.9)	-2.3 (-20.4, 15.8)			
p-value[a]		0.3892	0.7966			

[a] Estimates are from a mixed-effect model with repeated measures (MMRM) with baseline UPDRS score as a covariate, treatment group and visit and treatment group*visit as fixed effects, and subject within treatment group as a random effect.

Note: Lower scores represent better functioning. End of study visit data are included in the appropriate visit week. Data for subject 45 are excluded from analysis.

Source: Listing 17.2.2.1, Dataset: ADQUPDRS, Program: t_updrs_mmrm.sas, Output: t_16-2-2-2-1-updrs.rtf, Generated on: 28JUL2017 05:54

Page 1 of 1

Table 16.2.2.2.2 OFF State UPDRS ADL Score (Part II): Change and Percentage Change from Baseline to Week 80/e40 – MMRM, ITT Overall Population

Visit Statistic	GDNF/GDNF (N=21)			Placebo/GDNF (N=20)		
	Value	Change From Baseline	Percentage Change From Baseline	Value	Change From Baseline	Percentage Change From Baseline
Week 0 (Baseline)						
n	20			20		
Mean (SD)	18.5 (6.38)			16.9 (5.82)		
Median	18.0			17.5		
Min, Max	6, 30			8, 27		
Week 40/e0						
n	20	20	20	20	20	20
Mean (SD)	15.8 (7.32)	-2.7 (5.04)	-14.6 (25.94)	15.9 (5.34)	-1.0 (3.71)	-2.9 (26.00)
Median	14.5	-3.0	-17.9	16.0	-1.0	-4.8
Min, Max	4, 32	-13, 6	-59, 35	4, 26	-8, 5	-50, 50
Week 80/e40						
n	20	20	20	20	20	20
Mean (SD)	11.7 (4.89)	-6.9 (5.46)	-34.3 (22.34)	12.3 (6.60)	-4.6 (4.71)	-28.2 (26.17)
Median	12.0	-5.5	-31.3	11.5	-3.5	-22.6
Min, Max	3, 20	-19, 0	-86, 0	3, 29	-15, 2	-70, 15
Least squares mean[a] (95% CI)		-6.6 (-8.6, -4.5)	-33.5 (-44.6, -22.3)		-4.9 (-6.9, -2.8)	-29.1 (-40.2, -17.9)
Least squares mean difference versus placebo[a] (95% CI)		-1.7 (-4.6, 1.2)	-4.4 (-20.2, 11.4)			
p-value[a]		0.2455	0.5746			

[a] Estimates are from a mixed-effect model with repeated measures (MMRM) with baseline UPDRS score as a covariate, treatment group and visit and treatment group*visit as fixed effects, and subject within treatment group as a random effect.

Note: Lower scores represent better functioning. End of study visit data are included in the appropriate visit week. Data for subject 45 are excluded from analysis.

Source: Listing 17.2.2.1, Dataset: ADQUPDRS, Program: t_updrs_mmrm.sas, Output: t_16-2-2-2-2-updrs.rtf, Generated on: 28JUL2017 05:54
Page 1 of 1

Table 16.2.2.3 ON State UPDRS ADL Score (Part II): Change and Percentage Change from Baseline to Week 80/e40 – MMRM, ITT Overall Population

Visit Statistic	GDNF/GDNF (N=21)			Placebo/GDNF (N=20)		
	Value	Change From Baseline	Percentage Change From Baseline	Value	Change From Baseline	Percentage Change From Baseline
Week 0 (Baseline)						
n	20			20		
Mean (SD)	5.5 (4.07)			5.7 (3.67)		
Median	4.0			5.5		
Min, Max	1, 14			0, 15		
Week 40/e0						
n	20	20	20	20	20	19
Mean (SD)	5.4 (4.27)	-0.1 (3.49)	13.1 (109.56)	5.5 (4.14)	-0.2 (3.44)	-9.8 (53.14)
Median	5.0	0.0	0.0	5.5	-0.5	-6.7
Min, Max	0, 14	-6, 11	-100, 367	0, 15	-6, 9	-100, 150
Week 80/e40						
n	20	20	20	20	20	19
Mean (SD)	2.9 (3.02)	-2.6 (4.21)	-33.9 (62.58)	3.9 (3.21)	-1.8 (3.51)	-32.3 (51.98)
Median	2.0	-2.0	-39.7	4.0	-1.0	-33.3
Min, Max	0, 10	-12, 6	-100, 150	0, 13	-10, 7	-100, 117
Least squares mean[a] (95% CI)		-2.6 (-4.1, -1.1)	-34.5 (-60.3, -8.7)		-1.7 (-3.3, -0.2)	-31.3 (-57.6, -5.0)
Least squares mean difference versus placebo[a] (95% CI)		-0.8 (-3.0, 1.3)	-3.2 (-40.0, 33.7)			
p-value[a]		0.4279	0.8628			

[a] Estimates are from a mixed-effect model with repeated measures (MMRM) with baseline UPDRS score as a covariate, treatment group and visit and treatment group*visit as fixed effects, and subject within treatment group as a random effect.
Note: Lower scores represent better functioning. End of study visit data are included in the appropriate visit week. Data for subject 45 are excluded from analysis.
Source: Listing 17.2.2.1, Dataset: ADQUPDRS, Program: t_updrs_mmrm.sas, Output: t_16-2-2-3-updrs.rtf, Generated on: 28JUL2017 05:54
Page 1 of 1

Table 16.2.2.4.1 OFF State UPDRS Total Score: Change and Percentage Change from Baseline to Week 80/e40 – MMRM, ITT Primary Population

Visit Statistic	GDNF/GDNF (N=17)			Placebo/GDNF (N=18)		
	Value	Change From Baseline	Percentage Change From Baseline	Value	Change From Baseline	Percentage Change From Baseline
Week 0 (Baseline)						
n	16			18		
Mean (SD)	54.3 (13.80)			49.1 (11.57)		
Median	54.5			53.0		
Min, Max	25, 77			30, 66		
Week 40/e0						
n	16	16	16	18	18	18
Mean (SD)	45.9 (15.26)	-8.4 (10.32)	-15.2 (16.54)	45.0 (12.93)	-4.1 (5.19)	-9.2 (10.28)
Median	45.0	-8.5	-16.5	48.0	-4.0	-9.6
Min, Max	19, 90	-25, 15	-41, 20	26, 66	-12, 5	-26, 9
Week 80/e40						
n	16	16	16	18	18	18
Mean (SD)	38.4 (10.98)	-15.8 (9.14)	-28.4 (13.60)	35.3 (13.77)	-13.8 (10.51)	-28.8 (20.81)
Median	37.5	-13.5	-23.1	34.0	-14.5	-28.6
Min, Max	20, 54	-33, -4	-53, -7	13, 65	-32, 10	-60, 18
Least squares mean[a] (95% CI)		-15.3 (-20.0, -10.5)	-28.0 (-37.1, -18.8)		-14.3 (-18.8, -9.9)	-29.2 (-37.8, -20.5)
Least squares mean difference versus placebo[a] (95% CI)		-0.9 (-7.4, 5.6)	1.2 (-11.5, 13.8)			
p-value[a]		0.7746	0.8497			

[a] Estimates are from a mixed-effect model with repeated measures (MMRM) with baseline UPDRS score as a covariate, treatment group and visit and treatment group*visit as fixed effects, and subject within treatment group as a random effect.
Note: Lower scores represent better functioning. End of study visit data are included in the appropriate visit week. Data for subject 45 are excluded from analysis.
Source: Listing 17.2.2.1, Dataset: ADQUPDRS, Program: t_updrs_mmrm.sas, Output: t_16-2-2-4-1-updrs.rtf, Generated on: 28JUL2017 05:55
Page 1 of 1

Table 16.2.2.4.2 OFF State UPDRS Total Score: Change and Percentage Change from Baseline to Week 80/e40 – MMRM, ITT Overall Population

Visit Statistic	GDNF/GDNF (N=21)			Placebo/GDNF (N=20)		
	Value	Change From Baseline	Percentage Change From Baseline	Value	Change From Baseline	Percentage Change From Baseline
Week 0 (Baseline)						
n	20			20		
Mean (SD)	55.0 (16.70)			49.1 (10.95)		
Median	52.0			52.5		
Min, Max	25, 100			30, 66		
Week 40/e0						
n	20	20	20	20	20	20
Mean (SD)	45.2 (18.38)	-9.8 (9.82)	-18.4 (17.19)	44.4 (12.40)	-4.7 (5.27)	-10.3 (10.42)
Median	44.5	-10.5	-18.5	45.0	-4.5	-11.1
Min, Max	19, 90	-25, 15	-47, 20	26, 66	-12, 5	-26, 9
Week 80/e40						
n	20	20	20	20	20	20
Mean (SD)	37.9 (14.89)	-17.1 (8.64)	-31.3 (14.77)	35.5 (13.04)	-13.6 (9.97)	-28.3 (19.75)
Median	34.0	-16.0	-26.4	35.0	-12.5	-25.4
Min, Max	20, 78	-33, -4	-55, -7	13, 65	-32, 10	-60, 18
Least squares mean[a] (95% CI)		-16.6 (-20.7, -12.6)	-31.4 (-39.4, -23.5)		-14.0 (-18.1, -10.0)	-28.1 (-36.1, -20.2)
Least squares mean difference versus placebo[a] (95% CI)		-2.6 (-8.3, 3.2)	-3.3 (-14.6, 8.0)			
p-value[a]		0.3689	0.5571			

[a] Estimates are from a mixed-effect model with repeated measures (MMRM) with baseline UPDRS score as a covariate, treatment group and visit and treatment group*visit as fixed effects, and subject within treatment group as a random effect.

Note: Lower scores represent better functioning. End of study visit data are included in the appropriate visit week. Data for subject 45 are excluded from analysis.

Source: Listing 17.2.2.1, Dataset: ADQUPDRS, Program: t_updrs_mmrm.sas, Output: t_16-2-2-4-2-updrs.rtf, Generated on: 28JUL2017 05:55
Page 1 of 1

Table 16.2.2.5 ON State UPDRS Total Score: Change and Percentage Change from Baseline to Week 80/e40 – MMRM, ITT Overall Population

Visit Statistic	GDNF/GDNF (N=21)			Placebo/GDNF (N=20)		
	Value	Change From Baseline	Percentage Change From Baseline	Value	Change From Baseline	Percentage Change From Baseline
Week 0 (Baseline)						
n	20			20		
Mean (SD)	21.8 (8.35)			22.0 (8.53)		
Median	20.5			23.0		
Min, Max	8, 35			8, 49		
Week 40/e0						
n	20	20	20	20	20	20
Mean (SD)	20.3 (10.18)	-1.5 (7.92)	-6.1 (40.16)	22.6 (10.49)	0.7 (4.64)	2.4 (21.25)
Median	20.0	-2.5	-12.3	20.5	0.5	2.2
Min, Max	4, 46	-15, 26	-64, 130	10, 53	-9, 10	-39, 43
Week 80/e40						
n	20	20	20	19	19	19
Mean (SD)	17.4 (7.63)	-4.4 (6.88)	-17.5 (31.87)	18.6 (6.43)	-3.3 (6.09)	-11.3 (23.11)
Median	17.5	-3.0	-15.0	18.0	-3.0	-12.5
Min, Max	3, 32	-18, 8	-75, 62	7, 30	-19, 6	-55, 40
Least squares mean[a] (95% CI)		-4.4 (-7.0, -1.8)	-17.6 (-30.1, -5.1)		-2.9 (-5.5, -0.2)	-9.7 (-22.3, 3.0)
Least squares mean difference versus placebo[a] (95% CI)		-1.6 (-5.3, 2.2)	-7.9 (-25.7, 9.9)			
p-value[a]		0.4005	0.3730			

[a] Estimates are from a mixed-effect model with repeated measures (MMRM) with baseline UPDRS score as a covariate, treatment group and visit and treatment group*visit as fixed effects, and subject within treatment group as a random effect.
Note: Lower scores represent better functioning. End of study visit data are included in the appropriate visit week. Data for subject 45 are excluded from analysis.
Source: Listing 17.2.2.1, Dataset: ADQUPDRS, Program: t_updrs_mmrm.sas, Output: t_16-2-2-5-updrs.rtf, Generated on: 28JUL2017 05:55
Page 1 of 1

Table 16.2.2.6.1 OFF State UPDRS Motor Score (Part III): Change from Baseline to Week 40/e0 for GDNF/GDNF Group Compared to Change from Baseline to Week 80/e40 for Placebo/GDNF Group – MMRM, ITT Overall Population

Visit Statistic	GDNF/GDNF (N=21)		Placebo/GDNF (N=20)	
	Value	Change From Baseline	Value	Change From Baseline
Week 0 (Baseline)				
n	21		20	
Mean (SD)	36.0 (11.73)		32.2 (8.29)	
Median	34.0		33.0	
Min, Max	19, 70		16, 45	
Week 40/e0				
n	21	21		
Mean (SD)	28.8 (12.53)	-7.1 (6.83)		
Median	27.0	-8.0		
Min, Max	14, 60	-16, 11		
Week 80/e40				
n			20	20
Mean (SD)			23.2 (8.99)	-9.0 (7.75)
Median			23.5	-8.0
Min, Max			8, 39	-24, 8
Least squares mean[a] (95% CI)		-6.9 (-9.5, -4.3)		-9.3 (-12.4, -6.2)
Least squares mean difference versus placebo[a] (95% CI)		2.4 (-1.6, 6.4)		
p-value[a]		0.2368		

[a] Estimates are from a mixed-effect model with repeated measures (MMRM) with baseline UPDRS score as a covariate, treatment group and visit and treatment group*visit as fixed effects, and subject within treatment group as a random effect.
Note: Lower scores represent better functioning. End of study visit data are included in the appropriate visit week. For subject 45, items 22, 27, 28, 29 and 30 are excluded from the score.
Source: Listing 17.2.2.1, Dataset: ADQUPDRS, Program: t_updrs_comp.sas, Output: t_16-2-2-6-1-updrs.rtf, Generated on: 28JUL2017 05:55
Page 1 of 1

Table 16.2.2.6.2 OFF State UPDRS ADL Score (Part II): Change from Baseline to Week 40/e0 for GDNF/GDNF Group Compared to Change from Baseline to Week 80/e40 for Placebo/GDNF Group – MMRM, ITT Overall Population

Visit Statistic	GDNF/GDNF (N=21)		Placebo/GDNF (N=20)	
	Value	Change From Baseline	Value	Change From Baseline
Week 0 (Baseline)				
n	20		20	
Mean (SD)	18.5 (6.38)		16.9 (5.82)	
Median	18.0		17.5	
Min, Max	6, 30		8, 27	
Week 40/e0				
n	20	20		
Mean (SD)	15.8 (7.32)	-2.7 (5.04)		
Median	14.5	-3.0		
Min, Max	4, 32	-13, 6		
Week 80/e40				
n			20	20
Mean (SD)			12.3 (6.60)	-4.6 (4.71)
Median			11.5	-3.5
Min, Max			3, 29	-15, 2
Least squares mean[a] (95% CI)		-2.4 (-4.4, -0.5)		-4.9 (-6.9, -2.8)
Least squares mean difference versus placebo[a] (95% CI)		2.5 (-0.3, 5.3)		
p-value[a]		0.0852		

[a] Estimates are from a mixed-effect model with repeated measures (MMRM) with baseline UPDRS score as a covariate, treatment group and visit and treatment group*visit as fixed effects, and subject within treatment group as a random effect.
Note: Lower scores represent better functioning. End of study visit data are included in the appropriate visit week. Data for subject 45 are excluded from analysis.
Source: Listing 17.2.2.1, Dataset: ADQUPDRS, Program: t_updrs_comp.sas, Output: t_16-2-2-6-2-updrs.rtf, Generated on: 28JUL2017 05:55
Page 1 of 1

Table 16.2.2.6.3 OFF State UPDRS Total Score: Change from Baseline to Week 40/e0 for GDNF/GDNF Group Compared to Change from Baseline to Week 80/e40 for Placebo/GDNF Group – MMRM, ITT Overall Population

Visit Statistic	GDNF/GDNF (N=21)		Placebo/GDNF (N=20)	
	Value	Change From Baseline	Value	Change From Baseline
Week 0 (Baseline)				
n	20		20	
Mean (SD)	55.0 (16.70)		49.1 (10.95)	
Median	52.0		52.5	
Min, Max	25, 100		30, 66	
Week 40/e0				
n	20	20		
Mean (SD)	45.2 (18.38)	-9.8 (9.82)		
Median	44.5	-10.5		
Min, Max	19, 90	-25, 15		
Week 80/e40				
n			20	20
Mean (SD)			35.5 (13.04)	-13.6 (9.97)
Median			35.0	-12.5
Min, Max			13, 65	-32, 10
Least squares mean[a] (95% CI)		-9.3 (-13.0, -5.6)		-14.0 (-18.1, -10.0)
Least squares mean difference versus placebo[a] (95% CI)		4.7 (-0.7, 10.1)		
p-value[a]		0.0867		

[a] Estimates are from a mixed-effect model with repeated measures (MMRM) with baseline UPDRS score as a covariate, treatment group and visit and treatment group*visit as fixed effects, and subject within treatment group as a random effect.
Note: Lower scores represent better functioning. End of study visit data are included in the appropriate visit week. Data for subject 45 are excluded from analysis.
Source: Listing 17.2.2.1, Dataset: ADQUPDRS, Program: t_updrs_comp.sas, Output: t_16-2-2-6-3-updrs.rtf, Generated on: 28JUL2017 05:55
Page 1 of 1

Table 16.2.2.7.1 OFF State UPDRS Motor Score (Part III): Change from Baseline to Week 80/e40 for GDNF/GDNF Group Compared to Change from Baseline to Week 40/e0 for Placebo/GDNF Group – MMRM, ITT Overall Population

Visit Statistic	GDNF/GDNF (N=21)		Placebo/GDNF (N=20)	
	Value	Change From Baseline	Value	Change From Baseline
Week 0 (Baseline)				
n	21		20	
Mean (SD)	36.0 (11.73)		32.2 (8.29)	
Median	34.0		33.0	
Min, Max	19, 70		16, 45	
Week 40/e0				
n			20	20
Mean (SD)			28.5 (9.29)	-3.8 (4.20)
Median			28.5	-5.0
Min, Max			11, 44	-9, 6
Week 80/e40				
n	21	21		
Mean (SD)	26.4 (11.33)	-9.6 (6.70)		
Median	26.0	-10.0		
Min, Max	9, 58	-21, 3		
Least squares mean[a] (95% CI)		-9.3 (-12.4, -6.3)		-4.0 (-6.7, -1.4)
Least squares mean difference versus placebo[a] (95% CI)		-5.3 (-9.3, -1.3)		
p-value[a]		0.0108		

[a] Estimates are from a mixed-effect model with repeated measures (MMRM) with baseline UPDRS score as a covariate, treatment group and visit and treatment group*visit as fixed effects, and subject within treatment group as a random effect.
Note: Lower scores represent better functioning. End of study visit data are included in the appropriate visit week. For subject 45, items 22, 27, 28, 29 and 30 are excluded from the score.
Source: Listing 17.2.2.1, Dataset: ADQUPDRS, Program: t_updrs_comp.sas, Output: t_16-2-2-7-1-updrs.rtf, Generated on: 28JUL2017 05:55
Page 1 of 1

Table 16.2.2.7.2 OFF State UPDRS ADL Score (Part II): Change from Baseline to Week 80/e40 for GDNF/GDNF Group Compared to Change from Baseline to Week 40/e0 for Placebo/GDNF Group – MMRM, ITT Overall Population

Visit Statistic	GDNF/GDNF (N=21)		Placebo/GDNF (N=20)	
	Value	Change From Baseline	Value	Change From Baseline
Week 0 (Baseline)				
n	20		20	
Mean (SD)	18.5 (6.38)		16.9 (5.82)	
Median	18.0		17.5	
Min, Max	6, 30		8, 27	
Week 40/e0				
n			20	20
Mean (SD)			15.9 (5.34)	-1.0 (3.71)
Median			16.0	-1.0
Min, Max			4, 26	-8, 5
Week 80/e40				
n	20	20		
Mean (SD)	11.7 (4.89)	-6.9 (5.46)		
Median	12.0	-5.5		
Min, Max	3, 20	-19, 0		
Least squares mean[a] (95% CI)		-6.6 (-8.6, -4.5)		-1.2 (-3.2, 0.7)
Least squares mean difference versus placebo[a] (95% CI)		-5.3 (-8.1, -2.5)		
p-value[a]		0.0003		

[a] Estimates are from a mixed-effect model with repeated measures (MMRM) with baseline UPDRS score as a covariate, treatment group and visit and treatment group*visit as fixed effects, and subject within treatment group as a random effect.
Note: Lower scores represent better functioning. End of study visit data are included in the appropriate visit week. Data for subject 45 are excluded from analysis.
Source: Listing 17.2.2.1, Dataset: ADQUPDRS, Program: t_updrs_comp.sas, Output: t_16-2-2-7-2-updrs.rtf, Generated on: 28JUL2017 05:55
Page 1 of 1

Table 16.2.2.7.3 OFF State UPDRS Total Score: Change from Baseline to Week 80/e40 for GDNF/GDNF Group Compared to Change from Baseline to Week 40/e0 for Placebo/GDNF Group – MMRM, ITT Overall Population

Visit Statistic	GDNF/GDNF (N=21)		Placebo/GDNF (N=20)	
	Value	Change From Baseline	Value	Change From Baseline
Week 0 (Baseline)				
n	20		20	
Mean (SD)	55.0 (16.70)		49.1 (10.95)	
Median	52.0		52.5	
Min, Max	25, 100		30, 66	
Week 40/e0				
n			20	20
Mean (SD)			44.4 (12.40)	-4.7 (5.27)
Median			45.0	-4.5
Min, Max			26, 66	-12, 5
Week 80/e40				
n	20	20		
Mean (SD)	37.9 (14.89)	-17.1 (8.64)		
Median	34.0	-16.0		
Min, Max	20, 78	-33, -4		
Least squares mean[a] (95% CI)		-16.6 (-20.7, -12.6)		-5.1 (-8.8, -1.5)
Least squares mean difference versus placebo[a] (95% CI)		-11.5 (-16.9, -6.1)		
p-value[a]		<0.0001		

[a] Estimates are from a mixed-effect model with repeated measures (MMRM) with baseline UPDRS score as a covariate, treatment group and visit and treatment group*visit as fixed effects, and subject within treatment group as a random effect.
Note: Lower scores represent better functioning. End of study visit data are included in the appropriate visit week. Data for subject 45 are excluded from analysis.
Source: Listing 17.2.2.1, Dataset: ADQUPDRS, Program: t_updrs_comp.sas, Output: t_16-2-2-7-3-updrs.rtf, Generated on: 28JUL2017 05:55
Page 1 of 1

Table 16.2.3.1 Motor Fluctuation Diary Ratings by Visit: Change from Baseline – MMRM, ITT Primary Population

Parameter Visit Statistic	GDNF/GDNF (N=17)		Placebo/GDNF (N=18)	
	Value	Change From Baseline	Value	Change From Baseline
OFF Time Per Day (hours)				
Week 0 (Baseline)				
n	17		18	
Mean (SD)	6.11 (1.819)		4.76 (2.284)	
Median	5.67		4.25	
Min, Max	3.2, 9.7		1.2, 10.0	
Week 40/e0				
n	15	15	17	17
Mean (SD)	5.11 (2.398)	-1.01 (1.902)	5.04 (2.457)	0.42 (2.052)
Median	4.75	-1.17	5.33	1.00
Min, Max	2.0, 10.2	-4.8, 2.7	0.8, 9.8	-3.3, 3.8
Week 80/e40				
n	16	16	18	18
Mean (SD)	4.53 (1.888)	-1.46 (1.101)	3.88 (2.161)	-0.88 (2.838)
Median	4.33	-1.42	4.25	-0.75
Min, Max	1.3, 7.8	-3.0, 0.5	0.5, 9.3	-6.2, 4.3
Least squares mean[a] (95% CI)		-1.194 (-2.156, -0.231)		-1.130 (-2.050, -0.210)
Least squares mean difference versus placebo[a] (95% CI)		-0.064 (-1.420, 1.292)		
p-value[a]		0.9243		

[a] Estimates are from a mixed-effect model with repeated measures (MMRM) with baseline variable as a covariate, treatment group and visit and treatment group*visit as fixed effects, and subject within treatment group as a random effect.
Note: End of study visit data are included in the appropriate visit week.
Note: Total good-quality ON time per day is defined as the sum of ON time per day without dyskinesias + ON time per day with non-troublesome dyskinesias.
Source: Listing 17.2.2.2, Dataset: ADDIA, Program: t_pddiary.sas, Output: t_16-2-3-1-pddiary.rtf, Generated on: 28JUL2017 05:56
Page 1 of 5

Table 16.2.3.1 Motor Fluctuation Diary Ratings by Visit: Change from Baseline – MMRM, ITT Primary Population

Parameter Visit Statistic	GDNF/GDNF (N=17)		Placebo/GDNF (N=18)	
	Value	Change From Baseline	Value	Change From Baseline
Good-quality ON Time Per Day (hours)				
Week 0 (Baseline)				
n	17		18	
Mean (SD)	10.33 (2.112)		12.50 (2.683)	
Median	10.67		12.42	
Min, Max	5.8, 13.2		5.7, 16.0	
Week 40/e0				
n	15	15	17	17
Mean (SD)	11.41 (3.312)	1.30 (1.886)	12.09 (2.643)	-0.43 (1.858)
Median	12.67	1.33	12.00	-0.67
Min, Max	2.3, 16.3	-3.4, 5.0	6.0, 16.5	-4.3, 2.7
Week 80/e40				
n	16	16	18	18
Mean (SD)	12.00 (2.282)	1.70 (1.630)	13.15 (3.201)	0.65 (3.086)
Median	11.67	1.42	12.58	1.17
Min, Max	8.7, 16.3	-1.0, 5.9	8.3, 19.7	-5.3, 5.8
Least squares mean[a] (95% CI)		1.427 (0.227, 2.627)		0.959 (-0.196, 2.114)
Least squares mean difference versus placebo[a] (95% CI)		0.468 (-1.240, 2.176)		
p-value[a]		0.5818		

[a] Estimates are from a mixed-effect model with repeated measures (MMRM) with baseline variable as a covariate, treatment group and visit and treatment group*visit as fixed effects, and subject within treatment group as a random effect.
Note: End of study visit data are included in the appropriate visit week.
Note: Total good-quality ON time per day is defined as the sum of ON time per day without dyskinesias + ON time per day with non-troublesome dyskinesias.
Source: Listing 17.2.2.2, Dataset: ADDIA, Program: t_pddiary.sas, Output: t_16-2-3-1-pddiary.rtf, Generated on: 28JUL2017 05:56
Page 2 of 5

Table 16.2.3.1 Motor Fluctuation Diary Ratings by Visit: Change from Baseline – MMRM, ITT Primary Population

Parameter Visit Statistic	GDNF/GDNF (N=17)		Placebo/GDNF (N=18)	
	Value	Change From Baseline	Value	Change From Baseline
ON Time Per Day Without Dyskinesias (hours)				
Week 0 (Baseline)				
n	17		18	
Mean (SD)	9.18 (2.810)		10.23 (2.903)	
Median	9.00		11.25	
Min, Max	3.5, 12.5		5.0, 15.7	
Week 40/e0				
n	15	15	17	17
Mean (SD)	10.08 (3.297)	1.15 (2.231)	10.41 (3.490)	0.27 (2.824)
Median	10.33	0.67	11.17	0.33
Min, Max	2.3, 16.3	-2.7, 5.3	3.5, 16.0	-4.7, 6.2
Week 80/e40				
n	16	16	18	18
Mean (SD)	11.00 (3.347)	1.84 (2.837)	11.36 (3.905)	1.13 (3.679)
Median	11.58	2.08	11.00	1.58
Min, Max	0.8, 15.7	-3.7, 6.7	6.2, 18.2	-5.5, 8.3
Least squares mean[a] (95% CI)		1.704 (0.133, 3.276)		1.359 (-0.156, 2.874)
Least squares mean difference versus placebo[a] (95% CI)		0.345 (-1.848, 2.538)		
p-value[a]		0.7508		

[a] Estimates are from a mixed-effect model with repeated measures (MMRM) with baseline variable as a covariate, treatment group and visit and treatment group*visit as fixed effects, and subject within treatment group as a random effect.
Note: End of study visit data are included in the appropriate visit week.
Note: Total good-quality ON time per day is defined as the sum of ON time per day without dyskinesias + ON time per day with non-troublesome dyskinesias.
Source: Listing 17.2.2.2, Dataset: ADDIA, Program: t_pddiary.sas, Output: t_16-2-3-1-pddiary.rtf, Generated on: 28JUL2017 05:56
Page 3 of 5

Table 16.2.3.1 Motor Fluctuation Diary Ratings by Visit: Change from Baseline – MMRM, ITT Primary Population

Parameter Visit Statistic	GDNF/GDNF (N=17)		Placebo/GDNF (N=18)	
	Value	Change From Baseline	Value	Change From Baseline
ON Time Per Day With Non-troublesome Dyskinesias (hours)				
Week 0 (Baseline)				
n	17		18	
Mean (SD)	1.15 (1.481)		2.27 (2.748)	
Median	0.67		1.17	
Min, Max	0.0, 4.8		0.0, 10.0	
Week 40/e0				
n	15	15	17	17
Mean (SD)	1.32 (2.138)	0.15 (2.012)	1.69 (2.113)	-0.70 (2.563)
Median	0.00	0.00	0.50	0.00
Min, Max	0.0, 7.3	-4.8, 3.7	0.0, 6.8	-8.5, 3.2
Week 80/e40				
n	16	16	18	18
Mean (SD)	1.00 (1.976)	-0.14 (1.960)	1.79 (1.767)	-0.48 (2.498)
Median	0.00	0.00	1.75	-0.17
Min, Max	0.0, 7.8	-4.8, 4.2	0.0, 6.0	-6.3, 2.8
Least squares mean[a] (95% CI)		-0.503 (-1.366, 0.361)		-0.158 (-0.984, 0.667)
Least squares mean difference versus placebo[a] (95% CI)		-0.344 (-1.549, 0.861)		
p-value[a]		0.5653		

[a] Estimates are from a mixed-effect model with repeated measures (MMRM) with baseline variable as a covariate, treatment group and visit and treatment group*visit as fixed effects, and subject within treatment group as a random effect.
Note: End of study visit data are included in the appropriate visit week.
Note: Total good-quality ON time per day is defined as the sum of ON time per day without dyskinesias + ON time per day with non-troublesome dyskinesias.
Source: Listing 17.2.2.2, Dataset: ADDIA, Program: t_pddiary.sas, Output: t_16-2-3-1-pddiary.rtf, Generated on: 28JUL2017 05:56
Page 4 of 5

Table 16.2.3.1 Motor Fluctuation Diary Ratings by Visit: Change from Baseline – MMRM, ITT Primary Population

Parameter Visit Statistic	GDNF/GDNF (N=17)		Placebo/GDNF (N=18)	
	Value	Change From Baseline	Value	Change From Baseline
ON Time Per Day With Troublesome Dyskinesias (hours)				
Week 0 (Baseline)				
n	17		18	
Mean (SD)	0.48 (1.065)		0.50 (0.998)	
Median	0.00		0.00	
Min, Max	0.0, 3.0		0.0, 3.5	
Week 40/e0				
n	15	15	17	17
Mean (SD)	0.42 (1.324)	-0.12 (1.190)	0.42 (1.143)	-0.11 (0.549)
Median	0.00	0.00	0.00	0.00
Min, Max	0.0, 5.2	-3.0, 2.4	0.0, 4.7	-1.5, 1.2
Week 80/e40				
n	16	16	18	18
Mean (SD)	0.33 (1.095)	-0.17 (0.809)	0.39 (0.769)	-0.11 (1.223)
Median	0.00	0.00	0.00	0.00
Min, Max	0.0, 4.3	-2.3, 1.3	0.0, 3.0	-2.5, 3.0
Least squares mean[a] (95% CI)		-0.151 (-0.589, 0.287)		-0.117 (-0.530, 0.297)
Least squares mean difference versus placebo[a] (95% CI)		-0.034 (-0.636, 0.568)		
p-value[a]		0.9113		

[a] Estimates are from a mixed-effect model with repeated measures (MMRM) with baseline variable as a covariate, treatment group and visit and treatment group*visit as fixed effects, and subject within treatment group as a random effect.
Note: End of study visit data are included in the appropriate visit week.
Note: Total good-quality ON time per day is defined as the sum of ON time per day without dyskinesias + ON time per day with non-troublesome dyskinesias.
Source: Listing 17.2.2.2, Dataset: ADDIA, Program: t_pddiary.sas, Output: t_16-2-3-1-pddiary.rtf, Generated on: 28JUL2017 05:56
Page 5 of 5

Table 16.2.3.2 Motor Fluctuation Diary Ratings by Visit: Change from Baseline – MMRM, ITT Overall Population

Parameter Visit Statistic	GDNF/GDNF (N=21)		Placebo/GDNF (N=20)	
	Value	Change From Baseline	Value	Change From Baseline
OFF Time Per Day (hours)				
Week 0 (Baseline)				
n	21		19	
Mean (SD)	6.11 (1.689)		4.83 (2.243)	
Median	5.83		4.50	
Min, Max	3.2, 9.7		1.2, 10.0	
Week 40/e0				
n	18	18	19	18
Mean (SD)	5.04 (2.194)	-0.99 (1.736)	5.02 (2.546)	0.50 (2.018)
Median	4.54	-1.08	5.33	1.00
Min, Max	2.0, 10.2	-4.8, 2.7	0.8, 9.8	-3.3, 3.8
Week 80/e40				
n	20	20	20	19
Mean (SD)	4.54 (1.770)	-1.47 (1.388)	3.97 (2.124)	-0.82 (2.768)
Median	4.42	-1.33	4.25	-0.67
Min, Max	1.3, 7.8	-5.0, 0.5	0.5, 9.3	-6.2, 4.3
Least squares mean[a] (95% CI)		-1.236 (-2.084, -0.389)		-1.077 (-1.959, -0.196)
Least squares mean difference versus placebo[a] (95% CI)		-0.159 (-1.403, 1.085)		
p-value[a]		0.7975		

[a] Estimates are from a mixed-effect model with repeated measures (MMRM) with baseline variable as a covariate, treatment group and visit and treatment group*visit as fixed effects, and subject within treatment group as a random effect.
Note: End of study visit data are included in the appropriate visit week.
Note: Total good-quality ON time per day is defined as the sum of ON time per day without dyskinesias + ON time per day with non-troublesome dyskinesias.
Source: Listing 17.2.2.2, Dataset: ADDIA, Program: t_pddiary.sas, Output: t_16-2-3-2-pddiary.rtf, Generated on: 28JUL2017 05:56
Page 1 of 5

Table 16.2.3.2 Motor Fluctuation Diary Ratings by Visit: Change from Baseline – MMRM, ITT Overall Population

Parameter Visit Statistic	GDNF/GDNF (N=21)		Placebo/GDNF (N=20)	
	Value	Change From Baseline	Value	Change From Baseline
Good-quality ON Time Per Day (hours)				
Week 0 (Baseline)				
n	21		19	
Mean (SD)	10.19 (1.996)		12.48 (2.609)	
Median	10.50		12.17	
Min, Max	5.8, 13.2		5.7, 16.0	
Week 40/e0				
n	18	18	19	18
Mean (SD)	11.20 (3.094)	1.18 (1.739)	12.20 (2.591)	-0.46 (1.808)
Median	11.58	0.92	12.00	-0.79
Min, Max	2.3, 16.3	-3.4, 5.0	6.0, 16.5	-4.3, 2.7
Week 80/e40				
n	20	20	20	19
Mean (SD)	11.80 (2.202)	1.64 (1.487)	13.09 (3.085)	0.54 (3.034)
Median	11.58	1.42	12.58	0.83
Min, Max	8.3, 16.3	-1.0, 5.9	8.3, 19.7	-5.3, 5.8
Least squares mean[a] (95% CI)		1.409 (0.381, 2.438)		0.838 (-0.239, 1.916)
Least squares mean difference versus placebo[a] (95% CI)		0.571 (-0.965, 2.107)		
p-value[a]		0.4573		

[a] Estimates are from a mixed-effect model with repeated measures (MMRM) with baseline variable as a covariate, treatment group and visit and treatment group*visit as fixed effects, and subject within treatment group as a random effect.
Note: End of study visit data are included in the appropriate visit week.
Note: Total good-quality ON time per day is defined as the sum of ON time per day without dyskinesias + ON time per day with non-troublesome dyskinesias.
Source: Listing 17.2.2.2, Dataset: ADDIA, Program: t_pddiary.sas, Output: t_16-2-3-2-pddiary.rtf, Generated on: 28JUL2017 05:56
Page 2 of 5

Table 16.2.3.2 Motor Fluctuation Diary Ratings by Visit: Change from Baseline – MMRM, ITT Overall Population

Parameter Visit Statistic	GDNF/GDNF (N=21)		Placebo/GDNF (N=20)	
	Value	Change From Baseline	Value	Change From Baseline
ON Time Per Day Without Dyskinesias (hours)				
Week 0 (Baseline)				
n	21		19	
Mean (SD)	8.86 (2.894)		10.33 (2.856)	
Median	9.00		11.33	
Min, Max	3.3, 12.5		5.0, 15.7	
Week 40/e0				
n	18	18	19	18
Mean (SD)	9.58 (3.465)	1.00 (2.157)	10.64 (3.394)	0.20 (2.756)
Median	9.67	0.67	11.17	0.33
Min, Max	2.3, 16.3	-2.7, 5.3	3.5, 16.0	-4.7, 6.2
Week 80/e40				
n	20	20	20	19
Mean (SD)	10.59 (3.299)	1.77 (2.733)	11.43 (3.719)	1.00 (3.620)
Median	11.25	1.92	11.08	1.17
Min, Max	0.8, 15.7	-3.7, 6.7	6.2, 18.2	-5.5, 8.3
Least squares mean[a] (95% CI)		1.588 (0.232, 2.945)		1.306 (-0.112, 2.725)
Least squares mean difference versus placebo[a] (95% CI)		0.282 (-1.698, 2.262)		
p-value[a]		0.7749		

[a] Estimates are from a mixed-effect model with repeated measures (MMRM) with baseline variable as a covariate, treatment group and visit and treatment group*visit as fixed effects, and subject within treatment group as a random effect.
Note: End of study visit data are included in the appropriate visit week.
Note: Total good-quality ON time per day is defined as the sum of ON time per day without dyskinesias + ON time per day with non-troublesome dyskinesias.
Source: Listing 17.2.2.2, Dataset: ADDIA, Program: t_pddiary.sas, Output: t_16-2-3-2-pddiary.rtf, Generated on: 28JUL2017 05:56
Page 3 of 5

Table 16.2.3.2 Motor Fluctuation Diary Ratings by Visit: Change from Baseline – MMRM, ITT Overall Population

Parameter Visit Statistic	GDNF/GDNF (N=21)		Placebo/GDNF (N=20)	
	Value	Change From Baseline	Value	Change From Baseline
ON Time Per Day With Non-troublesome Dyskinesias (hours)				
Week 0 (Baseline)				
n	21		19	
Mean (SD)	1.34 (1.677)		2.15 (2.721)	
Median	0.67		0.67	
Min, Max	0.0, 4.8		0.0, 10.0	
Week 40/e0				
n	18	18	19	18
Mean (SD)	1.62 (2.205)	0.17 (1.932)	1.56 (2.034)	-0.66 (2.491)
Median	0.58	0.00	0.50	0.00
Min, Max	0.0, 7.3	-4.8, 3.7	0.0, 6.8	-8.5, 3.2
Week 80/e40				
n	20	20	20	19
Mean (SD)	1.21 (1.896)	-0.13 (2.143)	1.67 (1.723)	-0.46 (2.430)
Median	0.67	0.00	1.42	0.00
Min, Max	0.0, 7.8	-4.8, 4.2	0.0, 6.0	-6.3, 2.8
Least squares mean[a] (95% CI)		-0.375 (-1.148, 0.398)		-0.229 (-1.030, 0.573)
Least squares mean difference versus placebo[a] (95% CI)		-0.146 (-1.264, 0.972)		
p-value[a]		0.7926		

[a] Estimates are from a mixed-effect model with repeated measures (MMRM) with baseline variable as a covariate, treatment group and visit and treatment group*visit as fixed effects, and subject within treatment group as a random effect.
Note: End of study visit data are included in the appropriate visit week.
Note: Total good-quality ON time per day is defined as the sum of ON time per day without dyskinesias + ON time per day with non-troublesome dyskinesias.
Source: Listing 17.2.2.2, Dataset: ADDIA, Program: t_pddiary.sas, Output: t_16-2-3-2-pddiary.rtf, Generated on: 28JUL2017 05:56
Page 4 of 5

Table 16.2.3.2 Motor Fluctuation Diary Ratings by Visit: Change from Baseline – MMRM, ITT Overall Population

Parameter Visit Statistic	GDNF/GDNF (N=21)		Placebo/GDNF (N=20)	
	Value	Change From Baseline	Value	Change From Baseline
ON Time Per Day With Troublesome Dyskinesias (hours)				
Week 0 (Baseline)				
n	21		19	
Mean (SD)	0.56 (1.202)		0.47 (0.977)	
Median	0.00		0.00	
Min, Max	0.0, 3.7		0.0, 3.5	
Week 40/e0				
n	18	18	19	18
Mean (SD)	0.48 (1.252)	-0.17 (1.166)	0.38 (1.086)	-0.10 (0.534)
Median	0.00	0.00	0.00	0.00
Min, Max	0.0, 5.2	-3.0, 2.4	0.0, 4.7	-1.5, 1.2
Week 80/e40				
n	20	20	20	19
Mean (SD)	0.36 (1.041)	-0.23 (0.814)	0.35 (0.737)	-0.11 (1.189)
Median	0.00	0.00	0.00	0.00
Min, Max	0.0, 4.3	-2.3, 1.3	0.0, 3.0	-2.5, 3.0
Least squares mean[a] (95% CI)		-0.199 (-0.561, 0.164)		-0.133 (-0.506, 0.240)
Least squares mean difference versus placebo[a] (95% CI)		-0.066 (-0.585, 0.454)		
p-value[a]		0.7997		

[a] Estimates are from a mixed-effect model with repeated measures (MMRM) with baseline variable as a covariate, treatment group and visit and treatment group*visit as fixed effects, and subject within treatment group as a random effect.
Note: End of study visit data are included in the appropriate visit week.
Note: Total good-quality ON time per day is defined as the sum of ON time per day without dyskinesias + ON time per day with non-troublesome dyskinesias.
Source: Listing 17.2.2.2, Dataset: ADDIA, Program: t_pddiary.sas, Output: t_16-2-3-2-pddiary.rtf, Generated on: 28JUL2017 05:56
Page 5 of 5

Table 16.2.3.3.1 Treatment Response at Week 40/e0 and Week 80/e40 - ITT Overall Population

Treatment Response Criteria	Visit	GDNF/GDNF (N=21) n (%)	Placebo/GDNF (N=20) n (%)	Total (N=41) n (%)
Decrease from baseline by >= 10 points in OFF state UPDRS motor score (part III)	Week 40/e0	9 (42.9)	0	9 (22.0)
p-value		0.0013		
	Week 80/e40	11 (52.4)	9 (45.0)	20 (48.8)
p-value		0.7579		
Increase from baseline by >= 1 hour in total good-quality ON time per day (ON without dyskinesias or ON with non-troublesome dyskinesias)	Week 40/e0	9 (42.9)	3 (15.0)	12 (29.3)
p-value		0.0750		
	Week 80/e40	15 (71.4)	9 (45.0)	24 (58.5)
p-value		0.1053		
Both of the above criteria	Week 40/e0	4 (19.0)	0	4 (9.8)
p-value		0.1060		
	Week 80/e40	7 (33.3)	6 (30.0)	13 (31.7)
p-value		>0.9999		

Note: For subject 45, items 22, 27, 28, 29 and 30 are excluded from the UPDRS score. P-values are from a Fisher's exact test.
Source: Listing 17.2.2.3, Dataset: ADQUPDRS, ADDIA, Program: t_trtresp.sas, Output: t_16-2-3-3-1-trtresp.rtf, Generated on: 28JUL2017 05:56
Page 1 of 1

Table 16.2.3.3.2 UPDRS Responder at Week 80/e40 Compared to Week 40/e0 - ITT Overall Population

| | GDNF/GDNF (N=21) | | Placebo/GDNF (N=20) | |
| | UPDRS Responder at Week 80/e40 | | UPDRS Responder at Week 80/e40 | |
UPDRS Responder at Week 40/e0	Yes n (%)	No n (%)	Yes n (%)	No n (%)
Yes	7 (33.3)	2 (9.5)	0	0
No	4 (19.0)	8 (38.1)	9 (45.0)	11 (55.0)

Note: UPDRS responder is defined as a decrease from baseline by >=10 points in OFF state UPDRS motor score (part III). For subject 45, items 22, 27, 28, 29 and 30 are excluded from the UPDRS score.
Source: Listing 17.2.2.3, Dataset: ADQUPDRS, Program: t_updrsresp.sas, Output: t_16-2-3-3-2-updrsresp.rtf, Generated on: 28JUL2017 05:56
Page 1 of 1

Table 16.2.4.1 OFF and ON State Timed Walking Test by Visit: Change from Baseline – MMRM, ITT Overall Population

Parameter Visit Statistic	GDNF/GDNF (N=21)		Placebo/GDNF (N=20)	
	Value	Change From Baseline	Value	Change From Baseline
OFF State Timed Walking Test (seconds)				
Week 0 (Baseline)				
n	20		19	
Mean (SD)	45.25 (59.933)		17.58 (10.812)	
Median	17.00		13.00	
Min, Max	9.5, 203.0		10.0, 49.0	
Week 40/e0				
n	17	17	20	19
Mean (SD)	21.71 (31.158)	-20.03 (43.769)	16.28 (15.092)	-4.53 (8.061)
Median	13.50	-2.00	11.25	-1.50
Min, Max	8.0, 140.5	-175.5, 1.0	8.0, 77.5	-25.5, 4.0

[a] Estimates are from a mixed-effect model with repeated measures (MMRM) with baseline time as a covariate, treatment group and visit and treatment group*visit as fixed effects, and subject within treatment group as a random effect.

Note: Shorter times represent better function. Two trials per state per visit are averaged for analysis. If only the first trial is completed for a particular state, then the second trial result will be imputed with the worst non-missing second trial result from all subjects for that particular state during the study. If both trials are missing, then the endpoint is not reported for that visit. End of study visit data are included in the appropriate visit week. Data for subject 45 are excluded from analysis.

Source: Listing 17.2.2.4.1, Dataset: ADQSE, Program: t_timedtest.sas, Output: t_16-2-4-1-timedwalk.rtf, Generated on: 28JUL2017 05:56

Page 1 of 4

Table 16.2.4.1 OFF and ON State Timed Walking Test by Visit: Change from Baseline – MMRM, ITT Overall Population

Parameter Visit Statistic	GDNF/GDNF (N=21)		Placebo/GDNF (N=20)	
	Value	Change From Baseline	Value	Change From Baseline
OFF State Timed Walking Test (seconds)				
Week 80/e40				
n	19	19	19	18
Mean (SD)	27.63 (52.003)	-13.18 (72.569)	11.68 (2.916)	-4.33 (6.403)
Median	13.00	-4.00	11.00	-2.75
Min, Max	8.0, 238.0	-176.5, 200.0	8.0, 17.5	-24.0, 4.0
Least squares mean[a] (95% CI)		-6.52 (-24.19, 11.15)		-11.53 (-29.62, 6.56)
Least squares mean difference				
versus placebo[a] (95% CI)		5.01 (-20.47, 30.49)		
p-value[a]		0.6987		

[a] Estimates are from a mixed-effect model with repeated measures (MMRM) with baseline time as a covariate, treatment group and visit and treatment group*visit as fixed effects, and subject within treatment group as a random effect.

Note: Shorter times represent better function. Two trials per state per visit are averaged for analysis. If only the first trial is completed for a particular state, then the second trial result will be imputed with the worst non-missing second trial result from all subjects for that particular state during the study. If both trials are missing, then the endpoint is not reported for that visit. End of study visit data are included in the appropriate visit week. Data for subject 45 are excluded from analysis.

Source: Listing 17.2.2.4.1, Dataset: ADQSE, Program: t_timedtest.sas, Output: t_16-2-4-1-timedwalk.rtf, Generated on: 28JUL2017 05:56

Page 2 of 4

Table 16.2.4.1 OFF and ON State Timed Walking Test by Visit: Change from Baseline – MMRM, ITT Overall Population

Parameter Visit Statistic	GDNF/GDNF (N=21)		Placebo/GDNF (N=20)	
	Value	Change From Baseline	Value	Change From Baseline
ON State Timed Walking Test (seconds)				
Week 0 (Baseline)				
n	20		20	
Mean (SD)	10.95 (2.620)		10.43 (1.935)	
Median	10.25		10.50	
Min, Max	8.0, 16.5		8.0, 15.0	
Week 40/e0				
n	20	20	20	20
Mean (SD)	10.75 (2.112)	-0.20 (1.446)	10.00 (1.755)	-0.43 (1.104)
Median	10.25	0.00	9.50	-0.75
Min, Max	7.5, 15.0	-3.5, 3.5	7.0, 14.0	-2.5, 1.5

[a] Estimates are from a mixed-effect model with repeated measures (MMRM) with baseline time as a covariate, treatment group and visit and treatment group*visit as fixed effects, and subject within treatment group as a random effect.

Note: Shorter times represent better function. Two trials per state per visit are averaged for analysis. If only the first trial is completed for a particular state, then the second trial result will be imputed with the worst non-missing second trial result from all subjects for that particular state during the study. If both trials are missing, then the endpoint is not reported for that visit. End of study visit data are included in the appropriate visit week. Data for subject 45 are excluded from analysis.

Source: Listing 17.2.2.4.1, Dataset: ADQSE, Program: t_timedtest.sas, Output: t_16-2-4-1-timedwalk.rtf, Generated on: 28JUL2017 05:56

Page 3 of 4

Table 16.2.4.1 OFF and ON State Timed Walking Test by Visit: Change from Baseline – MMRM, ITT Overall Population

Parameter Visit Statistic	GDNF/GDNF (N=21)		Placebo/GDNF (N=20)	
	Value	Change From Baseline	Value	Change From Baseline
ON State Timed Walking Test (seconds)				
Week 80/e40				
n	20	20	19	19
Mean (SD)	10.38 (1.798)	-0.58 (1.801)	9.76 (1.584)	-0.66 (1.375)
Median	10.25	0.00	10.00	0.00
Min, Max	7.0, 13.0	-4.5, 2.5	7.0, 13.0	-4.0, 2.0
Least squares mean[a] (95% CI)		-0.45 (-0.99, 0.08)		-0.73 (-1.27, -0.19)
Least squares mean difference versus placebo[a] (95% CI)		0.27 (-0.49, 1.04)		
p-value[a]		0.4694		

[a] Estimates are from a mixed-effect model with repeated measures (MMRM) with baseline time as a covariate, treatment group and visit and treatment group*visit as fixed effects, and subject within treatment group as a random effect.

Note: Shorter times represent better function. Two trials per state per visit are averaged for analysis. If only the first trial is completed for a particular state, then the second trial result will be imputed with the worst non-missing second trial result from all subjects for that particular state during the study. If both trials are missing, then the endpoint is not reported for that visit. End of study visit data are included in the appropriate visit week. Data for subject 45 are excluded from analysis.

Source: Listing 17.2.2.4.1, Dataset: ADQSE, Program: t_timedtest.sas, Output: t_16-2-4-1-timedwalk.rtf, Generated on: 28JUL2017 05:56
Page 4 of 4

Table 16.2.4.2 OFF and ON State Timed Tapping Test by Visit: Change from Baseline – MMRM, ITT Overall Population

Parameter Visit Statistic	GDNF/GDNF (N=21)		Placebo/GDNF (N=20)	
	Value	Change From Baseline	Value	Change From Baseline
OFF State Timed Tapping Test				
Week 0 (Baseline)				
n	21		20	
Mean (SD)	43.11 (15.010)		42.38 (9.437)	
Median	36.25		41.25	
Min, Max	18.3, 74.5		24.8, 65.0	
Week 40/e0				
n	21	21	20	20
Mean (SD)	54.79 (18.549)	11.68 (8.289)	53.19 (15.954)	10.81 (11.009)
Median	49.00	10.25	54.00	9.25
Min, Max	18.5, 86.3	-2.0, 31.5	28.0, 88.3	-4.3, 38.0

[a] Estimates are from a mixed-effect model with repeated measures (MMRM) with baseline number of taps as a covariate, treatment group and visit and treatment group*visit as fixed effects, and subject within treatment group as a random effect.

Note: More taps represent better function. Four trials per state for each visit are averaged for analysis. If any trial is not completed for a particular state, then the trial result will be imputed with the worst non-missing applicable trial result (for example, first left hand trial) from all subjects for that particular state during the study. If all four trials are missing, then the endpoint is not reported for that visit. End of study visit data are included in the appropriate visit week.

Source: Listing 17.2.2.4.2, Dataset: ADQSE, Program: t_timedtest.sas, Output: t_16-2-4-2-timedtap.rtf, Generated on: 28JUL2017 05:57
Page 1 of 4

Table 16.2.4.2 OFF and ON State Timed Tapping Test by Visit: Change from Baseline – MMRM, ITT Overall Population

Parameter Visit Statistic	GDNF/GDNF (N=21)		Placebo/GDNF (N=20)	
	Value	Change From Baseline	Value	Change From Baseline
OFF State Timed Tapping Test				
Week 80/e40				
n	21	21	20	20
Mean (SD)	63.76 (22.566)	20.65 (15.379)	59.13 (17.799)	16.75 (12.912)
Median	59.75	20.50	60.63	14.13
Min, Max	32.0, 101.3	-2.0, 52.8	28.3, 90.5	-12.5, 40.3
Least squares mean[a] (95% CI)		20.64 (14.38, 26.89)		16.78 (10.36, 23.19)
Least squares mean difference versus placebo[a] (95% CI)		3.86 (-5.10, 12.82)		
p-value[a]		0.3889		

[a] Estimates are from a mixed-effect model with repeated measures (MMRM) with baseline number of taps as a covariate, treatment group and visit and treatment group*visit as fixed effects, and subject within treatment group as a random effect.

Note: More taps represent better function. Four trials per state for each visit are averaged for analysis. If any trial is not completed for a particular state, then the trial result will be imputed with the worst non-missing applicable trial result (for example, first left hand trial) from all subjects for that particular state during the study. If all four trials are missing, then the endpoint is not reported for that visit. End of study visit data are included in the appropriate visit week.

Source: Listing 17.2.2.4.2, Dataset: ADQSE, Program: t_timedtest.sas, Output: t_16-2-4-2-timedtap.rtf, Generated on: 28JUL2017 05:57

Page 2 of 4

Table 16.2.4.2 OFF and ON State Timed Tapping Test by Visit: Change from Baseline – MMRM, ITT Overall Population

Parameter Visit Statistic	GDNF/GDNF (N=21)		Placebo/GDNF (N=20)	
	Value	Change From Baseline	Value	Change From Baseline
ON State Timed Tapping Test				
Week 0 (Baseline)				
n	21		20	
Mean (SD)	64.20 (17.643)		61.00 (17.388)	
Median	64.00		59.50	
Min, Max	32.8, 102.3		30.8, 104.5	
Week 40/e0				
n	21	21	20	20
Mean (SD)	73.52 (18.073)	9.32 (9.441)	68.06 (18.041)	7.06 (8.984)
Median	68.25	9.50	67.25	5.75
Min, Max	39.3, 104.3	-5.3, 26.8	40.0, 103.5	-14.3, 26.0

[a] Estimates are from a mixed-effect model with repeated measures (MMRM) with baseline number of taps as a covariate, treatment group and visit and treatment group*visit as fixed effects, and subject within treatment group as a random effect.

Note: More taps represent better function. Four trials per state for each visit are averaged for analysis. If any trial is not completed for a particular state, then the trial result will be imputed with the worst non-missing applicable trial result (for example, first left hand trial) from all subjects for that particular state during the study. If all four trials are missing, then the endpoint is not reported for that visit. End of study visit data are included in the appropriate visit week.

Source: Listing 17.2.2.4.2, Dataset: ADQSE, Program: t_timedtest.sas, Output: t_16-2-4-2-timedtap.rtf, Generated on: 28JUL2017 05:57
Page 3 of 4

Table 16.2.4.2 OFF and ON State Timed Tapping Test by Visit: Change from Baseline – MMRM, ITT Overall Population

Parameter Visit Statistic	GDNF/GDNF (N=21)		Placebo/GDNF (N=20)	
	Value	Change From Baseline	Value	Change From Baseline
ON State Timed Tapping Test				
Week 80/e40				
n	21	21	19	19
Mean (SD)	79.89 (22.665)	15.69 (13.556)	73.55 (19.171)	12.72 (9.988)
Median	83.75	18.00	72.00	12.75
Min, Max	38.0, 111.8	-7.0, 44.3	41.5, 105.0	-2.0, 28.5
Least squares mean[a] (95% CI)		15.79 (10.52, 21.06)		12.41 (6.97, 17.85)
Least squares mean difference versus placebo[a] (95% CI)		3.38 (-4.20, 10.96)		
p-value[a]		0.3728		

[a] Estimates are from a mixed-effect model with repeated measures (MMRM) with baseline number of taps as a covariate, treatment group and visit and treatment group*visit as fixed effects, and subject within treatment group as a random effect.

Note: More taps represent better function. Four trials per state for each visit are averaged for analysis. If any trial is not completed for a particular state, then the trial result will be imputed with the worst non-missing applicable trial result (for example, first left hand trial) from all subjects for that particular state during the study. If all four trials are missing, then the endpoint is not reported for that visit. End of study visit data are included in the appropriate visit week.

Source: Listing 17.2.2.4.2, Dataset: ADQSE, Program: t_timedtest.sas, Output: t_16-2-4-2-timedtap.rtf, Generated on: 28JUL2017 05:57

Page 4 of 4

Table 16.2.4.3 NMSS Score by Visit: Change from Baseline – MMRM, ITT Overall Population

Parameter Visit Statistic	GDNF/GDNF (N=21)		Placebo/GDNF (N=20)	
	Value	Change From Baseline	Value	Change From Baseline
NMSS Total Score				
Screening (Baseline)				
n	20		20	
Mean (SD)	40.4 (22.54)		36.9 (29.83)	
Median	34.5		30.0	
Min, Max	11, 90		6, 127	
Week 40/e0				
n	20	20	20	20
Mean (SD)	25.7 (17.36)	-14.7 (21.20)	29.2 (27.30)	-7.8 (20.83)
Median	23.5	-10.5	24.0	-2.0
Min, Max	5, 73	-83, 21	3, 125	-76, 21

[a] Estimates are from a mixed-effect model with repeated measures (MMRM) with baseline score as a covariate, treatment group and visit and treatment group*visit as fixed effects, and subject within treatment group as a random effect.

Note: The NMSS is a 30-item interview-based scale that rates non-motor symptoms that occurred in the preceding month in 9 domains. Each item is rated from 0 (none) to 3 (severe) for severity and from 1 (rarely) to 4 (very frequent) for frequency. The maximum score for an individual item is 12. The higher the score, the worse the subject's condition. The maximum NMSS total score is 360. Missing individual item scores are imputed using LOCF. End of study visit data are included in the appropriate visit week. Data for subject 45 are excluded from analysis.

Source: Listing 17.2.2.5, Dataset: ADQSE, Program: t_nmss.sas, Output: t_16-2-4-3-nmss.rtf, Generated on: 28JUL2017 05:57

Page 1 of 20

Table 16.2.4.3 NMSS Score by Visit: Change from Baseline – MMRM, ITT Overall Population

Parameter Visit Statistic	GDNF/GDNF (N=21)		Placebo/GDNF (N=20)	
	Value	Change From Baseline	Value	Change From Baseline
NMSS Total Score				
Week 80/e40				
n	20	20	20	20
Mean (SD)	27.9 (20.00)	-12.5 (21.71)	26.7 (22.24)	-10.3 (19.32)
Median	25.0	-7.5	27.5	-9.5
Min, Max	3, 68	-50, 34	1, 80	-56, 30
Least squares mean[a] (95% CI)		-11.4 (-19.0, -3.9)		-11.3 (-18.9, -3.8)
Least squares mean difference versus placebo[a] (95% CI)		-0.1 (-10.8, 10.6)		
p-value[a]		0.9833		

[a] Estimates are from a mixed-effect model with repeated measures (MMRM) with baseline score as a covariate, treatment group and visit and treatment group*visit as fixed effects, and subject within treatment group as a random effect.

Note: The NMSS is a 30-item interview-based scale that rates non-motor symptoms that occurred in the preceding month in 9 domains. Each item is rated from 0 (none) to 3 (severe) for severity and from 1 (rarely) to 4 (very frequent) for frequency. The maximum score for an individual item is 12. The higher the score, the worse the subject's condition. The maximum NMSS total score is 360. Missing individual item scores are imputed using LOCF. End of study visit data are included in the appropriate visit week. Data for subject 45 are excluded from analysis.

Source: Listing 17.2.2.5, Dataset: ADQSE, Program: t_nmss.sas, Output: t_16-2-4-3-nmss.rtf, Generated on: 28JUL2017 05:57

Page 2 of 20

Table 16.2.4.3 NMSS Score by Visit: Change from Baseline – MMRM, ITT Overall Population

Parameter Visit Statistic	GDNF/GDNF (N=21)		Placebo/GDNF (N=20)	
	Value	Change From Baseline	Value	Change From Baseline
Cardiovascular Including Falls Score				
Screening (Baseline)				
n	20		20	
Mean (SD)	1.6 (2.52)		1.0 (1.36)	
Median	0.0		0.0	
Min, Max	0, 8		0, 4	
Week 40/e0				
n	20	20	20	20
Mean (SD)	0.3 (0.66)	-1.3 (2.38)	1.7 (2.64)	0.7 (2.05)
Median	0.0	0.0	0.0	0.0
Min, Max	0, 2	-8, 2	0, 8	-2, 6

[a] Estimates are from a mixed-effect model with repeated measures (MMRM) with baseline score as a covariate, treatment group and visit and treatment group*visit as fixed effects, and subject within treatment group as a random effect.
Note: The NMSS is a 30-item interview-based scale that rates non-motor symptoms that occurred in the preceding month in 9 domains. Each item is rated from 0 (none) to 3 (severe) for severity and from 1 (rarely) to 4 (very frequent) for frequency. The maximum score for an individual item is 12. The higher the score, the worse the subject's condition. The maximum NMSS total score is 360. Missing individual item scores are imputed using LOCF. End of study visit data are included in the appropriate visit week. Data for subject 45 are excluded from analysis.
Source: Listing 17.2.2.5, Dataset: ADQSE, Program: t_nmss.sas, Output: t_16-2-4-3-nmss.rtf, Generated on: 28JUL2017 05:57
Page 3 of 20

Table 16.2.4.3 NMSS Score by Visit: Change from Baseline – MMRM, ITT Overall Population

Parameter Visit Statistic	GDNF/GDNF (N=21)		Placebo/GDNF (N=20)	
	Value	Change From Baseline	Value	Change From Baseline
Cardiovascular Including Falls Score				
Week 80/e40				
n	20	20	20	20
Mean (SD)	0.5 (0.89)	-1.1 (2.67)	0.7 (1.04)	-0.3 (1.03)
Median	0.0	0.0	0.0	0.0
Min, Max	0, 3	-8, 3	0, 3	-3, 1
Least squares mean[a] (95% CI)		-0.8 (-1.3, -0.4)		-0.5 (-1.0, -0.1)
Least squares mean difference				
versus placebo[a] (95% CI)		-0.3 (-0.9, 0.3)		
p-value[a]		0.3476		

[a] Estimates are from a mixed-effect model with repeated measures (MMRM) with baseline score as a covariate, treatment group and visit and treatment group*visit as fixed effects, and subject within treatment group as a random effect.

Note: The NMSS is a 30-item interview-based scale that rates non-motor symptoms that occurred in the preceding month in 9 domains. Each item is rated from 0 (none) to 3 (severe) for severity and from 1 (rarely) to 4 (very frequent) for frequency. The maximum score for an individual item is 12. The higher the score, the worse the subject's condition. The maximum NMSS total score is 360. Missing individual item scores are imputed using LOCF. End of study visit data are included in the appropriate visit week. Data for subject 45 are excluded from analysis.

Source: Listing 17.2.2.5, Dataset: ADQSE, Program: t_nmss.sas, Output: t_16-2-4-3-nmss.rtf, Generated on: 28JUL2017 05:57
Page 4 of 20

Table 16.2.4.3 NMSS Score by Visit: Change from Baseline – MMRM, ITT Overall Population

Parameter Visit Statistic	GDNF/GDNF (N=21)		Placebo/GDNF (N=20)	
	Value	Change From Baseline	Value	Change From Baseline
Sleep/Fatigue Score				
Screening (Baseline)				
n	20		20	
Mean (SD)	11.5 (6.79)		10.3 (8.76)	
Median	12.0		6.5	
Min, Max	0, 28		0, 26	
Week 40/e0				
n	20	20	20	20
Mean (SD)	7.3 (5.54)	-4.2 (4.29)	9.1 (8.10)	-1.2 (6.73)
Median	7.0	-4.0	7.0	0.0
Min, Max	0, 18	-11, 4	0, 27	-24, 7

[a] Estimates are from a mixed-effect model with repeated measures (MMRM) with baseline score as a covariate, treatment group and visit and treatment group*visit as fixed effects, and subject within treatment group as a random effect.

Note: The NMSS is a 30-item interview-based scale that rates non-motor symptoms that occurred in the preceding month in 9 domains. Each item is rated from 0 (none) to 3 (severe) for severity and from 1 (rarely) to 4 (very frequent) for frequency. The maximum score for an individual item is 12. The higher the score, the worse the subject's condition. The maximum NMSS total score is 360. Missing individual item scores are imputed using LOCF. End of study visit data are included in the appropriate visit week. Data for subject 45 are excluded from analysis.

Source: Listing 17.2.2.5, Dataset: ADQSE, Program: t_nmss.sas, Output: t_16-2-4-3-nmss.rtf, Generated on: 28JUL2017 05:57

Table 16.2.4.3 NMSS Score by Visit: Change from Baseline – MMRM, ITT Overall Population

Parameter Visit Statistic	GDNF/GDNF (N=21)		Placebo/GDNF (N=20)	
	Value	Change From Baseline	Value	Change From Baseline
Sleep/Fatigue Score				
Week 80/e40				
n	20	20	20	20
Mean (SD)	6.9 (4.88)	-4.7 (5.23)	8.9 (9.23)	-1.4 (5.22)
Median	9.0	-3.0	5.0	0.0
Min, Max	0, 13	-17, 4	0, 28	-16, 8
Least squares mean[a] (95% CI)		-4.4 (-6.6, -2.2)		-1.6 (-3.8, 0.6)
Least squares mean difference				
versus placebo[a] (95% CI)		-2.8 (-5.9, 0.3)		
p-value[a]		0.0776		

[a] Estimates are from a mixed-effect model with repeated measures (MMRM) with baseline score as a covariate, treatment group and visit and treatment group*visit as fixed effects, and subject within treatment group as a random effect.

Note: The NMSS is a 30-item interview-based scale that rates non-motor symptoms that occurred in the preceding month in 9 domains. Each item is rated from 0 (none) to 3 (severe) for severity and from 1 (rarely) to 4 (very frequent) for frequency. The maximum score for an individual item is 12. The higher the score, the worse the subject's condition. The maximum NMSS total score is 360. Missing individual item scores are imputed using LOCF. End of study visit data are included in the appropriate visit week. Data for subject 45 are excluded from analysis.

Source: Listing 17.2.2.5, Dataset: ADQSE, Program: t_nmss.sas, Output: t_16-2-4-3-nmss.rtf, Generated on: 28JUL2017 05:57

Table 16.2.4.3 NMSS Score by Visit: Change from Baseline – MMRM, ITT Overall Population

Parameter Visit Statistic	GDNF/GDNF (N=21)		Placebo/GDNF (N=20)	
	Value	Change From Baseline	Value	Change From Baseline
Mood/Cognition Score				
Screening (Baseline)				
n	20		20	
Mean (SD)	2.4 (3.28)		2.5 (7.95)	
Median	0.5		0.0	
Min, Max	0, 12		0, 36	
Week 40/e0				
n	20	20	20	20
Mean (SD)	2.7 (6.83)	0.3 (4.66)	1.1 (1.89)	-1.4 (7.48)
Median	0.0	0.0	0.0	0.0
Min, Max	0, 29	-6, 17	0, 7	-32, 7

[a] Estimates are from a mixed-effect model with repeated measures (MMRM) with baseline score as a covariate, treatment group and visit and treatment group*visit as fixed effects, and subject within treatment group as a random effect.

Note: The NMSS is a 30-item interview-based scale that rates non-motor symptoms that occurred in the preceding month in 9 domains. Each item is rated from 0 (none) to 3 (severe) for severity and from 1 (rarely) to 4 (very frequent) for frequency. The maximum score for an individual item is 12. The higher the score, the worse the subject's condition. The maximum NMSS total score is 360. Missing individual item scores are imputed using LOCF. End of study visit data are included in the appropriate visit week. Data for subject 45 are excluded from analysis.

Source: Listing 17.2.2.5, Dataset: ADQSE, Program: t_nmss.sas, Output: t_16-2-4-3-nmss.rtf, Generated on: 28JUL2017 05:57

Page 7 of 20

Table 16.2.4.3 NMSS Score by Visit: Change from Baseline – MMRM, ITT Overall Population

Parameter Visit Statistic	GDNF/GDNF (N=21)		Placebo/GDNF (N=20)	
	Value	Change From Baseline	Value	Change From Baseline
Mood/Cognition Score				
Week 80/e40				
n	20	20	20	20
Mean (SD)	1.6 (2.62)	-0.8 (4.11)	1.2 (2.98)	-1.3 (7.83)
Median	0.0	0.0	0.0	0.0
Min, Max	0, 10	-8, 10	0, 12	-32, 12
Least squares mean[a] (95% CI)		-0.8 (-2.1, 0.4)		-1.3 (-2.5, 0.0)
Least squares mean difference				
versus placebo[a] (95% CI)		0.4 (-1.4, 2.2)		
p-value[a]		0.6449		

[a] Estimates are from a mixed-effect model with repeated measures (MMRM) with baseline score as a covariate, treatment group and visit and treatment group*visit as fixed effects, and subject within treatment group as a random effect.

Note: The NMSS is a 30-item interview-based scale that rates non-motor symptoms that occurred in the preceding month in 9 domains. Each item is rated from 0 (none) to 3 (severe) for severity and from 1 (rarely) to 4 (very frequent) for frequency. The maximum score for an individual item is 12. The higher the score, the worse the subject's condition. The maximum NMSS total score is 360. Missing individual item scores are imputed using LOCF. End of study visit data are included in the appropriate visit week. Data for subject 45 are excluded from analysis.

Source: Listing 17.2.2.5, Dataset: ADQSE, Program: t_nmss.sas, Output: t_16-2-4-3-nmss.rtf, Generated on: 28JUL2017 05:57

Table 16.2.4.3 NMSS Score by Visit: Change from Baseline – MMRM, ITT Overall Population

Parameter Visit Statistic	GDNF/GDNF (N=21)		Placebo/GDNF (N=20)	
	Value	Change From Baseline	Value	Change From Baseline
Perceptual Problems/Hallucinations Score				
Screening (Baseline)				
n	20		20	
Mean (SD)	0.3 (0.91)		0.5 (1.57)	
Median	0.0		0.0	
Min, Max	0, 4		0, 6	
Week 40/e0				
n	20	20	20	20
Mean (SD)	0.3 (0.79)	0.0 (0.56)	0.3 (0.98)	-0.2 (1.94)
Median	0.0	0.0	0.0	0.0
Min, Max	0, 3	-1, 2	0, 4	-6, 4

[a] Estimates are from a mixed-effect model with repeated measures (MMRM) with baseline score as a covariate, treatment group and visit and treatment group*visit as fixed effects, and subject within treatment group as a random effect.

Note: The NMSS is a 30-item interview-based scale that rates non-motor symptoms that occurred in the preceding month in 9 domains. Each item is rated from 0 (none) to 3 (severe) for severity and from 1 (rarely) to 4 (very frequent) for frequency. The maximum score for an individual item is 12. The higher the score, the worse the subject's condition. The maximum NMSS total score is 360. Missing individual item scores are imputed using LOCF. End of study visit data are included in the appropriate visit week. Data for subject 45 are excluded from analysis.

Source: Listing 17.2.2.5, Dataset: ADQSE, Program: t_nmss.sas, Output: t_16-2-4-3-nmss.rtf, Generated on: 28JUL2017 05:57

Page 9 of 20

Table 16.2.4.3 NMSS Score by Visit: Change from Baseline – MMRM, ITT Overall Population

Parameter Visit Statistic	GDNF/GDNF (N=21)		Placebo/GDNF (N=20)	
	Value	Change From Baseline	Value	Change From Baseline
Perceptual Problems/Hallucinations Score				
Week 80/e40				
n	20	20	20	20
Mean (SD)	1.1 (2.96)	0.8 (2.26)	0.2 (0.62)	-0.3 (1.34)
Median	0.0	0.0	0.0	0.0
Min, Max	0, 12	-1, 8	0, 2	-4, 2
Least squares mean[a] (95% CI)		0.7 (-0.2, 1.6)		-0.2 (-1.1, 0.7)
Least squares mean difference				
versus placebo[a] (95% CI)		0.9 (-0.3, 2.2)		
p-value[a]		0.1399		

[a] Estimates are from a mixed-effect model with repeated measures (MMRM) with baseline score as a covariate, treatment group and visit and treatment group*visit as fixed effects, and subject within treatment group as a random effect.
Note: The NMSS is a 30-item interview-based scale that rates non-motor symptoms that occurred in the preceding month in 9 domains. Each item is rated from 0 (none) to 3 (severe) for severity and from 1 (rarely) to 4 (very frequent) for frequency. The maximum score for an individual item is 12. The higher the score, the worse the subject's condition. The maximum NMSS total score is 360. Missing individual item scores are imputed using LOCF. End of study visit data are included in the appropriate visit week. Data for subject 45 are excluded from analysis.
Source: Listing 17.2.2.5, Dataset: ADQSE, Program: t_nmss.sas, Output: t_16-2-4-3-nmss.rtf, Generated on: 28JUL2017 05:57
Page 10 of 20

Table 16.2.4.3 NMSS Score by Visit: Change from Baseline – MMRM, ITT Overall Population

Parameter Visit Statistic	GDNF/GDNF (N=21)		Placebo/GDNF (N=20)	
	Value	Change From Baseline	Value	Change From Baseline
Attention/Memory Score				
Screening (Baseline)				
n	20		20	
Mean (SD)	5.1 (6.27)		3.8 (6.40)	
Median	3.0		1.0	
Min, Max	0, 24		0, 21	
Week 40/e0				
n	20	20	20	20
Mean (SD)	2.5 (3.32)	-2.6 (6.18)	1.9 (3.02)	-1.9 (6.13)
Median	1.5	-1.0	1.0	0.0
Min, Max	0, 13	-19, 5	0, 12	-19, 8

[a] Estimates are from a mixed-effect model with repeated measures (MMRM) with baseline score as a covariate, treatment group and visit and treatment group*visit as fixed effects, and subject within treatment group as a random effect.

Note: The NMSS is a 30-item interview-based scale that rates non-motor symptoms that occurred in the preceding month in 9 domains. Each item is rated from 0 (none) to 3 (severe) for severity and from 1 (rarely) to 4 (very frequent) for frequency. The maximum score for an individual item is 12. The higher the score, the worse the subject's condition. The maximum NMSS total score is 360. Missing individual item scores are imputed using LOCF. End of study visit data are included in the appropriate visit week. Data for subject 45 are excluded from analysis.

Source: Listing 17.2.2.5, Dataset: ADQSE, Program: t_nmss.sas, Output: t_16-2-4-3-nmss.rtf, Generated on: 28JUL2017 05:57

Table 16.2.4.3 NMSS Score by Visit: Change from Baseline – MMRM, ITT Overall Population

Parameter Visit Statistic	GDNF/GDNF (N=21)		Placebo/GDNF (N=20)	
	Value	Change From Baseline	Value	Change From Baseline
Attention/Memory Score				
Week 80/e40				
n	20	20	20	20
Mean (SD)	4.2 (5.41)	-0.9 (5.36)	2.2 (2.91)	-1.6 (6.18)
Median	1.0	-2.0	0.0	-0.5
Min, Max	0, 16	-10, 11	0, 8	-20, 7
Least squares mean[a] (95% CI)		-0.3 (-2.2, 1.6)		-2.2 (-4.0, -0.3)
Least squares mean difference				
versus placebo[a] (95% CI)		1.9 (-0.8, 4.5)		
p-value[a]		0.1609		

[a] Estimates are from a mixed-effect model with repeated measures (MMRM) with baseline score as a covariate, treatment group and visit and treatment group*visit as fixed effects, and subject within treatment group as a random effect.

Note: The NMSS is a 30-item interview-based scale that rates non-motor symptoms that occurred in the preceding month in 9 domains. Each item is rated from 0 (none) to 3 (severe) for severity and from 1 (rarely) to 4 (very frequent) for frequency. The maximum score for an individual item is 12. The higher the score, the worse the subject's condition. The maximum NMSS total score is 360. Missing individual item scores are imputed using LOCF. End of study visit data are included in the appropriate visit week. Data for subject 45 are excluded from analysis.

Source: Listing 17.2.2.5, Dataset: ADQSE, Program: t_nmss.sas, Output: t_16-2-4-3-nmss.rtf, Generated on: 28JUL2017 05:57
Page 12 of 20

Table 16.2.4.3 NMSS Score by Visit: Change from Baseline – MMRM, ITT Overall Population

Parameter Visit Statistic	GDNF/GDNF (N=21)		Placebo/GDNF (N=20)	
	Value	Change From Baseline	Value	Change From Baseline
Gastrointestinal Tract Score				
Screening (Baseline)				
n	20		20	
Mean (SD)	2.5 (2.50)		3.1 (3.52)	
Median	2.0		2.0	
Min, Max	0, 8		0, 11	
Week 40/e0				
n	20	20	20	20
Mean (SD)	1.7 (3.07)	-0.9 (3.38)	2.6 (3.07)	-0.5 (3.19)
Median	0.0	0.0	2.0	0.0
Min, Max	0, 12	-8, 6	0, 12	-9, 4

[a] Estimates are from a mixed-effect model with repeated measures (MMRM) with baseline score as a covariate, treatment group and visit and treatment group*visit as fixed effects, and subject within treatment group as a random effect.
Note: The NMSS is a 30-item interview-based scale that rates non-motor symptoms that occurred in the preceding month in 9 domains. Each item is rated from 0 (none) to 3 (severe) for severity and from 1 (rarely) to 4 (very frequent) for frequency. The maximum score for an individual item is 12. The higher the score, the worse the subject's condition. The maximum NMSS total score is 360. Missing individual item scores are imputed using LOCF. End of study visit data are included in the appropriate visit week. Data for subject 45 are excluded from analysis.
Source: Listing 17.2.2.5, Dataset: ADQSE, Program: t_nmss.sas, Output: t_16-2-4-3-nmss.rtf, Generated on: 28JUL2017 05:57
Page 13 of 20

Table 16.2.4.3 NMSS Score by Visit: Change from Baseline – MMRM, ITT Overall Population

Parameter Visit Statistic	GDNF/GDNF (N=21)		Placebo/GDNF (N=20)	
	Value	Change From Baseline	Value	Change From Baseline
Gastrointestinal Tract Score				
Week 80/e40				
n	20	20	20	20
Mean (SD)	1.7 (3.28)	-0.9 (3.51)	3.2 (3.87)	0.1 (3.65)
Median	0.0	-0.5	1.5	0.0
Min, Max	0, 12	-5, 8	0, 12	-5, 9
Least squares mean[a] (95% CI)		-1.1 (-2.6, 0.4)		0.3 (-1.2, 1.8)
Least squares mean difference				
versus placebo[a] (95% CI)		-1.3 (-3.4, 0.8)		
p-value[a]		0.2193		

[a] Estimates are from a mixed-effect model with repeated measures (MMRM) with baseline score as a covariate, treatment group and visit and treatment group*visit as fixed effects, and subject within treatment group as a random effect.

Note: The NMSS is a 30-item interview-based scale that rates non-motor symptoms that occurred in the preceding month in 9 domains. Each item is rated from 0 (none) to 3 (severe) for severity and from 1 (rarely) to 4 (very frequent) for frequency. The maximum score for an individual item is 12. The higher the score, the worse the subject's condition. The maximum NMSS total score is 360. Missing individual item scores are imputed using LOCF. End of study visit data are included in the appropriate visit week. Data for subject 45 are excluded from analysis.

Source: Listing 17.2.2.5, Dataset: ADQSE, Program: t_nmss.sas, Output: t_16-2-4-3-nmss.rtf, Generated on: 28JUL2017 05:57

Page 14 of 20

Table 16.2.4.3 NMSS Score by Visit: Change from Baseline – MMRM, ITT Overall Population

Parameter Visit Statistic	GDNF/GDNF (N=21)		Placebo/GDNF (N=20)	
	Value	Change From Baseline	Value	Change From Baseline
Urinary Score				
Screening (Baseline)				
n	20		20	
Mean (SD)	7.2 (7.26)		4.5 (6.84)	
Median	5.5		3.5	
Min, Max	0, 26		0, 28	
Week 40/e0				
n	20	20	20	20
Mean (SD)	3.6 (4.13)	-3.6 (6.98)	5.2 (8.46)	0.7 (7.19)
Median	3.0	-1.0	2.0	0.0
Min, Max	0, 12	-23, 8	0, 36	-18, 20

[a] Estimates are from a mixed-effect model with repeated measures (MMRM) with baseline score as a covariate, treatment group and visit and treatment group*visit as fixed effects, and subject within treatment group as a random effect.

Note: The NMSS is a 30-item interview-based scale that rates non-motor symptoms that occurred in the preceding month in 9 domains. Each item is rated from 0 (none) to 3 (severe) for severity and from 1 (rarely) to 4 (very frequent) for frequency. The maximum score for an individual item is 12. The higher the score, the worse the subject's condition. The maximum NMSS total score is 360. Missing individual item scores are imputed using LOCF. End of study visit data are included in the appropriate visit week. Data for subject 45 are excluded from analysis.

Source: Listing 17.2.2.5, Dataset: ADQSE, Program: t_nmss.sas, Output: t_16-2-4-3-nmss.rtf, Generated on: 28JUL2017 05:57

Table 16.2.4.3 NMSS Score by Visit: Change from Baseline – MMRM, ITT Overall Population

Parameter Visit Statistic	GDNF/GDNF (N=21)		Placebo/GDNF (N=20)	
	Value	Change From Baseline	Value	Change From Baseline
Urinary Score				
Week 80/e40				
n	20	20	20	20
Mean (SD)	6.4 (6.95)	-0.8 (5.79)	5.0 (7.03)	0.5 (5.19)
Median	4.5	0.0	2.5	0.0
Min, Max	0, 20	-11, 14	0, 28	-14, 12
Least squares mean[a] (95% CI)		0.1 (-2.5, 2.6)		-0.4 (-2.9, 2.2)
Least squares mean difference versus placebo[a] (95% CI)		0.4 (-3.2, 4.1)		
p-value[a]		0.8060		

[a] Estimates are from a mixed-effect model with repeated measures (MMRM) with baseline score as a covariate, treatment group and visit and treatment group*visit as fixed effects, and subject within treatment group as a random effect.

Note: The NMSS is a 30-item interview-based scale that rates non-motor symptoms that occurred in the preceding month in 9 domains. Each item is rated from 0 (none) to 3 (severe) for severity and from 1 (rarely) to 4 (very frequent) for frequency. The maximum score for an individual item is 12. The higher the score, the worse the subject's condition. The maximum NMSS total score is 360. Missing individual item scores are imputed using LOCF. End of study visit data are included in the appropriate visit week. Data for subject 45 are excluded from analysis.

Source: Listing 17.2.2.5, Dataset: ADQSE, Program: t_nmss.sas, Output: t_16-2-4-3-nmss.rtf, Generated on: 28JUL2017 05:57

Page 16 of 20

Table 16.2.4.3 NMSS Score by Visit: Change from Baseline – MMRM, ITT Overall Population

Parameter Visit Statistic	GDNF/GDNF (N=21)		Placebo/GDNF (N=20)	
	Value	Change From Baseline	Value	Change From Baseline
Sexual Function Score				
Screening (Baseline)				
n	20		20	
Mean (SD)	1.6 (2.62)		3.9 (5.20)	
Median	0.0		1.5	
Min, Max	0, 10		0, 20	
Week 40/e0				
n	20	20	20	20
Mean (SD)	2.3 (5.92)	0.7 (5.98)	2.3 (5.49)	-1.6 (3.28)
Median	0.0	0.0	0.0	-0.5
Min, Max	0, 24	-4, 24	0, 24	-12, 4

[a] Estimates are from a mixed-effect model with repeated measures (MMRM) with baseline score as a covariate, treatment group and visit and treatment group*visit as fixed effects, and subject within treatment group as a random effect.
Note: The NMSS is a 30-item interview-based scale that rates non-motor symptoms that occurred in the preceding month in 9 domains. Each item is rated
from 0 (none) to 3 (severe) for severity and from 1 (rarely) to 4 (very frequent) for frequency. The maximum score for an individual item is 12.
The higher the score, the worse the subject's condition. The maximum NMSS total score is 360. Missing individual item scores are imputed
using LOCF. End of study visit data are included in the appropriate visit week. Data for subject 45 are excluded from analysis.
Source: Listing 17.2.2.5, Dataset: ADQSE, Program: t_nmss.sas, Output: t_16-2-4-3-nmss.rtf, Generated on: 28JUL2017 05:57
Page 17 of 20

Table 16.2.4.3 NMSS Score by Visit: Change from Baseline – MMRM, ITT Overall Population

Parameter Visit Statistic	GDNF/GDNF (N=21)		Placebo/GDNF (N=20)	
	Value	Change From Baseline	Value	Change From Baseline
Sexual Function Score				
Week 80/e40				
n	20	20	20	20
Mean (SD)	1.3 (3.02)	-0.4 (2.83)	0.5 (1.15)	-3.4 (5.15)
Median	0.0	0.0	0.0	-1.0
Min, Max	0, 11	-4, 8	0, 4	-20, 1
Least squares mean[a] (95% CI)		-1.1 (-2.2, -0.1)		-2.6 (-3.7, -1.5)
Least squares mean difference				
versus placebo[a] (95% CI)		1.5 (-0.1, 3.0)		
p-value[a]		0.0617		

[a] Estimates are from a mixed-effect model with repeated measures (MMRM) with baseline score as a covariate, treatment group and visit and treatment group*visit as fixed effects, and subject within treatment group as a random effect.

Note: The NMSS is a 30-item interview-based scale that rates non-motor symptoms that occurred in the preceding month in 9 domains. Each item is rated from 0 (none) to 3 (severe) for severity and from 1 (rarely) to 4 (very frequent) for frequency. The maximum score for an individual item is 12. The higher the score, the worse the subject's condition. The maximum NMSS total score is 360. Missing individual item scores are imputed using LOCF. End of study visit data are included in the appropriate visit week. Data for subject 45 are excluded from analysis.

Source: Listing 17.2.2.5, Dataset: ADQSE, Program: t_nmss.sas, Output: t_16-2-4-3-nmss.rtf, Generated on: 28JUL2017 05:57

Page 18 of 20

Table 16.2.4.3 NMSS Score by Visit: Change from Baseline – MMRM, ITT Overall Population

Parameter Visit Statistic	GDNF/GDNF (N=21)		Placebo/GDNF (N=20)	
	Value	Change From Baseline	Value	Change From Baseline
Miscellaneous Score				
Screening (Baseline)				
n	20		20	
Mean (SD)	8.3 (6.55)		7.4 (8.43)	
Median	7.5		5.0	
Min, Max	0, 19		0, 32	
Week 40/e0				
n	20	20	20	20
Mean (SD)	5.1 (5.51)	-3.2 (6.20)	5.1 (6.57)	-2.4 (8.95)
Median	3.5	-2.0	2.5	-0.5
Min, Max	0, 16	-19, 8	0, 24	-21, 13

[a] Estimates are from a mixed-effect model with repeated measures (MMRM) with baseline score as a covariate, treatment group and visit and treatment group*visit as fixed effects, and subject within treatment group as a random effect.
Note: The NMSS is a 30-item interview-based scale that rates non-motor symptoms that occurred in the preceding month in 9 domains. Each item is rated
    from 0 (none) to 3 (severe) for severity and from 1 (rarely) to 4 (very frequent) for frequency. The maximum score for an individual item is 12.
    The higher the score, the worse the subject's condition. The maximum NMSS total score is 360. Missing individual item scores are imputed
    using LOCF. End of study visit data are included in the appropriate visit week. Data for subject 45 are excluded from analysis.
Source: Listing 17.2.2.5, Dataset: ADQSE, Program: t_nmss.sas, Output: t_16-2-4-3-nmss.rtf, Generated on: 28JUL2017 05:57
Page 19 of 20

Table 16.2.4.3 NMSS Score by Visit: Change from Baseline – MMRM, ITT Overall Population

Parameter Visit Statistic	GDNF/GDNF (N=21)		Placebo/GDNF (N=20)	
	Value	Change From Baseline	Value	Change From Baseline
Miscellaneous Score				
Week 80/e40				
n	20	20	20	20
Mean (SD)	4.4 (5.39)	-3.9 (9.12)	4.9 (5.93)	-2.6 (9.10)
Median	3.5	-4.0	2.5	-0.5
Min, Max	0, 20	-19, 12	0, 20	-23, 10
Least squares mean[a] (95% CI)		-3.5 (-6.2, -0.9)		-2.9 (-5.5, -0.3)
Least squares mean difference				
versus placebo[a] (95% CI)		-0.6 (-4.4, 3.1)		
p-value[a]		0.7291		

[a] Estimates are from a mixed-effect model with repeated measures (MMRM) with baseline score as a covariate, treatment group and visit and treatment group*visit as fixed effects, and subject within treatment group as a random effect.

Note: The NMSS is a 30-item interview-based scale that rates non-motor symptoms that occurred in the preceding month in 9 domains. Each item is rated from 0 (none) to 3 (severe) for severity and from 1 (rarely) to 4 (very frequent) for frequency. The maximum score for an individual item is 12. The higher the score, the worse the subject's condition. The maximum NMSS total score is 360. Missing individual item scores are imputed using LOCF. End of study visit data are included in the appropriate visit week. Data for subject 45 are excluded from analysis.

Source: Listing 17.2.2.5, Dataset: ADQSE, Program: t_nmss.sas, Output: t_16-2-4-3-nmss.rtf, Generated on: 28JUL2017 05:57
Page 20 of 20

Table 16.2.4.4 PDQ-39 Score: Change from Baseline to Week 80/e40 – ANCOVA, ITT Overall Population

Parameter Visit Statistic	GDNF/GDNF (N=21)		Placebo/GDNF (N=20)	
	Value	Change From Baseline	Value	Change From Baseline
Single Index (Total) PDQ-39 Score				
Screening (Baseline)				
n	20		20	
Mean (SD)	25.487 (13.066)		28.414 (15.665)	
Median	25.807		28.203	
Min, Max	6.094, 56.042		4.740, 69.479	
Week 40/e0				
n	20	20	20	20
Mean (SD)	24.393 (14.499)	-1.094 (11.365)	22.534 (13.822)	-5.880 (8.651)
Median	24.479	-1.120	21.641	-4.844
Min, Max	1.042, 50.885	-27.500, 18.437	2.344, 57.396	-22.604, 9.583

[a] Estimates are from an analysis of covariance (ANCOVA) model with baseline score as a covariate and treatment group as a factor.

Note: The PDQ-39 is a self-administered 39-item PD-specific scale that rates symptoms that occurred in the preceding month in 8 dimensions. Each item is rated from 0 (never) to 4 (always) for frequency. The score for each dimension is the average of responses in the dimension, weighted by the number of questions and multiplied by 100. PDQ-39 dimension and total scores range from 0 to 100 (0 = no problem, 100 = problem as worse as possible). The higher the score, the worse the subject's condition. Only subjects with a Week 80/e40 value are included in the observed data analysis. If an individual question response is missing, then that dimension score and the single index (total) score are also missing. Data for subject 45 are excluded from analysis.

Source: Listing 17.2.2.6, Dataset: ADQSE, Program: t_effqsum.sas, Output: t_16-2-4-4-pdq39.rtf, Generated on: 28JUL2017 05:57

Page 1 of 18

Table 16.2.4.4 PDQ-39 Score: Change from Baseline to Week 80/e40 – ANCOVA, ITT Overall Population

Parameter Visit Statistic	GDNF/GDNF (N=21)		Placebo/GDNF (N=20)	
	Value	Change From Baseline	Value	Change From Baseline
Single Index (Total) PDQ-39 Score				
Week 80/e40				
n	20	20	20	20
Mean (SD)	25.065 (16.323)	-0.422 (15.343)	21.812 (12.986)	-6.602 (11.394)
Median	21.771	-2.786	19.036	-5.911
Min, Max	1.667, 63.698	-35.313, 34.740	2.083, 48.490	-26.094, 13.594
Mean difference versus placebo[a]				
(95% CI)		4.962 (-2.943, 12.866)		
p-value[a]		0.2114		

[a] Estimates are from an analysis of covariance (ANCOVA) model with baseline score as a covariate and treatment group as a factor.
Note: The PDQ-39 is a self-administered 39-item PD-specific scale that rates symptoms that occurred in the preceding month in 8 dimensions. Each item is rated from 0 (never) to 4 (always) for frequency. The score for each dimension is the average of responses in the dimension, weighted by the number of questions and multiplied by 100. PDQ-39 dimension and total scores range from 0 to 100 (0 = no problem, 100 = problem as worse as possible). The higher the score, the worse the subject's condition. Only subjects with a Week 80/e40 value are included in the observed data analysis. If an individual question response is missing, then that dimension score and the single index (total) score are also missing. Data for subject 45 are excluded from analysis.
Source: Listing 17.2.2.6, Dataset: ADQSE, Program: t_effqsum.sas, Output: t_16-2-4-4-pdq39.rtf, Generated on: 28JUL2017 05:57
Page 2 of 18

Table 16.2.4.4 PDQ-39 Score: Change from Baseline to Week 80/e40 – ANCOVA, ITT Overall Population

Parameter Visit Statistic	GDNF/GDNF (N=21)		Placebo/GDNF (N=20)	
	Value	Change From Baseline	Value	Change From Baseline
Mobility Dimension				
Screening (Baseline)				
n	20		20	
Mean (SD)	32.13 (20.250)		33.25 (22.509)	
Median	37.50		35.00	
Min, Max	2.5, 77.5		0.0, 85.0	
Week 40/e0				
n	20	20	20	20
Mean (SD)	32.13 (23.202)	0.00 (15.623)	26.00 (18.144)	-7.25 (14.710)
Median	28.75	1.25	27.50	-2.50
Min, Max	0.0, 75.0	-27.5, 27.5	0.0, 57.5	-47.5, 12.5

[a] Estimates are from an analysis of covariance (ANCOVA) model with baseline score as a covariate and treatment group as a factor.

Note: The PDQ-39 is a self-administered 39-item PD-specific scale that rates symptoms that occurred in the preceding month in 8 dimensions. Each item is rated from 0 (never) to 4 (always) for frequency. The score for each dimension is the average of responses in the dimension, weighted by the number of questions and multiplied by 100. PDQ-39 dimension and total scores range from 0 to 100 (0 = no problem, 100 = problem as worse as possible). The higher the score, the worse the subject's condition. Only subjects with a Week 80/e40 value are included in the observed data analysis. If an individual question response is missing, then that dimension score and the single index (total) score are also missing. Data for subject 45 are excluded from analysis.

Source: Listing 17.2.2.6, Dataset: ADQSE, Program: t_effqsum.sas, Output: t_16-2-4-4-pdq39.rtf, Generated on: 28JUL2017 05:57

Page 3 of 18

Table 16.2.4.4 PDQ-39 Score: Change from Baseline to Week 80/e40 – ANCOVA, ITT Overall Population

Parameter Visit Statistic	GDNF/GDNF (N=21)		Placebo/GDNF (N=20)	
	Value	Change From Baseline	Value	Change From Baseline
Mobility Dimension				
Week 80/e40				
n	20	20	20	20
Mean (SD)	31.88 (21.381)	-0.25 (19.158)	23.25 (19.670)	-10.00 (19.348)
Median	37.50	2.50	17.50	-5.00
Min, Max	0.0, 82.5	-45.0, 30.0	0.0, 75.0	-52.5, 17.5
Mean difference versus placebo[a]				
(95% CI)		9.25 (-1.63, 20.13)		
p-value[a]		0.0932		

[a] Estimates are from an analysis of covariance (ANCOVA) model with baseline score as a covariate and treatment group as a factor.

Note: The PDQ-39 is a self-administered 39-item PD-specific scale that rates symptoms that occurred in the preceding month in 8 dimensions. Each item is rated from 0 (never) to 4 (always) for frequency. The score for each dimension is the average of responses in the dimension, weighted by the number of questions and multiplied by 100. PDQ-39 dimension and total scores range from 0 to 100 (0 = no problem, 100 = problem as worse as possible). The higher the score, the worse the subject's condition. Only subjects with a Week 80/e40 value are included in the observed data analysis. If an individual question response is missing, then that dimension score and the single index (total) score are also missing. Data for subject 45 are excluded from analysis.

Source: Listing 17.2.2.6, Dataset: ADQSE, Program: t_effqsum.sas, Output: t_16-2-4-4-pdq39.rtf, Generated on: 28JUL2017 05:57

Page 4 of 18

Table 16.2.4.4 PDQ-39 Score: Change from Baseline to Week 80/e40 – ANCOVA, ITT Overall Population

Parameter Visit Statistic	GDNF/GDNF (N=21)		Placebo/GDNF (N=20)	
	Value	Change From Baseline	Value	Change From Baseline
ADL Dimension				
Screening (Baseline)				
n	20		20	
Mean (SD)	32.917 (18.776)		39.375 (21.607)	
Median	29.167		41.667	
Min, Max	8.333, 79.167		0.000, 75.000	
Week 40/e0				
n	20	20	20	20
Mean (SD)	33.125 (21.480)	0.208 (20.434)	30.417 (18.242)	-8.958 (17.692)
Median	31.250	-2.083	31.250	-4.167
Min, Max	4.167, 75.000	-41.667, 50.000	0.000, 66.667	-54.167, 12.500

[a] Estimates are from an analysis of covariance (ANCOVA) model with baseline score as a covariate and treatment group as a factor.

Note: The PDQ-39 is a self-administered 39-item PD-specific scale that rates symptoms that occurred in the preceding month in 8 dimensions. Each item is rated from 0 (never) to 4 (always) for frequency. The score for each dimension is the average of responses in the dimension, weighted by the number of questions and multiplied by 100. PDQ-39 dimension and total scores range from 0 to 100 (0 = no problem, 100 = problem as worse as possible). The higher the score, the worse the subject's condition. Only subjects with a Week 80/e40 value are included in the observed data analysis. If an individual question response is missing, then that dimension score and the single index (total) score are also missing. Data for subject 45 are excluded from analysis.

Source: Listing 17.2.2.6, Dataset: ADQSE, Program: t_effqsum.sas, Output: t_16-2-4-4-pdq39.rtf, Generated on: 28JUL2017 05:57

Page 5 of 18

Table 16.2.4.4 PDQ-39 Score: Change from Baseline to Week 80/e40 – ANCOVA, ITT Overall Population

Parameter Visit Statistic	GDNF/GDNF (N=21)		Placebo/GDNF (N=20)	
	Value	Change From Baseline	Value	Change From Baseline
ADL Dimension				
Week 80/e40				
n	20	20	20	20
Mean (SD)	27.708 (19.603)	-5.208 (24.253)	24.375 (19.131)	-15.000 (23.663)
Median	22.917	-6.250	16.667	-8.333
Min, Max	4.167, 75.000	-58.333, 45.833	4.167, 70.833	-62.500, 29.167
Mean difference versus placebo[a]				
(95% CI)		4.994 (-7.281, 17.270)		
p-value[a]		0.4150		

[a] Estimates are from an analysis of covariance (ANCOVA) model with baseline score as a covariate and treatment group as a factor.
Note: The PDQ-39 is a self-administered 39-item PD-specific scale that rates symptoms that occurred in the preceding month in 8 dimensions. Each item is rated from 0 (never) to 4 (always) for frequency. The score for each dimension is the average of responses in the dimension, weighted by the number of questions and multiplied by 100. PDQ-39 dimension and total scores range from 0 to 100 (0 = no problem, 100 = problem as worse as possible). The higher the score, the worse the subject's condition. Only subjects with a Week 80/e40 value are included in the observed data analysis. If an individual question response is missing, then that dimension score and the single index (total) score are also missing. Data for subject 45 are excluded from analysis.
Source: Listing 17.2.2.6, Dataset: ADQSE, Program: t_effqsum.sas, Output: t_16-2-4-4-pdq39.rtf, Generated on: 28JUL2017 05:57
Page 6 of 18

Table 16.2.4.4 PDQ-39 Score: Change from Baseline to Week 80/e40 – ANCOVA, ITT Overall Population

Parameter Visit Statistic	GDNF/GDNF (N=21)		Placebo/GDNF (N=20)	
	Value	Change From Baseline	Value	Change From Baseline
Emotional Well Being Dimension				
Screening (Baseline)				
n	20		20	
Mean (SD)	18.750 (13.072)		17.292 (14.196)	
Median	20.833		16.667	
Min, Max	0.000, 37.500		0.000, 54.167	
Week 40/e0				
n	20	20	20	20
Mean (SD)	19.583 (16.617)	0.833 (10.348)	16.042 (14.260)	-1.250 (10.125)
Median	22.917	0.000	14.583	0.000
Min, Max	0.000, 58.333	-12.500, 20.833	0.000, 50.000	-20.833, 16.667

[a] Estimates are from an analysis of covariance (ANCOVA) model with baseline score as a covariate and treatment group as a factor.
Note: The PDQ-39 is a self-administered 39-item PD-specific scale that rates symptoms that occurred in the preceding month in 8 dimensions. Each item is rated from 0 (never) to 4 (always) for frequency. The score for each dimension is the average of responses in the dimension, weighted by the number of questions and multiplied by 100. PDQ-39 dimension and total scores range from 0 to 100 (0 = no problem, 100 = problem as worse as possible). The higher the score, the worse the subject's condition. Only subjects with a Week 80/e40 value are included in the observed data analysis. If an individual question response is missing, then that dimension score and the single index (total) score are also missing. Data for subject 45 are excluded from analysis.
Source: Listing 17.2.2.6, Dataset: ADQSE, Program: t_effqsum.sas, Output: t_16-2-4-4-pdq39.rtf, Generated on: 28JUL2017 05:57
Page 7 of 18

Table 16.2.4.4 PDQ-39 Score: Change from Baseline to Week 80/e40 – ANCOVA, ITT Overall Population

Parameter Visit Statistic	GDNF/GDNF (N=21)		Placebo/GDNF (N=20)	
	Value	Change From Baseline	Value	Change From Baseline
Emotional Well Being Dimension				
Week 80/e40				
n	20	20	20	20
Mean (SD)	21.458 (16.627)	2.708 (12.187)	17.292 (15.896)	0.000 (14.497)
Median	22.917	4.167	10.417	0.000
Min, Max	0.000, 62.500	-20.833, 25.000	0.000, 62.500	-25.000, 25.000
Mean difference versus placebo[a]				
(95% CI)		3.104 (-5.266, 11.474)		
p-value[a]		0.4572		

[a] Estimates are from an analysis of covariance (ANCOVA) model with baseline score as a covariate and treatment group as a factor.
Note: The PDQ-39 is a self-administered 39-item PD-specific scale that rates symptoms that occurred in the preceding month in 8 dimensions. Each item is rated from 0 (never) to 4 (always) for frequency. The score for each dimension is the average of responses in the dimension, weighted by the number of questions and multiplied by 100. PDQ-39 dimension and total scores range from 0 to 100 (0 = no problem, 100 = problem as worse as possible). The higher the score, the worse the subject's condition. Only subjects with a Week 80/e40 value are included in the observed data analysis. If an individual question response is missing, then that dimension score and the single index (total) score are also missing. Data for subject 45 are excluded from analysis.
Source: Listing 17.2.2.6, Dataset: ADQSE, Program: t_effqsum.sas, Output: t_16-2-4-4-pdq39.rtf, Generated on: 28JUL2017 05:57
Page 8 of 18

Table 16.2.4.4 PDQ-39 Score: Change from Baseline to Week 80/e40 – ANCOVA, ITT Overall Population

Parameter Visit Statistic	GDNF/GDNF (N=21)		Placebo/GDNF (N=20)	
	Value	Change From Baseline	Value	Change From Baseline
Stigma Dimension				
Screening (Baseline)				
n	20		20	
Mean (SD)	18.750 (18.023)		29.063 (24.016)	
Median	12.500		18.750	
Min, Max	0.00, 62.50		0.00, 87.50	
Week 40/e0				
n	20	20	20	20
Mean (SD)	15.000 (15.363)	-3.750 (16.399)	21.250 (22.342)	-7.813 (15.691)
Median	12.500	0.000	18.750	-6.250
Min, Max	0.00, 62.50	-50.00, 18.75	0.00, 75.00	-43.75, 31.25

[a] Estimates are from an analysis of covariance (ANCOVA) model with baseline score as a covariate and treatment group as a factor.

Note: The PDQ-39 is a self-administered 39-item PD-specific scale that rates symptoms that occurred in the preceding month in 8 dimensions. Each item is rated from 0 (never) to 4 (always) for frequency. The score for each dimension is the average of responses in the dimension, weighted by the number of questions and multiplied by 100. PDQ-39 dimension and total scores range from 0 to 100 (0 = no problem, 100 = problem as worse as possible). The higher the score, the worse the subject's condition. Only subjects with a Week 80/e40 value are included in the observed data analysis. If an individual question response is missing, then that dimension score and the single index (total) score are also missing. Data for subject 45 are excluded from analysis.

Source: Listing 17.2.2.6, Dataset: ADQSE, Program: t_effqsum.sas, Output: t_16-2-4-4-pdq39.rtf, Generated on: 28JUL2017 05:57

GDNF

Table 16.2.4.4 PDQ-39 Score: Change from Baseline to Week 80/e40 – ANCOVA, ITT Overall Population

Parameter Visit Statistic	GDNF/GDNF (N=21)		Placebo/GDNF (N=20)	
	Value	Change From Baseline	Value	Change From Baseline
Stigma Dimension				
Week 80/e40				
n	20	20	20	20
Mean (SD)	17.500 (21.613)	-1.250 (20.838)	22.500 (20.318)	-6.563 (15.103)
Median	12.500	0.000	25.000	-3.125
Min, Max	0.00, 75.00	-50.00, 43.75	0.00, 68.75	-37.50, 18.75
Mean difference versus placebo[a]				
(95% CI)		1.401 (-9.519, 12.321)		
p-value[a]		0.7964		

[a] Estimates are from an analysis of covariance (ANCOVA) model with baseline score as a covariate and treatment group as a factor.

Note: The PDQ-39 is a self-administered 39-item PD-specific scale that rates symptoms that occurred in the preceding month in 8 dimensions. Each item is rated from 0 (never) to 4 (always) for frequency. The score for each dimension is the average of responses in the dimension, weighted by the number of questions and multiplied by 100. PDQ-39 dimension and total scores range from 0 to 100 (0 = no problem, 100 = problem as worse as possible). The higher the score, the worse the subject's condition. Only subjects with a Week 80/e40 value are included in the observed data analysis. If an individual question response is missing, then that dimension score and the single index (total) score are also missing. Data for subject 45 are excluded from analysis.

Source: Listing 17.2.2.6, Dataset: ADQSE, Program: t_effqsum.sas, Output: t_16-2-4-4-pdq39.rtf, Generated on: 28JUL2017 05:57

Table 16.2.4.4 PDQ-39 Score: Change from Baseline to Week 80/e40 – ANCOVA, ITT Overall Population

Parameter Visit Statistic	GDNF/GDNF (N=21)		Placebo/GDNF (N=20)	
	Value	Change From Baseline	Value	Change From Baseline
Social Support Dimension				
Screening (Baseline)				
n	20		20	
Mean (SD)	15.000 (23.234)		15.833 (19.896)	
Median	4.167		8.333	
Min, Max	0.000, 75.000		0.000, 75.000	
Week 40/e0				
n	20	20	20	20
Mean (SD)	14.583 (18.511)	-0.417 (14.236)	11.667 (14.722)	-4.167 (18.437)
Median	8.333	0.000	8.333	0.000
Min, Max	0.000, 75.000	-50.000, 25.000	0.000, 50.000	-41.667, 25.000

[a] Estimates are from an analysis of covariance (ANCOVA) model with baseline score as a covariate and treatment group as a factor.
Note: The PDQ-39 is a self-administered 39-item PD-specific scale that rates symptoms that occurred in the preceding month in 8 dimensions. Each item is rated from 0 (never) to 4 (always) for frequency. The score for each dimension is the average of responses in the dimension, weighted by the number of questions and multiplied by 100. PDQ-39 dimension and total scores range from 0 to 100 (0 = no problem, 100 = problem as worse as possible). The higher the score, the worse the subject's condition. Only subjects with a Week 80/e40 value are included in the observed data analysis. If an individual question response is missing, then that dimension score and the single index (total) score are also missing. Data for subject 45 are excluded from analysis.
Source: Listing 17.2.2.6, Dataset: ADQSE, Program: t_effqsum.sas, Output: t_16-2-4-4-pdq39.rtf, Generated on: 28JUL2017 05:57
Page 11 of 18

Table 16.2.4.4 PDQ-39 Score: Change from Baseline to Week 80/e40 – ANCOVA, ITT Overall Population

Parameter Visit Statistic	GDNF/GDNF (N=21)		Placebo/GDNF (N=20)	
	Value	Change From Baseline	Value	Change From Baseline
Social Support Dimension				
Week 80/e40				
n	20	20	20	20
Mean (SD)	16.042 (20.514)	1.042 (14.924)	12.083 (19.017)	-3.750 (14.364)
Median	8.333	0.000	8.333	0.000
Min, Max	0.000, 58.333	-25.000, 41.667	0.000, 75.000	-41.667, 16.667
Mean difference versus placebo[a]				
(95% CI)		4.532 (-3.917, 12.981)		
p-value[a]		0.2841		

[a] Estimates are from an analysis of covariance (ANCOVA) model with baseline score as a covariate and treatment group as a factor.
Note: The PDQ-39 is a self-administered 39-item PD-specific scale that rates symptoms that occurred in the preceding month in 8 dimensions. Each item is rated from 0 (never) to 4 (always) for frequency. The score for each dimension is the average of responses in the dimension, weighted by the number of questions and multiplied by 100. PDQ-39 dimension and total scores range from 0 to 100 (0 = no problem, 100 = problem as worse as possible). The higher the score, the worse the subject's condition. Only subjects with a Week 80/e40 value are included in the observed data analysis. If an individual question response is missing, then that dimension score and the single index (total) score are also missing. Data for subject 45 are excluded from analysis.
Source: Listing 17.2.2.6, Dataset: ADQSE, Program: t_effqsum.sas, Output: t_16-2-4-4-pdq39.rtf, Generated on: 28JUL2017 05:57
Page 12 of 18

Table 16.2.4.4 PDQ-39 Score: Change from Baseline to Week 80/e40 – ANCOVA, ITT Overall Population

Parameter Visit Statistic	GDNF/GDNF (N=21)		Placebo/GDNF (N=20)	
	Value	Change From Baseline	Value	Change From Baseline
Cognitions Dimension				
Screening (Baseline)				
n	20		20	
Mean (SD)	24.688 (16.408)		17.500 (17.631)	
Median	21.875		12.500	
Min, Max	6.25, 56.25		0.00, 62.50	
Week 40/e0				
n	20	20	20	20
Mean (SD)	21.563 (17.143)	-3.125 (17.384)	14.063 (13.278)	-3.438 (11.906)
Median	18.750	-3.125	9.375	0.000
Min, Max	0.00, 68.75	-37.50, 31.25	0.00, 43.75	-31.25, 18.75

[a] Estimates are from an analysis of covariance (ANCOVA) model with baseline score as a covariate and treatment group as a factor.

Note: The PDQ-39 is a self-administered 39-item PD-specific scale that rates symptoms that occurred in the preceding month in 8 dimensions. Each item is rated from 0 (never) to 4 (always) for frequency. The score for each dimension is the average of responses in the dimension, weighted by the number of questions and multiplied by 100. PDQ-39 dimension and total scores range from 0 to 100 (0 = no problem, 100 = problem as worse as possible). The higher the score, the worse the subject's condition. Only subjects with a Week 80/e40 value are included in the observed data analysis. If an individual question response is missing, then that dimension score and the single index (total) score are also missing. Data for subject 45 are excluded from analysis.

Source: Listing 17.2.2.6, Dataset: ADQSE, Program: t_effqsum.sas, Output: t_16-2-4-4-pdq39.rtf, Generated on: 28JUL2017 05:57

Page 13 of 18

Table 16.2.4.4 PDQ-39 Score: Change from Baseline to Week 80/e40 – ANCOVA, ITT Overall Population

Parameter Visit Statistic	GDNF/GDNF (N=21)		Placebo/GDNF (N=20)	
	Value	Change From Baseline	Value	Change From Baseline
Cognitions Dimension				
Week 80/e40				
n	20	20	20	20
Mean (SD)	22.188 (16.902)	-2.500 (17.134)	13.750 (11.578)	-3.750 (12.566)
Median	21.875	-3.125	15.625	0.000
Min, Max	0.00, 56.25	-31.25, 37.50	0.00, 37.50	-31.25, 18.75
Mean difference versus placebo[a]				
(95% CI)		5.041 (-2.962, 13.043)		
p-value[a]		0.2098		

[a] Estimates are from an analysis of covariance (ANCOVA) model with baseline score as a covariate and treatment group as a factor.

Note: The PDQ-39 is a self-administered 39-item PD-specific scale that rates symptoms that occurred in the preceding month in 8 dimensions. Each item is rated from 0 (never) to 4 (always) for frequency. The score for each dimension is the average of responses in the dimension, weighted by the number of questions and multiplied by 100. PDQ-39 dimension and total scores range from 0 to 100 (0 = no problem, 100 = problem as worse as possible). The higher the score, the worse the subject's condition. Only subjects with a Week 80/e40 value are included in the observed data analysis. If an individual question response is missing, then that dimension score and the single index (total) score are also missing. Data for subject 45 are excluded from analysis.

Source: Listing 17.2.2.6, Dataset: ADQSE, Program: t_effqsum.sas, Output: t_16-2-4-4-pdq39.rtf, Generated on: 28JUL2017 05:57

Page 14 of 18

Table 16.2.4.4 PDQ-39 Score: Change from Baseline to Week 80/e40 – ANCOVA, ITT Overall Population

Parameter Visit Statistic	GDNF/GDNF (N=21)		Placebo/GDNF (N=20)	
	Value	Change From Baseline	Value	Change From Baseline
Communication Dimension				
Screening (Baseline)				
n	20		20	
Mean (SD)	18.750 (18.312)		26.667 (27.386)	
Median	12.500		20.833	
Min, Max	0.000, 66.667		0.000, 100.000	
Week 40/e0				
n	20	20	20	20
Mean (SD)	22.917 (21.608)	4.167 (15.413)	21.250 (27.101)	-5.417 (12.471)
Median	16.667	0.000	8.333	0.000
Min, Max	0.000, 58.333	-25.000, 33.333	0.000, 100.000	-25.000, 16.667

[a] Estimates are from an analysis of covariance (ANCOVA) model with baseline score as a covariate and treatment group as a factor.

Note: The PDQ-39 is a self-administered 39-item PD-specific scale that rates symptoms that occurred in the preceding month in 8 dimensions. Each item is rated from 0 (never) to 4 (always) for frequency. The score for each dimension is the average of responses in the dimension, weighted by the number of questions and multiplied by 100. PDQ-39 dimension and total scores range from 0 to 100 (0 = no problem, 100 = problem as worse as possible). The higher the score, the worse the subject's condition. Only subjects with a Week 80/e40 value are included in the observed data analysis. If an individual question response is missing, then that dimension score and the single index (total) score are also missing. Data for subject 45 are excluded from analysis.

Source: Listing 17.2.2.6, Dataset: ADQSE, Program: t_effqsum.sas, Output: t_16-2-4-4-pdq39.rtf, Generated on: 28JUL2017 05:57
Page 15 of 18

Table 16.2.4.4 PDQ-39 Score: Change from Baseline to Week 80/e40 – ANCOVA, ITT Overall Population

Parameter Visit Statistic	GDNF/GDNF (N=21)		Placebo/GDNF (N=20)	
	Value	Change From Baseline	Value	Change From Baseline
Communication Dimension				
Week 80/e40				
n	20	20	20	20
Mean (SD)	25.000 (24.483)	6.250 (26.056)	20.417 (25.859)	-6.250 (15.736)
Median	16.667	0.000	12.500	-8.333
Min, Max	0.000, 75.000	-50.000, 66.667	0.000, 91.667	-33.333, 33.333
Mean difference versus placebo[a]				
(95% CI)		9.787 (-3.388, 22.963)		
p-value[a]		0.1408		

[a] Estimates are from an analysis of covariance (ANCOVA) model with baseline score as a covariate and treatment group as a factor.

Note: The PDQ-39 is a self-administered 39-item PD-specific scale that rates symptoms that occurred in the preceding month in 8 dimensions. Each item is rated from 0 (never) to 4 (always) for frequency. The score for each dimension is the average of responses in the dimension, weighted by the number of questions and multiplied by 100. PDQ-39 dimension and total scores range from 0 to 100 (0 = no problem, 100 = problem as worse as possible). The higher the score, the worse the subject's condition. Only subjects with a Week 80/e40 value are included in the observed data analysis. If an individual question response is missing, then that dimension score and the single index (total) score are also missing. Data for subject 45 are excluded from analysis.

Source: Listing 17.2.2.6, Dataset: ADQSE, Program: t_effqsum.sas, Output: t_16-2-4-4-pdq39.rtf, Generated on: 28JUL2017 05:57

Table 16.2.4.4 PDQ-39 Score: Change from Baseline to Week 80/e40 – ANCOVA, ITT Overall Population

Parameter Visit Statistic	GDNF/GDNF (N=21)		Placebo/GDNF (N=20)	
	Value	Change From Baseline	Value	Change From Baseline
Bodily Discomfort Dimension				
Screening (Baseline)				
n	20		20	
Mean (SD)	42.917 (22.503)		48.333 (26.710)	
Median	45.833		54.167	
Min, Max	0.000, 75.000		8.333, 100.000	
Week 40/e0				
n	20	20	20	20
Mean (SD)	36.250 (24.073)	-6.667 (20.160)	39.583 (23.706)	-8.750 (18.432)
Median	41.667	-8.333	37.500	-8.333
Min, Max	0.000, 75.000	-50.000, 33.333	0.000, 83.333	-41.667, 33.333

[a] Estimates are from an analysis of covariance (ANCOVA) model with baseline score as a covariate and treatment group as a factor.

Note: The PDQ-39 is a self-administered 39-item PD-specific scale that rates symptoms that occurred in the preceding month in 8 dimensions. Each item is rated from 0 (never) to 4 (always) for frequency. The score for each dimension is the average of responses in the dimension, weighted by the number of questions and multiplied by 100. PDQ-39 dimension and total scores range from 0 to 100 (0 = no problem, 100 = problem as worse as possible). The higher the score, the worse the subject's condition. Only subjects with a Week 80/e40 value are included in the observed data analysis. If an individual question response is missing, then that dimension score and the single index (total) score are also missing. Data for subject 45 are excluded from analysis.

Source: Listing 17.2.2.6, Dataset: ADQSE, Program: t_effqsum.sas, Output: t_16-2-4-4-pdq39.rtf, Generated on: 28JUL2017 05:57

Page 17 of 18

Table 16.2.4.4 PDQ-39 Score: Change from Baseline to Week 80/e40 – ANCOVA, ITT Overall Population

Parameter Visit Statistic	GDNF/GDNF (N=21)		Placebo/GDNF (N=20)	
	Value	Change From Baseline	Value	Change From Baseline
Bodily Discomfort Dimension				
Week 80/e40				
n	20	20	20	20
Mean (SD)	38.750 (23.144)	-4.167 (18.237)	40.833 (23.399)	-7.500 (26.752)
Median	37.500	-8.333	41.667	-8.333
Min, Max	0.000, 75.000	-33.333, 33.333	0.000, 91.667	-50.000, 66.667
Mean difference versus placebo[a]				
(95% CI)		0.702 (-12.039, 13.444)		
p-value[a]		0.9117		

[a] Estimates are from an analysis of covariance (ANCOVA) model with baseline score as a covariate and treatment group as a factor.
Note: The PDQ-39 is a self-administered 39-item PD-specific scale that rates symptoms that occurred in the preceding month in 8 dimensions. Each item is rated from 0 (never) to 4 (always) for frequency. The score for each dimension is the average of responses in the dimension, weighted by the number of questions and multiplied by 100. PDQ-39 dimension and total scores range from 0 to 100 (0 = no problem, 100 = problem as worse as possible). The higher the score, the worse the subject's condition. Only subjects with a Week 80/e40 value are included in the observed data analysis. If an individual question response is missing, then that dimension score and the single index (total) score are also missing. Data for subject 45 are excluded from analysis.
Source: Listing 17.2.2.6, Dataset: ADQSE, Program: t_effqsum.sas, Output: t_16-2-4-4-pdq39.rtf, Generated on: 28JUL2017 05:57
Page 18 of 18

Table 16.2.4.5.1 EQ-5D Questionnaire: Baseline, Week 40/e0, and Week 80/e40 – Observed Data, ITT Overall Population

EQ-5D Dimension Visit Response Level	GDNF/GDNF (N=21) n (%)	Placebo/GDNF (N=20) n (%)
Mobility		
Screening (Baseline)		
No problem	8 (38.1)	10 (50.0)
Moderate problem	12 (57.1)	10 (50.0)
Severe problem	0	0
Week 40/e0		
No problem	10 (47.6)	8 (40.0)
Moderate problem	10 (47.6)	12 (60.0)
Severe problem	0	0
Week 80/e40		
No problem	12 (57.1)	11 (55.0)
Moderate problem	8 (38.1)	9 (45.0)
Severe problem	0	0

Note: The EQ-5D is a self-administered 5-item scale with three possible answers for each item (1=no problem, 2=moderate problem, 3=severe problem), and a visual analog scale ranging from 0 to 100, where 0 indicates worst health and 100 indicates best health. Only subjects with a Week 80/e40 value are included in the observed data analysis. Data for subject 45 are excluded from analysis.
Source: Listing 17.2.2.7, Dataset: ADQSE, Program: t_eq5d.sas, Output: t_16-2-4-5-1-eq5d.rtf, Generated on: 28JUL2017 05:57
Page 1 of 5

Table 16.2.4.5.1 EQ-5D Questionnaire: Baseline, Week 40/e0, and Week 80/e40 – Observed Data, ITT Overall Population

EQ-5D Dimension Visit Response Level	GDNF/GDNF (N=21) n (%)	Placebo/GDNF (N=20) n (%)
Self-Care		
Screening (Baseline)		
No problem	14 (66.7)	10 (50.0)
Moderate problem	6 (28.6)	10 (50.0)
Severe problem	0	0
Week 40/e0		
No problem	14 (66.7)	12 (60.0)
Moderate problem	5 (23.8)	8 (40.0)
Severe problem	1 (4.8)	0
Week 80/e40		
No problem	16 (76.2)	14 (70.0)
Moderate problem	4 (19.0)	6 (30.0)
Severe problem	0	0

Note: The EQ-5D is a self-administered 5-item scale with three possible answers for each item (1=no problem, 2=moderate problem, 3=severe problem), and a visual analog scale ranging from 0 to 100, where 0 indicates worst health and 100 indicates best health. Only subjects with a Week 80/e40 value are included in the observed data analysis. Data for subject 45 are excluded from analysis.
Source: Listing 17.2.2.7, Dataset: ADQSE, Program: t_eq5d.sas, Output: t_16-2-4-5-1-eq5d.rtf, Generated on: 28JUL2017 05:57
Page 2 of 5

Table 16.2.4.5.1 EQ-5D Questionnaire: Baseline, Week 40/e0, and Week 80/e40 – Observed Data, ITT Overall Population

EQ-5D Dimension Visit Response Level	GDNF/GDNF (N=21) n (%)	Placebo/GDNF (N=20) n (%)
Usual Activities		
Screening (Baseline)		
No problem	8 (38.1)	10 (50.0)
Moderate problem	12 (57.1)	10 (50.0)
Severe problem	0	0
Week 40/e0		
No problem	10 (47.6)	12 (60.0)
Moderate problem	10 (47.6)	8 (40.0)
Severe problem	0	0
Week 80/e40		
No problem	11 (52.4)	12 (60.0)
Moderate problem	9 (42.9)	8 (40.0)
Severe problem	0	0

Note: The EQ-5D is a self-administered 5-item scale with three possible answers for each item (1=no problem, 2=moderate problem, 3=severe problem), and a visual analog scale ranging from 0 to 100, where 0 indicates worst health and 100 indicates best health. Only subjects with a Week 80/e40 value are included in the observed data analysis. Data for subject 45 are excluded from analysis.
Source: Listing 17.2.2.7, Dataset: ADQSE, Program: t_eq5d.sas, Output: t_16-2-4-5-1-eq5d.rtf, Generated on: 28JUL2017 05:57
Page 3 of 5

Table 16.2.4.5.1 EQ-5D Questionnaire: Baseline, Week 40/e0, and Week 80/e40 – Observed Data, ITT Overall Population

EQ-5D Dimension Visit Response Level	GDNF/GDNF (N=21) n (%)	Placebo/GDNF (N=20) n (%)
Pain/Discomfort		
Screening (Baseline)		
No problem	7 (33.3)	11 (55.0)
Moderate problem	13 (61.9)	8 (40.0)
Severe problem	0	1 (5.0)
Week 40/e0		
No problem	7 (33.3)	6 (30.0)
Moderate problem	13 (61.9)	13 (65.0)
Severe problem	0	1 (5.0)
Week 80/e40		
No problem	9 (42.9)	11 (55.0)
Moderate problem	11 (52.4)	9 (45.0)
Severe problem	0	0

Note: The EQ-5D is a self-administered 5-item scale with three possible answers for each item (1=no problem, 2=moderate problem, 3=severe problem), and a visual analog scale ranging from 0 to 100, where 0 indicates worst health and 100 indicates best health. Only subjects with a Week 80/e40 value are included in the observed data analysis. Data for subject 45 are excluded from analysis.
Source: Listing 17.2.2.7, Dataset: ADQSE, Program: t_eq5d.sas, Output: t_16-2-4-5-1-eq5d.rtf, Generated on: 28JUL2017 05:57
Page 4 of 5

Table 16.2.4.5.1 EQ-5D Questionnaire: Baseline, Week 40/e0, and Week 80/e40 – Observed Data, ITT Overall Population

EQ-5D Dimension Visit Response Level	GDNF/GDNF (N=21) n (%)	Placebo/GDNF (N=20) n (%)
Anxiety/Depression		
Screening (Baseline)		
No problem	18 (85.7)	18 (90.0)
Moderate problem	2 (9.5)	1 (5.0)
Severe problem	0	1 (5.0)
Week 40/e0		
No problem	18 (85.7)	17 (85.0)
Moderate problem	2 (9.5)	3 (15.0)
Severe problem	0	0
Week 80/e40		
No problem	20 (95.2)	19 (95.0)
Moderate problem	0	1 (5.0)
Severe problem	0	0

Note: The EQ-5D is a self-administered 5-item scale with three possible answers for each item (1=no problem, 2=moderate problem, 3=severe problem), and a visual analog scale ranging from 0 to 100, where 0 indicates worst health and 100 indicates best health. Only subjects with a Week 80/e40 value are included in the observed data analysis. Data for subject 45 are excluded from analysis.
Source: Listing 17.2.2.7, Dataset: ADQSE, Program: t_eq5d.sas, Output: t_16-2-4-5-1-eq5d.rtf, Generated on: 28JUL2017 05:57

Table 16.2.4.5.2 EQ-5D Visual Analog Scale: Change from Baseline to Week 80/e40 – ANCOVA, ITT Overall Population

Parameter Visit Statistic	GDNF/GDNF (N=21)		Placebo/GDNF (N=20)	
	Value	Change From Baseline	Value	Change From Baseline
EQ VAS Score				
Screening (Baseline)				
n	20		20	
Mean (SD)	69.35 (13.441)		71.18 (14.621)	
Median	71.00		75.00	
Min, Max	50.0, 90.0		40.0, 94.5	
Week 40/e0				
n	20	20	20	20
Mean (SD)	76.05 (11.194)	6.70 (14.042)	75.00 (12.945)	3.83 (18.173)
Median	75.00	6.50	75.00	5.00
Min, Max	40.0, 90.0	-20.0, 30.0	40.0, 94.0	-24.5, 46.0

[a] Estimates are from an analysis of covariance (ANCOVA) model with baseline score as a covariate and treatment group as a factor.
Note: The EQ-5D is a self-administered 5-item scale with three possible answers for each item (1=no problem, 2=moderate problem, 3=severe problem), and a visual analog scale ranging from 0 to 100, where 0 indicates worst health and 100 indicates best health. Only subjects with a Week 80/e40 value are included in the analysis. Data for subject 45 are excluded from analysis.
Source: Listing 17.2.2.7, Dataset: ADQSE, Program: t_effqsum.sas, Output: t_16-2-4-5-2-eq5d.rtf, Generated on: 28JUL2017 05:57
Page 1 of 2

Table 16.2.4.5.2 EQ-5D Visual Analog Scale: Change from Baseline to Week 80/e40 – ANCOVA, ITT Overall Population

Parameter Visit Statistic	GDNF/GDNF (N=21)		Placebo/GDNF (N=20)	
	Value	Change From Baseline	Value	Change From Baseline
EQ VAS Score				
Week 80/e40				
n	20	20	20	20
Mean (SD)	77.25 (13.357)	7.90 (15.570)	80.65 (9.938)	9.48 (14.369)
Median	80.00	5.00	82.50	8.00
Min, Max	35.0, 99.0	-20.0, 35.0	60.0, 100.0	-24.5, 47.0
Mean difference versus placebo[a]				
(95% CI)		-2.88 (-10.10, 4.33)		
p-value[a]		0.4230		

[a] Estimates are from an analysis of covariance (ANCOVA) model with baseline score as a covariate and treatment group as a factor.
Note: The EQ-5D is a self-administered 5-item scale with three possible answers for each item (1=no problem, 2=moderate problem, 3=severe problem), and a visual analog scale ranging from 0 to 100, where 0 indicates worst health and 100 indicates best health. Only subjects with a Week 80/e40 value are included in the analysis. Data for subject 45 are excluded from analysis.
Source: Listing 17.2.2.7, Dataset: ADQSE, Program: t_effqsum.sas, Output: t_16-2-4-5-2-eq5d.rtf, Generated on: 28JUL2017 05:57
Page 2 of 2

Table 16.2.4.6 SNAQ Score: Change from Baseline to Week 80/e40 – ANCOVA, ITT Overall Population

Parameter Visit Statistic	GDNF/GDNF (N=21)		Placebo/GDNF (N=20)	
	Value	Change From Baseline	Value	Change From Baseline
SNAQ Total Score				
Screening (Baseline)				
n	17		17	
Mean (SD)	15.8 (1.67)		15.8 (1.95)	
Median	16.0		16.0	
Min, Max	13, 18		12, 18	
Week 40/e0				
n	16	16	18	17
Mean (SD)	15.3 (1.35)	-0.7 (1.25)	15.8 (1.66)	0.0 (1.46)
Median	15.0	-0.5	16.0	0.0
Min, Max	13, 18	-3, 1	13, 19	-4, 2

[a] Estimates are from an analysis of covariance (ANCOVA) model with baseline score as a covariate and treatment group as a factor.
Note: The SNAQ is a self-administered 4-question instrument with total scores ranging from 4 to 20 (4=poor appetite, 20=good appetite). Only subjects
   with a Week 80/e40 value are included in the analysis. If an individual question is not answered, then the total score is considered missing.
Source: Listing 17.2.2.8, Dataset: ADQSE, Program: t_effqsum.sas, Output: t_16-2-4-6-snaq.rtf, Generated on: 28JUL2017 05:57
Page 1 of 2

Table 16.2.4.6 SNAQ Score: Change from Baseline to Week 80/e40 – ANCOVA, ITT Overall Population

Parameter Visit Statistic	GDNF/GDNF (N=21)		Placebo/GDNF (N=20)	
	Value	Change From Baseline	Value	Change From Baseline
SNAQ Total Score				
Week 80/e40				
n	21	17	20	17
Mean (SD)	15.7 (2.24)	-0.1 (1.45)	16.9 (1.76)	0.8 (1.86)
Median	16.0	0.0	17.0	1.0
Min, Max	9, 18	-4, 3	13, 20	-3, 4
Mean difference versus placebo[a]				
(95% CI)		-0.9 (-1.9, 0.2)		
p-value[a]		0.1166		

[a] Estimates are from an analysis of covariance (ANCOVA) model with baseline score as a covariate and treatment group as a factor.
Note: The SNAQ is a self-administered 4-question instrument with total scores ranging from 4 to 20 (4=poor appetite, 20=good appetite). Only subjects
    with a Week 80/e40 value are included in the analysis. If an individual question is not answered, then the total score is considered missing.
Source: Listing 17.2.2.8, Dataset: ADQSE, Program: t_effqsum.sas, Output: t_16-2-4-6-snaq.rtf, Generated on: 28JUL2017 05:57
Page 2 of 2

Table 16.2.4.7 Total Daily Levodopa Dose (mg): Change From Baseline to Week 80/e40 – ANCOVA, ITT Overall Population

Visit Statistic	GDNF/GDNF (N=21)		Placebo/GDNF (N=20)	
	Value	Change From Baseline	Value	Change From Baseline
Week 0 (Baseline)				
n	21		20	
Mean (SD)	638.95 (305.969)		560.80 (283.570)	
Median	525.00		532.00	
Min, Max	300.0, 1596.0		100.0, 1200.0	
Week 40/e0				
n	21	21	20	20
Mean (SD)	628.63 (275.698)	-10.32 (191.673)	610.28 (289.995)	49.48 (107.792)
Median	575.00	0.00	561.88	0.00
Min, Max	300.0, 1596.0	-390.5, 423.0	100.0, 1214.5	-133.3, 314.5
Week 80/e40				
n	21	21	20	20
Mean (SD)	674.82 (309.695)	35.87 (186.313)	721.00 (390.982)	160.20 (230.317)
Median	599.00	0.00	641.00	66.75
Min, Max	300.0, 1729.0	-375.0, 423.0	100.0, 1350.0	-83.3, 707.0
Mean difference versus placebo[a] (95% CI)		-121.12 (-255.98, 13.74)		
p-value[a]		0.0769		

[a] Estimates are from an analysis of covariance (ANCOVA) model with baseline levodopa dose as a covariate and treatment group as a factor.
Note: Only subjects with a Week 80/e40 levodopa value are included in the analysis.
Source: Listing 17.2.2.9.1, Dataset: ADCM, Program: t_levdose.sas, Output: t_16-2-4-7-levdose.rtf, Generated on: 28JUL2017 05:57
Page 1 of 1

Table 16.2.4.8 Total Daily Levodopa Equivalent Dose (mg): Change From Baseline to Week 80/e40 – ANCOVA, ITT Overall Population

Visit Statistic	GDNF/GDNF (N=21)		Placebo/GDNF (N=20)	
	Value	Change From Baseline	Value	Change From Baseline
Week 0 (Baseline)				
n	21		20	
Mean (SD)	1011.26 (340.357)		953.67 (383.393)	
Median	930.00		930.00	
Min, Max	400.0, 1990.0		299.5, 1860.0	
Week 40/e0				
n	21	21	20	20
Mean (SD)	1021.21 (367.424)	9.95 (214.208)	1057.14 (401.426)	103.48 (149.372)
Median	1000.00	0.00	1067.00	50.00
Min, Max	400.0, 2262.8	-420.0, 423.0	494.0, 2100.0	-133.3, 510.0
Week 80/e40				
n	21	21	20	20
Mean (SD)	1070.63 (395.559)	59.37 (193.563)	1242.68 (552.209)	289.01 (364.820)
Median	1033.10	18.00	1184.25	150.00
Min, Max	400.0, 2470.0	-290.8, 480.0	441.0, 2208.0	-83.3, 1154.0
Mean difference versus placebo[a] (95% CI)		-232.66 (-418.65, -46.67)		
p-value[a]		0.0156		

[a] Estimates are from an analysis of covariance (ANCOVA) model with baseline levodopa equivalent dose as a covariate and treatment group as a factor.
Note: Only subjects with a Week 80/e40 levodopa equivalent value are included in the analysis.
Source: Listing 17.2.2.9.2, Dataset: ADCM, Program: t_levdose.sas, Output: t_16-2-4-8-levdose.rtf, Generated on: 28JUL2017 05:57
Page 1 of 1

Table 16.3.1 Volume of Distribution of Infusate as Determined by Contrast-Enhanced T1-Weighted MRI: Change from Baseline to Week 80/e40 – ANCOVA, ITT Primary Population

Parameter Visit Statistic	GDNF/GDNF (N=17)		Placebo/GDNF (N=18)	
	Value	Change From Baseline	Value	Change From Baseline
Volume of Distribution (mL), Left				
Healing Phase (Baseline)				
n	16		18	
Mean (SD)	4.894 (1.453)		4.833 (1.738)	
Median	5.171		4.843	
Min, Max	2.051, 7.121		2.538, 8.076	
Week 40/e0				
n	17	16	18	18
Mean (SD)	6.443 (1.511)	1.587 (1.411)	6.489 (2.228)	1.655 (2.737)
Median	6.047	1.756	6.451	2.528
Min, Max	3.765, 9.200	-1.354, 3.465	1.915, 11.265	-4.957, 5.612
Week 80/e40				
n	16	15	18	18
Mean (SD)	6.419 (1.703)	1.502 (1.883)	7.189 (2.123)	2.356 (2.539)
Median	6.133	1.569	6.395	2.315
Min, Max	3.731, 9.370	-1.927, 4.972	4.628, 11.137	-2.744, 6.861
Mean difference versus placebo[a]				
(95% CI)		-0.738 (-2.131, 0.654)		
p-value[a]		0.2874		

[a] Estimates are from an analysis of covariance (ANCOVA) model with baseline result as a covariate and treatment group as a factor.
Source: Listing 17.2.3.1, Dataset: ADPR, Program: t_mri.sas, Output: t_16-3-1-mri.rtf, Generated on: 28JUL2017 05:57
Page 1 of 2

**Table 16.3.1 Volume of Distribution of Infusate as Determined by Contrast-Enhanced T1-Weighted MRI: Change from Baseline to Week 80/e40 –
ANCOVA, ITT Primary Population**

Parameter Visit Statistic	GDNF/GDNF (N=17)		Placebo/GDNF (N=18)	
	Value	Change From Baseline	Value	Change From Baseline
Volume of Distribution (mL), Right				
Healing Phase (Baseline)				
n	16		18	
Mean (SD)	4.914 (1.582)		4.567 (1.557)	
Median	5.141		4.377	
Min, Max	2.113, 8.032		2.049, 7.676	
Week 40/e0				
n	17	16	18	18
Mean (SD)	6.564 (1.507)	1.687 (1.789)	6.710 (1.653)	2.143 (2.568)
Median	7.039	1.731	6.540	2.246
Min, Max	3.299, 8.523	-1.202, 5.342	2.949, 9.321	-3.411, 6.545
Week 80/e40				
n	16	15	17	17
Mean (SD)	6.300 (1.884)	1.370 (2.300)	6.248 (1.675)	1.864 (1.964)
Median	6.000	1.601	6.069	2.168
Min, Max	2.680, 9.699	-3.547, 4.672	3.371, 10.036	-2.596, 5.754
Mean difference versus placebo[a]				
(95% CI)		-0.025 (-1.359, 1.309)		
p-value[a]		0.9699		

[a] Estimates are from an analysis of covariance (ANCOVA) model with baseline result as a covariate and treatment group as a factor.
Source: Listing 17.2.3.1, Dataset: ADPR, Program: t_mri.sas, Output: t_16-3-1-mri.rtf, Generated on: 28JUL2017 05:57
Page 2 of 2

Table 16.3.2.1 Volume of Interest Coverage as Determined by Contrast-Enhanced T1-Weighted MRI: Change from Baseline to Week 80/e40 – ANCOVA, ITT Primary Population

Parameter Visit Statistic	GDNF/GDNF (N=17)		Placebo/GDNF (N=18)	
	Value	Change From Baseline	Value	Change From Baseline
Volume of Interest Coverage (%), Left Healing Phase (Baseline)				
n	16		18	
Mean (SD)	74.225 (15.292)		67.222 (11.200)	
Median	74.250		65.250	
Min, Max	42.40, 94.30		47.90, 94.70	
Week 40/e0				
n	17	16	18	18
Mean (SD)	78.539 (14.237)	5.292 (13.730)	68.749 (19.641)	1.527 (25.481)
Median	80.400	4.900	71.150	3.150
Min, Max	51.00, 99.40	-14.30, 38.30	31.94, 100.00	-51.90, 38.00
Week 80/e40				
n	16	15	18	18
Mean (SD)	71.869 (21.342)	-2.520 (22.253)	74.333 (14.499)	7.111 (19.210)
Median	76.450	-2.600	75.650	10.150
Min, Max	29.80, 99.70	-55.70, 25.50	42.10, 95.10	-33.60, 26.70
Mean difference versus placebo[a] (95% CI)		-4.232 (-17.785, 9.321)		
p-value[a]		0.5285		

[a] Estimates are from an analysis of covariance (ANCOVA) model with baseline result as a covariate and treatment group as a factor.
Source: Listing 17.2.3.1, Dataset: ADPR, Program: t_mri.sas, Output: t_16-3-2-1-mri.rtf, Generated on: 28JUL2017 05:57
Page 1 of 3

Table 16.3.2.1 Volume of Interest Coverage as Determined by Contrast-Enhanced T1-Weighted MRI: Change from Baseline to Week 80/e40 – ANCOVA, ITT Primary Population

Parameter Visit Statistic	GDNF/GDNF (N=17)		Placebo/GDNF (N=18)	
	Value	Change From Baseline	Value	Change From Baseline
Volume of Interest Coverage (%), Right Healing Phase (Baseline)				
n	16		18	
Mean (SD)	70.563 (17.154)		67.122 (15.320)	
Median	72.600		66.500	
Min, Max	40.20, 93.20		34.90, 90.40	
Week 40/e0				
n	17	16	18	18
Mean (SD)	78.405 (15.060)	7.893 (13.822)	71.026 (23.832)	3.903 (28.649)
Median	79.600	7.800	76.650	7.850
Min, Max	43.10, 100.00	-21.60, 33.90	18.00, 100.00	-57.60, 48.20
Week 80/e40				
n	16	15	17	17
Mean (SD)	69.963 (21.477)	-2.840 (27.813)	67.912 (21.931)	-1.106 (24.150)
Median	69.950	-0.300	68.400	-6.600
Min, Max	19.80, 100.00	-62.30, 46.50	34.00, 100.00	-39.00, 48.20
Mean difference versus placebo[a] (95% CI)		1.398 (-14.938, 17.733)		
p-value[a]		0.8623		

[a] Estimates are from an analysis of covariance (ANCOVA) model with baseline result as a covariate and treatment group as a factor.
Source: Listing 17.2.3.1, Dataset: ADPR, Program: t_mri.sas, Output: t_16-3-2-1-mri.rtf, Generated on: 28JUL2017 05:57
Page 2 of 3

Table 16.3.2.1 Volume of Interest Coverage as Determined by Contrast-Enhanced T1-Weighted MRI: Change from Baseline to Week 80/e40 – ANCOVA, ITT Primary Population

Parameter Visit Statistic	GDNF/GDNF (N=17)		Placebo/GDNF (N=18)	
	Value	Change From Baseline	Value	Change From Baseline
Volume of Interest Coverage (%), Both Healing Phase (Baseline)				
n	16		18	
Mean (SD)	72.394 (12.611)		67.172 (10.777)	
Median	73.325		68.675	
Min, Max	46.000, 92.200		49.100, 88.750	
Week 40/e0				
n	17	16	18	18
Mean (SD)	78.472 (13.243)	6.593 (9.067)	69.888 (18.244)	2.715 (23.806)
Median	75.950	4.550	73.975	1.850
Min, Max	53.700, 99.700	-4.720, 24.100	32.270, 93.550	-51.830, 39.600
Week 80/e40				
n	16	15	18	18
Mean (SD)	70.916 (17.627)	-2.680 (19.335)	70.603 (16.020)	3.431 (18.845)
Median	72.050	1.950	70.150	3.700
Min, Max	29.000, 99.850	-39.900, 19.600	45.700, 95.100	-36.300, 36.750
Mean difference versus placebo[a]				
(95% CI)		-1.280 (-13.977, 11.417)		
p-value[a]		0.8382		

[a] Estimates are from an analysis of covariance (ANCOVA) model with baseline result as a covariate and treatment group as a factor.
Source: Listing 17.2.3.1, Dataset: ADPR, Program: t_mri.sas, Output: t_16-3-2-1-mri.rtf, Generated on: 28JUL2017 05:57
Page 3 of 3

Table 16.3.2.2 Total Putamenal Coverage as Determined by Contrast-Enhanced T1-Weighted MRI: Change from Baseline to Week 80/e40 – ANCOVA, ITT Primary Population

Parameter Visit Statistic	GDNF/GDNF (N=17)		Placebo/GDNF (N=18)	
	Value	Change From Baseline	Value	Change From Baseline
Total Putamenal Coverage (%), Left Randomization (Baseline)				
n	16		18	
Mean (SD)	54.968 (17.087)		50.253 (15.530)	
Median	54.512		49.005	
Min, Max	14.944, 77.156		22.013, 75.832	
Week 40/e0				
n	17	16	18	18
Mean (SD)	54.789 (17.817)	1.553 (15.073)	47.745 (13.508)	-2.508 (20.289)
Median	60.404	4.472	49.473	0.496
Min, Max	24.178, 78.385	-36.603, 20.675	24.805, 70.776	-51.027, 28.732
Week 80/e40				
n	16	15	18	18
Mean (SD)	57.150 (21.547)	2.324 (21.455)	54.192 (13.243)	3.939 (11.944)
Median	59.438	5.461	54.536	4.268
Min, Max	16.290, 84.484	-45.952, 40.390	30.861, 75.516	-15.972, 23.484
Mean difference versus placebo[a] (95% CI)		0.920 (-10.300, 12.141)		
p-value[a]		0.8681		

[a] Estimates are from an analysis of covariance (ANCOVA) model with baseline result as a covariate and treatment group as a factor.
Source: Listing 17.2.3.1, Dataset: ADPR, Program: t_mri.sas, Output: t_16-3-2-2-mri.rtf, Generated on: 28JUL2017 05:57
Page 1 of 3

Table 16.3.2.2 Total Putamenal Coverage as Determined by Contrast-Enhanced T1-Weighted MRI: Change from Baseline to Week 80/e40 – ANCOVA, ITT Primary Population

Parameter Visit Statistic	GDNF/GDNF (N=17)		Placebo/GDNF (N=18)	
	Value	Change From Baseline	Value	Change From Baseline
Total Putamenal Coverage (%), Right Randomization (Baseline)				
n	16		18	
Mean (SD)	50.744 (14.932)		50.204 (14.127)	
Median	51.614		54.106	
Min, Max	23.404, 76.042		20.475, 68.717	
Week 40/e0				
n	17	16	18	18
Mean (SD)	53.370 (16.487)	3.614 (12.956)	48.121 (15.286)	-2.083 (18.700)
Median	54.097	4.934	46.200	1.820
Min, Max	28.674, 82.631	-24.569, 29.020	21.368, 78.008	-34.627, 19.996
Week 80/e40				
n	16	15	17	17
Mean (SD)	48.505 (15.533)	-2.905 (19.371)	51.116 (17.933)	1.124 (16.830)
Median	47.781	-9.626	48.704	-1.279
Min, Max	22.148, 77.892	-38.079, 34.070	17.558, 83.329	-25.771, 23.618
Mean difference versus placebo[a] (95% CI) p-value[a]		-2.504 (-14.255, 9.247) 0.6662		

[a] Estimates are from an analysis of covariance (ANCOVA) model with baseline result as a covariate and treatment group as a factor.
Source: Listing 17.2.3.1, Dataset: ADPR, Program: t_mri.sas, Output: t_16-3-2-2-mri.rtf, Generated on: 28JUL2017 05:57
Page 2 of 3

Table 16.3.2.2 Total Putamenal Coverage as Determined by Contrast-Enhanced T1-Weighted MRI: Change from Baseline to Week 80/e40 – ANCOVA, ITT Primary Population

Parameter Visit Statistic	GDNF/GDNF (N=17)		Placebo/GDNF (N=18)	
	Value	Change From Baseline	Value	Change From Baseline
Total Putamenal Coverage (%), Both Randomization (Baseline)				
n	16		18	
Mean (SD)	52.856 (14.769)		50.228 (14.013)	
Median	53.076		50.185	
Min, Max	19.174, 72.850		22.971, 67.589	
Week 40/e0				
n	17	16	18	18
Mean (SD)	54.079 (15.867)	2.584 (12.407)	47.933 (11.489)	-2.296 (16.447)
Median	55.733	4.836	44.232	-0.272
Min, Max	26.426, 78.183	-30.586, 22.665	27.166, 74.392	-36.547, 24.127
Week 80/e40				
n	16	15	18	18
Mean (SD)	52.828 (17.597)	-0.291 (18.171)	52.229 (13.590)	2.000 (12.960)
Median	53.698	-1.537	49.195	5.315
Min, Max	19.307, 81.188	-27.924, 37.230	26.136, 79.422	-20.871, 20.720
Mean difference versus placebo[a]				
(95% CI)		-0.323 (-10.480, 9.834)		
p-value[a]		0.9487		

[a] Estimates are from an analysis of covariance (ANCOVA) model with baseline result as a covariate and treatment group as a factor.
Source: Listing 17.2.3.1, Dataset: ADPR, Program: t_mri.sas, Output: t_16-3-2-2-mri.rtf, Generated on: 28JUL2017 05:57
Page 3 of 3

Table 16.3.3.1 Correlation Analyses of Percentage Change from Baseline to Week 80/e40 in OFF State UPDRS Motor Score (Part III) to Volume of Interest Coverage and Total Putamenal Coverage at Baseline as Determined by Contrast-Enhanced T1-Weighted MRI – ITT Primary Population

Parameters	GDNF/GDNF (N=17) n Spearman Rank Correlation (95% CI) p-value	Placebo/GDNF (N=18) n Spearman Rank Correlation (95% CI) p-value
Percentage change from baseline to Week 80/e40 in OFF state UPDRS motor score (part III)		
versus	16 0.085 (-0.429, 0.557)	18 0.024 (-0.448, 0.486)
VOI coverage at baseline, both putamina combined	0.7498	0.9233
Percentage change from baseline to Week 80/e40 in OFF state UPDRS motor score (part III)		
versus	16 -0.080 (-0.553, 0.433)	18 -0.143 (-0.571, 0.347)
Total putamenal coverage at baseline, both putamina combined	0.7660	0.5665

Note: For subject 45, items 22, 27, 28, 29 and 30 are excluded from the UPDRS score.
Source: Listing 17.2.2.1, 17.2.3.1, Dataset: ADPR, ADQUPDRS, Program: t_correl.sas, Output: t_16-3-3-1-correl.rtf, Generated on: 28JUL2017 05:57
Page 1 of 1

Table 16.3.3.2 Correlation Analysis of Percentage Change from Baseline to Week 80/e40 in OFF State UPDRS Motor Score (Part III) to Change from Baseline to Week 40/e0 in ^{18}F-DOPA Uptake as Determined by PET Scan – ITT Primary Population

Parameters	GDNF/GDNF (N=17) n Spearman Rank Correlation (95% CI) p-value	Placebo/GDNF (N=18) n Spearman Rank Correlation (95% CI) p-value
Percentage change from baseline to Week 80/e40 in OFF state UPDRS motor score (part III)		
versus		
Change from baseline to Week 40/e0 in ^{18}F-DOPA uptake rate constant, dorsal caudate nucleus, both hemispheres combined	17 -0.264 (-0.661, 0.248) 0.2964	18 -0.370 (-0.714, 0.117) 0.1216
Percentage change from baseline to Week 80/e40 in OFF state UPDRS motor score (part III)		
versus		
Change from baseline to Week 40/e0 in ^{18}F-DOPA uptake rate constant, dorsal anterior putamen, both hemispheres combined	17 -0.384 (-0.730, 0.118) 0.1185	18 0.281 (-0.214, 0.661) 0.2496

Note: For subject 45, items 22, 27, 28, 29 and 30 are excluded from the UPDRS score.
Source: Listing 17.2.2.1, Dataset: ADPR, ADQUPDRS, Program: t_correl.sas, Output: t_16-3-3-2-correl.rtf, Generated on: 28JUL2017 05:57
Page 1 of 3

Table 16.3.3.2 Correlation Analysis of Percentage Change from Baseline to Week 80/e40 in OFF State UPDRS Motor Score (Part III) to Change from Baseline to Week 40/e0 in ^{18}F-DOPA Uptake as Determined by PET Scan – ITT Primary Population

Parameters	GDNF/GDNF (N=17) n Spearman Rank Correlation (95% CI) p-value	Placebo/GDNF (N=18) n Spearman Rank Correlation (95% CI) p-value
Percentage change from baseline to Week 80/e40 in OFF state UPDRS motor score (part III)		
versus		
Change from baseline to Week 40/e0 in ^{18}F-DOPA uptake rate constant, dorsal central/posterior putamen, both hemispheres combined	17 -0.290 (-0.677, 0.221) 0.2485	18 0.415 (-0.064, 0.739) 0.0786
Percentage change from baseline to Week 80/e40 in OFF state UPDRS motor score (part III)		
versus		
Change from baseline to Week 40/e0 in ^{18}F-DOPA uptake rate constant, ventral striatum, both hemispheres combined	17 0.095 (-0.404, 0.551) 0.7129	18 -0.242 (-0.637, 0.253) 0.3247

Note: For subject 45, items 22, 27, 28, 29 and 30 are excluded from the UPDRS score.
Source: Listing 17.2.2.1, Dataset: ADPR, ADQUPDRS, Program: t_correl.sas, Output: t_16-3-3-2-correl.rtf, Generated on: 28JUL2017 05:57
Page 2 of 3

Table 16.3.3.2 Correlation Analysis of Percentage Change from Baseline to Week 80/e40 in OFF State UPDRS Motor Score (Part III) to Change from Baseline to Week 40/e0 in ^{18}F-DOPA Uptake as Determined by PET Scan – ITT Primary Population

Parameters	GDNF/GDNF (N=17) n Spearman Rank Correlation (95% CI) p-value	Placebo/GDNF (N=18) n Spearman Rank Correlation (95% CI) p-value
Percentage change from baseline to Week 80/e40 in OFF state UPDRS motor score (part III)		
versus		
Change from baseline to Week 40/e0 in ^{18}F-DOPA uptake rate constant, substantia nigra, both hemispheres combined	17 0.131 (-0.373, 0.575) 0.6118	18 -0.266 (-0.652, 0.230) 0.2777

Note: For subject 45, items 22, 27, 28, 29 and 30 are excluded from the UPDRS score.
Source: Listing 17.2.2.1, Dataset: ADPR, ADQUPDRS, Program: t_correl.sas, Output: t_16-3-3-2-correl.rtf, Generated on: 28JUL2017 05:57
Page 3 of 3

GDNF

Clinical Study Report
Study No. 2797

Table 16.3.3.3 Correlation Analysis of Percentage Change from Baseline to Week 80/e40 in OFF State UPDRS Motor Score (Part III) to Change from Baseline to Week 40/e0 in ^{18}F-DOPA Uptake as Determined by PET Scan – ITT Overall Population

Parameters	GDNF/GDNF (N=21) n Spearman Rank Correlation (95% CI) p-value	Placebo/GDNF (N=20) n Spearman Rank Correlation (95% CI) p-value
Percentage change from baseline to Week 80/e40 in OFF state UPDRS motor score (part III)		
versus		
Change from baseline to Week 40/e0 in ^{18}F-DOPA uptake rate constant, dorsal caudate nucleus, both hemispheres combined	21 -0.202 (-0.583, 0.252) 0.3741	20 -0.373 (-0.700, 0.084) 0.0978
Percentage change from baseline to Week 80/e40 in OFF state UPDRS motor score (part III)		
versus		
Change from baseline to Week 40/e0 in ^{18}F-DOPA uptake rate constant, dorsal anterior putamen, both hemispheres combined	21 -0.065 (-0.483, 0.378) 0.7784	20 0.269 (-0.197, 0.636) 0.2429

Note: For subject 45, items 22, 27, 28, 29 and 30 are excluded from the UPDRS score.
Source: Listing 17.2.2.1, Dataset: ADPR, ADQUPDRS, Program: t_correl.sas, Output: t_16-3-3-3-correl.rtf, Generated on: 28JUL2017 05:57
Page 1 of 3

CONFIDENTIAL

Page 310

Table 16.3.3.3 Correlation Analysis of Percentage Change from Baseline to Week 80/e40 in OFF State UPDRS Motor Score (Part III) to Change from Baseline to Week 40/e0 in ^{18}F-DOPA Uptake as Determined by PET Scan – ITT Overall Population

Parameters	GDNF/GDNF (N=21) n Spearman Rank Correlation (95% CI) p-value	Placebo/GDNF (N=20) n Spearman Rank Correlation (95% CI) p-value
Percentage change from baseline to Week 80/e40 in OFF state UPDRS motor score (part III)		
versus		
Change from baseline to Week 40/e0 in ^{18}F-DOPA uptake rate constant, dorsal central/posterior putamen, both hemispheres combined	21 -0.371 (-0.692, 0.072) 0.0904	20 0.399 (-0.053, 0.715) 0.0744
Percentage change from baseline to Week 80/e40 in OFF state UPDRS motor score (part III)		
versus		
Change from baseline to Week 40/e0 in ^{18}F-DOPA uptake rate constant, ventral striatum, both hemispheres combined	21 -0.005 (-0.436, 0.428) 0.9824	20 -0.247 (-0.621, 0.220) 0.2866

Note: For subject 45, items 22, 27, 28, 29 and 30 are excluded from the UPDRS score.
Source: Listing 17.2.2.1, Dataset: ADPR, ADQUPDRS, Program: t_correl.sas, Output: t_16-3-3-3-correl.rtf, Generated on: 28JUL2017 05:57
Page 2 of 3

Table 16.3.3.3 Correlation Analysis of Percentage Change from Baseline to Week 80/e40 in OFF State UPDRS Motor Score (Part III) to Change from Baseline to Week 40/e0 in ^{18}F-DOPA Uptake as Determined by PET Scan – ITT Overall Population

Parameters	GDNF/GDNF (N=21) n Spearman Rank Correlation (95% CI) p-value	Placebo/GDNF (N=20) n Spearman Rank Correlation (95% CI) p-value
Percentage change from baseline to Week 80/e40 in OFF state UPDRS motor score (part III)		
versus		
Change from baseline to Week 40/e0 in ^{18}F-DOPA uptake rate constant, substantia nigra, both hemispheres combined	21 -0.180 (-0.568, 0.273) 0.4287	20 -0.258 (-0.629, 0.208) 0.2641

Note: For subject 45, items 22, 27, 28, 29 and 30 are excluded from the UPDRS score.
Source: Listing 17.2.2.1, Dataset: ADPR, ADQUPDRS, Program: t_correl.sas, Output: t_16-3-3-3-correl.rtf, Generated on: 28JUL2017 05:57
Page 3 of 3

Table 16.4.1.1 Exposure to Study Medication - Safety Overall Population

Extension Part Variable	GDNF/GDNF (N=21)	Placebo/GDNF (N=20)	Total (N=41)
Initial Extension			
Number of infusions of study medication			
n	21	20	41
Mean (SD)	9.6 (1.16)	10.0 (0.00)	9.8 (0.85)
Median	10.0	10.0	10.0
Min, Max	5, 10	10, 10	5, 10
Total GDNF exposure[a] (mg)			
n	21	20	41
Mean (SD)	2.297 (0.280)	2.400 (0.000)	2.347 (0.204)
Median	2.400	2.400	2.400
Min, Max	1.20, 2.40	2.40, 2.40	1.20, 2.40
Pilot Extension			
Number of infusions of study medication			
n	3	2	5
Mean (SD)	12.0 (6.08)	17.0 (2.83)	14.0 (5.29)
Median	9.0	17.0	15.0
Min, Max	8, 19	15, 19	8, 19
Total GDNF exposure[a] (mg)			
n	3	2	5
Mean (SD)	2.880 (1.460)	4.080 (0.679)	3.360 (1.270)
Median	2.160	4.080	3.600
Min, Max	1.92, 4.56	3.60, 4.56	1.92, 4.56

[a] Total exposure in mg assumes the entire infusion was completed at each administration.
Source: Listing 17.2.4.1.1, Dataset: ADEX, Program: t_exp.sas, Output: t_16-4-1-1-exp.rtf, Generated on: 28JUL2017 05:57
Page 1 of 2

Table 16.4.1.1 Exposure to Study Medication - Safety Overall Population

Extension Part Variable	GDNF/GDNF (N=21)	Placebo/GDNF (N=20)	Total (N=41)
Supplemental Extension			
Number of infusions of study medication			
n	11	12	23
Mean (SD)	6.2 (3.76)	5.8 (3.24)	6.0 (3.42)
Median	4.0	6.0	5.0
Min, Max	2, 12	2, 11	2, 12
Total GDNF exposure[a] (mg)			
n	11	12	23
Mean (SD)	1.484 (0.903)	1.400 (0.778)	1.440 (0.822)
Median	0.960	1.440	1.200
Min, Max	0.48, 2.88	0.48, 2.64	0.48, 2.88
Overall			
Number of infusions of study medication			
n	21	20	41
Mean (SD)	14.5 (6.10)	15.2 (6.63)	14.9 (6.30)
Median	14.0	13.0	13.0
Min, Max	5, 31	10, 36	5, 36
Total GDNF exposure[a] (mg)			
n	21	20	41
Mean (SD)	3.486 (1.465)	3.648 (1.591)	3.565 (1.511)
Median	3.360	3.120	3.120
Min, Max	1.20, 7.44	2.40, 8.64	1.20, 8.64

[a] Total exposure in mg assumes the entire infusion was completed at each administration.
Source: Listing 17.2.4.1.1, Dataset: ADEX, Program: t_exp.sas, Output: t_16-4-1-1-exp.rtf, Generated on: 28JUL2017 05:57
Page 2 of 2

Table 16.4.1.2 Study Medication Infusion Details by Visit - Safety Overall Population

Visit Variable	GDNF/GDNF (N=21)	Placebo/GDNF (N=20)	Total (N=41)
Week e0			
Duration of infusion[a] (minutes)			
n	21	20	41
Mean (SD)	127.7 (28.15)	126.2 (27.59)	127.0 (27.54)
Median	102.0	102.5	102.0
Min, Max	101, 164	101, 162	101, 164
Any infusion interruption/early termination [n (%)]			
No	21 (100)	20 (100)	41 (100)
Yes	0	0	0
Week 44/e4			
Duration of infusion[a] (minutes)			
n	20	20	40
Mean (SD)	123.2 (27.56)	118.0 (26.24)	120.6 (26.69)
Median	102.0	102.0	102.0
Min, Max	100, 162	94, 162	94, 162
Any infusion interruption/early termination [n (%)]			
No	19 (90.5)	19 (95.0)	38 (92.7)
Yes	1 (4.8)	1 (5.0)	2 (4.9)

[a] Duration of infusion of study medication in minutes is calculated as (infusion end time – infusion start time + 1). Interruptions are not subtracted.
Source: Listing 17.2.4.1.2, 17.2.4.1.3, Dataset: ADEX, Program: t_infmed.sas, Output: t_16-4-1-2-infmed.rtf, Generated on: 28JUL2017 05:57
Page 1 of 21

Table 16.4.1.2 Study Medication Infusion Details by Visit - Safety Overall Population

Visit Variable	GDNF/GDNF (N=21)	Placebo/GDNF (N=20)	Total (N=41)
Week 48/e8			
Duration of infusion[a] (minutes)			
n	21	20	41
Mean (SD)	120.2 (33.70)	118.8 (25.74)	119.5 (29.72)
Median	102.0	102.0	102.0
Min, Max	34, 165	101, 162	34, 165
Any infusion interruption/early termination [n (%)]			
No	19 (90.5)	19 (95.0)	38 (92.7)
Yes	2 (9.5)	1 (5.0)	3 (7.3)
Week 52/e12			
Duration of infusion[a] (minutes)			
n	18	20	38
Mean (SD)	124.6 (37.03)	115.8 (25.20)	119.9 (31.24)
Median	102.0	102.0	102.0
Min, Max	101, 225	101, 162	101, 225
Any infusion interruption/early termination [n (%)]			
No	14 (66.7)	19 (95.0)	33 (80.5)
Yes	4 (19.0)	1 (5.0)	5 (12.2)

[a] Duration of infusion of study medication in minutes is calculated as (infusion end time – infusion start time + 1). Interruptions are not subtracted.
Source: Listing 17.2.4.1.2, 17.2.4.1.3, Dataset: ADEX, Program: t_infmed.sas, Output: t_16-4-1-2-infmed.rtf, Generated on: 28JUL2017 05:57
Page 2 of 21

Table 16.4.1.2 Study Medication Infusion Details by Visit - Safety Overall Population

Visit Variable	GDNF/GDNF (N=21)	Placebo/GDNF (N=20)	Total (N=41)
Week 56/e16			
Duration of infusion[a] (minutes)			
n	21	20	41
Mean (SD)	117.2 (25.54)	115.8 (25.19)	116.5 (25.06)
Median	102.0	102.0	102.0
Min, Max	98, 162	101, 162	98, 162
Any infusion interruption/early termination [n (%)]			
No	18 (85.7)	18 (90.0)	36 (87.8)
Yes	3 (14.3)	2 (10.0)	5 (12.2)
Week 60/e20			
Duration of infusion[a] (minutes)			
n	19	20	39
Mean (SD)	118.4 (35.57)	118.1 (25.61)	118.2 (30.45)
Median	101.0	102.0	102.0
Min, Max	47, 198	101, 162	47, 198
Any infusion interruption/early termination [n (%)]			
No	14 (66.7)	17 (85.0)	31 (75.6)
Yes	5 (23.8)	3 (15.0)	8 (19.5)

[a] Duration of infusion of study medication in minutes is calculated as (infusion end time – infusion start time + 1). Interruptions are not subtracted.
Source: Listing 17.2.4.1.2, 17.2.4.1.3, Dataset: ADEX, Program: t_infmed.sas, Output: t_16-4-1-2-infmed.rtf, Generated on: 28JUL2017 05:57
Page 3 of 21

Table 16.4.1.2 Study Medication Infusion Details by Visit - Safety Overall Population

Visit Variable	GDNF/GDNF (N=21)	Placebo/GDNF (N=20)	Total (N=41)
Week 64/e24			
Duration of infusion[a] (minutes)			
n	20	20	40
Mean (SD)	115.1 (24.11)	115.4 (24.50)	115.2 (24.00)
Median	102.0	102.0	102.0
Min, Max	101, 163	101, 162	101, 163
Any infusion interruption/early termination [n (%)]			
No	16 (76.2)	19 (95.0)	35 (85.4)
Yes	4 (19.0)	1 (5.0)	5 (12.2)
Week 68/e28			
Duration of infusion[a] (minutes)			
n	19	20	39
Mean (SD)	113.2 (22.88)	116.2 (25.48)	114.7 (23.97)
Median	102.0	102.0	102.0
Min, Max	101, 161	101, 164	101, 164
Any infusion interruption/early termination [n (%)]			
No	17 (81.0)	18 (90.0)	35 (85.4)
Yes	2 (9.5)	2 (10.0)	4 (9.8)

[a] Duration of infusion of study medication in minutes is calculated as (infusion end time – infusion start time + 1). Interruptions are not subtracted.
Source: Listing 17.2.4.1.2, 17.2.4.1.3, Dataset: ADEX, Program: t_infmed.sas, Output: t_16-4-1-2-infmed.rtf, Generated on: 28JUL2017 05:57
Page 4 of 21

Table 16.4.1.2 Study Medication Infusion Details by Visit - Safety Overall Population

Visit Variable	GDNF/GDNF (N=21)	Placebo/GDNF (N=20)	Total (N=41)
Week 72/e32			
Duration of infusion[a] (minutes)			
n	21	20	41
Mean (SD)	112.8 (26.01)	115.7 (25.15)	114.2 (25.32)
Median	102.0	102.0	102.0
Min, Max	59, 161	101, 162	59, 162
Any infusion interruption/early termination [n (%)]			
No	16 (76.2)	18 (90.0)	34 (82.9)
Yes	5 (23.8)	2 (10.0)	7 (17.1)
Week 76/e36			
Duration of infusion[a] (minutes)			
n	18	19	37
Mean (SD)	113.8 (23.64)	116.3 (25.19)	115.1 (24.14)
Median	102.0	102.0	102.0
Min, Max	101, 161	101, 161	101, 161
Any infusion interruption/early termination [n (%)]			
No	14 (66.7)	14 (70.0)	28 (68.3)
Yes	4 (19.0)	5 (25.0)	9 (22.0)

[a] Duration of infusion of study medication in minutes is calculated as (infusion end time – infusion start time + 1). Interruptions are not subtracted.
Source: Listing 17.2.4.1.2, 17.2.4.1.3, Dataset: ADEX, Program: t_infmed.sas, Output: t_16-4-1-2-infmed.rtf, Generated on: 28JUL2017 05:57
Page 5 of 21

Table 16.4.1.2 Study Medication Infusion Details by Visit - Safety Overall Population

Visit Variable	GDNF/GDNF (N=21)	Placebo/GDNF (N=20)	Total (N=41)
Week e2-4			
Duration of infusion[a] (minutes)			
n	3	2	5
Mean (SD)	155.0 (0.00)	154.5 (0.71)	154.8 (0.45)
Median	155.0	154.5	155.0
Min, Max	155, 155	154, 155	154, 155
Any infusion interruption/early termination [n (%)]			
No	2 (9.5)	0	2 (4.9)
Yes	1 (4.8)	2 (10.0)	3 (7.3)
Week e2-8			
Duration of infusion[a] (minutes)			
n	3	2	5
Mean (SD)	167.3 (20.50)	155.5 (0.71)	162.6 (15.88)
Median	156.0	155.5	156.0
Min, Max	155, 191	155, 156	155, 191
Any infusion interruption/early termination [n (%)]			
No	1 (4.8)	0	1 (2.4)
Yes	2 (9.5)	2 (10.0)	4 (9.8)

[a] Duration of infusion of study medication in minutes is calculated as (infusion end time – infusion start time + 1). Interruptions are not subtracted.
Source: Listing 17.2.4.1.2, 17.2.4.1.3, Dataset: ADEX, Program: t_infmed.sas, Output: t_16-4-1-2-infmed.rtf, Generated on: 28JUL2017 05:57
Page 6 of 21

Table 16.4.1.2 Study Medication Infusion Details by Visit - Safety Overall Population

Visit Variable	GDNF/GDNF (N=21)	Placebo/GDNF (N=20)	Total (N=41)
Week e2-12			
Duration of infusion[a] (minutes)			
n	3	2	5
Mean (SD)	154.7 (0.58)	185.5 (40.31)	167.0 (26.30)
Median	155.0	185.5	155.0
Min, Max	154, 155	157, 214	154, 214
Any infusion interruption/early termination [n (%)]			
No	2 (9.5)	0	2 (4.9)
Yes	1 (4.8)	2 (10.0)	3 (7.3)
Week e2-16			
Duration of infusion[a] (minutes)			
n	3	2	5
Mean (SD)	155.3 (0.58)	149.0 (8.49)	152.8 (5.50)
Median	155.0	149.0	155.0
Min, Max	155, 156	143, 155	143, 156
Any infusion interruption/early termination [n (%)]			
No	2 (9.5)	0	2 (4.9)
Yes	1 (4.8)	2 (10.0)	3 (7.3)

[a] Duration of infusion of study medication in minutes is calculated as (infusion end time – infusion start time + 1). Interruptions are not subtracted.
Source: Listing 17.2.4.1.2, 17.2.4.1.3, Dataset: ADEX, Program: t_infmed.sas, Output: t_16-4-1-2-infmed.rtf, Generated on: 28JUL2017 05:57
Page 7 of 21

Table 16.4.1.2 Study Medication Infusion Details by Visit - Safety Overall Population

Visit Variable	GDNF/GDNF (N=21)	Placebo/GDNF (N=20)	Total (N=41)
Week e2-20			
Duration of infusion[a] (minutes)			
n	3	2	5
Mean (SD)	156.7 (0.58)	84.5 (26.16)	127.8 (41.64)
Median	157.0	84.5	156.0
Min, Max	156, 157	66, 103	66, 157
Any infusion interruption/early termination [n (%)]			
No	2 (9.5)	0	2 (4.9)
Yes	1 (4.8)	2 (10.0)	3 (7.3)
Week e2-24			
Duration of infusion[a] (minutes)			
n	3	2	5
Mean (SD)	155.3 (0.58)	159.5 (3.54)	157.0 (2.92)
Median	155.0	159.5	156.0
Min, Max	155, 156	157, 162	155, 162
Any infusion interruption/early termination [n (%)]			
No	1 (4.8)	1 (5.0)	2 (4.9)
Yes	2 (9.5)	1 (5.0)	3 (7.3)

[a] Duration of infusion of study medication in minutes is calculated as (infusion end time – infusion start time + 1). Interruptions are not subtracted.
Source: Listing 17.2.4.1.2, 17.2.4.1.3, Dataset: ADEX, Program: t_infmed.sas, Output: t_16-4-1-2-infmed.rtf, Generated on: 28JUL2017 05:57
Page 8 of 21

Table 16.4.1.2 Study Medication Infusion Details by Visit - Safety Overall Population

Visit Variable	GDNF/GDNF (N=21)	Placebo/GDNF (N=20)	Total (N=41)
Week e2-28			
Duration of infusion[a] (minutes)			
n	3	2	5
Mean (SD)	157.0 (3.46)	111.5 (70.00)	138.8 (43.04)
Median	155.0	111.5	155.0
Min, Max	155, 161	62, 161	62, 161
Any infusion interruption/early termination [n (%)]			
No	2 (9.5)	0	2 (4.9)
Yes	1 (4.8)	2 (10.0)	3 (7.3)
Week e2-32			
Duration of infusion[a] (minutes)			
n	3	2	5
Mean (SD)	119.7 (30.60)	147.0 (11.31)	130.6 (26.91)
Median	102.0	147.0	139.0
Min, Max	102, 155	139, 155	102, 155
Any infusion interruption/early termination [n (%)]			
No	1 (4.8)	0	1 (2.4)
Yes	2 (9.5)	2 (10.0)	4 (9.8)

[a] Duration of infusion of study medication in minutes is calculated as (infusion end time – infusion start time + 1). Interruptions are not subtracted.
Source: Listing 17.2.4.1.2, 17.2.4.1.3, Dataset: ADEX, Program: t_infmed.sas, Output: t_16-4-1-2-infmed.rtf, Generated on: 28JUL2017 05:57
Page 9 of 21

Table 16.4.1.2 Study Medication Infusion Details by Visit - Safety Overall Population

Visit Variable	GDNF/GDNF (N=21)	Placebo/GDNF (N=20)	Total (N=41)
Week e2-36			
Duration of infusion[a] (minutes)			
n	2	2	4
Mean (SD)	158.5 (4.95)	112.0 (69.30)	135.3 (48.27)
Median	158.5	112.0	158.0
Min, Max	155, 162	63, 161	63, 162
Any infusion interruption/early termination [n (%)]			
No	1 (4.8)	1 (5.0)	2 (4.9)
Yes	1 (4.8)	1 (5.0)	2 (4.9)
Week e2-40			
Duration of infusion[a] (minutes)			
n	1	2	3
Mean (SD)	161.0	83.0 (24.04)	109.0 (48.14)
Median	161.0	83.0	100.0
Min, Max	161, 161	66, 100	66, 161
Any infusion interruption/early termination [n (%)]			
No	0	0	0
Yes	1 (4.8)	2 (10.0)	3 (7.3)

[a] Duration of infusion of study medication in minutes is calculated as (infusion end time – infusion start time + 1). Interruptions are not subtracted.
Source: Listing 17.2.4.1.2, 17.2.4.1.3, Dataset: ADEX, Program: t_infmed.sas, Output: t_16-4-1-2-infmed.rtf, Generated on: 28JUL2017 05:57
Page 10 of 21

Table 16.4.1.2 Study Medication Infusion Details by Visit - Safety Overall Population

Visit Variable	GDNF/GDNF (N=21)	Placebo/GDNF (N=20)	Total (N=41)
Week e2-44			
Duration of infusion[a] (minutes)			
n	1	2	3
Mean (SD)	164.0	58.5 (4.95)	93.7 (61.01)
Median	164.0	58.5	62.0
Min, Max	164, 164	55, 62	55, 164
Any infusion interruption/early termination [n (%)]			
No	0	0	0
Yes	1 (4.8)	2 (10.0)	3 (7.3)
Week e2-48			
Duration of infusion[a] (minutes)			
n	1	2	3
Mean (SD)	48.0	60.5 (0.71)	56.3 (7.23)
Median	48.0	60.5	60.0
Min, Max	48, 48	60, 61	48, 61
Any infusion interruption/early termination [n (%)]			
No	0	0	0
Yes	1 (4.8)	2 (10.0)	3 (7.3)

[a] Duration of infusion of study medication in minutes is calculated as (infusion end time – infusion start time + 1). Interruptions are not subtracted.
Source: Listing 17.2.4.1.2, 17.2.4.1.3, Dataset: ADEX, Program: t_infmed.sas, Output: t_16-4-1-2-infmed.rtf, Generated on: 28JUL2017 05:57

Table 16.4.1.2 Study Medication Infusion Details by Visit - Safety Overall Population

Visit Variable	GDNF/GDNF (N=21)	Placebo/GDNF (N=20)	Total (N=41)
Week e2-52			
Duration of infusion[a] (minutes)			
n	1	2	3
Mean (SD)	162.0	57.0 (2.83)	92.0 (60.65)
Median	162.0	57.0	59.0
Min, Max	162, 162	55, 59	55, 162
Any infusion interruption/early termination [n (%)]			
No	0	0	0
Yes	1 (4.8)	2 (10.0)	3 (7.3)
Week e2-56			
Duration of infusion[a] (minutes)			
n	1	2	3
Mean (SD)	81.0	65.5 (4.95)	70.7 (9.61)
Median	81.0	65.5	69.0
Min, Max	81, 81	62, 69	62, 81
Any infusion interruption/early termination [n (%)]			
No	0	0	0
Yes	1 (4.8)	2 (10.0)	3 (7.3)

[a] Duration of infusion of study medication in minutes is calculated as (infusion end time – infusion start time + 1). Interruptions are not subtracted.
Source: Listing 17.2.4.1.2, 17.2.4.1.3, Dataset: ADEX, Program: t_infmed.sas, Output: t_16-4-1-2-infmed.rtf, Generated on: 28JUL2017 05:57

Table 16.4.1.2 Study Medication Infusion Details by Visit - Safety Overall Population

Visit Variable	GDNF/GDNF (N=21)	Placebo/GDNF (N=20)	Total (N=41)
Week e2-60			
Duration of infusion[a] (minutes)			
n	1	2	3
Mean (SD)	162.0	60.5 (2.12)	94.3 (58.62)
Median	162.0	60.5	62.0
Min, Max	162, 162	59, 62	59, 162
Any infusion interruption/early termination [n (%)]			
No	0	0	0
Yes	1 (4.8)	2 (10.0)	3 (7.3)
Week e2-64			
Duration of infusion[a] (minutes)			
n	1	1	2
Mean (SD)	75.0	70.0	72.5 (3.54)
Median	75.0	70.0	72.5
Min, Max	75, 75	70, 70	70, 75
Any infusion interruption/early termination [n (%)]			
No	0	0	0
Yes	1 (4.8)	1 (5.0)	2 (4.9)

[a] Duration of infusion of study medication in minutes is calculated as (infusion end time – infusion start time + 1). Interruptions are not subtracted.
Source: Listing 17.2.4.1.2, 17.2.4.1.3, Dataset: ADEX, Program: t_infmed.sas, Output: t_16-4-1-2-infmed.rtf, Generated on: 28JUL2017 05:57
Page 13 of 21

Table 16.4.1.2 Study Medication Infusion Details by Visit - Safety Overall Population

Visit Variable	GDNF/GDNF (N=21)	Placebo/GDNF (N=20)	Total (N=41)
Week e2-68			
Duration of infusion[a] (minutes)			
n	1	1	2
Mean (SD)	61.0	60.0	60.5 (0.71)
Median	61.0	60.0	60.5
Min, Max	61, 61	60, 60	60, 61
Any infusion interruption/early termination [n (%)]			
No	0	0	0
Yes	1 (4.8)	1 (5.0)	2 (4.9)
Week e2-72			
Duration of infusion[a] (minutes)			
n	1	1	2
Mean (SD)	61.0	63.0	62.0 (1.41)
Median	61.0	63.0	62.0
Min, Max	61, 61	63, 63	61, 63
Any infusion interruption/early termination [n (%)]			
No	0	0	0
Yes	1 (4.8)	1 (5.0)	2 (4.9)

[a] Duration of infusion of study medication in minutes is calculated as (infusion end time – infusion start time + 1). Interruptions are not subtracted.
Source: Listing 17.2.4.1.2, 17.2.4.1.3, Dataset: ADEX, Program: t_infmed.sas, Output: t_16-4-1-2-infmed.rtf, Generated on: 28JUL2017 05:57
Page 14 of 21

Table 16.4.1.2 Study Medication Infusion Details by Visit - Safety Overall Population

Visit Variable	GDNF/GDNF (N=21)	Placebo/GDNF (N=20)	Total (N=41)
Week e2-76			
Duration of infusion[a] (minutes)			
n	1	1	2
Mean (SD)	71.0	65.0	68.0 (4.24)
Median	71.0	65.0	68.0
Min, Max	71, 71	65, 65	65, 71
Any infusion interruption/early termination [n (%)]			
No	0	0	0
Yes	1 (4.8)	1 (5.0)	2 (4.9)
Week e3-0			
Duration of infusion[a] (minutes)			
n	11	12	23
Mean (SD)	98.3 (11.40)	114.7 (27.72)	106.8 (22.66)
Median	102.0	101.5	102.0
Min, Max	64, 102	86, 162	64, 162
Any infusion interruption/early termination [n (%)]			
No	10 (47.6)	10 (50.0)	20 (48.8)
Yes	1 (4.8)	2 (10.0)	3 (7.3)

[a] Duration of infusion of study medication in minutes is calculated as (infusion end time – infusion start time + 1). Interruptions are not subtracted.
Source: Listing 17.2.4.1.2, 17.2.4.1.3, Dataset: ADEX, Program: t_infmed.sas, Output: t_16-4-1-2-infmed.rtf, Generated on: 28JUL2017 05:57
Page 15 of 21

Table 16.4.1.2 Study Medication Infusion Details by Visit - Safety Overall Population

Visit Variable	GDNF/GDNF (N=21)	Placebo/GDNF (N=20)	Total (N=41)
Week e3-4			
Duration of infusion[a] (minutes)			
n	11	12	23
Mean (SD)	98.0 (12.28)	107.9 (26.22)	103.2 (20.93)
Median	102.0	102.0	102.0
Min, Max	61, 102	61, 162	61, 162
Any infusion interruption/early termination [n (%)]			
No	10 (47.6)	9 (45.0)	19 (46.3)
Yes	1 (4.8)	3 (15.0)	4 (9.8)
Week e3-8			
Duration of infusion[a] (minutes)			
n	9	10	19
Mean (SD)	101.9 (0.60)	109.3 (28.38)	105.8 (20.43)
Median	102.0	101.5	102.0
Min, Max	101, 103	65, 162	65, 162
Any infusion interruption/early termination [n (%)]			
No	9 (42.9)	7 (35.0)	16 (39.0)
Yes	0	3 (15.0)	3 (7.3)

[a] Duration of infusion of study medication in minutes is calculated as (infusion end time – infusion start time + 1). Interruptions are not subtracted.
Source: Listing 17.2.4.1.2, 17.2.4.1.3, Dataset: ADEX, Program: t_infmed.sas, Output: t_16-4-1-2-infmed.rtf, Generated on: 28JUL2017 05:57

Table 16.4.1.2 Study Medication Infusion Details by Visit - Safety Overall Population

Visit Variable	GDNF/GDNF (N=21)	Placebo/GDNF (N=20)	Total (N=41)
Week e3-12			
Duration of infusion[a] (minutes)			
n	8	7	15
Mean (SD)	103.6 (5.04)	123.6 (36.99)	112.9 (26.55)
Median	102.0	102.0	102.0
Min, Max	101, 116	74, 162	74, 162
Any infusion interruption/early termination [n (%)]			
No	7 (33.3)	5 (25.0)	12 (29.3)
Yes	1 (4.8)	2 (10.0)	3 (7.3)
Week e3-16			
Duration of infusion[a] (minutes)			
n	5	7	12
Mean (SD)	103.0 (2.24)	123.7 (38.63)	115.1 (30.49)
Median	102.0	115.0	102.0
Min, Max	102, 107	63, 162	63, 162
Any infusion interruption/early termination [n (%)]			
No	5 (23.8)	4 (20.0)	9 (22.0)
Yes	0	3 (15.0)	3 (7.3)

[a] Duration of infusion of study medication in minutes is calculated as (infusion end time – infusion start time + 1). Interruptions are not subtracted.
Source: Listing 17.2.4.1.2, 17.2.4.1.3, Dataset: ADEX, Program: t_infmed.sas, Output: t_16-4-1-2-infmed.rtf, Generated on: 28JUL2017 05:57
Page 17 of 21

Table 16.4.1.2 Study Medication Infusion Details by Visit - Safety Overall Population

Visit Variable	GDNF/GDNF (N=21)	Placebo/GDNF (N=20)	Total (N=41)
Week e3-20			
Duration of infusion[a] (minutes)			
n	4	6	10
Mean (SD)	97.0 (10.00)	100.8 (37.19)	99.3 (28.39)
Median	102.0	101.5	102.0
Min, Max	82, 102	59, 161	59, 161
Any infusion interruption/early termination [n (%)]			
No	3 (14.3)	3 (15.0)	6 (14.6)
Yes	1 (4.8)	3 (15.0)	4 (9.8)
Week e3-24			
Duration of infusion[a] (minutes)			
n	4	6	10
Mean (SD)	101.3 (0.50)	100.3 (34.78)	100.7 (25.93)
Median	101.0	101.5	101.0
Min, Max	101, 102	61, 162	61, 162
Any infusion interruption/early termination [n (%)]			
No	4 (19.0)	3 (15.0)	7 (17.1)
Yes	0	3 (15.0)	3 (7.3)

[a] Duration of infusion of study medication in minutes is calculated as (infusion end time – infusion start time + 1). Interruptions are not subtracted.
Source: Listing 17.2.4.1.2, 17.2.4.1.3, Dataset: ADEX, Program: t_infmed.sas, Output: t_16-4-1-2-infmed.rtf, Generated on: 28JUL2017 05:57
Page 18 of 21

Table 16.4.1.2 Study Medication Infusion Details by Visit - Safety Overall Population

Visit Variable	GDNF/GDNF (N=21)	Placebo/GDNF (N=20)	Total (N=41)
Week e3-28			
Duration of infusion[a] (minutes)			
n	4	4	8
Mean (SD)	101.5 (0.58)	101.3 (0.50)	101.4 (0.52)
Median	101.5	101.0	101.0
Min, Max	101, 102	101, 102	101, 102
Any infusion interruption/early termination [n (%)]			
No	4 (19.0)	2 (10.0)	6 (14.6)
Yes	0	2 (10.0)	2 (4.9)
Week e3-32			
Duration of infusion[a] (minutes)			
n	4	3	7
Mean (SD)	101.8 (0.50)	102.0 (0.00)	101.9 (0.38)
Median	102.0	102.0	102.0
Min, Max	101, 102	102, 102	101, 102
Any infusion interruption/early termination [n (%)]			
No	4 (19.0)	2 (10.0)	6 (14.6)
Yes	0	1 (5.0)	1 (2.4)

[a] Duration of infusion of study medication in minutes is calculated as (infusion end time – infusion start time + 1). Interruptions are not subtracted.
Source: Listing 17.2.4.1.2, 17.2.4.1.3, Dataset: ADEX, Program: t_infmed.sas, Output: t_16-4-1-2-infmed.rtf, Generated on: 28JUL2017 05:57
Page 19 of 21

Table 16.4.1.2 Study Medication Infusion Details by Visit - Safety Overall Population

Visit Variable	GDNF/GDNF (N=21)	Placebo/GDNF (N=20)	Total (N=41)
Week e3-36			
Duration of infusion[a] (minutes)			
n	4	2	6
Mean (SD)	101.8 (0.50)	128.5 (37.48)	110.7 (21.72)
Median	102.0	128.5	102.0
Min, Max	101, 102	102, 155	101, 155
Any infusion interruption/early termination [n (%)]			
No	4 (19.0)	1 (5.0)	5 (12.2)
Yes	0	1 (5.0)	1 (2.4)
Week e3-40			
Duration of infusion[a] (minutes)			
n	3	1	4
Mean (SD)	101.7 (0.58)	102.0	101.8 (0.50)
Median	102.0	102.0	102.0
Min, Max	101, 102	102, 102	101, 102
Any infusion interruption/early termination [n (%)]			
No	3 (14.3)	1 (5.0)	4 (9.8)
Yes	0	0	0

[a] Duration of infusion of study medication in minutes is calculated as (infusion end time – infusion start time + 1). Interruptions are not subtracted.
Source: Listing 17.2.4.1.2, 17.2.4.1.3, Dataset: ADEX, Program: t_infmed.sas, Output: t_16-4-1-2-infmed.rtf, Generated on: 28JUL2017 05:57
Page 20 of 21

Table 16.4.1.2 Study Medication Infusion Details by Visit - Safety Overall Population

Visit Variable	GDNF/GDNF (N=21)	Placebo/GDNF (N=20)	Total (N=41)
Week e3-44			
Duration of infusion[a] (minutes)			
n	1	0	1
Mean (SD)	102.0		102.0
Median	102.0		102.0
Min, Max	102, 102		102, 102
Any infusion interruption/early termination [n (%)]			
No	1 (4.8)	0	1 (2.4)
Yes	0	0	0

[a] Duration of infusion of study medication in minutes is calculated as (infusion end time – infusion start time + 1). Interruptions are not subtracted.
Source: Listing 17.2.4.1.2, 17.2.4.1.3, Dataset: ADEX, Program: t_infmed.sas, Output: t_16-4-1-2-infmed.rtf, Generated on: 28JUL2017 05:57
Page 21 of 21

Table 16.4.2.1.1 Overall Summary of Adverse Events - Safety Overall Population

Adverse Event Category	GDNF/GDNF (N=21) n (%)	Placebo/GDNF (N=20) n (%)	Total (N=41) n (%)
Any TEAE	21 (100)	20 (100)	41 (100)
Any severe TEAE	10 (47.6)	12 (60.0)	22 (53.7)
Any serious TEAE	7 (33.3)	3 (15.0)	10 (24.4)
Any TEAE leading to permanent discontinuation of study medication	2 (9.5)	0	2 (4.9)
Any study medication-related TEAE	16 (76.2)	18 (90.0)	34 (82.9)
Any serious study medication-related TEAE	0	0	0
Any device-related TEAE	9 (42.9)	10 (50.0)	19 (46.3)
Any serious device-related TEAE	3 (14.3)	0	3 (7.3)

Note: For each category, subjects are included only once, even if they experienced multiple events in that category. All AEs reported during the study period are considered TEAEs. TEAEs that are present or ongoing at the beginning of Study 2797 (date of consent or date of last visit in Study 2553, if consent was obtained earlier) are considered pre-existing, if the event term, severity, and date and time of onset in Study 2797 are identical to the corresponding information given for the TEAE in Study 2553. If any of these conditions is not met, the TEAE is considered new or worsening. Only new or worsening TEAEs are summarized.

Source: Listing 17.2.4.2, Dataset: ADAE, Program: t_oae.sas, Output: t_16-4-2-1-1-oae.rtf, Generated on: 03AUG2017 09:44

Page 1 of 1

Table 16.4.2.1.2 Overall Summary of Adverse Events During the Initial Extension - Safety Overall Population

Adverse Event Category	GDNF/GDNF (N=21) n (%)	Placebo/GDNF (N=20) n (%)	Total (N=41) n (%)
Any TEAE	21 (100)	20 (100)	41 (100)
Any severe TEAE	9 (42.9)	9 (45.0)	18 (43.9)
Any serious TEAE	7 (33.3)	1 (5.0)	8 (19.5)
Any TEAE leading to permanent discontinuation of study medication	0	0	0
Any study medication-related TEAE	16 (76.2)	18 (90.0)	34 (82.9)
Any serious study medication-related TEAE	0	0	0
Any device-related TEAE	9 (42.9)	10 (50.0)	19 (46.3)
Any serious device-related TEAE	3 (14.3)	0	3 (7.3)

Note: For each category, subjects are included only once, even if they experienced multiple events in that category. All AEs reported during the study period are considered TEAEs. TEAEs that are present or ongoing at the beginning of Study 2797 (date of consent or date of last visit in Study 2553, if consent was obtained earlier) are considered pre-existing, if the event term, severity, and date and time of onset in Study 2797 are identical to the corresponding information given for the TEAE in Study 2553. If any of these conditions is not met, the TEAE is considered new or worsening. Only new or worsening TEAEs are summarized.
Source: Listing 17.2.4.2, Dataset: ADAE, Program: t_oae.sas, Output: t_16-4-2-1-2-oae.rtf, Generated on: 03AUG2017 09:44
Page 1 of 1

Table 16.4.2.1.3 Overall Summary of Adverse Events During the Pilot and Supplemental Extensions - Safety Overall Population

Adverse Event Category	GDNF/GDNF (N=13) n (%)	Placebo/GDNF (N=13) n (%)	Total (N=26) n (%)
Any TEAE	13 (100)	12 (92.3)	25 (96.2)
Any severe TEAE	3 (23.1)	4 (30.8)	7 (26.9)
Any serious TEAE	3 (23.1)	2 (15.4)	5 (19.2)
Any TEAE leading to permanent discontinuation of study medication	2 (15.4)	0	2 (7.7)
Any study medication-related TEAE	5 (38.5)	4 (30.8)	9 (34.6)
Any serious study medication-related TEAE	0	0	0
Any device-related TEAE	6 (46.2)	2 (15.4)	8 (30.8)
Any serious device-related TEAE	2 (15.4)	0	2 (7.7)

Note: For each category, subjects are included only once, even if they experienced multiple events in that category. All AEs reported during the study period are considered TEAEs. TEAEs that are present or ongoing at the beginning of Study 2797 (date of consent or date of last visit in Study 2553, if consent was obtained earlier) are considered pre-existing, if the event term, severity, and date and time of onset in Study 2797 are identical to the corresponding information given for the TEAE in Study 2553. If any of these conditions is not met, the TEAE is considered new or worsening. Only new or worsening TEAEs are summarized. Percentages are based on the number of subjects that entered either the Pilot or Supplemental Extensions.

Source: Listing 17.2.4.2, Dataset: ADAE, Program: t_oae.sas, Output: t_16-4-2-1-3-oae.rtf, Generated on: 03AUG2017 09:44
Page 1 of 1

Table 16.4.2.2 Treatment-Emergent Adverse Events by System Organ Class and Preferred Term - Safety Overall Population

System Organ Class Preferred Term	GDNF/GDNF (N=21) n (%)	Placebo/GDNF (N=20) n (%)	Total (N=41) n (%)
Subjects with at least one TEAE	21 (100)	20 (100)	41 (100)
Blood and lymphatic system disorders	5 (23.8)	2 (10.0)	7 (17.1)
Anaemia	4 (19.0)	0	4 (9.8)
Anaemia macrocytic	0	1 (5.0)	1 (2.4)
Anaemia megaloblastic	0	1 (5.0)	1 (2.4)
Iron deficiency anaemia	0	1 (5.0)	1 (2.4)
Lymphopenia	1 (4.8)	0	1 (2.4)
Cardiac disorders	3 (14.3)	0	3 (7.3)
Atrial flutter	1 (4.8)	0	1 (2.4)
Palpitations	1 (4.8)	0	1 (2.4)
Tachycardia	1 (4.8)	0	1 (2.4)
Congenital, familial and genetic disorders	0	1 (5.0)	1 (2.4)
Type IIa hyperlipidaemia	0	1 (5.0)	1 (2.4)
Ear and labyrinth disorders	1 (4.8)	1 (5.0)	2 (4.9)
Ear haemorrhage	0	1 (5.0)	1 (2.4)
Tinnitus	1 (4.8)	0	1 (2.4)

Note: Adverse events are coded using MedDRA version 19.0. All AEs reported during the study period are considered TEAEs. TEAEs that are present or ongoing at the beginning of Study 2797 (date of consent or date of last visit in Study 2553, if consent was obtained earlier) are considered pre-existing, if the event term, severity, and date and time of onset in Study 2797 are identical to the corresponding information given for the TEAE in Study 2553. If any of these conditions is not met, the TEAE is considered new or worsening. Only new or worsening TEAEs are summarized. For each system organ class and preferred term, subjects are included only once, even if they experienced multiple events in that system organ class or preferred term.
Source: Listing 17.2.4.2, Dataset: ADAE, Program: t_aesoc.sas, Output: t_16-4-2-2-aesoc.rtf, Generated on: 28JUL2017 05:57
Page 1 of 20

Table 16.4.2.2 Treatment-Emergent Adverse Events by System Organ Class and Preferred Term - Safety Overall Population

System Organ Class Preferred Term	GDNF/GDNF (N=21) n (%)	Placebo/GDNF (N=20) n (%)	Total (N=41) n (%)
Endocrine disorders	1 (4.8)	1 (5.0)	2 (4.9)
Hypothyroidism	1 (4.8)	1 (5.0)	2 (4.9)
Eye disorders	6 (28.6)	4 (20.0)	10 (24.4)
Blepharospasm	0	2 (10.0)	2 (4.9)
Cataract	0	1 (5.0)	1 (2.4)
Diplopia	2 (9.5)	0	2 (4.9)
Dry eye	1 (4.8)	0	1 (2.4)
Excessive eye blinking	1 (4.8)	0	1 (2.4)
Eye pain	2 (9.5)	0	2 (4.9)
Eyelid dermatochalasis	1 (4.8)	0	1 (2.4)
Ocular hyperaemia	0	1 (5.0)	1 (2.4)
Photophobia	1 (4.8)	0	1 (2.4)
Vision blurred	2 (9.5)	1 (5.0)	3 (7.3)
Vitreous detachment	1 (4.8)	0	1 (2.4)
Vitreous floaters	2 (9.5)	0	2 (4.9)

Note: Adverse events are coded using MedDRA version 19.0. All AEs reported during the study period are considered TEAEs. TEAEs that are present or ongoing at the beginning of Study 2797 (date of consent or date of last visit in Study 2553, if consent was obtained earlier) are considered pre-existing, if the event term, severity, and date and time of onset in Study 2797 are identical to the corresponding information given for the TEAE in Study 2553. If any of these conditions is not met, the TEAE is considered new or worsening. Only new or worsening TEAEs are summarized. For each system organ class and preferred term, subjects are included only once, even if they experienced multiple events in that system organ class or preferred term.
Source: Listing 17.2.4.2, Dataset: ADAE, Program: t_aesoc.sas, Output: t_16-4-2-2-aesoc.rtf, Generated on: 28JUL2017 05:57

Table 16.4.2.2 Treatment-Emergent Adverse Events by System Organ Class and Preferred Term - Safety Overall Population

System Organ Class Preferred Term	GDNF/GDNF (N=21) n (%)	Placebo/GDNF (N=20) n (%)	Total (N=41) n (%)
Gastrointestinal disorders	10 (47.6)	9 (45.0)	19 (46.3)
Abdominal discomfort	1 (4.8)	0	1 (2.4)
Abdominal pain lower	0	1 (5.0)	1 (2.4)
Abdominal pain upper	3 (14.3)	0	3 (7.3)
Constipation	2 (9.5)	3 (15.0)	5 (12.2)
Dental caries	0	2 (10.0)	2 (4.9)
Diarrhoea	3 (14.3)	2 (10.0)	5 (12.2)
Dry mouth	0	1 (5.0)	1 (2.4)
Dysphagia	1 (4.8)	3 (15.0)	4 (9.8)
Haemorrhoids	1 (4.8)	0	1 (2.4)
Intestinal obstruction	0	1 (5.0)	1 (2.4)
Irritable bowel syndrome	0	1 (5.0)	1 (2.4)
Nausea	5 (23.8)	2 (10.0)	7 (17.1)
Paraesthesia oral	0	1 (5.0)	1 (2.4)
Toothache	1 (4.8)	0	1 (2.4)
Vomiting	2 (9.5)	2 (10.0)	4 (9.8)

Note: Adverse events are coded using MedDRA version 19.0. All AEs reported during the study period are considered TEAEs. TEAEs that are present or ongoing at the beginning of Study 2797 (date of consent or date of last visit in Study 2553, if consent was obtained earlier) are considered pre-existing, if the event term, severity, and date and time of onset in Study 2797 are identical to the corresponding information given for the TEAE in Study 2553. If any of these conditions is not met, the TEAE is considered new or worsening. Only new or worsening TEAEs are summarized. For each system organ class and preferred term, subjects are included only once, even if they experienced multiple events in that system organ class or preferred term.
Source: Listing 17.2.4.2, Dataset: ADAE, Program: t_aesoc.sas, Output: t_16-4-2-2-aesoc.rtf, Generated on: 28JUL2017 05:57
Page 3 of 20

Table 16.4.2.2 Treatment-Emergent Adverse Events by System Organ Class and Preferred Term - Safety Overall Population

System Organ Class Preferred Term	GDNF/GDNF (N=21) n (%)	Placebo/GDNF (N=20) n (%)	Total (N=41) n (%)
General disorders and administration site conditions	14 (66.7)	13 (65.0)	27 (65.9)
Application site discharge	1 (4.8)	1 (5.0)	2 (4.9)
Application site erosion	1 (4.8)	0	1 (2.4)
Application site erythema	3 (14.3)	4 (20.0)	7 (17.1)
Application site haemorrhage	1 (4.8)	2 (10.0)	3 (7.3)
Application site hypertrophy	1 (4.8)	1 (5.0)	2 (4.9)
Application site hypoaesthesia	0	1 (5.0)	1 (2.4)
Application site inflammation	3 (14.3)	1 (5.0)	4 (9.8)
Application site laceration	0	1 (5.0)	1 (2.4)
Application site pain	2 (9.5)	1 (5.0)	3 (7.3)
Application site pruritus	0	1 (5.0)	1 (2.4)
Application site reaction	3 (14.3)	1 (5.0)	4 (9.8)
Application site swelling	3 (14.3)	2 (10.0)	5 (12.2)
Application site ulcer	1 (4.8)	1 (5.0)	2 (4.9)
Asthenia	1 (4.8)	0	1 (2.4)
Chest discomfort	1 (4.8)	0	1 (2.4)

Note: Adverse events are coded using MedDRA version 19.0. All AEs reported during the study period are considered TEAEs. TEAEs that are present or ongoing at the beginning of Study 2797 (date of consent or date of last visit in Study 2553, if consent was obtained earlier) are considered pre-existing, if the event term, severity, and date and time of onset in Study 2797 are identical to the corresponding information given for the TEAE in Study 2553. If any of these conditions is not met, the TEAE is considered new or worsening. Only new or worsening TEAEs are summarized. For each system organ class and preferred term, subjects are included only once, even if they experienced multiple events in that system organ class or preferred term.
Source: Listing 17.2.4.2, Dataset: ADAE, Program: t_aesoc.sas, Output: t_16-4-2-2-aesoc.rtf, Generated on: 28JUL2017 05:57
Page 4 of 20

Table 16.4.2.2 Treatment-Emergent Adverse Events by System Organ Class and Preferred Term - Safety Overall Population

System Organ Class Preferred Term	GDNF/GDNF (N=21) n (%)	Placebo/GDNF (N=20) n (%)	Total (N=41) n (%)
General disorders and administration site conditions			
Crying	0	1 (5.0)	1 (2.4)
Discomfort	1 (4.8)	0	1 (2.4)
Drug effect decreased	2 (9.5)	3 (15.0)	5 (12.2)
Drug ineffective	3 (14.3)	1 (5.0)	4 (9.8)
Drug intolerance	0	1 (5.0)	1 (2.4)
Facial pain	2 (9.5)	0	2 (4.9)
Fatigue	3 (14.3)	2 (10.0)	5 (12.2)
Feeling abnormal	1 (4.8)	2 (10.0)	3 (7.3)
Feeling cold	1 (4.8)	0	1 (2.4)
Feeling hot	1 (4.8)	0	1 (2.4)
Gait disturbance	2 (9.5)	1 (5.0)	3 (7.3)
Influenza like illness	0	1 (5.0)	1 (2.4)
Peripheral swelling	1 (4.8)	0	1 (2.4)
Pre-existing condition improved	2 (9.5)	0	2 (4.9)
Pyrexia	1 (4.8)	1 (5.0)	2 (4.9)
Sluggishness	1 (4.8)	0	1 (2.4)

Note: Adverse events are coded using MedDRA version 19.0. All AEs reported during the study period are considered TEAEs. TEAEs that are present or ongoing at the beginning of Study 2797 (date of consent or date of last visit in Study 2553, if consent was obtained earlier) are considered pre-existing, if the event term, severity, and date and time of onset in Study 2797 are identical to the corresponding information given for the TEAE in Study 2553. If any of these conditions is not met, the TEAE is considered new or worsening. Only new or worsening TEAEs are summarized. For each system organ class and preferred term, subjects are included only once, even if they experienced multiple events in that system organ class or preferred term.
Source: Listing 17.2.4.2, Dataset: ADAE, Program: t_aesoc.sas, Output: t_16-4-2-2-aesoc.rtf, Generated on: 28JUL2017 05:57
Page 5 of 20

Table 16.4.2.2 Treatment-Emergent Adverse Events by System Organ Class and Preferred Term - Safety Overall Population

System Organ Class Preferred Term	GDNF/GDNF (N=21) n (%)	Placebo/GDNF (N=20) n (%)	Total (N=41) n (%)
Immune system disorders	4 (19.0)	1 (5.0)	5 (12.2)
Allergy to arthropod sting	1 (4.8)	0	1 (2.4)
Food allergy	0	1 (5.0)	1 (2.4)
Hypersensitivity	1 (4.8)	0	1 (2.4)
Seasonal allergy	2 (9.5)	0	2 (4.9)
Infections and infestations	18 (85.7)	15 (75.0)	33 (80.5)
Abscess	0	1 (5.0)	1 (2.4)
Abscess oral	0	1 (5.0)	1 (2.4)
Appendicitis	0	1 (5.0)	1 (2.4)
Application site infection	6 (28.6)	4 (20.0)	10 (24.4)
Candida infection	1 (4.8)	0	1 (2.4)
Cellulitis	1 (4.8)	0	1 (2.4)
Conjunctivitis	1 (4.8)	2 (10.0)	3 (7.3)
Cystitis	1 (4.8)	0	1 (2.4)
Device related infection	1 (4.8)	0	1 (2.4)
Ear infection	1 (4.8)	0	1 (2.4)

Note: Adverse events are coded using MedDRA version 19.0. All AEs reported during the study period are considered TEAEs. TEAEs that are present or ongoing at the beginning of Study 2797 (date of consent or date of last visit in Study 2553, if consent was obtained earlier) are considered pre-existing, if the event term, severity, and date and time of onset in Study 2797 are identical to the corresponding information given for the TEAE in Study 2553. If any of these conditions is not met, the TEAE is considered new or worsening. Only new or worsening TEAEs are summarized. For each system organ class and preferred term, subjects are included only once, even if they experienced multiple events in that system organ class or preferred term.
Source: Listing 17.2.4.2, Dataset: ADAE, Program: t_aesoc.sas, Output: t_16-4-2-2-aesoc.rtf, Generated on: 28JUL2017 05:57

Table 16.4.2.2 Treatment-Emergent Adverse Events by System Organ Class and Preferred Term - Safety Overall Population

System Organ Class Preferred Term	GDNF/GDNF (N=21) n (%)	Placebo/GDNF (N=20) n (%)	Total (N=41) n (%)
Infections and infestations			
Fungal infection	1 (4.8)	0	1 (2.4)
Gastroenteritis	2 (9.5)	0	2 (4.9)
Gastroenteritis viral	1 (4.8)	0	1 (2.4)
Herpes zoster	1 (4.8)	0	1 (2.4)
Hordeolum	0	1 (5.0)	1 (2.4)
Impetigo	1 (4.8)	0	1 (2.4)
Laryngitis	1 (4.8)	0	1 (2.4)
Lower respiratory tract infection	2 (9.5)	1 (5.0)	3 (7.3)
Nasopharyngitis	9 (42.9)	8 (40.0)	17 (41.5)
Nosocomial infection	1 (4.8)	0	1 (2.4)
Post procedural infection	1 (4.8)	0	1 (2.4)
Postoperative wound infection	1 (4.8)	0	1 (2.4)
Pyelonephritis	0	1 (5.0)	1 (2.4)
Sinusitis	2 (9.5)	0	2 (4.9)
Skin infection	1 (4.8)	0	1 (2.4)
Tinea versicolour	1 (4.8)	0	1 (2.4)

Note: Adverse events are coded using MedDRA version 19.0. All AEs reported during the study period are considered TEAEs. TEAEs that are present or ongoing at the beginning of Study 2797 (date of consent or date of last visit in Study 2553, if consent was obtained earlier) are considered pre-existing, if the event term, severity, and date and time of onset in Study 2797 are identical to the corresponding information given for the TEAE in Study 2553. If any of these conditions is not met, the TEAE is considered new or worsening. Only new or worsening TEAEs are summarized. For each system organ class and preferred term, subjects are included only once, even if they experienced multiple events in that system organ class or preferred term.
Source: Listing 17.2.4.2, Dataset: ADAE, Program: t_aesoc.sas, Output: t_16-4-2-2-aesoc.rtf, Generated on: 28JUL2017 05:57
Page 7 of 20

Table 16.4.2.2 Treatment-Emergent Adverse Events by System Organ Class and Preferred Term - Safety Overall Population

System Organ Class Preferred Term	GDNF/GDNF (N=21) n (%)	Placebo/GDNF (N=20) n (%)	Total (N=41) n (%)
Infections and infestations			
Upper respiratory tract infection	1 (4.8)	0	1 (2.4)
Urinary tract infection	4 (19.0)	4 (20.0)	8 (19.5)
Viral infection	1 (4.8)	0	1 (2.4)
Vulval abscess	1 (4.8)	0	1 (2.4)
Injury, poisoning and procedural complications	13 (61.9)	14 (70.0)	27 (65.9)
Arthropod bite	0	1 (5.0)	1 (2.4)
Chest injury	1 (4.8)	0	1 (2.4)
Contusion	5 (23.8)	4 (20.0)	9 (22.0)
Corneal abrasion	1 (4.8)	0	1 (2.4)
Epicondylitis	0	2 (10.0)	2 (4.9)
Eye contusion	1 (4.8)	0	1 (2.4)
Facial bones fracture	0	1 (5.0)	1 (2.4)
Fall	6 (28.6)	10 (50.0)	16 (39.0)
Foreign body	1 (4.8)	0	1 (2.4)
Hair injury	0	1 (5.0)	1 (2.4)
Head injury	2 (9.5)	2 (10.0)	4 (9.8)

Note: Adverse events are coded using MedDRA version 19.0. All AEs reported during the study period are considered TEAEs. TEAEs that are present or ongoing at the beginning of Study 2797 (date of consent or date of last visit in Study 2553, if consent was obtained earlier) are considered pre-existing, if the event term, severity, and date and time of onset in Study 2797 are identical to the corresponding information given for the TEAE in Study 2553. If any of these conditions is not met, the TEAE is considered new or worsening. Only new or worsening TEAEs are summarized. For each system organ class and preferred term, subjects are included only once, even if they experienced multiple events in that system organ class or preferred term.
Source: Listing 17.2.4.2, Dataset: ADAE, Program: t_aesoc.sas, Output: t_16-4-2-2-aesoc.rtf, Generated on: 28JUL2017 05:57
Page 8 of 20

Table 16.4.2.2 Treatment-Emergent Adverse Events by System Organ Class and Preferred Term - Safety Overall Population

System Organ Class Preferred Term	GDNF/GDNF (N=21) n (%)	Placebo/GDNF (N=20) n (%)	Total (N=41) n (%)
Injury, poisoning and procedural complications			
Inflammation of wound	1 (4.8)	0	1 (2.4)
Joint injury	4 (19.0)	2 (10.0)	6 (14.6)
Laceration	0	1 (5.0)	1 (2.4)
Muscle rupture	1 (4.8)	1 (5.0)	2 (4.9)
Post procedural complication	1 (4.8)	0	1 (2.4)
Post procedural contusion	1 (4.8)	0	1 (2.4)
Post procedural oedema	1 (4.8)	0	1 (2.4)
Postoperative fever	1 (4.8)	0	1 (2.4)
Procedural complication	1 (4.8)	0	1 (2.4)
Procedural headache	1 (4.8)	0	1 (2.4)
Psychosis postoperative	1 (4.8)	0	1 (2.4)
Rib fracture	0	1 (5.0)	1 (2.4)
Skeletal injury	1 (4.8)	0	1 (2.4)
Skin abrasion	1 (4.8)	2 (10.0)	3 (7.3)
Spinal column injury	0	1 (5.0)	1 (2.4)
Sternal fracture	1 (4.8)	0	1 (2.4)

Note: Adverse events are coded using MedDRA version 19.0. All AEs reported during the study period are considered TEAEs. TEAEs that are present or ongoing at the beginning of Study 2797 (date of consent or date of last visit in Study 2553, if consent was obtained earlier) are considered pre-existing, if the event term, severity, and date and time of onset in Study 2797 are identical to the corresponding information given for the TEAE in Study 2553. If any of these conditions is not met, the TEAE is considered new or worsening. Only new or worsening TEAEs are summarized. For each system organ class and preferred term, subjects are included only once, even if they experienced multiple events in that system organ class or preferred term.
Source: Listing 17.2.4.2, Dataset: ADAE, Program: t_aesoc.sas, Output: t_16-4-2-2-aesoc.rtf, Generated on: 28JUL2017 05:57
Page 9 of 20

Table 16.4.2.2 Treatment-Emergent Adverse Events by System Organ Class and Preferred Term - Safety Overall Population

System Organ Class Preferred Term	GDNF/GDNF (N=21) n (%)	Placebo/GDNF (N=20) n (%)	Total (N=41) n (%)
Injury, poisoning and procedural complications			
Tooth fracture	0	1 (5.0)	1 (2.4)
Vaccination complication	0	1 (5.0)	1 (2.4)
Wrist fracture	1 (4.8)	0	1 (2.4)
Investigations	3 (14.3)	4 (20.0)	7 (17.1)
Blood cholesterol increased	0	1 (5.0)	1 (2.4)
Blood pressure increased	0	1 (5.0)	1 (2.4)
Body temperature increased	0	1 (5.0)	1 (2.4)
C-reactive protein increased	0	1 (5.0)	1 (2.4)
Electrocardiogram abnormal	1 (4.8)	0	1 (2.4)
Haemoglobin decreased	1 (4.8)	0	1 (2.4)
Renal function test abnormal	0	1 (5.0)	1 (2.4)
Vitamin D decreased	0	1 (5.0)	1 (2.4)
Weight decreased	1 (4.8)	1 (5.0)	2 (4.9)
Metabolism and nutrition disorders	0	5 (25.0)	5 (12.2)
Dehydration	0	1 (5.0)	1 (2.4)
Hyperglycaemia	0	1 (5.0)	1 (2.4)

Note: Adverse events are coded using MedDRA version 19.0. All AEs reported during the study period are considered TEAEs. TEAEs that are present or ongoing at the beginning of Study 2797 (date of consent or date of last visit in Study 2553, if consent was obtained earlier) are considered pre-existing, if the event term, severity, and date and time of onset in Study 2797 are identical to the corresponding information given for the TEAE in Study 2553. If any of these conditions is not met, the TEAE is considered new or worsening. Only new or worsening TEAEs are summarized. For each system organ class and preferred term, subjects are included only once, even if they experienced multiple events in that system organ class or preferred term.
Source: Listing 17.2.4.2, Dataset: ADAE, Program: t_aesoc.sas, Output: t_16-4-2-2-aesoc.rtf, Generated on: 28JUL2017 05:57
Page 10 of 20

Table 16.4.2.2 Treatment-Emergent Adverse Events by System Organ Class and Preferred Term - Safety Overall Population

System Organ Class Preferred Term	GDNF/GDNF (N=21) n (%)	Placebo/GDNF (N=20) n (%)	Total (N=41) n (%)
Metabolism and nutrition disorders			
Hypoalbuminaemia	0	2 (10.0)	2 (4.9)
Hypocalcaemia	0	1 (5.0)	1 (2.4)
Musculoskeletal and connective tissue disorders	15 (71.4)	13 (65.0)	28 (68.3)
Arthralgia	2 (9.5)	3 (15.0)	5 (12.2)
Arthritis	1 (4.8)	0	1 (2.4)
Back pain	5 (23.8)	5 (25.0)	10 (24.4)
Bursitis	1 (4.8)	0	1 (2.4)
Foot deformity	2 (9.5)	0	2 (4.9)
Joint swelling	1 (4.8)	0	1 (2.4)
Limb discomfort	3 (14.3)	0	3 (7.3)
Lumbar spinal stenosis	0	1 (5.0)	1 (2.4)
Mobility decreased	0	1 (5.0)	1 (2.4)
Muscle rigidity	0	2 (10.0)	2 (4.9)
Muscle spasms	4 (19.0)	7 (35.0)	11 (26.8)
Muscular weakness	2 (9.5)	0	2 (4.9)
Musculoskeletal chest pain	0	1 (5.0)	1 (2.4)

Note: Adverse events are coded using MedDRA version 19.0. All AEs reported during the study period are considered TEAEs. TEAEs that are present or ongoing at the beginning of Study 2797 (date of consent or date of last visit in Study 2553, if consent was obtained earlier) are considered pre-existing, if the event term, severity, and date and time of onset in Study 2797 are identical to the corresponding information given for the TEAE in Study 2553. If any of these conditions is not met, the TEAE is considered new or worsening. Only new or worsening TEAEs are summarized. For each system organ class and preferred term, subjects are included only once, even if they experienced multiple events in that system organ class or preferred term.
Source: Listing 17.2.4.2, Dataset: ADAE, Program: t_aesoc.sas, Output: t_16-4-2-2-aesoc.rtf, Generated on: 28JUL2017 05:57

Table 16.4.2.2 Treatment-Emergent Adverse Events by System Organ Class and Preferred Term - Safety Overall Population

System Organ Class Preferred Term	GDNF/GDNF (N=21) n (%)	Placebo/GDNF (N=20) n (%)	Total (N=41) n (%)
Musculoskeletal and connective tissue disorders			
Musculoskeletal pain	3 (14.3)	1 (5.0)	4 (9.8)
Musculoskeletal stiffness	1 (4.8)	0	1 (2.4)
Neck pain	2 (9.5)	1 (5.0)	3 (7.3)
Osteoarthritis	2 (9.5)	1 (5.0)	3 (7.3)
Osteoporosis	0	1 (5.0)	1 (2.4)
Pain in extremity	6 (28.6)	2 (10.0)	8 (19.5)
Pain in jaw	0	1 (5.0)	1 (2.4)
Trigger finger	1 (4.8)	0	1 (2.4)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (9.5)	1 (5.0)	3 (7.3)
Chondromatosis	1 (4.8)	0	1 (2.4)
Lipoma	0	1 (5.0)	1 (2.4)
Melanocytic naevus	1 (4.8)	0	1 (2.4)
Nervous system disorders	18 (85.7)	16 (80.0)	34 (82.9)
Aphasia	2 (9.5)	0	2 (4.9)
Balance disorder	2 (9.5)	1 (5.0)	3 (7.3)
Bradykinesia	2 (9.5)	0	2 (4.9)

Note: Adverse events are coded using MedDRA version 19.0. All AEs reported during the study period are considered TEAEs. TEAEs that are present or ongoing at the beginning of Study 2797 (date of consent or date of last visit in Study 2553, if consent was obtained earlier) are considered pre-existing, if the event term, severity, and date and time of onset in Study 2797 are identical to the corresponding information given for the TEAE in Study 2553. If any of these conditions is not met, the TEAE is considered new or worsening. Only new or worsening TEAEs are summarized. For each system organ class and preferred term, subjects are included only once, even if they experienced multiple events in that system organ class or preferred term.
Source: Listing 17.2.4.2, Dataset: ADAE, Program: t_aesoc.sas, Output: t_16-4-2-2-aesoc.rtf, Generated on: 28JUL2017 05:57
Page 12 of 20

Table 16.4.2.2 Treatment-Emergent Adverse Events by System Organ Class and Preferred Term - Safety Overall Population

System Organ Class Preferred Term	GDNF/GDNF (N=21) n (%)	Placebo/GDNF (N=20) n (%)	Total (N=41) n (%)
Nervous system disorders			
Burning sensation	1 (4.8)	1 (5.0)	2 (4.9)
Cognitive disorder	0	1 (5.0)	1 (2.4)
Coordination abnormal	0	1 (5.0)	1 (2.4)
Dizziness	3 (14.3)	3 (15.0)	6 (14.6)
Dizziness postural	0	1 (5.0)	1 (2.4)
Drooling	1 (4.8)	0	1 (2.4)
Dysaesthesia	0	1 (5.0)	1 (2.4)
Dysgeusia	1 (4.8)	1 (5.0)	2 (4.9)
Dyskinesia	10 (47.6)	9 (45.0)	19 (46.3)
Dysstasia	1 (4.8)	0	1 (2.4)
Dystonia	6 (28.6)	5 (25.0)	11 (26.8)
Freezing phenomenon	8 (38.1)	3 (15.0)	11 (26.8)
Head discomfort	3 (14.3)	1 (5.0)	4 (9.8)
Headache	6 (28.6)	5 (25.0)	11 (26.8)
Hypoaesthesia	1 (4.8)	2 (10.0)	3 (7.3)
Hypokinesia	0	1 (5.0)	1 (2.4)

Note: Adverse events are coded using MedDRA version 19.0. All AEs reported during the study period are considered TEAEs. TEAEs that are present or ongoing at the beginning of Study 2797 (date of consent or date of last visit in Study 2553, if consent was obtained earlier) are considered pre-existing, if the event term, severity, and date and time of onset in Study 2797 are identical to the corresponding information given for the TEAE in Study 2553. If any of these conditions is not met, the TEAE is considered new or worsening. Only new or worsening TEAEs are summarized. For each system organ class and preferred term, subjects are included only once, even if they experienced multiple events in that system organ class or preferred term.
Source: Listing 17.2.4.2, Dataset: ADAE, Program: t_aesoc.sas, Output: t_16-4-2-2-aesoc.rtf, Generated on: 28JUL2017 05:57
Page 13 of 20

Table 16.4.2.2 Treatment-Emergent Adverse Events by System Organ Class and Preferred Term - Safety Overall Population

System Organ Class Preferred Term	GDNF/GDNF (N=21) n (%)	Placebo/GDNF (N=20) n (%)	Total (N=41) n (%)
Nervous system disorders			
Lethargy	1 (4.8)	0	1 (2.4)
Lhermitte's sign	9 (42.9)	4 (20.0)	13 (31.7)
Migraine	0	1 (5.0)	1 (2.4)
Motor dysfunction	1 (4.8)	0	1 (2.4)
On and off phenomenon	7 (33.3)	7 (35.0)	14 (34.1)
Paraesthesia	6 (28.6)	7 (35.0)	13 (31.7)
Parkinson's disease	5 (23.8)	1 (5.0)	6 (14.6)
Parosmia	1 (4.8)	0	1 (2.4)
Poor quality sleep	2 (9.5)	0	2 (4.9)
Psychomotor hyperactivity	1 (4.8)	0	1 (2.4)
Restless legs syndrome	2 (9.5)	2 (10.0)	4 (9.8)
Sciatica	1 (4.8)	1 (5.0)	2 (4.9)
Sensory disturbance	2 (9.5)	1 (5.0)	3 (7.3)
Somnolence	0	1 (5.0)	1 (2.4)
Tension headache	1 (4.8)	0	1 (2.4)
Tremor	2 (9.5)	0	2 (4.9)

Note: Adverse events are coded using MedDRA version 19.0. All AEs reported during the study period are considered TEAEs. TEAEs that are present or ongoing at the beginning of Study 2797 (date of consent or date of last visit in Study 2553, if consent was obtained earlier) are considered pre-existing, if the event term, severity, and date and time of onset in Study 2797 are identical to the corresponding information given for the TEAE in Study 2553. If any of these conditions is not met, the TEAE is considered new or worsening. Only new or worsening TEAEs are summarized. For each system organ class and preferred term, subjects are included only once, even if they experienced multiple events in that system organ class or preferred term.
Source: Listing 17.2.4.2, Dataset: ADAE, Program: t_aesoc.sas, Output: t_16-4-2-2-aesoc.rtf, Generated on: 28JUL2017 05:57

Table 16.4.2.2 Treatment-Emergent Adverse Events by System Organ Class and Preferred Term - Safety Overall Population

System Organ Class Preferred Term	GDNF/GDNF (N=21) n (%)	Placebo/GDNF (N=20) n (%)	Total (N=41) n (%)
Product issues	2 (9.5)	0	2 (4.9)
Device occlusion	2 (9.5)	0	2 (4.9)
Psychiatric disorders	15 (71.4)	13 (65.0)	28 (68.3)
Abnormal dreams	3 (14.3)	1 (5.0)	4 (9.8)
Affective disorder	1 (4.8)	0	1 (2.4)
Agitation	0	1 (5.0)	1 (2.4)
Anorgasmia	1 (4.8)	0	1 (2.4)
Anxiety	2 (9.5)	2 (10.0)	4 (9.8)
Bruxism	1 (4.8)	0	1 (2.4)
Compulsive shopping	0	1 (5.0)	1 (2.4)
Confusional state	1 (4.8)	0	1 (2.4)
Depressed mood	4 (19.0)	3 (15.0)	7 (17.1)
Depression	1 (4.8)	0	1 (2.4)
Dopamine dysregulation syndrome	0	1 (5.0)	1 (2.4)
Dysphemia	1 (4.8)	0	1 (2.4)
Feeling of despair	1 (4.8)	0	1 (2.4)

Note: Adverse events are coded using MedDRA version 19.0. All AEs reported during the study period are considered TEAEs. TEAEs that are present or ongoing at the beginning of Study 2797 (date of consent or date of last visit in Study 2553, if consent was obtained earlier) are considered pre-existing, if the event term, severity, and date and time of onset in Study 2797 are identical to the corresponding information given for the TEAE in Study 2553. If any of these conditions is not met, the TEAE is considered new or worsening. Only new or worsening TEAEs are summarized. For each system organ class and preferred term, subjects are included only once, even if they experienced multiple events in that system organ class or preferred term.
Source: Listing 17.2.4.2, Dataset: ADAE, Program: t_aesoc.sas, Output: t_16-4-2-2-aesoc.rtf, Generated on: 28JUL2017 05:57

Table 16.4.2.2 Treatment-Emergent Adverse Events by System Organ Class and Preferred Term - Safety Overall Population

System Organ Class Preferred Term	GDNF/GDNF (N=21) n (%)	Placebo/GDNF (N=20) n (%)	Total (N=41) n (%)
Psychiatric disorders			
Hallucination	1 (4.8)	1 (5.0)	2 (4.9)
Hallucination, olfactory	0	1 (5.0)	1 (2.4)
Hallucination, visual	0	1 (5.0)	1 (2.4)
Hypersexuality	0	1 (5.0)	1 (2.4)
Hypomania	0	1 (5.0)	1 (2.4)
Impulsive behaviour	1 (4.8)	0	1 (2.4)
Insomnia	2 (9.5)	3 (15.0)	5 (12.2)
Irritability	0	1 (5.0)	1 (2.4)
Libido increased	2 (9.5)	0	2 (4.9)
Obsessive-compulsive disorder	2 (9.5)	1 (5.0)	3 (7.3)
Paranoia	1 (4.8)	0	1 (2.4)
Rapid eye movement sleep behaviour disorder	2 (9.5)	3 (15.0)	5 (12.2)
Rapid eye movements sleep abnormal	0	1 (5.0)	1 (2.4)
Restlessness	0	1 (5.0)	1 (2.4)
Sleep disorder	2 (9.5)	0	2 (4.9)
Stress	2 (9.5)	0	2 (4.9)

Note: Adverse events are coded using MedDRA version 19.0. All AEs reported during the study period are considered TEAEs. TEAEs that are present or ongoing at the beginning of Study 2797 (date of consent or date of last visit in Study 2553, if consent was obtained earlier) are considered pre-existing, if the event term, severity, and date and time of onset in Study 2797 are identical to the corresponding information given for the TEAE in Study 2553. If any of these conditions is not met, the TEAE is considered new or worsening. Only new or worsening TEAEs are summarized. For each system organ class and preferred term, subjects are included only once, even if they experienced multiple events in that system organ class or preferred term.
Source: Listing 17.2.4.2, Dataset: ADAE, Program: t_aesoc.sas, Output: t_16-4-2-2-aesoc.rtf, Generated on: 28JUL2017 05:57

Table 16.4.2.2 Treatment-Emergent Adverse Events by System Organ Class and Preferred Term - Safety Overall Population

System Organ Class Preferred Term	GDNF/GDNF (N=21) n (%)	Placebo/GDNF (N=20) n (%)	Total (N=41) n (%)
Psychiatric disorders			
Tearfulness	0	1 (5.0)	1 (2.4)
Renal and urinary disorders	2 (9.5)	5 (25.0)	7 (17.1)
Bladder disorder	1 (4.8)	0	1 (2.4)
Dysuria	0	1 (5.0)	1 (2.4)
Haematuria	0	1 (5.0)	1 (2.4)
Micturition urgency	1 (4.8)	0	1 (2.4)
Pollakiuria	0	2 (10.0)	2 (4.9)
Renal impairment	0	1 (5.0)	1 (2.4)
Urinary retention	0	1 (5.0)	1 (2.4)
Reproductive system and breast disorders	4 (19.0)	2 (10.0)	6 (14.6)
Breast cyst	1 (4.8)	0	1 (2.4)
Dyspareunia	0	1 (5.0)	1 (2.4)
Ejaculation disorder	1 (4.8)	0	1 (2.4)
Endometrial thickening	1 (4.8)	0	1 (2.4)
Menorrhagia	2 (9.5)	0	2 (4.9)
Pelvic pain	0	1 (5.0)	1 (2.4)

Note: Adverse events are coded using MedDRA version 19.0. All AEs reported during the study period are considered TEAEs. TEAEs that are present or ongoing at the beginning of Study 2797 (date of consent or date of last visit in Study 2553, if consent was obtained earlier) are considered pre-existing, if the event term, severity, and date and time of onset in Study 2797 are identical to the corresponding information given for the TEAE in Study 2553. If any of these conditions is not met, the TEAE is considered new or worsening. Only new or worsening TEAEs are summarized. For each system organ class and preferred term, subjects are included only once, even if they experienced multiple events in that system organ class or preferred term.
Source: Listing 17.2.4.2, Dataset: ADAE, Program: t_aesoc.sas, Output: t_16-4-2-2-aesoc.rtf, Generated on: 28JUL2017 05:57
Page 17 of 20

Table 16.4.2.2 Treatment-Emergent Adverse Events by System Organ Class and Preferred Term - Safety Overall Population

System Organ Class Preferred Term	GDNF/GDNF (N=21) n (%)	Placebo/GDNF (N=20) n (%)	Total (N=41) n (%)
Respiratory, thoracic and mediastinal disorders	8 (38.1)	4 (20.0)	12 (29.3)
Cough	4 (19.0)	1 (5.0)	5 (12.2)
Dysphonia	1 (4.8)	0	1 (2.4)
Dyspnoea	2 (9.5)	0	2 (4.9)
Epistaxis	1 (4.8)	0	1 (2.4)
Laryngospasm	0	1 (5.0)	1 (2.4)
Nasal obstruction	1 (4.8)	0	1 (2.4)
Oropharyngeal pain	0	1 (5.0)	1 (2.4)
Productive cough	1 (4.8)	0	1 (2.4)
Respiratory disorder	1 (4.8)	0	1 (2.4)
Rhinorrhoea	0	1 (5.0)	1 (2.4)
Sinus congestion	0	1 (5.0)	1 (2.4)
Skin and subcutaneous tissue disorders	6 (28.6)	6 (30.0)	12 (29.3)
Acne	0	1 (5.0)	1 (2.4)
Alopecia	1 (4.8)	0	1 (2.4)
Dermatitis	1 (4.8)	0	1 (2.4)

Note: Adverse events are coded using MedDRA version 19.0. All AEs reported during the study period are considered TEAEs. TEAEs that are present or ongoing at the beginning of Study 2797 (date of consent or date of last visit in Study 2553, if consent was obtained earlier) are considered pre-existing, if the event term, severity, and date and time of onset in Study 2797 are identical to the corresponding information given for the TEAE in Study 2553. If any of these conditions is not met, the TEAE is considered new or worsening. Only new or worsening TEAEs are summarized. For each system organ class and preferred term, subjects are included only once, even if they experienced multiple events in that system organ class or preferred term.
Source: Listing 17.2.4.2, Dataset: ADAE, Program: t_aesoc.sas, Output: t_16-4-2-2-aesoc.rtf, Generated on: 28JUL2017 05:57
Page 18 of 20

Table 16.4.2.2 Treatment-Emergent Adverse Events by System Organ Class and Preferred Term - Safety Overall Population

System Organ Class Preferred Term	GDNF/GDNF (N=21) n (%)	Placebo/GDNF (N=20) n (%)	Total (N=41) n (%)
Skin and subcutaneous tissue disorders			
Dermatitis allergic	1 (4.8)	0	1 (2.4)
Drug eruption	1 (4.8)	0	1 (2.4)
Hirsutism	0	1 (5.0)	1 (2.4)
Hyperhidrosis	0	2 (10.0)	2 (4.9)
Itching scar	1 (4.8)	0	1 (2.4)
Lichenoid keratosis	0	1 (5.0)	1 (2.4)
Night sweats	1 (4.8)	0	1 (2.4)
Rash	1 (4.8)	1 (5.0)	2 (4.9)
Rash generalised	0	1 (5.0)	1 (2.4)
Rash pruritic	1 (4.8)	0	1 (2.4)
Skin exfoliation	0	1 (5.0)	1 (2.4)
Skin hypopigmentation	1 (4.8)	0	1 (2.4)
Skin lesion	0	1 (5.0)	1 (2.4)
Skin reaction	1 (4.8)	0	1 (2.4)
Skin ulcer	2 (9.5)	0	2 (4.9)
Stasis dermatitis	0	1 (5.0)	1 (2.4)

Note: Adverse events are coded using MedDRA version 19.0. All AEs reported during the study period are considered TEAEs. TEAEs that are present or ongoing at the beginning of Study 2797 (date of consent or date of last visit in Study 2553, if consent was obtained earlier) are considered pre-existing, if the event term, severity, and date and time of onset in Study 2797 are identical to the corresponding information given for the TEAE in Study 2553. If any of these conditions is not met, the TEAE is considered new or worsening. Only new or worsening TEAEs are summarized. For each system organ class and preferred term, subjects are included only once, even if they experienced multiple events in that system organ class or preferred term.
Source: Listing 17.2.4.2, Dataset: ADAE, Program: t_aesoc.sas, Output: t_16-4-2-2-aesoc.rtf, Generated on: 28JUL2017 05:57
Page 19 of 20

Table 16.4.2.2 Treatment-Emergent Adverse Events by System Organ Class and Preferred Term - Safety Overall Population

System Organ Class Preferred Term	GDNF/GDNF (N=21) n (%)	Placebo/GDNF (N=20) n (%)	Total (N=41) n (%)
Skin and subcutaneous tissue disorders			
Swelling face	1 (4.8)	0	1 (2.4)
Vascular disorders	6 (28.6)	1 (5.0)	7 (17.1)
Flushing	1 (4.8)	0	1 (2.4)
Hot flush	1 (4.8)	0	1 (2.4)
Hypertension	2 (9.5)	0	2 (4.9)
Orthostatic hypotension	2 (9.5)	1 (5.0)	3 (7.3)

Note: Adverse events are coded using MedDRA version 19.0. All AEs reported during the study period are considered TEAEs. TEAEs that are present or ongoing at the beginning of Study 2797 (date of consent or date of last visit in Study 2553, if consent was obtained earlier) are considered pre-existing, if the event term, severity, and date and time of onset in Study 2797 are identical to the corresponding information given for the TEAE in Study 2553. If any of these conditions is not met, the TEAE is considered new or worsening. Only new or worsening TEAEs are summarized. For each system organ class and preferred term, subjects are included only once, even if they experienced multiple events in that system organ class or preferred term.
Source: Listing 17.2.4.2, Dataset: ADAE, Program: t_aesoc.sas, Output: t_16-4-2-2-aesoc.rtf, Generated on: 28JUL2017 05:57
Page 20 of 20

Table 16.4.2.3.1 Treatment-Emergent Adverse Events Experienced by at Least 3 Subjects in Any Treatment Group by Preferred Term - Safety Overall Population

Preferred Term	GDNF/GDNF (N=21)		Placebo/GDNF (N=20)		Total (N=41)	
	n Subjects (%)	n Events	n Subjects (%)	n Events	n Subjects (%)	n Events
Dyskinesia	10 (47.6)	12	9 (45.0)	13	19 (46.3)	25
Nasopharyngitis	9 (42.9)	10	8 (40.0)	9	17 (41.5)	19
Fall	6 (28.6)	18	10 (50.0)	20	16 (39.0)	38
On and off phenomenon	7 (33.3)	14	7 (35.0)	13	14 (34.1)	27
Lhermitte's sign	9 (42.9)	12	4 (20.0)	4	13 (31.7)	16
Paraesthesia	6 (28.6)	14	7 (35.0)	8	13 (31.7)	22
Dystonia	6 (28.6)	11	5 (25.0)	7	11 (26.8)	18
Freezing phenomenon	8 (38.1)	13	3 (15.0)	5	11 (26.8)	18
Headache	6 (28.6)	17	5 (25.0)	8	11 (26.8)	25
Muscle spasms	4 (19.0)	8	7 (35.0)	10	11 (26.8)	18
Application site infection	6 (28.6)	15	4 (20.0)	7	10 (24.4)	22
Back pain	5 (23.8)	5	5 (25.0)	5	10 (24.4)	10
Contusion	5 (23.8)	6	4 (20.0)	4	9 (22.0)	10
Pain in extremity	6 (28.6)	7	2 (10.0)	2	8 (19.5)	9
Urinary tract infection	4 (19.0)	4	4 (20.0)	6	8 (19.5)	10
Application site erythema	3 (14.3)	4	4 (20.0)	4	7 (17.1)	8

Note: Adverse events are coded using MedDRA version 19.0. All AEs reported during the study period are considered TEAEs. TEAEs that are present or ongoing at the beginning of Study 2797 (date of consent or date of last visit in Study 2553, if consent was obtained earlier) are considered pre-existing, if the event term, severity, and date and time of onset in Study 2797 are identical to the corresponding information given for the TEAE in Study 2553. If any of these conditions is not met, the TEAE is considered new or worsening. Only new or worsening TEAEs are summarized. For each preferred term, subjects are included only once, even if they experienced multiple events in that preferred term.
Source: Listing 17.2.4.2, Dataset: ADAE, Program: t_aept.sas, Output: t_16-4-2-3-1-aept.rtf, Generated on: 28JUL2017 05:57
Page 1 of 3

Table 16.4.2.3.1 Treatment-Emergent Adverse Events Experienced by at Least 3 Subjects in Any Treatment Group by Preferred Term - Safety Overall Population

Preferred Term	GDNF/GDNF (N=21)		Placebo/GDNF (N=20)		Total (N=41)	
	n Subjects (%)	n Events	n Subjects (%)	n Events	n Subjects (%)	n Events
Depressed mood	4 (19.0)	4	3 (15.0)	3	7 (17.1)	7
Nausea	5 (23.8)	5	2 (10.0)	2	7 (17.1)	7
Dizziness	3 (14.3)	3	3 (15.0)	3	6 (14.6)	6
Joint injury	4 (19.0)	5	2 (10.0)	2	6 (14.6)	7
Parkinson's disease	5 (23.8)	5	1 (5.0)	2	6 (14.6)	7
Application site swelling	3 (14.3)	3	2 (10.0)	2	5 (12.2)	5
Arthralgia	2 (9.5)	2	3 (15.0)	3	5 (12.2)	5
Constipation	2 (9.5)	2	3 (15.0)	3	5 (12.2)	5
Cough	4 (19.0)	5	1 (5.0)	1	5 (12.2)	6
Diarrhoea	3 (14.3)	9	2 (10.0)	2	5 (12.2)	11
Drug effect decreased	2 (9.5)	2	3 (15.0)	3	5 (12.2)	5
Fatigue	3 (14.3)	7	2 (10.0)	4	5 (12.2)	11
Insomnia	2 (9.5)	3	3 (15.0)	7	5 (12.2)	10
Rapid eye movement sleep behaviour disorder	2 (9.5)	2	3 (15.0)	3	5 (12.2)	5
Abnormal dreams	3 (14.3)	3	1 (5.0)	1	4 (9.8)	4
Anaemia	4 (19.0)	6	0	0	4 (9.8)	6

Note: Adverse events are coded using MedDRA version 19.0. All AEs reported during the study period are considered TEAEs. TEAEs that are present or ongoing at the beginning of Study 2797 (date of consent or date of last visit in Study 2553, if consent was obtained earlier) are considered pre-existing, if the event term, severity, and date and time of onset in Study 2797 are identical to the corresponding information given for the TEAE in Study 2553. If any of these conditions is not met, the TEAE is considered new or worsening. Only new or worsening TEAEs are summarized. For each preferred term, subjects are included only once, even if they experienced multiple events in that preferred term.
Source: Listing 17.2.4.2, Dataset: ADAE, Program: t_aept.sas, Output: t_16-4-2-3-1-aept.rtf, Generated on: 28JUL2017 05:57
Page 2 of 3

Table 16.4.2.3.1 Treatment-Emergent Adverse Events Experienced by at Least 3 Subjects in Any Treatment Group by Preferred Term - Safety Overall Population

Preferred Term	GDNF/GDNF (N=21)		Placebo/GDNF (N=20)		Total (N=41)	
	n Subjects (%)	n Events	n Subjects (%)	n Events	n Subjects (%)	n Events
Application site inflammation	3 (14.3)	5	1 (5.0)	1	4 (9.8)	6
Application site reaction	3 (14.3)	4	1 (5.0)	1	4 (9.8)	5
Drug ineffective	3 (14.3)	4	1 (5.0)	1	4 (9.8)	5
Dysphagia	1 (4.8)	1	3 (15.0)	3	4 (9.8)	4
Head discomfort	3 (14.3)	11	1 (5.0)	1	4 (9.8)	12
Musculoskeletal pain	3 (14.3)	3	1 (5.0)	2	4 (9.8)	5
Abdominal pain upper	3 (14.3)	4	0	0	3 (7.3)	4
Limb discomfort	3 (14.3)	4	0	0	3 (7.3)	4

Note: Adverse events are coded using MedDRA version 19.0. All AEs reported during the study period are considered TEAEs. TEAEs that are present or ongoing at the beginning of Study 2797 (date of consent or date of last visit in Study 2553, if consent was obtained earlier) are considered pre-existing, if the event term, severity, and date and time of onset in Study 2797 are identical to the corresponding information given for the TEAE in Study 2553. If any of these conditions is not met, the TEAE is considered new or worsening. Only new or worsening TEAEs are summarized. For each preferred term, subjects are included only once, even if they experienced multiple events in that preferred term.
Source: Listing 17.2.4.2, Dataset: ADAE, Program: t_aept.sas, Output: t_16-4-2-3-1-aept.rtf, Generated on: 28JUL2017 05:57
Page 3 of 3

Table 16.4.2.3.2 Treatment-Emergent Adverse Events Experienced by at Least 3 Subjects in Any Treatment Group During the Initial Extension by Preferred Term - Safety Overall Population

Preferred Term	GDNF/GDNF (N=21)		Placebo/GDNF (N=20)		Total (N=41)	
	n Subjects (%)	n Events	n Subjects (%)	n Events	n Subjects (%)	n Events
Dyskinesia	8 (38.1)	9	9 (45.0)	10	17 (41.5)	19
Lhermitte's sign	9 (42.9)	12	4 (20.0)	4	13 (31.7)	16
Nasopharyngitis	7 (33.3)	8	6 (30.0)	7	13 (31.7)	15
Paraesthesia	6 (28.6)	13	7 (35.0)	8	13 (31.7)	21
Fall	5 (23.8)	14	7 (35.0)	14	12 (29.3)	28
On and off phenomenon	4 (19.0)	8	7 (35.0)	11	11 (26.8)	19
Freezing phenomenon	7 (33.3)	10	3 (15.0)	4	10 (24.4)	14
Application site infection	5 (23.8)	11	4 (20.0)	7	9 (22.0)	18
Dystonia	5 (23.8)	10	4 (20.0)	6	9 (22.0)	16
Headache	4 (19.0)	8	5 (25.0)	8	9 (22.0)	16
Back pain	3 (14.3)	3	5 (25.0)	5	8 (19.5)	8
Muscle spasms	2 (9.5)	4	6 (30.0)	9	8 (19.5)	13
Contusion	4 (19.0)	5	3 (15.0)	3	7 (17.1)	8
Pain in extremity	5 (23.8)	5	2 (10.0)	2	7 (17.1)	7
Urinary tract infection	3 (14.3)	3	4 (20.0)	6	7 (17.1)	9
Application site erythema	2 (9.5)	3	4 (20.0)	4	6 (14.6)	7

Note: Adverse events are coded using MedDRA version 19.0. All AEs reported during the study period are considered TEAEs. TEAEs that are present or ongoing at the beginning of Study 2797 (date of consent or date of last visit in Study 2553, if consent was obtained earlier) are considered pre-existing, if the event term, severity, and date and time of onset in Study 2797 are identical to the corresponding information given for the TEAE in Study 2553. If any of these conditions is not met, the TEAE is considered new or worsening. Only new or worsening TEAEs are summarized. For each preferred term, subjects are included only once, even if they experienced multiple events in that preferred term.
Source: Listing 17.2.4.2, Dataset: ADAE, Program: t_aept.sas, Output: t_16-4-2-3-2-aept.rtf, Generated on: 28JUL2017 05:57
Page 1 of 2

Table 16.4.2.3.2 Treatment-Emergent Adverse Events Experienced by at Least 3 Subjects in Any Treatment Group During the Initial Extension by Preferred Term - Safety Overall Population

Preferred Term	GDNF/GDNF (N=21)		Placebo/GDNF (N=20)		Total (N=41)	
	n Subjects (%)	n Events	n Subjects (%)	n Events	n Subjects (%)	n Events
Dizziness	3 (14.3)	3	3 (15.0)	3	6 (14.6)	6
Joint injury	4 (19.0)	5	2 (10.0)	2	6 (14.6)	7
Nausea	4 (19.0)	4	2 (10.0)	2	6 (14.6)	6
Constipation	2 (9.5)	2	3 (15.0)	3	5 (12.2)	5
Drug effect decreased	2 (9.5)	2	3 (15.0)	3	5 (12.2)	5
Abnormal dreams	3 (14.3)	3	1 (5.0)	1	4 (9.8)	4
Application site inflammation	3 (14.3)	4	1 (5.0)	1	4 (9.8)	5
Application site reaction	3 (14.3)	4	1 (5.0)	1	4 (9.8)	5
Cough	3 (14.3)	3	1 (5.0)	1	4 (9.8)	4
Diarrhoea	3 (14.3)	7	1 (5.0)	1	4 (9.8)	8
Insomnia	1 (4.8)	1	3 (15.0)	7	4 (9.8)	8
Abdominal pain upper	3 (14.3)	4	0	0	3 (7.3)	4
Anaemia	3 (14.3)	3	0	0	3 (7.3)	3
Dysphagia	0	0	3 (15.0)	3	3 (7.3)	3
Head discomfort	3 (14.3)	11	0	0	3 (7.3)	11

Note: Adverse events are coded using MedDRA version 19.0. All AEs reported during the study period are considered TEAEs. TEAEs that are present or ongoing at the beginning of Study 2797 (date of consent or date of last visit in Study 2553, if consent was obtained earlier) are considered pre-existing, if the event term, severity, and date and time of onset in Study 2797 are identical to the corresponding information given for the TEAE in Study 2553. If any of these conditions is not met, the TEAE is considered new or worsening. Only new or worsening TEAEs are summarized. For each preferred term, subjects are included only once, even if they experienced multiple events in that preferred term.
Source: Listing 17.2.4.2, Dataset: ADAE, Program: t_aept.sas, Output: t_16-4-2-3-2-aept.rtf, Generated on: 28JUL2017 05:57
Page 2 of 2

Table 16.4.2.3.3 Treatment-Emergent Adverse Events Experienced by at Least 3 Subjects in Any Treatment Group During the Pilot and Supplemental Extensions by Preferred Term - Safety Overall Population

Preferred Term	GDNF/GDNF (N=13)		Placebo/GDNF (N=13)		Total (N=26)	
	n Subjects (%)	n Events	n Subjects (%)	n Events	n Subjects (%)	n Events
Fall	3 (23.1)	4	5 (38.5)	6	8 (30.8)	10
On and off phenomenon	5 (38.5)	6	2 (15.4)	2	7 (26.9)	8
Dyskinesia	3 (23.1)	3	3 (23.1)	3	6 (23.1)	6
Depressed mood	3 (23.1)	3	1 (7.7)	1	4 (15.4)	4
Application site infection	3 (23.1)	4	0	0	3 (11.5)	4
Headache	3 (23.1)	9	0	0	3 (11.5)	9
Parkinson's disease	3 (23.1)	3	0	0	3 (11.5)	3

Note: Adverse events are coded using MedDRA version 19.0. All AEs reported during the study period are considered TEAEs. TEAEs that are present or ongoing at the beginning of Study 2797 (date of consent or date of last visit in Study 2553, if consent was obtained earlier) are considered pre-existing, if the event term, severity, and date and time of onset in Study 2797 are identical to the corresponding information given for the TEAE in Study 2553. If any of these conditions is not met, the TEAE is considered new or worsening. Only new or worsening TEAEs are summarized. For each preferred term, subjects are included only once, even if they experienced multiple events in that preferred term. Percentages are based on the number of subjects that entered either the Pilot or Supplemental Extensions.
Source: Listing 17.2.4.2, Dataset: ADAE, Program: t_aept.sas, Output: t_16-4-2-3-3-aept.rtf, Generated on: 28JUL2017 05:57
Page 1 of 1

Table 16.4.2.4 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Maximum Severity - Safety Overall Population

System Organ Class Preferred Term	GDNF/GDNF (N=21)				Placebo/GDNF (N=20)			
	Mild n (%)	Moderate n (%)	Severe n (%)	Total n (%)	Mild n (%)	Moderate n (%)	Severe n (%)	Total n (%)
Subjects with at least one TEAE	5 (23.8)	6 (28.6)	10 (47.6)	21 (100)	3 (15.0)	5 (25.0)	12 (60.0)	20 (100)
Blood and lymphatic system disorders	5 (23.8)	0	0	5 (23.8)	2 (10.0)	0	0	2 (10.0)
Anaemia	4 (19.0)	0	0	4 (19.0)	0	0	0	0
Anaemia macrocytic	0	0	0	0	1 (5.0)	0	0	1 (5.0)
Anaemia megaloblastic	0	0	0	0	1 (5.0)	0	0	1 (5.0)
Iron deficiency anaemia	0	0	0	0	1 (5.0)	0	0	1 (5.0)
Lymphopenia	1 (4.8)	0	0	1 (4.8)	0	0	0	0
Cardiac disorders	1 (4.8)	2 (9.5)	0	3 (14.3)	0	0	0	0
Atrial flutter	1 (4.8)	0	0	1 (4.8)	0	0	0	0
Palpitations	0	1 (4.8)	0	1 (4.8)	0	0	0	0
Tachycardia	0	1 (4.8)	0	1 (4.8)	0	0	0	0
Congenital, familial and genetic disorders	0	0	0	0	1 (5.0)	0	0	1 (5.0)
Type IIa hyperlipidaemia	0	0	0	0	1 (5.0)	0	0	1 (5.0)

Note: Adverse events are coded using MedDRA version 19.0. All AEs reported during the study period are considered TEAEs. TEAEs that are present or ongoing at the beginning of Study 2797 (date of consent or date of last visit in Study 2553, if consent was obtained earlier) are considered pre-existing, if the event term, severity, and date and time of onset in Study 2797 are identical to the corresponding information given for the TEAE in Study 2553. If any of these conditions is not met, the TEAE is considered new or worsening. Only new or worsening TEAEs are summarized. For each system organ class and preferred term, subjects are included only once, in the maximum severity, for that TEAE. TEAEs without severity information are counted in the respective Total column for severity only.
Source: Listing 17.2.4.2, Dataset: ADAE, Program: t_aesev.sas, Output: t_16-4-2-4-aesev.rtf, Generated on: 28JUL2017 05:57
Page 1 of 38

Table 16.4.2.4 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Maximum Severity - Safety Overall Population

System Organ Class Preferred Term	Total (N=41)			
	Mild n (%)	Moderate n (%)	Severe n (%)	Total n (%)
Subjects with at least one TEAE	8 (19.5)	11 (26.8)	22 (53.7)	41 (100)
Blood and lymphatic system disorders	7 (17.1)	0	0	7 (17.1)
Anaemia	4 (9.8)	0	0	4 (9.8)
Anaemia macrocytic	1 (2.4)	0	0	1 (2.4)
Anaemia megaloblastic	1 (2.4)	0	0	1 (2.4)
Iron deficiency anaemia	1 (2.4)	0	0	1 (2.4)
Lymphopenia	1 (2.4)	0	0	1 (2.4)
Cardiac disorders	1 (2.4)	2 (4.9)	0	3 (7.3)
Atrial flutter	1 (2.4)	0	0	1 (2.4)
Palpitations	0	1 (2.4)	0	1 (2.4)
Tachycardia	0	1 (2.4)	0	1 (2.4)
Congenital, familial and genetic disorders	1 (2.4)	0	0	1 (2.4)
Type IIa hyperlipidaemia	1 (2.4)	0	0	1 (2.4)

Note: Adverse events are coded using MedDRA version 19.0. All AEs reported during the study period are considered TEAEs. TEAEs that are present or ongoing at the beginning of Study 2797 (date of consent or date of last visit in Study 2553, if consent was obtained earlier) are considered pre-existing, if the event term, severity, and date and time of onset in Study 2797 are identical to the corresponding information given for the TEAE in Study 2553. If any of these conditions is not met, the TEAE is considered new or worsening. Only new or worsening TEAEs are summarized. For each system organ class and preferred term, subjects are included only once, in the maximum severity, for that TEAE. TEAEs without severity information are counted in the respective Total column for severity only.
Source: Listing 17.2.4.2, Dataset: ADAE, Program: t_aesev.sas, Output: t_16-4-2-4-aesev.rtf, Generated on: 28JUL2017 05:57
Page 2 of 38

Table 16.4.2.4 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Maximum Severity - Safety Overall Population

System Organ Class Preferred Term	GDNF/GDNF (N=21)				Placebo/GDNF (N=20)			
	Mild n (%)	Moderate n (%)	Severe n (%)	Total n (%)	Mild n (%)	Moderate n (%)	Severe n (%)	Total n (%)
Ear and labyrinth disorders	1 (4.8)	0	0	1 (4.8)	1 (5.0)	0	0	1 (5.0)
Ear haemorrhage	0	0	0	0	1 (5.0)	0	0	1 (5.0)
Tinnitus	1 (4.8)	0	0	1 (4.8)	0	0	0	0
Endocrine disorders	1 (4.8)	0	0	1 (4.8)	1 (5.0)	0	0	1 (5.0)
Hypothyroidism	1 (4.8)	0	0	1 (4.8)	1 (5.0)	0	0	1 (5.0)
Eye disorders	3 (14.3)	2 (9.5)	1 (4.8)	6 (28.6)	4 (20.0)	0	0	4 (20.0)
Blepharospasm	0	0	0	0	2 (10.0)	0	0	2 (10.0)
Cataract	0	0	0	0	1 (5.0)	0	0	1 (5.0)
Diplopia	1 (4.8)	1 (4.8)	0	2 (9.5)	0	0	0	0
Dry eye	1 (4.8)	0	0	1 (4.8)	0	0	0	0
Excessive eye blinking	1 (4.8)	0	0	1 (4.8)	0	0	0	0
Eye pain	2 (9.5)	0	0	2 (9.5)	0	0	0	0
Eyelid dermatochalasis	0	0	1 (4.8)	1 (4.8)	0	0	0	0
Ocular hyperaemia	0	0	0	0	1 (5.0)	0	0	1 (5.0)
Photophobia	1 (4.8)	0	0	1 (4.8)	0	0	0	0
Vision blurred	1 (4.8)	1 (4.8)	0	2 (9.5)	1 (5.0)	0	0	1 (5.0)
Vitreous detachment	1 (4.8)	0	0	1 (4.8)	0	0	0	0
Vitreous floaters	2 (9.5)	0	0	2 (9.5)	0	0	0	0

Note: Adverse events are coded using MedDRA version 19.0. All AEs reported during the study period are considered TEAEs. TEAEs that are present or ongoing at the beginning of Study 2797 (date of consent or date of last visit in Study 2553, if consent was obtained earlier) are considered pre-existing, if the event term, severity, and date and time of onset in Study 2797 are identical to the corresponding information given for the TEAE in Study 2553. If any of these conditions is not met, the TEAE is considered new or worsening. Only new or worsening TEAEs are summarized. For each system organ class and preferred term, subjects are included only once, in the maximum severity, for that TEAE. TEAEs without severity information are counted in the respective Total column for severity only.
Source: Listing 17.2.4.2, Dataset: ADAE, Program: t_aesev.sas, Output: t_16-4-2-4-aesev.rtf, Generated on: 28JUL2017 05:57
Page 3 of 38

Table 16.4.2.4 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Maximum Severity - Safety Overall Population

System Organ Class Preferred Term	Total (N=41)			
	Mild n (%)	Moderate n (%)	Severe n (%)	Total n (%)
Ear and labyrinth disorders	2 (4.9)	0	0	2 (4.9)
Ear haemorrhage	1 (2.4)	0	0	1 (2.4)
Tinnitus	1 (2.4)	0	0	1 (2.4)
Endocrine disorders	2 (4.9)	0	0	2 (4.9)
Hypothyroidism	2 (4.9)	0	0	2 (4.9)
Eye disorders	7 (17.1)	2 (4.9)	1 (2.4)	10 (24.4)
Blepharospasm	2 (4.9)	0	0	2 (4.9)
Cataract	1 (2.4)	0	0	1 (2.4)
Diplopia	1 (2.4)	1 (2.4)	0	2 (4.9)
Dry eye	1 (2.4)	0	0	1 (2.4)
Excessive eye blinking	1 (2.4)	0	0	1 (2.4)
Eye pain	2 (4.9)	0	0	2 (4.9)
Eyelid dermatochalasis	0	0	1 (2.4)	1 (2.4)
Ocular hyperaemia	1 (2.4)	0	0	1 (2.4)
Photophobia	1 (2.4)	0	0	1 (2.4)
Vision blurred	2 (4.9)	1 (2.4)	0	3 (7.3)
Vitreous detachment	1 (2.4)	0	0	1 (2.4)
Vitreous floaters	2 (4.9)	0	0	2 (4.9)

Note: Adverse events are coded using MedDRA version 19.0. All AEs reported during the study period are considered TEAEs. TEAEs that are present or ongoing at the beginning of Study 2797 (date of consent or date of last visit in Study 2553, if consent was obtained earlier) are considered pre-existing, if the event term, severity, and date and time of onset in Study 2797 are identical to the corresponding information given for the TEAE in Study 2553. If any of these conditions is not met, the TEAE is considered new or worsening. Only new or worsening TEAEs are summarized. For each system organ class and preferred term, subjects are included only once, in the maximum severity, for that TEAE. TEAEs without severity information are counted in the respective Total column for severity only.
Source: Listing 17.2.4.2, Dataset: ADAE, Program: t_aesev.sas, Output: t_16-4-2-4-aesev.rtf, Generated on: 28JUL2017 05:57
Page 4 of 38

Table 16.4.2.4 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Maximum Severity - Safety Overall Population

System Organ Class Preferred Term	GDNF/GDNF (N=21)				Placebo/GDNF (N=20)			
	Mild n (%)	Moderate n (%)	Severe n (%)	Total n (%)	Mild n (%)	Moderate n (%)	Severe n (%)	Total n (%)
Gastrointestinal disorders	8 (38.1)	2 (9.5)	0	10 (47.6)	2 (10.0)	3 (15.0)	4 (20.0)	9 (45.0)
Abdominal discomfort	1 (4.8)	0	0	1 (4.8)	0	0	0	0
Abdominal pain lower	0	0	0	0	1 (5.0)	0	0	1 (5.0)
Abdominal pain upper	2 (9.5)	1 (4.8)	0	3 (14.3)	0	0	0	0
Constipation	2 (9.5)	0	0	2 (9.5)	0	1 (5.0)	2 (10.0)	3 (15.0)
Dental caries	0	0	0	0	2 (10.0)	0	0	2 (10.0)
Diarrhoea	2 (9.5)	1 (4.8)	0	3 (14.3)	0	0	2 (10.0)	2 (10.0)
Dry mouth	0	0	0	0	1 (5.0)	0	0	1 (5.0)
Dysphagia	0	1 (4.8)	0	1 (4.8)	2 (10.0)	1 (5.0)	0	3 (15.0)
Haemorrhoids	1 (4.8)	0	0	1 (4.8)	0	0	0	0
Intestinal obstruction	0	0	0	0	1 (5.0)	0	0	1 (5.0)
Irritable bowel syndrome	0	0	0	0	0	1 (5.0)	0	1 (5.0)
Nausea	5 (23.8)	0	0	5 (23.8)	1 (5.0)	0	1 (5.0)	2 (10.0)
Paraesthesia oral	0	0	0	0	1 (5.0)	0	0	1 (5.0)
Toothache	1 (4.8)	0	0	1 (4.8)	0	0	0	0
Vomiting	2 (9.5)	0	0	2 (9.5)	2 (10.0)	0	0	2 (10.0)

Note: Adverse events are coded using MedDRA version 19.0. All AEs reported during the study period are considered TEAEs. TEAEs that are present or ongoing at the beginning of Study 2797 (date of consent or date of last visit in Study 2553, if consent was obtained earlier) are considered pre-existing, if the event term, severity, and date and time of onset in Study 2797 are identical to the corresponding information given for the TEAE in Study 2553. If any of these conditions is not met, the TEAE is considered new or worsening. Only new or worsening TEAEs are summarized. For each system organ class and preferred term, subjects are included only once, in the maximum severity, for that TEAE. TEAEs without severity information are counted in the respective Total column for severity only.

Source: Listing 17.2.4.2, Dataset: ADAE, Program: t_aesev.sas, Output: t_16-4-2-4-aesev.rtf, Generated on: 28JUL2017 05:57

Table 16.4.2.4 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Maximum Severity - Safety Overall Population

System Organ Class Preferred Term	Total (N=41)			
	Mild n (%)	Moderate n (%)	Severe n (%)	Total n (%)
Gastrointestinal disorders	10 (24.4)	5 (12.2)	4 (9.8)	19 (46.3)
Abdominal discomfort	1 (2.4)	0	0	1 (2.4)
Abdominal pain lower	1 (2.4)	0	0	1 (2.4)
Abdominal pain upper	2 (4.9)	1 (2.4)	0	3 (7.3)
Constipation	2 (4.9)	1 (2.4)	2 (4.9)	5 (12.2)
Dental caries	2 (4.9)	0	0	2 (4.9)
Diarrhoea	2 (4.9)	1 (2.4)	2 (4.9)	5 (12.2)
Dry mouth	1 (2.4)	0	0	1 (2.4)
Dysphagia	2 (4.9)	2 (4.9)	0	4 (9.8)
Haemorrhoids	1 (2.4)	0	0	1 (2.4)
Intestinal obstruction	1 (2.4)	0	0	1 (2.4)
Irritable bowel syndrome	0	1 (2.4)	0	1 (2.4)
Nausea	6 (14.6)	0	1 (2.4)	7 (17.1)
Paraesthesia oral	1 (2.4)	0	0	1 (2.4)
Toothache	1 (2.4)	0	0	1 (2.4)
Vomiting	4 (9.8)	0	0	4 (9.8)

Note: Adverse events are coded using MedDRA version 19.0. All AEs reported during the study period are considered TEAEs. TEAEs that are present or ongoing at the beginning of Study 2797 (date of consent or date of last visit in Study 2553, if consent was obtained earlier) are considered pre-existing, if the event term, severity, and date and time of onset in Study 2797 are identical to the corresponding information given for the TEAE in Study 2553. If any of these conditions is not met, the TEAE is considered new or worsening. Only new or worsening TEAEs are summarized. For each system organ class and preferred term, subjects are included only once, in the maximum severity, for that TEAE. TEAEs without severity information are counted in the respective Total column for severity only.
Source: Listing 17.2.4.2, Dataset: ADAE, Program: t_aesev.sas, Output: t_16-4-2-4-aesev.rtf, Generated on: 28JUL2017 05:57
Page 6 of 38

Table 16.4.2.4 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Maximum Severity - Safety Overall Population

System Organ Class Preferred Term	GDNF/GDNF (N=21)				Placebo/GDNF (N=20)			
	Mild n (%)	Moderate n (%)	Severe n (%)	Total n (%)	Mild n (%)	Moderate n (%)	Severe n (%)	Total n (%)
General disorders and administration site conditions	7 (33.3)	6 (28.6)	1 (4.8)	14 (66.7)	6 (30.0)	5 (25.0)	2 (10.0)	13 (65.0)
Application site discharge	1 (4.8)	0	0	1 (4.8)	1 (5.0)	0	0	1 (5.0)
Application site erosion	0	1 (4.8)	0	1 (4.8)	0	0	0	0
Application site erythema	2 (9.5)	1 (4.8)	0	3 (14.3)	4 (20.0)	0	0	4 (20.0)
Application site haemorrhage	0	1 (4.8)	0	1 (4.8)	2 (10.0)	0	0	2 (10.0)
Application site hypertrophy	1 (4.8)	0	0	1 (4.8)	0	1 (5.0)	0	1 (5.0)
Application site hypoaesthesia	0	0	0	0	1 (5.0)	0	0	1 (5.0)
Application site inflammation	2 (9.5)	1 (4.8)	0	3 (14.3)	1 (5.0)	0	0	1 (5.0)
Application site laceration	0	0	0	0	1 (5.0)	0	0	1 (5.0)
Application site pain	1 (4.8)	1 (4.8)	0	2 (9.5)	1 (5.0)	0	0	1 (5.0)
Application site pruritus	0	0	0	0	1 (5.0)	0	0	1 (5.0)
Application site reaction	2 (9.5)	1 (4.8)	0	3 (14.3)	1 (5.0)	0	0	1 (5.0)
Application site swelling	2 (9.5)	1 (4.8)	0	3 (14.3)	2 (10.0)	0	0	2 (10.0)

Note: Adverse events are coded using MedDRA version 19.0. All AEs reported during the study period are considered TEAEs. TEAEs that are present or ongoing at the beginning of Study 2797 (date of consent or date of last visit in Study 2553, if consent was obtained earlier) are considered pre-existing, if the event term, severity, and date and time of onset in Study 2797 are identical to the corresponding information given for the TEAE in Study 2553. If any of these conditions is not met, the TEAE is considered new or worsening. Only new or worsening TEAEs are summarized. For each system organ class and preferred term, subjects are included only once, in the maximum severity, for that TEAE. TEAEs without severity information are counted in the respective Total column for severity only.

Source: Listing 17.2.4.2, Dataset: ADAE, Program: t_aesev.sas, Output: t_16-4-2-4-aesev.rtf, Generated on: 28JUL2017 05:57

Table 16.4.2.4 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Maximum Severity - Safety Overall Population

System Organ Class Preferred Term	Total (N=41)			
	Mild n (%)	Moderate n (%)	Severe n (%)	Total n (%)
General disorders and administration site conditions	13 (31.7)	11 (26.8)	3 (7.3)	27 (65.9)
Application site discharge	2 (4.9)	0	0	2 (4.9)
Application site erosion	0	1 (2.4)	0	1 (2.4)
Application site erythema	6 (14.6)	1 (2.4)	0	7 (17.1)
Application site haemorrhage	2 (4.9)	1 (2.4)	0	3 (7.3)
Application site hypertrophy	1 (2.4)	1 (2.4)	0	2 (4.9)
Application site hypoaesthesia	1 (2.4)	0	0	1 (2.4)
Application site inflammation	3 (7.3)	1 (2.4)	0	4 (9.8)
Application site laceration	1 (2.4)	0	0	1 (2.4)
Application site pain	2 (4.9)	1 (2.4)	0	3 (7.3)
Application site pruritus	1 (2.4)	0	0	1 (2.4)
Application site reaction	3 (7.3)	1 (2.4)	0	4 (9.8)
Application site swelling	4 (9.8)	1 (2.4)	0	5 (12.2)

Note: Adverse events are coded using MedDRA version 19.0. All AEs reported during the study period are considered TEAEs. TEAEs that are present or ongoing at the beginning of Study 2797 (date of consent or date of last visit in Study 2553, if consent was obtained earlier) are considered pre-existing, if the event term, severity, and date and time of onset in Study 2797 are identical to the corresponding information given for the TEAE in Study 2553. If any of these conditions is not met, the TEAE is considered new or worsening. Only new or worsening TEAEs are summarized. For each system organ class and preferred term, subjects are included only once, in the maximum severity, for that TEAE. TEAEs without severity information are counted in the respective Total column for severity only.
Source: Listing 17.2.4.2, Dataset: ADAE, Program: t_aesev.sas, Output: t_16-4-2-4-aesev.rtf, Generated on: 28JUL2017 05:57
Page 8 of 38

Table 16.4.2.4 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Maximum Severity - Safety Overall Population

System Organ Class Preferred Term	GDNF/GDNF (N=21)				Placebo/GDNF (N=20)			
	Mild n (%)	Moderate n (%)	Severe n (%)	Total n (%)	Mild n (%)	Moderate n (%)	Severe n (%)	Total n (%)
General disorders and administration site conditions								
Application site ulcer	1 (4.8)	0	0	1 (4.8)	1 (5.0)	0	0	1 (5.0)
Asthenia	1 (4.8)	0	0	1 (4.8)	0	0	0	0
Chest discomfort	1 (4.8)	0	0	1 (4.8)	0	0	0	0
Crying	0	0	0	0	0	1 (5.0)	0	1 (5.0)
Discomfort	1 (4.8)	0	0	1 (4.8)	0	0	0	0
Drug effect decreased	0	2 (9.5)	0	2 (9.5)	0	3 (15.0)	0	3 (15.0)
Drug ineffective	1 (4.8)	1 (4.8)	1 (4.8)	3 (14.3)	0	0	1 (5.0)	1 (5.0)
Drug intolerance	0	0	0	0	1 (5.0)	0	0	1 (5.0)
Facial pain	1 (4.8)	1 (4.8)	0	2 (9.5)	0	0	0	0
Fatigue	3 (14.3)	0	0	3 (14.3)	0	1 (5.0)	1 (5.0)	2 (10.0)
Feeling abnormal	1 (4.8)	0	0	1 (4.8)	1 (5.0)	1 (5.0)	0	2 (10.0)
Feeling cold	1 (4.8)	0	0	1 (4.8)	0	0	0	0
Feeling hot	1 (4.8)	0	0	1 (4.8)	0	0	0	0
Gait disturbance	1 (4.8)	1 (4.8)	0	2 (9.5)	1 (5.0)	0	0	1 (5.0)
Influenza like illness	0	0	0	0	1 (5.0)	0	0	1 (5.0)
Peripheral swelling	1 (4.8)	0	0	1 (4.8)	0	0	0	0
Pre-existing condition improved	1 (4.8)	1 (4.8)	0	2 (9.5)	0	0	0	0

Note: Adverse events are coded using MedDRA version 19.0. All AEs reported during the study period are considered TEAEs. TEAEs that are present or ongoing at the beginning of Study 2797 (date of consent or date of last visit in Study 2553, if consent was obtained earlier) are considered pre-existing, if the event term, severity, and date and time of onset in Study 2797 are identical to the corresponding information given for the TEAE in Study 2553. If any of these conditions is not met, the TEAE is considered new or worsening. Only new or worsening TEAEs are summarized. For each system organ class and preferred term, subjects are included only once, in the maximum severity, for that TEAE. TEAEs without severity information are counted in the respective Total column for severity only.
Source: Listing 17.2.4.2, Dataset: ADAE, Program: t_aesev.sas, Output: t_16-4-2-4-aesev.rtf, Generated on: 28JUL2017 05:57

Table 16.4.2.4 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Maximum Severity - Safety Overall Population

System Organ Class Preferred Term	Total (N=41)			
	Mild n (%)	Moderate n (%)	Severe n (%)	Total n (%)
General disorders and administration site conditions				
Application site ulcer	2 (4.9)	0	0	2 (4.9)
Asthenia	1 (2.4)	0	0	1 (2.4)
Chest discomfort	1 (2.4)	0	0	1 (2.4)
Crying	0	1 (2.4)	0	1 (2.4)
Discomfort	1 (2.4)	0	0	1 (2.4)
Drug effect decreased	0	5 (12.2)	0	5 (12.2)
Drug ineffective	1 (2.4)	1 (2.4)	2 (4.9)	4 (9.8)
Drug intolerance	1 (2.4)	0	0	1 (2.4)
Facial pain	1 (2.4)	1 (2.4)	0	2 (4.9)
Fatigue	3 (7.3)	1 (2.4)	1 (2.4)	5 (12.2)
Feeling abnormal	2 (4.9)	1 (2.4)	0	3 (7.3)
Feeling cold	1 (2.4)	0	0	1 (2.4)
Feeling hot	1 (2.4)	0	0	1 (2.4)
Gait disturbance	2 (4.9)	1 (2.4)	0	3 (7.3)
Influenza like illness	1 (2.4)	0	0	1 (2.4)
Peripheral swelling	1 (2.4)	0	0	1 (2.4)
Pre-existing condition improved	1 (2.4)	1 (2.4)	0	2 (4.9)

Note: Adverse events are coded using MedDRA version 19.0. All AEs reported during the study period are considered TEAEs. TEAEs that are present or ongoing at the beginning of Study 2797 (date of consent or date of last visit in Study 2553, if consent was obtained earlier) are considered pre-existing, if the event term, severity, and date and time of onset in Study 2797 are identical to the corresponding information given for the TEAE in Study 2553. If any of these conditions is not met, the TEAE is considered new or worsening. Only new or worsening TEAEs are summarized. For each system organ class and preferred term, subjects are included only once, in the maximum severity, for that TEAE. TEAEs without severity information are counted in the respective Total column for severity only.
Source: Listing 17.2.4.2, Dataset: ADAE, Program: t_aesev.sas, Output: t_16-4-2-4-aesev.rtf, Generated on: 28JUL2017 05:57
Page 10 of 38

Table 16.4.2.4 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Maximum Severity - Safety Overall Population

System Organ Class Preferred Term	GDNF/GDNF (N=21)				Placebo/GDNF (N=20)			
	Mild n (%)	Moderate n (%)	Severe n (%)	Total n (%)	Mild n (%)	Moderate n (%)	Severe n (%)	Total n (%)
General disorders and administration site conditions								
Pyrexia	1 (4.8)	0	0	1 (4.8)	1 (5.0)	0	0	1 (5.0)
Sluggishness	1 (4.8)	0	0	1 (4.8)	0	0	0	0
Immune system disorders	3 (14.3)	1 (4.8)	0	4 (19.0)	1 (5.0)	0	0	1 (5.0)
Allergy to arthropod sting	1 (4.8)	0	0	1 (4.8)	0	0	0	0
Food allergy	0	0	0	0	1 (5.0)	0	0	1 (5.0)
Hypersensitivity	1 (4.8)	0	0	1 (4.8)	0	0	0	0
Seasonal allergy	1 (4.8)	1 (4.8)	0	2 (9.5)	0	0	0	0
Infections and infestations	12 (57.1)	4 (19.0)	2 (9.5)	18 (85.7)	7 (35.0)	7 (35.0)	1 (5.0)	15 (75.0)
Abscess	0	0	0	0	1 (5.0)	0	0	1 (5.0)
Abscess oral	0	0	0	0	0	1 (5.0)	0	1 (5.0)
Appendicitis	0	0	0	0	0	1 (5.0)	0	1 (5.0)
Application site infection	2 (9.5)	4 (19.0)	0	6 (28.6)	3 (15.0)	1 (5.0)	0	4 (20.0)
Candida infection	1 (4.8)	0	0	1 (4.8)	0	0	0	0
Cellulitis	0	1 (4.8)	0	1 (4.8)	0	0	0	0
Conjunctivitis	1 (4.8)	0	0	1 (4.8)	2 (10.0)	0	0	2 (10.0)
Cystitis	1 (4.8)	0	0	1 (4.8)	0	0	0	0
Device related infection	0	0	1 (4.8)	1 (4.8)	0	0	0	0
Ear infection	1 (4.8)	0	0	1 (4.8)	0	0	0	0

Note: Adverse events are coded using MedDRA version 19.0. All AEs reported during the study period are considered TEAEs. TEAEs that are present or ongoing at the beginning of Study 2797 (date of consent or date of last visit in Study 2553, if consent was obtained earlier) are considered pre-existing, if the event term, severity, and date and time of onset in Study 2797 are identical to the corresponding information given for the TEAE in Study 2553. If any of these conditions is not met, the TEAE is considered new or worsening. Only new or worsening TEAEs are summarized. For each system organ class and preferred term, subjects are included only once, in the maximum severity, for that TEAE. TEAEs without severity information are counted in the respective Total column for severity only.
Source: Listing 17.2.4.2, Dataset: ADAE, Program: t_aesev.sas, Output: t_16-4-2-4-aesev.rtf, Generated on: 28JUL2017 05:57
Page 11 of 38

Table 16.4.2.4 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Maximum Severity - Safety Overall Population

System Organ Class Preferred Term	Total (N=41)			
	Mild n (%)	Moderate n (%)	Severe n (%)	Total n (%)
General disorders and administration site conditions				
Pyrexia	2 (4.9)	0	0	2 (4.9)
Sluggishness	1 (2.4)	0	0	1 (2.4)
Immune system disorders	4 (9.8)	1 (2.4)	0	5 (12.2)
Allergy to arthropod sting	1 (2.4)	0	0	1 (2.4)
Food allergy	1 (2.4)	0	0	1 (2.4)
Hypersensitivity	1 (2.4)	0	0	1 (2.4)
Seasonal allergy	1 (2.4)	1 (2.4)	0	2 (4.9)
Infections and infestations	19 (46.3)	11 (26.8)	3 (7.3)	33 (80.5)
Abscess	1 (2.4)	0	0	1 (2.4)
Abscess oral	0	1 (2.4)	0	1 (2.4)
Appendicitis	0	1 (2.4)	0	1 (2.4)
Application site infection	5 (12.2)	5 (12.2)	0	10 (24.4)
Candida infection	1 (2.4)	0	0	1 (2.4)
Cellulitis	0	1 (2.4)	0	1 (2.4)
Conjunctivitis	3 (7.3)	0	0	3 (7.3)
Cystitis	1 (2.4)	0	0	1 (2.4)
Device related infection	0	0	1 (2.4)	1 (2.4)
Ear infection	1 (2.4)	0	0	1 (2.4)

Note: Adverse events are coded using MedDRA version 19.0. All AEs reported during the study period are considered TEAEs. TEAEs that are present or ongoing at the beginning of Study 2797 (date of consent or date of last visit in Study 2553, if consent was obtained earlier) are considered pre-existing, if the event term, severity, and date and time of onset in Study 2797 are identical to the corresponding information given for the TEAE in Study 2553. If any of these conditions is not met, the TEAE is considered new or worsening. Only new or worsening TEAEs are summarized. For each system organ class and preferred term, subjects are included only once, in the maximum severity, for that TEAE. TEAEs without severity information are counted in the respective Total column for severity only.
Source: Listing 17.2.4.2, Dataset: ADAE, Program: t_aesev.sas, Output: t_16-4-2-4-aesev.rtf, Generated on: 28JUL2017 05:57
Page 12 of 38

Table 16.4.2.4 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Maximum Severity - Safety Overall Population

System Organ Class Preferred Term	GDNF/GDNF (N=21)				Placebo/GDNF (N=20)			
	Mild n (%)	Moderate n (%)	Severe n (%)	Total n (%)	Mild n (%)	Moderate n (%)	Severe n (%)	Total n (%)
Infections and infestations								
Fungal infection	1 (4.8)	0	0	1 (4.8)	0	0	0	0
Gastroenteritis	1 (4.8)	0	1 (4.8)	2 (9.5)	0	0	0	0
Gastroenteritis viral	1 (4.8)	0	0	1 (4.8)	0	0	0	0
Herpes zoster	1 (4.8)	0	0	1 (4.8)	0	0	0	0
Hordeolum	0	0	0	0	1 (5.0)	0	0	1 (5.0)
Impetigo	1 (4.8)	0	0	1 (4.8)	0	0	0	0
Laryngitis	1 (4.8)	0	0	1 (4.8)	0	0	0	0
Lower respiratory tract infection	2 (9.5)	0	0	2 (9.5)	0	1 (5.0)	0	1 (5.0)
Nasopharyngitis	9 (42.9)	0	0	9 (42.9)	5 (25.0)	3 (15.0)	0	8 (40.0)
Nosocomial infection	1 (4.8)	0	0	1 (4.8)	0	0	0	0
Post procedural infection	0	1 (4.8)	0	1 (4.8)	0	0	0	0
Postoperative wound infection	1 (4.8)	0	0	1 (4.8)	0	0	0	0
Pyelonephritis	0	0	0	0	0	0	1 (5.0)	1 (5.0)
Sinusitis	2 (9.5)	0	0	2 (9.5)	0	0	0	0
Skin infection	1 (4.8)	0	0	1 (4.8)	0	0	0	0
Tinea versicolour	1 (4.8)	0	0	1 (4.8)	0	0	0	0

Note: Adverse events are coded using MedDRA version 19.0. All AEs reported during the study period are considered TEAEs. TEAEs that are present or ongoing at the beginning of Study 2797 (date of consent or date of last visit in Study 2553, if consent was obtained earlier) are considered pre-existing, if the event term, severity, and date and time of onset in Study 2797 are identical to the corresponding information given for the TEAE in Study 2553. If any of these conditions is not met, the TEAE is considered new or worsening. Only new or worsening TEAEs are summarized. For each system organ class and preferred term, subjects are included only once, in the maximum severity, for that TEAE. TEAEs without severity information are counted in the respective Total column for severity only.
Source: Listing 17.2.4.2, Dataset: ADAE, Program: t_aesev.sas, Output: t_16-4-2-4-aesev.rtf, Generated on: 28JUL2017 05:57
Page 13 of 38

Table 16.4.2.4 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Maximum Severity - Safety Overall Population

System Organ Class Preferred Term	Total (N=41)			
	Mild n (%)	Moderate n (%)	Severe n (%)	Total n (%)
Infections and infestations				
Fungal infection	1 (2.4)	0	0	1 (2.4)
Gastroenteritis	1 (2.4)	0	1 (2.4)	2 (4.9)
Gastroenteritis viral	1 (2.4)	0	0	1 (2.4)
Herpes zoster	1 (2.4)	0	0	1 (2.4)
Hordeolum	1 (2.4)	0	0	1 (2.4)
Impetigo	1 (2.4)	0	0	1 (2.4)
Laryngitis	1 (2.4)	0	0	1 (2.4)
Lower respiratory tract infection	2 (4.9)	1 (2.4)	0	3 (7.3)
Nasopharyngitis	14 (34.1)	3 (7.3)	0	17 (41.5)
Nosocomial infection	1 (2.4)	0	0	1 (2.4)
Post procedural infection	0	1 (2.4)	0	1 (2.4)
Postoperative wound infection	1 (2.4)	0	0	1 (2.4)
Pyelonephritis	0	0	1 (2.4)	1 (2.4)
Sinusitis	2 (4.9)	0	0	2 (4.9)
Skin infection	1 (2.4)	0	0	1 (2.4)
Tinea versicolour	1 (2.4)	0	0	1 (2.4)

Note: Adverse events are coded using MedDRA version 19.0. All AEs reported during the study period are considered TEAEs. TEAEs that are present or ongoing at the beginning of Study 2797 (date of consent or date of last visit in Study 2553, if consent was obtained earlier) are considered pre-existing, if the event term, severity, and date and time of onset in Study 2797 are identical to the corresponding information given for the TEAE in Study 2553. If any of these conditions is not met, the TEAE is considered new or worsening. Only new or worsening TEAEs are summarized. For each system organ class and preferred term, subjects are included only once, in the maximum severity, for that TEAE. TEAEs without severity information are counted in the respective Total column for severity only.
Source: Listing 17.2.4.2, Dataset: ADAE, Program: t_aesev.sas, Output: t_16-4-2-4-aesev.rtf, Generated on: 28JUL2017 05:57
Page 14 of 38

Table 16.4.2.4 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Maximum Severity - Safety Overall Population

System Organ Class Preferred Term	GDNF/GDNF (N=21)				Placebo/GDNF (N=20)			
	Mild n (%)	Moderate n (%)	Severe n (%)	Total n (%)	Mild n (%)	Moderate n (%)	Severe n (%)	Total n (%)
Infections and infestations								
Upper respiratory tract infection	1 (4.8)	0	0	1 (4.8)	0	0	0	0
Urinary tract infection	4 (19.0)	0	0	4 (19.0)	4 (20.0)	0	0	4 (20.0)
Viral infection	1 (4.8)	0	0	1 (4.8)	0	0	0	0
Vulval abscess	1 (4.8)	0	0	1 (4.8)	0	0	0	0
Injury, poisoning and procedural complications	7 (33.3)	5 (23.8)	1 (4.8)	13 (61.9)	11 (55.0)	3 (15.0)	0	14 (70.0)
Arthropod bite	0	0	0	0	1 (5.0)	0	0	1 (5.0)
Chest injury	0	1 (4.8)	0	1 (4.8)	0	0	0	0
Contusion	4 (19.0)	1 (4.8)	0	5 (23.8)	3 (15.0)	1 (5.0)	0	4 (20.0)
Corneal abrasion	1 (4.8)	0	0	1 (4.8)	0	0	0	0
Epicondylitis	0	0	0	0	2 (10.0)	0	0	2 (10.0)
Eye contusion	1 (4.8)	0	0	1 (4.8)	0	0	0	0
Facial bones fracture	0	0	0	0	1 (5.0)	0	0	1 (5.0)
Fall	5 (23.8)	0	1 (4.8)	6 (28.6)	7 (35.0)	3 (15.0)	0	10 (50.0)
Foreign body	1 (4.8)	0	0	1 (4.8)	0	0	0	0
Hair injury	0	0	0	0	1 (5.0)	0	0	1 (5.0)
Head injury	1 (4.8)	1 (4.8)	0	2 (9.5)	2 (10.0)	0	0	2 (10.0)
Inflammation of wound	1 (4.8)	0	0	1 (4.8)	0	0	0	0

Note: Adverse events are coded using MedDRA version 19.0. All AEs reported during the study period are considered TEAEs. TEAEs that are present or ongoing at the beginning of Study 2797 (date of consent or date of last visit in Study 2553, if consent was obtained earlier) are considered pre-existing, if the event term, severity, and date and time of onset in Study 2797 are identical to the corresponding information given for the TEAE in Study 2553. If any of these conditions is not met, the TEAE is considered new or worsening. Only new or worsening TEAEs are summarized. For each system organ class and preferred term, subjects are included only once, in the maximum severity, for that TEAE. TEAEs without severity information are counted in the respective Total column for severity only.

Source: Listing 17.2.4.2, Dataset: ADAE, Program: t_aesev.sas, Output: t_16-4-2-4-aesev.rtf, Generated on: 28JUL2017 05:57
Page 15 of 38

Table 16.4.2.4 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Maximum Severity - Safety Overall Population

System Organ Class Preferred Term	Total (N=41)			
	Mild n (%)	Moderate n (%)	Severe n (%)	Total n (%)
Infections and infestations				
Upper respiratory tract infection	1 (2.4)	0	0	1 (2.4)
Urinary tract infection	8 (19.5)	0	0	8 (19.5)
Viral infection	1 (2.4)	0	0	1 (2.4)
Vulval abscess	1 (2.4)	0	0	1 (2.4)
Injury, poisoning and procedural complications	18 (43.9)	8 (19.5)	1 (2.4)	27 (65.9)
Arthropod bite	1 (2.4)	0	0	1 (2.4)
Chest injury	0	1 (2.4)	0	1 (2.4)
Contusion	7 (17.1)	2 (4.9)	0	9 (22.0)
Corneal abrasion	1 (2.4)	0	0	1 (2.4)
Epicondylitis	2 (4.9)	0	0	2 (4.9)
Eye contusion	1 (2.4)	0	0	1 (2.4)
Facial bones fracture	1 (2.4)	0	0	1 (2.4)
Fall	12 (29.3)	3 (7.3)	1 (2.4)	16 (39.0)
Foreign body	1 (2.4)	0	0	1 (2.4)
Hair injury	1 (2.4)	0	0	1 (2.4)
Head injury	3 (7.3)	1 (2.4)	0	4 (9.8)
Inflammation of wound	1 (2.4)	0	0	1 (2.4)

Note: Adverse events are coded using MedDRA version 19.0. All AEs reported during the study period are considered TEAEs. TEAEs that are present or ongoing at the beginning of Study 2797 (date of consent or date of last visit in Study 2553, if consent was obtained earlier) are considered pre-existing, if the event term, severity, and date and time of onset in Study 2797 are identical to the corresponding information given for the TEAE in Study 2553. If any of these conditions is not met, the TEAE is considered new or worsening. Only new or worsening TEAEs are summarized. For each system organ class and preferred term, subjects are included only once, in the maximum severity, for that TEAE. TEAEs without severity information are counted in the respective Total column for severity only.
Source: Listing 17.2.4.2, Dataset: ADAE, Program: t_aesev.sas, Output: t_16-4-2-4-aesev.rtf, Generated on: 28JUL2017 05:57
Page 16 of 38

Table 16.4.2.4 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Maximum Severity - Safety Overall Population

System Organ Class Preferred Term	GDNF/GDNF (N=21)				Placebo/GDNF (N=20)			
	Mild n (%)	Moderate n (%)	Severe n (%)	Total n (%)	Mild n (%)	Moderate n (%)	Severe n (%)	Total n (%)
Injury, poisoning and procedural complications								
Joint injury	1 (4.8)	3 (14.3)	0	4 (19.0)	1 (5.0)	1 (5.0)	0	2 (10.0)
Laceration	0	0	0	0	1 (5.0)	0	0	1 (5.0)
Muscle rupture	0	1 (4.8)	0	1 (4.8)	1 (5.0)	0	0	1 (5.0)
Post procedural complication	1 (4.8)	0	0	1 (4.8)	0	0	0	0
Post procedural contusion	0	1 (4.8)	0	1 (4.8)	0	0	0	0
Post procedural oedema	1 (4.8)	0	0	1 (4.8)	0	0	0	0
Postoperative fever	1 (4.8)	0	0	1 (4.8)	0	0	0	0
Procedural complication	0	0	1 (4.8)	1 (4.8)	0	0	0	0
Procedural headache	0	1 (4.8)	0	1 (4.8)	0	0	0	0
Psychosis postoperative	0	1 (4.8)	0	1 (4.8)	0	0	0	0
Rib fracture	0	0	0	0	1 (5.0)	0	0	1 (5.0)
Skeletal injury	0	1 (4.8)	0	1 (4.8)	0	0	0	0
Skin abrasion	1 (4.8)	0	0	1 (4.8)	2 (10.0)	0	0	2 (10.0)
Spinal column injury	0	0	0	0	1 (5.0)	0	0	1 (5.0)
Sternal fracture	1 (4.8)	0	0	1 (4.8)	0	0	0	0
Tooth fracture	0	0	0	0	1 (5.0)	0	0	1 (5.0)
Vaccination complication	0	0	0	0	1 (5.0)	0	0	1 (5.0)

Note: Adverse events are coded using MedDRA version 19.0. All AEs reported during the study period are considered TEAEs. TEAEs that are present or ongoing at the beginning of Study 2797 (date of consent or date of last visit in Study 2553, if consent was obtained earlier) are considered pre-existing, if the event term, severity, and date and time of onset in Study 2797 are identical to the corresponding information given for the TEAE in Study 2553. If any of these conditions is not met, the TEAE is considered new or worsening. Only new or worsening TEAEs are summarized. For each system organ class and preferred term, subjects are included only once, in the maximum severity, for that TEAE. TEAEs without severity information are counted in the respective Total column for severity only.
Source: Listing 17.2.4.2, Dataset: ADAE, Program: t_aesev.sas, Output: t_16-4-2-4-aesev.rtf, Generated on: 28JUL2017 05:57

Table 16.4.2.4 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Maximum Severity - Safety Overall Population

System Organ Class Preferred Term	Total (N=41)			
	Mild n (%)	Moderate n (%)	Severe n (%)	Total n (%)
Injury, poisoning and procedural complications				
Joint injury	2 (4.9)	4 (9.8)	0	6 (14.6)
Laceration	1 (2.4)	0	0	1 (2.4)
Muscle rupture	1 (2.4)	1 (2.4)	0	2 (4.9)
Post procedural complication	1 (2.4)	0	0	1 (2.4)
Post procedural contusion	0	1 (2.4)	0	1 (2.4)
Post procedural oedema	1 (2.4)	0	0	1 (2.4)
Postoperative fever	1 (2.4)	0	0	1 (2.4)
Procedural complication	0	0	1 (2.4)	1 (2.4)
Procedural headache	0	1 (2.4)	0	1 (2.4)
Psychosis postoperative	0	1 (2.4)	0	1 (2.4)
Rib fracture	1 (2.4)	0	0	1 (2.4)
Skeletal injury	0	1 (2.4)	0	1 (2.4)
Skin abrasion	3 (7.3)	0	0	3 (7.3)
Spinal column injury	1 (2.4)	0	0	1 (2.4)
Sternal fracture	1 (2.4)	0	0	1 (2.4)
Tooth fracture	1 (2.4)	0	0	1 (2.4)
Vaccination complication	1 (2.4)	0	0	1 (2.4)

Note: Adverse events are coded using MedDRA version 19.0. All AEs reported during the study period are considered TEAEs. TEAEs that are present or ongoing at the beginning of Study 2797 (date of consent or date of last visit in Study 2553, if consent was obtained earlier) are considered pre-existing, if the event term, severity, and date and time of onset in Study 2797 are identical to the corresponding information given for the TEAE in Study 2553. If any of these conditions is not met, the TEAE is considered new or worsening. Only new or worsening TEAEs are summarized. For each system organ class and preferred term, subjects are included only once, in the maximum severity, for that TEAE. TEAEs without severity information are counted in the respective Total column for severity only.
Source: Listing 17.2.4.2, Dataset: ADAE, Program: t_aesev.sas, Output: t_16-4-2-4-aesev.rtf, Generated on: 28JUL2017 05:57
Page 18 of 38

Table 16.4.2.4 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Maximum Severity - Safety Overall Population

System Organ Class Preferred Term	GDNF/GDNF (N=21)				Placebo/GDNF (N=20)			
	Mild n (%)	Moderate n (%)	Severe n (%)	Total n (%)	Mild n (%)	Moderate n (%)	Severe n (%)	Total n (%)
Injury, poisoning and procedural complications								
Wrist fracture	0	1 (4.8)	0	1 (4.8)	0	0	0	0
Investigations	3 (14.3)	0	0	3 (14.3)	3 (15.0)	1 (5.0)	0	4 (20.0)
Blood cholesterol increased	0	0	0	0	1 (5.0)	0	0	1 (5.0)
Blood pressure increased	0	0	0	0	0	1 (5.0)	0	1 (5.0)
Body temperature increased	0	0	0	0	1 (5.0)	0	0	1 (5.0)
C-reactive protein increased	0	0	0	0	1 (5.0)	0	0	1 (5.0)
Electrocardiogram abnormal	1 (4.8)	0	0	1 (4.8)	0	0	0	0
Haemoglobin decreased	1 (4.8)	0	0	1 (4.8)	0	0	0	0
Renal function test abnormal	0	0	0	0	1 (5.0)	0	0	1 (5.0)
Vitamin D decreased	0	0	0	0	1 (5.0)	0	0	1 (5.0)
Weight decreased	1 (4.8)	0	0	1 (4.8)	1 (5.0)	0	0	1 (5.0)
Metabolism and nutrition disorders	0	0	0	0	4 (20.0)	0	1 (5.0)	5 (25.0)
Dehydration	0	0	0	0	0	0	1 (5.0)	1 (5.0)
Hyperglycaemia	0	0	0	0	1 (5.0)	0	0	1 (5.0)

Note: Adverse events are coded using MedDRA version 19.0. All AEs reported during the study period are considered TEAEs. TEAEs that are present or ongoing at the beginning of Study 2797 (date of consent or date of last visit in Study 2553, if consent was obtained earlier) are considered pre-existing, if the event term, severity, and date and time of onset in Study 2797 are identical to the corresponding information given for the TEAE in Study 2553. If any of these conditions is not met, the TEAE is considered new or worsening. Only new or worsening TEAEs are summarized. For each system organ class and preferred term, subjects are included only once, in the maximum severity, for that TEAE. TEAEs without severity information are counted in the respective Total column for severity only.
Source: Listing 17.2.4.2, Dataset: ADAE, Program: t_aesev.sas, Output: t_16-4-2-4-aesev.rtf, Generated on: 28JUL2017 05:57
Page 19 of 38

Table 16.4.2.4 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Maximum Severity - Safety Overall Population

System Organ Class Preferred Term	Total (N=41)			
	Mild n (%)	Moderate n (%)	Severe n (%)	Total n (%)
Injury, poisoning and procedural complications				
Wrist fracture	0	1 (2.4)	0	1 (2.4)
Investigations	6 (14.6)	1 (2.4)	0	7 (17.1)
Blood cholesterol increased	1 (2.4)	0	0	1 (2.4)
Blood pressure increased	0	1 (2.4)	0	1 (2.4)
Body temperature increased	1 (2.4)	0	0	1 (2.4)
C-reactive protein increased	1 (2.4)	0	0	1 (2.4)
Electrocardiogram abnormal	1 (2.4)	0	0	1 (2.4)
Haemoglobin decreased	1 (2.4)	0	0	1 (2.4)
Renal function test abnormal	1 (2.4)	0	0	1 (2.4)
Vitamin D decreased	1 (2.4)	0	0	1 (2.4)
Weight decreased	2 (4.9)	0	0	2 (4.9)
Metabolism and nutrition disorders	4 (9.8)	0	1 (2.4)	5 (12.2)
Dehydration	0	0	1 (2.4)	1 (2.4)
Hyperglycaemia	1 (2.4)	0	0	1 (2.4)

Note: Adverse events are coded using MedDRA version 19.0. All AEs reported during the study period are considered TEAEs. TEAEs that are present or ongoing at the beginning of Study 2797 (date of consent or date of last visit in Study 2553, if consent was obtained earlier) are considered pre-existing, if the event term, severity, and date and time of onset in Study 2797 are identical to the corresponding information given for the TEAE in Study 2553. If any of these conditions is not met, the TEAE is considered new or worsening. Only new or worsening TEAEs are summarized. For each system organ class and preferred term, subjects are included only once, in the maximum severity, for that TEAE. TEAEs without severity information are counted in the respective Total column for severity only.
Source: Listing 17.2.4.2, Dataset: ADAE, Program: t_aesev.sas, Output: t_16-4-2-4-aesev.rtf, Generated on: 28JUL2017 05:57
Page 20 of 38

Table 16.4.2.4 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Maximum Severity - Safety Overall Population

System Organ Class Preferred Term	GDNF/GDNF (N=21)				Placebo/GDNF (N=20)			
	Mild n (%)	Moderate n (%)	Severe n (%)	Total n (%)	Mild n (%)	Moderate n (%)	Severe n (%)	Total n (%)
Metabolism and nutrition disorders								
Hypoalbuminaemia	0	0	0	0	2 (10.0)	0	0	2 (10.0)
Hypocalcaemia	0	0	0	0	1 (5.0)	0	0	1 (5.0)
Musculoskeletal and connective tissue disorders	8 (38.1)	2 (9.5)	5 (23.8)	15 (71.4)	3 (15.0)	5 (25.0)	5 (25.0)	13 (65.0)
Arthralgia	2 (9.5)	0	0	2 (9.5)	1 (5.0)	1 (5.0)	1 (5.0)	3 (15.0)
Arthritis	1 (4.8)	0	0	1 (4.8)	0	0	0	0
Back pain	2 (9.5)	1 (4.8)	2 (9.5)	5 (23.8)	3 (15.0)	0	2 (10.0)	5 (25.0)
Bursitis	1 (4.8)	0	0	1 (4.8)	0	0	0	0
Foot deformity	1 (4.8)	0	1 (4.8)	2 (9.5)	0	0	0	0
Joint swelling	1 (4.8)	0	0	1 (4.8)	0	0	0	0
Limb discomfort	2 (9.5)	0	1 (4.8)	3 (14.3)	0	0	0	0
Lumbar spinal stenosis	0	0	0	0	0	1 (5.0)	0	1 (5.0)
Mobility decreased	0	0	0	0	0	0	1 (5.0)	1 (5.0)
Muscle rigidity	0	0	0	0	1 (5.0)	1 (5.0)	0	2 (10.0)
Muscle spasms	1 (4.8)	1 (4.8)	2 (9.5)	4 (19.0)	3 (15.0)	3 (15.0)	1 (5.0)	7 (35.0)
Muscular weakness	0	1 (4.8)	1 (4.8)	2 (9.5)	0	0	0	0
Musculoskeletal chest pain	0	0	0	0	1 (5.0)	0	0	1 (5.0)
Musculoskeletal pain	3 (14.3)	0	0	3 (14.3)	0	1 (5.0)	0	1 (5.0)

Note: Adverse events are coded using MedDRA version 19.0. All AEs reported during the study period are considered TEAEs. TEAEs that are present or ongoing at the beginning of Study 2797 (date of consent or date of last visit in Study 2553, if consent was obtained earlier) are considered pre-existing, if the event term, severity, and date and time of onset in Study 2797 are identical to the corresponding information given for the TEAE in Study 2553. If any of these conditions is not met, the TEAE is considered new or worsening. Only new or worsening TEAEs are summarized. For each system organ class and preferred term, subjects are included only once, in the maximum severity, for that TEAE. TEAEs without severity information are counted in the respective Total column for severity only.
Source: Listing 17.2.4.2, Dataset: ADAE, Program: t_aesev.sas, Output: t_16-4-2-4-aesev.rtf, Generated on: 28JUL2017 05:57
Page 21 of 38

Table 16.4.2.4 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Maximum Severity - Safety Overall Population

System Organ Class Preferred Term	Total (N=41)			
	Mild n (%)	Moderate n (%)	Severe n (%)	Total n (%)
Metabolism and nutrition disorders				
Hypoalbuminaemia	2 (4.9)	0	0	2 (4.9)
Hypocalcaemia	1 (2.4)	0	0	1 (2.4)
Musculoskeletal and connective tissue disorders	11 (26.8)	7 (17.1)	10 (24.4)	28 (68.3)
Arthralgia	3 (7.3)	1 (2.4)	1 (2.4)	5 (12.2)
Arthritis	1 (2.4)	0	0	1 (2.4)
Back pain	5 (12.2)	1 (2.4)	4 (9.8)	10 (24.4)
Bursitis	1 (2.4)	0	0	1 (2.4)
Foot deformity	1 (2.4)	0	1 (2.4)	2 (4.9)
Joint swelling	1 (2.4)	0	0	1 (2.4)
Limb discomfort	2 (4.9)	0	1 (2.4)	3 (7.3)
Lumbar spinal stenosis	0	1 (2.4)	0	1 (2.4)
Mobility decreased	0	0	1 (2.4)	1 (2.4)
Muscle rigidity	1 (2.4)	1 (2.4)	0	2 (4.9)
Muscle spasms	4 (9.8)	4 (9.8)	3 (7.3)	11 (26.8)
Muscular weakness	0	1 (2.4)	1 (2.4)	2 (4.9)
Musculoskeletal chest pain	1 (2.4)	0	0	1 (2.4)
Musculoskeletal pain	3 (7.3)	1 (2.4)	0	4 (9.8)

Note: Adverse events are coded using MedDRA version 19.0. All AEs reported during the study period are considered TEAEs. TEAEs that are present or ongoing at the beginning of Study 2797 (date of consent or date of last visit in Study 2553, if consent was obtained earlier) are considered pre-existing, if the event term, severity, and date and time of onset in Study 2797 are identical to the corresponding information given for the TEAE in Study 2553. If any of these conditions is not met, the TEAE is considered new or worsening. Only new or worsening TEAEs are summarized. For each system organ class and preferred term, subjects are included only once, in the maximum severity, for that TEAE. TEAEs without severity information are counted in the respective Total column for severity only.
Source: Listing 17.2.4.2, Dataset: ADAE, Program: t_aesev.sas, Output: t_16-4-2-4-aesev.rtf, Generated on: 28JUL2017 05:57
Page 22 of 38

Table 16.4.2.4 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Maximum Severity - Safety Overall Population

System Organ Class Preferred Term	GDNF/GDNF (N=21)				Placebo/GDNF (N=20)			
	Mild n (%)	Moderate n (%)	Severe n (%)	Total n (%)	Mild n (%)	Moderate n (%)	Severe n (%)	Total n (%)
Musculoskeletal and connective tissue disorders								
Musculoskeletal stiffness	1 (4.8)	0	0	1 (4.8)	0	0	0	0
Neck pain	2 (9.5)	0	0	2 (9.5)	0	1 (5.0)	0	1 (5.0)
Osteoarthritis	1 (4.8)	1 (4.8)	0	2 (9.5)	0	1 (5.0)	0	1 (5.0)
Osteoporosis	0	0	0	0	1 (5.0)	0	0	1 (5.0)
Pain in extremity	2 (9.5)	3 (14.3)	1 (4.8)	6 (28.6)	2 (10.0)	0	0	2 (10.0)
Pain in jaw	0	0	0	0	1 (5.0)	0	0	1 (5.0)
Trigger finger	1 (4.8)	0	0	1 (4.8)	0	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (9.5)	0	0	2 (9.5)	1 (5.0)	0	0	1 (5.0)
Chondromatosis	1 (4.8)	0	0	1 (4.8)	0	0	0	0
Lipoma	0	0	0	0	1 (5.0)	0	0	1 (5.0)
Melanocytic naevus	1 (4.8)	0	0	1 (4.8)	0	0	0	0
Nervous system disorders	6 (28.6)	8 (38.1)	4 (19.0)	18 (85.7)	5 (25.0)	7 (35.0)	4 (20.0)	16 (80.0)
Aphasia	2 (9.5)	0	0	2 (9.5)	0	0	0	0
Balance disorder	1 (4.8)	0	1 (4.8)	2 (9.5)	0	1 (5.0)	0	1 (5.0)
Bradykinesia	1 (4.8)	0	1 (4.8)	2 (9.5)	0	0	0	0
Burning sensation	1 (4.8)	0	0	1 (4.8)	0	1 (5.0)	0	1 (5.0)
Cognitive disorder	0	0	0	0	1 (5.0)	0	0	1 (5.0)

Note: Adverse events are coded using MedDRA version 19.0. All AEs reported during the study period are considered TEAEs. TEAEs that are present or ongoing at the beginning of Study 2797 (date of consent or date of last visit in Study 2553, if consent was obtained earlier) are considered pre-existing, if the event term, severity, and date and time of onset in Study 2797 are identical to the corresponding information given for the TEAE in Study 2553. If any of these conditions is not met, the TEAE is considered new or worsening. Only new or worsening TEAEs are summarized. For each system organ class and preferred term, subjects are included only once, in the maximum severity, for that TEAE. TEAEs without severity information are counted in the respective Total column for severity only.
Source: Listing 17.2.4.2, Dataset: ADAE, Program: t_aesev.sas, Output: t_16-4-2-4-aesev.rtf, Generated on: 28JUL2017 05:57
Page 23 of 38

Table 16.4.2.4 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Maximum Severity - Safety Overall Population

System Organ Class Preferred Term	Total (N=41)			
	Mild n (%)	Moderate n (%)	Severe n (%)	Total n (%)
Musculoskeletal and connective tissue disorders				
Musculoskeletal stiffness	1 (2.4)	0	0	1 (2.4)
Neck pain	2 (4.9)	1 (2.4)	0	3 (7.3)
Osteoarthritis	1 (2.4)	2 (4.9)	0	3 (7.3)
Osteoporosis	1 (2.4)	0	0	1 (2.4)
Pain in extremity	4 (9.8)	3 (7.3)	1 (2.4)	8 (19.5)
Pain in jaw	1 (2.4)	0	0	1 (2.4)
Trigger finger	1 (2.4)	0	0	1 (2.4)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3 (7.3)	0	0	3 (7.3)
Chondromatosis	1 (2.4)	0	0	1 (2.4)
Lipoma	1 (2.4)	0	0	1 (2.4)
Melanocytic naevus	1 (2.4)	0	0	1 (2.4)
Nervous system disorders	11 (26.8)	15 (36.6)	8 (19.5)	34 (82.9)
Aphasia	2 (4.9)	0	0	2 (4.9)
Balance disorder	1 (2.4)	1 (2.4)	1 (2.4)	3 (7.3)
Bradykinesia	1 (2.4)	0	1 (2.4)	2 (4.9)
Burning sensation	1 (2.4)	1 (2.4)	0	2 (4.9)
Cognitive disorder	1 (2.4)	0	0	1 (2.4)

Note: Adverse events are coded using MedDRA version 19.0. All AEs reported during the study period are considered TEAEs. TEAEs that are present or ongoing at the beginning of Study 2797 (date of consent or date of last visit in Study 2553, if consent was obtained earlier) are considered pre-existing, if the event term, severity, and date and time of onset in Study 2797 are identical to the corresponding information given for the TEAE in Study 2553. If any of these conditions is not met, the TEAE is considered new or worsening. Only new or worsening TEAEs are summarized. For each system organ class and preferred term, subjects are included only once, in the maximum severity, for that TEAE. TEAEs without severity information are counted in the respective Total column for severity only.

Source: Listing 17.2.4.2, Dataset: ADAE, Program: t_aesev.sas, Output: t_16-4-2-4-aesev.rtf, Generated on: 28JUL2017 05:57

Table 16.4.2.4 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Maximum Severity - Safety Overall Population

System Organ Class Preferred Term	GDNF/GDNF (N=21)				Placebo/GDNF (N=20)			
	Mild n (%)	Moderate n (%)	Severe n (%)	Total n (%)	Mild n (%)	Moderate n (%)	Severe n (%)	Total n (%)
Nervous system disorders								
Coordination abnormal	0	0	0	0	0	0	1 (5.0)	1 (5.0)
Dizziness	3 (14.3)	0	0	3 (14.3)	3 (15.0)	0	0	3 (15.0)
Dizziness postural	0	0	0	0	1 (5.0)	0	0	1 (5.0)
Drooling	1 (4.8)	0	0	1 (4.8)	0	0	0	0
Dysaesthesia	0	0	0	0	1 (5.0)	0	0	1 (5.0)
Dysgeusia	1 (4.8)	0	0	1 (4.8)	1 (5.0)	0	0	1 (5.0)
Dyskinesia	5 (23.8)	4 (19.0)	1 (4.8)	10 (47.6)	5 (25.0)	3 (15.0)	1 (5.0)	9 (45.0)
Dysstasia	0	1 (4.8)	0	1 (4.8)	0	0	0	0
Dystonia	2 (9.5)	1 (4.8)	3 (14.3)	6 (28.6)	4 (20.0)	1 (5.0)	0	5 (25.0)
Freezing phenomenon	3 (14.3)	4 (19.0)	1 (4.8)	8 (38.1)	1 (5.0)	2 (10.0)	0	3 (15.0)
Head discomfort	3 (14.3)	0	0	3 (14.3)	1 (5.0)	0	0	1 (5.0)
Headache	3 (14.3)	3 (14.3)	0	6 (28.6)	2 (10.0)	2 (10.0)	1 (5.0)	5 (25.0)
Hypoaesthesia	1 (4.8)	0	0	1 (4.8)	2 (10.0)	0	0	2 (10.0)
Hypokinesia	0	0	0	0	1 (5.0)	0	0	1 (5.0)
Lethargy	1 (4.8)	0	0	1 (4.8)	0	0	0	0
Lhermitte's sign	7 (33.3)	2 (9.5)	0	9 (42.9)	4 (20.0)	0	0	4 (20.0)
Migraine	0	0	0	0	1 (5.0)	0	0	1 (5.0)
Motor dysfunction	0	1 (4.8)	0	1 (4.8)	0	0	0	0

Note: Adverse events are coded using MedDRA version 19.0. All AEs reported during the study period are considered TEAEs. TEAEs that are present or ongoing at the beginning of Study 2797 (date of consent or date of last visit in Study 2553, if consent was obtained earlier) are considered pre-existing, if the event term, severity, and date and time of onset in Study 2797 are identical to the corresponding information given for the TEAE in Study 2553. If any of these conditions is not met, the TEAE is considered new or worsening. Only new or worsening TEAEs are summarized. For each system organ class and preferred term, subjects are included only once, in the maximum severity, for that TEAE. TEAEs without severity information are counted in the respective Total column for severity only.

Source: Listing 17.2.4.2, Dataset: ADAE, Program: t_aesev.sas, Output: t_16-4-2-4-aesev.rtf, Generated on: 28JUL2017 05:57

Table 16.4.2.4 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Maximum Severity - Safety Overall Population

| System Organ Class
Preferred Term | Total
(N=41) | | | |
	Mild n (%)	Moderate n (%)	Severe n (%)	Total n (%)
Nervous system disorders				
Coordination abnormal	0	0	1 (2.4)	1 (2.4)
Dizziness	6 (14.6)	0	0	6 (14.6)
Dizziness postural	1 (2.4)	0	0	1 (2.4)
Drooling	1 (2.4)	0	0	1 (2.4)
Dysaesthesia	1 (2.4)	0	0	1 (2.4)
Dysgeusia	2 (4.9)	0	0	2 (4.9)
Dyskinesia	10 (24.4)	7 (17.1)	2 (4.9)	19 (46.3)
Dysstasia	0	1 (2.4)	0	1 (2.4)
Dystonia	6 (14.6)	2 (4.9)	3 (7.3)	11 (26.8)
Freezing phenomenon	4 (9.8)	6 (14.6)	1 (2.4)	11 (26.8)
Head discomfort	4 (9.8)	0	0	4 (9.8)
Headache	5 (12.2)	5 (12.2)	1 (2.4)	11 (26.8)
Hypoaesthesia	3 (7.3)	0	0	3 (7.3)
Hypokinesia	1 (2.4)	0	0	1 (2.4)
Lethargy	1 (2.4)	0	0	1 (2.4)
Lhermitte's sign	11 (26.8)	2 (4.9)	0	13 (31.7)
Migraine	1 (2.4)	0	0	1 (2.4)
Motor dysfunction	0	1 (2.4)	0	1 (2.4)

Note: Adverse events are coded using MedDRA version 19.0. All AEs reported during the study period are considered TEAEs. TEAEs that are present or ongoing at the beginning of Study 2797 (date of consent or date of last visit in Study 2553, if consent was obtained earlier) are considered pre-existing, if the event term, severity, and date and time of onset in Study 2797 are identical to the corresponding information given for the TEAE in Study 2553. If any of these conditions is not met, the TEAE is considered new or worsening. Only new or worsening TEAEs are summarized. For each system organ class and preferred term, subjects are included only once, in the maximum severity, for that TEAE. TEAEs without severity information are counted in the respective Total column for severity only.
Source: Listing 17.2.4.2, Dataset: ADAE, Program: t_aesev.sas, Output: t_16-4-2-4-aesev.rtf, Generated on: 28JUL2017 05:57

Table 16.4.2.4 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Maximum Severity - Safety Overall Population

System Organ Class Preferred Term	GDNF/GDNF (N=21)				Placebo/GDNF (N=20)			
	Mild n (%)	Moderate n (%)	Severe n (%)	Total n (%)	Mild n (%)	Moderate n (%)	Severe n (%)	Total n (%)
Nervous system disorders								
On and off phenomenon	3 (14.3)	2 (9.5)	2 (9.5)	7 (33.3)	1 (5.0)	6 (30.0)	0	7 (35.0)
Paraesthesia	6 (28.6)	0	0	6 (28.6)	7 (35.0)	0	0	7 (35.0)
Parkinson's disease	5 (23.8)	0	0	5 (23.8)	1 (5.0)	0	0	1 (5.0)
Parosmia	1 (4.8)	0	0	1 (4.8)	0	0	0	0
Poor quality sleep	1 (4.8)	1 (4.8)	0	2 (9.5)	0	0	0	0
Psychomotor hyperactivity	0	1 (4.8)	0	1 (4.8)	0	0	0	0
Restless legs syndrome	1 (4.8)	1 (4.8)	0	2 (9.5)	2 (10.0)	0	0	2 (10.0)
Sciatica	1 (4.8)	0	0	1 (4.8)	0	0	1 (5.0)	1 (5.0)
Sensory disturbance	2 (9.5)	0	0	2 (9.5)	1 (5.0)	0	0	1 (5.0)
Somnolence	0	0	0	0	1 (5.0)	0	0	1 (5.0)
Tension headache	1 (4.8)	0	0	1 (4.8)	0	0	0	0
Tremor	2 (9.5)	0	0	2 (9.5)	0	0	0	0
Product issues	0	2 (9.5)	0	2 (9.5)	0	0	0	0
Device occlusion	0	2 (9.5)	0	2 (9.5)	0	0	0	0
Psychiatric disorders	8 (38.1)	7 (33.3)	0	15 (71.4)	6 (30.0)	6 (30.0)	1 (5.0)	13 (65.0)
Abnormal dreams	3 (14.3)	0	0	3 (14.3)	1 (5.0)	0	0	1 (5.0)
Affective disorder	0	1 (4.8)	0	1 (4.8)	0	0	0	0
Agitation	0	0	0	0	1 (5.0)	0	0	1 (5.0)

Note: Adverse events are coded using MedDRA version 19.0. All AEs reported during the study period are considered TEAEs. TEAEs that are present or ongoing at the beginning of Study 2797 (date of consent or date of last visit in Study 2553, if consent was obtained earlier) are considered pre-existing, if the event term, severity, and date and time of onset in Study 2797 are identical to the corresponding information given for the TEAE in Study 2553. If any of these conditions is not met, the TEAE is considered new or worsening. Only new or worsening TEAEs are summarized. For each system organ class and preferred term, subjects are included only once, in the maximum severity, for that TEAE. TEAEs without severity information are counted in the respective Total column for severity only.
Source: Listing 17.2.4.2, Dataset: ADAE, Program: t_aesev.sas, Output: t_16-4-2-4-aesev.rtf, Generated on: 28JUL2017 05:57
Page 27 of 38

Table 16.4.2.4 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Maximum Severity - Safety Overall Population

System Organ Class Preferred Term	Total (N=41)			
	Mild n (%)	Moderate n (%)	Severe n (%)	Total n (%)
Nervous system disorders				
On and off phenomenon	4 (9.8)	8 (19.5)	2 (4.9)	14 (34.1)
Paraesthesia	13 (31.7)	0	0	13 (31.7)
Parkinson's disease	6 (14.6)	0	0	6 (14.6)
Parosmia	1 (2.4)	0	0	1 (2.4)
Poor quality sleep	1 (2.4)	1 (2.4)	0	2 (4.9)
Psychomotor hyperactivity	0	1 (2.4)	0	1 (2.4)
Restless legs syndrome	3 (7.3)	1 (2.4)	0	4 (9.8)
Sciatica	1 (2.4)	0	1 (2.4)	2 (4.9)
Sensory disturbance	3 (7.3)	0	0	3 (7.3)
Somnolence	1 (2.4)	0	0	1 (2.4)
Tension headache	1 (2.4)	0	0	1 (2.4)
Tremor	2 (4.9)	0	0	2 (4.9)
Product issues	0	2 (4.9)	0	2 (4.9)
Device occlusion	0	2 (4.9)	0	2 (4.9)
Psychiatric disorders	14 (34.1)	13 (31.7)	1 (2.4)	28 (68.3)
Abnormal dreams	4 (9.8)	0	0	4 (9.8)
Affective disorder	0	1 (2.4)	0	1 (2.4)
Agitation	1 (2.4)	0	0	1 (2.4)

Note: Adverse events are coded using MedDRA version 19.0. All AEs reported during the study period are considered TEAEs. TEAEs that are present or ongoing at the beginning of Study 2797 (date of consent or date of last visit in Study 2553, if consent was obtained earlier) are considered pre-existing, if the event term, severity, and date and time of onset in Study 2797 are identical to the corresponding information given for the TEAE in Study 2553. If any of these conditions is not met, the TEAE is considered new or worsening. Only new or worsening TEAEs are summarized. For each system organ class and preferred term, subjects are included only once, in the maximum severity, for that TEAE. TEAEs without severity information are counted in the respective Total column for severity only.
Source: Listing 17.2.4.2, Dataset: ADAE, Program: t_aesev.sas, Output: t_16-4-2-4-aesev.rtf, Generated on: 28JUL2017 05:57
Page 28 of 38

Table 16.4.2.4 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Maximum Severity - Safety Overall Population

System Organ Class Preferred Term	GDNF/GDNF (N=21)				Placebo/GDNF (N=20)			
	Mild n (%)	Moderate n (%)	Severe n (%)	Total n (%)	Mild n (%)	Moderate n (%)	Severe n (%)	Total n (%)
Psychiatric disorders								
Anorgasmia	1 (4.8)	0	0	1 (4.8)	0	0	0	0
Anxiety	1 (4.8)	1 (4.8)	0	2 (9.5)	2 (10.0)	0	0	2 (10.0)
Bruxism	1 (4.8)	0	0	1 (4.8)	0	0	0	0
Compulsive shopping	0	0	0	0	1 (5.0)	0	0	1 (5.0)
Confusional state	0	1 (4.8)	0	1 (4.8)	0	0	0	0
Depressed mood	4 (19.0)	0	0	4 (19.0)	2 (10.0)	1 (5.0)	0	3 (15.0)
Depression	0	1 (4.8)	0	1 (4.8)	0	0	0	0
Dopamine dysregulation syndrome	0	0	0	0	0	1 (5.0)	0	1 (5.0)
Dysphemia	1 (4.8)	0	0	1 (4.8)	0	0	0	0
Feeling of despair	0	1 (4.8)	0	1 (4.8)	0	0	0	0
Hallucination	1 (4.8)	0	0	1 (4.8)	1 (5.0)	0	0	1 (5.0)
Hallucination, olfactory	0	0	0	0	1 (5.0)	0	0	1 (5.0)
Hallucination, visual	0	0	0	0	1 (5.0)	0	0	1 (5.0)
Hypersexuality	0	0	0	0	1 (5.0)	0	0	1 (5.0)
Hypomania	0	0	0	0	0	0	1 (5.0)	1 (5.0)
Impulsive behaviour	0	1 (4.8)	0	1 (4.8)	0	0	0	0
Insomnia	1 (4.8)	1 (4.8)	0	2 (9.5)	2 (10.0)	1 (5.0)	0	3 (15.0)

Note: Adverse events are coded using MedDRA version 19.0. All AEs reported during the study period are considered TEAEs. TEAEs that are present or ongoing at the beginning of Study 2797 (date of consent or date of last visit in Study 2553, if consent was obtained earlier) are considered pre-existing, if the event term, severity, and date and time of onset in Study 2797 are identical to the corresponding information given for the TEAE in Study 2553. If any of these conditions is not met, the TEAE is considered new or worsening. Only new or worsening TEAEs are summarized. For each system organ class and preferred term, subjects are included only once, in the maximum severity, for that TEAE. TEAEs without severity information are counted in the respective Total column for severity only.
Source: Listing 17.2.4.2, Dataset: ADAE, Program: t_aesev.sas, Output: t_16-4-2-4-aesev.rtf, Generated on: 28JUL2017 05:57

Table 16.4.2.4 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Maximum Severity - Safety Overall Population

System Organ Class Preferred Term	Total (N=41)			
	Mild n (%)	Moderate n (%)	Severe n (%)	Total n (%)
Psychiatric disorders				
Anorgasmia	1 (2.4)	0	0	1 (2.4)
Anxiety	3 (7.3)	1 (2.4)	0	4 (9.8)
Bruxism	1 (2.4)	0	0	1 (2.4)
Compulsive shopping	1 (2.4)	0	0	1 (2.4)
Confusional state	0	1 (2.4)	0	1 (2.4)
Depressed mood	6 (14.6)	1 (2.4)	0	7 (17.1)
Depression	0	1 (2.4)	0	1 (2.4)
Dopamine dysregulation syndrome	0	1 (2.4)	0	1 (2.4)
Dysphemia	1 (2.4)	0	0	1 (2.4)
Feeling of despair	0	1 (2.4)	0	1 (2.4)
Hallucination	2 (4.9)	0	0	2 (4.9)
Hallucination, olfactory	1 (2.4)	0	0	1 (2.4)
Hallucination, visual	1 (2.4)	0	0	1 (2.4)
Hypersexuality	1 (2.4)	0	0	1 (2.4)
Hypomania	0	0	1 (2.4)	1 (2.4)
Impulsive behaviour	0	1 (2.4)	0	1 (2.4)
Insomnia	3 (7.3)	2 (4.9)	0	5 (12.2)

Note: Adverse events are coded using MedDRA version 19.0. All AEs reported during the study period are considered TEAEs. TEAEs that are present or ongoing at the beginning of Study 2797 (date of consent or date of last visit in Study 2553, if consent was obtained earlier) are considered pre-existing, if the event term, severity, and date and time of onset in Study 2797 are identical to the corresponding information given for the TEAE in Study 2553. If any of these conditions is not met, the TEAE is considered new or worsening. Only new or worsening TEAEs are summarized. For each system organ class and preferred term, subjects are included only once, in the maximum severity, for that TEAE. TEAEs without severity information are counted in the respective Total column for severity only.
Source: Listing 17.2.4.2, Dataset: ADAE, Program: t_aesev.sas, Output: t_16-4-2-4-aesev.rtf, Generated on: 28JUL2017 05:57
Page 30 of 38

Table 16.4.2.4 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Maximum Severity - Safety Overall Population

System Organ Class Preferred Term	GDNF/GDNF (N=21)				Placebo/GDNF (N=20)			
	Mild n (%)	Moderate n (%)	Severe n (%)	Total n (%)	Mild n (%)	Moderate n (%)	Severe n (%)	Total n (%)
Psychiatric disorders								
Irritability	0	0	0	0	0	1 (5.0)	0	1 (5.0)
Libido increased	2 (9.5)	0	0	2 (9.5)	0	0	0	0
Obsessive-compulsive disorder	2 (9.5)	0	0	2 (9.5)	0	1 (5.0)	0	1 (5.0)
Paranoia	0	1 (4.8)	0	1 (4.8)	0	0	0	0
Rapid eye movement sleep behaviour disorder	1 (4.8)	1 (4.8)	0	2 (9.5)	2 (10.0)	1 (5.0)	0	3 (15.0)
Rapid eye movements sleep abnormal	0	0	0	0	0	1 (5.0)	0	1 (5.0)
Restlessness	0	0	0	0	0	1 (5.0)	0	1 (5.0)
Sleep disorder	2 (9.5)	0	0	2 (9.5)	0	0	0	0
Stress	2 (9.5)	0	0	2 (9.5)	0	0	0	0
Tearfulness	0	0	0	0	1 (5.0)	0	0	1 (5.0)
Renal and urinary disorders	1 (4.8)	0	1 (4.8)	2 (9.5)	4 (20.0)	1 (5.0)	0	5 (25.0)
Bladder disorder	1 (4.8)	0	0	1 (4.8)	0	0	0	0
Dysuria	0	0	0	0	1 (5.0)	0	0	1 (5.0)
Haematuria	0	0	0	0	1 (5.0)	0	0	1 (5.0)
Micturition urgency	0	0	1 (4.8)	1 (4.8)	0	0	0	0

Note: Adverse events are coded using MedDRA version 19.0. All AEs reported during the study period are considered TEAEs. TEAEs that are present or ongoing at the beginning of Study 2797 (date of consent or date of last visit in Study 2553, if consent was obtained earlier) are considered pre-existing, if the event term, severity, and date and time of onset in Study 2797 are identical to the corresponding information given for the TEAE in Study 2553. If any of these conditions is not met, the TEAE is considered new or worsening. Only new or worsening TEAEs are summarized. For each system organ class and preferred term, subjects are included only once, in the maximum severity, for that TEAE. TEAEs without severity information are counted in the respective Total column for severity only.
Source: Listing 17.2.4.2, Dataset: ADAE, Program: t_aesev.sas, Output: t_16-4-2-4-aesev.rtf, Generated on: 28JUL2017 05:57

Table 16.4.2.4 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Maximum Severity - Safety Overall Population

System Organ Class Preferred Term	Total (N=41)			
	Mild n (%)	Moderate n (%)	Severe n (%)	Total n (%)
Psychiatric disorders				
Irritability	0	1 (2.4)	0	1 (2.4)
Libido increased	2 (4.9)	0	0	2 (4.9)
Obsessive-compulsive disorder	2 (4.9)	1 (2.4)	0	3 (7.3)
Paranoia	0	1 (2.4)	0	1 (2.4)
Rapid eye movement sleep behaviour disorder	3 (7.3)	2 (4.9)	0	5 (12.2)
Rapid eye movements sleep abnormal	0	1 (2.4)	0	1 (2.4)
Restlessness	0	1 (2.4)	0	1 (2.4)
Sleep disorder	2 (4.9)	0	0	2 (4.9)
Stress	2 (4.9)	0	0	2 (4.9)
Tearfulness	1 (2.4)	0	0	1 (2.4)
Renal and urinary disorders	5 (12.2)	1 (2.4)	1 (2.4)	7 (17.1)
Bladder disorder	1 (2.4)	0	0	1 (2.4)
Dysuria	1 (2.4)	0	0	1 (2.4)
Haematuria	1 (2.4)	0	0	1 (2.4)
Micturition urgency	0	0	1 (2.4)	1 (2.4)

Note: Adverse events are coded using MedDRA version 19.0. All AEs reported during the study period are considered TEAEs. TEAEs that are present or ongoing at the beginning of Study 2797 (date of consent or date of last visit in Study 2553, if consent was obtained earlier) are considered pre-existing, if the event term, severity, and date and time of onset in Study 2797 are identical to the corresponding information given for the TEAE in Study 2553. If any of these conditions is not met, the TEAE is considered new or worsening. Only new or worsening TEAEs are summarized. For each system organ class and preferred term, subjects are included only once, in the maximum severity, for that TEAE. TEAEs without severity information are counted in the respective Total column for severity only.
Source: Listing 17.2.4.2, Dataset: ADAE, Program: t_aesev.sas, Output: t_16-4-2-4-aesev.rtf, Generated on: 28JUL2017 05:57
Page 32 of 38

Table 16.4.2.4 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Maximum Severity - Safety Overall Population

System Organ Class Preferred Term	GDNF/GDNF (N=21)				Placebo/GDNF (N=20)			
	Mild n (%)	Moderate n (%)	Severe n (%)	Total n (%)	Mild n (%)	Moderate n (%)	Severe n (%)	Total n (%)
Renal and urinary disorders								
Pollakiuria	0	0	0	0	1 (5.0)	1 (5.0)	0	2 (10.0)
Renal impairment	0	0	0	0	1 (5.0)	0	0	1 (5.0)
Urinary retention	0	0	0	0	0	1 (5.0)	0	1 (5.0)
Reproductive system and breast disorders	2 (9.5)	2 (9.5)	0	4 (19.0)	1 (5.0)	1 (5.0)	0	2 (10.0)
Breast cyst	1 (4.8)	0	0	1 (4.8)	0	0	0	0
Dyspareunia	0	0	0	0	0	1 (5.0)	0	1 (5.0)
Ejaculation disorder	1 (4.8)	0	0	1 (4.8)	0	0	0	0
Endometrial thickening	1 (4.8)	0	0	1 (4.8)	0	0	0	0
Menorrhagia	0	2 (9.5)	0	2 (9.5)	0	0	0	0
Pelvic pain	0	0	0	0	1 (5.0)	0	0	1 (5.0)
Respiratory, thoracic and mediastinal disorders	5 (23.8)	2 (9.5)	1 (4.8)	8 (38.1)	3 (15.0)	0	1 (5.0)	4 (20.0)
Cough	2 (9.5)	2 (9.5)	0	4 (19.0)	1 (5.0)	0	0	1 (5.0)
Dysphonia	1 (4.8)	0	0	1 (4.8)	0	0	0	0
Dyspnoea	0	1 (4.8)	1 (4.8)	2 (9.5)	0	0	0	0
Epistaxis	1 (4.8)	0	0	1 (4.8)	0	0	0	0
Laryngospasm	0	0	0	0	0	0	1 (5.0)	1 (5.0)

Note: Adverse events are coded using MedDRA version 19.0. All AEs reported during the study period are considered TEAEs. TEAEs that are present or ongoing at the beginning of Study 2797 (date of consent or date of last visit in Study 2553, if consent was obtained earlier) are considered pre-existing, if the event term, severity, and date and time of onset in Study 2797 are identical to the corresponding information given for the TEAE in Study 2553. If any of these conditions is not met, the TEAE is considered new or worsening. Only new or worsening TEAEs are summarized. For each system organ class and preferred term, subjects are included only once, in the maximum severity, for that TEAE. TEAEs without severity information are counted in the respective Total column for severity only.
Source: Listing 17.2.4.2, Dataset: ADAE, Program: t_aesev.sas, Output: t_16-4-2-4-aesev.rtf, Generated on: 28JUL2017 05:57
Page 33 of 38

Table 16.4.2.4 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Maximum Severity - Safety Overall Population

System Organ Class Preferred Term	Total (N=41)			
	Mild n (%)	Moderate n (%)	Severe n (%)	Total n (%)
Renal and urinary disorders				
Pollakiuria	1 (2.4)	1 (2.4)	0	2 (4.9)
Renal impairment	1 (2.4)	0	0	1 (2.4)
Urinary retention	0	1 (2.4)	0	1 (2.4)
Reproductive system and breast disorders	3 (7.3)	3 (7.3)	0	6 (14.6)
Breast cyst	1 (2.4)	0	0	1 (2.4)
Dyspareunia	0	1 (2.4)	0	1 (2.4)
Ejaculation disorder	1 (2.4)	0	0	1 (2.4)
Endometrial thickening	1 (2.4)	0	0	1 (2.4)
Menorrhagia	0	2 (4.9)	0	2 (4.9)
Pelvic pain	1 (2.4)	0	0	1 (2.4)
Respiratory, thoracic and mediastinal disorders	8 (19.5)	2 (4.9)	2 (4.9)	12 (29.3)
Cough	3 (7.3)	2 (4.9)	0	5 (12.2)
Dysphonia	1 (2.4)	0	0	1 (2.4)
Dyspnoea	0	1 (2.4)	1 (2.4)	2 (4.9)
Epistaxis	1 (2.4)	0	0	1 (2.4)
Laryngospasm	0	0	1 (2.4)	1 (2.4)

Note: Adverse events are coded using MedDRA version 19.0. All AEs reported during the study period are considered TEAEs. TEAEs that are present or ongoing at the beginning of Study 2797 (date of consent or date of last visit in Study 2553, if consent was obtained earlier) are considered pre-existing, if the event term, severity, and date and time of onset in Study 2797 are identical to the corresponding information given for the TEAE in Study 2553. If any of these conditions is not met, the TEAE is considered new or worsening. Only new or worsening TEAEs are summarized. For each system organ class and preferred term, subjects are included only once, in the maximum severity, for that TEAE. TEAEs without severity information are counted in the respective Total column for severity only.
Source: Listing 17.2.4.2, Dataset: ADAE, Program: t_aesev.sas, Output: t_16-4-2-4-aesev.rtf, Generated on: 28JUL2017 05:57
Page 34 of 38

Table 16.4.2.4 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Maximum Severity - Safety Overall Population

System Organ Class Preferred Term	GDNF/GDNF (N=21)				Placebo/GDNF (N=20)			
	Mild n (%)	Moderate n (%)	Severe n (%)	Total n (%)	Mild n (%)	Moderate n (%)	Severe n (%)	Total n (%)
Respiratory, thoracic and mediastinal disorders								
Nasal obstruction	1 (4.8)	0	0	1 (4.8)	0	0	0	0
Oropharyngeal pain	0	0	0	0	1 (5.0)	0	0	1 (5.0)
Productive cough	1 (4.8)	0	0	1 (4.8)	0	0	0	0
Respiratory disorder	1 (4.8)	0	0	1 (4.8)	0	0	0	0
Rhinorrhoea	0	0	0	0	1 (5.0)	0	0	1 (5.0)
Sinus congestion	0	0	0	0	1 (5.0)	0	0	1 (5.0)
Skin and subcutaneous tissue disorders	5 (23.8)	1 (4.8)	0	6 (28.6)	3 (15.0)	2 (10.0)	1 (5.0)	6 (30.0)
Acne	0	0	0	0	1 (5.0)	0	0	1 (5.0)
Alopecia	1 (4.8)	0	0	1 (4.8)	0	0	0	0
Dermatitis	1 (4.8)	0	0	1 (4.8)	0	0	0	0
Dermatitis allergic	1 (4.8)	0	0	1 (4.8)	0	0	0	0
Drug eruption	1 (4.8)	0	0	1 (4.8)	0	0	0	0
Hirsutism	0	0	0	0	1 (5.0)	0	0	1 (5.0)
Hyperhidrosis	0	0	0	0	0	1 (5.0)	1 (5.0)	2 (10.0)
Itching scar	1 (4.8)	0	0	1 (4.8)	0	0	0	0
Lichenoid keratosis	0	0	0	0	0	1 (5.0)	0	1 (5.0)
Night sweats	1 (4.8)	0	0	1 (4.8)	0	0	0	0

Note: Adverse events are coded using MedDRA version 19.0. All AEs reported during the study period are considered TEAEs. TEAEs that are present or ongoing at the beginning of Study 2797 (date of consent or date of last visit in Study 2553, if consent was obtained earlier) are considered pre-existing, if the event term, severity, and date and time of onset in Study 2797 are identical to the corresponding information given for the TEAE in Study 2553. If any of these conditions is not met, the TEAE is considered new or worsening. Only new or worsening TEAEs are summarized. For each system organ class and preferred term, subjects are included only once, in the maximum severity, for that TEAE. TEAEs without severity information are counted in the respective Total column for severity only.
Source: Listing 17.2.4.2, Dataset: ADAE, Program: t_aesev.sas, Output: t_16-4-2-4-aesev.rtf, Generated on: 28JUL2017 05:57
Page 35 of 38

Table 16.4.2.4 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Maximum Severity - Safety Overall Population

System Organ Class Preferred Term	Total (N=41)			
	Mild n (%)	Moderate n (%)	Severe n (%)	Total n (%)
Respiratory, thoracic and mediastinal disorders				
Nasal obstruction	1 (2.4)	0	0	1 (2.4)
Oropharyngeal pain	1 (2.4)	0	0	1 (2.4)
Productive cough	1 (2.4)	0	0	1 (2.4)
Respiratory disorder	1 (2.4)	0	0	1 (2.4)
Rhinorrhoea	1 (2.4)	0	0	1 (2.4)
Sinus congestion	1 (2.4)	0	0	1 (2.4)
Skin and subcutaneous tissue disorders	8 (19.5)	3 (7.3)	1 (2.4)	12 (29.3)
Acne	1 (2.4)	0	0	1 (2.4)
Alopecia	1 (2.4)	0	0	1 (2.4)
Dermatitis	1 (2.4)	0	0	1 (2.4)
Dermatitis allergic	1 (2.4)	0	0	1 (2.4)
Drug eruption	1 (2.4)	0	0	1 (2.4)
Hirsutism	1 (2.4)	0	0	1 (2.4)
Hyperhidrosis	0	1 (2.4)	1 (2.4)	2 (4.9)
Itching scar	1 (2.4)	0	0	1 (2.4)
Lichenoid keratosis	0	1 (2.4)	0	1 (2.4)
Night sweats	1 (2.4)	0	0	1 (2.4)

Note: Adverse events are coded using MedDRA version 19.0. All AEs reported during the study period are considered TEAEs. TEAEs that are present or ongoing at the beginning of Study 2797 (date of consent or date of last visit in Study 2553, if consent was obtained earlier) are considered pre-existing, if the event term, severity, and date and time of onset in Study 2797 are identical to the corresponding information given for the TEAE in Study 2553. If any of these conditions is not met, the TEAE is considered new or worsening. Only new or worsening TEAEs are summarized. For each system organ class and preferred term, subjects are included only once, in the maximum severity, for that TEAE. TEAEs without severity information are counted in the respective Total column for severity only.
Source: Listing 17.2.4.2, Dataset: ADAE, Program: t_aesev.sas, Output: t_16-4-2-4-aesev.rtf, Generated on: 28JUL2017 05:57
Page 36 of 38

Table 16.4.2.4 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Maximum Severity - Safety Overall Population

System Organ Class Preferred Term	GDNF/GDNF (N=21)				Placebo/GDNF (N=20)			
	Mild n (%)	Moderate n (%)	Severe n (%)	Total n (%)	Mild n (%)	Moderate n (%)	Severe n (%)	Total n (%)
Skin and subcutaneous tissue disorders								
Rash	1 (4.8)	0	0	1 (4.8)	1 (5.0)	0	0	1 (5.0)
Rash generalised	0	0	0	0	1 (5.0)	0	0	1 (5.0)
Rash pruritic	1 (4.8)	0	0	1 (4.8)	0	0	0	0
Skin exfoliation	0	0	0	0	1 (5.0)	0	0	1 (5.0)
Skin hypopigmentation	1 (4.8)	0	0	1 (4.8)	0	0	0	0
Skin lesion	0	0	0	0	1 (5.0)	0	0	1 (5.0)
Skin reaction	1 (4.8)	0	0	1 (4.8)	0	0	0	0
Skin ulcer	2 (9.5)	0	0	2 (9.5)	0	0	0	0
Stasis dermatitis	0	0	0	0	1 (5.0)	0	0	1 (5.0)
Swelling face	0	1 (4.8)	0	1 (4.8)	0	0	0	0
Vascular disorders	6 (28.6)	0	0	6 (28.6)	1 (5.0)	0	0	1 (5.0)
Flushing	1 (4.8)	0	0	1 (4.8)	0	0	0	0
Hot flush	1 (4.8)	0	0	1 (4.8)	0	0	0	0
Hypertension	2 (9.5)	0	0	2 (9.5)	0	0	0	0
Orthostatic hypotension	2 (9.5)	0	0	2 (9.5)	1 (5.0)	0	0	1 (5.0)

Note: Adverse events are coded using MedDRA version 19.0. All AEs reported during the study period are considered TEAEs. TEAEs that are present or ongoing at the beginning of Study 2797 (date of consent or date of last visit in Study 2553, if consent was obtained earlier) are considered pre-existing, if the event term, severity, and date and time of onset in Study 2797 are identical to the corresponding information given for the TEAE in Study 2553. If any of these conditions is not met, the TEAE is considered new or worsening. Only new or worsening TEAEs are summarized. For each system organ class and preferred term, subjects are included only once, in the maximum severity, for that TEAE. TEAEs without severity information are counted in the respective Total column for severity only.
Source: Listing 17.2.4.2, Dataset: ADAE, Program: t_aesev.sas, Output: t_16-4-2-4-aesev.rtf, Generated on: 28JUL2017 05:57

Table 16.4.2.4 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Maximum Severity - Safety Overall Population

System Organ Class Preferred Term	Total (N=41)			
	Mild n (%)	Moderate n (%)	Severe n (%)	Total n (%)
Skin and subcutaneous tissue disorders				
Rash	2 (4.9)	0	0	2 (4.9)
Rash generalised	1 (2.4)	0	0	1 (2.4)
Rash pruritic	1 (2.4)	0	0	1 (2.4)
Skin exfoliation	1 (2.4)	0	0	1 (2.4)
Skin hypopigmentation	1 (2.4)	0	0	1 (2.4)
Skin lesion	1 (2.4)	0	0	1 (2.4)
Skin reaction	1 (2.4)	0	0	1 (2.4)
Skin ulcer	2 (4.9)	0	0	2 (4.9)
Stasis dermatitis	1 (2.4)	0	0	1 (2.4)
Swelling face	0	1 (2.4)	0	1 (2.4)
Vascular disorders	7 (17.1)	0	0	7 (17.1)
Flushing	1 (2.4)	0	0	1 (2.4)
Hot flush	1 (2.4)	0	0	1 (2.4)
Hypertension	2 (4.9)	0	0	2 (4.9)
Orthostatic hypotension	3 (7.3)	0	0	3 (7.3)

Note: Adverse events are coded using MedDRA version 19.0. All AEs reported during the study period are considered TEAEs. TEAEs that are present or ongoing at the beginning of Study 2797 (date of consent or date of last visit in Study 2553, if consent was obtained earlier) are considered pre-existing, if the event term, severity, and date and time of onset in Study 2797 are identical to the corresponding information given for the TEAE in Study 2553. If any of these conditions is not met, the TEAE is considered new or worsening. Only new or worsening TEAEs are summarized. For each system organ class and preferred term, subjects are included only once, in the maximum severity, for that TEAE. TEAEs without severity information are counted in the respective Total column for severity only.
Source: Listing 17.2.4.2, Dataset: ADAE, Program: t_aesev.sas, Output: t_16-4-2-4-aesev.rtf, Generated on: 28JUL2017 05:57
Page 38 of 38

Table 16.4.2.5.1 Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term - Safety Overall Population

System Organ Class Preferred Term	GDNF/GDNF (N=21) n (%)	Placebo/GDNF (N=20) n (%)	Total (N=41) n (%)
Subjects with at least one serious TEAE	7 (33.3)	3 (15.0)	10 (24.4)
General disorders and administration site conditions	2 (9.5)	0	2 (4.9)
Application site hypertrophy	1 (4.8)	0	1 (2.4)
Application site inflammation	1 (4.8)	0	1 (2.4)
Infections and infestations	3 (14.3)	1 (5.0)	4 (9.8)
Appendicitis	0	1 (5.0)	1 (2.4)
Application site infection	1 (4.8)	0	1 (2.4)
Device related infection	1 (4.8)	0	1 (2.4)
Post procedural infection	1 (4.8)	0	1 (2.4)
Injury, poisoning and procedural complications	2 (9.5)	0	2 (4.9)
Muscle rupture	1 (4.8)	0	1 (2.4)
Procedural complication	1 (4.8)	0	1 (2.4)
Psychosis postoperative	1 (4.8)	0	1 (2.4)
Metabolism and nutrition disorders	0	1 (5.0)	1 (2.4)
Dehydration	0	1 (5.0)	1 (2.4)

Note: Adverse events are coded using MedDRA version 19.0. All AEs reported during the study period are considered TEAEs. TEAEs that are present or ongoing at the beginning of Study 2797 (date of consent or date of last visit in Study 2553, if consent was obtained earlier) are considered pre-existing, if the event term, severity, and date and time of onset in Study 2797 are identical to the corresponding information given for the TEAE in Study 2553. If any of these conditions is not met, the TEAE is considered new or worsening. Only new or worsening TEAEs are summarized. For each system organ class and preferred term, subjects are included only once, even if they experienced multiple events in that system organ class or preferred term.
Source: Listing 17.2.4.2, Dataset: ADAE, Program: t_aesoc.sas, Output: t_16-4-2-5-1-aesoc.rtf, Generated on: 28JUL2017 05:57
Page 1 of 2

Table 16.4.2.5.1 Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term - Safety Overall Population

System Organ Class Preferred Term	GDNF/GDNF (N=21) n (%)	Placebo/GDNF (N=20) n (%)	Total (N=41) n (%)
Musculoskeletal and connective tissue disorders	0	1 (5.0)	1 (2.4)
Osteoarthritis	0	1 (5.0)	1 (2.4)
Product issues	2 (9.5)	0	2 (4.9)
Device occlusion	2 (9.5)	0	2 (4.9)
Psychiatric disorders	2 (9.5)	0	2 (4.9)
Confusional state	1 (4.8)	0	1 (2.4)
Depression	1 (4.8)	0	1 (2.4)
Paranoia	1 (4.8)	0	1 (2.4)
Reproductive system and breast disorders	1 (4.8)	0	1 (2.4)
Menorrhagia	1 (4.8)	0	1 (2.4)

Note: Adverse events are coded using MedDRA version 19.0. All AEs reported during the study period are considered TEAEs. TEAEs that are present or ongoing at the beginning of Study 2797 (date of consent or date of last visit in Study 2553, if consent was obtained earlier) are considered pre-existing, if the event term, severity, and date and time of onset in Study 2797 are identical to the corresponding information given for the TEAE in Study 2553. If any of these conditions is not met, the TEAE is considered new or worsening. Only new or worsening TEAEs are summarized. For each system organ class and preferred term, subjects are included only once, even if they experienced multiple events in that system organ class or preferred term.
Source: Listing 17.2.4.2, Dataset: ADAE, Program: t_aesoc.sas, Output: t_16-4-2-5-1-aesoc.rtf, Generated on: 28JUL2017 05:57
Page 2 of 2

Table 16.4.2.5.2 Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term During the Initial Extension - Safety Overall Population

System Organ Class Preferred Term	GDNF/GDNF (N=21) n (%)	Placebo/GDNF (N=20) n (%)	Total (N=41) n (%)
Subjects with at least one serious TEAE during the Initial Extension	7 (33.3)	1 (5.0)	8 (19.5)
General disorders and administration site conditions	1 (4.8)	0	1 (2.4)
Application site inflammation	1 (4.8)	0	1 (2.4)
Infections and infestations	1 (4.8)	0	1 (2.4)
Post procedural infection	1 (4.8)	0	1 (2.4)
Injury, poisoning and procedural complications	1 (4.8)	0	1 (2.4)
Muscle rupture	1 (4.8)	0	1 (2.4)
Musculoskeletal and connective tissue disorders	0	1 (5.0)	1 (2.4)
Osteoarthritis	0	1 (5.0)	1 (2.4)
Product issues	2 (9.5)	0	2 (4.9)
Device occlusion	2 (9.5)	0	2 (4.9)
Psychiatric disorders	2 (9.5)	0	2 (4.9)
Confusional state	1 (4.8)	0	1 (2.4)
Depression	1 (4.8)	0	1 (2.4)
Reproductive system and breast disorders	1 (4.8)	0	1 (2.4)
Menorrhagia	1 (4.8)	0	1 (2.4)

Note: Adverse events are coded using MedDRA version 19.0. All AEs reported during the study period are considered TEAEs. TEAEs that are present or ongoing at the beginning of Study 2797 (date of consent or date of last visit in Study 2553, if consent was obtained earlier) are considered pre-existing, if the event term, severity, and date and time of onset in Study 2797 are identical to the corresponding information given for the TEAE in Study 2553. If any of these conditions is not met, the TEAE is considered new or worsening. Only new or worsening TEAEs are summarized. For each system organ class and preferred term, subjects are included only once, even if they experienced multiple events in that system organ class or preferred term.
Source: Listing 17.2.4.2, Dataset: ADAE, Program: t_aesoc.sas, Output: t_16-4-2-5-2-aesoc.rtf, Generated on: 28JUL2017 05:57
Page 1 of 1

Table 16.4.2.5.3 Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term During the Pilot and Supplemental Extensions - Safety Overall Population

System Organ Class Preferred Term	GDNF/GDNF (N=13) n (%)	Placebo/GDNF (N=13) n (%)	Total (N=26) n (%)
Subjects with at least one serious TEAE during the Pilot and Supplemental Extensions	3 (23.1)	2 (15.4)	5 (19.2)
General disorders and administration site conditions	1 (7.7)	0	1 (3.8)
Application site hypertrophy	1 (7.7)	0	1 (3.8)
Infections and infestations	2 (15.4)	1 (7.7)	3 (11.5)
Appendicitis	0	1 (7.7)	1 (3.8)
Application site infection	1 (7.7)	0	1 (3.8)
Device related infection	1 (7.7)	0	1 (3.8)
Injury, poisoning and procedural complications	1 (7.7)	0	1 (3.8)
Procedural complication	1 (7.7)	0	1 (3.8)
Psychosis postoperative	1 (7.7)	0	1 (3.8)
Metabolism and nutrition disorders	0	1 (7.7)	1 (3.8)
Dehydration	0	1 (7.7)	1 (3.8)
Psychiatric disorders	1 (7.7)	0	1 (3.8)
Paranoia	1 (7.7)	0	1 (3.8)

Note: Adverse events are coded using MedDRA version 19.0. All AEs reported during the study period are considered TEAEs. TEAEs that are present or ongoing at the beginning of Study 2797 (date of consent or date of last visit in Study 2553, if consent was obtained earlier) are considered pre-existing, if the event term, severity, and date and time of onset in Study 2797 are identical to the corresponding information given for the TEAE in Study 2553. If any of these conditions is not met, the TEAE is considered new or worsening. Only new or worsening TEAEs are summarized. For each system organ class and preferred term, subjects are included only once, even if they experienced multiple events in that system organ class or preferred term. Percentages are based on the number of subjects that entered either the Pilot or Supplemental Extensions.
Source: Listing 17.2.4.2, Dataset: ADAE, Program: t_aesoc.sas, Output: t_16-4-2-5-3-aesoc.rtf, Generated on: 28JUL2017 05:57
Page 1 of 1

Table 16.4.2.6 Study Medication-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term - Safety Overall Population

System Organ Class Preferred Term	GDNF/GDNF (N=21) n (%)	Placebo/GDNF (N=20) n (%)	Total (N=41) n (%)
Subjects with at least one study medication-related TEAE	16 (76.2)	18 (90.0)	34 (82.9)
Eye disorders	1 (4.8)	0	1 (2.4)
Eye pain	1 (4.8)	0	1 (2.4)
Gastrointestinal disorders	2 (9.5)	1 (5.0)	3 (7.3)
Diarrhoea	1 (4.8)	0	1 (2.4)
Nausea	1 (4.8)	1 (5.0)	2 (4.9)
General disorders and administration site conditions	4 (19.0)	2 (10.0)	6 (14.6)
Discomfort	1 (4.8)	0	1 (2.4)
Fatigue	0	1 (5.0)	1 (2.4)
Feeling abnormal	0	1 (5.0)	1 (2.4)
Gait disturbance	1 (4.8)	0	1 (2.4)
Pyrexia	1 (4.8)	0	1 (2.4)
Sluggishness	1 (4.8)	0	1 (2.4)
Injury, poisoning and procedural complications	2 (9.5)	1 (5.0)	3 (7.3)
Fall	1 (4.8)	1 (5.0)	2 (4.9)
Procedural headache	1 (4.8)	0	1 (2.4)

Note: Adverse events are coded using MedDRA version 19.0. All AEs reported during the study period are considered TEAEs. TEAEs that are present or ongoing at the beginning of Study 2797 (date of consent or date of last visit in Study 2553, if consent was obtained earlier) are considered pre-existing, if the event term, severity, and date and time of onset in Study 2797 are identical to the corresponding information given for the TEAE in Study 2553. If any of these conditions is not met, the TEAE is considered new or worsening. Only new or worsening TEAEs are summarized. For each system organ class and preferred term, subjects are included only once, even if they experienced multiple events in that system organ class or preferred term.
Source: Listing 17.2.4.2, Dataset: ADAE, Program: t_aesoc.sas, Output: t_16-4-2-6-aesoc.rtf, Generated on: 28JUL2017 05:57
Page 1 of 4

Table 16.4.2.6 Study Medication-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term - Safety Overall Population

System Organ Class Preferred Term	GDNF/GDNF (N=21) n (%)	Placebo/GDNF (N=20) n (%)	Total (N=41) n (%)
Investigations	1 (4.8)	1 (5.0)	2 (4.9)
Weight decreased	1 (4.8)	1 (5.0)	2 (4.9)
Metabolism and nutrition disorders	0	2 (10.0)	2 (4.9)
Hypoalbuminaemia	0	2 (10.0)	2 (4.9)
Musculoskeletal and connective tissue disorders	3 (14.3)	2 (10.0)	5 (12.2)
Foot deformity	1 (4.8)	0	1 (2.4)
Limb discomfort	1 (4.8)	0	1 (2.4)
Muscle spasms	1 (4.8)	2 (10.0)	3 (7.3)
Nervous system disorders	15 (71.4)	15 (75.0)	30 (73.2)
Balance disorder	1 (4.8)	0	1 (2.4)
Dysaesthesia	0	1 (5.0)	1 (2.4)
Dysgeusia	0	1 (5.0)	1 (2.4)
Dyskinesia	7 (33.3)	9 (45.0)	16 (39.0)
Freezing phenomenon	2 (9.5)	2 (10.0)	4 (9.8)
Head discomfort	3 (14.3)	0	3 (7.3)
Headache	5 (23.8)	1 (5.0)	6 (14.6)

Note: Adverse events are coded using MedDRA version 19.0. All AEs reported during the study period are considered TEAEs. TEAEs that are present or ongoing at the beginning of Study 2797 (date of consent or date of last visit in Study 2553, if consent was obtained earlier) are considered pre-existing, if the event term, severity, and date and time of onset in Study 2797 are identical to the corresponding information given for the TEAE in Study 2553. If any of these conditions is not met, the TEAE is considered new or worsening. Only new or worsening TEAEs are summarized. For each system organ class and preferred term, subjects are included only once, even if they experienced multiple events in that system organ class or preferred term.
Source: Listing 17.2.4.2, Dataset: ADAE, Program: t_aesoc.sas, Output: t_16-4-2-6-aesoc.rtf, Generated on: 28JUL2017 05:57

Table 16.4.2.6 Study Medication-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term - Safety Overall Population

System Organ Class 　Preferred Term	GDNF/GDNF (N=21) n (%)	Placebo/GDNF (N=20) n (%)	Total (N=41) n (%)
Nervous system disorders			
Hypoaesthesia	0	1 (5.0)	1 (2.4)
Lhermitte's sign	9 (42.9)	4 (20.0)	13 (31.7)
On and off phenomenon	1 (4.8)	1 (5.0)	2 (4.9)
Paraesthesia	6 (28.6)	2 (10.0)	8 (19.5)
Parkinson's disease	4 (19.0)	1 (5.0)	5 (12.2)
Parosmia	1 (4.8)	0	1 (2.4)
Poor quality sleep	2 (9.5)	0	2 (4.9)
Psychomotor hyperactivity	1 (4.8)	0	1 (2.4)
Sensory disturbance	1 (4.8)	1 (5.0)	2 (4.9)
Psychiatric disorders	4 (19.0)	7 (35.0)	11 (26.8)
Abnormal dreams	1 (4.8)	0	1 (2.4)
Agitation	0	1 (5.0)	1 (2.4)
Compulsive shopping	0	1 (5.0)	1 (2.4)
Dopamine dysregulation syndrome	0	1 (5.0)	1 (2.4)
Hypomania	0	1 (5.0)	1 (2.4)
Impulsive behaviour	1 (4.8)	0	1 (2.4)

Note: Adverse events are coded using MedDRA version 19.0. All AEs reported during the study period are considered TEAEs. TEAEs that are present or ongoing at the beginning of Study 2797 (date of consent or date of last visit in Study 2553, if consent was obtained earlier) are considered pre-existing, if the event term, severity, and date and time of onset in Study 2797 are identical to the corresponding information given for the TEAE in Study 2553. If any of these conditions is not met, the TEAE is considered new or worsening. Only new or worsening TEAEs are summarized. For each system organ class and preferred term, subjects are included only once, even if they experienced multiple events in that system organ class or preferred term.
Source: Listing 17.2.4.2, Dataset: ADAE, Program: t_aesoc.sas, Output: t_16-4-2-6-aesoc.rtf, Generated on: 28JUL2017 05:57
Page 3 of 4

Table 16.4.2.6 Study Medication-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term - Safety Overall Population

System Organ Class Preferred Term	GDNF/GDNF (N=21) n (%)	Placebo/GDNF (N=20) n (%)	Total (N=41) n (%)
Psychiatric disorders			
Insomnia	0	2 (10.0)	2 (4.9)
Libido increased	1 (4.8)	0	1 (2.4)
Obsessive-compulsive disorder	1 (4.8)	1 (5.0)	2 (4.9)
Rapid eye movement sleep behaviour disorder	0	1 (5.0)	1 (2.4)
Restlessness	0	1 (5.0)	1 (2.4)
Renal and urinary disorders	0	1 (5.0)	1 (2.4)
Pollakiuria	0	1 (5.0)	1 (2.4)
Urinary retention	0	1 (5.0)	1 (2.4)

Note: Adverse events are coded using MedDRA version 19.0. All AEs reported during the study period are considered TEAEs. TEAEs that are present or ongoing at the beginning of Study 2797 (date of consent or date of last visit in Study 2553, if consent was obtained earlier) are considered pre-existing, if the event term, severity, and date and time of onset in Study 2797 are identical to the corresponding information given for the TEAE in Study 2553. If any of these conditions is not met, the TEAE is considered new or worsening. Only new or worsening TEAEs are summarized. For each system organ class and preferred term, subjects are included only once, even if they experienced multiple events in that system organ class or preferred term.

Source: Listing 17.2.4.2, Dataset: ADAE, Program: t_aesoc.sas, Output: t_16-4-2-6-aesoc.rtf, Generated on: 28JUL2017 05:57

Table 16.4.2.7 Serious Study Medication-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term - Safety Overall Population

System Organ Class Preferred Term	GDNF/GDNF (N=21) n (%)	Placebo/GDNF (N=20) n (%)	Total (N=41) n (%)
Subjects with at least one serious study medication-related TEAE	0	0	0

Note: Adverse events are coded using MedDRA version 19.0. All AEs reported during the study period are considered TEAEs. TEAEs that are present or ongoing at the beginning of Study 2797 (date of consent or date of last visit in Study 2553, if consent was obtained earlier) are considered pre-existing, if the event term, severity, and date and time of onset in Study 2797 are identical to the corresponding information given for the TEAE in Study 2553. If any of these conditions is not met, the TEAE is considered new or worsening. Only new or worsening TEAEs are summarized. For each system organ class and preferred term, subjects are included only once, even if they experienced multiple events in that system organ class or preferred term.
Source: Listing 17.2.4.2, Dataset: ADAE, Program: t_aesoc.sas, Output: t_16-4-2-7-aesoc.rtf, Generated on: 28JUL2017 05:58
Page 1 of 1

Table 16.4.2.8 Device-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term - Safety Overall Population

System Organ Class Preferred Term	GDNF/GDNF (N=21) n (%)	Placebo/GDNF (N=20) n (%)	Total (N=41) n (%)
Subjects with at least one device-related TEAE	9 (42.9)	10 (50.0)	19 (46.3)
Gastrointestinal disorders	2 (9.5)	0	2 (4.9)
Dysphagia	1 (4.8)	0	1 (2.4)
Nausea	1 (4.8)	0	1 (2.4)
General disorders and administration site conditions	8 (38.1)	10 (50.0)	18 (43.9)
Application site discharge	1 (4.8)	1 (5.0)	2 (4.9)
Application site erosion	1 (4.8)	0	1 (2.4)
Application site erythema	3 (14.3)	4 (20.0)	7 (17.1)
Application site haemorrhage	1 (4.8)	2 (10.0)	3 (7.3)
Application site hypertrophy	1 (4.8)	1 (5.0)	2 (4.9)
Application site hypoaesthesia	0	1 (5.0)	1 (2.4)
Application site inflammation	3 (14.3)	1 (5.0)	4 (9.8)
Application site laceration	0	1 (5.0)	1 (2.4)
Application site pain	2 (9.5)	1 (5.0)	3 (7.3)
Application site pruritus	0	1 (5.0)	1 (2.4)
Application site reaction	3 (14.3)	1 (5.0)	4 (9.8)

Note: Adverse events are coded using MedDRA version 19.0. All AEs reported during the study period are considered TEAEs. TEAEs that are present or ongoing at the beginning of Study 2797 (date of consent or date of last visit in Study 2553, if consent was obtained earlier) are considered pre-existing, if the event term, severity, and date and time of onset in Study 2797 are identical to the corresponding information given for the TEAE in Study 2553. If any of these conditions is not met, the TEAE is considered new or worsening. Only new or worsening TEAEs are summarized. For each system organ class and preferred term, subjects are included only once, even if they experienced multiple events in that system organ class or preferred term.
Source: Listing 17.2.4.2, Dataset: ADAE, Program: t_aesoc.sas, Output: t_16-4-2-8-aesoc.rtf, Generated on: 28JUL2017 05:58
Page 1 of 3

Table 16.4.2.8 Device-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term - Safety Overall Population

System Organ Class Preferred Term	GDNF/GDNF (N=21) n (%)	Placebo/GDNF (N=20) n (%)	Total (N=41) n (%)
General disorders and administration site conditions			
Application site swelling	3 (14.3)	2 (10.0)	5 (12.2)
Application site ulcer	1 (4.8)	1 (5.0)	2 (4.9)
Facial pain	1 (4.8)	0	1 (2.4)
Pyrexia	1 (4.8)	0	1 (2.4)
Infections and infestations	6 (28.6)	4 (20.0)	10 (24.4)
Application site infection	6 (28.6)	4 (20.0)	10 (24.4)
Device related infection	1 (4.8)	0	1 (2.4)
Nosocomial infection	1 (4.8)	0	1 (2.4)
Injury, poisoning and procedural complications	1 (4.8)	0	1 (2.4)
Eye contusion	1 (4.8)	0	1 (2.4)
Inflammation of wound	1 (4.8)	0	1 (2.4)
Procedural complication	1 (4.8)	0	1 (2.4)
Psychosis postoperative	1 (4.8)	0	1 (2.4)
Nervous system disorders	1 (4.8)	0	1 (2.4)
Motor dysfunction	1 (4.8)	0	1 (2.4)

Note: Adverse events are coded using MedDRA version 19.0. All AEs reported during the study period are considered TEAEs. TEAEs that are present or ongoing at the beginning of Study 2797 (date of consent or date of last visit in Study 2553, if consent was obtained earlier) are considered pre-existing, if the event term, severity, and date and time of onset in Study 2797 are identical to the corresponding information given for the TEAE in Study 2553. If any of these conditions is not met, the TEAE is considered new or worsening. Only new or worsening TEAEs are summarized. For each system organ class and preferred term, subjects are included only once, even if they experienced multiple events in that system organ class or preferred term.
Source: Listing 17.2.4.2, Dataset: ADAE, Program: t_aesoc.sas, Output: t_16-4-2-8-aesoc.rtf, Generated on: 28JUL2017 05:58
Page 2 of 3

Table 16.4.2.8 Device-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term - Safety Overall Population

System Organ Class Preferred Term	GDNF/GDNF (N=21) n (%)	Placebo/GDNF (N=20) n (%)	Total (N=41) n (%)
Product issues	2 (9.5)	0	2 (4.9)
Device occlusion	2 (9.5)	0	2 (4.9)
Psychiatric disorders	1 (4.8)	0	1 (2.4)
Affective disorder	1 (4.8)	0	1 (2.4)
Skin and subcutaneous tissue disorders	2 (9.5)	0	2 (4.9)
Dermatitis	1 (4.8)	0	1 (2.4)
Swelling face	1 (4.8)	0	1 (2.4)
Vascular disorders	1 (4.8)	0	1 (2.4)
Flushing	1 (4.8)	0	1 (2.4)

Note: Adverse events are coded using MedDRA version 19.0. All AEs reported during the study period are considered TEAEs. TEAEs that are present or ongoing at the beginning of Study 2797 (date of consent or date of last visit in Study 2553, if consent was obtained earlier) are considered pre-existing, if the event term, severity, and date and time of onset in Study 2797 are identical to the corresponding information given for the TEAE in Study 2553. If any of these conditions is not met, the TEAE is considered new or worsening. Only new or worsening TEAEs are summarized. For each system organ class and preferred term, subjects are included only once, even if they experienced multiple events in that system organ class or preferred term.
Source: Listing 17.2.4.2, Dataset: ADAE, Program: t_aesoc.sas, Output: t_16-4-2-8-aesoc.rtf, Generated on: 28JUL2017 05:58
Page 3 of 3

Table 16.4.2.9 Serious Device-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term - Safety Overall Population

System Organ Class Preferred Term	GDNF/GDNF (N=21) n (%)	Placebo/GDNF (N=20) n (%)	Total (N=41) n (%)
Subjects with at least one serious device-related TEAE	3 (14.3)	0	3 (7.3)
General disorders and administration site conditions	2 (9.5)	0	2 (4.9)
Application site hypertrophy	1 (4.8)	0	1 (2.4)
Application site inflammation	1 (4.8)	0	1 (2.4)
Infections and infestations	2 (9.5)	0	2 (4.9)
Application site infection	1 (4.8)	0	1 (2.4)
Device related infection	1 (4.8)	0	1 (2.4)
Injury, poisoning and procedural complications	1 (4.8)	0	1 (2.4)
Procedural complication	1 (4.8)	0	1 (2.4)
Psychosis postoperative	1 (4.8)	0	1 (2.4)
Product issues	2 (9.5)	0	2 (4.9)
Device occlusion	2 (9.5)	0	2 (4.9)

Note: Adverse events are coded using MedDRA version 19.0. All AEs reported during the study period are considered TEAEs. TEAEs that are present or ongoing at the beginning of Study 2797 (date of consent or date of last visit in Study 2553, if consent was obtained earlier) are considered pre-existing, if the event term, severity, and date and time of onset in Study 2797 are identical to the corresponding information given for the TEAE in Study 2553. If any of these conditions is not met, the TEAE is considered new or worsening. Only new or worsening TEAEs are summarized. For each system organ class and preferred term, subjects are included only once, even if they experienced multiple events in that system organ class or preferred term.
Source: Listing 17.2.4.2, Dataset: ADAE, Program: t_aesoc.sas, Output: t_16-4-2-9-aesoc.rtf, Generated on: 28JUL2017 05:58
Page 1 of 1

Table 16.4.2.10 Treatment-Emergent Adverse Events of Special Interest by Preferred Term - Safety Overall Population

AESI Category Preferred Term	GDNF/GDNF (N=21) n (%)	Placebo/GDNF (N=20) n (%)	Total (N=41) n (%)
Subjects with at least one treatment-emergent AESI	16 (76.2)	17 (85.0)	33 (80.5)
Dyskinesias	13 (61.9)	11 (55.0)	24 (58.5)
Blepharospasm	0	2 (10.0)	2 (4.9)
Dyskinesia	10 (47.6)	9 (45.0)	19 (46.3)
Dystonia	6 (28.6)	5 (25.0)	11 (26.8)
Excessive eye blinking	1 (4.8)	0	1 (2.4)
Falls	6 (28.6)	10 (50.0)	16 (39.0)
Fall	6 (28.6)	10 (50.0)	16 (39.0)
Adverse Changes in Mood	8 (38.1)	7 (35.0)	15 (36.6)
Affective disorder	1 (4.8)	0	1 (2.4)
Agitation	0	1 (5.0)	1 (2.4)
Anxiety	2 (9.5)	2 (10.0)	4 (9.8)
Crying	0	1 (5.0)	1 (2.4)
Depressed mood	4 (19.0)	3 (15.0)	7 (17.1)
Depression	1 (4.8)	0	1 (2.4)
Feeling of despair	1 (4.8)	0	1 (2.4)
Hypomania	0	1 (5.0)	1 (2.4)

Note: Adverse events are coded using MedDRA version 19.0. All AEs reported during the study period are considered TEAEs. TEAEs that are present or ongoing at the beginning of Study 2797 (date of consent or date of last visit in Study 2553, if consent was obtained earlier) are considered pre-existing, if the event term, severity, and date and time of onset in Study 2797 are identical to the corresponding information given for the TEAE in Study 2553. If any of these conditions is not met, the TEAE is considered new or worsening. Only new or worsening TEAEs are summarized. For each category and preferred term, subjects are included only once, even if they experienced multiple events in that category or preferred term.
Source: Listing 17.2.4.3.1, 17.2.4.3.2, 17.2.4.3.3, 17.2.4.3.4, Dataset: ADAE, Program: t_aesi.sas, Output: t_16-4-2-10-aesi.rtf, Generated on: 28JUL2017 05:58

Table 16.4.2.10 Treatment-Emergent Adverse Events of Special Interest by Preferred Term - Safety Overall Population

AESI Category Preferred Term	GDNF/GDNF (N=21) n (%)	Placebo/GDNF (N=20) n (%)	Total (N=41) n (%)
Irritability	0	1 (5.0)	1 (2.4)
Tearfulness	0	1 (5.0)	1 (2.4)
Impulsivity	4 (19.0)	2 (10.0)	6 (14.6)
Compulsive shopping	0	1 (5.0)	1 (2.4)
Dopamine dysregulation syndrome	0	1 (5.0)	1 (2.4)
Hypersexuality	0	1 (5.0)	1 (2.4)
Impulsive behaviour	1 (4.8)	0	1 (2.4)
Libido increased	2 (9.5)	0	2 (4.9)
Obsessive-compulsive disorder	2 (9.5)	1 (5.0)	3 (7.3)

Note: Adverse events are coded using MedDRA version 19.0. All AEs reported during the study period are considered TEAEs. TEAEs that are present or ongoing at the beginning of Study 2797 (date of consent or date of last visit in Study 2553, if consent was obtained earlier) are considered pre-existing, if the event term, severity, and date and time of onset in Study 2797 are identical to the corresponding information given for the TEAE in Study 2553. If any of these conditions is not met, the TEAE is considered new or worsening. Only new or worsening TEAEs are summarized. For each category and preferred term, subjects are included only once, even if they experienced multiple events in that category or preferred term.
Source: Listing 17.2.4.3.1, 17.2.4.3.2, 17.2.4.3.3, 17.2.4.3.4, Dataset: ADAE, Program: t_aesi.sas, Output: t_16-4-2-10-aesi.rtf, Generated on: 28JUL2017 05:58
Page 2 of 2

Table 16.4.3.1 Clinically Significant Postbaseline Hematology Results - Safety Overall Population

Parameter	GDNF/GDNF (N=21) n (%)	Placebo/GDNF (N=20) n (%)
Erythrocytes (10/L) - Low	0	1 (5.0)
Hematocrit (fraction of 1) - Low	1 (4.8)	1 (5.0)
Hemoglobin (g/L) - Low	2 (9.5)	1 (5.0)
Neutrophils (10/L) - High	0	1 (5.0)

Note: Results were rated by the investigator as clinically significant on the CRF based on medical judgment, not using any pre-specified numerical criteria. For each parameter, subjects are included only once, even if they experienced more than one clinically significant result.
Source: Listing 17.2.4.5, Dataset: ADLB, Program: t_labcs.sas, Output: t_16-4-3-1-hemcs.rtf, Generated on: 28JUL2017 05:58
Page 1 of 1

Table 16.4.3.2 Clinically Significant Postbaseline Serum Chemistry Results - Safety Overall Population

Parameter	GDNF/GDNF (N=21) n (%)	Placebo/GDNF (N=20) n (%)
Creatinine (umol/L) - Normal	0	1 (5.0)
Urea (mmol/L) - High	0	1 (5.0)
Glomerular Filtration Rate (mL/min) - Low	0	1 (5.0)
Albumin (g/L) - Low	0	1 (5.0)
Glucose (mmol/L) - High	1 (4.8)	0

Note: Results were rated by the investigator as clinically significant on the CRF based on medical judgment, not using any pre-specified numerical criteria. For each parameter, subjects are included only once, even if they experienced more than one clinically significant result.
Source: Listing 17.2.4.6, Dataset: ADLB, Program: t_labcs.sas, Output: t_16-4-3-2-chemcs.rtf, Generated on: 28JUL2017 05:58
Page 1 of 1

Table 16.4.4.1 Anti-GDNF Binding Serum Antibodies by Visit – Safety Overall Population

Visit Variable	GDNF/GDNF (N=21) n (%)	Placebo/GDNF (N=20) n (%)
All visits[a]		
All Negative	21 (100)	20 (100)
1 Positive	0	0
> 1 Positive	0	0
1 Missing or Not Done	1 (4.8)	2 (10.0)
2 Missing or Not Done	0	0
> 2 Missing or Not Done	0	0
Screening (Baseline)		
Positive	0	0
Negative	21 (100)	20 (100)
Not done	0	0
Missing	0	0
Week 40/e0		
Positive	0	0
Negative	21 (100)	20 (100)
Not done	0	0
Missing	0	0
Week 44/e4		
Positive	0	0
Negative	20 (95.2)	20 (100)
Not done	0	0
Missing	0	0

[a] "All visits" includes all postbaseline visits from Study 2553 and Study 2797. "All Negative" includes all subjects without a positive result even if some results are missing or not done.
Source: Listing 17.2.4.8, Dataset: ADAB, Program: t_antigdnf.sas, Output: t_16-4-4-1-bind.rtf, Generated on: 28JUL2017 05:58
Page 1 of 3

Table 16.4.4.1 Anti-GDNF Binding Serum Antibodies by Visit – Safety Overall Population

Visit Variable	GDNF/GDNF (N=21) n (%)	Placebo/GDNF (N=20) n (%)
Week 56/e16		
Positive	0	0
Negative	21 (100)	20 (100)
Not done	0	0
Missing	0	0
Week 68/e28		
Positive	0	0
Negative	20 (95.2)	19 (95.0)
Not done	0	0
Missing	0	1 (5.0)
Week 80/e40		
Positive	0	0
Negative	20 (95.2)	19 (95.0)
Not done	0	0
Missing	1 (4.8)	1 (5.0)
Week e2-24		
Positive	0	0
Negative	3 (14.3)	2 (10.0)
Not done	0	0
Missing	0	0

[a] "All visits" includes all postbaseline visits from Study 2553 and Study 2797. "All Negative" includes all subjects without a positive result even if some results are missing or not done.
Source: Listing 17.2.4.8, Dataset: ADAB, Program: t_antigdnf.sas, Output: t_16-4-4-1-bind.rtf, Generated on: 28JUL2017 05:58
Page 2 of 3

Table 16.4.4.1 Anti-GDNF Binding Serum Antibodies by Visit – Safety Overall Population

Visit Variable	GDNF/GDNF (N=21) n (%)	Placebo/GDNF (N=20) n (%)
Week e2-48		
Positive	0	0
Negative	1 (4.8)	2 (10.0)
Not done	0	0
Missing	0	0
Week e2-72		
Positive	0	0
Negative	1 (4.8)	2 (10.0)
Not done	0	0
Missing	0	0
Last Study Visit in the Supplemental Extension		
Positive	0	0
Negative	10 (47.6)	11 (55.0)
Not done	0	0
Missing	0	0

[a] "All visits" includes all postbaseline visits from Study 2553 and Study 2797. "All Negative" includes all subjects without a positive result even if some results are missing or not done.
Source: Listing 17.2.4.8, Dataset: ADAB, Program: t_antigdnf.sas, Output: t_16-4-4-1-bind.rtf, Generated on: 28JUL2017 05:58
Page 3 of 3

Table 16.4.4.2 Anti-GDNF Neutralizing Serum Antibodies by Visit - Safety Overall Population

Visit Variable	GDNF/GDNF (N=21) n (%)	Placebo/GDNF (N=20) n (%)
All visits[a]		
All Negative	0	0
1 Positive	0	0
> 1 Positive	0	0
1 Missing or Not Done	0	0
2 Missing or Not Done	0	0
> 2 Missing or Not Done	21 (100)	20 (100)
Screening (Baseline)		
Positive	0	0
Negative	0	0
Not done	21 (100)	20 (100)
Missing	0	0
Week 40/e0		
Positive	0	0
Negative	0	0
Not done	21 (100)	20 (100)
Missing	0	0
Week 44/e4		
Positive	0	0
Negative	0	0
Not done	20 (95.2)	20 (100)
Missing	0	0

[a] "All visits" includes all postbaseline visits from Study 2553 and Study 2797. "All Negative" includes all subjects without a positive result even if some results are missing or not done.
Source: Listing 17.2.4.8, Dataset: ADAB, Program: t_antigdnf.sas, Output: t_16-4-4-2-neut.rtf, Generated on: 28JUL2017 05:58
Page 1 of 3

Table 16.4.4.2 Anti-GDNF Neutralizing Serum Antibodies by Visit - Safety Overall Population

Visit Variable	GDNF/GDNF (N=21) n (%)	Placebo/GDNF (N=20) n (%)
Week 56/e16		
Positive	0	0
Negative	0	0
Not done	21 (100)	20 (100)
Missing	0	0
Week 68/e28		
Positive	0	0
Negative	0	0
Not done	20 (95.2)	19 (95.0)
Missing	0	1 (5.0)
Week 80/e40		
Positive	0	0
Negative	0	0
Not done	20 (95.2)	19 (95.0)
Missing	1 (4.8)	1 (5.0)
Week e2-24		
Positive	0	0
Negative	0	0
Not done	3 (14.3)	2 (10.0)
Missing	0	0

[a] "All visits" includes all postbaseline visits from Study 2553 and Study 2797. "All Negative" includes all subjects without a positive result even if some results are missing or not done.
Source: Listing 17.2.4.8, Dataset: ADAB, Program: t_antigdnf.sas, Output: t_16-4-4-2-neut.rtf, Generated on: 28JUL2017 05:58
Page 2 of 3

Table 16.4.4.2 Anti-GDNF Neutralizing Serum Antibodies by Visit - Safety Overall Population

Visit Variable	GDNF/GDNF (N=21) n (%)	Placebo/GDNF (N=20) n (%)
Week e2-48		
Positive	0	0
Negative	0	0
Not done	1 (4.8)	2 (10.0)
Missing	0	0
Week e2-72		
Positive	0	0
Negative	0	0
Not done	1 (4.8)	2 (10.0)
Missing	0	0
Last Study Visit in the Supplemental Extension		
Positive	0	0
Negative	0	0
Not done	10 (47.6)	11 (55.0)
Missing	0	0

[a] "All visits" includes all postbaseline visits from Study 2553 and Study 2797. "All Negative" includes all subjects without a positive result even if some results are missing or not done.
Source: Listing 17.2.4.8, Dataset: ADAB, Program: t_antigdnf.sas, Output: t_16-4-4-2-neut.rtf, Generated on: 28JUL2017 05:58
Page 3 of 3

Table 16.4.5 Plasma GDNF Concentrations by Visit - Safety Overall Population

Plasma GDNF Concentration (ng/mL) Visit Statistic	GDNF/GDNF (N=21)		Placebo/GDNF (N=20)	
	Value	Change From Baseline	Value	Change From Baseline
Screening (Baseline)				
n	0		1	
Mean (SD)			0.290	
Median			0.290	
Min, Max			0.290, 0.290	
Not Done	0		0	
Missing	0		0	
Week 40/e0				
n	0	0	1	1
Mean (SD)			0.447	0.157
Median			0.447	0.157
Min, Max			0.447, 0.447	0.157, 0.157
Not Done	0		0	
Missing	0		0	
Week 44/e4				
n	1	0	0	0
Mean (SD)	1.458			
Median	1.458			
Min, Max	1.458, 1.458			
Not Done	0		1	
Missing	0		0	

Note: Results of <LOD and <LLOQ are not included in the summary statistics.
Source: Listing 17.2.4.9, Dataset: ADAB, Program: t_plasmagdnf.sas, Output: t_16-4-5-plasmagdnf.rtf, Generated on: 28JUL2017 05:58
Page 1 of 4

Table 16.4.5 Plasma GDNF Concentrations by Visit - Safety Overall Population

Plasma GDNF Concentration (ng/mL) Visit Statistic	GDNF/GDNF (N=21)		Placebo/GDNF (N=20)	
	Value	Change From Baseline	Value	Change From Baseline
Week 56/e16				
n	1	0	1	1
Mean (SD)	1.328		7.857	7.567
Median	1.328		7.857	7.567
Min, Max	1.328, 1.328		7.857, 7.857	7.567, 7.567
Not Done	1		0	
Missing	0		0	
Week 68/e28				
n	1	0	1	1
Mean (SD)	1.800		7.331	7.041
Median	1.800		7.331	7.041
Min, Max	1.800, 1.800		7.331, 7.331	7.041, 7.041
Not Done	0		0	
Missing	0		1	
Week 80/e40				
n	0	0	1	1
Mean (SD)			7.183	6.893
Median			7.183	6.893
Min, Max			7.183, 7.183	6.893, 6.893
Not Done	1		0	
Missing	0		1	

Note: Results of <LOD and <LLOQ are not included in the summary statistics.
Source: Listing 17.2.4.9, Dataset: ADAB, Program: t_plasmagdnf.sas, Output: t_16-4-5-plasmagdnf.rtf, Generated on: 28JUL2017 05:58
Page 2 of 4

Table 16.4.5 Plasma GDNF Concentrations by Visit - Safety Overall Population

Plasma GDNF Concentration (ng/mL) Visit Statistic	GDNF/GDNF (N=21)		Placebo/GDNF (N=20)	
	Value	Change From Baseline	Value	Change From Baseline
Week e2-24				
n	1	0	0	0
Mean (SD)	1.269			
Median	1.269			
Min, Max	1.269, 1.269			
Not Done	0		0	
Missing	0		0	
Week e2-48				
n	1	0	0	0
Mean (SD)	1.600			
Median	1.600			
Min, Max	1.600, 1.600			
Not Done	0		0	
Missing	0		0	
Week e2-72				
n	0	0	0	0
Mean (SD)				
Median				
Min, Max				
Not Done	1		0	
Missing	0		0	

Note: Results of <LOD and <LLOQ are not included in the summary statistics.
Source: Listing 17.2.4.9, Dataset: ADAB, Program: t_plasmagdnf.sas, Output: t_16-4-5-plasmagdnf.rtf, Generated on: 28JUL2017 05:58
Page 3 of 4

Table 16.4.5 Plasma GDNF Concentrations by Visit - Safety Overall Population

Plasma GDNF Concentration (ng/mL) Visit Statistic	GDNF/GDNF (N=21)		Placebo/GDNF (N=20)	
	Value	Change From Baseline	Value	Change From Baseline
Last Study Visit in the Supplemental Extension				
n	1	0	1	0
Mean (SD)	1.341		0.276	
Median	1.341		0.276	
Min, Max	1.341, 1.341		0.276, 0.276	
Not Done	0		0	
Missing	0		0	

Note: Results of <LOD and <LLOQ are not included in the summary statistics.
Source: Listing 17.2.4.9, Dataset: ADAB, Program: t_plasmagdnf.sas, Output: t_16-4-5-plasmagdnf.rtf, Generated on: 28JUL2017 05:58
Page 4 of 4

Table 16.4.6 Clinically Relevant Postbaseline Abnormalities in Vital Sign Results in the Initial Extension - Safety Overall Population

Parameter and Criterion
  Visit
    Time Point
	GDNF/GDNF
	(N=21)
	n (%)
		Placebo/GDNF
		(N=20)
		n (%)

Sitting Pulse < 50 bpm at any visit in Initial Extension	2 (9.5)	5 (25.0)
Week e0	0	2 (10.0)
105 mins after start of infusion	0	1 (5.0)
120 mins after start of infusion	0	1 (5.0)
Post-dose	0	1 (5.0)
Week 44/e4	1 (4.8)	0
120 mins after start of infusion	1 (4.8)	0
Week 48/e8	1 (4.8)	2 (10.0)
60 mins after start of infusion	0	2 (10.0)
90 mins after start of infusion	0	1 (5.0)
120 mins after start of infusion	0	1 (5.0)
Post-dose	1 (4.8)	0
Week 52/e12	1 (4.8)	3 (15.0)
30 mins after start of infusion	0	1 (5.0)
60 mins after start of infusion	0	3 (15.0)
90 mins after start of infusion	1 (4.8)	3 (15.0)
120 mins after start of infusion	1 (4.8)	1 (5.0)

Note: bpm = beats per minute. For each parameter and criterion, visit, and time point, subjects are included only once, even if they experienced more
    than one clinically relevant abnormality. For the comparisons of values during or after infusion with pre-infusion values, the baseline is the
    pre-infusion value.
Source: Listing 17.2.4.11, Dataset: ADVS, Program: t_vsabnorm.sas, Output: t_16-4-6-vsabnorm.rtf, Generated on: 28JUL2017 05:58
Page 1 of 27

Table 16.4.6 Clinically Relevant Postbaseline Abnormalities in Vital Sign Results in the Initial Extension - Safety Overall Population

Parameter and Criterion Visit Time Point	GDNF/GDNF (N=21) n (%)	Placebo/GDNF (N=20) n (%)
Sitting Pulse < 50 bpm at any visit in Initial Extension		
Week 52/e12		
Post-dose	1 (4.8)	1 (5.0)
Week 56/e16	1 (4.8)	2 (10.0)
30 mins after start of infusion	1 (4.8)	1 (5.0)
60 mins after start of infusion	1 (4.8)	1 (5.0)
90 mins after start of infusion	1 (4.8)	2 (10.0)
120 mins after start of infusion	0	1 (5.0)
Post-dose	1 (4.8)	1 (5.0)
Week 60/e20	1 (4.8)	1 (5.0)
30 mins after start of infusion	0	1 (5.0)
90 mins after start of infusion	0	1 (5.0)
120 mins after start of infusion	0	1 (5.0)
Post-dose	1 (4.8)	1 (5.0)
Week 64/e24	1 (4.8)	3 (15.0)
60 mins after start of infusion	1 (4.8)	2 (10.0)
90 mins after start of infusion	1 (4.8)	0
120 mins after start of infusion	0	1 (5.0)
Post-dose	0	3 (15.0)

Note: bpm = beats per minute. For each parameter and criterion, visit, and time point, subjects are included only once, even if they experienced more
than one clinically relevant abnormality. For the comparisons of values during or after infusion with pre-infusion values, the baseline is the
pre-infusion value.
Source: Listing 17.2.4.11, Dataset: ADVS, Program: t_vsabnorm.sas, Output: t_16-4-6-vsabnorm.rtf, Generated on: 28JUL2017 05:58
Page 2 of 27

Table 16.4.6 Clinically Relevant Postbaseline Abnormalities in Vital Sign Results in the Initial Extension - Safety Overall Population

Parameter and Criterion Visit Time Point	GDNF/GDNF (N=21) n (%)	Placebo/GDNF (N=20) n (%)
Sitting Pulse < 50 bpm at any visit in Initial Extension		
Week 68/e28	0	3 (15.0)
60 mins after start of infusion	0	2 (10.0)
90 mins after start of infusion	0	2 (10.0)
Post-dose	0	2 (10.0)
Week 72/e32	0	1 (5.0)
30 mins after start of infusion	0	1 (5.0)
60 mins after start of infusion	0	1 (5.0)
90 mins after start of infusion	0	1 (5.0)
120 mins after start of infusion	0	1 (5.0)
Week 80/e40	1 (4.8)	1 (5.0)
60 mins after start of infusion	1 (4.8)	1 (5.0)
90 mins after start of infusion	1 (4.8)	0
Post-dose	1 (4.8)	0
Sitting Pulse ≥ 120 bpm or an increase from pre-dose of > 20 bpm at any visit in Initial Extension	4 (19.0)	1 (5.0)
Week e0	0	1 (5.0)
60 mins after start of infusion	0	1 (5.0)
75 mins after start of infusion	0	1 (5.0)

Note: bpm = beats per minute. For each parameter and criterion, visit, and time point, subjects are included only once, even if they experienced more
    than one clinically relevant abnormality. For the comparisons of values during or after infusion with pre-infusion values, the baseline is the
    pre-infusion value.
Source: Listing 17.2.4.11, Dataset: ADVS, Program: t_vsabnorm.sas, Output: t_16-4-6-vsabnorm.rtf, Generated on: 28JUL2017 05:58
Page 3 of 27

Table 16.4.6 Clinically Relevant Postbaseline Abnormalities in Vital Sign Results in the Initial Extension - Safety Overall Population

Parameter and Criterion Visit Time Point	GDNF/GDNF (N=21) n (%)	Placebo/GDNF (N=20) n (%)
Sitting Pulse >= 120 bpm or an increase from pre-dose of > 20 bpm at any visit in Initial Extension		
Week e0		
90 mins after start of infusion	0	1 (5.0)
Week 52/e12	0	1 (5.0)
Post-dose	0	1 (5.0)
Week 56/e16	2 (9.5)	0
30 mins after start of infusion	1 (4.8)	0
60 mins after start of infusion	1 (4.8)	0
90 mins after start of infusion	1 (4.8)	0
120 mins after start of infusion	1 (4.8)	0
Post-dose	1 (4.8)	0
Week 60/e20	1 (4.8)	0
30 mins after start of infusion	1 (4.8)	0
Week 64/e24	2 (9.5)	0
90 mins after start of infusion	1 (4.8)	0
120 mins after start of infusion	1 (4.8)	0
Post-dose	2 (9.5)	0

Note: bpm = beats per minute. For each parameter and criterion, visit, and time point, subjects are included only once, even if they experienced more than one clinically relevant abnormality. For the comparisons of values during or after infusion with pre-infusion values, the baseline is the pre-infusion value.
Source: Listing 17.2.4.11, Dataset: ADVS, Program: t_vsabnorm.sas, Output: t_16-4-6-vsabnorm.rtf, Generated on: 28JUL2017 05:58
Page 4 of 27

Table 16.4.6 Clinically Relevant Postbaseline Abnormalities in Vital Sign Results in the Initial Extension - Safety Overall Population

Parameter and Criterion
  Visit
    Time Point
	GDNF/GDNF
	(N=21)
	n (%)
		Placebo/GDNF
		(N=20)
		n (%)

Standing Pulse < 50 bpm at any visit in Initial Extension	1 (4.8)	2 (10.0)
Week 60/e20	1 (4.8)	0
Post-dose	1 (4.8)	0
Week 64/e24	0	2 (10.0)
Post-dose	0	2 (10.0)
Standing Pulse ≥ 120 bpm or an increase from pre-dose of > 20 bpm at any visit in Initial Extension	4 (19.0)	2 (10.0)
Week e0	0	1 (5.0)
Post-dose	0	1 (5.0)
Week 44/e4	1 (4.8)	0
Post-dose	1 (4.8)	0
Week 52/e12	0	1 (5.0)
Post-dose	0	1 (5.0)
Week 60/e20	0	1 (5.0)
Post-dose	0	1 (5.0)
Week 64/e24	1 (4.8)	0
Post-dose	1 (4.8)	0

Note: bpm = beats per minute. For each parameter and criterion, visit, and time point, subjects are included only once, even if they experienced more than one clinically relevant abnormality. For the comparisons of values during or after infusion with pre-infusion values, the baseline is the pre-infusion value.
Source: Listing 17.2.4.11, Dataset: ADVS, Program: t_vsabnorm.sas, Output: t_16-4-6-vsabnorm.rtf, Generated on: 28JUL2017 05:58
Page 5 of 27

Table 16.4.6 Clinically Relevant Postbaseline Abnormalities in Vital Sign Results in the Initial Extension - Safety Overall Population

Parameter and Criterion Visit Time Point	GDNF/GDNF (N=21) n (%)	Placebo/GDNF (N=20) n (%)
Standing Pulse >= 120 bpm or an increase from pre-dose of > 20 bpm at any visit in Initial Extension		
Week 68/e28	1 (4.8)	0
Post-dose	1 (4.8)	0
Week 72/e32	1 (4.8)	0
Post-dose	1 (4.8)	0
Week 76/e36	0	1 (5.0)
Post-dose	0	1 (5.0)

Note: bpm = beats per minute. For each parameter and criterion, visit, and time point, subjects are included only once, even if they experienced more than one clinically relevant abnormality. For the comparisons of values during or after infusion with pre-infusion values, the baseline is the pre-infusion value.
Source: Listing 17.2.4.11, Dataset: ADVS, Program: t_vsabnorm.sas, Output: t_16-4-6-vsabnorm.rtf, Generated on: 28JUL2017 05:58
Page 6 of 27

Table 16.4.6 Clinically Relevant Postbaseline Abnormalities in Vital Sign Results in the Initial Extension - Safety Overall Population

Parameter and Criterion Visit Time Point	GDNF/GDNF (N=21) n (%)	Placebo/GDNF (N=20) n (%)
Respiration < 12 or > 20 breaths/min at any visit in Initial Extension	2 (9.5)	2 (10.0)
Week 48/e8	0	1 (5.0)
60 mins after start of infusion	0	1 (5.0)
Week 56/e16	1 (4.8)	0
60 mins after start of infusion	1 (4.8)	0
Week 68/e28	1 (4.8)	0
90 mins after start of infusion	1 (4.8)	0
Week 72/e32	0	1 (5.0)
90 mins after start of infusion	0	1 (5.0)
Week 76/e36	0	1 (5.0)
30 mins after start of infusion	0	1 (5.0)

Note: bpm = beats per minute. For each parameter and criterion, visit, and time point, subjects are included only once, even if they experienced more
than one clinically relevant abnormality. For the comparisons of values during or after infusion with pre-infusion values, the baseline is the
pre-infusion value.
Source: Listing 17.2.4.11, Dataset: ADVS, Program: t_vsabnorm.sas, Output: t_16-4-6-vsabnorm.rtf, Generated on: 28JUL2017 05:58

Table 16.4.6 Clinically Relevant Postbaseline Abnormalities in Vital Sign Results in the Initial Extension - Safety Overall Population

Parameter and Criterion Visit Time Point	GDNF/GDNF (N=21) n (%)	Placebo/GDNF (N=20) n (%)
Sitting Systolic Blood Pressure < 90 mmHg or a decrease from pre-dose of ≥ 30 mmHg at any visit in Initial Extension	13 (61.9)	12 (60.0)
Week e0	5 (23.8)	3 (15.0)
15 mins after start of infusion	1 (4.8)	0
45 mins after start of infusion	1 (4.8)	1 (5.0)
60 mins after start of infusion	1 (4.8)	0
75 mins after start of infusion	1 (4.8)	0
90 mins after start of infusion	2 (9.5)	1 (5.0)
105 mins after start of infusion	1 (4.8)	0
120 mins after start of infusion	1 (4.8)	1 (5.0)
Post-dose	2 (9.5)	1 (5.0)
Week 44/e4	2 (9.5)	1 (5.0)
30 mins after start of infusion	0	1 (5.0)
90 mins after start of infusion	1 (4.8)	0
Post-dose	1 (4.8)	0
Week 48/e8	2 (9.5)	2 (10.0)
30 mins after start of infusion	0	1 (5.0)
90 mins after start of infusion	2 (9.5)	0

Note: bpm = beats per minute. For each parameter and criterion, visit, and time point, subjects are included only once, even if they experienced more
than one clinically relevant abnormality. For the comparisons of values during or after infusion with pre-infusion values, the baseline is the
pre-infusion value.
Source: Listing 17.2.4.11, Dataset: ADVS, Program: t_vsabnorm.sas, Output: t_16-4-6-vsabnorm.rtf, Generated on: 28JUL2017 05:58
Page 8 of 27

Table 16.4.6 Clinically Relevant Postbaseline Abnormalities in Vital Sign Results in the Initial Extension - Safety Overall Population

Parameter and Criterion Visit Time Point	GDNF/GDNF (N=21) n (%)	Placebo/GDNF (N=20) n (%)
Sitting Systolic Blood Pressure < 90 mmHg or a decrease from pre-dose of >= 30 mmHg at any visit in Initial Extension		
Week 48/e8		
120 mins after start of infusion	0	1 (5.0)
Post-dose	0	1 (5.0)
Week 52/e12	0	1 (5.0)
60 mins after start of infusion	0	1 (5.0)
Week 56/e16	3 (14.3)	3 (15.0)
30 mins after start of infusion	1 (4.8)	1 (5.0)
60 mins after start of infusion	2 (9.5)	1 (5.0)
90 mins after start of infusion	2 (9.5)	2 (10.0)
120 mins after start of infusion	0	1 (5.0)
Post-dose	1 (4.8)	0
Week 60/e20	3 (14.3)	1 (5.0)
30 mins after start of infusion	1 (4.8)	0
60 mins after start of infusion	1 (4.8)	1 (5.0)
Post-dose	1 (4.8)	0
Week 64/e24	2 (9.5)	4 (20.0)
30 mins after start of infusion	1 (4.8)	0
60 mins after start of infusion	2 (9.5)	4 (20.0)

Note: bpm = beats per minute. For each parameter and criterion, visit, and time point, subjects are included only once, even if they experienced more than one clinically relevant abnormality. For the comparisons of values during or after infusion with pre-infusion values, the baseline is the pre-infusion value.
Source: Listing 17.2.4.11, Dataset: ADVS, Program: t_vsabnorm.sas, Output: t_16-4-6-vsabnorm.rtf, Generated on: 28JUL2017 05:58
Page 9 of 27

Table 16.4.6 Clinically Relevant Postbaseline Abnormalities in Vital Sign Results in the Initial Extension - Safety Overall Population

Parameter and Criterion
  Visit
    Time Point
	GDNF/GDNF
	(N=21)
	n (%)
		Placebo/GDNF
		(N=20)
		n (%)

Sitting Systolic Blood Pressure < 90 mmHg or a decrease from pre-dose of >= 30 mmHg at any visit in Initial Extension		
Week 64/e24		
90 mins after start of infusion	2 (9.5)	0
Week 68/e28	1 (4.8)	5 (25.0)
30 mins after start of infusion	1 (4.8)	2 (10.0)
60 mins after start of infusion	1 (4.8)	2 (10.0)
90 mins after start of infusion	1 (4.8)	0
Post-dose	0	2 (10.0)
Week 72/e32	2 (9.5)	2 (10.0)
60 mins after start of infusion	1 (4.8)	1 (5.0)
90 mins after start of infusion	1 (4.8)	1 (5.0)
120 mins after start of infusion	1 (4.8)	1 (5.0)
Post-dose	1 (4.8)	2 (10.0)
Week 76/e36	4 (19.0)	2 (10.0)
30 mins after start of infusion	3 (14.3)	1 (5.0)
90 mins after start of infusion	0	1 (5.0)
Post-dose	1 (4.8)	0

Note: bpm = beats per minute. For each parameter and criterion, visit, and time point, subjects are included only once, even if they experienced more
    than one clinically relevant abnormality. For the comparisons of values during or after infusion with pre-infusion values, the baseline is the
    pre-infusion value.
Source: Listing 17.2.4.11, Dataset: ADVS, Program: t_vsabnorm.sas, Output: t_16-4-6-vsabnorm.rtf, Generated on: 28JUL2017 05:58
Page 10 of 27

Table 16.4.6 Clinically Relevant Postbaseline Abnormalities in Vital Sign Results in the Initial Extension - Safety Overall Population

Parameter and Criterion Visit Time Point	GDNF/GDNF (N=21) n (%)	Placebo/GDNF (N=20) n (%)
Sitting Systolic Blood Pressure < 90 mmHg or a decrease from pre-dose of >= 30 mmHg at any visit in Initial Extension		
Week 80/e40	5 (23.8)	2 (10.0)
30 mins after start of infusion	1 (4.8)	2 (10.0)
60 mins after start of infusion	2 (9.5)	1 (5.0)
90 mins after start of infusion	1 (4.8)	2 (10.0)
Post-dose	3 (14.3)	0
Sitting Systolic Blood Pressure ≥ 180 mmHg or an increase from pre-dose of ≥ 30 mmHg at any visit in Initial Extension	5 (23.8)	10 (50.0)
Week e0	1 (4.8)	1 (5.0)
90 mins after start of infusion	1 (4.8)	0
120 mins after start of infusion	0	1 (5.0)
Post-dose	1 (4.8)	0
Week 44/e4	1 (4.8)	1 (5.0)
60 mins after start of infusion	1 (4.8)	0
90 mins after start of infusion	0	1 (5.0)
Post-dose	1 (4.8)	1 (5.0)
Week 48/e8	0	3 (15.0)
90 mins after start of infusion	0	2 (10.0)
Post-dose	0	1 (5.0)

Note: bpm = beats per minute. For each parameter and criterion, visit, and time point, subjects are included only once, even if they experienced more than one clinically relevant abnormality. For the comparisons of values during or after infusion with pre-infusion values, the baseline is the pre-infusion value.
Source: Listing 17.2.4.11, Dataset: ADVS, Program: t_vsabnorm.sas, Output: t_16-4-6-vsabnorm.rtf, Generated on: 28JUL2017 05:58
Page 11 of 27

Table 16.4.6 Clinically Relevant Postbaseline Abnormalities in Vital Sign Results in the Initial Extension - Safety Overall Population

Parameter and Criterion Visit Time Point	GDNF/GDNF (N=21) n (%)	Placebo/GDNF (N=20) n (%)
Sitting Systolic Blood Pressure >= 180 mmHg or an increase from pre-dose of >= 30 mmHg at any visit in Initial Extension		
Week 52/e12	1 (4.8)	1 (5.0)
30 mins after start of infusion	1 (4.8)	0
60 mins after start of infusion	1 (4.8)	0
90 mins after start of infusion	1 (4.8)	1 (5.0)
Post-dose	1 (4.8)	1 (5.0)
Week 56/e16	3 (14.3)	3 (15.0)
60 mins after start of infusion	1 (4.8)	0
90 mins after start of infusion	0	1 (5.0)
120 mins after start of infusion	0	1 (5.0)
Post-dose	2 (9.5)	2 (10.0)
Week 60/e20	0	2 (10.0)
30 mins after start of infusion	0	1 (5.0)
90 mins after start of infusion	0	1 (5.0)
Week 64/e24	1 (4.8)	2 (10.0)
30 mins after start of infusion	0	1 (5.0)
90 mins after start of infusion	1 (4.8)	0
Post-dose	1 (4.8)	1 (5.0)

Note: bpm = beats per minute. For each parameter and criterion, visit, and time point, subjects are included only once, even if they experienced more than one clinically relevant abnormality. For the comparisons of values during or after infusion with pre-infusion values, the baseline is the pre-infusion value.
Source: Listing 17.2.4.11, Dataset: ADVS, Program: t_vsabnorm.sas, Output: t_16-4-6-vsabnorm.rtf, Generated on: 28JUL2017 05:58
Page 12 of 27

Table 16.4.6 Clinically Relevant Postbaseline Abnormalities in Vital Sign Results in the Initial Extension - Safety Overall Population

Parameter and Criterion Visit Time Point	GDNF/GDNF (N=21) n (%)	Placebo/GDNF (N=20) n (%)
Sitting Systolic Blood Pressure >= 180 mmHg or an increase from pre-dose of >= 30 mmHg at any visit in Initial Extension		
Week 68/e28	0	2 (10.0)
30 mins after start of infusion	0	1 (5.0)
60 mins after start of infusion	0	2 (10.0)
90 mins after start of infusion	0	1 (5.0)
Post-dose	0	1 (5.0)
Week 76/e36	1 (4.8)	1 (5.0)
60 mins after start of infusion	1 (4.8)	1 (5.0)

Note: bpm = beats per minute. For each parameter and criterion, visit, and time point, subjects are included only once, even if they experienced more than one clinically relevant abnormality. For the comparisons of values during or after infusion with pre-infusion values, the baseline is the pre-infusion value.
Source: Listing 17.2.4.11, Dataset: ADVS, Program: t_vsabnorm.sas, Output: t_16-4-6-vsabnorm.rtf, Generated on: 28JUL2017 05:58
Page 13 of 27

Table 16.4.6 Clinically Relevant Postbaseline Abnormalities in Vital Sign Results in the Initial Extension - Safety Overall Population

Parameter and Criterion Visit Time Point	GDNF/GDNF (N=21) n (%)	Placebo/GDNF (N=20) n (%)
Standing Systolic Blood Pressure < 90 mmHg or a decrease from pre-dose of ≥ 30 mmHg at any visit in Initial Extension	6 (28.6)	4 (20.0)
Week e0	2 (9.5)	2 (10.0)
Post-dose	2 (9.5)	2 (10.0)
Week 52/e12	1 (4.8)	0
Post-dose	1 (4.8)	0
Week 60/e20	1 (4.8)	0
Post-dose	1 (4.8)	0
Week 64/e24	0	1 (5.0)
Post-dose	0	1 (5.0)
Week 68/e28	0	1 (5.0)
Post-dose	0	1 (5.0)
Week 72/e32	1 (4.8)	1 (5.0)
Post-dose	1 (4.8)	1 (5.0)
Week 76/e36	2 (9.5)	0
Post-dose	2 (9.5)	0

Note: bpm = beats per minute. For each parameter and criterion, visit, and time point, subjects are included only once, even if they experienced more than one clinically relevant abnormality. For the comparisons of values during or after infusion with pre-infusion values, the baseline is the pre-infusion value.
Source: Listing 17.2.4.11, Dataset: ADVS, Program: t_vsabnorm.sas, Output: t_16-4-6-vsabnorm.rtf, Generated on: 28JUL2017 05:58
Page 14 of 27

Table 16.4.6 Clinically Relevant Postbaseline Abnormalities in Vital Sign Results in the Initial Extension - Safety Overall Population

Parameter and Criterion Visit Time Point	GDNF/GDNF (N=21) n (%)	Placebo/GDNF (N=20) n (%)
Standing Systolic Blood Pressure ≥ 180 mmHg or an increase from pre-dose of ≥ 30 mmHg at any visit in		
Initial Extension	6 (28.6)	7 (35.0)
Week 44/e4	1 (4.8)	2 (10.0)
Post-dose	1 (4.8)	2 (10.0)
Week 48/e8	2 (9.5)	2 (10.0)
Post-dose	2 (9.5)	2 (10.0)
Week 52/e12	0	2 (10.0)
Post-dose	0	2 (10.0)
Week 56/e16	1 (4.8)	0
Post-dose	1 (4.8)	0
Week 60/e20	0	1 (5.0)
Post-dose	0	1 (5.0)
Week 64/e24	2 (9.5)	1 (5.0)
Post-dose	2 (9.5)	1 (5.0)
Week 68/e28	0	1 (5.0)
Post-dose	0	1 (5.0)

Note: bpm = beats per minute. For each parameter and criterion, visit, and time point, subjects are included only once, even if they experienced more than one clinically relevant abnormality. For the comparisons of values during or after infusion with pre-infusion values, the baseline is the pre-infusion value.
Source: Listing 17.2.4.11, Dataset: ADVS, Program: t_vsabnorm.sas, Output: t_16-4-6-vsabnorm.rtf, Generated on: 28JUL2017 05:58
Page 15 of 27

Table 16.4.6 Clinically Relevant Postbaseline Abnormalities in Vital Sign Results in the Initial Extension - Safety Overall Population

Parameter and Criterion Visit Time Point	GDNF/GDNF (N=21) n (%)	Placebo/GDNF (N=20) n (%)
Standing Systolic Blood Pressure >= 180 mmHg or an increase from pre-dose of >= 30 mmHg at any visit in Initial Extension		
Week 72/e32	1 (4.8)	0
Post-dose	1 (4.8)	0
Week 76/e36	1 (4.8)	0
Post-dose	1 (4.8)	0

Note: bpm = beats per minute. For each parameter and criterion, visit, and time point, subjects are included only once, even if they experienced more than one clinically relevant abnormality. For the comparisons of values during or after infusion with pre-infusion values, the baseline is the pre-infusion value.
Source: Listing 17.2.4.11, Dataset: ADVS, Program: t_vsabnorm.sas, Output: t_16-4-6-vsabnorm.rtf, Generated on: 28JUL2017 05:58
Page 16 of 27

Table 16.4.6 Clinically Relevant Postbaseline Abnormalities in Vital Sign Results in the Initial Extension - Safety Overall Population

Parameter and Criterion
    Visit
        Time Point
	GDNF/GDNF
	(N=21)
	n (%)
		Placebo/GDNF
		(N=20)
		n (%)

Sitting Diastolic Blood Pressure < 50 mmHg or a decrease from pre-dose of ≥ 20 mmHg at any visit in Initial Extension	17 (81.0)	17 (85.0)
Week e0	7 (33.3)	6 (30.0)
15 mins after start of infusion	2 (9.5)	1 (5.0)
45 mins after start of infusion	0	2 (10.0)
60 mins after start of infusion	3 (14.3)	0
75 mins after start of infusion	3 (14.3)	2 (10.0)
90 mins after start of infusion	3 (14.3)	3 (15.0)
105 mins after start of infusion	2 (9.5)	1 (5.0)
120 mins after start of infusion	2 (9.5)	0
Post-dose	4 (19.0)	4 (20.0)
Week 44/e4	6 (28.6)	5 (25.0)
30 mins after start of infusion	2 (9.5)	2 (10.0)
60 mins after start of infusion	2 (9.5)	3 (15.0)
90 mins after start of infusion	4 (19.0)	1 (5.0)
Post-dose	2 (9.5)	1 (5.0)

Note: bpm = beats per minute. For each parameter and criterion, visit, and time point, subjects are included only once, even if they experienced more
    than one clinically relevant abnormality. For the comparisons of values during or after infusion with pre-infusion values, the baseline is the
    pre-infusion value.
Source: Listing 17.2.4.11, Dataset: ADVS, Program: t_vsabnorm.sas, Output: t_16-4-6-vsabnorm.rtf, Generated on: 28JUL2017 05:58
Page 17 of 27

Table 16.4.6 Clinically Relevant Postbaseline Abnormalities in Vital Sign Results in the Initial Extension - Safety Overall Population

Parameter and Criterion
  Visit
    Time Point
	GDNF/GDNF
	(N=21)
	n (%)
		Placebo/GDNF
		(N=20)
		n (%)

Sitting Diastolic Blood Pressure < 50 mmHg or a decrease from pre-dose of >= 20 mmHg at any visit in Initial Extension		
Week 48/e8	5 (23.8)	7 (35.0)
30 mins after start of infusion	2 (9.5)	5 (25.0)
60 mins after start of infusion	2 (9.5)	1 (5.0)
90 mins after start of infusion	2 (9.5)	3 (15.0)
120 mins after start of infusion	0	1 (5.0)
Post-dose	1 (4.8)	4 (20.0)
Week 52/e12	4 (19.0)	3 (15.0)
30 mins after start of infusion	1 (4.8)	1 (5.0)
60 mins after start of infusion	1 (4.8)	1 (5.0)
90 mins after start of infusion	1 (4.8)	1 (5.0)
120 mins after start of infusion	1 (4.8)	0
Post-dose	2 (9.5)	3 (15.0)
Week 56/e16	4 (19.0)	7 (35.0)
30 mins after start of infusion	2 (9.5)	4 (20.0)
60 mins after start of infusion	2 (9.5)	4 (20.0)
90 mins after start of infusion	3 (14.3)	3 (15.0)
120 mins after start of infusion	1 (4.8)	2 (10.0)

Note: bpm = beats per minute. For each parameter and criterion, visit, and time point, subjects are included only once, even if they experienced more than one clinically relevant abnormality. For the comparisons of values during or after infusion with pre-infusion values, the baseline is the pre-infusion value.
Source: Listing 17.2.4.11, Dataset: ADVS, Program: t_vsabnorm.sas, Output: t_16-4-6-vsabnorm.rtf, Generated on: 28JUL2017 05:58
Page 18 of 27

Table 16.4.6 Clinically Relevant Postbaseline Abnormalities in Vital Sign Results in the Initial Extension - Safety Overall Population

Parameter and Criterion Visit Time Point	GDNF/GDNF (N=21) n (%)	Placebo/GDNF (N=20) n (%)
Sitting Diastolic Blood Pressure < 50 mmHg or a decrease from pre-dose of >= 20 mmHg at any visit in Initial Extension		
Week 56/e16		
Post-dose	3 (14.3)	3 (15.0)
Week 60/e20	4 (19.0)	1 (5.0)
30 mins after start of infusion	0	1 (5.0)
60 mins after start of infusion	1 (4.8)	0
90 mins after start of infusion	1 (4.8)	0
Post-dose	3 (14.3)	0
Week 64/e24	5 (23.8)	7 (35.0)
30 mins after start of infusion	2 (9.5)	5 (25.0)
60 mins after start of infusion	4 (19.0)	2 (10.0)
90 mins after start of infusion	2 (9.5)	3 (15.0)
120 mins after start of infusion	0	1 (5.0)
Post-dose	3 (14.3)	0
Week 68/e28	5 (23.8)	6 (30.0)
30 mins after start of infusion	3 (14.3)	1 (5.0)
60 mins after start of infusion	1 (4.8)	2 (10.0)
90 mins after start of infusion	2 (9.5)	3 (15.0)
Post-dose	1 (4.8)	2 (10.0)

Note: bpm = beats per minute. For each parameter and criterion, visit, and time point, subjects are included only once, even if they experienced more than one clinically relevant abnormality. For the comparisons of values during or after infusion with pre-infusion values, the baseline is the pre-infusion value.
Source: Listing 17.2.4.11, Dataset: ADVS, Program: t_vsabnorm.sas, Output: t_16-4-6-vsabnorm.rtf, Generated on: 28JUL2017 05:58
Page 19 of 27

Table 16.4.6 Clinically Relevant Postbaseline Abnormalities in Vital Sign Results in the Initial Extension - Safety Overall Population

Parameter and Criterion 　Visit 　　Time Point	GDNF/GDNF (N=21) n (%)	Placebo/GDNF (N=20) n (%)
Sitting Diastolic Blood Pressure < 50 mmHg or a decrease from pre-dose of >= 20 mmHg at any visit in Initial Extension		
Week 72/e32	0	3 (15.0)
30 mins after start of infusion	0	2 (10.0)
60 mins after start of infusion	0	1 (5.0)
90 mins after start of infusion	0	1 (5.0)
Post-dose	0	2 (10.0)
Week 76/e36	2 (9.5)	4 (20.0)
30 mins after start of infusion	1 (4.8)	1 (5.0)
60 mins after start of infusion	1 (4.8)	2 (10.0)
90 mins after start of infusion	1 (4.8)	3 (15.0)
Post-dose	2 (9.5)	0
Week 80/e40	6 (28.6)	4 (20.0)
30 mins after start of infusion	3 (14.3)	2 (10.0)
60 mins after start of infusion	3 (14.3)	1 (5.0)
90 mins after start of infusion	3 (14.3)	2 (10.0)
Post-dose	2 (9.5)	0

Note: bpm = beats per minute. For each parameter and criterion, visit, and time point, subjects are included only once, even if they experienced more than one clinically relevant abnormality. For the comparisons of values during or after infusion with pre-infusion values, the baseline is the pre-infusion value.
Source: Listing 17.2.4.11, Dataset: ADVS, Program: t_vsabnorm.sas, Output: t_16-4-6-vsabnorm.rtf, Generated on: 28JUL2017 05:58
Page 20 of 27

Table 16.4.6 Clinically Relevant Postbaseline Abnormalities in Vital Sign Results in the Initial Extension - Safety Overall Population

Parameter and Criterion
  Visit
    Time Point
	GDNF/GDNF
	(N=21)
	n (%)
		Placebo/GDNF
		(N=20)
		n (%)

Sitting Diastolic Blood Pressure ≥ 105 mmHg or an increase from pre-dose of ≥ 20 mmHg at any visit in Initial Extension	12 (57.1)	12 (60.0)
Week e0	1 (4.8)	4 (20.0)
30 mins after start of infusion	0	2 (10.0)
45 mins after start of infusion	1 (4.8)	2 (10.0)
60 mins after start of infusion	0	1 (5.0)
75 mins after start of infusion	1 (4.8)	2 (10.0)
90 mins after start of infusion	0	2 (10.0)
105 mins after start of infusion	0	1 (5.0)
120 mins after start of infusion	0	1 (5.0)
Week 44/e4	2 (9.5)	1 (5.0)
Post-dose	2 (9.5)	1 (5.0)
Week 48/e8	1 (4.8)	4 (20.0)
30 mins after start of infusion	1 (4.8)	1 (5.0)
60 mins after start of infusion	0	1 (5.0)
90 mins after start of infusion	1 (4.8)	1 (5.0)
120 mins after start of infusion	1 (4.8)	0
Post-dose	0	1 (5.0)

Note: bpm = beats per minute. For each parameter and criterion, visit, and time point, subjects are included only once, even if they experienced more than one clinically relevant abnormality. For the comparisons of values during or after infusion with pre-infusion values, the baseline is the pre-infusion value.
Source: Listing 17.2.4.11, Dataset: ADVS, Program: t_vsabnorm.sas, Output: t_16-4-6-vsabnorm.rtf, Generated on: 28JUL2017 05:58
Page 21 of 27

Table 16.4.6 Clinically Relevant Postbaseline Abnormalities in Vital Sign Results in the Initial Extension - Safety Overall Population

Parameter and Criterion Visit Time Point	GDNF/GDNF (N=21) n (%)	Placebo/GDNF (N=20) n (%)
Sitting Diastolic Blood Pressure >= 105 mmHg or an increase from pre-dose of >= 20 mmHg at any visit in Initial Extension		
Week 52/e12	2 (9.5)	2 (10.0)
30 mins after start of infusion	1 (4.8)	0
60 mins after start of infusion	1 (4.8)	0
90 mins after start of infusion	0	2 (10.0)
Week 56/e16	2 (9.5)	2 (10.0)
30 mins after start of infusion	1 (4.8)	0
60 mins after start of infusion	0	2 (10.0)
90 mins after start of infusion	0	1 (5.0)
Post-dose	1 (4.8)	1 (5.0)
Week 60/e20	3 (14.3)	4 (20.0)
30 mins after start of infusion	0	2 (10.0)
60 mins after start of infusion	1 (4.8)	0
90 mins after start of infusion	2 (9.5)	1 (5.0)
120 mins after start of infusion	1 (4.8)	0
Post-dose	0	2 (10.0)

Note: bpm = beats per minute. For each parameter and criterion, visit, and time point, subjects are included only once, even if they experienced more than one clinically relevant abnormality. For the comparisons of values during or after infusion with pre-infusion values, the baseline is the pre-infusion value.
Source: Listing 17.2.4.11, Dataset: ADVS, Program: t_vsabnorm.sas, Output: t_16-4-6-vsabnorm.rtf, Generated on: 28JUL2017 05:58
Page 22 of 27

Table 16.4.6 Clinically Relevant Postbaseline Abnormalities in Vital Sign Results in the Initial Extension - Safety Overall Population

Parameter and Criterion Visit Time Point	GDNF/GDNF (N=21) n (%)	Placebo/GDNF (N=20) n (%)
Sitting Diastolic Blood Pressure >= 105 mmHg or an increase from pre-dose of >= 20 mmHg at any visit in Initial Extension		
Week 64/e24	3 (14.3)	1 (5.0)
120 mins after start of infusion	1 (4.8)	0
Post-dose	3 (14.3)	1 (5.0)
Week 68/e28	2 (9.5)	4 (20.0)
30 mins after start of infusion	1 (4.8)	2 (10.0)
60 mins after start of infusion	1 (4.8)	1 (5.0)
90 mins after start of infusion	1 (4.8)	2 (10.0)
Post-dose	2 (9.5)	3 (15.0)
Week 72/e32	3 (14.3)	1 (5.0)
60 mins after start of infusion	1 (4.8)	1 (5.0)
90 mins after start of infusion	3 (14.3)	0
Post-dose	2 (9.5)	1 (5.0)
Week 76/e36	0	2 (10.0)
30 mins after start of infusion	0	1 (5.0)
60 mins after start of infusion	0	2 (10.0)
90 mins after start of infusion	0	1 (5.0)
Post-dose	0	2 (10.0)

Note: bpm = beats per minute. For each parameter and criterion, visit, and time point, subjects are included only once, even if they experienced more
    than one clinically relevant abnormality. For the comparisons of values during or after infusion with pre-infusion values, the baseline is the
    pre-infusion value.
Source: Listing 17.2.4.11, Dataset: ADVS, Program: t_vsabnorm.sas, Output: t_16-4-6-vsabnorm.rtf, Generated on: 28JUL2017 05:58
Page 23 of 27

Table 16.4.6 Clinically Relevant Postbaseline Abnormalities in Vital Sign Results in the Initial Extension - Safety Overall Population

Parameter and Criterion
  Visit
    Time Point
	GDNF/GDNF
	(N=21)
	n (%)
		Placebo/GDNF
		(N=20)
		n (%)

Sitting Diastolic Blood Pressure >= 105 mmHg or an increase from pre-dose of >= 20 mmHg at any visit in Initial Extension		
Week 80/e40	1 (4.8)	0
30 mins after start of infusion	1 (4.8)	0
90 mins after start of infusion	1 (4.8)	0
Post-dose	1 (4.8)	0

Note: bpm = beats per minute. For each parameter and criterion, visit, and time point, subjects are included only once, even if they experienced more than one clinically relevant abnormality. For the comparisons of values during or after infusion with pre-infusion values, the baseline is the pre-infusion value.
Source: Listing 17.2.4.11, Dataset: ADVS, Program: t_vsabnorm.sas, Output: t_16-4-6-vsabnorm.rtf, Generated on: 28JUL2017 05:58
Page 24 of 27

Table 16.4.6 Clinically Relevant Postbaseline Abnormalities in Vital Sign Results in the Initial Extension - Safety Overall Population

Parameter and Criterion Visit Time Point	GDNF/GDNF (N=21) n (%)	Placebo/GDNF (N=20) n (%)
Standing Diastolic Blood Pressure < 50 mmHg or a decrease from pre-dose of ≥ 20 mmHg at any visit in		
Initial Extension	6 (28.6)	4 (20.0)
Week e0	1 (4.8)	1 (5.0)
Post-dose	1 (4.8)	1 (5.0)
Week 44/e4	2 (9.5)	0
Post-dose	2 (9.5)	0
Week 48/e8	1 (4.8)	2 (10.0)
Post-dose	1 (4.8)	2 (10.0)
Week 52/e12	1 (4.8)	0
Post-dose	1 (4.8)	0
Week 60/e20	2 (9.5)	1 (5.0)
Post-dose	2 (9.5)	1 (5.0)
Week 64/e24	0	2 (10.0)
Post-dose	0	2 (10.0)
Week 68/e28	2 (9.5)	1 (5.0)
Post-dose	2 (9.5)	1 (5.0)

Note: bpm = beats per minute. For each parameter and criterion, visit, and time point, subjects are included only once, even if they experienced more than one clinically relevant abnormality. For the comparisons of values during or after infusion with pre-infusion values, the baseline is the pre-infusion value.
Source: Listing 17.2.4.11, Dataset: ADVS, Program: t_vsabnorm.sas, Output: t_16-4-6-vsabnorm.rtf, Generated on: 28JUL2017 05:58
Page 25 of 27

Table 16.4.6 Clinically Relevant Postbaseline Abnormalities in Vital Sign Results in the Initial Extension - Safety Overall Population

Parameter and Criterion Visit Time Point	GDNF/GDNF (N=21) n (%)	Placebo/GDNF (N=20) n (%)
Standing Diastolic Blood Pressure < 50 mmHg or a decrease from pre-dose of >= 20 mmHg at any visit in Initial Extension		
Week 72/e32	0	1 (5.0)
Post-dose	0	1 (5.0)
Week 76/e36	2 (9.5)	0
Post-dose	2 (9.5)	0
Standing Diastolic Blood Pressure ≥ 105 mmHg or an increase from pre-dose of ≥ 20 mmHg at any visit in Initial Extension	11 (52.4)	6 (30.0)
Week e0	2 (9.5)	1 (5.0)
Post-dose	2 (9.5)	1 (5.0)
Week 44/e4	1 (4.8)	2 (10.0)
Post-dose	1 (4.8)	2 (10.0)
Week 52/e12	1 (4.8)	1 (5.0)
Post-dose	1 (4.8)	1 (5.0)
Week 56/e16	3 (14.3)	2 (10.0)
Post-dose	3 (14.3)	2 (10.0)
Week 60/e20	0	1 (5.0)
Post-dose	0	1 (5.0)

Note: bpm = beats per minute. For each parameter and criterion, visit, and time point, subjects are included only once, even if they experienced more than one clinically relevant abnormality. For the comparisons of values during or after infusion with pre-infusion values, the baseline is the pre-infusion value.
Source: Listing 17.2.4.11, Dataset: ADVS, Program: t_vsabnorm.sas, Output: t_16-4-6-vsabnorm.rtf, Generated on: 28JUL2017 05:58
Page 26 of 27

Table 16.4.6 Clinically Relevant Postbaseline Abnormalities in Vital Sign Results in the Initial Extension - Safety Overall Population

Parameter and Criterion Visit Time Point	GDNF/GDNF (N=21) n (%)	Placebo/GDNF (N=20) n (%)
Standing Diastolic Blood Pressure >= 105 mmHg or an increase from pre-dose of >= 20 mmHg at any visit in Initial Extension		
Week 64/e24	3 (14.3)	1 (5.0)
Post-dose	3 (14.3)	1 (5.0)
Week 68/e28	0	1 (5.0)
Post-dose	0	1 (5.0)
Week 72/e32	2 (9.5)	1 (5.0)
Post-dose	2 (9.5)	1 (5.0)
Week 80/e40	1 (4.8)	0
Post-dose	1 (4.8)	0

Note: bpm = beats per minute. For each parameter and criterion, visit, and time point, subjects are included only once, even if they experienced more than one clinically relevant abnormality. For the comparisons of values during or after infusion with pre-infusion values, the baseline is the pre-infusion value.
Source: Listing 17.2.4.11, Dataset: ADVS, Program: t_vsabnorm.sas, Output: t_16-4-6-vsabnorm.rtf, Generated on: 28JUL2017 05:58
Page 27 of 27

Table 16.4.7.1 Electrocardiogram Results by Visit – Safety Overall Population

Parameter (unit) Visit Statistic	GDNF/GDNF (N=21)		Placebo/GDNF (N=20)	
	Value	Change From Baseline	Value	Change From Baseline
Heart Rate (beats/min)				
Screening (Baseline)				
n	21		20	
Mean (SD)	67.7 (9.79)		67.5 (11.57)	
Median	67.0		67.0	
Min, Max	54, 84		49, 89	
Week 40/e0				
n	21	21	20	20
Mean (SD)	68.2 (11.45)	0.5 (10.46)	68.6 (12.16)	1.2 (7.54)
Median	68.0	1.0	69.5	1.0
Min, Max	45, 92	-19, 22	43, 100	-9, 16
Week 80/e40				
n	21	21	20	20
Mean (SD)	67.0 (9.95)	-0.7 (9.25)	67.4 (11.97)	-0.1 (9.03)
Median	66.0	0.0	66.0	-1.5
Min, Max	48, 87	-15, 18	49, 99	-17, 19

Note: Hodges QT correction formula was used.
Source: Listing 17.2.4.13, Dataset: ADEG, Program: t_ecg.sas, Output: t_16-4-7-1-ecg.rtf, Generated on: 28JUL2017 05:58
Page 1 of 5

Table 16.4.7.1 Electrocardiogram Results by Visit – Safety Overall Population

Parameter (unit) Visit Statistic	GDNF/GDNF (N=21)		Placebo/GDNF (N=20)	
	Value	Change From Baseline	Value	Change From Baseline
PR Interval (ms)				
Screening (Baseline)				
n	21		20	
Mean (SD)	161.4 (22.23)		158.8 (29.10)	
Median	158.0		161.0	
Min, Max	124, 197		68, 198	
Week 40/e0				
n	21	21	20	20
Mean (SD)	190.0 (120.87)	28.7 (121.32)	159.2 (26.69)	0.4 (33.98)
Median	158.0	4.0	162.0	-2.5
Min, Max	127, 706	-47, 550	80, 194	-66, 88
Week 80/e40				
n	21	21	20	20
Mean (SD)	164.2 (18.90)	2.9 (16.16)	164.1 (19.93)	5.3 (28.44)
Median	163.0	1.0	168.5	3.0
Min, Max	126, 198	-26, 32	126, 194	-40, 88

Note: Hodges QT correction formula was used.
Source: Listing 17.2.4.13, Dataset: ADEG, Program: t_ecg.sas, Output: t_16-4-7-1-ecg.rtf, Generated on: 28JUL2017 05:58
Page 2 of 5

Table 16.4.7.1 Electrocardiogram Results by Visit – Safety Overall Population

Parameter (unit) Visit Statistic	GDNF/GDNF (N=21)		Placebo/GDNF (N=20)	
	Value	Change From Baseline	Value	Change From Baseline
QRS Interval (ms)				
Screening (Baseline)				
n	21		20	
Mean (SD)	94.2 (10.15)		95.2 (10.00)	
Median	92.0		95.0	
Min, Max	76, 114		80, 120	
Week 40/e0				
n	21	21	20	20
Mean (SD)	96.2 (8.96)	2.0 (6.04)	96.8 (14.53)	1.6 (11.24)
Median	96.0	2.0	92.0	2.0
Min, Max	80, 108	-11, 16	72, 128	-22, 24
Week 80/e40				
n	21	21	20	20
Mean (SD)	96.9 (8.73)	2.7 (6.23)	96.9 (11.49)	1.7 (6.45)
Median	96.0	2.0	97.0	3.0
Min, Max	82, 122	-15, 16	78, 122	-14, 11

Note: Hodges QT correction formula was used.
Source: Listing 17.2.4.13, Dataset: ADEG, Program: t_ecg.sas, Output: t_16-4-7-1-ecg.rtf, Generated on: 28JUL2017 05:58
Page 3 of 5

Table 16.4.7.1 Electrocardiogram Results by Visit – Safety Overall Population

Parameter (unit) Visit Statistic	GDNF/GDNF (N=21)		Placebo/GDNF (N=20)	
	Value	Change From Baseline	Value	Change From Baseline
QT Interval (ms)				
Screening (Baseline)				
n	21		20	
Mean (SD)	400.8 (35.68)		393.1 (29.72)	
Median	400.0		397.0	
Min, Max	308, 458		328, 442	
Week 40/e0				
n	21	21	20	20
Mean (SD)	404.1 (27.87)	3.3 (31.36)	391.7 (28.90)	-1.5 (23.46)
Median	408.0	8.0	395.0	-1.0
Min, Max	362, 456	-52, 68	326, 439	-58, 34
Week 80/e40				
n	21	21	20	20
Mean (SD)	405.9 (27.11)	5.1 (38.43)	389.6 (31.96)	-3.6 (24.48)
Median	400.0	-2.0	396.0	2.0
Min, Max	368, 456	-54, 118	320, 432	-65, 34

Note: Hodges QT correction formula was used.
Source: Listing 17.2.4.13, Dataset: ADEG, Program: t_ecg.sas, Output: t_16-4-7-1-ecg.rtf, Generated on: 28JUL2017 05:58
Page 4 of 5

Table 16.4.7.1 Electrocardiogram Results by Visit – Safety Overall Population

Parameter (unit) Visit Statistic	GDNF/GDNF (N=21)		Placebo/GDNF (N=20)	
	Value	Change From Baseline	Value	Change From Baseline
QTc Interval (ms)				
Screening (Baseline)				
n	21		20	
Mean (SD)	413.7 (23.93)		405.6 (23.05)	
Median	416.0		406.0	
Min, Max	342, 450		362, 466	
Week 40/e0				
n	21	21	20	20
Mean (SD)	417.0 (19.48)	3.2 (23.39)	405.4 (22.95)	-0.2 (22.55)
Median	418.0	6.0	403.5	2.0
Min, Max	383, 453	-39, 41	354, 448	-63, 34
Week 80/e40				
n	21	21	20	20
Mean (SD)	417.8 (18.97)	4.1 (29.21)	405.1 (19.74)	-0.6 (18.38)
Median	419.0	3.0	405.5	0.5
Min, Max	383, 460	-50, 89	353, 438	-48, 34

Note: Hodges QT correction formula was used.
Source: Listing 17.2.4.13, Dataset: ADEG, Program: t_ecg.sas, Output: t_16-4-7-1-ecg.rtf, Generated on: 28JUL2017 05:58
Page 5 of 5

Table 16.4.7.2 Summary of Electrocardiogram Results at Week 80/e40 - Safety Overall Population

ECG Evaluation	GDNF/GDNF (N=21) n (%)	Placebo/GDNF (N=20) n (%)
Overall impression		
Normal Week 80/e40 result	16 (76.2)	18 (90.0)
Any abnormal Week 80/e40 result	5 (23.8)	2 (10.0)
Any clinically significant abnormal Week 80/e40 result	0	0
Any clinically relevant abnormal Week 80/e40 QTc Interval result based on criteria below	3 (14.3)	2 (10.0)
> 450 ms	1 (4.8)	0
> 500 ms	0	0
Change from Baseline > 30 ms	1 (4.8)	2 (10.0)
Change from Baseline > 60 ms	1 (4.8)	0

Note: Overall ECG impression was rated by the investigator as abnormal and clinically significant on the CRF based on medical judgment. Hodges QT correction formula was used.

Source: Listing 17.2.4.13, 17.2.4.14, Dataset: ADEG, Program: t_ecgabnorm.sas, Output: t_16-4-7-2-ecgabnorm.rtf, Generated on: 28JUL2017 05:58
Page 1 of 1

Table 16.4.8 Glasgow Coma Scale Score = 15 or < 15 During or After Infusion by Visit and Time Point in the Initial Extension – Safety
Overall Population

Visit and Time Point Glasgow Coma Scale Score	GDNF/GDNF (N=21) n (%)	Placebo/GDNF (N=20) n (%)
Week e0 at any time during or after infusion		
All Scores = 15	20 (95.2)	19 (95.0)
Any Score < 15	0	1 (5.0)
No score < 15 but at least one score is missing	1 (4.8)	0
Missing	0	0
Week 44/e4 at any time during or after infusion		
All Scores = 15	20 (95.2)	20 (100)
Any Score < 15	0	0
No score < 15 but at least one score is missing	0	0
Missing	1 (4.8)	0
Week 48/e8 at any time during or after infusion		
All Scores = 15	21 (100)	20 (100)
Any Score < 15	0	0
No score < 15 but at least one score is missing	0	0
Missing	0	0
Week 52/e12 at any time during or after infusion		
All Scores = 15	18 (85.7)	20 (100)
Any Score < 15	0	0
No score < 15 but at least one score is missing	0	0
Missing	3 (14.3)	0

Note: Glasgow Coma Scale items include visual response, verbal ability, and motor skills. Each item has 4-6 possible responses. The best possible total
    score is 15.
Source: Listing 17.2.4.15, Dataset: ADQSS, Program: t_gcs.sas, Output: t_16-4-8-gcs.rtf, Generated on: 28JUL2017 05:58
Page 1 of 4

Table 16.4.8 Glasgow Coma Scale Score = 15 or < 15 During or After Infusion by Visit and Time Point in the Initial Extension – Safety Overall Population

Visit and Time Point Glasgow Coma Scale Score	GDNF/GDNF (N=21) n (%)	Placebo/GDNF (N=20) n (%)
Week 56/e16 at any time during or after infusion		
All Scores = 15	20 (95.2)	20 (100)
Any Score < 15	1 (4.8)	0
No score < 15 but at least one score is missing	0	0
Missing	0	0
Week 60/e20 at any time during or after infusion		
All Scores = 15	19 (90.5)	20 (100)
Any Score < 15	0	0
No score < 15 but at least one score is missing	0	0
Missing	2 (9.5)	0
Week 64/e24 at any time during or after infusion		
All Scores = 15	20 (95.2)	20 (100)
Any Score < 15	0	0
No score < 15 but at least one score is missing	0	0
Missing	1 (4.8)	0
Week 68/e28 at any time during or after infusion		
All Scores = 15	19 (90.5)	20 (100)
Any Score < 15	0	0
No score < 15 but at least one score is missing	0	0
Missing	2 (9.5)	0

Note: Glasgow Coma Scale items include visual response, verbal ability, and motor skills. Each item has 4-6 possible responses. The best possible total score is 15.
Source: Listing 17.2.4.15, Dataset: ADQSS, Program: t_gcs.sas, Output: t_16-4-8-gcs.rtf, Generated on: 28JUL2017 05:58
Page 2 of 4

Table 16.4.8 Glasgow Coma Scale Score = 15 or < 15 During or After Infusion by Visit and Time Point in the Initial Extension – Safety Overall Population

Visit and Time Point Glasgow Coma Scale Score	GDNF/GDNF (N=21) n (%)	Placebo/GDNF (N=20) n (%)
Week 72/e32 at any time during or after infusion		
All Scores = 15	21 (100)	19 (95.0)
Any Score < 15	0	0
No score < 15 but at least one score is missing	0	1 (5.0)
Missing	0	0
Week 76/e36 at any time during or after infusion		
All Scores = 15	16 (76.2)	19 (95.0)
Any Score < 15	0	0
No score < 15 but at least one score is missing	2 (9.5)	0
Missing	3 (14.3)	1 (5.0)
Week 80/e40 at any time during or after infusion		
All Scores = 15	18 (85.7)	18 (90.0)
Any Score < 15	0	0
No score < 15 but at least one score is missing	0	0
Missing	3 (14.3)	2 (10.0)

Note: Glasgow Coma Scale items include visual response, verbal ability, and motor skills. Each item has 4-6 possible responses. The best possible total score is 15.
Source: Listing 17.2.4.15, Dataset: ADQSS, Program: t_gcs.sas, Output: t_16-4-8-gcs.rtf, Generated on: 28JUL2017 05:58
Page 3 of 4

**Table 16.4.8 Glasgow Coma Scale Score = 15 or < 15 During or After Infusion by Visit and Time Point in the Initial Extension – Safety
Overall Population**

Glasgow Coma Scale Scoring		
Visual Response	**Verbal Ability**	**Motor Skills**
1. No eye opening	1. No verbal response	1. No motor response
2. Eye opening to pain	2. Incomprehensible sounds	2. Extension to pain
3. Eye opening to verbal command	3. Inappropriate words	3. Flexion to pain
4. Eyes open spontaneously	4. Confused	4. Withdrawal from pain
	5. Orientated	5. Localizing pain
		6. Obeys commands

Note: Glasgow Coma Scale items include visual response, verbal ability, and motor skills. Each item has 4-6 possible responses. The best possible total
score is 15.
Source: Listing 17.2.4.15, Dataset: ADQSS, Program: t_gcs.sas, Output: t_16-4-8-gcs.rtf, Generated on: 28JUL2017 05:58
Page 4 of 4

Table 16.4.9.1 QUIP by Visit - Safety Overall Population

Assessor Parameter Visit Baseline Value	GDNF/GDNF (N=21) Postbaseline Value			Placebo/GDNF (N=20) Postbaseline Value		
	Positive n (%)	Negative n (%)	Missing n (%)	Positive n (%)	Negative n (%)	Missing n (%)
Subject						
Compulsive Gambling						
Week 48/e8						
Positive	0	0	0	0	0	0
Negative	0	20 (95.2)	0	0	20 (100)	0
Missing	0	1 (4.8)	0	0	0	0
Week 56/e16						
Positive	0	0	0	0	0	0
Negative	0	20 (95.2)	0	0	20 (100)	0
Missing	0	1 (4.8)	0	0	0	0
Week 64/e24						
Positive	0	0	0	0	0	0
Negative	0	20 (95.2)	0	0	20 (100)	0
Missing	0	1 (4.8)	0	0	0	0
Week 72/e32						
Positive	0	0	0	0	0	0
Negative	0	20 (95.2)	0	0	20 (100)	0
Missing	0	1 (4.8)	0	0	0	0

Note: The QUIP is a self-administered or informant-completed scale that includes 13 questions covering symptoms related to the 4 commonest impulse control disorders in PD, other behaviors, and problematic use of medication. The number of "Yes" responses is compared to the number required for a positive result. Missing individual responses are imputed using LOCF. Each impulse control disorder, other behavior, and problematic use of medication is rated as a positive result (ie, present) or a negative result (ie, not present). Percentages are based on the total number of observations for that visit.
Source: Listing 17.2.4.16, Dataset: ADQSS, Program: t_quip.sas, Output: t_16-4-9-1-quip.rtf, Generated on: 28JUL2017 05:58
Page 1 of 64

Table 16.4.9.1 QUIP by Visit - Safety Overall Population

Assessor Parameter Visit Baseline Value	GDNF/GDNF (N=21) Postbaseline Value			Placebo/GDNF (N=20) Postbaseline Value		
	Positive n (%)	Negative n (%)	Missing n (%)	Positive n (%)	Negative n (%)	Missing n (%)
Subject						
Compulsive Gambling						
Week 80/e40						
Positive	0	0	0	0	0	0
Negative	0	20 (95.2)	0	0	20 (100)	0
Missing	0	1 (4.8)	0	0	0	0
Week e2-16						
Positive	0	0	0	0	0	0
Negative	0	2 (9.5)	0	0	2 (10.0)	0
Missing	0	1 (4.8)	0	0	0	0
Week e2-32						
Positive	0	0	0	0	0	0
Negative	0	2 (9.5)	0	0	2 (10.0)	0
Missing	0	1 (4.8)	0	0	0	0
Week e2-48						
Positive	0	0	0	0	0	0
Negative	0	2 (9.5)	0	0	2 (10.0)	0
Missing	0	1 (4.8)	0	0	0	0

Note: The QUIP is a self-administered or informant-completed scale that includes 13 questions covering symptoms related to the 4 commonest impulse control disorders in PD, other behaviors, and problematic use of medication. The number of "Yes" responses is compared to the number required for a positive result. Missing individual responses are imputed using LOCF. Each impulse control disorder, other behavior, and problematic use of medication is rated as a positive result (ie, present) or a negative result (ie, not present). Percentages are based on the total number of observations for that visit.
Source: Listing 17.2.4.16, Dataset: ADQSS, Program: t_quip.sas, Output: t_16-4-9-1-quip.rtf, Generated on: 28JUL2017 05:58
Page 2 of 64

Table 16.4.9.1 QUIP by Visit - Safety Overall Population

Assessor Parameter Visit Baseline Value	GDNF/GDNF (N=21) Postbaseline Value			Placebo/GDNF (N=20) Postbaseline Value		
	Positive n (%)	Negative n (%)	Missing n (%)	Positive n (%)	Negative n (%)	Missing n (%)
Subject						
Compulsive Gambling						
Week e2-64						
Positive	0	0	0	0	0	0
Negative	0	2 (9.5)	0	0	2 (10.0)	0
Missing	0	1 (4.8)	0	0	0	0
Week e2-80						
Positive	0	0	0	0	0	0
Negative	0	2 (9.5)	0	0	2 (10.0)	0
Missing	0	1 (4.8)	0	0	0	0
Week e3-16						
Positive	0	0	0	0	0	0
Negative	0	11 (52.4)	0	0	13 (65.0)	0
Missing	0	1 (4.8)	0	0	0	0
Week e3-32						
Positive	0	0	0	0	0	0
Negative	0	11 (52.4)	0	0	13 (65.0)	0
Missing	0	1 (4.8)	0	0	0	0

Note: The QUIP is a self-administered or informant-completed scale that includes 13 questions covering symptoms related to the 4 commonest impulse control disorders in PD, other behaviors, and problematic use of medication. The number of "Yes" responses is compared to the number required for a positive result. Missing individual responses are imputed using LOCF. Each impulse control disorder, other behavior, and problematic use of medication is rated as a positive result (ie, present) or a negative result (ie, not present). Percentages are based on the total number of observations for that visit.
Source: Listing 17.2.4.16, Dataset: ADQSS, Program: t_quip.sas, Output: t_16-4-9-1-quip.rtf, Generated on: 28JUL2017 05:58
Page 3 of 64

Table 16.4.9.1 QUIP by Visit - Safety Overall Population

Assessor Parameter Visit Baseline Value	GDNF/GDNF (N=21) Postbaseline Value			Placebo/GDNF (N=20) Postbaseline Value		
	Positive n (%)	Negative n (%)	Missing n (%)	Positive n (%)	Negative n (%)	Missing n (%)
Subject						
Compulsive Gambling						
Last Study Visit in the Supplemental Extension						
Positive	0	0	0	0	0	0
Negative	1 (4.8)	10 (47.6)	0	0	13 (65.0)	0
Missing	0	1 (4.8)	0	0	0	0

Note: The QUIP is a self-administered or informant-completed scale that includes 13 questions covering symptoms related to the 4 commonest impulse control disorders in PD, other behaviors, and problematic use of medication. The number of "Yes" responses is compared to the number required for a positive result. Missing individual responses are imputed using LOCF. Each impulse control disorder, other behavior, and problematic use of medication is rated as a positive result (ie, present) or a negative result (ie, not present). Percentages are based on the total number of observations for that visit.
Source: Listing 17.2.4.16, Dataset: ADQSS, Program: t_quip.sas, Output: t_16-4-9-1-quip.rtf, Generated on: 28JUL2017 05:58
Page 4 of 64

Table 16.4.9.1 QUIP by Visit - Safety Overall Population

Assessor Parameter Visit Baseline Value	GDNF/GDNF (N=21) Postbaseline Value			Placebo/GDNF (N=20) Postbaseline Value		
	Positive n (%)	Negative n (%)	Missing n (%)	Positive n (%)	Negative n (%)	Missing n (%)
Subject						
Compulsive Sexual Behaviour						
Week 48/e8						
Positive	1 (4.8)	1 (4.8)	0	1 (5.0)	2 (10.0)	0
Negative	0	18 (85.7)	0	1 (5.0)	16 (80.0)	0
Missing	0	1 (4.8)	0	0	0	0
Week 56/e16						
Positive	0	2 (9.5)	0	1 (5.0)	2 (10.0)	0
Negative	0	18 (85.7)	0	0	17 (85.0)	0
Missing	0	1 (4.8)	0	0	0	0
Week 64/e24						
Positive	0	2 (9.5)	0	1 (5.0)	2 (10.0)	0
Negative	0	18 (85.7)	0	1 (5.0)	16 (80.0)	0
Missing	0	1 (4.8)	0	0	0	0
Week 72/e32						
Positive	1 (4.8)	1 (4.8)	0	1 (5.0)	2 (10.0)	0
Negative	0	18 (85.7)	0	0	17 (85.0)	0
Missing	0	1 (4.8)	0	0	0	0

Note: The QUIP is a self-administered or informant-completed scale that includes 13 questions covering symptoms related to the 4 commonest impulse control disorders in PD, other behaviors, and problematic use of medication. The number of "Yes" responses is compared to the number required for a positive result. Missing individual responses are imputed using LOCF. Each impulse control disorder, other behavior, and problematic use of medication is rated as a positive result (ie, present) or a negative result (ie, not present). Percentages are based on the total number of observations for that visit.
Source: Listing 17.2.4.16, Dataset: ADQSS, Program: t_quip.sas, Output: t_16-4-9-1-quip.rtf, Generated on: 28JUL2017 05:58
Page 5 of 64

Table 16.4.9.1 QUIP by Visit - Safety Overall Population

Assessor Parameter Visit Baseline Value	GDNF/GDNF (N=21) Postbaseline Value			Placebo/GDNF (N=20) Postbaseline Value		
	Positive n (%)	Negative n (%)	Missing n (%)	Positive n (%)	Negative n (%)	Missing n (%)
Subject						
Compulsive Sexual Behaviour						
Week 80/e40						
Positive	1 (4.8)	1 (4.8)	0	1 (5.0)	2 (10.0)	0
Negative	0	18 (85.7)	0	0	17 (85.0)	0
Missing	0	1 (4.8)	0	0	0	0
Week e2-16						
Positive	0	1 (4.8)	0	0	0	0
Negative	0	1 (4.8)	0	0	2 (10.0)	0
Missing	0	1 (4.8)	0	0	0	0
Week e2-32						
Positive	0	1 (4.8)	0	0	0	0
Negative	0	1 (4.8)	0	0	2 (10.0)	0
Missing	0	1 (4.8)	0	0	0	0
Week e2-48						
Positive	1 (4.8)	0	0	0	0	0
Negative	0	1 (4.8)	0	0	2 (10.0)	0
Missing	0	1 (4.8)	0	0	0	0

Note: The QUIP is a self-administered or informant-completed scale that includes 13 questions covering symptoms related to the 4 commonest impulse control disorders in PD, other behaviors, and problematic use of medication. The number of "Yes" responses is compared to the number required for a positive result. Missing individual responses are imputed using LOCF. Each impulse control disorder, other behavior, and problematic use of medication is rated as a positive result (ie, present) or a negative result (ie, not present). Percentages are based on the total number of observations for that visit.
Source: Listing 17.2.4.16, Dataset: ADQSS, Program: t_quip.sas, Output: t_16-4-9-1-quip.rtf, Generated on: 28JUL2017 05:58

Table 16.4.9.1 QUIP by Visit - Safety Overall Population

Assessor Parameter Visit Baseline Value	GDNF/GDNF (N=21) Postbaseline Value			Placebo/GDNF (N=20) Postbaseline Value		
	Positive n (%)	Negative n (%)	Missing n (%)	Positive n (%)	Negative n (%)	Missing n (%)
Subject						
Compulsive Sexual Behaviour						
Week e2-64						
Positive	0	1 (4.8)	0	0	0	0
Negative	0	1 (4.8)	0	0	2 (10.0)	0
Missing	0	1 (4.8)	0	0	0	0
Week e2-80						
Positive	0	1 (4.8)	0	0	0	0
Negative	0	1 (4.8)	0	0	2 (10.0)	0
Missing	0	1 (4.8)	0	0	0	0
Week e3-16						
Positive	2 (9.5)	0	0	1 (5.0)	2 (10.0)	0
Negative	0	9 (42.9)	0	0	10 (50.0)	0
Missing	0	1 (4.8)	0	0	0	0
Week e3-32						
Positive	1 (4.8)	1 (4.8)	0	1 (5.0)	2 (10.0)	0
Negative	0	9 (42.9)	0	0	10 (50.0)	0
Missing	0	1 (4.8)	0	0	0	0

Note: The QUIP is a self-administered or informant-completed scale that includes 13 questions covering symptoms related to the 4 commonest impulse control disorders in PD, other behaviors, and problematic use of medication. The number of "Yes" responses is compared to the number required for a positive result. Missing individual responses are imputed using LOCF. Each impulse control disorder, other behavior, and problematic use of medication is rated as a positive result (ie, present) or a negative result (ie, not present). Percentages are based on the total number of observations for that visit.
Source: Listing 17.2.4.16, Dataset: ADQSS, Program: t_quip.sas, Output: t_16-4-9-1-quip.rtf, Generated on: 28JUL2017 05:58
Page 7 of 64

Table 16.4.9.1 QUIP by Visit - Safety Overall Population

Assessor Parameter Visit Baseline Value	GDNF/GDNF (N=21)			Placebo/GDNF (N=20)		
	Postbaseline Value			Postbaseline Value		
	Positive n (%)	Negative n (%)	Missing n (%)	Positive n (%)	Negative n (%)	Missing n (%)
Subject						
Compulsive Sexual Behaviour						
Last Study Visit in the Supplemental Extension						
Positive	1 (4.8)	1 (4.8)	0	2 (10.0)	1 (5.0)	0
Negative	0	9 (42.9)	0	0	10 (50.0)	0
Missing	0	1 (4.8)	0	0	0	0

Note: The QUIP is a self-administered or informant-completed scale that includes 13 questions covering symptoms related to the 4 commonest impulse control disorders in PD, other behaviors, and problematic use of medication. The number of "Yes" responses is compared to the number required for a positive result. Missing individual responses are imputed using LOCF. Each impulse control disorder, other behavior, and problematic use of medication is rated as a positive result (ie, present) or a negative result (ie, not present). Percentages are based on the total number of observations for that visit.
Source: Listing 17.2.4.16, Dataset: ADQSS, Program: t_quip.sas, Output: t_16-4-9-1-quip.rtf, Generated on: 28JUL2017 05:58
Page 8 of 64

Table 16.4.9.1 QUIP by Visit - Safety Overall Population

Assessor Parameter Visit Baseline Value	GDNF/GDNF (N=21) Postbaseline Value			Placebo/GDNF (N=20) Postbaseline Value		
	Positive n (%)	Negative n (%)	Missing n (%)	Positive n (%)	Negative n (%)	Missing n (%)
Subject						
Compulsive Buying						
Week 48/e8						
Positive	0	2 (9.5)	0	2 (10.0)	1 (5.0)	0
Negative	0	18 (85.7)	0	0	17 (85.0)	0
Missing	0	1 (4.8)	0	0	0	0
Week 56/e16						
Positive	0	2 (9.5)	0	2 (10.0)	1 (5.0)	0
Negative	0	18 (85.7)	0	0	17 (85.0)	0
Missing	0	1 (4.8)	0	0	0	0
Week 64/e24						
Positive	0	2 (9.5)	0	1 (5.0)	2 (10.0)	0
Negative	0	18 (85.7)	0	0	17 (85.0)	0
Missing	0	1 (4.8)	0	0	0	0
Week 72/e32						
Positive	1 (4.8)	1 (4.8)	0	1 (5.0)	2 (10.0)	0
Negative	1 (4.8)	17 (81.0)	0	0	17 (85.0)	0
Missing	0	1 (4.8)	0	0	0	0

Note: The QUIP is a self-administered or informant-completed scale that includes 13 questions covering symptoms related to the 4 commonest impulse control disorders in PD, other behaviors, and problematic use of medication. The number of "Yes" responses is compared to the number required for a positive result. Missing individual responses are imputed using LOCF. Each impulse control disorder, other behavior, and problematic use of medication is rated as a positive result (ie, present) or a negative result (ie, not present). Percentages are based on the total number of observations for that visit.
Source: Listing 17.2.4.16, Dataset: ADQSS, Program: t_quip.sas, Output: t_16-4-9-1-quip.rtf, Generated on: 28JUL2017 05:58
Page 9 of 64

Table 16.4.9.1 QUIP by Visit - Safety Overall Population

Assessor Parameter Visit Baseline Value	GDNF/GDNF (N=21) Postbaseline Value			Placebo/GDNF (N=20) Postbaseline Value		
	Positive n (%)	Negative n (%)	Missing n (%)	Positive n (%)	Negative n (%)	Missing n (%)
Subject						
Compulsive Buying						
Week 80/e40						
Positive	1 (4.8)	1 (4.8)	0	1 (5.0)	2 (10.0)	0
Negative	0	18 (85.7)	0	1 (5.0)	16 (80.0)	0
Missing	0	1 (4.8)	0	0	0	0
Week e2-16						
Positive	0	1 (4.8)	0	0	0	0
Negative	0	1 (4.8)	0	0	2 (10.0)	0
Missing	0	1 (4.8)	0	0	0	0
Week e2-32						
Positive	0	1 (4.8)	0	0	0	0
Negative	0	1 (4.8)	0	0	2 (10.0)	0
Missing	0	1 (4.8)	0	0	0	0
Week e2-48						
Positive	1 (4.8)	0	0	0	0	0
Negative	0	1 (4.8)	0	0	2 (10.0)	0
Missing	0	1 (4.8)	0	0	0	0

Note: The QUIP is a self-administered or informant-completed scale that includes 13 questions covering symptoms related to the 4 commonest impulse control disorders in PD, other behaviors, and problematic use of medication. The number of "Yes" responses is compared to the number required for a positive result. Missing individual responses are imputed using LOCF. Each impulse control disorder, other behavior, and problematic use of medication is rated as a positive result (ie, present) or a negative result (ie, not present). Percentages are based on the total number of observations for that visit.
Source: Listing 17.2.4.16, Dataset: ADQSS, Program: t_quip.sas, Output: t_16-4-9-1-quip.rtf, Generated on: 28JUL2017 05:58
Page 10 of 64

Table 16.4.9.1 QUIP by Visit - Safety Overall Population

Assessor Parameter Visit Baseline Value	GDNF/GDNF (N=21) Postbaseline Value			Placebo/GDNF (N=20) Postbaseline Value		
	Positive n (%)	Negative n (%)	Missing n (%)	Positive n (%)	Negative n (%)	Missing n (%)
Subject						
Compulsive Buying						
Week e2-64						
Positive	0	1 (4.8)	0	0	0	0
Negative	0	1 (4.8)	0	0	2 (10.0)	0
Missing	0	1 (4.8)	0	0	0	0
Week e2-80						
Positive	1 (4.8)	0	0	0	0	0
Negative	0	1 (4.8)	0	0	2 (10.0)	0
Missing	0	1 (4.8)	0	0	0	0
Week e3-16						
Positive	1 (4.8)	1 (4.8)	0	0	2 (10.0)	0
Negative	0	9 (42.9)	0	1 (5.0)	10 (50.0)	0
Missing	0	1 (4.8)	0	0	0	0
Week e3-32						
Positive	1 (4.8)	1 (4.8)	0	0	2 (10.0)	0
Negative	0	9 (42.9)	0	1 (5.0)	10 (50.0)	0
Missing	0	1 (4.8)	0	0	0	0

Note: The QUIP is a self-administered or informant-completed scale that includes 13 questions covering symptoms related to the 4 commonest impulse control disorders in PD, other behaviors, and problematic use of medication. The number of "Yes" responses is compared to the number required for a positive result. Missing individual responses are imputed using LOCF. Each impulse control disorder, other behavior, and problematic use of medication is rated as a positive result (ie, present) or a negative result (ie, not present). Percentages are based on the total number of observations for that visit.
Source: Listing 17.2.4.16, Dataset: ADQSS, Program: t_quip.sas, Output: t_16-4-9-1-quip.rtf, Generated on: 28JUL2017 05:58
Page 11 of 64

Table 16.4.9.1 QUIP by Visit - Safety Overall Population

Assessor Parameter Visit Baseline Value	GDNF/GDNF (N=21)			Placebo/GDNF (N=20)		
	Postbaseline Value			Postbaseline Value		
	Positive n (%)	Negative n (%)	Missing n (%)	Positive n (%)	Negative n (%)	Missing n (%)
Subject						
Compulsive Buying						
Last Study Visit in the Supplemental Extension						
Positive	2 (9.5)	0	0	0	2 (10.0)	0
Negative	0	9 (42.9)	0	1 (5.0)	10 (50.0)	0
Missing	0	1 (4.8)	0	0	0	0

Note: The QUIP is a self-administered or informant-completed scale that includes 13 questions covering symptoms related to the 4 commonest impulse control disorders in PD, other behaviors, and problematic use of medication. The number of "Yes" responses is compared to the number required for a positive result. Missing individual responses are imputed using LOCF. Each impulse control disorder, other behavior, and problematic use of medication is rated as a positive result (ie, present) or a negative result (ie, not present). Percentages are based on the total number of observations for that visit.
Source: Listing 17.2.4.16, Dataset: ADQSS, Program: t_quip.sas, Output: t_16-4-9-1-quip.rtf, Generated on: 28JUL2017 05:58
Page 12 of 64

Table 16.4.9.1 QUIP by Visit - Safety Overall Population

Assessor Parameter Visit Baseline Value	GDNF/GDNF (N=21) Postbaseline Value			Placebo/GDNF (N=20) Postbaseline Value		
	Positive n (%)	Negative n (%)	Missing n (%)	Positive n (%)	Negative n (%)	Missing n (%)
Subject						
Compulsive Eating						
Week 48/e8						
Positive	0	0	0	1 (5.0)	1 (5.0)	0
Negative	1 (4.8)	19 (90.5)	0	0	18 (90.0)	0
Missing	0	1 (4.8)	0	0	0	0
Week 56/e16						
Positive	0	0	0	0	2 (10.0)	0
Negative	0	20 (95.2)	0	0	18 (90.0)	0
Missing	0	1 (4.8)	0	0	0	0
Week 64/e24						
Positive	0	0	0	0	2 (10.0)	0
Negative	0	20 (95.2)	0	0	18 (90.0)	0
Missing	0	1 (4.8)	0	0	0	0
Week 72/e32						
Positive	0	0	0	0	2 (10.0)	0
Negative	0	20 (95.2)	0	0	18 (90.0)	0
Missing	0	1 (4.8)	0	0	0	0

Note: The QUIP is a self-administered or informant-completed scale that includes 13 questions covering symptoms related to the 4 commonest impulse control disorders in PD, other behaviors, and problematic use of medication. The number of "Yes" responses is compared to the number required for a positive result. Missing individual responses are imputed using LOCF. Each impulse control disorder, other behavior, and problematic use of medication is rated as a positive result (ie, present) or a negative result (ie, not present). Percentages are based on the total number of observations for that visit.
Source: Listing 17.2.4.16, Dataset: ADQSS, Program: t_quip.sas, Output: t_16-4-9-1-quip.rtf, Generated on: 28JUL2017 05:58
Page 13 of 64

Table 16.4.9.1 QUIP by Visit - Safety Overall Population

Assessor Parameter Visit Baseline Value	GDNF/GDNF (N=21)			Placebo/GDNF (N=20)		
	Postbaseline Value			Postbaseline Value		
	Positive n (%)	Negative n (%)	Missing n (%)	Positive n (%)	Negative n (%)	Missing n (%)
Subject						
Compulsive Eating						
Week 80/e40						
Positive	0	0	0	1 (5.0)	1 (5.0)	0
Negative	0	20 (95.2)	0	0	18 (90.0)	0
Missing	0	1 (4.8)	0	0	0	0
Week e2-16						
Positive	0	0	0	0	0	0
Negative	0	2 (9.5)	0	0	2 (10.0)	0
Missing	0	1 (4.8)	0	0	0	0
Week e2-32						
Positive	0	0	0	0	0	0
Negative	0	2 (9.5)	0	0	2 (10.0)	0
Missing	0	1 (4.8)	0	0	0	0
Week e2-48						
Positive	0	0	0	0	0	0
Negative	1 (4.8)	1 (4.8)	0	0	2 (10.0)	0
Missing	0	1 (4.8)	0	0	0	0

Note: The QUIP is a self-administered or informant-completed scale that includes 13 questions covering symptoms related to the 4 commonest impulse control disorders in PD, other behaviors, and problematic use of medication. The number of "Yes" responses is compared to the number required for a positive result. Missing individual responses are imputed using LOCF. Each impulse control disorder, other behavior, and problematic use of medication is rated as a positive result (ie, present) or a negative result (ie, not present). Percentages are based on the total number of observations for that visit.
Source: Listing 17.2.4.16, Dataset: ADQSS, Program: t_quip.sas, Output: t_16-4-9-1-quip.rtf, Generated on: 28JUL2017 05:58
Page 14 of 64

Table 16.4.9.1 QUIP by Visit - Safety Overall Population

Assessor Parameter Visit Baseline Value	GDNF/GDNF (N=21) Postbaseline Value			Placebo/GDNF (N=20) Postbaseline Value		
	Positive n (%)	Negative n (%)	Missing n (%)	Positive n (%)	Negative n (%)	Missing n (%)
Subject						
Compulsive Eating						
Week e2-64						
Positive	0	0	0	0	0	0
Negative	0	2 (9.5)	0	0	2 (10.0)	0
Missing	0	1 (4.8)	0	0	0	0
Week e2-80						
Positive	0	0	0	0	0	0
Negative	1 (4.8)	1 (4.8)	0	0	2 (10.0)	0
Missing	0	1 (4.8)	0	0	0	0
Week e3-16						
Positive	0	0	0	0	2 (10.0)	0
Negative	0	11 (52.4)	0	0	11 (55.0)	0
Missing	0	1 (4.8)	0	0	0	0
Week e3-32						
Positive	0	0	0	0	2 (10.0)	0
Negative	0	11 (52.4)	0	0	11 (55.0)	0
Missing	0	1 (4.8)	0	0	0	0

Note: The QUIP is a self-administered or informant-completed scale that includes 13 questions covering symptoms related to the 4 commonest impulse control disorders in PD, other behaviors, and problematic use of medication. The number of "Yes" responses is compared to the number required for a positive result. Missing individual responses are imputed using LOCF. Each impulse control disorder, other behavior, and problematic use of medication is rated as a positive result (ie, present) or a negative result (ie, not present). Percentages are based on the total number of observations for that visit.
Source: Listing 17.2.4.16, Dataset: ADQSS, Program: t_quip.sas, Output: t_16-4-9-1-quip.rtf, Generated on: 28JUL2017 05:58

Table 16.4.9.1 QUIP by Visit - Safety Overall Population

Assessor Parameter Visit Baseline Value	GDNF/GDNF (N=21)			Placebo/GDNF (N=20)		
	Postbaseline Value			Postbaseline Value		
	Positive n (%)	Negative n (%)	Missing n (%)	Positive n (%)	Negative n (%)	Missing n (%)
Subject						
Compulsive Eating						
Last Study Visit in the Supplemental Extension						
Positive	0	0	0	0	2 (10.0)	0
Negative	1 (4.8)	10 (47.6)	0	0	11 (55.0)	0
Missing	0	1 (4.8)	0	0	0	0

Note: The QUIP is a self-administered or informant-completed scale that includes 13 questions covering symptoms related to the 4 commonest impulse control disorders in PD, other behaviors, and problematic use of medication. The number of "Yes" responses is compared to the number required for a positive result. Missing individual responses are imputed using LOCF. Each impulse control disorder, other behavior, and problematic use of medication is rated as a positive result (ie, present) or a negative result (ie, not present). Percentages are based on the total number of observations for that visit.
Source: Listing 17.2.4.16, Dataset: ADQSS, Program: t_quip.sas, Output: t_16-4-9-1-quip.rtf, Generated on: 28JUL2017 05:58
Page 16 of 64

Table 16.4.9.1 QUIP by Visit - Safety Overall Population

Assessor Parameter Visit Baseline Value	GDNF/GDNF (N=21) Postbaseline Value			Placebo/GDNF (N=20) Postbaseline Value		
	Positive n (%)	Negative n (%)	Missing n (%)	Positive n (%)	Negative n (%)	Missing n (%)
Subject						
Hobbyism						
Week 48/e8						
Positive	3 (14.3)	2 (9.5)	0	3 (15.0)	5 (25.0)	0
Negative	0	15 (71.4)	0	0	12 (60.0)	0
Missing	0	1 (4.8)	0	0	0	0
Week 56/e16						
Positive	4 (19.0)	1 (4.8)	0	2 (10.0)	6 (30.0)	0
Negative	0	15 (71.4)	0	1 (5.0)	11 (55.0)	0
Missing	0	1 (4.8)	0	0	0	0
Week 64/e24						
Positive	2 (9.5)	3 (14.3)	0	3 (15.0)	5 (25.0)	0
Negative	1 (4.8)	14 (66.7)	0	1 (5.0)	11 (55.0)	0
Missing	0	1 (4.8)	0	0	0	0
Week 72/e32						
Positive	2 (9.5)	3 (14.3)	0	2 (10.0)	6 (30.0)	0
Negative	2 (9.5)	13 (61.9)	0	1 (5.0)	11 (55.0)	0
Missing	1 (4.8)	0	0	0	0	0

Note: The QUIP is a self-administered or informant-completed scale that includes 13 questions covering symptoms related to the 4 commonest impulse control disorders in PD, other behaviors, and problematic use of medication. The number of "Yes" responses is compared to the number required for a positive result. Missing individual responses are imputed using LOCF. Each impulse control disorder, other behavior, and problematic use of medication is rated as a positive result (ie, present) or a negative result (ie, not present). Percentages are based on the total number of observations for that visit.
Source: Listing 17.2.4.16, Dataset: ADQSS, Program: t_quip.sas, Output: t_16-4-9-1-quip.rtf, Generated on: 28JUL2017 05:58
Page 17 of 64

Table 16.4.9.1 QUIP by Visit - Safety Overall Population

Assessor Parameter Visit Baseline Value	GDNF/GDNF (N=21) Postbaseline Value			Placebo/GDNF (N=20) Postbaseline Value		
	Positive n (%)	Negative n (%)	Missing n (%)	Positive n (%)	Negative n (%)	Missing n (%)
Subject						
Hobbyism						
Week 80/e40						
Positive	3 (14.3)	2 (9.5)	0	4 (20.0)	4 (20.0)	0
Negative	4 (19.0)	11 (52.4)	0	2 (10.0)	10 (50.0)	0
Missing	0	1 (4.8)	0	0	0	0
Week e2-16						
Positive	0	0	0	0	0	0
Negative	1 (4.8)	1 (4.8)	0	0	2 (10.0)	0
Missing	0	1 (4.8)	0	0	0	0
Week e2-32						
Positive	0	0	0	0	0	0
Negative	1 (4.8)	1 (4.8)	0	0	2 (10.0)	0
Missing	0	1 (4.8)	0	0	0	0
Week e2-48						
Positive	0	0	0	0	0	0
Negative	1 (4.8)	1 (4.8)	0	0	2 (10.0)	0
Missing	0	1 (4.8)	0	0	0	0

Note: The QUIP is a self-administered or informant-completed scale that includes 13 questions covering symptoms related to the 4 commonest impulse control disorders in PD, other behaviors, and problematic use of medication. The number of "Yes" responses is compared to the number required for a positive result. Missing individual responses are imputed using LOCF. Each impulse control disorder, other behavior, and problematic use of medication is rated as a positive result (ie, present) or a negative result (ie, not present). Percentages are based on the total number of observations for that visit.

Source: Listing 17.2.4.16, Dataset: ADQSS, Program: t_quip.sas, Output: t_16-4-9-1-quip.rtf, Generated on: 28JUL2017 05:58
Page 18 of 64

Table 16.4.9.1 QUIP by Visit - Safety Overall Population

Assessor Parameter Visit Baseline Value	GDNF/GDNF (N=21) Postbaseline Value			Placebo/GDNF (N=20) Postbaseline Value		
	Positive n (%)	Negative n (%)	Missing n (%)	Positive n (%)	Negative n (%)	Missing n (%)
Subject						
Hobbyism						
Week e2-64						
Positive	0	0	0	0	0	0
Negative	0	2 (9.5)	0	0	2 (10.0)	0
Missing	0	1 (4.8)	0	0	0	0
Week e2-80						
Positive	0	0	0	0	0	0
Negative	1 (4.8)	1 (4.8)	0	0	2 (10.0)	0
Missing	1 (4.8)	0	0	0	0	0
Week e3-16						
Positive	1 (4.8)	2 (9.5)	0	1 (5.0)	3 (15.0)	0
Negative	1 (4.8)	7 (33.3)	0	1 (5.0)	8 (40.0)	0
Missing	1 (4.8)	0	0	0	0	0
Week e3-32						
Positive	1 (4.8)	2 (9.5)	0	1 (5.0)	3 (15.0)	0
Negative	2 (9.5)	6 (28.6)	0	2 (10.0)	7 (35.0)	0
Missing	1 (4.8)	0	0	0	0	0

Note: The QUIP is a self-administered or informant-completed scale that includes 13 questions covering symptoms related to the 4 commonest impulse control disorders in PD, other behaviors, and problematic use of medication. The number of "Yes" responses is compared to the number required for a positive result. Missing individual responses are imputed using LOCF. Each impulse control disorder, other behavior, and problematic use of medication is rated as a positive result (ie, present) or a negative result (ie, not present). Percentages are based on the total number of observations for that visit.
Source: Listing 17.2.4.16, Dataset: ADQSS, Program: t_quip.sas, Output: t_16-4-9-1-quip.rtf, Generated on: 28JUL2017 05:58
Page 19 of 64

Table 16.4.9.1 QUIP by Visit - Safety Overall Population

Assessor Parameter Visit Baseline Value	GDNF/GDNF (N=21) Postbaseline Value			Placebo/GDNF (N=20) Postbaseline Value		
	Positive n (%)	Negative n (%)	Missing n (%)	Positive n (%)	Negative n (%)	Missing n (%)
Subject						
Hobbyism						
Last Study Visit in the Supplemental Extension						
Positive	1 (4.8)	2 (9.5)	0	2 (10.0)	2 (10.0)	0
Negative	2 (9.5)	6 (28.6)	0	2 (10.0)	7 (35.0)	0
Missing	1 (4.8)	0	0	0	0	0

Note: The QUIP is a self-administered or informant-completed scale that includes 13 questions covering symptoms related to the 4 commonest impulse control disorders in PD, other behaviors, and problematic use of medication. The number of "Yes" responses is compared to the number required for a positive result. Missing individual responses are imputed using LOCF. Each impulse control disorder, other behavior, and problematic use of medication is rated as a positive result (ie, present) or a negative result (ie, not present). Percentages are based on the total number of observations for that visit.
Source: Listing 17.2.4.16, Dataset: ADQSS, Program: t_quip.sas, Output: t_16-4-9-1-quip.rtf, Generated on: 28JUL2017 05:58
Page 20 of 64

Table 16.4.9.1 QUIP by Visit - Safety Overall Population

Assessor Parameter Visit Baseline Value	GDNF/GDNF (N=21) Postbaseline Value			Placebo/GDNF (N=20) Postbaseline Value		
	Positive n (%)	Negative n (%)	Missing n (%)	Positive n (%)	Negative n (%)	Missing n (%)
Subject						
Punding						
Week 48/e8						
Positive	1 (4.8)	1 (4.8)	0	2 (10.0)	0	0
Negative	1 (4.8)	17 (81.0)	0	2 (10.0)	16 (80.0)	0
Missing	0	1 (4.8)	0	0	0	0
Week 56/e16						
Positive	0	2 (9.5)	0	1 (5.0)	1 (5.0)	0
Negative	1 (4.8)	17 (81.0)	0	1 (5.0)	17 (85.0)	0
Missing	0	1 (4.8)	0	0	0	0
Week 64/e24						
Positive	1 (4.8)	1 (4.8)	0	1 (5.0)	1 (5.0)	0
Negative	0	18 (85.7)	0	0	18 (90.0)	0
Missing	0	1 (4.8)	0	0	0	0
Week 72/e32						
Positive	0	2 (9.5)	0	1 (5.0)	1 (5.0)	0
Negative	0	18 (85.7)	0	2 (10.0)	16 (80.0)	0
Missing	0	1 (4.8)	0	0	0	0

Note: The QUIP is a self-administered or informant-completed scale that includes 13 questions covering symptoms related to the 4 commonest impulse control disorders in PD, other behaviors, and problematic use of medication. The number of "Yes" responses is compared to the number required for a positive result. Missing individual responses are imputed using LOCF. Each impulse control disorder, other behavior, and problematic use of medication is rated as a positive result (ie, present) or a negative result (ie, not present). Percentages are based on the total number of observations for that visit.
Source: Listing 17.2.4.16, Dataset: ADQSS, Program: t_quip.sas, Output: t_16-4-9-1-quip.rtf, Generated on: 28JUL2017 05:58
Page 21 of 64

Table 16.4.9.1 QUIP by Visit - Safety Overall Population

Assessor Parameter Visit Baseline Value	GDNF/GDNF (N=21) Postbaseline Value			Placebo/GDNF (N=20) Postbaseline Value		
	Positive n (%)	Negative n (%)	Missing n (%)	Positive n (%)	Negative n (%)	Missing n (%)
Subject						
Punding						
Week 80/e40						
Positive	2 (9.5)	0	0	0	2 (10.0)	0
Negative	1 (4.8)	17 (81.0)	0	2 (10.0)	16 (80.0)	0
Missing	0	1 (4.8)	0	0	0	0
Week e2-16						
Positive	0	0	0	0	0	0
Negative	1 (4.8)	1 (4.8)	0	0	2 (10.0)	0
Missing	0	1 (4.8)	0	0	0	0
Week e2-32						
Positive	0	0	0	0	0	0
Negative	1 (4.8)	1 (4.8)	0	0	2 (10.0)	0
Missing	0	1 (4.8)	0	0	0	0
Week e2-48						
Positive	0	0	0	0	0	0
Negative	1 (4.8)	1 (4.8)	0	0	2 (10.0)	0
Missing	0	1 (4.8)	0	0	0	0

Note: The QUIP is a self-administered or informant-completed scale that includes 13 questions covering symptoms related to the 4 commonest impulse control disorders in PD, other behaviors, and problematic use of medication. The number of "Yes" responses is compared to the number required for a positive result. Missing individual responses are imputed using LOCF. Each impulse control disorder, other behavior, and problematic use of medication is rated as a positive result (ie, present) or a negative result (ie, not present). Percentages are based on the total number of observations for that visit.
Source: Listing 17.2.4.16, Dataset: ADQSS, Program: t_quip.sas, Output: t_16-4-9-1-quip.rtf, Generated on: 28JUL2017 05:58
Page 22 of 64

Table 16.4.9.1 QUIP by Visit - Safety Overall Population

Assessor Parameter Visit Baseline Value	GDNF/GDNF (N=21) Postbaseline Value			Placebo/GDNF (N=20) Postbaseline Value		
	Positive n (%)	Negative n (%)	Missing n (%)	Positive n (%)	Negative n (%)	Missing n (%)
Subject						
Punding						
Week e2-64						
Positive	0	0	0	0	0	0
Negative	0	2 (9.5)	0	0	2 (10.0)	0
Missing	0	1 (4.8)	0	0	0	0
Week e2-80						
Positive	0	0	0	0	0	0
Negative	1 (4.8)	1 (4.8)	0	0	2 (10.0)	0
Missing	0	1 (4.8)	0	0	0	0
Week e3-16						
Positive	1 (4.8)	0	0	0	1 (5.0)	0
Negative	1 (4.8)	9 (42.9)	0	0	12 (60.0)	0
Missing	0	1 (4.8)	0	0	0	0
Week e3-32						
Positive	0	1 (4.8)	0	0	1 (5.0)	0
Negative	1 (4.8)	9 (42.9)	0	0	12 (60.0)	0
Missing	0	1 (4.8)	0	0	0	0

Note: The QUIP is a self-administered or informant-completed scale that includes 13 questions covering symptoms related to the 4 commonest impulse control disorders in PD, other behaviors, and problematic use of medication. The number of "Yes" responses is compared to the number required for a positive result. Missing individual responses are imputed using LOCF. Each impulse control disorder, other behavior, and problematic use of medication is rated as a positive result (ie, present) or a negative result (ie, not present). Percentages are based on the total number of observations for that visit.
Source: Listing 17.2.4.16, Dataset: ADQSS, Program: t_quip.sas, Output: t_16-4-9-1-quip.rtf, Generated on: 28JUL2017 05:58

Table 16.4.9.1 QUIP by Visit - Safety Overall Population

Assessor Parameter Visit Baseline Value	GDNF/GDNF (N=21) Postbaseline Value			Placebo/GDNF (N=20) Postbaseline Value		
	Positive n (%)	Negative n (%)	Missing n (%)	Positive n (%)	Negative n (%)	Missing n (%)
Subject						
Punding						
Last Study Visit in the Supplemental Extension						
Positive	0	1 (4.8)	0	1 (5.0)	0	0
Negative	1 (4.8)	9 (42.9)	0	1 (5.0)	11 (55.0)	0
Missing	0	1 (4.8)	0	0	0	0

Note: The QUIP is a self-administered or informant-completed scale that includes 13 questions covering symptoms related to the 4 commonest impulse control disorders in PD, other behaviors, and problematic use of medication. The number of "Yes" responses is compared to the number required for a positive result. Missing individual responses are imputed using LOCF. Each impulse control disorder, other behavior, and problematic use of medication is rated as a positive result (ie, present) or a negative result (ie, not present). Percentages are based on the total number of observations for that visit.
Source: Listing 17.2.4.16, Dataset: ADQSS, Program: t_quip.sas, Output: t_16-4-9-1-quip.rtf, Generated on: 28JUL2017 05:58
Page 24 of 64

Table 16.4.9.1 QUIP by Visit - Safety Overall Population

Assessor Parameter Visit Baseline Value	GDNF/GDNF (N=21) Postbaseline Value			Placebo/GDNF (N=20) Postbaseline Value		
	Positive n (%)	Negative n (%)	Missing n (%)	Positive n (%)	Negative n (%)	Missing n (%)
Subject						
Walkabout						
Week 48/e8						
Positive	0	0	0	0	0	0
Negative	0	20 (95.2)	0	0	20 (100)	0
Missing	0	1 (4.8)	0	0	0	0
Week 56/e16						
Positive	0	0	0	0	0	0
Negative	0	20 (95.2)	0	0	20 (100)	0
Missing	0	1 (4.8)	0	0	0	0
Week 64/e24						
Positive	0	0	0	0	0	0
Negative	0	20 (95.2)	0	0	20 (100)	0
Missing	0	1 (4.8)	0	0	0	0
Week 72/e32						
Positive	0	0	0	0	0	0
Negative	0	20 (95.2)	0	0	20 (100)	0
Missing	0	1 (4.8)	0	0	0	0

Note: The QUIP is a self-administered or informant-completed scale that includes 13 questions covering symptoms related to the 4 commonest impulse control disorders in PD, other behaviors, and problematic use of medication. The number of "Yes" responses is compared to the number required for a positive result. Missing individual responses are imputed using LOCF. Each impulse control disorder, other behavior, and problematic use of medication is rated as a positive result (ie, present) or a negative result (ie, not present). Percentages are based on the total number of observations for that visit.
Source: Listing 17.2.4.16, Dataset: ADQSS, Program: t_quip.sas, Output: t_16-4-9-1-quip.rtf, Generated on: 28JUL2017 05:58

Table 16.4.9.1 QUIP by Visit - Safety Overall Population

Assessor Parameter Visit Baseline Value	GDNF/GDNF (N=21)			Placebo/GDNF (N=20)		
	Postbaseline Value			Postbaseline Value		
	Positive n (%)	Negative n (%)	Missing n (%)	Positive n (%)	Negative n (%)	Missing n (%)
Subject						
Walkabout						
Week 80/e40						
Positive	0	0	0	0	0	0
Negative	0	20 (95.2)	0	0	20 (100)	0
Missing	0	1 (4.8)	0	0	0	0
Week e2-16						
Positive	0	0	0	0	0	0
Negative	0	2 (9.5)	0	0	2 (10.0)	0
Missing	1 (4.8)	0	0	0	0	0
Week e2-32						
Positive	0	0	0	0	0	0
Negative	0	2 (9.5)	0	0	2 (10.0)	0
Missing	0	1 (4.8)	0	0	0	0
Week e2-48						
Positive	0	0	0	0	0	0
Negative	0	2 (9.5)	0	0	2 (10.0)	0
Missing	0	1 (4.8)	0	0	0	0

Note: The QUIP is a self-administered or informant-completed scale that includes 13 questions covering symptoms related to the 4 commonest impulse control disorders in PD, other behaviors, and problematic use of medication. The number of "Yes" responses is compared to the number required for a positive result. Missing individual responses are imputed using LOCF. Each impulse control disorder, other behavior, and problematic use of medication is rated as a positive result (ie, present) or a negative result (ie, not present). Percentages are based on the total number of observations for that visit.
Source: Listing 17.2.4.16, Dataset: ADQSS, Program: t_quip.sas, Output: t_16-4-9-1-quip.rtf, Generated on: 28JUL2017 05:58

Table 16.4.9.1 QUIP by Visit - Safety Overall Population

Assessor Parameter Visit Baseline Value	GDNF/GDNF (N=21) Postbaseline Value			Placebo/GDNF (N=20) Postbaseline Value		
	Positive n (%)	Negative n (%)	Missing n (%)	Positive n (%)	Negative n (%)	Missing n (%)
Subject						
Walkabout						
Week e2-64						
Positive	0	0	0	0	0	0
Negative	0	2 (9.5)	0	0	2 (10.0)	0
Missing	0	1 (4.8)	0	0	0	0
Week e2-80						
Positive	0	0	0	0	0	0
Negative	0	2 (9.5)	0	0	2 (10.0)	0
Missing	0	1 (4.8)	0	0	0	0
Week e3-16						
Positive	0	0	0	0	0	0
Negative	0	11 (52.4)	0	0	13 (65.0)	0
Missing	0	1 (4.8)	0	0	0	0
Week e3-32						
Positive	0	0	0	0	0	0
Negative	0	11 (52.4)	0	0	13 (65.0)	0
Missing	0	1 (4.8)	0	0	0	0

Note: The QUIP is a self-administered or informant-completed scale that includes 13 questions covering symptoms related to the 4 commonest impulse control disorders in PD, other behaviors, and problematic use of medication. The number of "Yes" responses is compared to the number required for a positive result. Missing individual responses are imputed using LOCF. Each impulse control disorder, other behavior, and problematic use of medication is rated as a positive result (ie, present) or a negative result (ie, not present). Percentages are based on the total number of observations for that visit.
Source: Listing 17.2.4.16, Dataset: ADQSS, Program: t_quip.sas, Output: t_16-4-9-1-quip.rtf, Generated on: 28JUL2017 05:58

Table 16.4.9.1 QUIP by Visit - Safety Overall Population

Assessor Parameter Visit Baseline Value	GDNF/GDNF (N=21)			Placebo/GDNF (N=20)		
	Postbaseline Value			Postbaseline Value		
	Positive n (%)	Negative n (%)	Missing n (%)	Positive n (%)	Negative n (%)	Missing n (%)
Subject						
Walkabout						
Last Study Visit in the Supplemental Extension						
Positive	0	0	0	0	0	0
Negative	0	11 (52.4)	0	0	13 (65.0)	0
Missing	0	1 (4.8)	0	0	0	0

Note: The QUIP is a self-administered or informant-completed scale that includes 13 questions covering symptoms related to the 4 commonest impulse control disorders in PD, other behaviors, and problematic use of medication. The number of "Yes" responses is compared to the number required for a positive result. Missing individual responses are imputed using LOCF. Each impulse control disorder, other behavior, and problematic use of medication is rated as a positive result (ie, present) or a negative result (ie, not present). Percentages are based on the total number of observations for that visit.
Source: Listing 17.2.4.16, Dataset: ADQSS, Program: t_quip.sas, Output: t_16-4-9-1-quip.rtf, Generated on: 28JUL2017 05:58

Table 16.4.9.1 QUIP by Visit - Safety Overall Population

Assessor Parameter Visit Baseline Value	GDNF/GDNF (N=21) Postbaseline Value			Placebo/GDNF (N=20) Postbaseline Value		
	Positive n (%)	Negative n (%)	Missing n (%)	Positive n (%)	Negative n (%)	Missing n (%)
Subject						
Medication Use						
Week 48/e8						
Positive	0	0	0	0	0	0
Negative	0	20 (95.2)	0	0	20 (100)	0
Missing	0	1 (4.8)	0	0	0	0
Week 56/e16						
Positive	0	0	0	0	0	0
Negative	0	20 (95.2)	0	0	20 (100)	0
Missing	0	1 (4.8)	0	0	0	0
Week 64/e24						
Positive	0	0	0	0	0	0
Negative	0	20 (95.2)	0	0	20 (100)	0
Missing	0	1 (4.8)	0	0	0	0
Week 72/e32						
Positive	0	0	0	0	0	0
Negative	0	20 (95.2)	0	0	20 (100)	0
Missing	0	1 (4.8)	0	0	0	0

Note: The QUIP is a self-administered or informant-completed scale that includes 13 questions covering symptoms related to the 4 commonest impulse control disorders in PD, other behaviors, and problematic use of medication. The number of "Yes" responses is compared to the number required for a positive result. Missing individual responses are imputed using LOCF. Each impulse control disorder, other behavior, and problematic use of medication is rated as a positive result (ie, present) or a negative result (ie, not present). Percentages are based on the total number of observations for that visit.
Source: Listing 17.2.4.16, Dataset: ADQSS, Program: t_quip.sas, Output: t_16-4-9-1-quip.rtf, Generated on: 28JUL2017 05:58
Page 29 of 64

Table 16.4.9.1 QUIP by Visit - Safety Overall Population

Assessor Parameter Visit Baseline Value	GDNF/GDNF (N=21) Postbaseline Value			Placebo/GDNF (N=20) Postbaseline Value		
	Positive n (%)	Negative n (%)	Missing n (%)	Positive n (%)	Negative n (%)	Missing n (%)
Subject Medication Use						
Week 80/e40						
Positive	0	0	0	0	0	0
Negative	0	20 (95.2)	0	0	20 (100)	0
Missing	0	1 (4.8)	0	0	0	0
Week e2-16						
Positive	0	0	0	0	0	0
Negative	0	2 (9.5)	0	0	2 (10.0)	0
Missing	0	1 (4.8)	0	0	0	0
Week e2-32						
Positive	0	0	0	0	0	0
Negative	0	2 (9.5)	0	0	2 (10.0)	0
Missing	0	1 (4.8)	0	0	0	0
Week e2-48						
Positive	0	0	0	0	0	0
Negative	0	2 (9.5)	0	0	2 (10.0)	0
Missing	0	1 (4.8)	0	0	0	0

Note: The QUIP is a self-administered or informant-completed scale that includes 13 questions covering symptoms related to the 4 commonest impulse control disorders in PD, other behaviors, and problematic use of medication. The number of "Yes" responses is compared to the number required for a positive result. Missing individual responses are imputed using LOCF. Each impulse control disorder, other behavior, and problematic use of medication is rated as a positive result (ie, present) or a negative result (ie, not present). Percentages are based on the total number of observations for that visit.
Source: Listing 17.2.4.16, Dataset: ADQSS, Program: t_quip.sas, Output: t_16-4-9-1-quip.rtf, Generated on: 28JUL2017 05:58
Page 30 of 64

Table 16.4.9.1 QUIP by Visit - Safety Overall Population

Assessor Parameter Visit Baseline Value	GDNF/GDNF (N=21)			Placebo/GDNF (N=20)		
	Postbaseline Value			Postbaseline Value		
	Positive n (%)	Negative n (%)	Missing n (%)	Positive n (%)	Negative n (%)	Missing n (%)

Subject
  Medication Use
    Week e2-64						

Positive	0	0	0	0	0	0
Negative	0	2 (9.5)	0	0	2 (10.0)	0
Missing	0	1 (4.8)	0	0	0	0
Week e2-80						
Positive	0	0	0	0	0	0
Negative	0	2 (9.5)	0	0	2 (10.0)	0
Missing	0	1 (4.8)	0	0	0	0
Week e3-16						
Positive	0	0	0	0	0	0
Negative	0	11 (52.4)	0	0	13 (65.0)	0
Missing	0	1 (4.8)	0	0	0	0
Week e3-32						
Positive	0	0	0	0	0	0
Negative	0	11 (52.4)	0	0	13 (65.0)	0
Missing	0	1 (4.8)	0	0	0	0

Note: The QUIP is a self-administered or informant-completed scale that includes 13 questions covering symptoms related to the 4 commonest impulse control disorders in PD, other behaviors, and problematic use of medication. The number of "Yes" responses is compared to the number required for a positive result. Missing individual responses are imputed using LOCF. Each impulse control disorder, other behavior, and problematic use of medication is rated as a positive result (ie, present) or a negative result (ie, not present). Percentages are based on the total number of observations for that visit.
Source: Listing 17.2.4.16, Dataset: ADQSS, Program: t_quip.sas, Output: t_16-4-9-1-quip.rtf, Generated on: 28JUL2017 05:58
Page 31 of 64

Table 16.4.9.1 QUIP by Visit - Safety Overall Population

Assessor Parameter Visit Baseline Value	GDNF/GDNF (N=21) Postbaseline Value			Placebo/GDNF (N=20) Postbaseline Value		
	Positive n (%)	Negative n (%)	Missing n (%)	Positive n (%)	Negative n (%)	Missing n (%)
Subject						
Medication Use						
Last Study Visit in the Supplemental Extension						
Positive	0	0	0	0	0	0
Negative	0	11 (52.4)	0	0	13 (65.0)	0
Missing	0	1 (4.8)	0	0	0	0

Note: The QUIP is a self-administered or informant-completed scale that includes 13 questions covering symptoms related to the 4 commonest impulse control disorders in PD, other behaviors, and problematic use of medication. The number of "Yes" responses is compared to the number required for a positive result. Missing individual responses are imputed using LOCF. Each impulse control disorder, other behavior, and problematic use of medication is rated as a positive result (ie, present) or a negative result (ie, not present). Percentages are based on the total number of observations for that visit.
Source: Listing 17.2.4.16, Dataset: ADQSS, Program: t_quip.sas, Output: t_16-4-9-1-quip.rtf, Generated on: 28JUL2017 05:58

Table 16.4.9.1 QUIP by Visit - Safety Overall Population

Assessor Parameter Visit Baseline Value	GDNF/GDNF (N=21) Postbaseline Value			Placebo/GDNF (N=20) Postbaseline Value		
	Positive n (%)	Negative n (%)	Missing n (%)	Positive n (%)	Negative n (%)	Missing n (%)
Informant						
Compulsive Gambling						
Week 48/e8						
Positive	0	0	0	0	0	0
Negative	0	0	0	0	2 (10.0)	0
Missing	0	1 (4.8)	20 (95.2)	0	1 (5.0)	17 (85.0)
Week 56/e16						
Positive	0	0	0	0	0	0
Negative	0	0	0	0	2 (10.0)	0
Missing	0	1 (4.8)	20 (95.2)	0	1 (5.0)	17 (85.0)
Week 64/e24						
Positive	0	0	0	0	0	0
Negative	0	0	0	0	4 (20.0)	0
Missing	0	3 (14.3)	18 (85.7)	0	1 (5.0)	15 (75.0)
Week 72/e32						
Positive	0	0	0	0	0	0
Negative	0	0	0	0	4 (20.0)	0
Missing	0	4 (19.0)	17 (81.0)	0	2 (10.0)	14 (70.0)

Note: The QUIP is a self-administered or informant-completed scale that includes 13 questions covering symptoms related to the 4 commonest impulse control disorders in PD, other behaviors, and problematic use of medication. The number of "Yes" responses is compared to the number required for a positive result. Missing individual responses are imputed using LOCF. Each impulse control disorder, other behavior, and problematic use of medication is rated as a positive result (ie, present) or a negative result (ie, not present). Percentages are based on the total number of observations for that visit.
Source: Listing 17.2.4.16, Dataset: ADQSS, Program: t_quip.sas, Output: t_16-4-9-1-quip.rtf, Generated on: 28JUL2017 05:58

Table 16.4.9.1 QUIP by Visit - Safety Overall Population

Assessor Parameter Visit Baseline Value	GDNF/GDNF (N=21) Postbaseline Value			Placebo/GDNF (N=20) Postbaseline Value		
	Positive n (%)	Negative n (%)	Missing n (%)	Positive n (%)	Negative n (%)	Missing n (%)
Informant						
Compulsive Gambling						
Week 80/e40						
Positive	0	0	0	0	0	0
Negative	0	0	0	0	4 (20.0)	0
Missing	0	6 (28.6)	15 (71.4)	0	2 (10.0)	14 (70.0)
Week e2-16						
Positive	0	0	0	0	0	0
Negative	0	0	0	0	0	0
Missing	0	0	3 (14.3)	0	0	2 (10.0)
Week e2-32						
Positive	0	0	0	0	0	0
Negative	0	0	0	0	0	0
Missing	0	0	3 (14.3)	0	0	2 (10.0)
Week e2-48						
Positive	0	0	0	0	0	0
Negative	0	0	0	0	0	0
Missing	0	0	3 (14.3)	0	0	2 (10.0)

Note: The QUIP is a self-administered or informant-completed scale that includes 13 questions covering symptoms related to the 4 commonest impulse control disorders in PD, other behaviors, and problematic use of medication. The number of "Yes" responses is compared to the number required for a positive result. Missing individual responses are imputed using LOCF. Each impulse control disorder, other behavior, and problematic use of medication is rated as a positive result (ie, present) or a negative result (ie, not present). Percentages are based on the total number of observations for that visit.
Source: Listing 17.2.4.16, Dataset: ADQSS, Program: t_quip.sas, Output: t_16-4-9-1-quip.rtf, Generated on: 28JUL2017 05:58

Table 16.4.9.1 QUIP by Visit - Safety Overall Population

Assessor Parameter Visit Baseline Value	GDNF/GDNF (N=21) Postbaseline Value			Placebo/GDNF (N=20) Postbaseline Value		
	Positive n (%)	Negative n (%)	Missing n (%)	Positive n (%)	Negative n (%)	Missing n (%)
Informant						
Compulsive Gambling						
Week e2-64						
Positive	0	0	0	0	0	0
Negative	0	0	0	0	0	0
Missing	0	0	3 (14.3)	0	0	2 (10.0)
Week e2-80						
Positive	0	0	0	0	0	0
Negative	0	0	0	0	0	0
Missing	0	0	3 (14.3)	0	0	2 (10.0)
Week e3-16						
Positive	0	0	0	0	0	0
Negative	0	0	0	0	3 (15.0)	0
Missing	0	1 (4.8)	11 (52.4)	0	2 (10.0)	8 (40.0)
Week e3-32						
Positive	0	0	0	0	0	0
Negative	0	0	0	0	3 (15.0)	0
Missing	0	1 (4.8)	11 (52.4)	0	2 (10.0)	8 (40.0)

Note: The QUIP is a self-administered or informant-completed scale that includes 13 questions covering symptoms related to the 4 commonest impulse control disorders in PD, other behaviors, and problematic use of medication. The number of "Yes" responses is compared to the number required for a positive result. Missing individual responses are imputed using LOCF. Each impulse control disorder, other behavior, and problematic use of medication is rated as a positive result (ie, present) or a negative result (ie, not present). Percentages are based on the total number of observations for that visit.
Source: Listing 17.2.4.16, Dataset: ADQSS, Program: t_quip.sas, Output: t_16-4-9-1-quip.rtf, Generated on: 28JUL2017 05:58
Page 35 of 64

Table 16.4.9.1 QUIP by Visit - Safety Overall Population

Assessor Parameter Visit Baseline Value	GDNF/GDNF (N=21) Postbaseline Value			Placebo/GDNF (N=20) Postbaseline Value		
	Positive n (%)	Negative n (%)	Missing n (%)	Positive n (%)	Negative n (%)	Missing n (%)
Informant						
Compulsive Gambling						
Last Study Visit in the Supplemental Extension						
Positive	0	0	0	0	0	0
Negative	0	0	0	0	3 (15.0)	0
Missing	0	1 (4.8)	11 (52.4)	0	2 (10.0)	8 (40.0)

Note: The QUIP is a self-administered or informant-completed scale that includes 13 questions covering symptoms related to the 4 commonest impulse control disorders in PD, other behaviors, and problematic use of medication. The number of "Yes" responses is compared to the number required for a positive result. Missing individual responses are imputed using LOCF. Each impulse control disorder, other behavior, and problematic use of medication is rated as a positive result (ie, present) or a negative result (ie, not present). Percentages are based on the total number of observations for that visit.
Source: Listing 17.2.4.16, Dataset: ADQSS, Program: t_quip.sas, Output: t_16-4-9-1-quip.rtf, Generated on: 28JUL2017 05:58
Page 36 of 64

Table 16.4.9.1 QUIP by Visit - Safety Overall Population

Assessor Parameter Visit Baseline Value	GDNF/GDNF (N=21)			Placebo/GDNF (N=20)		
	Postbaseline Value			Postbaseline Value		
	Positive n (%)	Negative n (%)	Missing n (%)	Positive n (%)	Negative n (%)	Missing n (%)
Informant						
Compulsive Sexual Behaviour						
Week 48/e8						
Positive	0	0	0	1 (5.0)	0	0
Negative	0	0	0	0	1 (5.0)	0
Missing	0	1 (4.8)	20 (95.2)	1 (5.0)	0	17 (85.0)
Week 56/e16						
Positive	0	0	0	0	1 (5.0)	0
Negative	0	0	0	0	1 (5.0)	0
Missing	0	1 (4.8)	20 (95.2)	1 (5.0)	0	17 (85.0)
Week 64/e24						
Positive	0	0	0	0	1 (5.0)	0
Negative	0	0	0	0	3 (15.0)	0
Missing	0	3 (14.3)	18 (85.7)	1 (5.0)	0	15 (75.0)
Week 72/e32						
Positive	0	0	0	1 (5.0)	0	0
Negative	0	0	0	0	3 (15.0)	0
Missing	0	4 (19.0)	17 (81.0)	1 (5.0)	1 (5.0)	14 (70.0)

Note: The QUIP is a self-administered or informant-completed scale that includes 13 questions covering symptoms related to the 4 commonest impulse control disorders in PD, other behaviors, and problematic use of medication. The number of "Yes" responses is compared to the number required for a positive result. Missing individual responses are imputed using LOCF. Each impulse control disorder, other behavior, and problematic use of medication is rated as a positive result (ie, present) or a negative result (ie, not present). Percentages are based on the total number of observations for that visit.
Source: Listing 17.2.4.16, Dataset: ADQSS, Program: t_quip.sas, Output: t_16-4-9-1-quip.rtf, Generated on: 28JUL2017 05:58
Page 37 of 64

Table 16.4.9.1 QUIP by Visit - Safety Overall Population

Assessor Parameter Visit Baseline Value	GDNF/GDNF (N=21) Postbaseline Value			Placebo/GDNF (N=20) Postbaseline Value		
	Positive n (%)	Negative n (%)	Missing n (%)	Positive n (%)	Negative n (%)	Missing n (%)
Informant						
Compulsive Sexual Behaviour						
Week 80/e40						
Positive	0	0	0	0	1 (5.0)	0
Negative	0	0	0	0	3 (15.0)	0
Missing	0	6 (28.6)	15 (71.4)	1 (5.0)	1 (5.0)	14 (70.0)
Week e2-16						
Positive	0	0	0	0	0	0
Negative	0	0	0	0	0	0
Missing	0	0	3 (14.3)	0	0	2 (10.0)
Week e2-32						
Positive	0	0	0	0	0	0
Negative	0	0	0	0	0	0
Missing	0	0	3 (14.3)	0	0	2 (10.0)
Week e2-48						
Positive	0	0	0	0	0	0
Negative	0	0	0	0	0	0
Missing	0	0	3 (14.3)	0	0	2 (10.0)

Note: The QUIP is a self-administered or informant-completed scale that includes 13 questions covering symptoms related to the 4 commonest impulse control disorders in PD, other behaviors, and problematic use of medication. The number of "Yes" responses is compared to the number required for a positive result. Missing individual responses are imputed using LOCF. Each impulse control disorder, other behavior, and problematic use of medication is rated as a positive result (ie, present) or a negative result (ie, not present). Percentages are based on the total number of observations for that visit.
Source: Listing 17.2.4.16, Dataset: ADQSS, Program: t_quip.sas, Output: t_16-4-9-1-quip.rtf, Generated on: 28JUL2017 05:58
Page 38 of 64

Table 16.4.9.1 QUIP by Visit - Safety Overall Population

Assessor Parameter Visit Baseline Value	GDNF/GDNF (N=21) Postbaseline Value			Placebo/GDNF (N=20) Postbaseline Value		
	Positive n (%)	Negative n (%)	Missing n (%)	Positive n (%)	Negative n (%)	Missing n (%)
Informant						
Compulsive Sexual Behaviour						
Week e2-64						
Positive	0	0	0	0	0	0
Negative	0	0	0	0	0	0
Missing	0	0	3 (14.3)	0	0	2 (10.0)
Week e2-80						
Positive	0	0	0	0	0	0
Negative	0	0	0	0	0	0
Missing	0	0	3 (14.3)	0	0	2 (10.0)
Week e3-16						
Positive	0	0	0	0	1 (5.0)	0
Negative	0	0	0	0	2 (10.0)	0
Missing	0	1 (4.8)	11 (52.4)	1 (5.0)	1 (5.0)	8 (40.0)
Week e3-32						
Positive	0	0	0	0	1 (5.0)	0
Negative	0	0	0	0	2 (10.0)	0
Missing	0	1 (4.8)	11 (52.4)	1 (5.0)	1 (5.0)	8 (40.0)

Note: The QUIP is a self-administered or informant-completed scale that includes 13 questions covering symptoms related to the 4 commonest impulse control disorders in PD, other behaviors, and problematic use of medication. The number of "Yes" responses is compared to the number required for a positive result. Missing individual responses are imputed using LOCF. Each impulse control disorder, other behavior, and problematic use of medication is rated as a positive result (ie, present) or a negative result (ie, not present). Percentages are based on the total number of observations for that visit.
Source: Listing 17.2.4.16, Dataset: ADQSS, Program: t_quip.sas, Output: t_16-4-9-1-quip.rtf, Generated on: 28JUL2017 05:58
Page 39 of 64

Table 16.4.9.1 QUIP by Visit - Safety Overall Population

Assessor Parameter Visit Baseline Value	GDNF/GDNF (N=21) Postbaseline Value			Placebo/GDNF (N=20) Postbaseline Value		
	Positive n (%)	Negative n (%)	Missing n (%)	Positive n (%)	Negative n (%)	Missing n (%)
Informant						
Compulsive Sexual Behaviour						
Last Study Visit in the Supplemental Extension						
Positive	0	0	0	0	1 (5.0)	0
Negative	0	0	0	0	2 (10.0)	0
Missing	0	1 (4.8)	11 (52.4)	1 (5.0)	1 (5.0)	8 (40.0)

Note: The QUIP is a self-administered or informant-completed scale that includes 13 questions covering symptoms related to the 4 commonest impulse control disorders in PD, other behaviors, and problematic use of medication. The number of "Yes" responses is compared to the number required for a positive result. Missing individual responses are imputed using LOCF. Each impulse control disorder, other behavior, and problematic use of medication is rated as a positive result (ie, present) or a negative result (ie, not present). Percentages are based on the total number of observations for that visit.
Source: Listing 17.2.4.16, Dataset: ADQSS, Program: t_quip.sas, Output: t_16-4-9-1-quip.rtf, Generated on: 28JUL2017 05:58
Page 40 of 64

Table 16.4.9.1 QUIP by Visit - Safety Overall Population

Assessor Parameter Visit Baseline Value	GDNF/GDNF (N=21)			Placebo/GDNF (N=20)		
	Postbaseline Value			Postbaseline Value		
	Positive n (%)	Negative n (%)	Missing n (%)	Positive n (%)	Negative n (%)	Missing n (%)
Informant						
Compulsive Buying						
Week 48/e8						
Positive	0	0	0	0	0	0
Negative	0	0	0	0	2 (10.0)	0
Missing	0	1 (4.8)	20 (95.2)	0	1 (5.0)	17 (85.0)
Week 56/e16						
Positive	0	0	0	0	0	0
Negative	0	0	0	1 (5.0)	1 (5.0)	0
Missing	0	1 (4.8)	20 (95.2)	0	1 (5.0)	17 (85.0)
Week 64/e24						
Positive	0	0	0	0	0	0
Negative	0	0	0	1 (5.0)	3 (15.0)	0
Missing	0	3 (14.3)	18 (85.7)	0	1 (5.0)	15 (75.0)
Week 72/e32						
Positive	0	0	0	0	0	0
Negative	0	0	0	0	4 (20.0)	0
Missing	0	4 (19.0)	17 (81.0)	0	2 (10.0)	14 (70.0)

Note: The QUIP is a self-administered or informant-completed scale that includes 13 questions covering symptoms related to the 4 commonest impulse control disorders in PD, other behaviors, and problematic use of medication. The number of "Yes" responses is compared to the number required for a positive result. Missing individual responses are imputed using LOCF. Each impulse control disorder, other behavior, and problematic use of medication is rated as a positive result (ie, present) or a negative result (ie, not present). Percentages are based on the total number of observations for that visit.
Source: Listing 17.2.4.16, Dataset: ADQSS, Program: t_quip.sas, Output: t_16-4-9-1-quip.rtf, Generated on: 28JUL2017 05:58
Page 41 of 64

Table 16.4.9.1 QUIP by Visit - Safety Overall Population

Assessor Parameter Visit Baseline Value	GDNF/GDNF (N=21) Postbaseline Value			Placebo/GDNF (N=20) Postbaseline Value		
	Positive n (%)	Negative n (%)	Missing n (%)	Positive n (%)	Negative n (%)	Missing n (%)
Informant						
Compulsive Buying						
Week 80/e40						
Positive	0	0	0	0	0	0
Negative	0	0	0	1 (5.0)	3 (15.0)	0
Missing	0	6 (28.6)	15 (71.4)	0	2 (10.0)	14 (70.0)
Week e2-16						
Positive	0	0	0	0	0	0
Negative	0	0	0	0	0	0
Missing	0	0	3 (14.3)	0	0	2 (10.0)
Week e2-32						
Positive	0	0	0	0	0	0
Negative	0	0	0	0	0	0
Missing	0	0	3 (14.3)	0	0	2 (10.0)
Week e2-48						
Positive	0	0	0	0	0	0
Negative	0	0	0	0	0	0
Missing	0	0	3 (14.3)	0	0	2 (10.0)

Note: The QUIP is a self-administered or informant-completed scale that includes 13 questions covering symptoms related to the 4 commonest impulse control disorders in PD, other behaviors, and problematic use of medication. The number of "Yes" responses is compared to the number required for a positive result. Missing individual responses are imputed using LOCF. Each impulse control disorder, other behavior, and problematic use of medication is rated as a positive result (ie, present) or a negative result (ie, not present). Percentages are based on the total number of observations for that visit.
Source: Listing 17.2.4.16, Dataset: ADQSS, Program: t_quip.sas, Output: t_16-4-9-1-quip.rtf, Generated on: 28JUL2017 05:58

Table 16.4.9.1 QUIP by Visit - Safety Overall Population

Assessor Parameter Visit Baseline Value	GDNF/GDNF (N=21) Postbaseline Value			Placebo/GDNF (N=20) Postbaseline Value		
	Positive n (%)	Negative n (%)	Missing n (%)	Positive n (%)	Negative n (%)	Missing n (%)
Informant						
Compulsive Buying						
Week e2-64						
Positive	0	0	0	0	0	0
Negative	0	0	0	0	0	0
Missing	0	0	3 (14.3)	0	0	2 (10.0)
Week e2-80						
Positive	0	0	0	0	0	0
Negative	0	0	0	0	0	0
Missing	0	0	3 (14.3)	0	0	2 (10.0)
Week e3-16						
Positive	0	0	0	0	0	0
Negative	0	0	0	1 (5.0)	2 (10.0)	0
Missing	0	1 (4.8)	11 (52.4)	0	2 (10.0)	8 (40.0)
Week e3-32						
Positive	0	0	0	0	0	0
Negative	0	0	0	1 (5.0)	2 (10.0)	0
Missing	0	1 (4.8)	11 (52.4)	0	2 (10.0)	8 (40.0)

Note: The QUIP is a self-administered or informant-completed scale that includes 13 questions covering symptoms related to the 4 commonest impulse control disorders in PD, other behaviors, and problematic use of medication. The number of "Yes" responses is compared to the number required for a positive result. Missing individual responses are imputed using LOCF. Each impulse control disorder, other behavior, and problematic use of medication is rated as a positive result (ie, present) or a negative result (ie, not present). Percentages are based on the total number of observations for that visit.
Source: Listing 17.2.4.16, Dataset: ADQSS, Program: t_quip.sas, Output: t_16-4-9-1-quip.rtf, Generated on: 28JUL2017 05:58
Page 43 of 64

Table 16.4.9.1 QUIP by Visit - Safety Overall Population

Assessor Parameter Visit Baseline Value	GDNF/GDNF (N=21) Postbaseline Value			Placebo/GDNF (N=20) Postbaseline Value		
	Positive n (%)	Negative n (%)	Missing n (%)	Positive n (%)	Negative n (%)	Missing n (%)
Informant						
Compulsive Buying						
Last Study Visit in the Supplemental Extension						
Positive	0	0	0	0	0	0
Negative	0	0	0	1 (5.0)	2 (10.0)	0
Missing	0	1 (4.8)	11 (52.4)	0	2 (10.0)	8 (40.0)

Note: The QUIP is a self-administered or informant-completed scale that includes 13 questions covering symptoms related to the 4 commonest impulse control disorders in PD, other behaviors, and problematic use of medication. The number of "Yes" responses is compared to the number required for a positive result. Missing individual responses are imputed using LOCF. Each impulse control disorder, other behavior, and problematic use of medication is rated as a positive result (ie, present) or a negative result (ie, not present). Percentages are based on the total number of observations for that visit.
Source: Listing 17.2.4.16, Dataset: ADQSS, Program: t_quip.sas, Output: t_16-4-9-1-quip.rtf, Generated on: 28JUL2017 05:58
Page 44 of 64

Table 16.4.9.1 QUIP by Visit - Safety Overall Population

Assessor Parameter Visit Baseline Value	GDNF/GDNF (N=21)			Placebo/GDNF (N=20)		
	Postbaseline Value			Postbaseline Value		
	Positive n (%)	Negative n (%)	Missing n (%)	Positive n (%)	Negative n (%)	Missing n (%)
Informant						
Compulsive Eating						
Week 48/e8						
Positive	0	0	0	1 (5.0)	0	0
Negative	0	0	0	0	1 (5.0)	0
Missing	0	1 (4.8)	20 (95.2)	0	1 (5.0)	17 (85.0)
Week 56/e16						
Positive	0	0	0	1 (5.0)	0	0
Negative	0	0	0	0	1 (5.0)	0
Missing	0	1 (4.8)	20 (95.2)	0	1 (5.0)	17 (85.0)
Week 64/e24						
Positive	0	0	0	1 (5.0)	0	0
Negative	0	0	0	0	3 (15.0)	0
Missing	0	3 (14.3)	18 (85.7)	0	1 (5.0)	15 (75.0)
Week 72/e32						
Positive	0	0	0	0	1 (5.0)	0
Negative	0	0	0	0	3 (15.0)	0
Missing	0	4 (19.0)	17 (81.0)	0	2 (10.0)	14 (70.0)

Note: The QUIP is a self-administered or informant-completed scale that includes 13 questions covering symptoms related to the 4 commonest impulse control disorders in PD, other behaviors, and problematic use of medication. The number of "Yes" responses is compared to the number required for a positive result. Missing individual responses are imputed using LOCF. Each impulse control disorder, other behavior, and problematic use of medication is rated as a positive result (ie, present) or a negative result (ie, not present). Percentages are based on the total number of observations for that visit.
Source: Listing 17.2.4.16, Dataset: ADQSS, Program: t_quip.sas, Output: t_16-4-9-1-quip.rtf, Generated on: 28JUL2017 05:58
Page 45 of 64

Table 16.4.9.1 QUIP by Visit - Safety Overall Population

Assessor Parameter Visit Baseline Value	GDNF/GDNF (N=21) Postbaseline Value			Placebo/GDNF (N=20) Postbaseline Value		
	Positive n (%)	Negative n (%)	Missing n (%)	Positive n (%)	Negative n (%)	Missing n (%)
Informant						
Compulsive Eating						
Week 80/e40						
Positive	0	0	0	0	1 (5.0)	0
Negative	0	0	0	0	3 (15.0)	0
Missing	0	6 (28.6)	15 (71.4)	0	2 (10.0)	14 (70.0)
Week e2-16						
Positive	0	0	0	0	0	0
Negative	0	0	0	0	0	0
Missing	0	0	3 (14.3)	0	0	2 (10.0)
Week e2-32						
Positive	0	0	0	0	0	0
Negative	0	0	0	0	0	0
Missing	0	0	3 (14.3)	0	0	2 (10.0)
Week e2-48						
Positive	0	0	0	0	0	0
Negative	0	0	0	0	0	0
Missing	0	0	3 (14.3)	0	0	2 (10.0)

Note: The QUIP is a self-administered or informant-completed scale that includes 13 questions covering symptoms related to the 4 commonest impulse control disorders in PD, other behaviors, and problematic use of medication. The number of "Yes" responses is compared to the number required for a positive result. Missing individual responses are imputed using LOCF. Each impulse control disorder, other behavior, and problematic use of medication is rated as a positive result (ie, present) or a negative result (ie, not present). Percentages are based on the total number of observations for that visit.
Source: Listing 17.2.4.16, Dataset: ADQSS, Program: t_quip.sas, Output: t_16-4-9-1-quip.rtf, Generated on: 28JUL2017 05:58

Table 16.4.9.1 QUIP by Visit - Safety Overall Population

Assessor Parameter Visit Baseline Value	GDNF/GDNF (N=21) Postbaseline Value			Placebo/GDNF (N=20) Postbaseline Value		
	Positive n (%)	Negative n (%)	Missing n (%)	Positive n (%)	Negative n (%)	Missing n (%)
Informant						
Compulsive Eating						
Week e2-64						
Positive	0	0	0	0	0	0
Negative	0	0	0	0	0	0
Missing	0	0	3 (14.3)	0	0	2 (10.0)
Week e2-80						
Positive	0	0	0	0	0	0
Negative	0	0	0	0	0	0
Missing	0	0	3 (14.3)	0	0	2 (10.0)
Week e3-16						
Positive	0	0	0	0	1 (5.0)	0
Negative	0	0	0	0	2 (10.0)	0
Missing	0	1 (4.8)	11 (52.4)	0	2 (10.0)	8 (40.0)
Week e3-32						
Positive	0	0	0	0	1 (5.0)	0
Negative	0	0	0	0	2 (10.0)	0
Missing	0	1 (4.8)	11 (52.4)	0	2 (10.0)	8 (40.0)

Note: The QUIP is a self-administered or informant-completed scale that includes 13 questions covering symptoms related to the 4 commonest impulse control disorders in PD, other behaviors, and problematic use of medication. The number of "Yes" responses is compared to the number required for a positive result. Missing individual responses are imputed using LOCF. Each impulse control disorder, other behavior, and problematic use of medication is rated as a positive result (ie, present) or a negative result (ie, not present). Percentages are based on the total number of observations for that visit.
Source: Listing 17.2.4.16, Dataset: ADQSS, Program: t_quip.sas, Output: t_16-4-9-1-quip.rtf, Generated on: 28JUL2017 05:58
Page 47 of 64

Table 16.4.9.1 QUIP by Visit - Safety Overall Population

Assessor Parameter Visit Baseline Value	GDNF/GDNF (N=21) Postbaseline Value			Placebo/GDNF (N=20) Postbaseline Value		
	Positive n (%)	Negative n (%)	Missing n (%)	Positive n (%)	Negative n (%)	Missing n (%)
Informant						
Compulsive Eating						
Last Study Visit in the Supplemental Extension						
Positive	0	0	0	0	1 (5.0)	0
Negative	0	0	0	0	2 (10.0)	0
Missing	0	1 (4.8)	11 (52.4)	0	2 (10.0)	8 (40.0)

Note: The QUIP is a self-administered or informant-completed scale that includes 13 questions covering symptoms related to the 4 commonest impulse control disorders in PD, other behaviors, and problematic use of medication. The number of "Yes" responses is compared to the number required for a positive result. Missing individual responses are imputed using LOCF. Each impulse control disorder, other behavior, and problematic use of medication is rated as a positive result (ie, present) or a negative result (ie, not present). Percentages are based on the total number of observations for that visit.
Source: Listing 17.2.4.16, Dataset: ADQSS, Program: t_quip.sas, Output: t_16-4-9-1-quip.rtf, Generated on: 28JUL2017 05:58

Table 16.4.9.1 QUIP by Visit - Safety Overall Population

Assessor Parameter Visit Baseline Value	GDNF/GDNF (N=21) Postbaseline Value			Placebo/GDNF (N=20) Postbaseline Value		
	Positive n (%)	Negative n (%)	Missing n (%)	Positive n (%)	Negative n (%)	Missing n (%)
Informant						
Hobbyism						
Week 48/e8						
Positive	0	0	0	0	0	0
Negative	0	0	0	1 (5.0)	1 (5.0)	0
Missing	0	1 (4.8)	20 (95.2)	0	1 (5.0)	17 (85.0)
Week 56/e16						
Positive	0	0	0	0	0	0
Negative	0	0	0	1 (5.0)	1 (5.0)	0
Missing	0	1 (4.8)	20 (95.2)	0	1 (5.0)	17 (85.0)
Week 64/e24						
Positive	0	0	0	1 (5.0)	0	0
Negative	0	0	0	1 (5.0)	2 (10.0)	0
Missing	0	3 (14.3)	18 (85.7)	0	1 (5.0)	15 (75.0)
Week 72/e32						
Positive	0	0	0	1 (5.0)	0	0
Negative	0	0	0	1 (5.0)	2 (10.0)	0
Missing	1 (4.8)	3 (14.3)	17 (81.0)	0	2 (10.0)	14 (70.0)

Note: The QUIP is a self-administered or informant-completed scale that includes 13 questions covering symptoms related to the 4 commonest impulse control disorders in PD, other behaviors, and problematic use of medication. The number of "Yes" responses is compared to the number required for a positive result. Missing individual responses are imputed using LOCF. Each impulse control disorder, other behavior, and problematic use of medication is rated as a positive result (ie, present) or a negative result (ie, not present). Percentages are based on the total number of observations for that visit.
Source: Listing 17.2.4.16, Dataset: ADQSS, Program: t_quip.sas, Output: t_16-4-9-1-quip.rtf, Generated on: 28JUL2017 05:58
Page 49 of 64

Table 16.4.9.1 QUIP by Visit - Safety Overall Population

Assessor Parameter Visit Baseline Value	GDNF/GDNF (N=21) Postbaseline Value			Placebo/GDNF (N=20) Postbaseline Value		
	Positive n (%)	Negative n (%)	Missing n (%)	Positive n (%)	Negative n (%)	Missing n (%)
Informant						
Hobbyism						
Week 80/e40						
Positive	0	0	0	1 (5.0)	0	0
Negative	0	0	0	1 (5.0)	2 (10.0)	0
Missing	2 (9.5)	4 (19.0)	15 (71.4)	0	2 (10.0)	14 (70.0)
Week e2-16						
Positive	0	0	0	0	0	0
Negative	0	0	0	0	0	0
Missing	0	0	3 (14.3)	0	0	2 (10.0)
Week e2-32						
Positive	0	0	0	0	0	0
Negative	0	0	0	0	0	0
Missing	0	0	3 (14.3)	0	0	2 (10.0)
Week e2-48						
Positive	0	0	0	0	0	0
Negative	0	0	0	0	0	0
Missing	0	0	3 (14.3)	0	0	2 (10.0)

Note: The QUIP is a self-administered or informant-completed scale that includes 13 questions covering symptoms related to the 4 commonest impulse control disorders in PD, other behaviors, and problematic use of medication. The number of "Yes" responses is compared to the number required for a positive result. Missing individual responses are imputed using LOCF. Each impulse control disorder, other behavior, and problematic use of medication is rated as a positive result (ie, present) or a negative result (ie, not present). Percentages are based on the total number of observations for that visit.
Source: Listing 17.2.4.16, Dataset: ADQSS, Program: t_quip.sas, Output: t_16-4-9-1-quip.rtf, Generated on: 28JUL2017 05:58

Table 16.4.9.1 QUIP by Visit - Safety Overall Population

Assessor Parameter Visit Baseline Value	GDNF/GDNF (N=21)			Placebo/GDNF (N=20)		
	Postbaseline Value			Postbaseline Value		
	Positive n (%)	Negative n (%)	Missing n (%)	Positive n (%)	Negative n (%)	Missing n (%)
Informant						
Hobbyism						
Week e2-64						
Positive	0	0	0	0	0	0
Negative	0	0	0	0	0	0
Missing	0	0	3 (14.3)	0	0	2 (10.0)
Week e2-80						
Positive	0	0	0	0	0	0
Negative	0	0	0	0	0	0
Missing	0	0	3 (14.3)	0	0	2 (10.0)
Week e3-16						
Positive	0	0	0	1 (5.0)	0	0
Negative	0	0	0	1 (5.0)	1 (5.0)	0
Missing	0	1 (4.8)	11 (52.4)	0	2 (10.0)	8 (40.0)
Week e3-32						
Positive	0	0	0	1 (5.0)	0	0
Negative	0	0	0	1 (5.0)	1 (5.0)	0
Missing	0	1 (4.8)	11 (52.4)	0	2 (10.0)	8 (40.0)

Note: The QUIP is a self-administered or informant-completed scale that includes 13 questions covering symptoms related to the 4 commonest impulse control disorders in PD, other behaviors, and problematic use of medication. The number of "Yes" responses is compared to the number required for a positive result. Missing individual responses are imputed using LOCF. Each impulse control disorder, other behavior, and problematic use of medication is rated as a positive result (ie, present) or a negative result (ie, not present). Percentages are based on the total number of observations for that visit.
Source: Listing 17.2.4.16, Dataset: ADQSS, Program: t_quip.sas, Output: t_16-4-9-1-quip.rtf, Generated on: 28JUL2017 05:58

Table 16.4.9.1 QUIP by Visit - Safety Overall Population

Assessor Parameter Visit Baseline Value	GDNF/GDNF (N=21) Postbaseline Value			Placebo/GDNF (N=20) Postbaseline Value		
	Positive n (%)	Negative n (%)	Missing n (%)	Positive n (%)	Negative n (%)	Missing n (%)
Informant						
Hobbyism						
Last Study Visit in the Supplemental Extension						
Positive	0	0	0	1 (5.0)	0	0
Negative	0	0	0	1 (5.0)	1 (5.0)	0
Missing	0	1 (4.8)	11 (52.4)	0	2 (10.0)	8 (40.0)

Note: The QUIP is a self-administered or informant-completed scale that includes 13 questions covering symptoms related to the 4 commonest impulse control disorders in PD, other behaviors, and problematic use of medication. The number of "Yes" responses is compared to the number required for a positive result. Missing individual responses are imputed using LOCF. Each impulse control disorder, other behavior, and problematic use of medication is rated as a positive result (ie, present) or a negative result (ie, not present). Percentages are based on the total number of observations for that visit.
Source: Listing 17.2.4.16, Dataset: ADQSS, Program: t_quip.sas, Output: t_16-4-9-1-quip.rtf, Generated on: 28JUL2017 05:58

Table 16.4.9.1 QUIP by Visit - Safety Overall Population

Assessor Parameter Visit Baseline Value	GDNF/GDNF (N=21) Postbaseline Value			Placebo/GDNF (N=20) Postbaseline Value		
	Positive n (%)	Negative n (%)	Missing n (%)	Positive n (%)	Negative n (%)	Missing n (%)
Informant						
Punding						
Week 48/e8						
Positive	0	0	0	0	0	0
Negative	0	0	0	0	2 (10.0)	0
Missing	0	1 (4.8)	20 (95.2)	0	1 (5.0)	17 (85.0)
Week 56/e16						
Positive	0	0	0	0	0	0
Negative	0	0	0	0	2 (10.0)	0
Missing	0	1 (4.8)	20 (95.2)	0	1 (5.0)	17 (85.0)
Week 64/e24						
Positive	0	0	0	1 (5.0)	0	0
Negative	0	0	0	0	3 (15.0)	0
Missing	0	3 (14.3)	18 (85.7)	0	1 (5.0)	15 (75.0)
Week 72/e32						
Positive	0	0	0	1 (5.0)	0	0
Negative	0	0	0	0	3 (15.0)	0
Missing	1 (4.8)	3 (14.3)	17 (81.0)	0	2 (10.0)	14 (70.0)

Note: The QUIP is a self-administered or informant-completed scale that includes 13 questions covering symptoms related to the 4 commonest impulse control disorders in PD, other behaviors, and problematic use of medication. The number of "Yes" responses is compared to the number required for a positive result. Missing individual responses are imputed using LOCF. Each impulse control disorder, other behavior, and problematic use of medication is rated as a positive result (ie, present) or a negative result (ie, not present). Percentages are based on the total number of observations for that visit.
Source: Listing 17.2.4.16, Dataset: ADQSS, Program: t_quip.sas, Output: t_16-4-9-1-quip.rtf, Generated on: 28JUL2017 05:58
Page 53 of 64

Table 16.4.9.1 QUIP by Visit - Safety Overall Population

Assessor Parameter Visit Baseline Value	GDNF/GDNF (N=21) Postbaseline Value			Placebo/GDNF (N=20) Postbaseline Value		
	Positive n (%)	Negative n (%)	Missing n (%)	Positive n (%)	Negative n (%)	Missing n (%)
Informant						
Punding						
Week 80/e40						
Positive	0	0	0	1 (5.0)	0	0
Negative	0	0	0	1 (5.0)	2 (10.0)	0
Missing	1 (4.8)	4 (19.0)	16 (76.2)	0	2 (10.0)	14 (70.0)
Week e2-16						
Positive	0	0	0	0	0	0
Negative	0	0	0	0	0	0
Missing	0	0	3 (14.3)	0	0	2 (10.0)
Week e2-32						
Positive	0	0	0	0	0	0
Negative	0	0	0	0	0	0
Missing	0	0	3 (14.3)	0	0	2 (10.0)
Week e2-48						
Positive	0	0	0	0	0	0
Negative	0	0	0	0	0	0
Missing	0	0	3 (14.3)	0	0	2 (10.0)

Note: The QUIP is a self-administered or informant-completed scale that includes 13 questions covering symptoms related to the 4 commonest impulse control disorders in PD, other behaviors, and problematic use of medication. The number of "Yes" responses is compared to the number required for a positive result. Missing individual responses are imputed using LOCF. Each impulse control disorder, other behavior, and problematic use of medication is rated as a positive result (ie, present) or a negative result (ie, not present). Percentages are based on the total number of observations for that visit.
Source: Listing 17.2.4.16, Dataset: ADQSS, Program: t_quip.sas, Output: t_16-4-9-1-quip.rtf, Generated on: 28JUL2017 05:58
Page 54 of 64

Table 16.4.9.1 QUIP by Visit - Safety Overall Population

Assessor Parameter Visit Baseline Value	GDNF/GDNF (N=21) Postbaseline Value			Placebo/GDNF (N=20) Postbaseline Value		
	Positive n (%)	Negative n (%)	Missing n (%)	Positive n (%)	Negative n (%)	Missing n (%)
Informant						
Punding						
Week e2-64						
Positive	0	0	0	0	0	0
Negative	0	0	0	0	0	0
Missing	0	0	3 (14.3)	0	0	2 (10.0)
Week e2-80						
Positive	0	0	0	0	0	0
Negative	0	0	0	0	0	0
Missing	0	0	3 (14.3)	0	0	2 (10.0)
Week e3-16						
Positive	0	0	0	1 (5.0)	0	0
Negative	0	0	0	1 (5.0)	1 (5.0)	0
Missing	0	1 (4.8)	11 (52.4)	0	2 (10.0)	8 (40.0)
Week e3-32						
Positive	0	0	0	1 (5.0)	0	0
Negative	0	0	0	1 (5.0)	1 (5.0)	0
Missing	0	1 (4.8)	11 (52.4)	0	2 (10.0)	8 (40.0)

Note: The QUIP is a self-administered or informant-completed scale that includes 13 questions covering symptoms related to the 4 commonest impulse control disorders in PD, other behaviors, and problematic use of medication. The number of "Yes" responses is compared to the number required for a positive result. Missing individual responses are imputed using LOCF. Each impulse control disorder, other behavior, and problematic use of medication is rated as a positive result (ie, present) or a negative result (ie, not present). Percentages are based on the total number of observations for that visit.
Source: Listing 17.2.4.16, Dataset: ADQSS, Program: t_quip.sas, Output: t_16-4-9-1-quip.rtf, Generated on: 28JUL2017 05:58
Page 55 of 64

Table 16.4.9.1 QUIP by Visit - Safety Overall Population

Assessor Parameter Visit Baseline Value	GDNF/GDNF (N=21) Postbaseline Value			Placebo/GDNF (N=20) Postbaseline Value		
	Positive n (%)	Negative n (%)	Missing n (%)	Positive n (%)	Negative n (%)	Missing n (%)
Informant						
Punding						
Last Study Visit in the Supplemental Extension						
Positive	0	0	0	1 (5.0)	0	0
Negative	0	0	0	1 (5.0)	1 (5.0)	0
Missing	0	1 (4.8)	11 (52.4)	0	2 (10.0)	8 (40.0)

Note: The QUIP is a self-administered or informant-completed scale that includes 13 questions covering symptoms related to the 4 commonest impulse control disorders in PD, other behaviors, and problematic use of medication. The number of "Yes" responses is compared to the number required for a positive result. Missing individual responses are imputed using LOCF. Each impulse control disorder, other behavior, and problematic use of medication is rated as a positive result (ie, present) or a negative result (ie, not present). Percentages are based on the total number of observations for that visit.
Source: Listing 17.2.4.16, Dataset: ADQSS, Program: t_quip.sas, Output: t_16-4-9-1-quip.rtf, Generated on: 28JUL2017 05:58
Page 56 of 64

Table 16.4.9.1 QUIP by Visit - Safety Overall Population

Assessor Parameter Visit Baseline Value	GDNF/GDNF (N=21) Postbaseline Value			Placebo/GDNF (N=20) Postbaseline Value		
	Positive n (%)	Negative n (%)	Missing n (%)	Positive n (%)	Negative n (%)	Missing n (%)
Informant						
Walkabout						
Week 48/e8						
Positive	0	0	0	0	0	0
Negative	0	0	0	0	2 (10.0)	0
Missing	0	1 (4.8)	20 (95.2)	0	1 (5.0)	17 (85.0)
Week 56/e16						
Positive	0	0	0	0	0	0
Negative	0	0	0	0	2 (10.0)	0
Missing	0	1 (4.8)	20 (95.2)	0	1 (5.0)	17 (85.0)
Week 64/e24						
Positive	0	0	0	0	0	0
Negative	0	0	0	0	4 (20.0)	0
Missing	0	3 (14.3)	18 (85.7)	0	1 (5.0)	15 (75.0)
Week 72/e32						
Positive	0	0	0	0	0	0
Negative	0	0	0	0	4 (20.0)	0
Missing	0	4 (19.0)	17 (81.0)	0	2 (10.0)	14 (70.0)

Note: The QUIP is a self-administered or informant-completed scale that includes 13 questions covering symptoms related to the 4 commonest impulse control disorders in PD, other behaviors, and problematic use of medication. The number of "Yes" responses is compared to the number required for a positive result. Missing individual responses are imputed using LOCF. Each impulse control disorder, other behavior, and problematic use of medication is rated as a positive result (ie, present) or a negative result (ie, not present). Percentages are based on the total number of observations for that visit.
Source: Listing 17.2.4.16, Dataset: ADQSS, Program: t_quip.sas, Output: t_16-4-9-1-quip.rtf, Generated on: 28JUL2017 05:58
Page 57 of 64

Table 16.4.9.1 QUIP by Visit - Safety Overall Population

Assessor Parameter Visit Baseline Value	GDNF/GDNF (N=21) Postbaseline Value			Placebo/GDNF (N=20) Postbaseline Value		
	Positive n (%)	Negative n (%)	Missing n (%)	Positive n (%)	Negative n (%)	Missing n (%)
Informant						
Walkabout						
Week 80/e40						
Positive	0	0	0	0	0	0
Negative	0	0	0	0	4 (20.0)	0
Missing	0	6 (28.6)	15 (71.4)	0	2 (10.0)	14 (70.0)
Week e2-16						
Positive	0	0	0	0	0	0
Negative	0	0	0	0	0	0
Missing	0	0	3 (14.3)	0	0	2 (10.0)
Week e2-32						
Positive	0	0	0	0	0	0
Negative	0	0	0	0	0	0
Missing	0	0	3 (14.3)	0	0	2 (10.0)
Week e2-48						
Positive	0	0	0	0	0	0
Negative	0	0	0	0	0	0
Missing	0	0	3 (14.3)	0	0	2 (10.0)

Note: The QUIP is a self-administered or informant-completed scale that includes 13 questions covering symptoms related to the 4 commonest impulse control disorders in PD, other behaviors, and problematic use of medication. The number of "Yes" responses is compared to the number required for a positive result. Missing individual responses are imputed using LOCF. Each impulse control disorder, other behavior, and problematic use of medication is rated as a positive result (ie, present) or a negative result (ie, not present). Percentages are based on the total number of observations for that visit.
Source: Listing 17.2.4.16, Dataset: ADQSS, Program: t_quip.sas, Output: t_16-4-9-1-quip.rtf, Generated on: 28JUL2017 05:58
Page 58 of 64

Table 16.4.9.1 QUIP by Visit - Safety Overall Population

Assessor Parameter Visit Baseline Value	GDNF/GDNF (N=21) Postbaseline Value			Placebo/GDNF (N=20) Postbaseline Value		
	Positive n (%)	Negative n (%)	Missing n (%)	Positive n (%)	Negative n (%)	Missing n (%)
Informant						
Walkabout						
Week e2-64						
Positive	0	0	0	0	0	0
Negative	0	0	0	0	0	0
Missing	0	0	3 (14.3)	0	0	2 (10.0)
Week e2-80						
Positive	0	0	0	0	0	0
Negative	0	0	0	0	0	0
Missing	0	0	3 (14.3)	0	0	2 (10.0)
Week e3-16						
Positive	0	0	0	0	0	0
Negative	0	0	0	0	3 (15.0)	0
Missing	0	1 (4.8)	11 (52.4)	0	2 (10.0)	8 (40.0)
Week e3-32						
Positive	0	0	0	0	0	0
Negative	0	0	0	0	3 (15.0)	0
Missing	0	1 (4.8)	11 (52.4)	0	2 (10.0)	8 (40.0)

Note: The QUIP is a self-administered or informant-completed scale that includes 13 questions covering symptoms related to the 4 commonest impulse control disorders in PD, other behaviors, and problematic use of medication. The number of "Yes" responses is compared to the number required for a positive result. Missing individual responses are imputed using LOCF. Each impulse control disorder, other behavior, and problematic use of medication is rated as a positive result (ie, present) or a negative result (ie, not present). Percentages are based on the total number of observations for that visit.
Source: Listing 17.2.4.16, Dataset: ADQSS, Program: t_quip.sas, Output: t_16-4-9-1-quip.rtf, Generated on: 28JUL2017 05:58

Table 16.4.9.1 QUIP by Visit - Safety Overall Population

Assessor Parameter Visit Baseline Value	GDNF/GDNF (N=21) Postbaseline Value			Placebo/GDNF (N=20) Postbaseline Value		
	Positive n (%)	Negative n (%)	Missing n (%)	Positive n (%)	Negative n (%)	Missing n (%)
Informant						
Walkabout						
Last Study Visit in the Supplemental Extension						
Positive	0	0	0	0	0	0
Negative	0	0	0	0	3 (15.0)	0
Missing	0	1 (4.8)	11 (52.4)	0	2 (10.0)	8 (40.0)

Note: The QUIP is a self-administered or informant-completed scale that includes 13 questions covering symptoms related to the 4 commonest impulse control disorders in PD, other behaviors, and problematic use of medication. The number of "Yes" responses is compared to the number required for a positive result. Missing individual responses are imputed using LOCF. Each impulse control disorder, other behavior, and problematic use of medication is rated as a positive result (ie, present) or a negative result (ie, not present). Percentages are based on the total number of observations for that visit.
Source: Listing 17.2.4.16, Dataset: ADQSS, Program: t_quip.sas, Output: t_16-4-9-1-quip.rtf, Generated on: 28JUL2017 05:58
Page 60 of 64

Table 16.4.9.1 QUIP by Visit - Safety Overall Population

Assessor Parameter Visit Baseline Value	GDNF/GDNF (N=21) Postbaseline Value			Placebo/GDNF (N=20) Postbaseline Value		
	Positive n (%)	Negative n (%)	Missing n (%)	Positive n (%)	Negative n (%)	Missing n (%)
Informant						
Medication Use						
Week 48/e8						
Positive	0	0	0	0	0	0
Negative	0	0	0	0	2 (10.0)	0
Missing	0	1 (4.8)	20 (95.2)	0	1 (5.0)	17 (85.0)
Week 56/e16						
Positive	0	0	0	0	0	0
Negative	0	0	0	0	2 (10.0)	0
Missing	0	1 (4.8)	20 (95.2)	0	1 (5.0)	17 (85.0)
Week 64/e24						
Positive	0	0	0	0	0	0
Negative	0	0	0	0	4 (20.0)	0
Missing	0	3 (14.3)	18 (85.7)	0	1 (5.0)	15 (75.0)
Week 72/e32						
Positive	0	0	0	0	0	0
Negative	0	0	0	0	4 (20.0)	0
Missing	0	4 (19.0)	17 (81.0)	0	2 (10.0)	14 (70.0)

Note: The QUIP is a self-administered or informant-completed scale that includes 13 questions covering symptoms related to the 4 commonest impulse control disorders in PD, other behaviors, and problematic use of medication. The number of "Yes" responses is compared to the number required for a positive result. Missing individual responses are imputed using LOCF. Each impulse control disorder, other behavior, and problematic use of medication is rated as a positive result (ie, present) or a negative result (ie, not present). Percentages are based on the total number of observations for that visit.
Source: Listing 17.2.4.16, Dataset: ADQSS, Program: t_quip.sas, Output: t_16-4-9-1-quip.rtf, Generated on: 28JUL2017 05:58

Table 16.4.9.1 QUIP by Visit - Safety Overall Population

Assessor Parameter Visit Baseline Value	GDNF/GDNF (N=21) Postbaseline Value			Placebo/GDNF (N=20) Postbaseline Value		
	Positive n (%)	Negative n (%)	Missing n (%)	Positive n (%)	Negative n (%)	Missing n (%)
Informant						
Medication Use						
Week 80/e40						
Positive	0	0	0	0	0	0
Negative	0	0	0	0	4 (20.0)	0
Missing	0	6 (28.6)	15 (71.4)	0	2 (10.0)	14 (70.0)
Week e2-16						
Positive	0	0	0	0	0	0
Negative	0	0	0	0	0	0
Missing	0	0	3 (14.3)	0	0	2 (10.0)
Week e2-32						
Positive	0	0	0	0	0	0
Negative	0	0	0	0	0	0
Missing	0	0	3 (14.3)	0	0	2 (10.0)
Week e2-48						
Positive	0	0	0	0	0	0
Negative	0	0	0	0	0	0
Missing	0	0	3 (14.3)	0	0	2 (10.0)

Note: The QUIP is a self-administered or informant-completed scale that includes 13 questions covering symptoms related to the 4 commonest impulse control disorders in PD, other behaviors, and problematic use of medication. The number of "Yes" responses is compared to the number required for a positive result. Missing individual responses are imputed using LOCF. Each impulse control disorder, other behavior, and problematic use of medication is rated as a positive result (ie, present) or a negative result (ie, not present). Percentages are based on the total number of observations for that visit.
Source: Listing 17.2.4.16, Dataset: ADQSS, Program: t_quip.sas, Output: t_16-4-9-1-quip.rtf, Generated on: 28JUL2017 05:58
Page 62 of 64

Table 16.4.9.1 QUIP by Visit - Safety Overall Population

Assessor Parameter Visit Baseline Value	GDNF/GDNF (N=21) Postbaseline Value			Placebo/GDNF (N=20) Postbaseline Value		
	Positive n (%)	Negative n (%)	Missing n (%)	Positive n (%)	Negative n (%)	Missing n (%)
Informant						
Medication Use						
Week e2-64						
Positive	0	0	0	0	0	0
Negative	0	0	0	0	0	0
Missing	0	0	3 (14.3)	0	0	2 (10.0)
Week e2-80						
Positive	0	0	0	0	0	0
Negative	0	0	0	0	0	0
Missing	0	0	3 (14.3)	0	0	2 (10.0)
Week e3-16						
Positive	0	0	0	0	0	0
Negative	0	0	0	0	3 (15.0)	0
Missing	0	1 (4.8)	11 (52.4)	0	2 (10.0)	8 (40.0)
Week e3-32						
Positive	0	0	0	0	0	0
Negative	0	0	0	0	3 (15.0)	0
Missing	0	1 (4.8)	11 (52.4)	0	2 (10.0)	8 (40.0)

Note: The QUIP is a self-administered or informant-completed scale that includes 13 questions covering symptoms related to the 4 commonest impulse control disorders in PD, other behaviors, and problematic use of medication. The number of "Yes" responses is compared to the number required for a positive result. Missing individual responses are imputed using LOCF. Each impulse control disorder, other behavior, and problematic use of medication is rated as a positive result (ie, present) or a negative result (ie, not present). Percentages are based on the total number of observations for that visit.
Source: Listing 17.2.4.16, Dataset: ADQSS, Program: t_quip.sas, Output: t_16-4-9-1-quip.rtf, Generated on: 28JUL2017 05:58

Table 16.4.9.1 QUIP by Visit - Safety Overall Population

Assessor Parameter Visit Baseline Value	GDNF/GDNF (N=21) Postbaseline Value			Placebo/GDNF (N=20) Postbaseline Value		
	Positive n (%)	Negative n (%)	Missing n (%)	Positive n (%)	Negative n (%)	Missing n (%)
Informant						
Medication Use						
Last Study Visit in the Supplemental Extension						
Positive	0	0	0	0	0	0
Negative	0	0	0	0	3 (15.0)	0
Missing	0	1 (4.8)	11 (52.4)	0	2 (10.0)	8 (40.0)

Note: The QUIP is a self-administered or informant-completed scale that includes 13 questions covering symptoms related to the 4 commonest impulse control disorders in PD, other behaviors, and problematic use of medication. The number of "Yes" responses is compared to the number required for a positive result. Missing individual responses are imputed using LOCF. Each impulse control disorder, other behavior, and problematic use of medication is rated as a positive result (ie, present) or a negative result (ie, not present). Percentages are based on the total number of observations for that visit.
Source: Listing 17.2.4.16, Dataset: ADQSS, Program: t_quip.sas, Output: t_16-4-9-1-quip.rtf, Generated on: 28JUL2017 05:58
Page 64 of 64

Table 16.4.9.2 MoCA by Visit - Safety Overall Population

Parameter Visit Statistic	GDNF/GDNF (N=21)		Placebo/GDNF (N=20)	
	Value	Change From Baseline	Value	Change From Baseline
MoCA Total Score				
Screening				
n	21		20	
Mean (SD)	27.9 (1.85)		27.5 (1.85)	
Median	28.0		28.0	
Min, Max	24, 30		24, 30	
Pre-test Infusion (Baseline)				
n	21		20	
Mean (SD)	27.6 (1.72)		27.9 (1.77)	
Median	28.0		28.5	
Min, Max	24, 30		25, 30	
Week 40/e0				
n	21	21	20	20
Mean (SD)	28.1 (1.81)	0.5 (2.34)	27.6 (2.14)	-0.3 (1.87)
Median	28.0	0.0	28.0	0.0
Min, Max	25, 30	-5, 4	24, 30	-4, 5
Week 56/e16				
n	21	21	20	20
Mean (SD)	27.8 (3.04)	0.2 (3.20)	27.9 (1.81)	-0.1 (1.39)
Median	29.0	1.0	28.5	0.0
Min, Max	16, 30	-12, 5	25, 30	-4, 2

Note: The MoCA is a rater-administered cognitive screening tool with 8 components. The total score ranges from 0 to 30, with lower scores representing poorer cognitive function. A total score of 26 or above is considered normal. Missing individual scores are imputed using LOCF if necessary.
Source: Listing 17.2.4.17, Dataset: ADQSS, Program: t_safqsum.sas, Output: t_16-4-9-2-moca.rtf, Generated on: 28JUL2017 05:58
Page 1 of 2

Table 16.4.9.2 MoCA by Visit - Safety Overall Population

Parameter Visit Statistic	GDNF/GDNF (N=21)		Placebo/GDNF (N=20)	
	Value	Change From Baseline	Value	Change From Baseline
MoCA Total Score				
Week 80/e40				
n	21	21	20	20
Mean (SD)	28.0 (2.44)	0.4 (2.42)	27.8 (2.21)	-0.1 (1.80)
Median	29.0	1.0	28.5	0.0
Min, Max	20, 30	-8, 4	22, 30	-3, 4
Week e2-80				
n	3	3	2	2
Mean (SD)	27.0 (2.65)	0.3 (3.21)	29.0 (1.41)	2.0 (1.41)
Median	28.0	-1.0	29.0	2.0
Min, Max	24, 29	-2, 4	28, 30	1, 3
Last Study Visit in the Supplemental Extension				
n	12	12	13	13
Mean (SD)	28.7 (1.61)	0.9 (1.56)	28.5 (1.56)	0.8 (1.82)
Median	29.0	1.0	29.0	0.0
Min, Max	25, 30	-1, 4	25, 30	-1, 5

Note: The MoCA is a rater-administered cognitive screening tool with 8 components. The total score ranges from 0 to 30, with lower scores representing poorer cognitive function. A total score of 26 or above is considered normal. Missing individual scores are imputed using LOCF if necessary.
Source: Listing 17.2.4.17, Dataset: ADQSS, Program: t_safqsum.sas, Output: t_16-4-9-2-moca.rtf, Generated on: 28JUL2017 05:58
Page 2 of 2

Table 16.4.9.3 MDRS by Visit - Safety Overall Population

Parameter Visit Statistic	GDNF/GDNF (N=21)		Placebo/GDNF (N=20)	
	Value	Change From Baseline	Value	Change From Baseline
AEMSS Total Score				
Screening (Baseline)				
n	21		20	
Mean (SD)	11.7 (1.68)		11.9 (1.89)	
Median	12.0		12.0	
Min, Max	9, 15		9, 15	
Week 40/e0				
n	21	21	20	20
Mean (SD)	12.0 (2.82)	0.3 (2.56)	12.6 (2.61)	0.7 (2.66)
Median	13.0	0.0	14.0	0.0
Min, Max	4, 15	-5, 4	8, 16	-4, 5
Week 56/e16				
n	21	21	19	19
Mean (SD)	12.0 (2.61)	0.3 (2.47)	12.1 (2.20)	0.1 (2.17)
Median	13.0	1.0	13.0	-1.0
Min, Max	3, 15	-6, 4	8, 16	-4, 4
Week 80/e40				
n	21	21	20	20
Mean (SD)	13.0 (2.13)	1.2 (1.84)	12.7 (2.01)	0.8 (2.20)
Median	14.0	1.0	12.5	0.0
Min, Max	8, 16	-2, 5	9, 16	-3, 6

Note: The MDRS is a rater-administered global scale of cognition including 5 subscales. The total score ranges from 0 to 144, with higher scores representing better cognitive function. A total score lower than 123 is associated with some degree of dementia in PD. The AEMSS total score ranges from 0 to 20, with higher scores representing better cognitive function.
Source: Listing 17.2.4.18, Dataset: ADQSS, Program: t_safqsum.sas, Output: t_16-4-9-3-mdrs.rtf, Generated on: 28JUL2017 05:58
Page 1 of 2

Table 16.4.9.3 MDRS by Visit - Safety Overall Population

Parameter Visit Statistic	GDNF/GDNF (N=21)		Placebo/GDNF (N=20)	
	Value	Change From Baseline	Value	Change From Baseline
AEMSS Total Score				
Week e2-80				
n	0	0	0	0
Mean (SD)				
Median				
Min, Max				
Last Study Visit in the Supplemental Extension				
n	11	11	11	11
Mean (SD)	12.9 (2.12)	0.9 (1.97)	12.5 (2.25)	0.5 (2.73)
Median	14.0	1.0	12.0	0.0
Min, Max	9, 16	-2, 4	9, 16	-4, 6

Note: The MDRS is a rater-administered global scale of cognition including 5 subscales. The total score ranges from 0 to 144, with higher scores
representing better cognitive function. A total score lower than 123 is associated with some degree of dementia in PD. The AEMSS total
score ranges from 0 to 20, with higher scores representing better cognitive function.
Source: Listing 17.2.4.18, Dataset: ADQSS, Program: t_safqsum.sas, Output: t_16-4-9-3-mdrs.rtf, Generated on: 28JUL2017 05:58
Page 2 of 2

Table 16.4.9.4 Stroop Test by Visit, Safety Overall Population

Parameter (unit) Visit Statistic	GDNF/GDNF (N=21)		Placebo/GDNF (N=20)	
	Value	Change From Baseline	Value	Change From Baseline
Color Naming (sec)				
Screening (Baseline)				
n	19		19	
Mean (SD)	28.8 (6.69)		32.5 (7.05)	
Median	28.0		32.0	
Min, Max	20, 42		21, 50	
Week 40/e0				
n	17	17	19	18
Mean (SD)	30.2 (6.34)	1.4 (3.79)	32.2 (6.47)	0.4 (3.43)
Median	28.0	2.0	31.0	0.5
Min, Max	22, 44	-10, 8	24, 48	-5, 9
Week 80/e40				
n	21	19	20	19
Mean (SD)	30.9 (7.20)	1.9 (5.75)	31.1 (5.77)	-1.3 (5.98)
Median	29.0	0.0	29.0	-1.0
Min, Max	22, 46	-7, 18	22, 45	-21, 5

Note: The Stroop test is a global scale of reaction time including 4 conditions. Total time to complete the test in each condition can range from 0 to 999 seconds, with lower time representing better reaction time.
Source: Listing 17.2.4.19, Dataset: ADQSS, Program: t_safqsum.sas, Output: t_16-4-9-4-stroop.rtf, Generated on: 28JUL2017 05:58
Page 1 of 4

Table 16.4.9.4 Stroop Test by Visit, Safety Overall Population

Parameter (unit) Visit Statistic	GDNF/GDNF (N=21)		Placebo/GDNF (N=20)	
	Value	Change From Baseline	Value	Change From Baseline
Word Reading (sec)				
Screening (Baseline)				
n	19		19	
Mean (SD)	22.4 (4.68)		23.7 (6.93)	
Median	22.0		22.0	
Min, Max	16, 33		18, 48	
Week 40/e0				
n	17	17	19	18
Mean (SD)	23.4 (5.87)	0.6 (3.26)	22.8 (4.71)	-0.4 (6.71)
Median	24.0	0.0	22.0	1.0
Min, Max	14, 32	-6, 6	16, 32	-26, 4
Week 80/e40				
n	21	19	20	19
Mean (SD)	24.5 (6.79)	2.5 (5.10)	23.8 (7.44)	0.2 (7.62)
Median	21.0	2.0	22.0	1.0
Min, Max	14, 39	-6, 15	10, 46	-23, 18

Note: The Stroop test is a global scale of reaction time including 4 conditions. Total time to complete the test in each condition can range from 0 to 999 seconds, with lower time representing better reaction time.
Source: Listing 17.2.4.19, Dataset: ADQSS, Program: t_safqsum.sas, Output: t_16-4-9-4-stroop.rtf, Generated on: 28JUL2017 05:58
Page 2 of 4

Table 16.4.9.4 Stroop Test by Visit, Safety Overall Population

Parameter (unit) Visit Statistic	GDNF/GDNF (N=21)		Placebo/GDNF (N=20)	
	Value	Change From Baseline	Value	Change From Baseline
Inhibition (sec)				
Screening (Baseline)				
n	19		19	
Mean (SD)	58.7 (14.69)		56.9 (9.94)	
Median	55.0		56.0	
Min, Max	35, 89		37, 77	
Week 40/e0				
n	17	17	19	18
Mean (SD)	59.2 (16.22)	-0.1 (9.50)	55.4 (8.34)	-0.1 (5.52)
Median	59.0	0.0	58.0	0.0
Min, Max	36, 85	-18, 15	38, 73	-8, 12
Week 80/e40				
n	21	19	20	19
Mean (SD)	56.2 (13.33)	-2.1 (10.04)	57.5 (13.61)	1.4 (8.91)
Median	54.0	-1.0	54.5	-2.0
Min, Max	36, 93	-24, 23	41, 91	-9, 26

Note: The Stroop test is a global scale of reaction time including 4 conditions. Total time to complete the test in each condition can range from 0 to 999 seconds, with lower time representing better reaction time.
Source: Listing 17.2.4.19, Dataset: ADQSS, Program: t_safqsum.sas, Output: t_16-4-9-4-stroop.rtf, Generated on: 28JUL2017 05:58
Page 3 of 4

Table 16.4.9.4 Stroop Test by Visit, Safety Overall Population

Parameter (unit) Visit Statistic	GDNF/GDNF (N=21)		Placebo/GDNF (N=20)	
	Value	Change From Baseline	Value	Change From Baseline
Inhibition/Switching (sec)				
Screening (Baseline)				
n	19		19	
Mean (SD)	61.8 (13.57)		78.4 (30.47)	
Median	63.0		70.0	
Min, Max	38, 89		44, 157	
Week 40/e0				
n	17	17	19	18
Mean (SD)	66.4 (15.16)	4.2 (13.13)	73.9 (31.78)	-0.5 (13.69)
Median	62.0	4.0	64.0	1.0
Min, Max	44, 95	-16, 39	39, 181	-33, 26
Week 80/e40				
n	21	19	19	18
Mean (SD)	64.4 (20.80)	3.0 (14.82)	71.0 (19.04)	-4.9 (20.34)
Median	63.0	-2.0	67.0	-1.0
Min, Max	40, 120	-18, 42	50, 118	-39, 41

Note: The Stroop test is a global scale of reaction time including 4 conditions. Total time to complete the test in each condition can range from 0 to 999 seconds, with lower time representing better reaction time.
Source: Listing 17.2.4.19, Dataset: ADQSS, Program: t_safqsum.sas, Output: t_16-4-9-4-stroop.rtf, Generated on: 28JUL2017 05:58
Page 4 of 4

Table 16.4.9.5 FrSBe by Visit - Safety Overall Population

Parameter Visit Statistic	GDNF/GDNF (N=21)		Placebo/GDNF (N=20)	
	Value	Change From Baseline	Value	Change From Baseline
Apathy Score				
Screening "Before"				
n	17		18	
Mean (SD)	22.4 (4.37)		22.2 (5.44)	
Median	22.0		22.0	
Min, Max	17, 35		14, 35	
Screening "After" (Baseline)				
n	17		18	
Mean (SD)	28.1 (7.03)		28.2 (7.64)	
Median	25.0		29.0	
Min, Max	18, 41		18, 48	
Week 40/e0 "After"				
n	17	17	18	18
Mean (SD)	29.8 (9.65)	1.8 (8.51)	28.3 (7.18)	0.1 (7.32)
Median	31.0	-1.0	29.0	0.5
Min, Max	16, 49	-9, 22	18, 48	-20, 10
Week 80/e40 "After"				
n	21	17	20	18
Mean (SD)	26.0 (8.75)	-0.7 (9.25)	24.9 (7.08)	-2.8 (6.54)
Median	23.0	-2.0	24.0	-0.5
Min, Max	17, 48	-13, 24	11, 45	-16, 6

Note: The FrSBe is a scale that assesses behavior related to frontal systems damage including 3 subscales. Higher subscale scores indicate greater pathology. Individual missing items are imputed using the average of non-missing scores in each subscale.
Source: Listing 17.2.4.20, Dataset: ADQSS, Program: t_safqsum.sas, Output: t_16-4-9-5-frsbe.rtf, Generated on: 28JUL2017 05:58
Page 1 of 3

Table 16.4.9.5 FrSBe by Visit - Safety Overall Population

Parameter Visit Statistic	GDNF/GDNF (N=21)		Placebo/GDNF (N=20)	
	Value	Change From Baseline	Value	Change From Baseline
Disinhibition Score				
Screening "Before"				
n	17		18	
Mean (SD)	26.7 (4.22)		26.8 (7.02)	
Median	28.0		25.5	
Min, Max	19, 33		19, 46	
Screening "After" (Baseline)				
n	17		18	
Mean (SD)	30.4 (6.43)		30.9 (8.04)	
Median	31.0		29.0	
Min, Max	18, 44		19, 49	
Week 40/e0 "After"				
n	17	17	18	18
Mean (SD)	32.9 (10.49)	2.5 (8.46)	28.2 (7.94)	-2.7 (5.17)
Median	35.0	1.0	28.5	-3.5
Min, Max	18, 54	-11, 23	15, 43	-14, 7
Week 80/e40 "After"				
n	21	17	20	18
Mean (SD)	30.1 (7.36)	0.1 (5.36)	26.8 (8.18)	-4.3 (5.51)
Median	32.0	0.0	27.0	-4.5
Min, Max	17, 40	-10, 10	15, 45	-16, 6

Note: The FrSBe is a scale that assesses behavior related to frontal systems damage including 3 subscales. Higher subscale scores indicate greater
pathology. Individual missing items are imputed using the average of non-missing scores in each subscale.
Source: Listing 17.2.4.20, Dataset: ADQSS, Program: t_safqsum.sas, Output: t_16-4-9-5-frsbe.rtf, Generated on: 28JUL2017 05:58
Page 2 of 3

Table 16.4.9.5 FrSBe by Visit - Safety Overall Population

Parameter Visit Statistic	GDNF/GDNF (N=21)		Placebo/GDNF (N=20)	
	Value	Change From Baseline	Value	Change From Baseline
Executive Dysfunction Score				
Screening "Before"				
n	17		18	
Mean (SD)	31.5 (7.54)		32.8 (6.39)	
Median	32.0		33.5	
Min, Max	20, 46		20, 46	
Screening "After" (Baseline)				
n	17		18	
Mean (SD)	36.7 (7.21)		37.1 (7.27)	
Median	36.0		37.0	
Min, Max	26, 51		25, 52	
Week 40/e0 "After"				
n	17	17	18	18
Mean (SD)	37.4 (11.12)	0.6 (8.57)	35.5 (8.37)	-1.6 (8.44)
Median	36.0	-1.0	34.0	-1.5
Min, Max	20, 58	-15, 13	22, 58	-18, 18
Week 80/e40 "After"				
n	21	17	20	18
Mean (SD)	36.9 (9.42)	-0.2 (10.74)	33.6 (10.56)	-3.9 (9.38)
Median	35.0	-4.0	33.5	-3.5
Min, Max	22, 58	-16, 26	15, 54	-19, 14

Note: The FrSBe is a scale that assesses behavior related to frontal systems damage including 3 subscales. Higher subscale scores indicate greater
      pathology. Individual missing items are imputed using the average of non-missing scores in each subscale.
Source: Listing 17.2.4.20, Dataset: ADQSS, Program: t_safqsum.sas, Output: t_16-4-9-5-frsbe.rtf, Generated on: 28JUL2017 05:58
Page 3 of 3

Table 16.4.9.6 Deary-Liewald Four-Choice Reaction Time by Visit - Safety Overall Population

Parameter (unit) Visit Statistic	GDNF/GDNF (N=21)		Placebo/GDNF (N=20)	
	Value	Change From Baseline	Value	Change From Baseline
Mean Reaction Time (msec)				
Screening (Baseline)				
n	17		17	
Mean (SD)	527.210 (125.182)		539.486 (92.990)	
Median	495.306		512.725	
Min, Max	348.514, 769.500		410.237, 718.225	
Week 40/e0				
n	17	17	18	17
Mean (SD)	582.378 (148.253)	55.168 (120.253)	600.090 (180.853)	58.650 (170.389)
Median	554.275	42.516	586.352	75.310
Min, Max	402.552, 881.108	-210.654, 274.633	404.225, 1232.946	-314.000, 555.125
Week 56/e16				
n	16	16	15	14
Mean (SD)	590.348 (138.220)	54.858 (112.325)	592.269 (96.015)	66.238 (132.491)
Median	578.794	34.833	567.200	77.390
Min, Max	390.649, 881.571	-130.449, 275.096	449.825, 813.076	-268.400, 326.365
Week 80/e40				
n	17	16	18	17
Mean (SD)	582.204 (133.211)	70.083 (82.145)	597.305 (93.320)	57.131 (112.295)
Median	537.564	62.423	587.350	57.856
Min, Max	409.236, 819.650	-66.475, 231.364	477.621, 891.205	-193.775, 255.514

Note: The Deary-Liewald RT is a computerized measure of simple and four-choice reaction time. The parameter is the mean reaction time, variance and SD for correct responses for four-choice reaction time. A shorter reaction time is better.
Source: Listing 17.2.4.21, Dataset: ADQSS, Program: t_safqsum.sas, Output: t_16-4-9-6-deary.rtf, Generated on: 28JUL2017 05:58
Page 1 of 3

Table 16.4.9.6 Deary-Liewald Four-Choice Reaction Time by Visit - Safety Overall Population

Parameter (unit) Visit Statistic	GDNF/GDNF (N=21)		Placebo/GDNF (N=20)	
	Value	Change From Baseline	Value	Change From Baseline
Variance				
Screening (Baseline)				
n	17		17	
Mean (SD)	17866.684 (15378.985)		15639.019 (14496.871)	
Median	11494.780		8318.904	
Min, Max	3199.420, 48530.410		1219.981, 56640.100	
Week 40/e0				
n	17	17	18	17
Mean (SD)	17232.057 (15930.170)	-634.627 (17317.397)	15346.812 (7870.538)	-660.505 (16226.682)
Median	10849.301	2.753	13516.560	1775.735
Min, Max	3530.018, 56196.099	-33977.645, 30645.588	5930.541, 38365.065	-44273.619, 31742.852
Week 56/e16				
n	16	16	15	14
Mean (SD)	17760.603 (13840.613)	-952.611 (16366.682)	19860.736 (15581.488)	2228.299 (20333.766)
Median	14959.548	395.829	12131.301	1422.940
Min, Max	3817.669, 51026.871	-33241.834, 33520.081	7017.822, 57177.925	-31425.144, 50508.438
Week 80/e40				
n	17	16	18	17
Mean (SD)	13591.297 (8138.066)	-3099.225 (9843.342)	16366.328 (10979.073)	1018.703 (17213.610)
Median	11614.940	24.804	13720.654	741.748
Min, Max	3727.772, 31648.435	-27810.490, 7363.713	3975.860, 44364.383	-40597.264, 42521.546

Note: The Deary-Liewald RT is a computerized measure of simple and four-choice reaction time. The parameter is the mean reaction time, variance and
SD for correct responses for four-choice reaction time. A shorter reaction time is better.
Source: Listing 17.2.4.21, Dataset: ADQSS, Program: t_safqsum.sas, Output: t_16-4-9-6-deary.rtf, Generated on: 28JUL2017 05:58
Page 2 of 3

Table 16.4.9.6 Deary-Liewald Four-Choice Reaction Time by Visit - Safety Overall Population

Parameter (unit) Visit Statistic	GDNF/GDNF (N=21)		Placebo/GDNF (N=20)	
	Value	Change From Baseline	Value	Change From Baseline
Standard Deviation				
Screening (Baseline)				
n	17		17	
Mean (SD)	122.419 (55.320)		127.111 (44.167)	
Median	107.214		126.070	
Min, Max	56.563, 220.296		76.779, 237.992	
Week 40/e0				
n	17	17	18	17
Mean (SD)	120.440 (54.152)	-1.979 (51.699)	121.781 (28.994)	-6.814 (50.137)
Median	104.160	0.016	116.261	-3.415
Min, Max	59.414, 237.037	-99.661, 84.167	77.010, 195.870	-126.787, 114.493
Week 56/e16				
n	16	16	15	14
Mean (SD)	139.380 (69.923)	13.419 (60.692)	132.868 (48.629)	2.266 (58.673)
Median	126.381	3.911	110.162	-14.581
Min, Max	61.787, 328.830	-96.649, 156.037	83.772, 239.119	-79.200, 157.452
Week 80/e40				
n	17	16	18	17
Mean (SD)	112.052 (33.172)	-5.356 (34.248)	122.209 (38.931)	-3.998 (45.883)
Median	107.773	0.650	116.963	-1.217
Min, Max	61.055, 177.900	-90.786, 41.352	63.054, 210.629	-111.331, 74.877

Note: The Deary-Liewald RT is a computerized measure of simple and four-choice reaction time. The parameter is the mean reaction time, variance and SD for correct responses for four-choice reaction time. A shorter reaction time is better.
Source: Listing 17.2.4.21, Dataset: ADQSS, Program: t_safqsum.sas, Output: t_16-4-9-6-deary.rtf, Generated on: 28JUL2017 05:58
Page 3 of 3

**Table 16.4.9.7 Verbal Fluency Assessment by Visit - Safety Overall Population**

Parameter Visit Statistic	GDNF/GDNF (N=21)		Placebo/GDNF (N=20)	
	Value	Change From Baseline	Value	Change From Baseline
Phonemic Verbal Fluency				
Screening (Baseline)				
n	17		17	
Mean (SD)	15.4 (4.46)		16.1 (4.52)	
Median	16.0		16.0	
Min, Max	8, 21		9, 24	
Week 40/e0				
n	17	17	18	17
Mean (SD)	17.4 (3.90)	2.0 (3.95)	16.8 (5.54)	0.9 (3.31)
Median	18.0	2.0	17.0	1.0
Min, Max	9, 24	-9, 8	5, 26	-6, 6
Week 80/e40				
n	21	17	20	17
Mean (SD)	16.2 (5.13)	0.9 (3.85)	17.5 (5.36)	1.4 (4.87)
Median	16.0	1.0	17.5	3.0
Min, Max	7, 26	-7, 9	8, 28	-8, 8

Note: The verbal fluency assessment measures verbal functioning in 2 categories. Scores represent number of correct words in one minute and range
     from 0 to 200. Higher scores represent better verbal functioning.
Source: Listing 17.2.4.22, Dataset: ADQSS, Program: t_safqsum.sas, Output: t_16-4-9-7-verbal.rtf, Generated on: 28JUL2017 05:58
Page 1 of 2

Table 16.4.9.7 Verbal Fluency Assessment by Visit - Safety Overall Population

Parameter Visit Statistic	GDNF/GDNF (N=21)		Placebo/GDNF (N=20)	
	Value	Change From Baseline	Value	Change From Baseline
Semantic Verbal Fluency				
Screening (Baseline)				
n	17		17	
Mean (SD)	23.5 (4.29)		22.1 (4.90)	
Median	24.0		22.0	
Min, Max	16, 32		14, 32	
Week 40/e0				
n	17	17	18	17
Mean (SD)	21.2 (4.38)	-2.3 (4.73)	21.6 (6.68)	-0.5 (6.67)
Median	21.0	-1.0	22.0	-1.0
Min, Max	14, 30	-14, 3	5, 33	-15, 15
Week 80/e40				
n	21	17	20	17
Mean (SD)	22.9 (6.32)	-0.6 (6.48)	23.1 (4.94)	0.8 (4.50)
Median	22.0	-1.0	23.0	0.0
Min, Max	11, 35	-9, 13	15, 33	-8, 9

Note: The verbal fluency assessment measures verbal functioning in 2 categories. Scores represent number of correct words in one minute and range
from 0 to 200. Higher scores represent better verbal functioning.
Source: Listing 17.2.4.22, Dataset: ADQSS, Program: t_safqsum.sas, Output: t_16-4-9-7-verbal.rtf, Generated on: 28JUL2017 05:58
Page 2 of 2

Table 16.4.9.8 BDI by Visit - Safety Overall Population

Parameter Visit Statistic	GDNF/GDNF (N=21)		Placebo/GDNF (N=20)	
	Value	Change From Baseline	Value	Change From Baseline
BDI Total Score				
Screening (Baseline)				
n	21		20	
Mean (SD)	7.24 (4.847)		5.50 (4.174)	
Median	8.00		4.50	
Min, Max	0.0, 17.0		0.0, 16.0	
Week 40/e0				
n	21	21	20	20
Mean (SD)	6.95 (5.380)	-0.29 (5.640)	5.20 (4.742)	-0.30 (4.857)
Median	7.00	0.00	3.00	-1.00
Min, Max	0.0, 17.0	-12.0, 12.0	0.0, 16.0	-8.0, 7.0
Week 80/e40				
n	21	21	20	20
Mean (SD)	6.52 (4.512)	-0.71 (5.100)	4.75 (4.711)	-0.75 (4.854)
Median	7.00	0.00	3.50	-0.50
Min, Max	0.0, 18.0	-13.0, 8.0	0.0, 15.0	-9.0, 7.0
Last Study Visit in the Pilot Extension				
n	2	2	2	2
Mean (SD)	6.50 (4.950)	-5.00 (1.414)	1.00 (1.414)	-5.50 (4.950)
Median	6.50	-5.00	1.00	-5.50
Min, Max	3.0, 10.0	-6.0, -4.0	0.0, 2.0	-9.0, -2.0

Note: The BDI is a self-administered test which consists of 21 questions that measure the severity of depression. Scores range from 0 to 63, with higher
　　scores representing worse depression. Individual missing items are imputed using the average of non-missing scores in each subscale.
Source: Listing 17.2.4.23, Dataset: ADQSS, Program: t_safqsum.sas, Output: t_16-4-9-8-bdi.rtf, Generated on: 28JUL2017 05:58
Page 1 of 2

Table 16.4.9.8 BDI by Visit - Safety Overall Population

Parameter Visit Statistic	GDNF/GDNF (N=21)		Placebo/GDNF (N=20)	
	Value	Change From Baseline	Value	Change From Baseline
BDI Total Score				
Last Study Visit in the Supplemental				
Extension				
n	12	12	11	11
Mean (SD)	6.37 (4.653)	-1.38 (5.300)	5.18 (5.250)	0.18 (7.125)
Median	6.50	-2.00	4.00	-1.00
Min, Max	0.0, 14.0	-14.0, 9.0	0.0, 15.0	-10.0, 13.0

Note: The BDI is a self-administered test which consists of 21 questions that measure the severity of depression. Scores range from 0 to 63, with higher scores representing worse depression. Individual missing items are imputed using the average of non-missing scores in each subscale.
Source: Listing 17.2.4.23, Dataset: ADQSS, Program: t_safqsum.sas, Output: t_16-4-9-8-bdi.rtf, Generated on: 28JUL2017 05:58
Page 2 of 2

Table 16.4.9.9 UPSIT by Visit - Safety Overall Population

Parameter Visit Statistic	GDNF/GDNF (N=21)		Placebo/GDNF (N=20)	
	Value	Change From Baseline	Value	Change From Baseline
UPSIT Total Correct Responses				
Screening (Baseline)				
n	18		20	
Mean (SD)	18.5 (7.16)		23.0 (5.15)	
Median	20.0		23.0	
Min, Max	0, 29		13, 32	
Week 40/e0				
n	17	15	19	19
Mean (SD)	16.5 (8.48)	-0.8 (1.82)	21.3 (7.50)	-1.5 (8.33)
Median	17.0	-1.0	21.0	-1.0
Min, Max	0, 29	-4, 3	0, 32	-32, 8
Week 80/e40				
n	21	18	20	20
Mean (SD)	19.8 (6.45)	1.4 (7.68)	21.2 (6.45)	-1.8 (5.15)
Median	20.0	0.5	20.0	-2.5
Min, Max	10, 32	-7, 29	8, 33	-11, 6

Note: The UPSIT is a self-administered test which can be used to identify and quantitate olfactory dysfunction in PD. The number of correct responses out
of 40 total items constitutes a subject's score. Lower scores represent greater olfactory dysfunction. Individual missing responses are imputed
as zeros (ie, incorrect responses).
Source: Listing 17.2.4.24, Dataset: ADQSS, Program: t_safqsum.sas, Output: t_16-4-9-9-upsit.rtf, Generated on: 28JUL2017 05:58
Page 1 of 2

Table 16.4.9.9 UPSIT by Visit - Safety Overall Population

UPSIT Score Interpretation		
Test Score (Males)	**Test Score (Females)**	**Olfactory Diagnosis**
0-5	0-5	Probable malingering
6-18	6-18	Total anosmia
19-25	19-25	Severe microsmia
26-29	26-30	Moderate microsmia
30-33	31-34	Mild microsmia
34-40	35-40	Normosmia

Note: The UPSIT is a self-administered test which can be used to identify and quantitate olfactory dysfunction in PD. The number of correct responses out of 40 total items constitutes a subject's score. Lower scores represent greater olfactory dysfunction. Individual missing responses are imputed as zeros (ie, incorrect responses).
Source: Listing 17.2.4.24, Dataset: ADQSS, Program: t_safqsum.sas, Output: t_16-4-9-9-upsit.rtf, Generated on: 28JUL2017 05:58
Page 2 of 2

Table of Contents
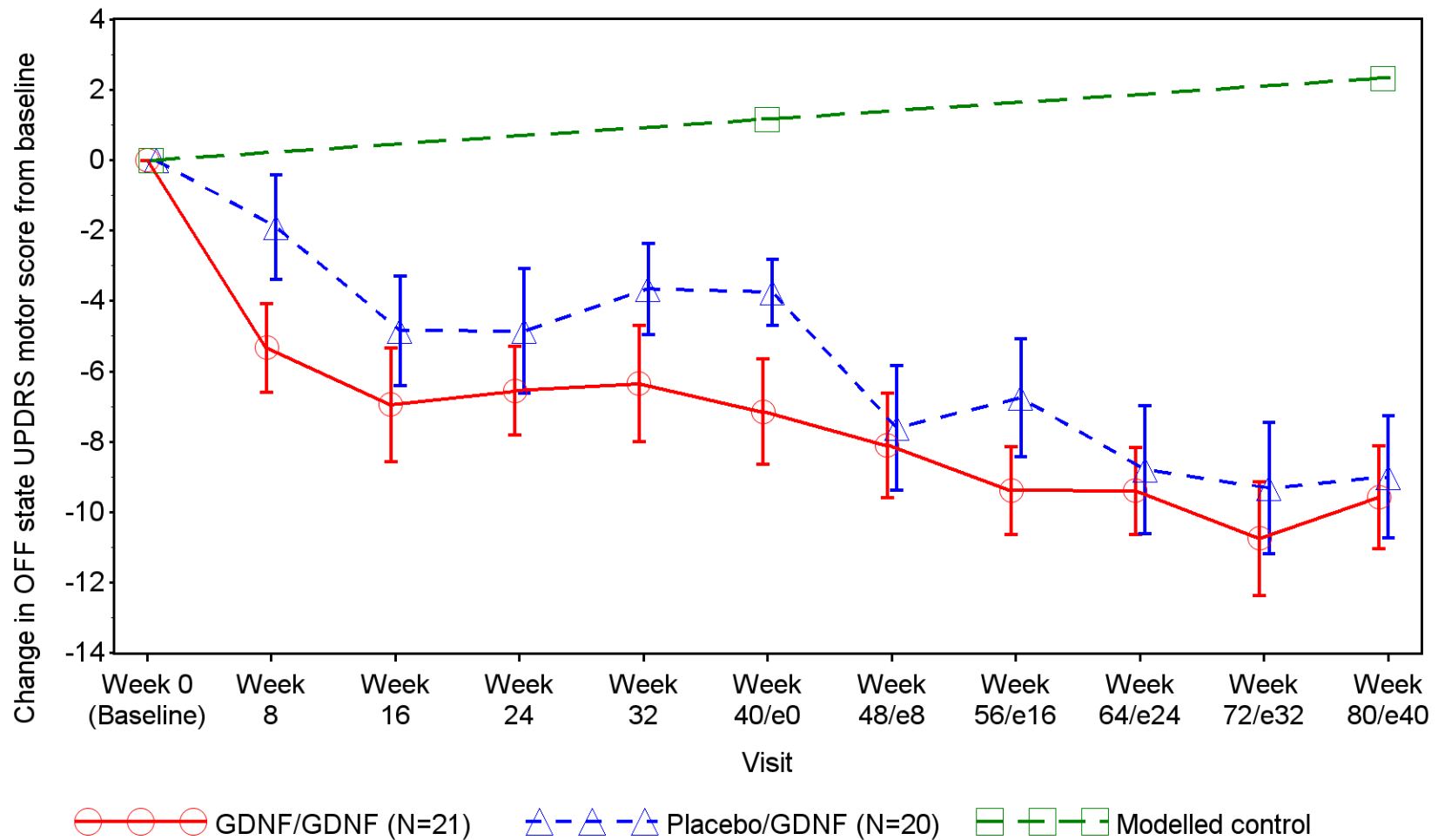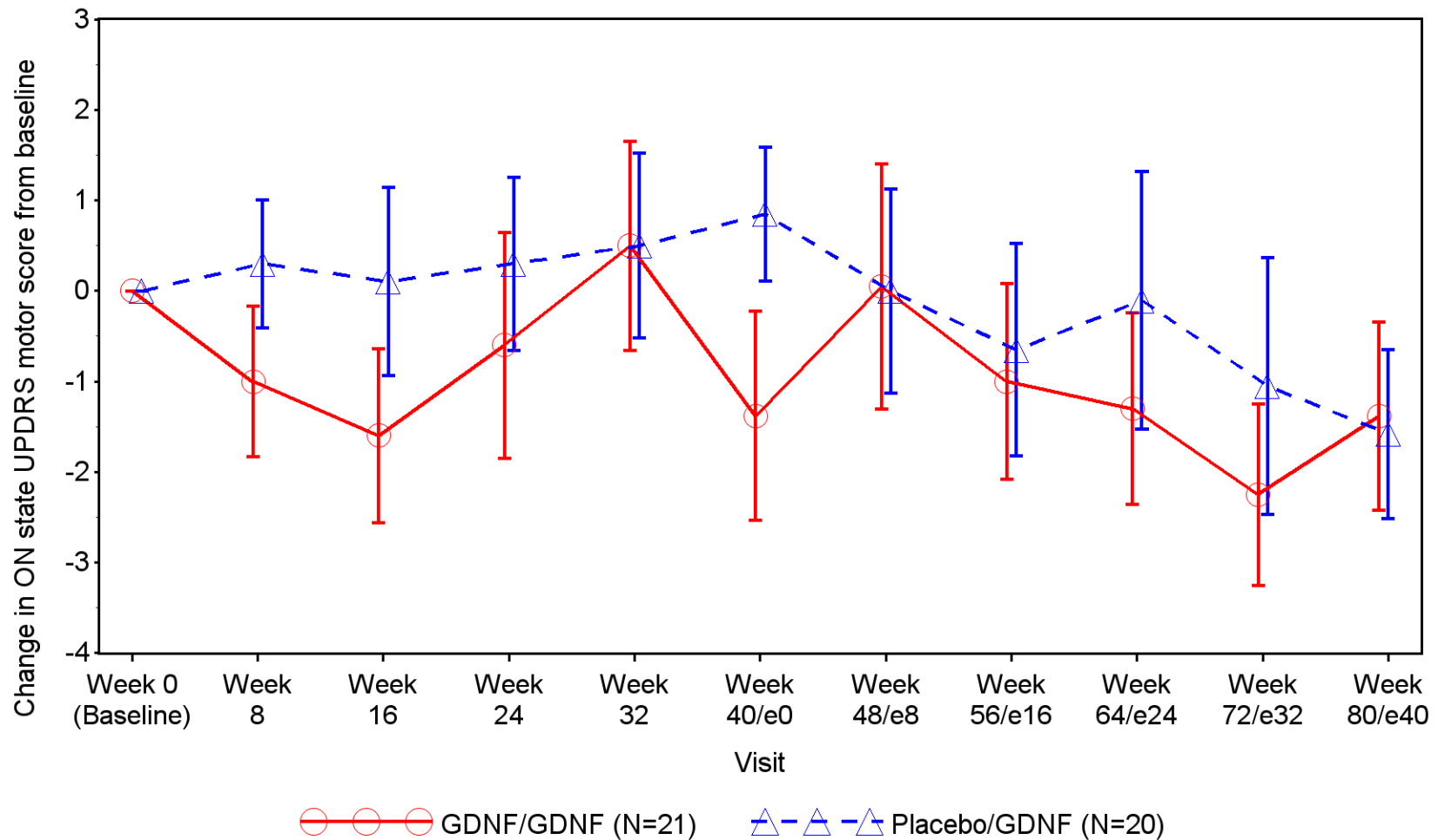
Table of Contents

Figure 16.5.1.1.1 OFF State UPDRS Motor Score (Part III): Percentage Change Over Time - ITT Primary Population
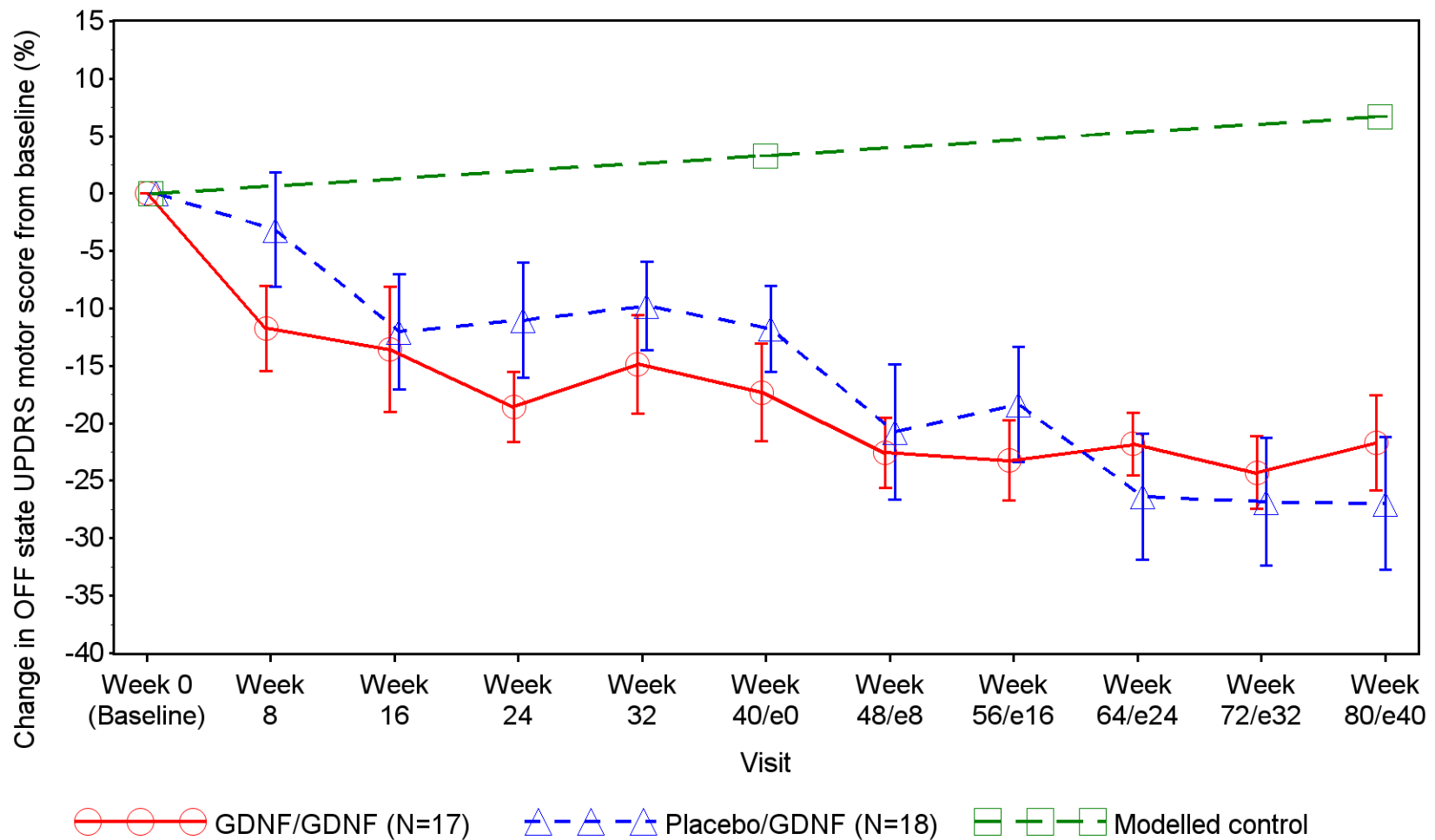
Note: Data points represent means, and error bars represent standard errors. For subject 45, items 22, 27, 28, 29 and 30 are excluded from the score. P-value from a mixed-effect model with repeated measures (MMRM) for the percentage change from baseline to Week 80/e40 between treatment groups is 0.4078.

Source: Listing 17.2.2.1, Dataset: ADQUPDRS, Program: f_updrs.sas, Output: f_16-5-1-1-1-updrs.rtf, Generated on: 28JUL2017 06:56
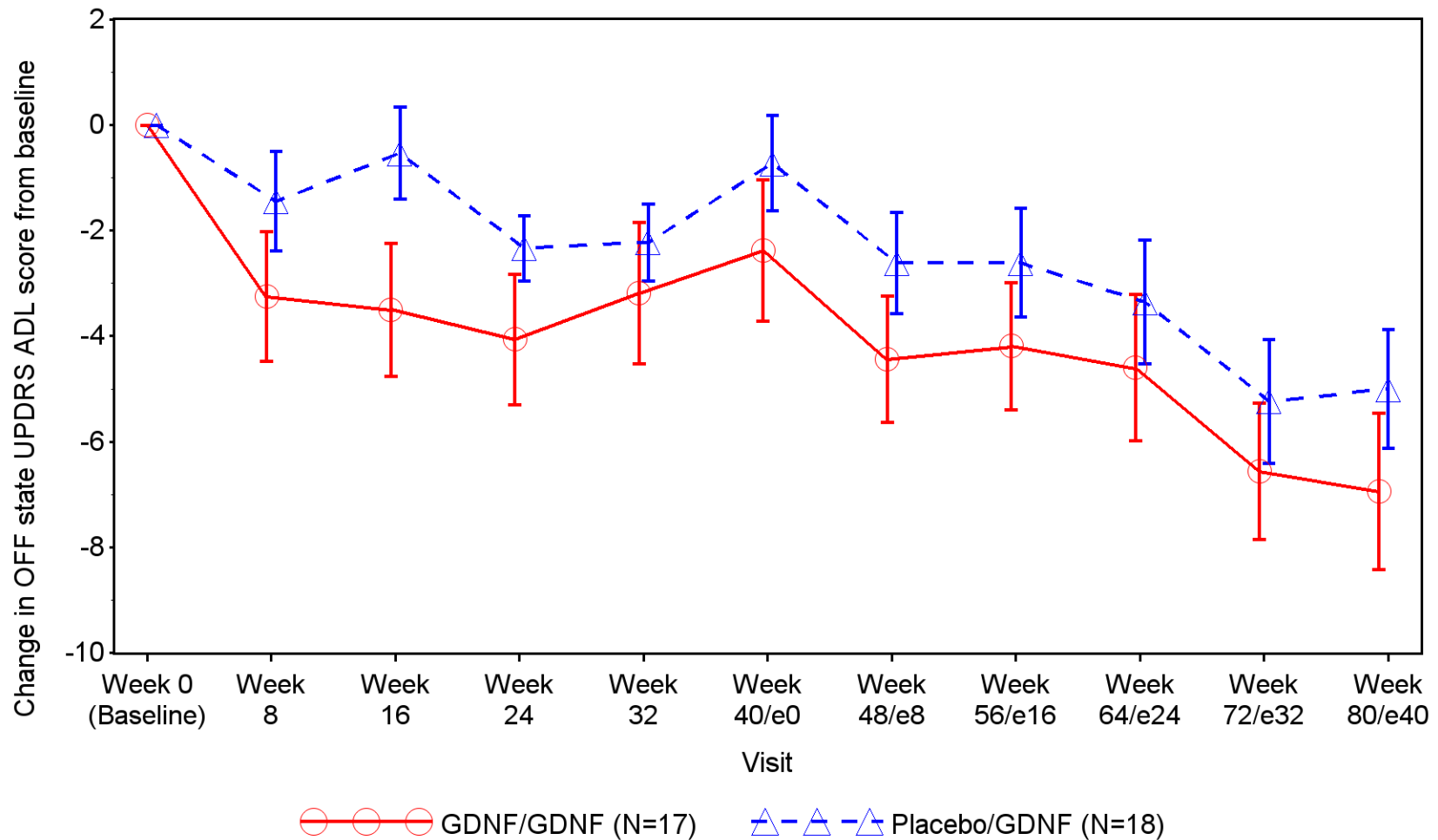
Figure 16.5.1.1.2 OFF State UPDRS Motor Score (Part III): Percentage Change Over Time - ITT Overall Population
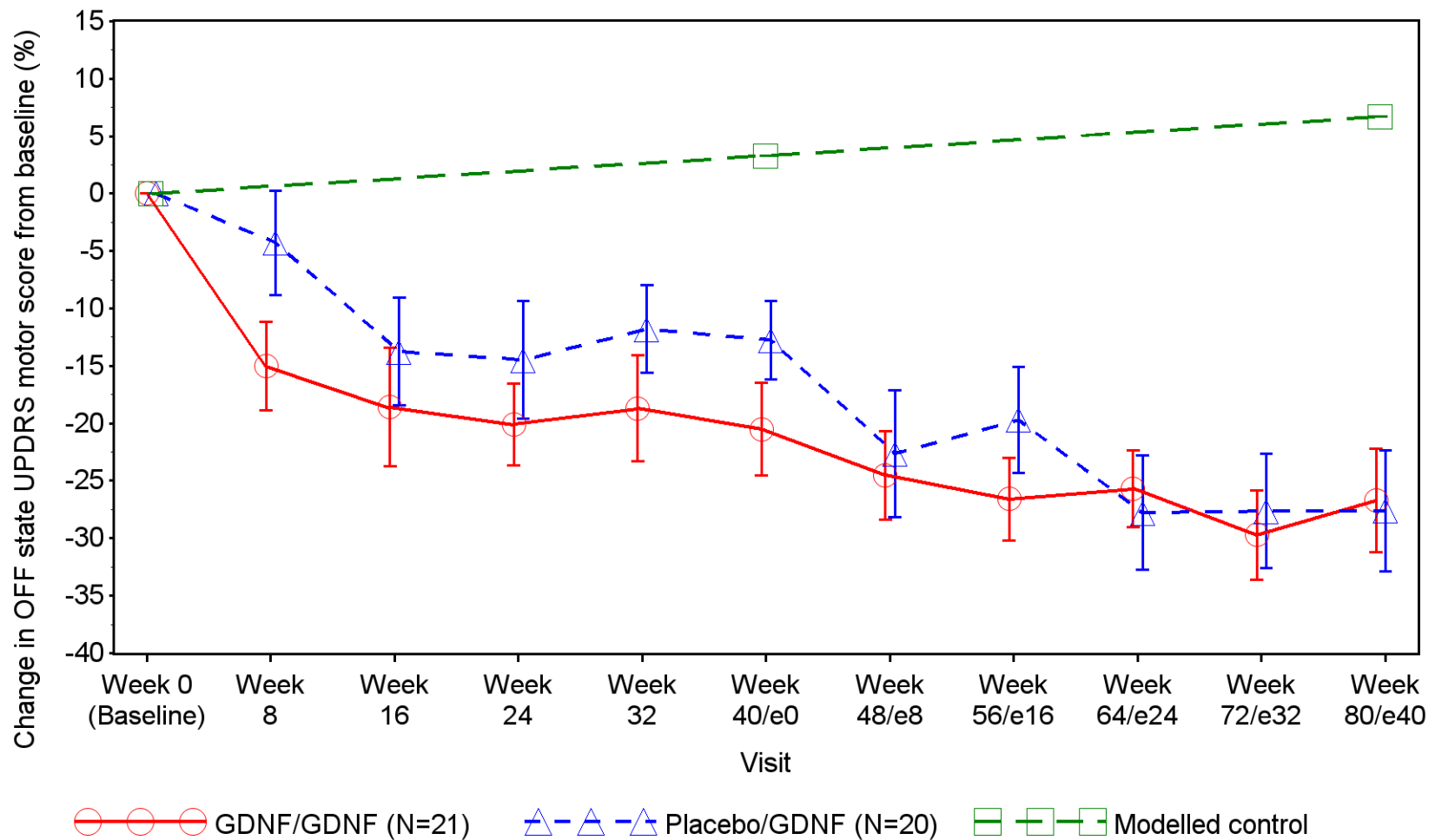
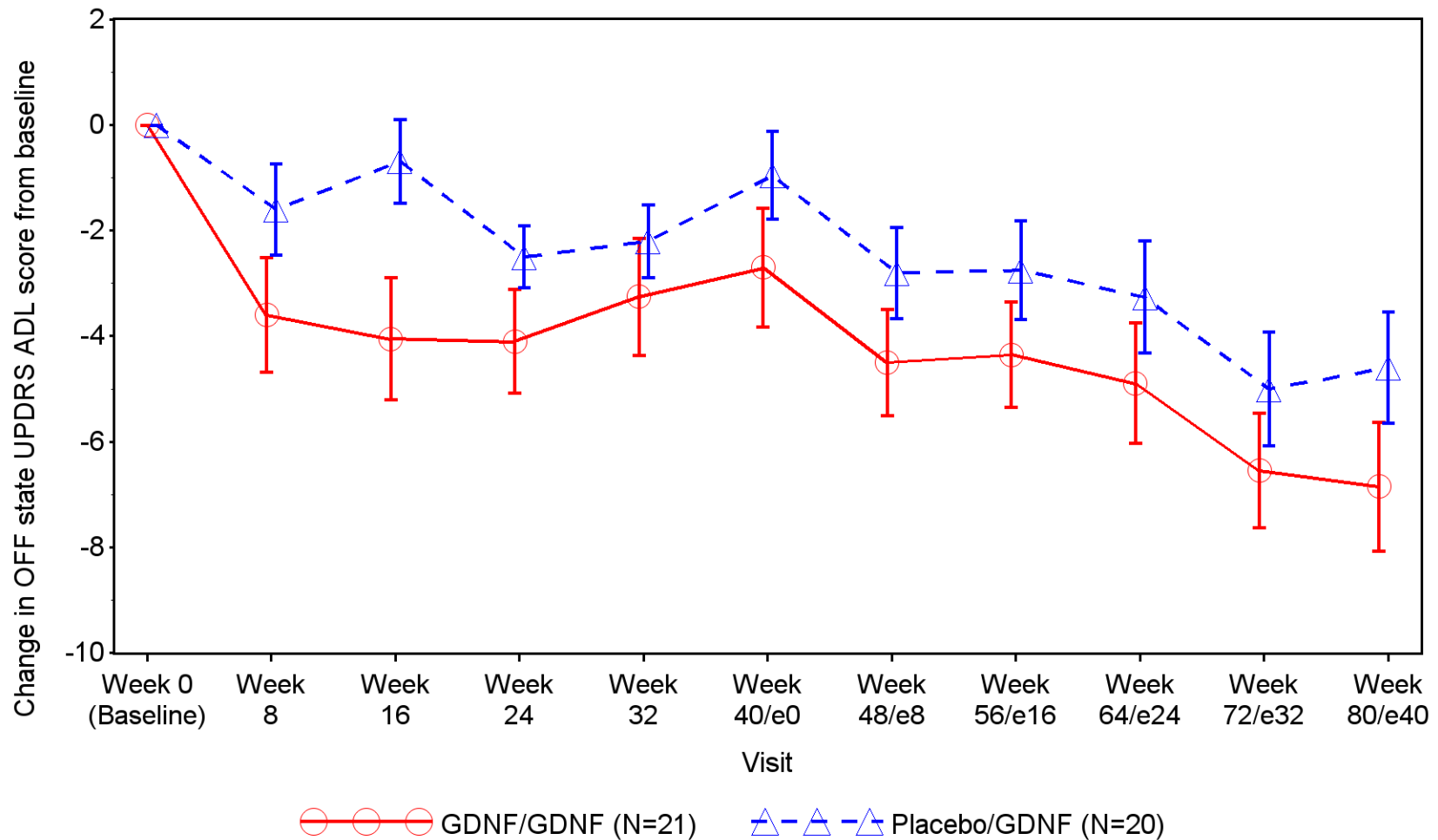Note: Data points represent means, and error bars represent standard errors. For subject 45, items 22, 27, 28, 29 and 30 are excluded from the score. P-value from a mixed-effect model with repeated measures (MMRM) for the percentage change from baseline to Week 80/e40 between treatment groups is 0.9587.

Source: Listing 17.2.2.1, Dataset: ADQUPDRS, Program: f_updrs.sas, Output: f_16-5-1-1-2-updrs.rtf, Generated on: 28JUL2017 06:57

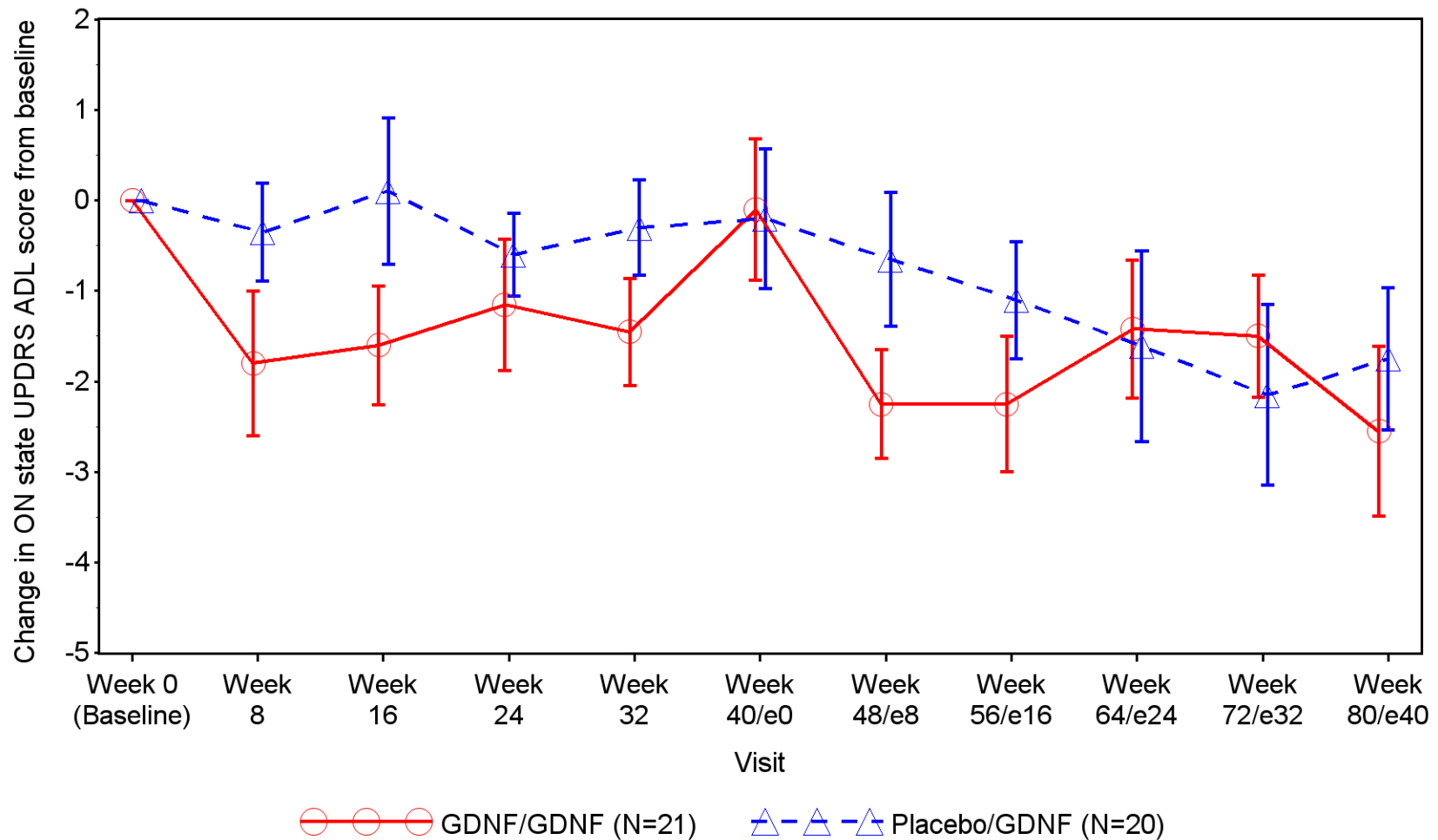**Figure 16.5.1.2.1 OFF State UPDRS Motor Score (Part III): Change Over Time - ITT Primary Population**
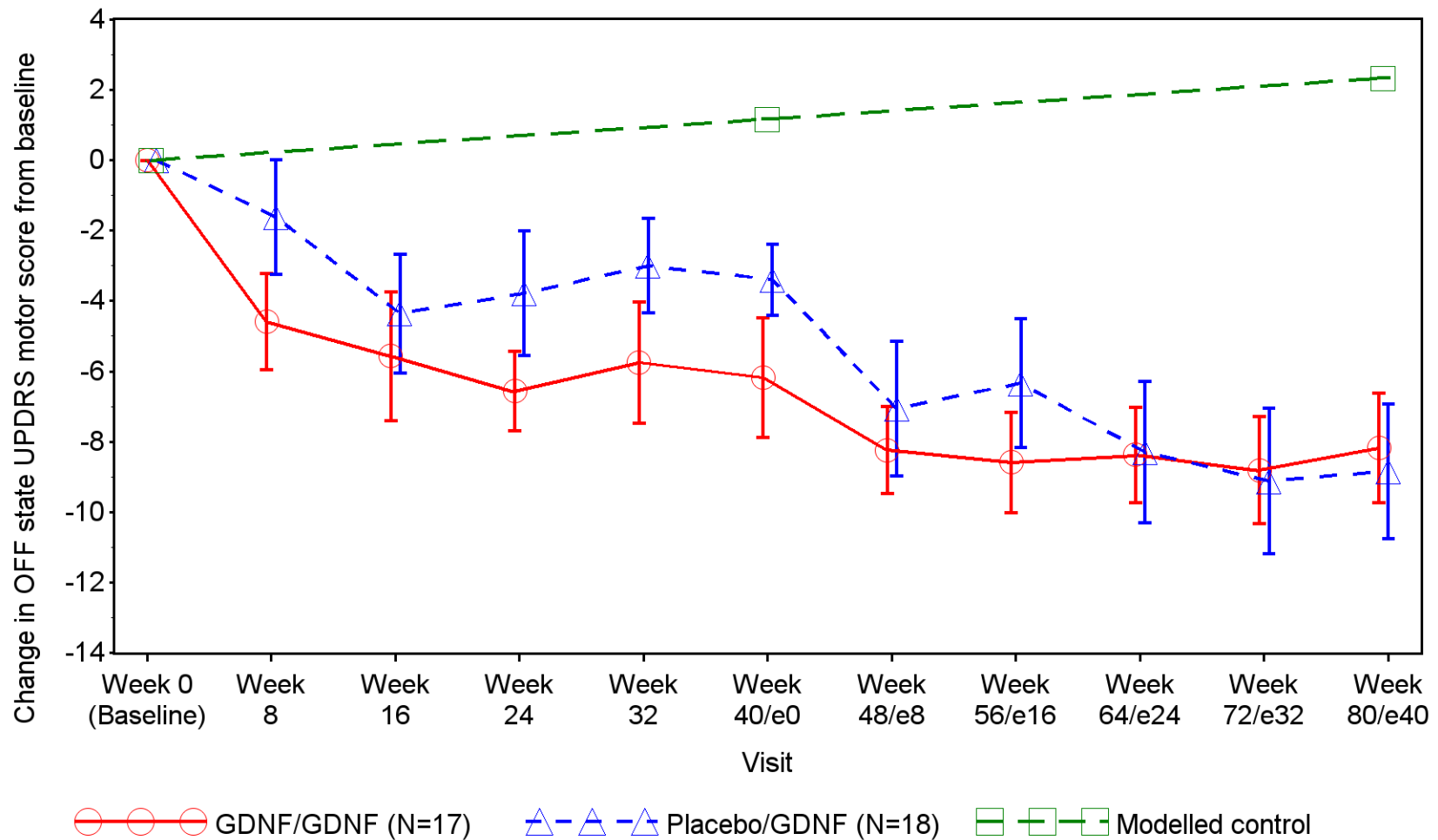
Note: Data points represent means, and error bars represent standard errors. For subject 45, items 22, 27, 28, 29 and 30 are excluded from the score. P-value from a mixed-effect model with repeated measures (MMRM) for the change from baseline to Week 80/e40 between treatment groups is 0.5564.

Source: Listing 17.2.2.1, Dataset: ADQUPDRS, Program: f_updrs.sas, Output: f_16-5-1-2-1-updrs.rtf, Generated on: 28JUL2017 06:57

Figure 16.5.1.2.2 OFF State UPDRS Motor Score (Part III): Change Over Time - ITT Overall Population

Note: Data points represent means, and error bars represent standard errors. For subject 45, items 22, 27, 28, 29 and 30 are excluded from the score. P-value from a mixed-effect model with repeated measures (MMRM) for the change from baseline to Week 80/e40 between treatment groups is 0.9929.

Source: Listing 17.2.2.1, Dataset: ADQUPDRS, Program: f_updrs.sas, Output: f_16-5-1-2-2-updrs.rtf, Generated on: 28JUL2017 06:57

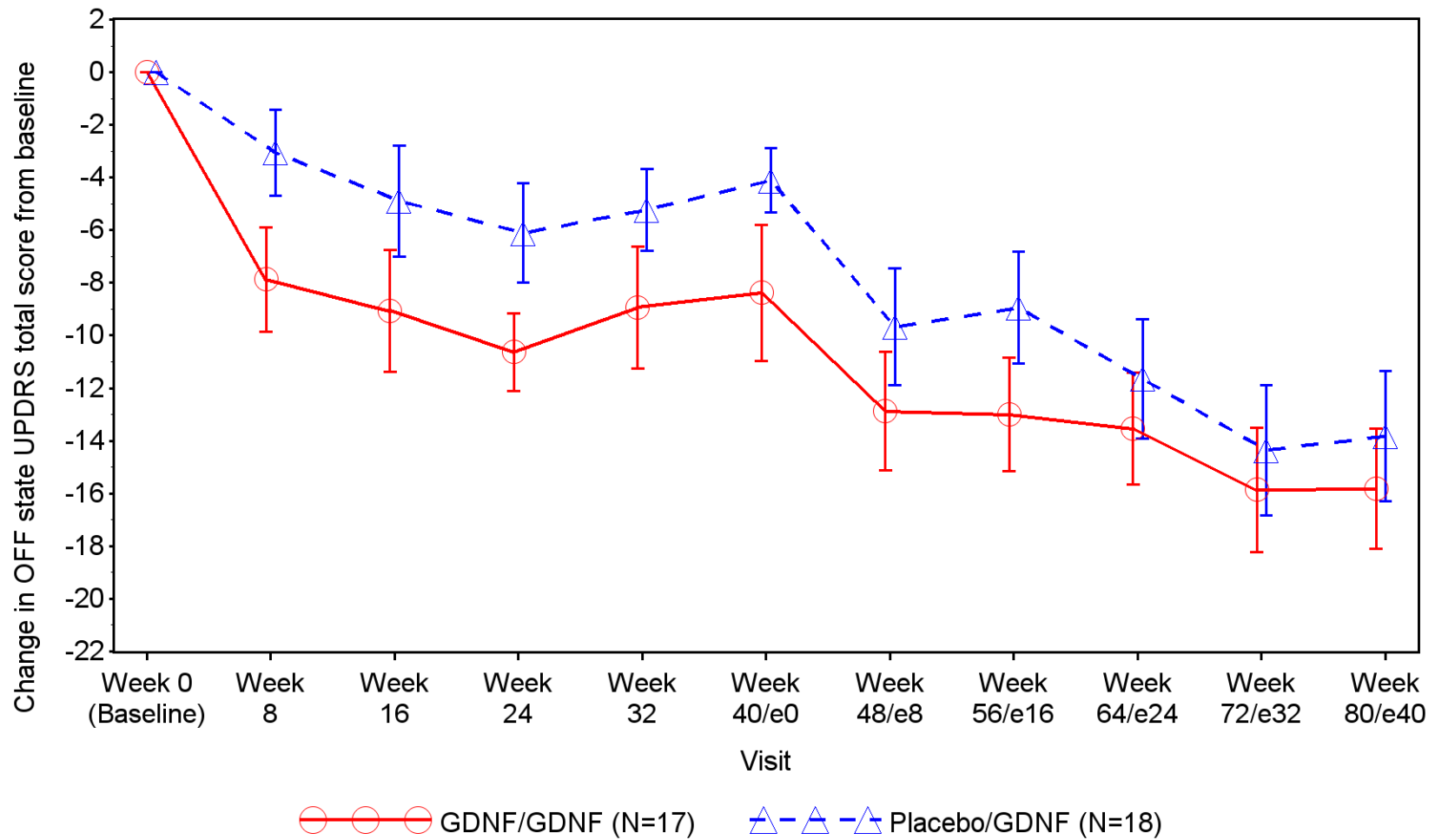**Figure 16.5.1.3 ON State UPDRS Motor Score (Part III): Change Over Time - ITT Overall Population**

Note: Data points represent means, and error bars represent standard errors. For subject 45, items 22, 27, 28, 29 and 30 are excluded from the score.
Source: Listing 17.2.2.1, Dataset: ADQUPDRS, Program: f_updrs.sas, Output: f_16-5-1-3-updrs.rtf, Generated on: 28JUL2017 06:57
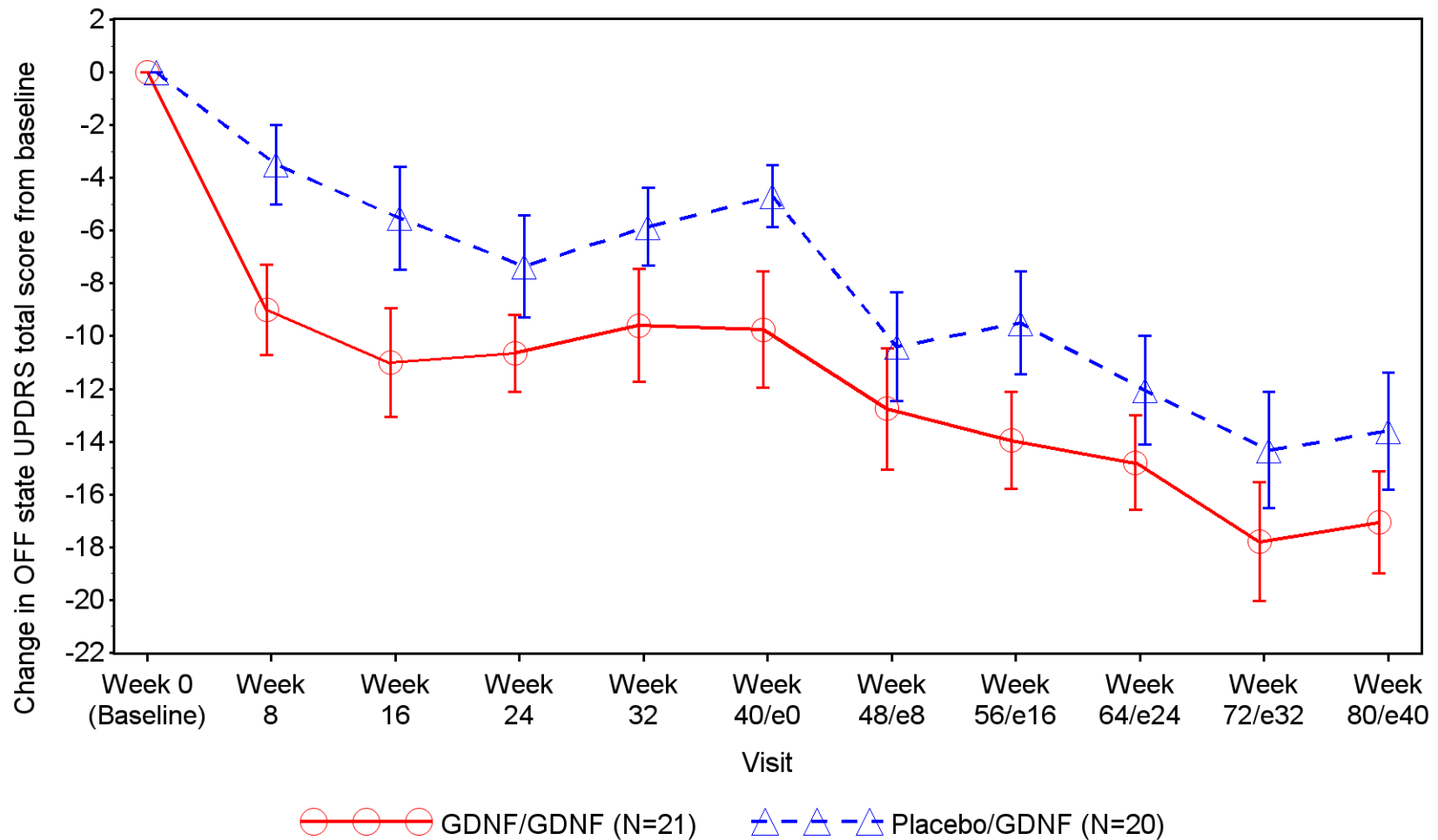
Figure 16.5.1.4.1 OFF State UPDRS ADL Score (Part II): Change Over Time - ITT Primary Population
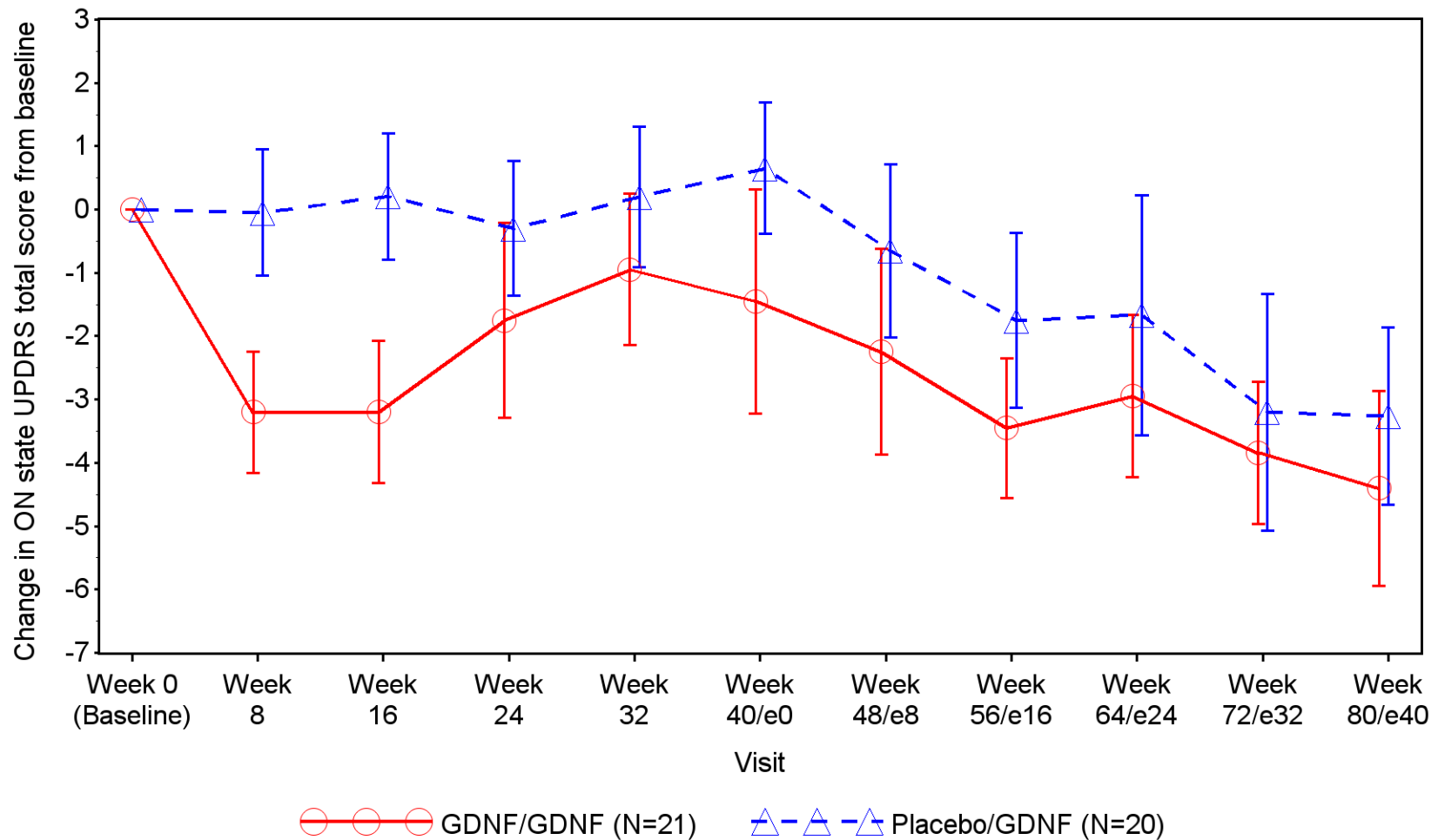

Note: Data points represent means, and error bars represent standard errors. Data for Subject 45 are excluded from analysis.
Source: Listing 17.2.2.1, Dataset: ADQUPDRS, Program: f_updrs.sas, Output: f_16-5-1-4-1-updrs.rtf, Generated on: 28JUL2017 06:57

Figure 16.5.1.4.2 OFF State UPDRS ADL Score (Part II): Change Over Time - ITT Overall Population

Note: Data points represent means, and error bars represent standard errors. Data for Subject 45 are excluded from analysis.
Source: Listing 17.2.2.1, Dataset: ADQUPDRS, Program: f_updrs.sas, Output: f_16-5-1-4-2-updrs.rtf, Generated on: 28JUL2017 06:57
Page 1 of 1

Figure 16.5.1.5 ON State UPDRS ADL Score (Part II): Change Over Time - ITT Overall Population

Note: Data points represent means, and error bars represent standard errors. Data for Subject 45 are excluded from analysis.
Source: Listing 17.2.2.1, Dataset: ADQUPDRS, Program: f_updrs.sas, Output: f_16-5-1-5-updrs.rtf, Generated on: 28JUL2017 06:57

Figure 16.5.1.6.1 OFF State UPDRS Total Score: Change Over Time - ITT Primary Population
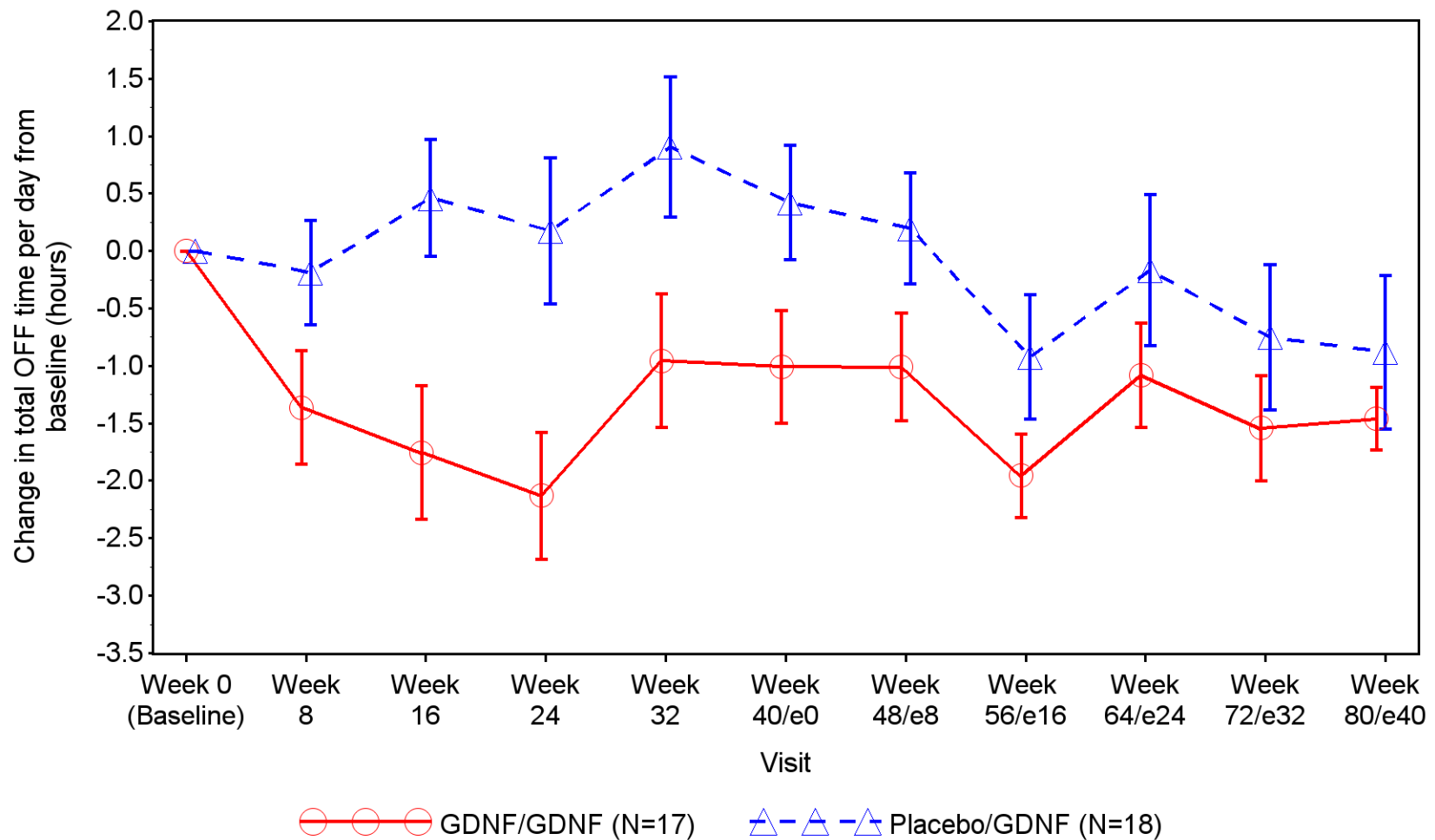

Note: Data points represent means, and error bars represent standard errors. Data for Subject 45 are excluded from analysis.
Source: Listing 17.2.2.1, Dataset: ADQUPDRS, Program: f_updrs.sas, Output: f_16-5-1-6-1-updrs.rtf, Generated on: 28JUL2017 06:57
Page 1 of 1

Figure 16.5.1.6.2 OFF State UPDRS Total Score: Change Over Time - ITT Overall Population

Note: Data points represent means, and error bars represent standard errors. Data for Subject 45 are excluded from analysis.
Source: Listing 17.2.2.1, Dataset: ADQUPDRS, Program: f_updrs.sas, Output: f_16-5-1-6-2-updrs.rtf, Generated on: 28JUL2017 06:57

Figure 16.5.1.7 ON State UPDRS Total Score: Change Over Time - ITT Overall Population

Note: Data points represent means, and error bars represent standard errors. Data for Subject 45 are excluded from analysis.
Source: Listing 17.2.2.1, Dataset: ADQUPDRS, Program: f_updrs.sas, Output: f_16-5-1-7-updrs.rtf, Generated on: 28JUL2017 06:57
Page 1 of 1   Page 563

Figure 16.5.2.1 Motor Fluctuation Diary Total OFF Time Per Day (Hours): Change Over Time - ITT Primary Population
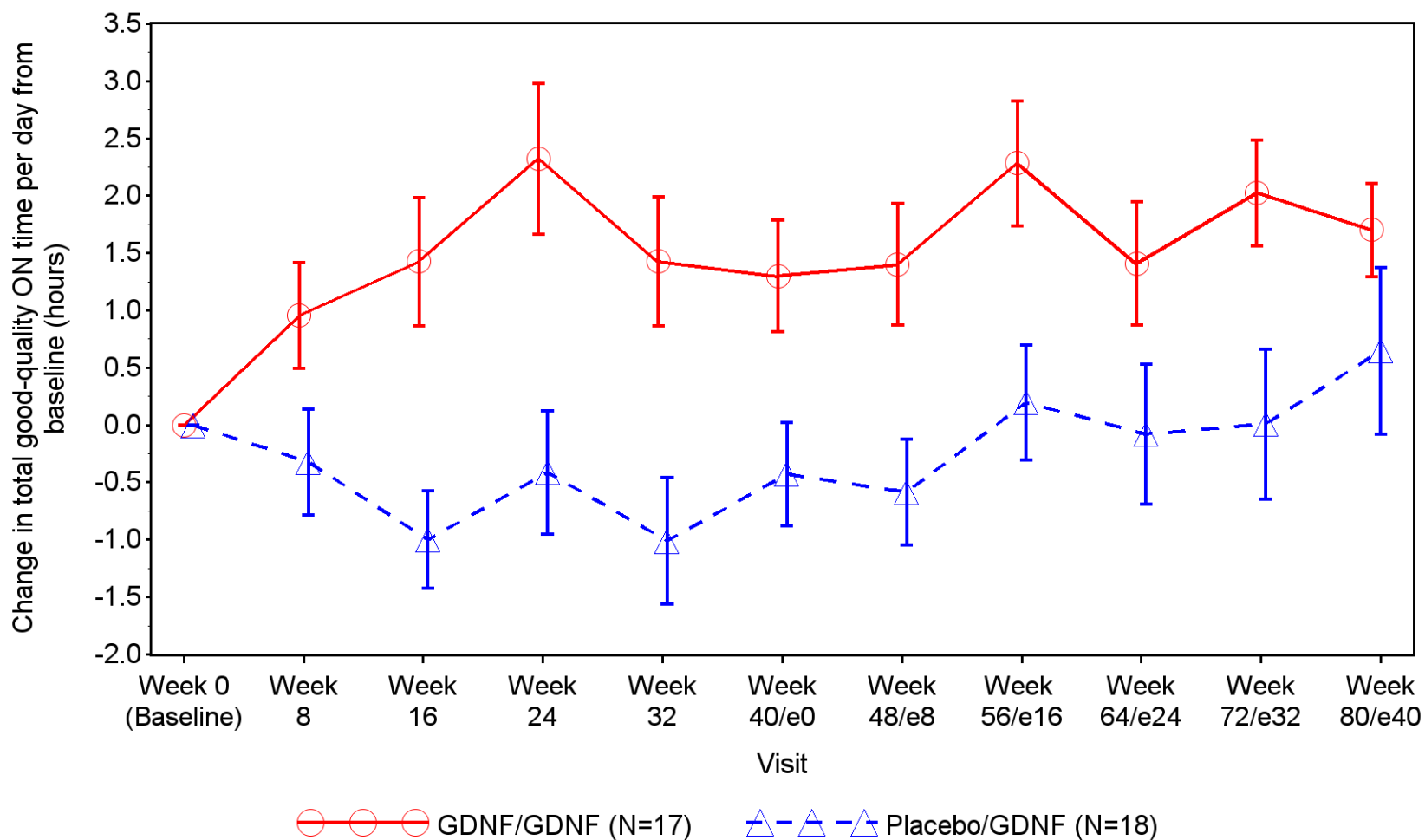

Note: Data points represent means, and error bars represent standard errors.
Source: Listing 17.2.2.2, Dataset: ADDIA, Program: f_pddiary.sas, Output: f_16-5-2-1-pddiary.rtf, Generated on: 28JUL2017 06:57
Page 1 of 1

Figure 16.5.2.2 Motor Fluctuation Diary Total OFF Time Per Day (Hours): Change Over Time - ITT Overall Population
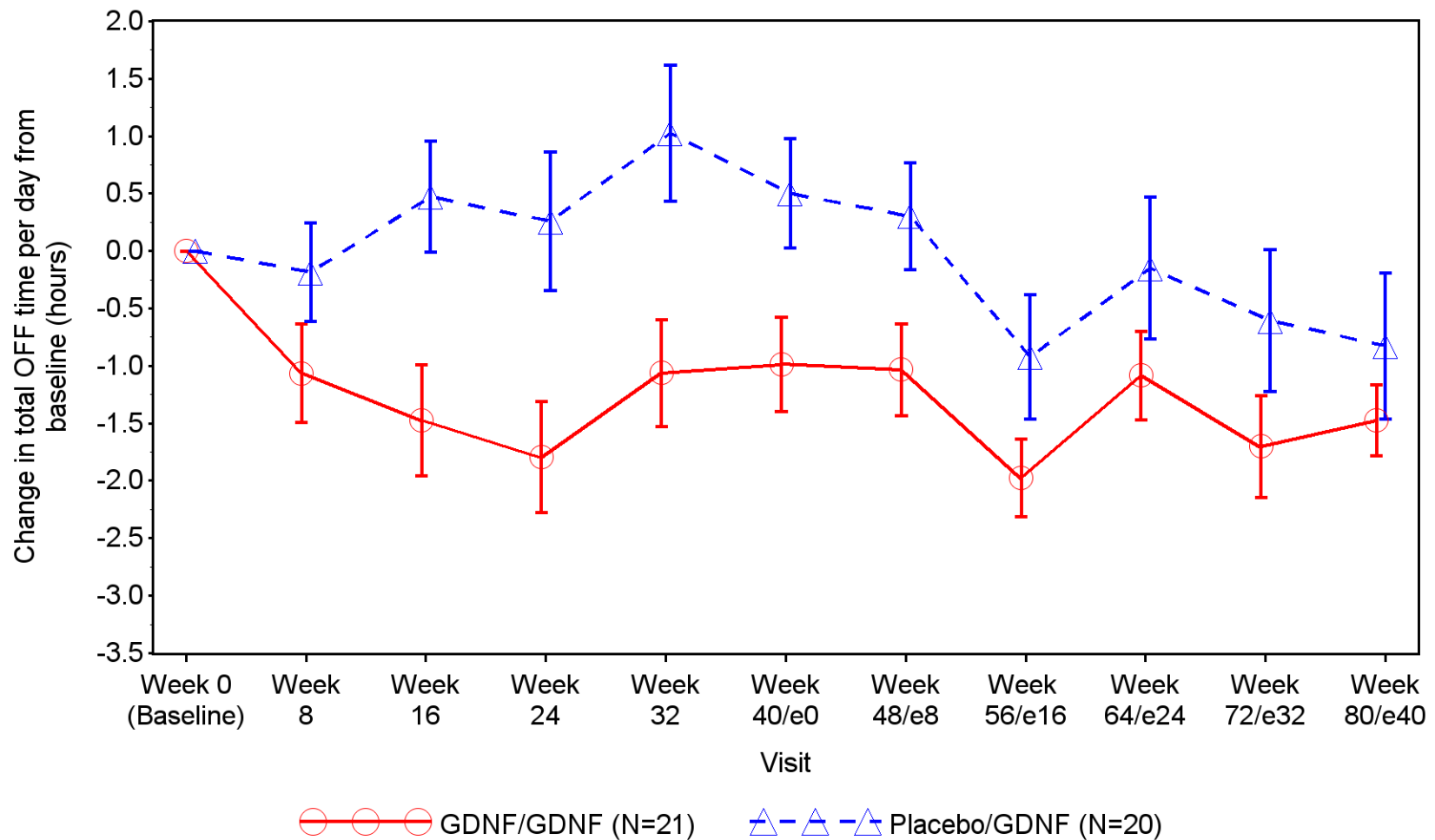
Note: Data points represent means, and error bars represent standard errors.
Source: Listing 17.2.2.2, Dataset: ADDIA, Program: f_pddiary.sas, Output: f_16-5-2-2-pddiary.rtf, Generated on: 28JUL2017 06:57
Page 1 of 1

Figure 16.5.2.3 Motor Fluctuation Diary Total Good-Quality ON Time Per Day (Hours): Change Over Time - ITT Primary Population
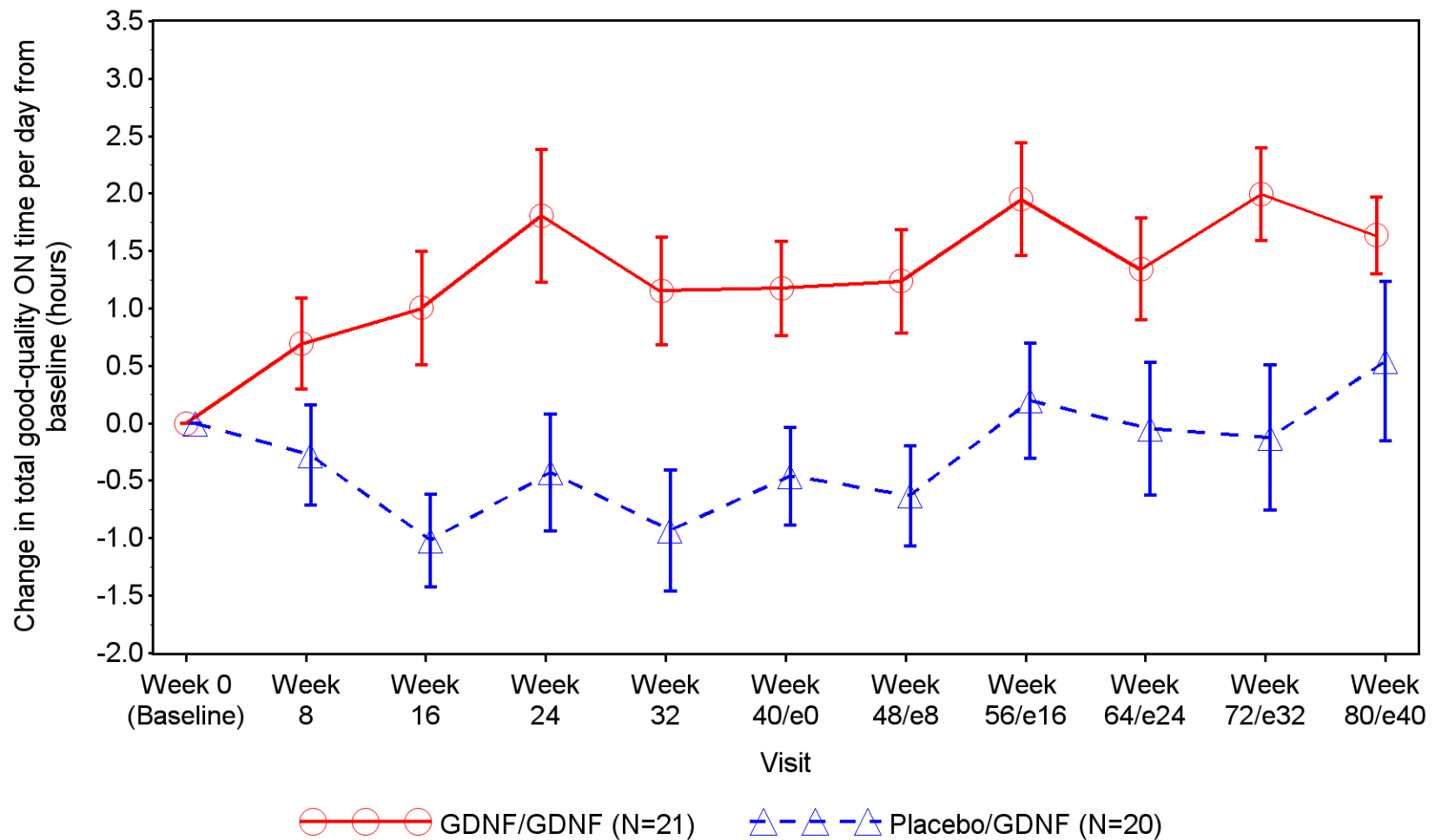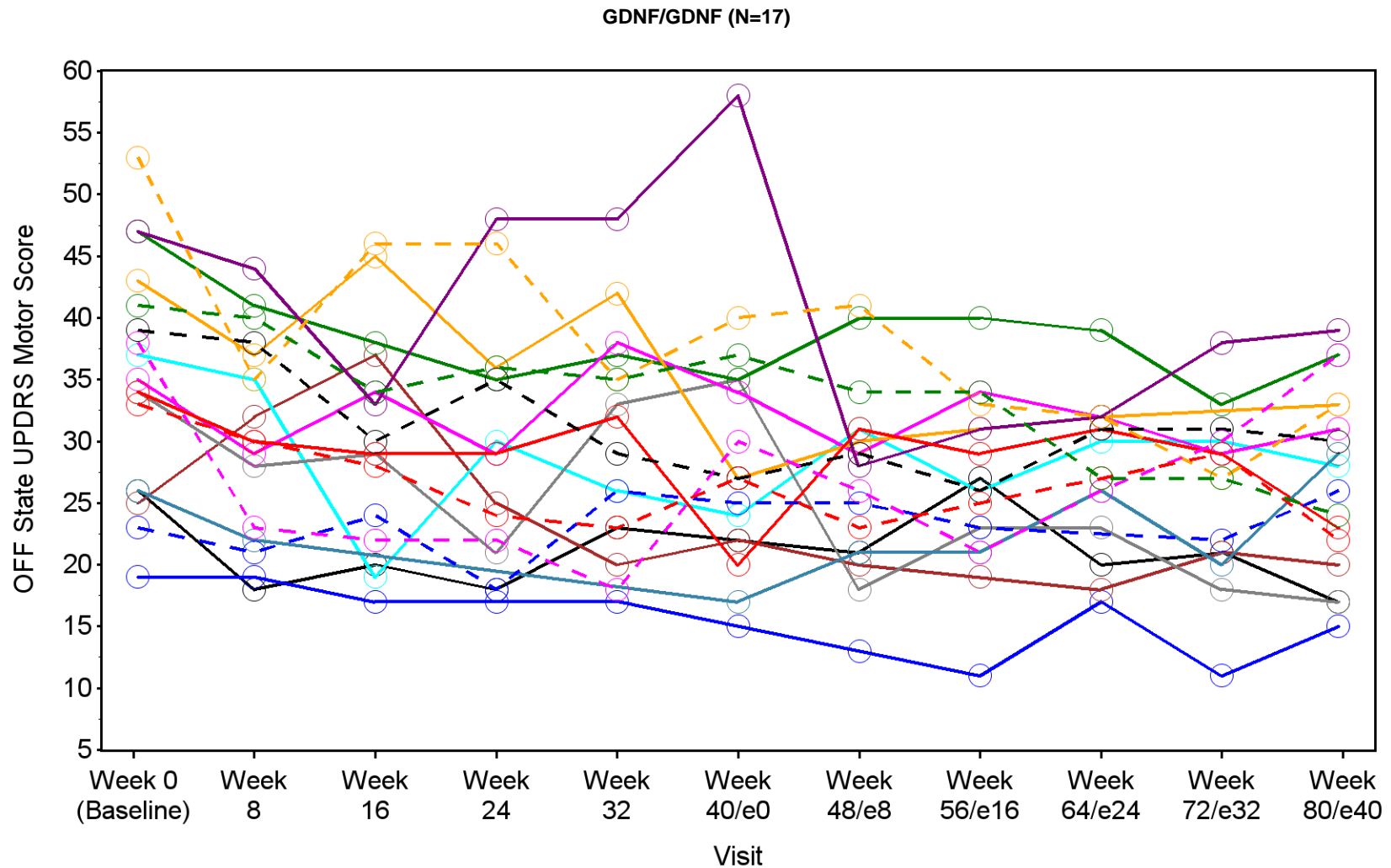

Note: Data points represent means, and error bars represent standard errors.
Note: Total good-quality ON time per day is defined as the sum of ON time per day without dyskinesias + ON time per day with non-troublesome dyskinesias.
Source: Listing 17.2.2.2, Dataset: ADDIA, Program: f_pddiary.sas, Output: f_16-5-2-3-pddiary.rtf, Generated on: 28JUL2017 06:57
Page 1 of 1

Figure 16.5.2.4 Motor Fluctuation Diary Total Good-Quality ON Time Per Day (Hours): Change Over Time - ITT Overall Population

Note: Data points represent means, and error bars represent standard errors.

Note: Total good-quality ON time per day is defined as the sum of ON time per day without dyskinesias + ON time per day with non-troublesome dyskinesias.

Source: Listing 17.2.2.2, Dataset: ADDIA, Program: f_pddiary.sas, Output: f_16-5-2-4-pddiary.rtf, Generated on: 28JUL2017 06:57
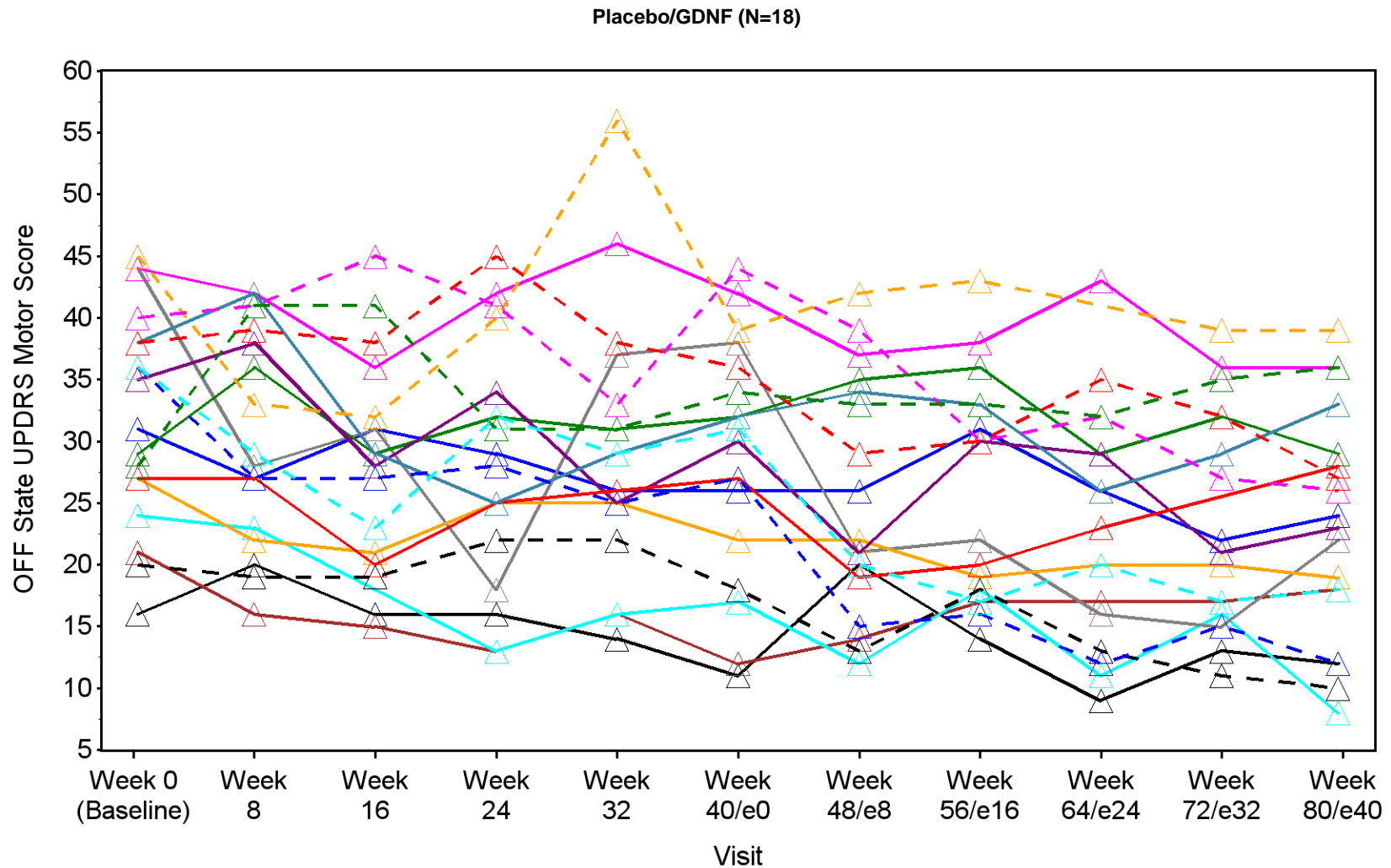
Page 1 of 1

Figure 16.5.3 OFF State UPDRS Motor Score (Part III): Subject Scores Over Time - ITT Primary Population

GDNF/GDNF (N=17)

Note: For subject 45, items 22, 27, 28, 29 and 30 are excluded from the score.
Source: Listing 17.2.2.1, Dataset: ADQUPDRS, Program: f_updrs-subj.sas, Output: f_16-5-3-updrs-subj.rtf, Generated on: 28JUL2017 06:57
Page 1 of 2   Page 568

Figure 16.5.3 OFF State UPDRS Motor Score (Part III): Subject Scores Over Time - ITT Primary Population

Placebo/GDNF (N=18)

Note: For subject 45, items 22, 27, 28, 29 and 30 are excluded from the score.
Source: Listing 17.2.2.1, Dataset: ADQUPDRS, Program: f_updrs-subj.sas, Output: f_16-5-3-updrs-subj.rtf, Generated on: 28JUL2017 06:57
Page 2 of 2   Page 569

Figure 16.5.4.1 OFF State UPDRS Motor Score (Part III): Frequency Distribution of Change at Week 40/e0 - ITT Overall Population

Change in OFF state UPDRS motor score at Week 40/e0 from baseline
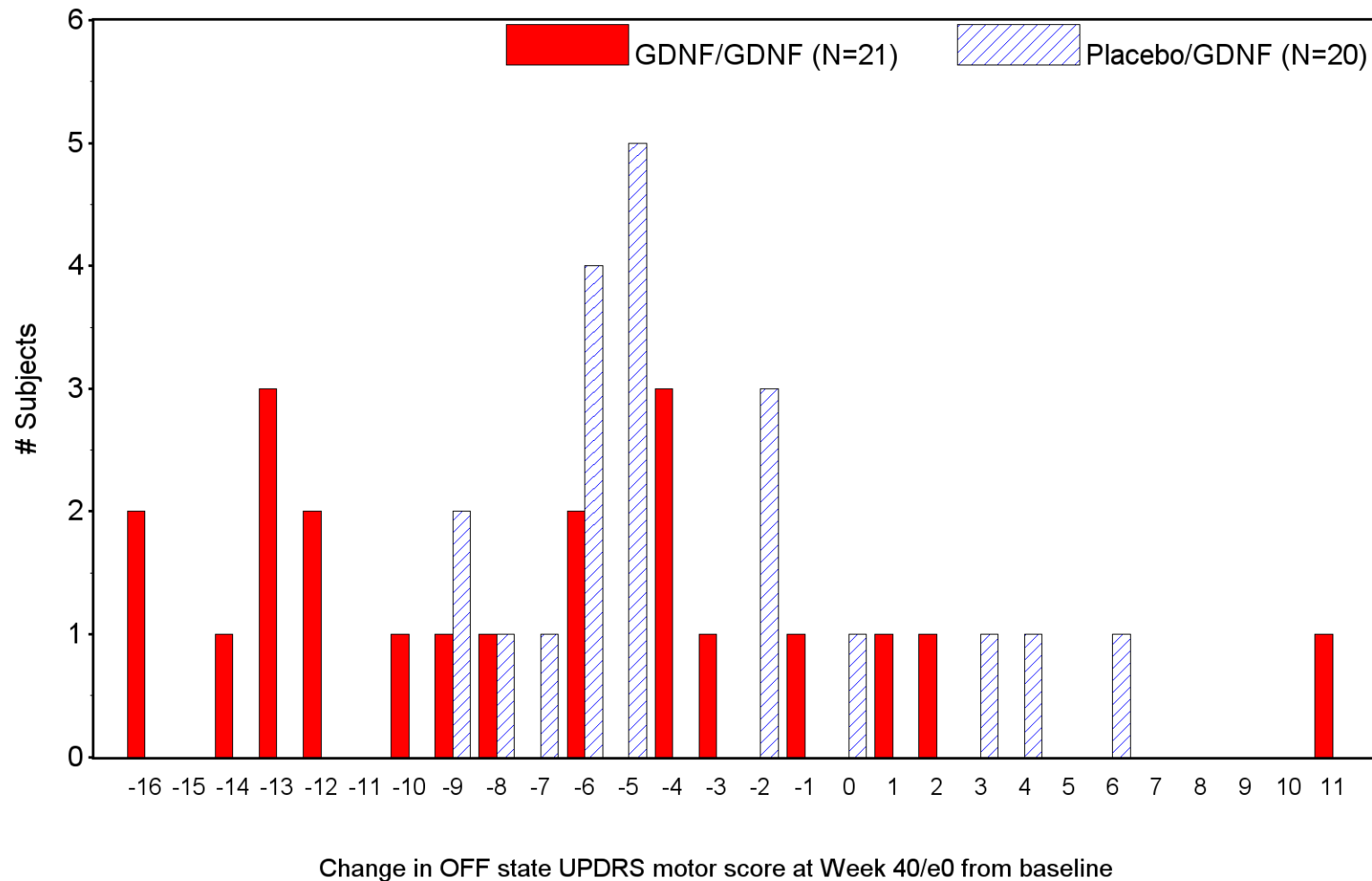
Note: For subject 45, items 22, 27, 28, 29 and 30 are excluded from the score.
Source: Listing 17.2.2.1, Dataset: ADQUPDRS, Program: f_updrs-freq.sas, Output: f_16-5-4-1-updrs-freq.rtf, Generated on: 28JUL2017 06:57

Figure 16.5.4.2 OFF State UPDRS Motor Score (Part III): Frequency Distribution of Change at Week 80/e40 - ITT Overall Population

Change in OFF state UPDRS motor score at Week 80/e40 from baseline
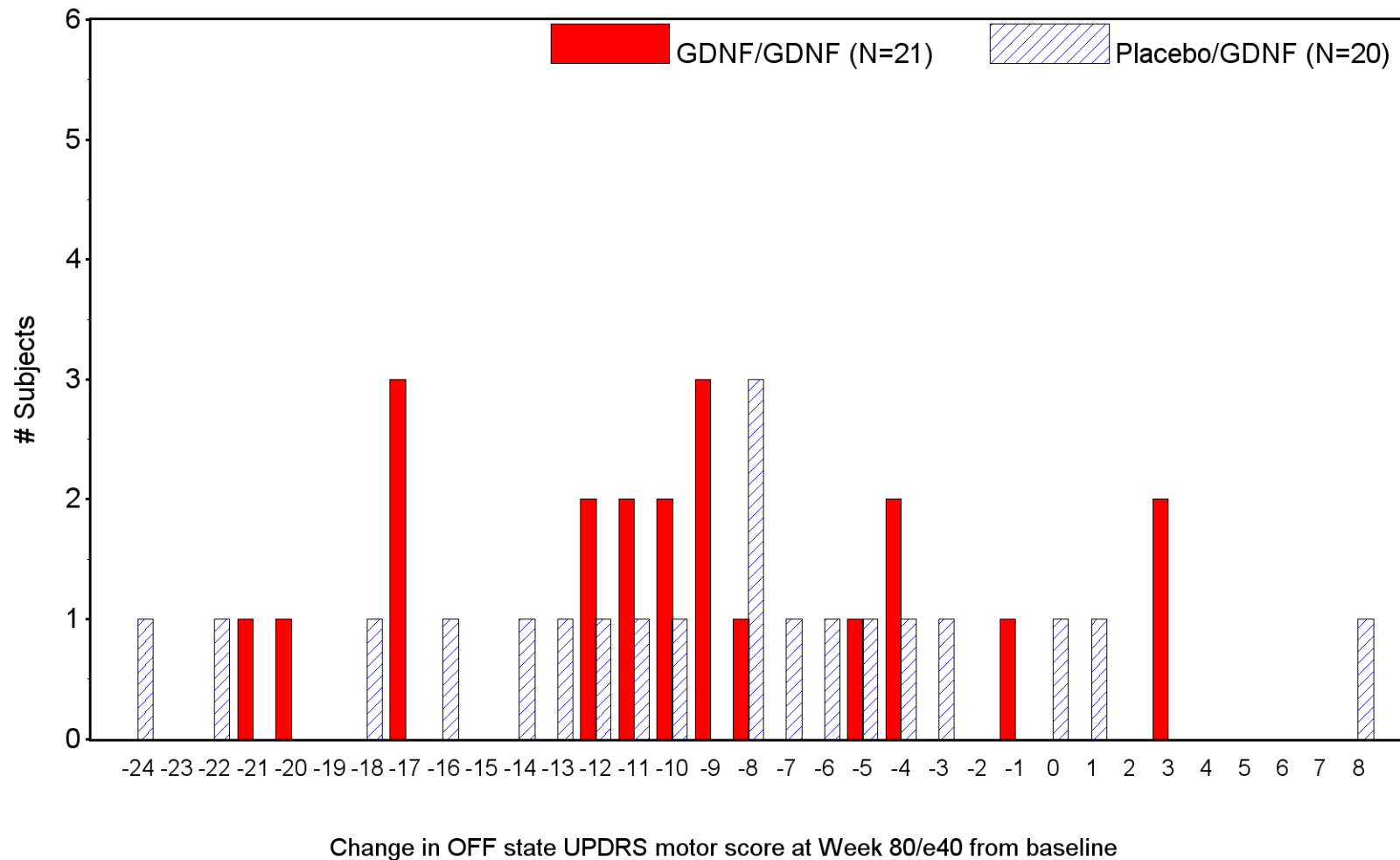
Note: For subject 45, items 22, 27, 28, 29 and 30 are excluded from the score.
Source: Listing 17.2.2.1, Dataset: ADQUPDRS, Program: f_updrs-freq.sas, Output: f_16-5-4-2-updrs-freq.rtf, Generated on: 28JUL2017 06:57

Figure 16.5.5.1 Correlation Analysis of Percentage Change from Baseline to Week 80/e40 in OFF State UPDRS Motor Score (Part III) to Volume of Interest Coverage at Baseline as Determined by Contrast-Enhanced T1-Weighted MRI - ITT Primary Population
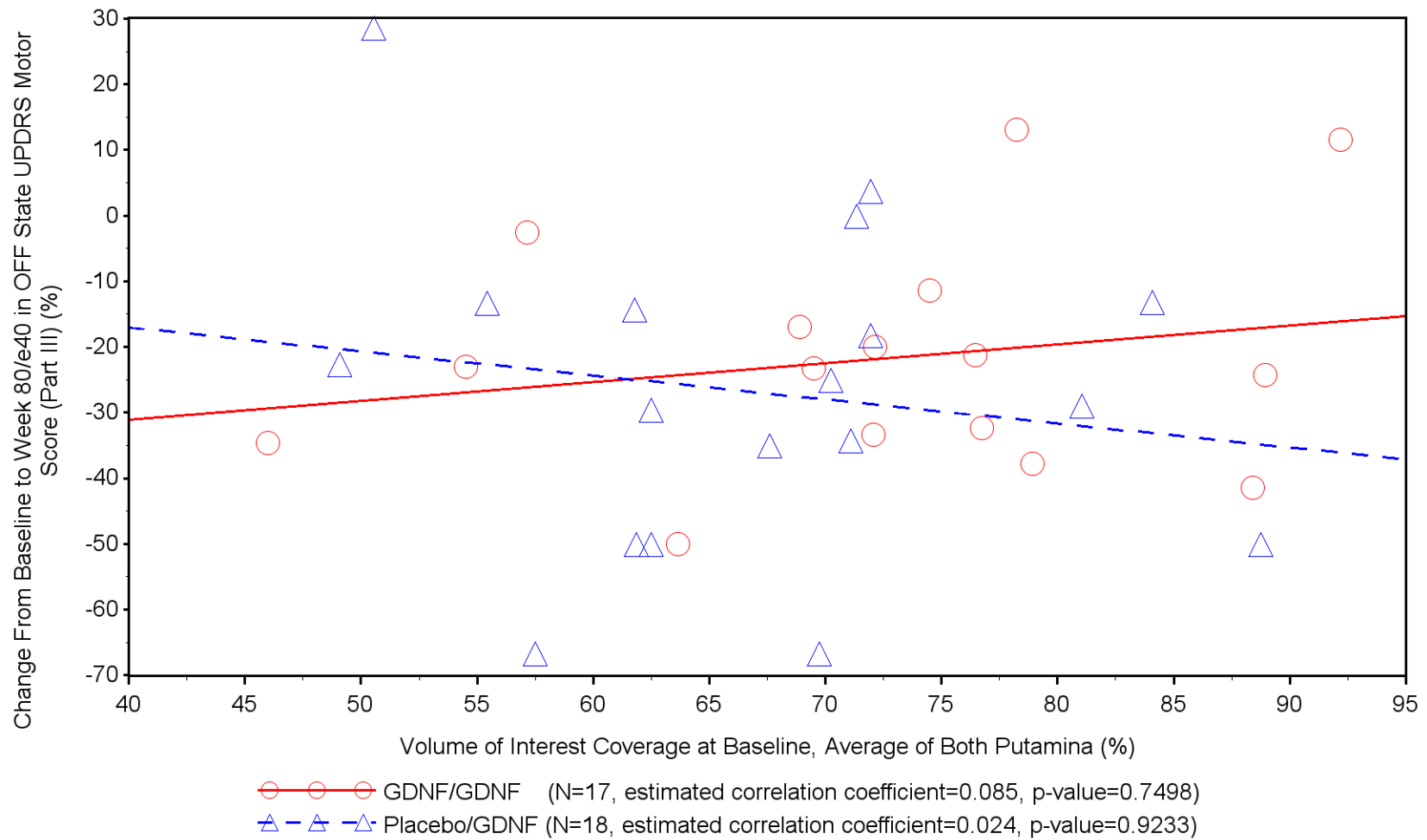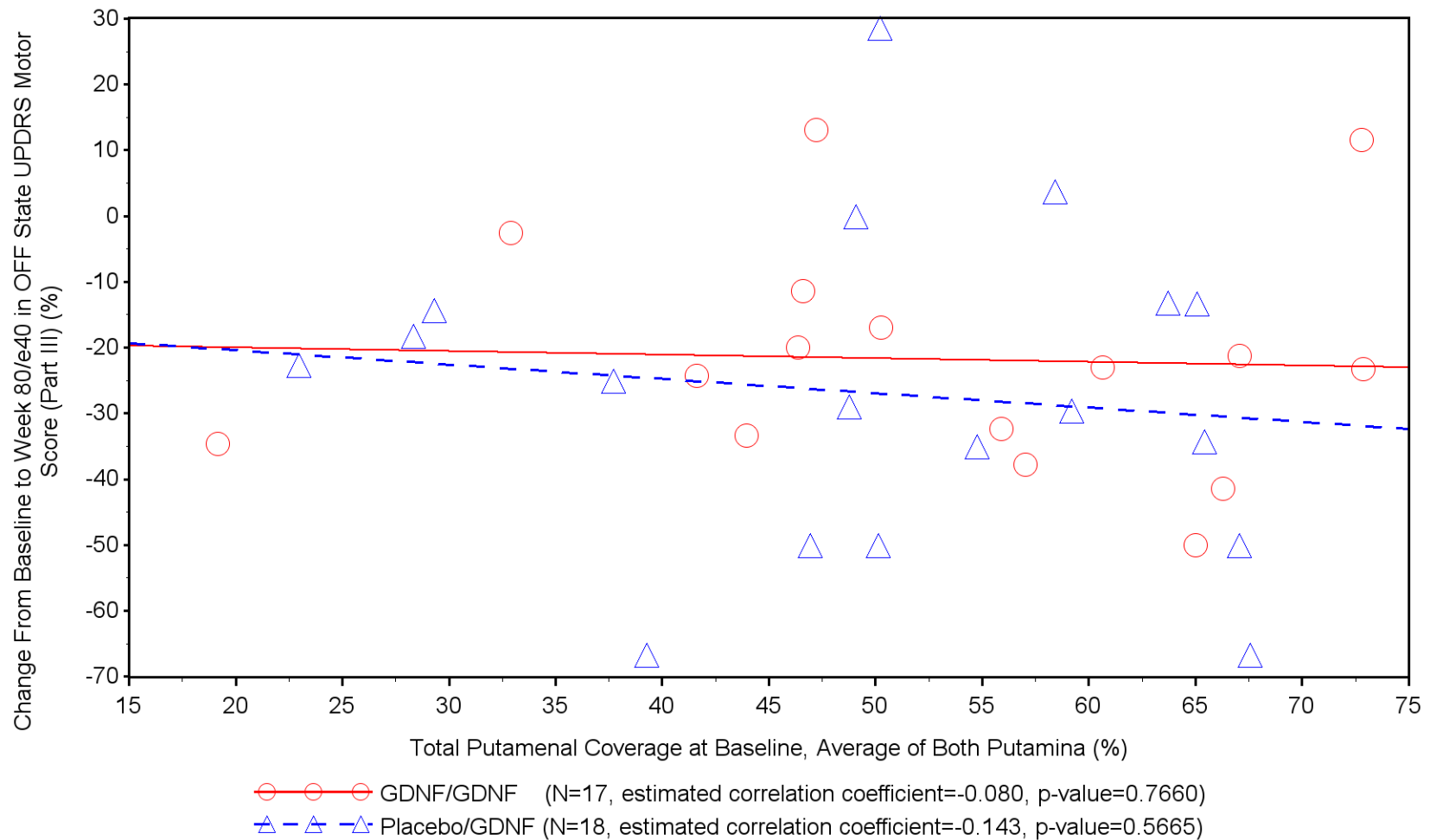

Note: Analysis uses non-parametric Spearman rank correlation. For subject 45, items 22, 27, 28, 29 and 30 are excluded from the score.
Source: Listing 17.2.2.1, 17.2.3.1, Dataset: ADPR, ADQUPDRS, Program: f_correl.sas, Output: f_16-5-5-1-correl.rtf, Generated on: 28JUL2017 06:57
Page 1 of 1

Figure 16.5.5.2 Correlation Analysis of Percentage Change from Baseline to Week 80/e40 in OFF State UPDRS Motor Score (Part III) to Total Putamenal Coverage at Baseline as Determined by Contrast-Enhanced T1-Weighted MRI - ITT Primary Population
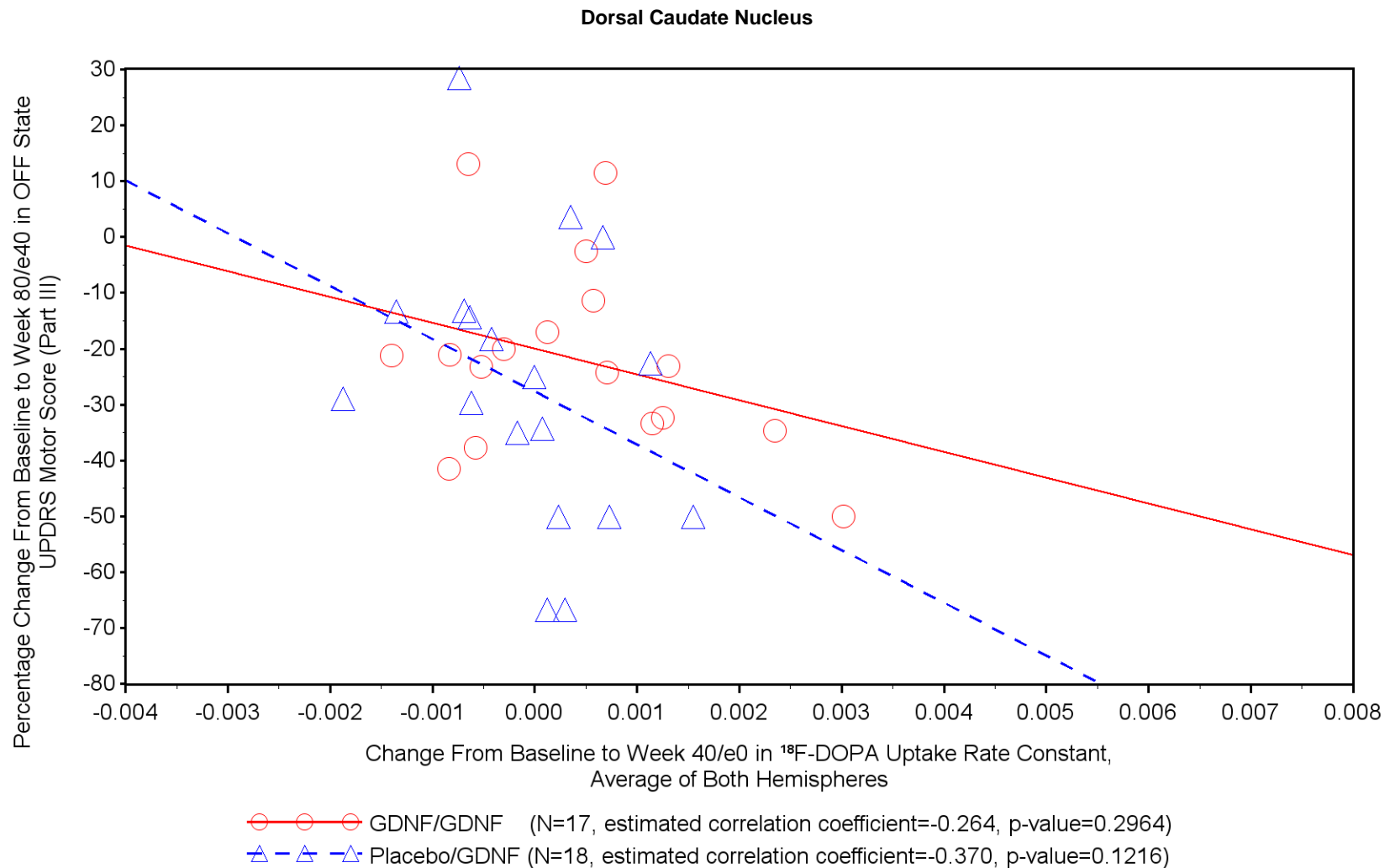

Note: Analysis uses non-parametric Spearman rank correlation. For subject 45, items 22, 27, 28, 29 and 30 are excluded from the score.
Source: Listing 17.2.2.1, 17.2.3.1, Dataset: ADPR, ADQUPDRS, Program: f_correl.sas, Output: f_16-5-5-2-correl.rtf, Generated on: 28JUL2017 06:57
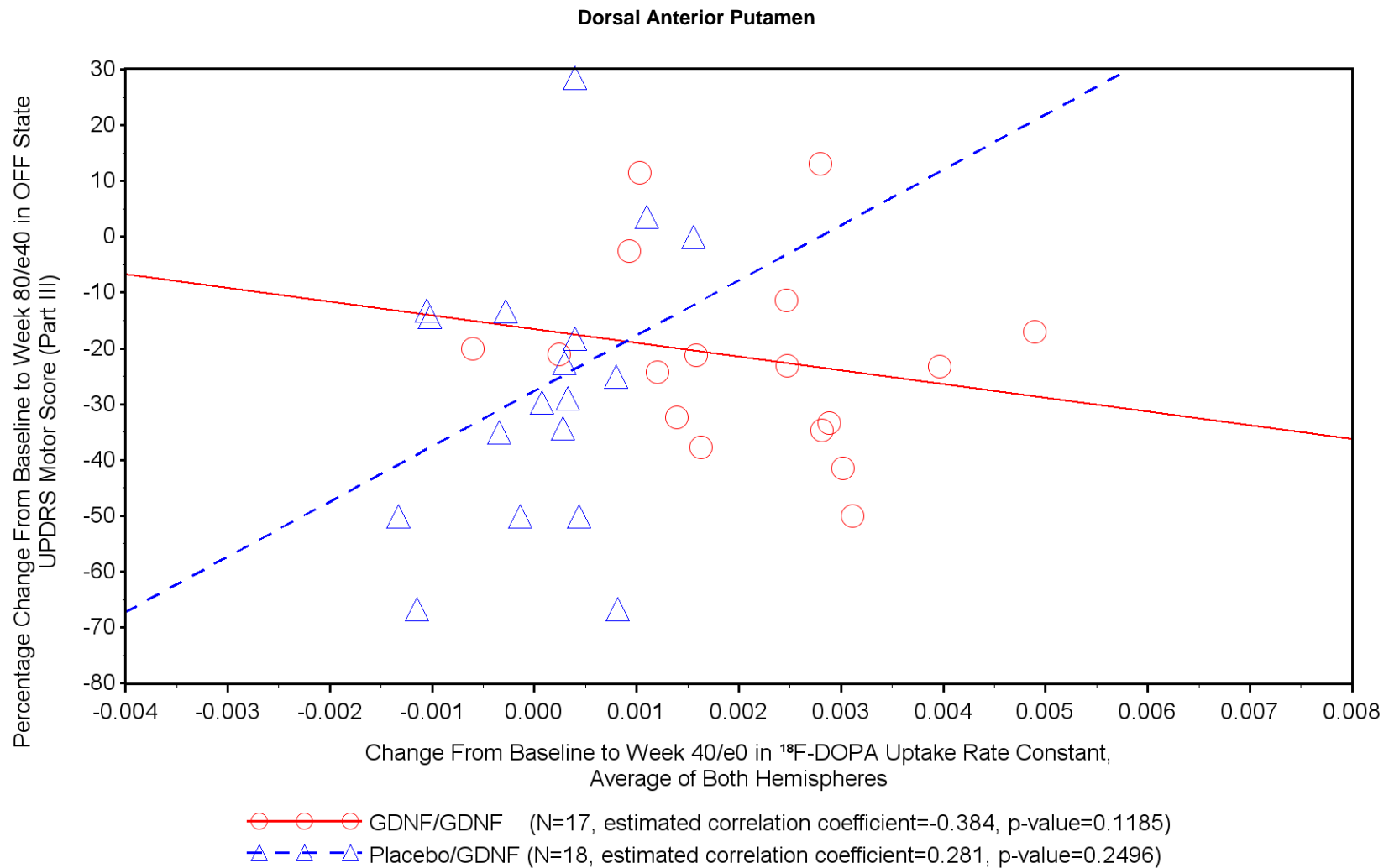
Figure 16.5.5.3 Correlation Analysis of Percentage Change from Baseline to Week 80/e40 in OFF State UPDRS Motor Score (Part III) to Change From Baseline to Week 40/e0 in ^{18}F-DOPA Uptake as Determined by PET Scan - ITT Primary Population

Dorsal Caudate Nucleus

Note: Analysis uses non-parametric Spearman rank correlation. For subject 45, items 22, 27, 28, 29 and 30 are excluded from the score.
Source: Listing 17.2.2.1, Dataset: ADPR, ADQUPDRS, Program: f_correl2.sas, Output: f_16-5-5-3-correl.rtf, Generated on: 28JUL2017 06:57
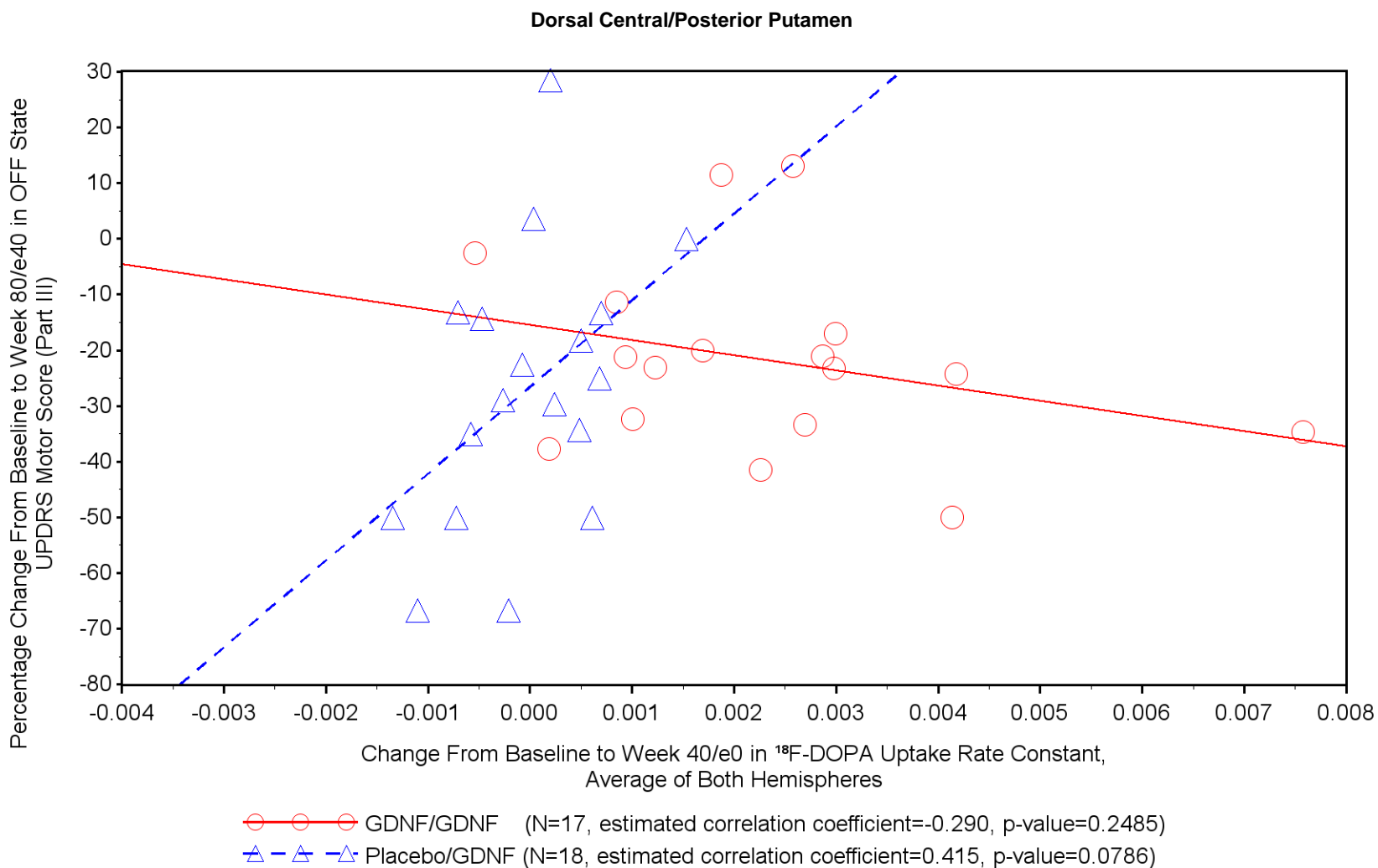
Figure 16.5.5.3 Correlation Analysis of Percentage Change from Baseline to Week 80/e40 in OFF State UPDRS Motor Score (Part III) to Change From Baseline to Week 40/e0 in ^{18}F-DOPA Uptake as Determined by PET Scan - ITT Primary Population

Dorsal Anterior Putamen

GDNF/GDNF   (N=17, estimated correlation coefficient=-0.384, p-value=0.1185)
Placebo/GDNF (N=18, estimated correlation coefficient=0.281, p-value=0.2496)

Note: Analysis uses non-parametric Spearman rank correlation. For subject 45, items 22, 27, 28, 29 and 30 are excluded from the score.
Source: Listing 17.2.2.1, Dataset: ADPR, ADQUPDRS, Program: f_correl2.sas, Output: f_16-5-5-3-correl.rtf, Generated on: 28JUL2017 06:57
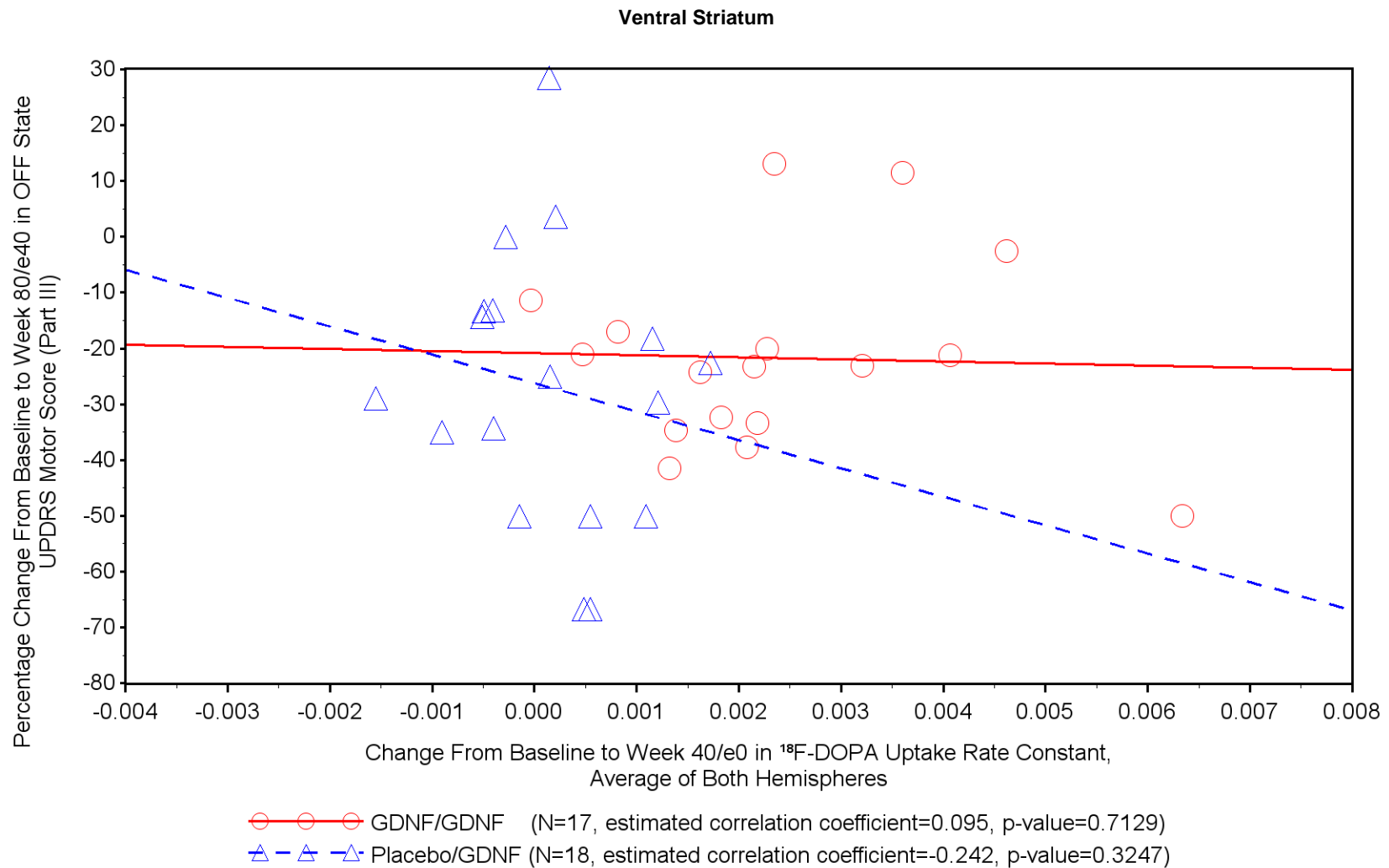
Figure 16.5.5.3 Correlation Analysis of Percentage Change from Baseline to Week 80/e40 in OFF State UPDRS Motor Score (Part III) to Change From Baseline to Week 40/e0 in ^{18}F-DOPA Uptake as Determined by PET Scan - ITT Primary Population

Dorsal Central/Posterior Putamen

Note: Analysis uses non-parametric Spearman rank correlation. For subject 45, items 22, 27, 28, 29 and 30 are excluded from the score.
Source: Listing 17.2.2.1, Dataset: ADPR, ADQUPDRS, Program: f_correl2.sas, Output: f_16-5-5-3-correl.rtf, Generated on: 28JUL2017 06:57
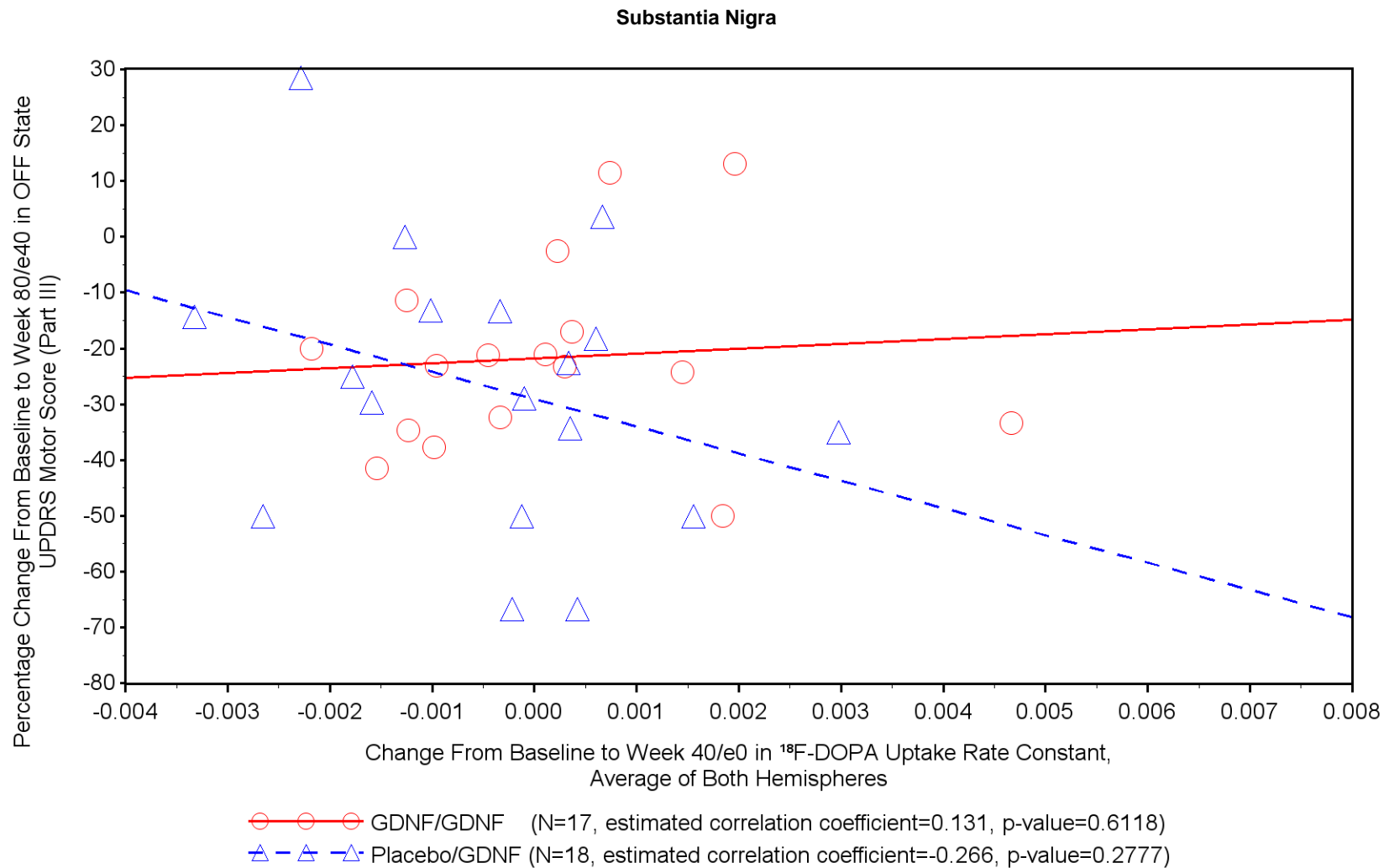
Figure 16.5.5.3 Correlation Analysis of Percentage Change from Baseline to Week 80/e40 in OFF State UPDRS Motor Score (Part III) to Change From Baseline to Week 40/e0 in ^{18}F-DOPA Uptake as Determined by PET Scan - ITT Primary Population

Ventral Striatum

GDNF/GDNF   (N=17, estimated correlation coefficient=0.095, p-value=0.7129)
Placebo/GDNF (N=18, estimated correlation coefficient=-0.242, p-value=0.3247)

Note: Analysis uses non-parametric Spearman rank correlation. For subject 45, items 22, 27, 28, 29 and 30 are excluded from the score.
Source: Listing 17.2.2.1, Dataset: ADPR, ADQUPDRS, Program: f_correl2.sas, Output: f_16-5-5-3-correl.rtf, Generated on: 28JUL2017 06:57
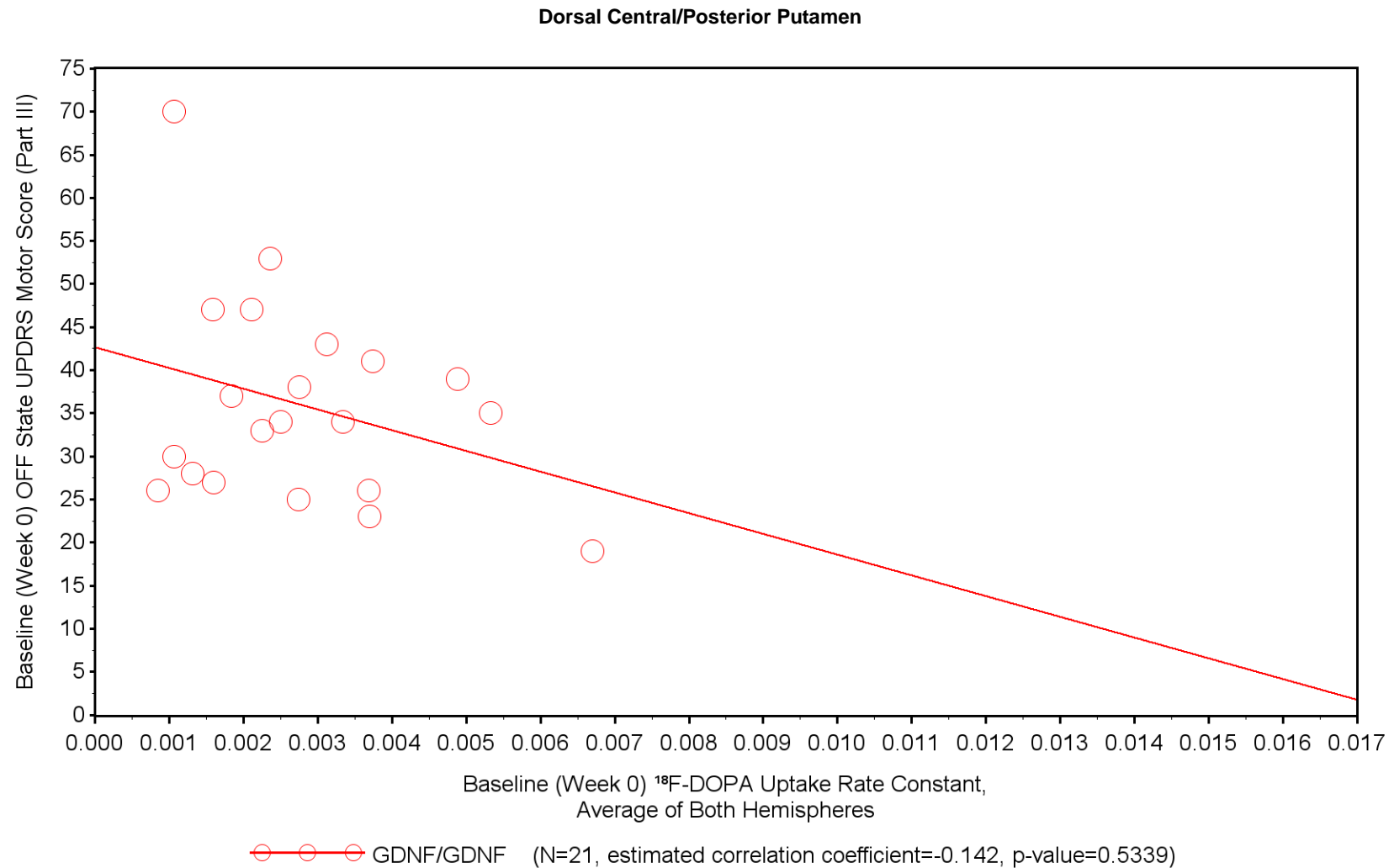
Figure 16.5.5.3 Correlation Analysis of Percentage Change from Baseline to Week 80/e40 in OFF State UPDRS Motor Score (Part III) to Change From Baseline to Week 40/e0 in ^{18}F-DOPA Uptake as Determined by PET Scan - ITT Primary Population

Substantia Nigra

GDNF/GDNF   (N=17, estimated correlation coefficient=0.131, p-value=0.6118)
Placebo/GDNF (N=18, estimated correlation coefficient=-0.266, p-value=0.2777)

Note: Analysis uses non-parametric Spearman rank correlation. For subject 45, items 22, 27, 28, 29 and 30 are excluded from the score.
Source: Listing 17.2.2.1, Dataset: ADPR, ADQUPDRS, Program: f_correl2.sas, Output: f_16-5-5-3-correl.rtf, Generated on: 28JUL2017 06:57
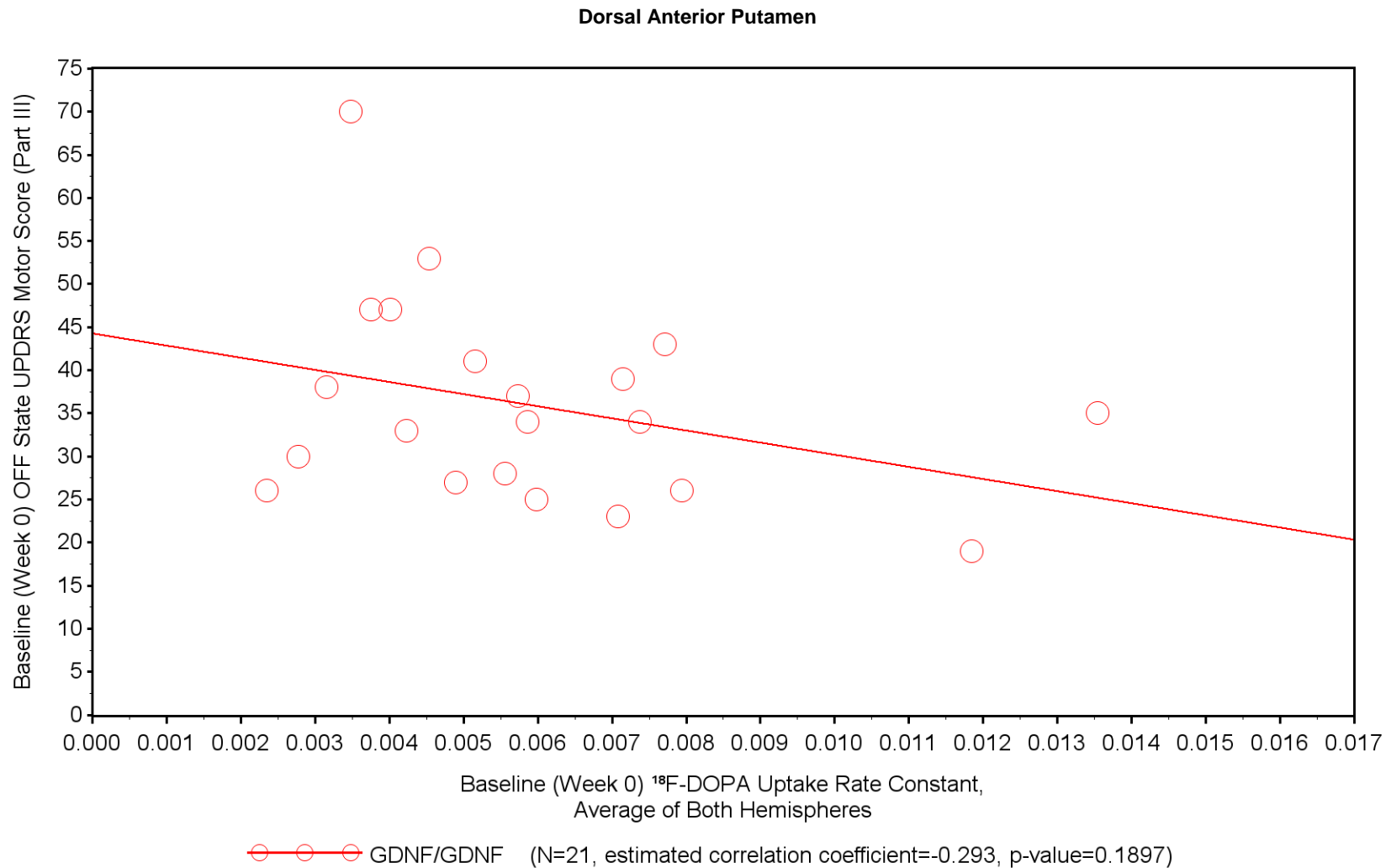
Figure 16.5.5.4 Correlation Analysis of Baseline (Week 0) OFF State UPDRS Motor Score (Part III) to Baseline (Week 0) ^{18}F-DOPA Uptake as Determined by PET Scan for GDNF/GDNF Subjects - ITT Overall Population

Dorsal Central/Posterior Putamen

GDNF/GDNF   (N=21, estimated correlation coefficient=-0.142, p-value=0.5339)

Note: Analysis uses non-parametric Spearman rank correlation. For subject 45, items 22, 27, 28, 29 and 30 are excluded from the score.
Source: Listing 17.2.2.1, Dataset: ADPR, ADQUPDRS, Program: f_correl3.sas, Output: f_16-5-5-4-correl.rtf, Generated on: 28JUL2017 06:57
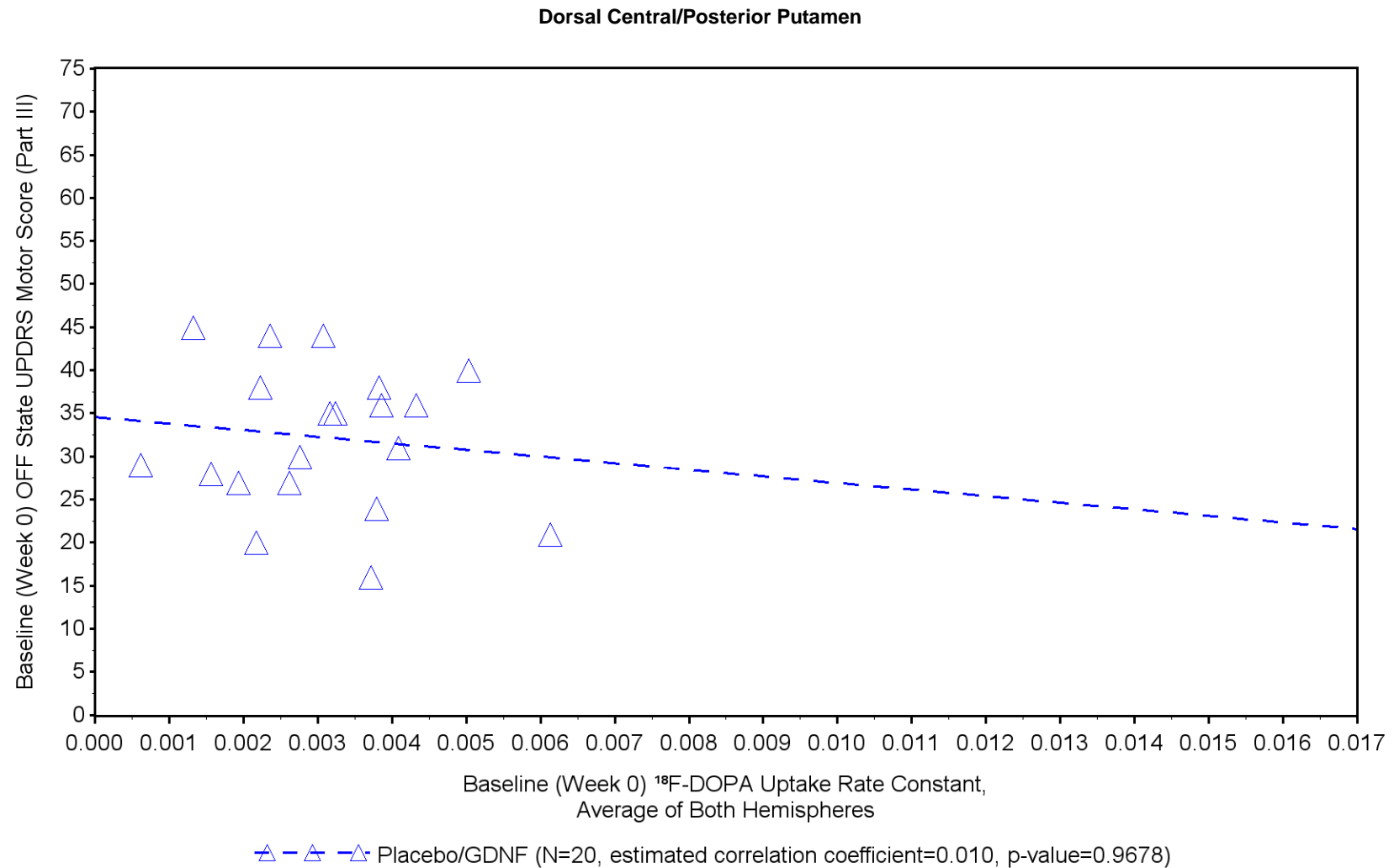
Figure 16.5.5.4 Correlation Analysis of Baseline (Week 0) OFF State UPDRS Motor Score (Part III) to Baseline (Week 0) ^{18}F-DOPA Uptake as Determined by PET Scan for GDNF/GDNF Subjects - ITT Overall Population

Dorsal Anterior Putamen

Note: Analysis uses non-parametric Spearman rank correlation. For subject 45, items 22, 27, 28, 29 and 30 are excluded from the score.
Source: Listing 17.2.2.1, Dataset: ADPR, ADQUPDRS, Program: f_correl3.sas, Output: f_16-5-5-4-correl.rtf, Generated on: 28JUL2017 06:57
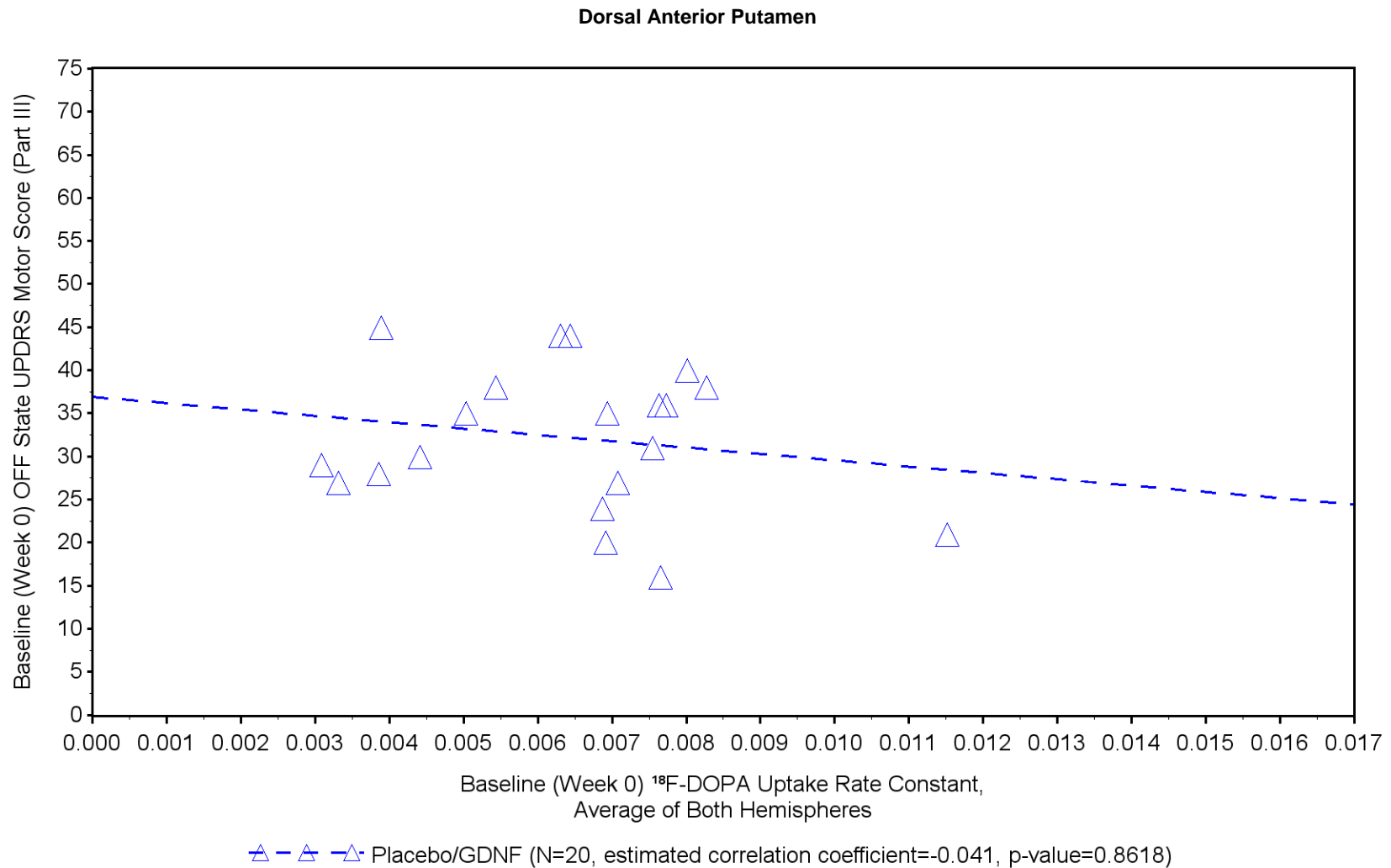**Page 2 of 2**
Page 580

Figure 16.5.5.5 Correlation Analysis of Baseline (Week 0) OFF State UPDRS Motor Score (Part III) to Baseline (Week 0) ^{18}F-DOPA Uptake as Determined by PET Scan for Placebo/GDNF Subjects - ITT Overall Population

Dorsal Central/Posterior Putamen

Note: Analysis uses non-parametric Spearman rank correlation.
Source: Listing 17.2.2.1, Dataset: ADPR, ADQUPDRS, Program: f_correl3.sas, Output: f_16-5-5-5-correl.rtf, Generated on: 28JUL2017 06:57
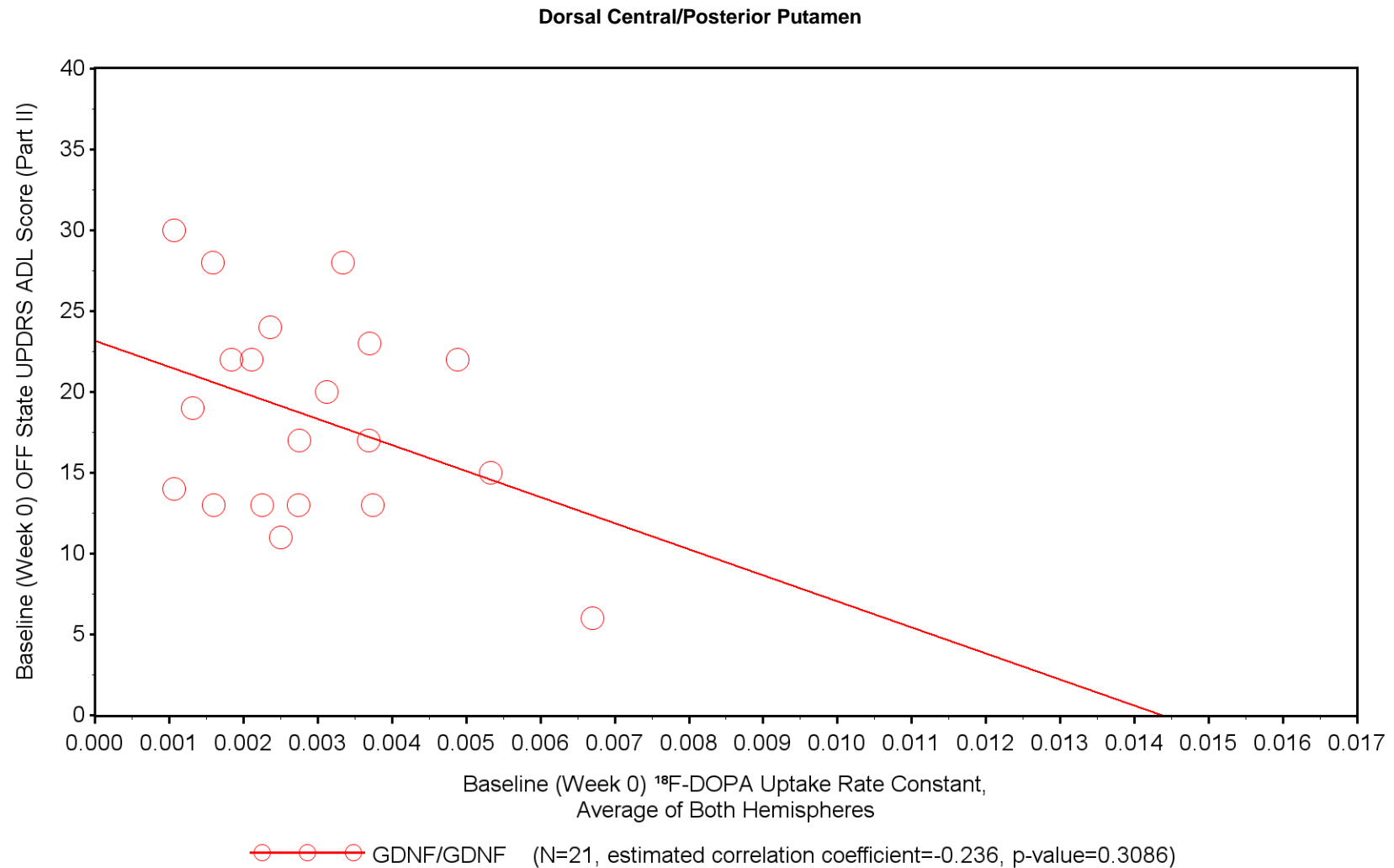
Figure 16.5.5.5 Correlation Analysis of Baseline (Week 0) OFF State UPDRS Motor Score (Part III) to Baseline (Week 0) ^{18}F-DOPA Uptake as Determined by PET Scan for Placebo/GDNF Subjects - ITT Overall Population

Dorsal Anterior Putamen

Placebo/GDNF (N=20, estimated correlation coefficient=-0.041, p-value=0.8618)

Note: Analysis uses non-parametric Spearman rank correlation.
Source: Listing 17.2.2.1, Dataset: ADPR, ADQUPDRS, Program: f_correl3.sas, Output: f_16-5-5-5-correl.rtf, Generated on: 28JUL2017 06:57
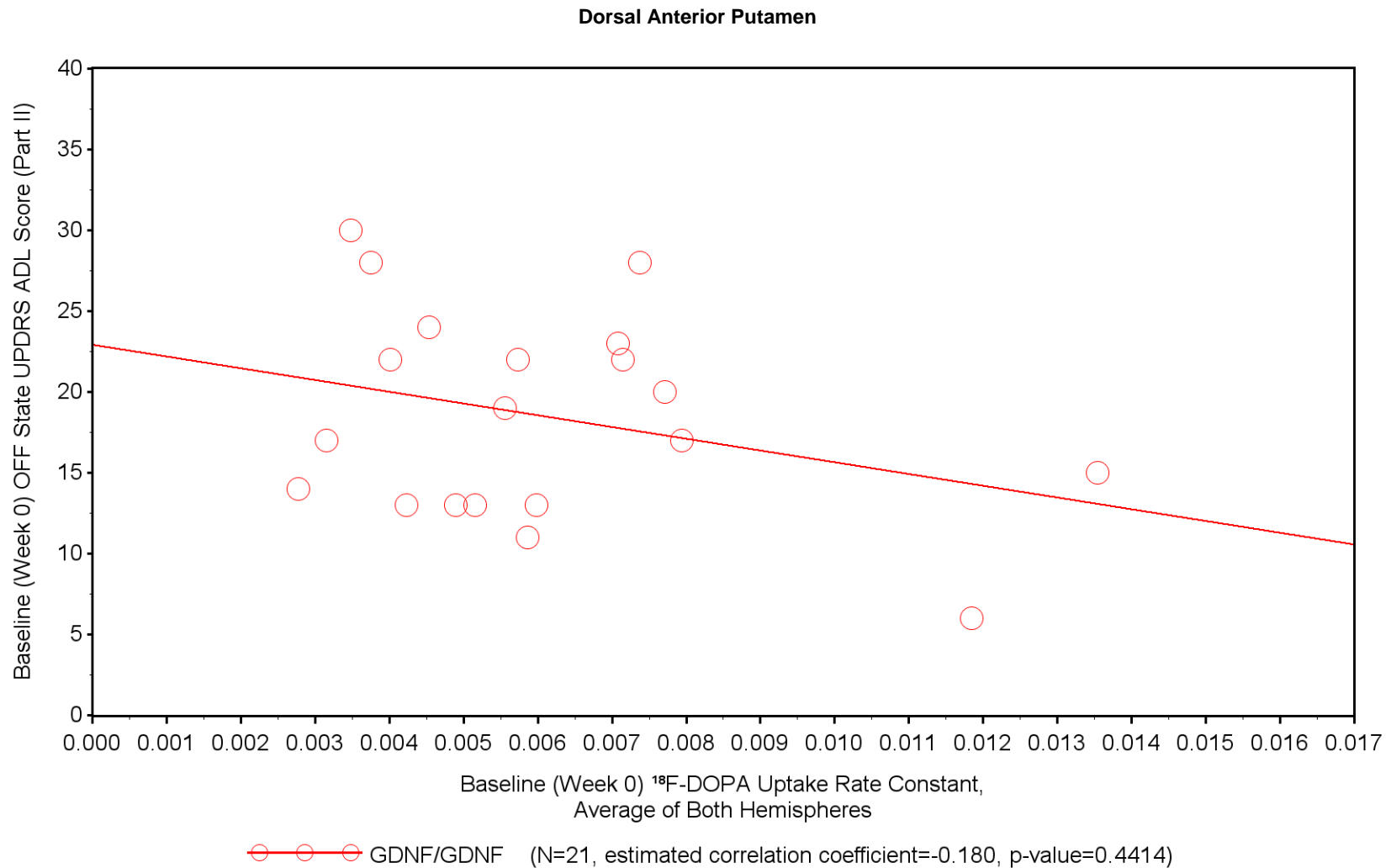
Figure 16.5.5.6 Correlation Analysis of Baseline (Week 0) OFF State UPDRS ADL Score (Part II) to Baseline (Week 0) ^{18}F-DOPA Uptake as Determined by PET Scan for GDNF/GDNF Subjects - ITT Overall Population

Dorsal Central/Posterior Putamen

Note: Analysis uses non-parametric Spearman rank correlation. Data for Subject 45 are excluded from analysis.
Source: Listing 17.2.2.1, Dataset: ADPR, ADQUPDRS, Program: f_correl3.sas, Output: f_16-5-5-6-correl.rtf, Generated on: 28JUL2017 06:57
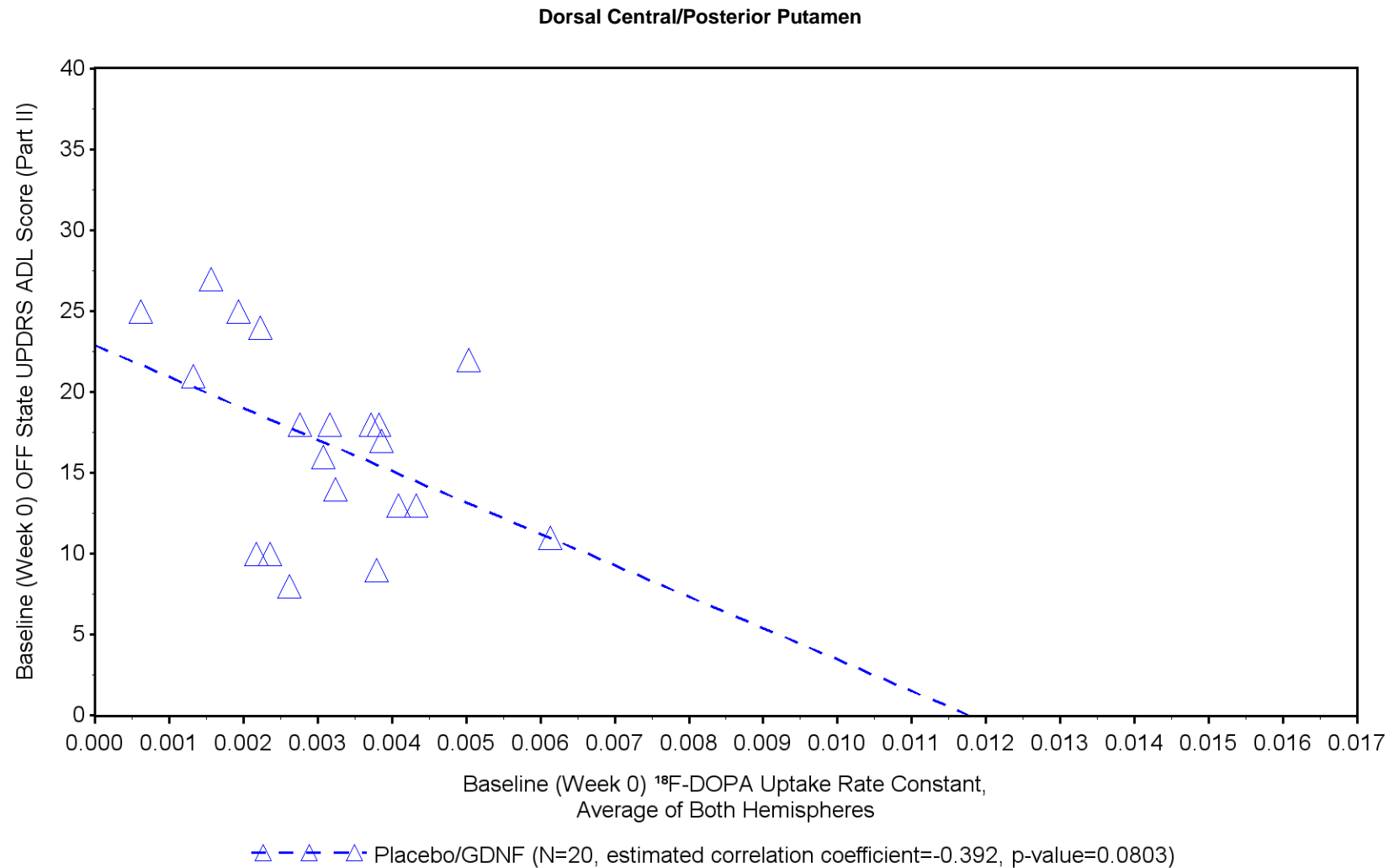
Figure 16.5.5.6 Correlation Analysis of Baseline (Week 0) OFF State UPDRS ADL Score (Part II) to Baseline (Week 0) ^{18}F-DOPA Uptake as Determined by PET Scan for GDNF/GDNF Subjects - ITT Overall Population

Dorsal Anterior Putamen

GDNF/GDNF   (N=21, estimated correlation coefficient=-0.180, p-value=0.4414)

Note: Analysis uses non-parametric Spearman rank correlation. Data for Subject 45 are excluded from analysis.
Source: Listing 17.2.2.1, Dataset: ADPR, ADQUPDRS, Program: f_correl3.sas, Output: f_16-5-5-6-correl.rtf, Generated on: 28JUL2017 06:57
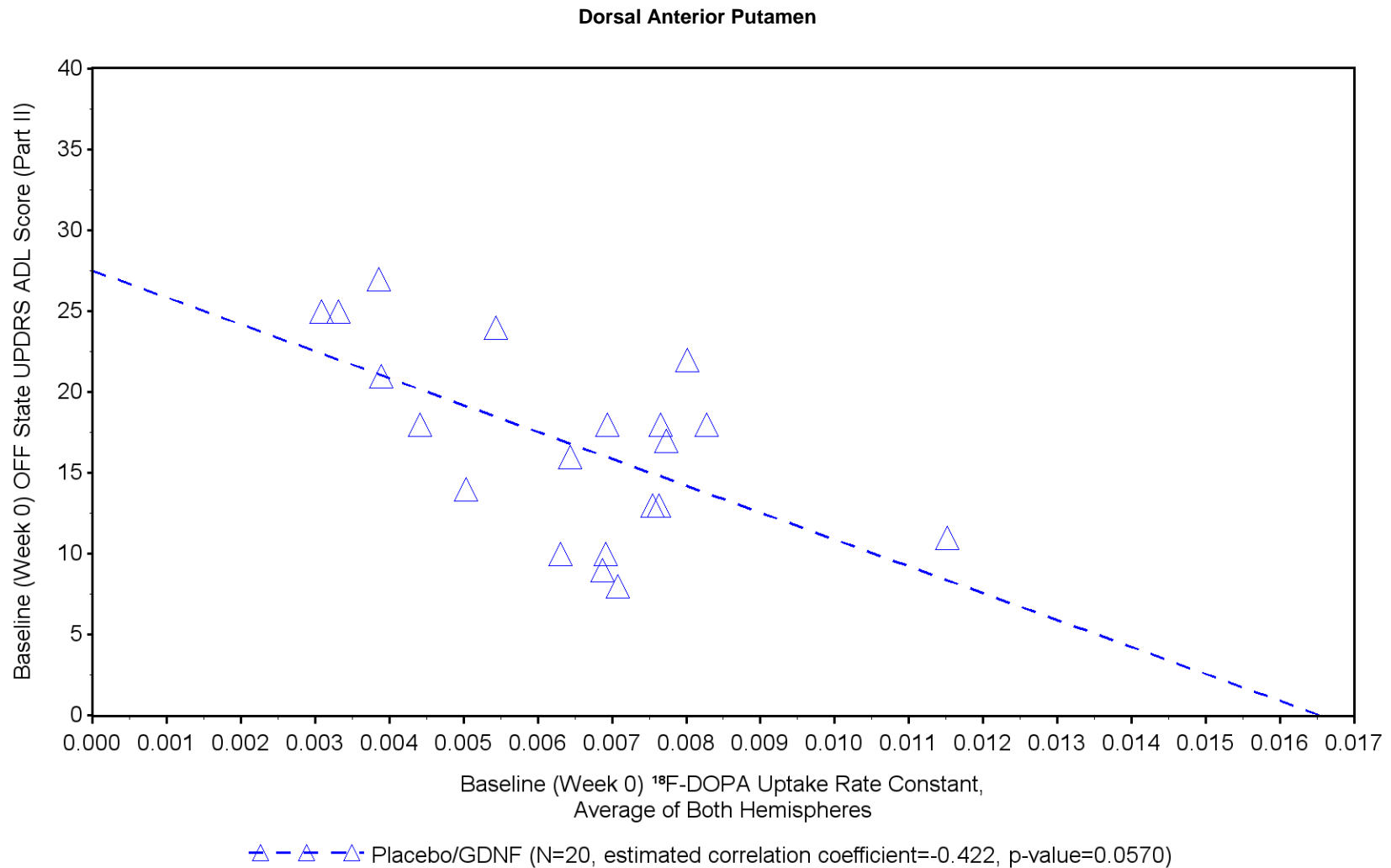
Figure 16.5.5.7 Correlation Analysis of Baseline (Week 0) OFF State UPDRS ADL Score (Part II) to Baseline (Week 0) ^{18}F-DOPA Uptake as Determined by PET Scan for Placebo/GDNF Subjects - ITT Overall Population

Dorsal Central/Posterior Putamen

Placebo/GDNF (N=20, estimated correlation coefficient=-0.392, p-value=0.0803)

Note: Analysis uses non-parametric Spearman rank correlation.
Source: Listing 17.2.2.1, Dataset: ADPR, ADQUPDRS, Program: f_correl3.sas, Output: f_16-5-5-7-correl.rtf, Generated on: 28JUL2017 06:58
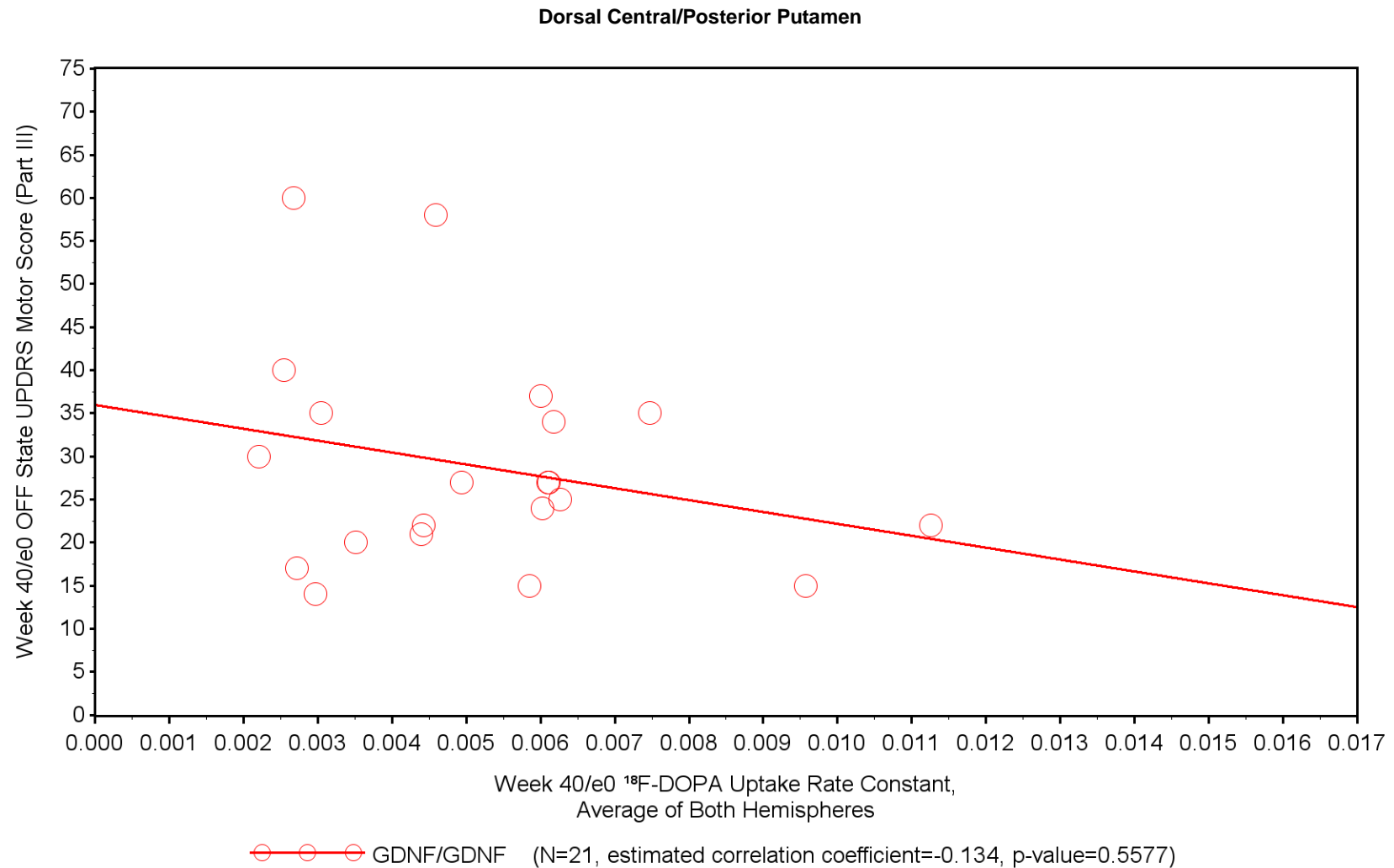
Figure 16.5.5.7 Correlation Analysis of Baseline (Week 0) OFF State UPDRS ADL Score (Part II) to Baseline (Week 0) ^{18}F-DOPA Uptake as Determined by PET Scan for Placebo/GDNF Subjects - ITT Overall Population

Dorsal Anterior Putamen

Placebo/GDNF (N=20, estimated correlation coefficient=-0.422, p-value=0.0570)

Note: Analysis uses non-parametric Spearman rank correlation.

Figure 16.5.5.8 Correlation Analysis of Week 40/e0 OFF State UPDRS Motor Score (Part III) to Week 40/e0 ^{18}F-DOPA Uptake as Determined by PET Scan for GDNF/GDNF Subjects - ITT Overall Population

Dorsal Central/Posterior Putamen

Note: Analysis uses non-parametric Spearman rank correlation. For subject 45, items 22, 27, 28, 29 and 30 are excluded from the score.
Source: Listing 17.2.2.1, Dataset: ADPR, ADQUPDRS, Program: f_correl3.sas, Output: f_16-5-5-8-correl.rtf, Generated on: 28JUL2017 06:58
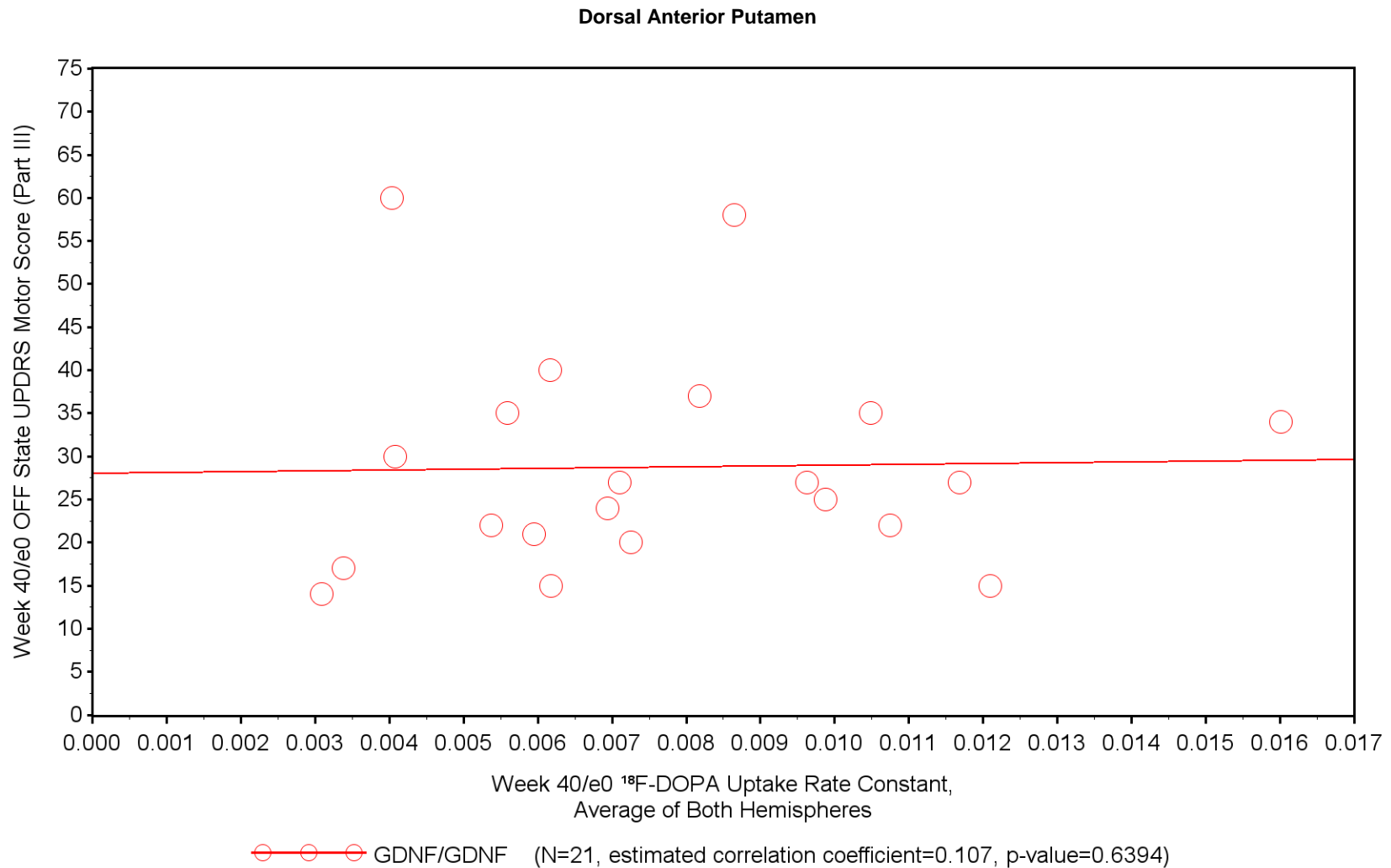
Figure 16.5.5.8 Correlation Analysis of Week 40/e0 OFF State UPDRS Motor Score (Part III) to Week 40/e0 ^{18}F-DOPA Uptake as Determined by PET Scan for GDNF/GDNF Subjects - ITT Overall Population

Dorsal Anterior Putamen

GDNF/GDNF (N=21, estimated correlation coefficient=0.107, p-value=0.6394)

Note: Analysis uses non-parametric Spearman rank correlation. For subject 45, items 22, 27, 28, 29 and 30 are excluded from the score.
Source: Listing 17.2.2.1, Dataset: ADPR, ADQUPDRS, Program: f_correl3.sas, Output: f_16-5-5-8-correl.rtf, Generated on: 28JUL2017 06:58
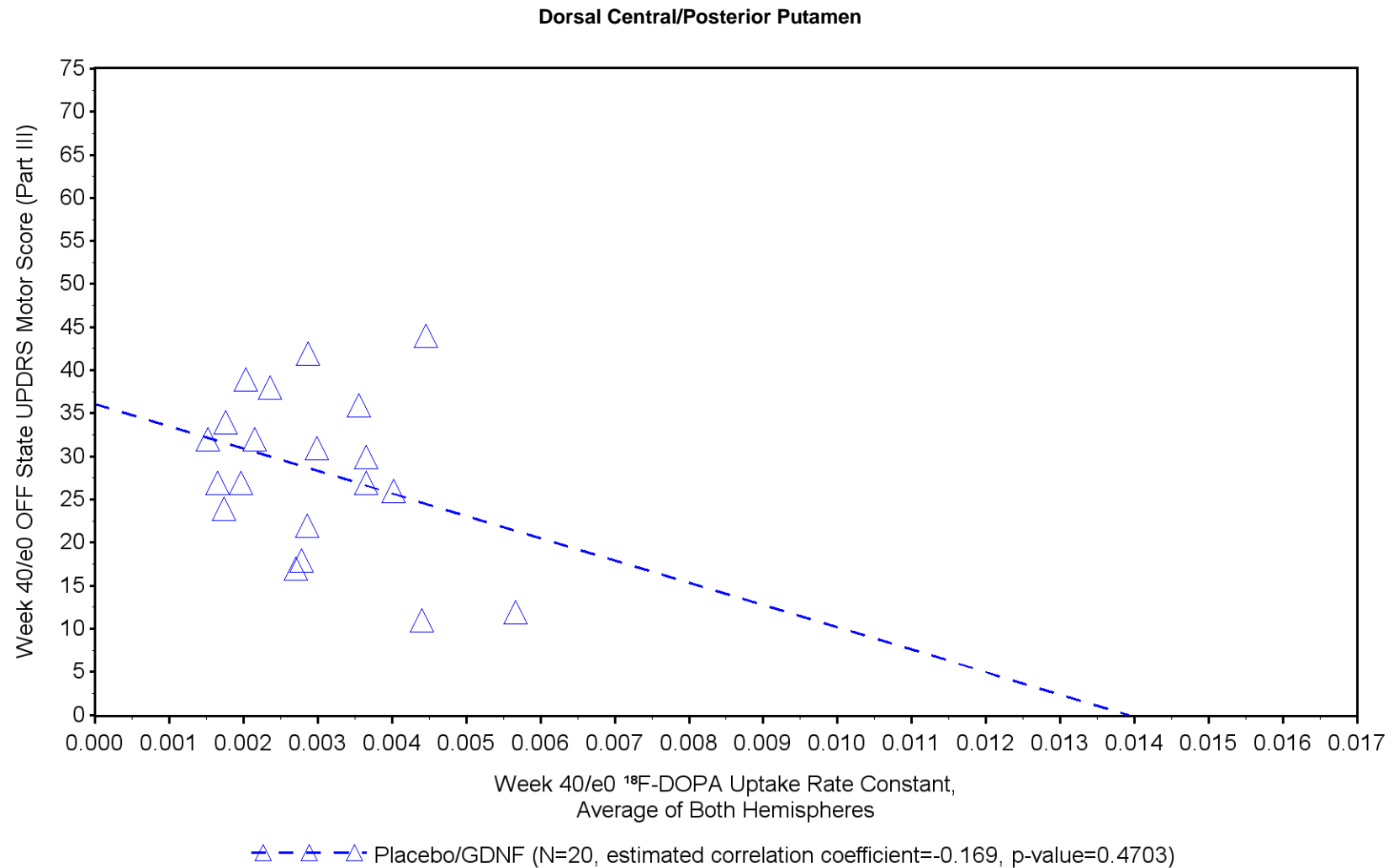
Figure 16.5.5.9 Correlation Analysis of Week 40/e0 OFF State UPDRS Motor Score (Part III) to Week 40/e0 ^{18}F-DOPA Uptake as Determined by PET Scan for Placebo/GDNF Subjects - ITT Overall Population

Dorsal Central/Posterior Putamen

Note: Analysis uses non-parametric Spearman rank correlation.
Source: Listing 17.2.2.1, Dataset: ADPR, ADQUPDRS, Program: f_correl3.sas, Output: f_16-5-5-9-correl.rtf, Generated on: 28JUL2017 06:58
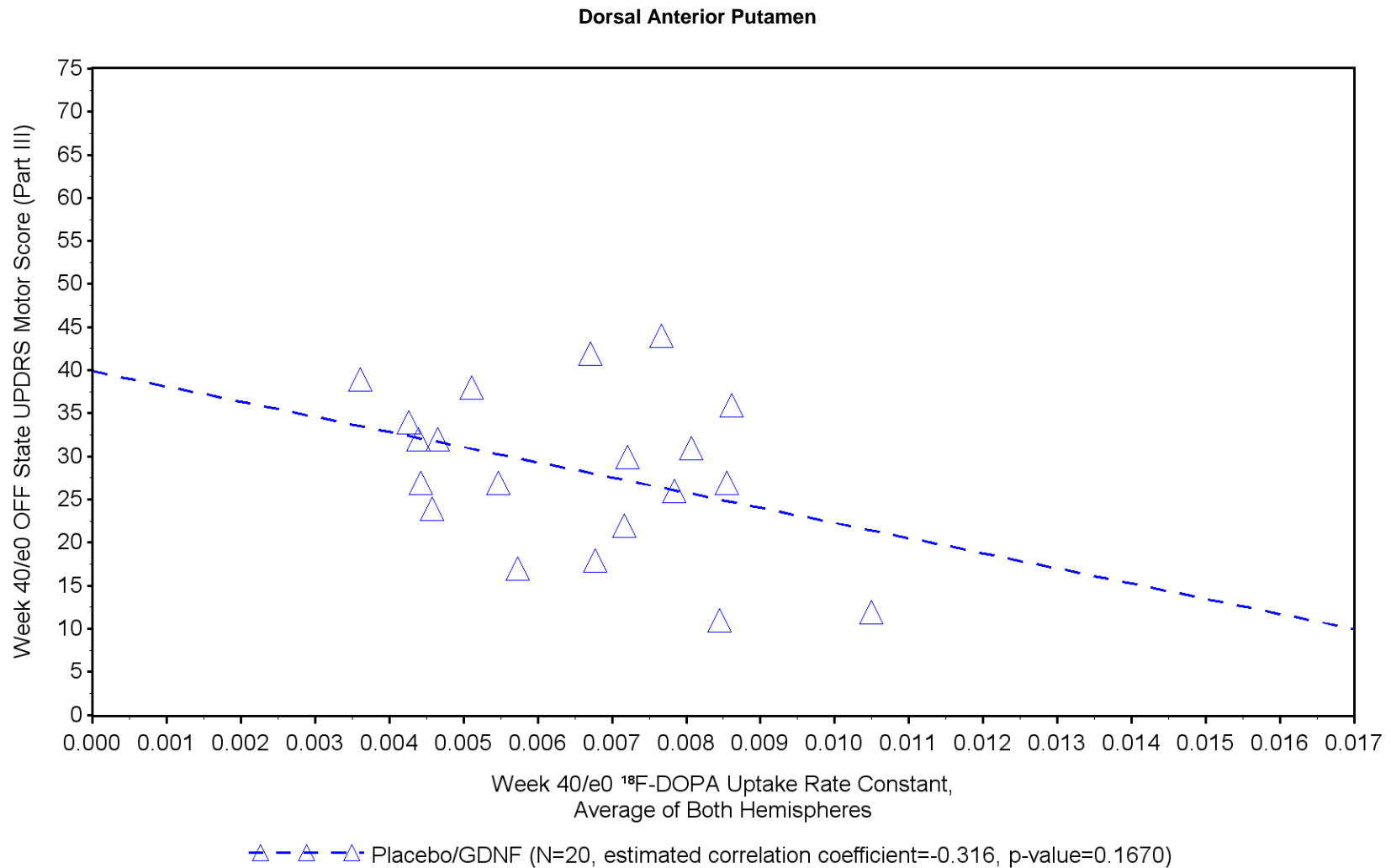
Figure 16.5.5.9 Correlation Analysis of Week 40/e0 OFF State UPDRS Motor Score (Part III) to Week 40/e0 ^{18}F-DOPA Uptake as Determined by PET Scan for Placebo/GDNF Subjects - ITT Overall Population

Dorsal Anterior Putamen

Note: Analysis uses non-parametric Spearman rank correlation.
Source: Listing 17.2.2.1, Dataset: ADPR, ADQUPDRS, Program: f_correl3.sas, Output: f_16-5-5-9-correl.rtf, Generated on: 28JUL2017 06:58
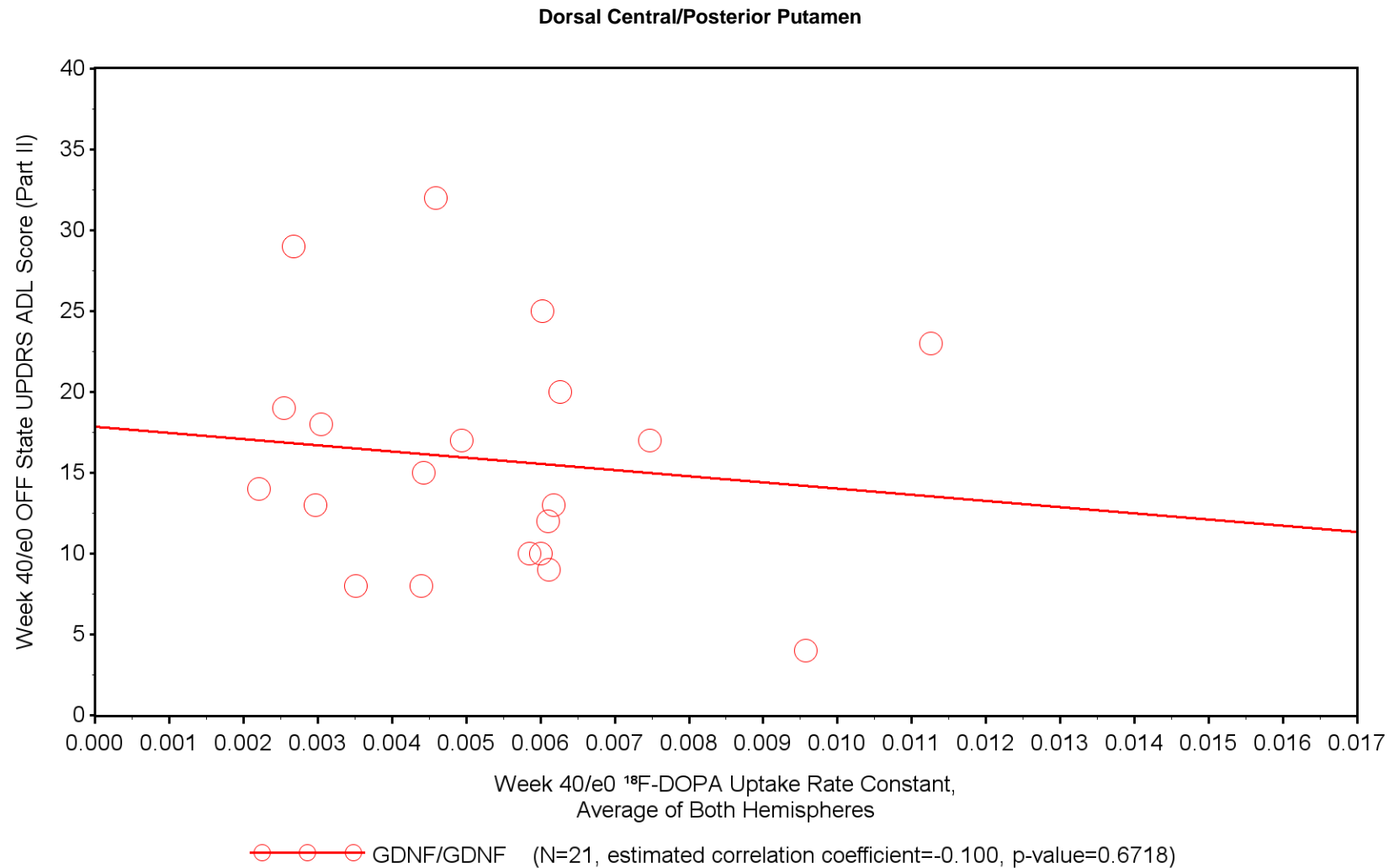
Figure 16.5.5.10 Correlation Analysis of Week 40/e0 OFF State UPDRS ADL Score (Part II) to Week 40/e0 ^{18}F-DOPA Uptake as Determined by PET Scan for GDNF/GDNF Subjects - ITT Overall Population

Dorsal Central/Posterior Putamen

Note: Analysis uses non-parametric Spearman rank correlation. Data for Subject 45 are excluded from analysis.
Source: Listing 17.2.2.1, Dataset: ADPR, ADQUPDRS, Program: f_correl3.sas, Output: f_16-5-5-10-correl.rtf, Generated on: 28JUL2017 06:58
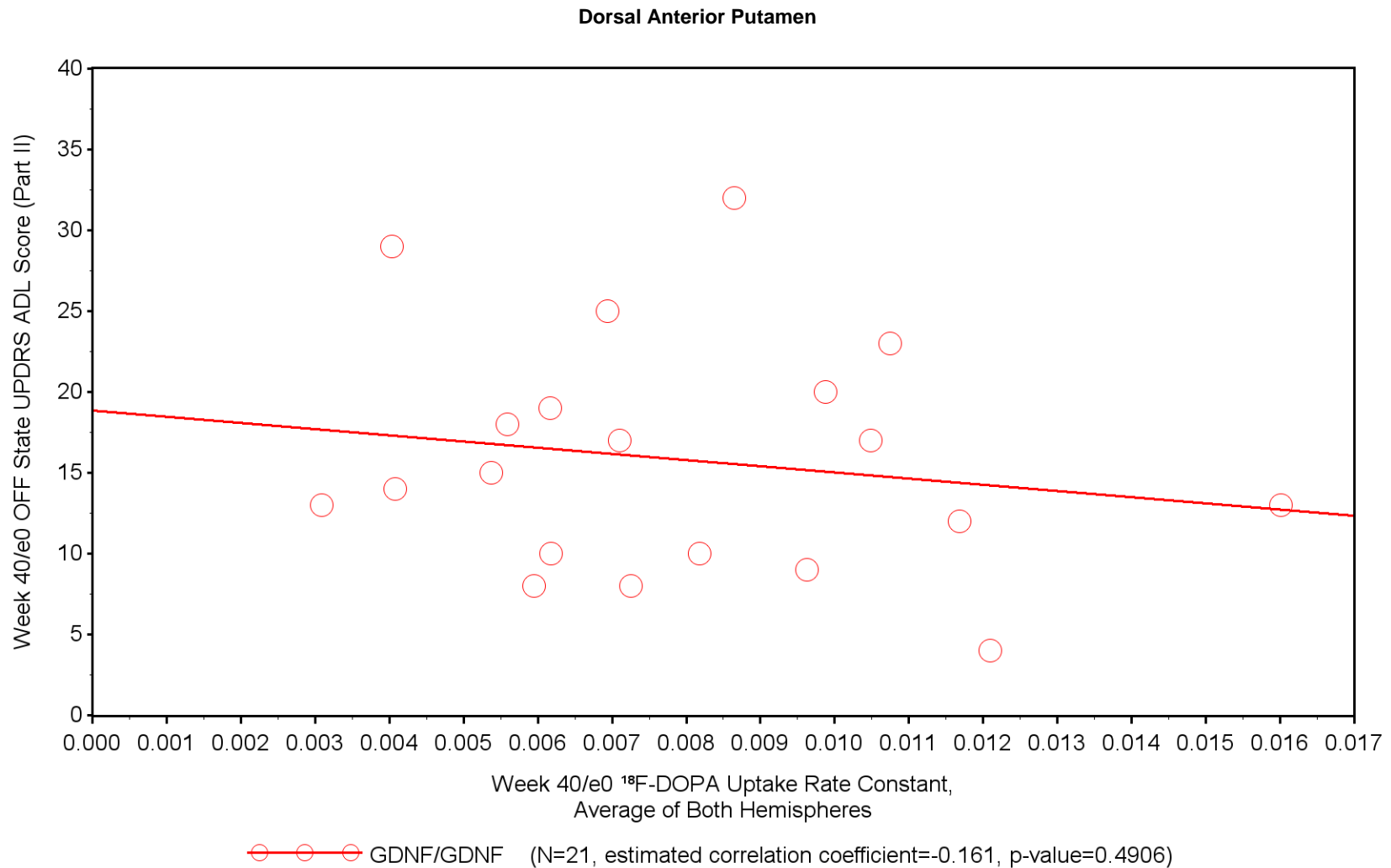
Figure 16.5.5.10 Correlation Analysis of Week 40/e0 OFF State UPDRS ADL Score (Part II) to Week 40/e0 ^{18}F-DOPA Uptake as Determined by PET Scan for GDNF/GDNF Subjects - ITT Overall Population

Dorsal Anterior Putamen

Note: Analysis uses non-parametric Spearman rank correlation. Data for Subject 45 are excluded from analysis.
Source: Listing 17.2.2.1, Dataset: ADPR, ADQUPDRS, Program: f_correl3.sas, Output: f_16-5-5-10-correl.rtf, Generated on: 28JUL2017 06:58
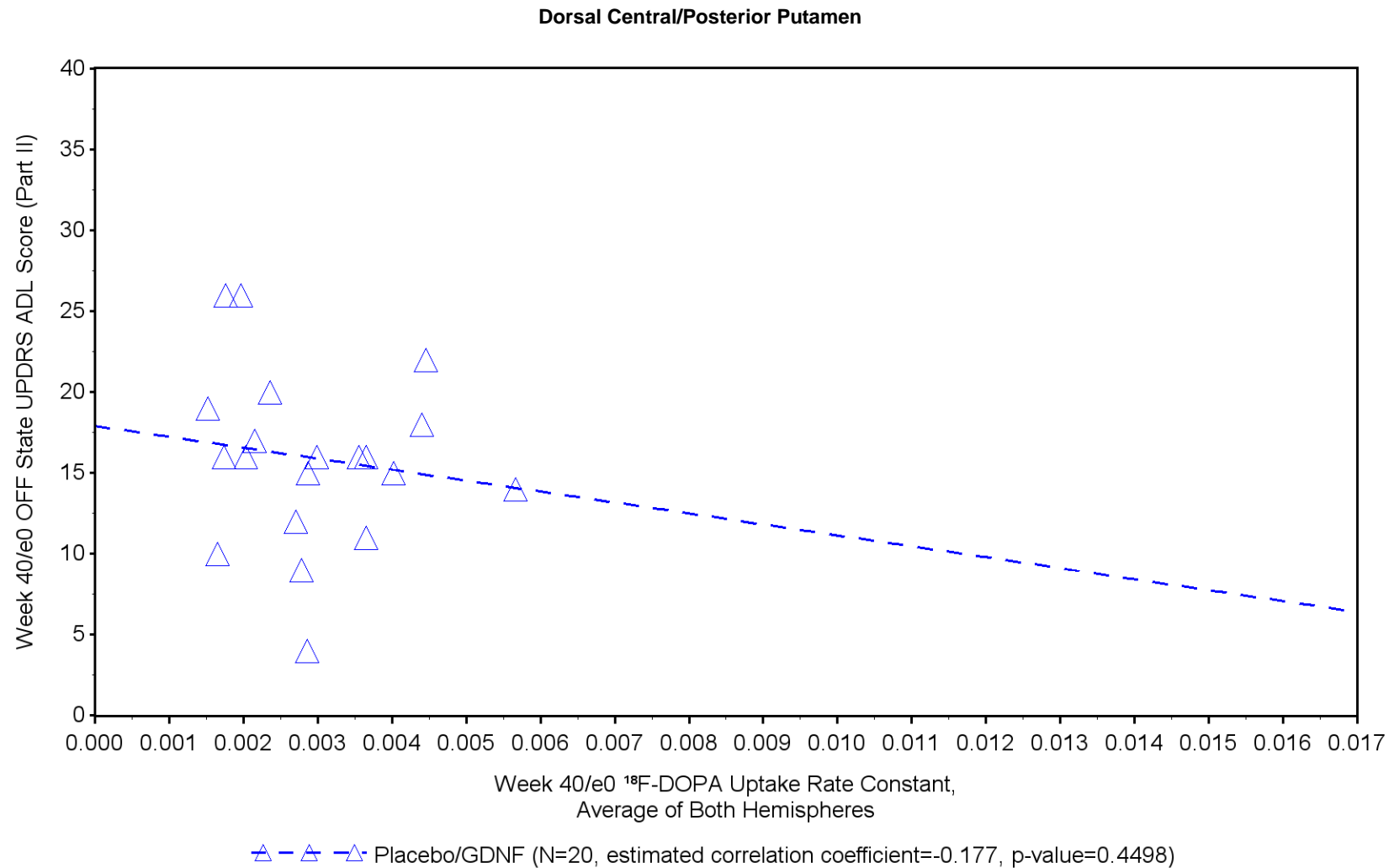
Figure 16.5.5.11 Correlation Analysis of Week 40/e0 OFF State UPDRS ADL Score (Part II) to Week 40/e0 ^{18}F-DOPA Uptake as Determined by PET Scan for Placebo/GDNF Subjects - ITT Overall Population

Dorsal Central/Posterior Putamen

Placebo/GDNF (N=20, estimated correlation coefficient=-0.177, p-value=0.4498)

Note: Analysis uses non-parametric Spearman rank correlation.
Source: Listing 17.2.2.1, Dataset: ADPR, ADQUPDRS, Program: f_correl3.sas, Output: f_16-5-5-11-correl.rtf, Generated on: 28JUL2017 06:58
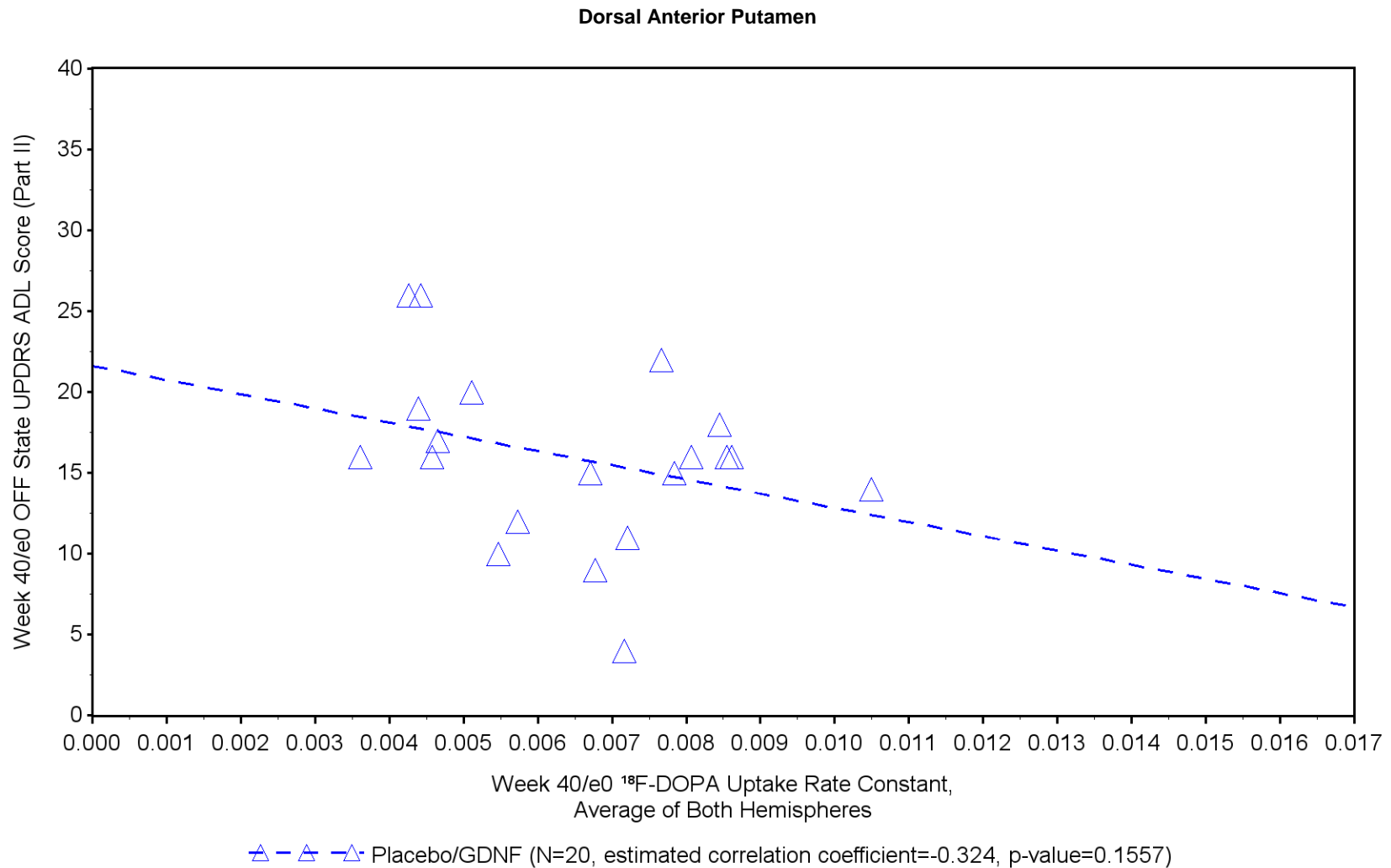
Figure 16.5.5.11 Correlation Analysis of Week 40/e0 OFF State UPDRS ADL Score (Part II) to Week 40/e0 ^{18}F-DOPA Uptake as Determined by PET Scan for Placebo/GDNF Subjects - ITT Overall Population

Dorsal Anterior Putamen

Placebo/GDNF (N=20, estimated correlation coefficient=-0.324, p-value=0.1557)

Note: Analysis uses non-parametric Spearman rank correlation.
Source: Listing 17.2.2.1, Dataset: ADPR, ADQUPDRS, Program: f_correl3.sas, Output: f_16-5-5-11-correl.rtf, Generated on: 28JUL2017 06:58

Figure 16.5.5.12 Correlation Analysis of Week 80/e40 OFF State UPDRS Motor Score (Part III) to Week 40/e0 ^{18}F-DOPA Uptake as Determined by PET Scan for GDNF/GDNF Subjects - ITT Overall Population

Dorsal Central/Posterior Putamen

Note: Analysis uses non-parametric Spearman rank correlation. For subject 45, items 22, 27, 28, 29 and 30 are excluded from the score.
Source: Listing 17.2.2.1, Dataset: ADPR, ADQUPDRS, Program: f_correl3.sas, Output: f_16-5-5-12-correl.rtf, Generated on: 28JUL2017 06:58
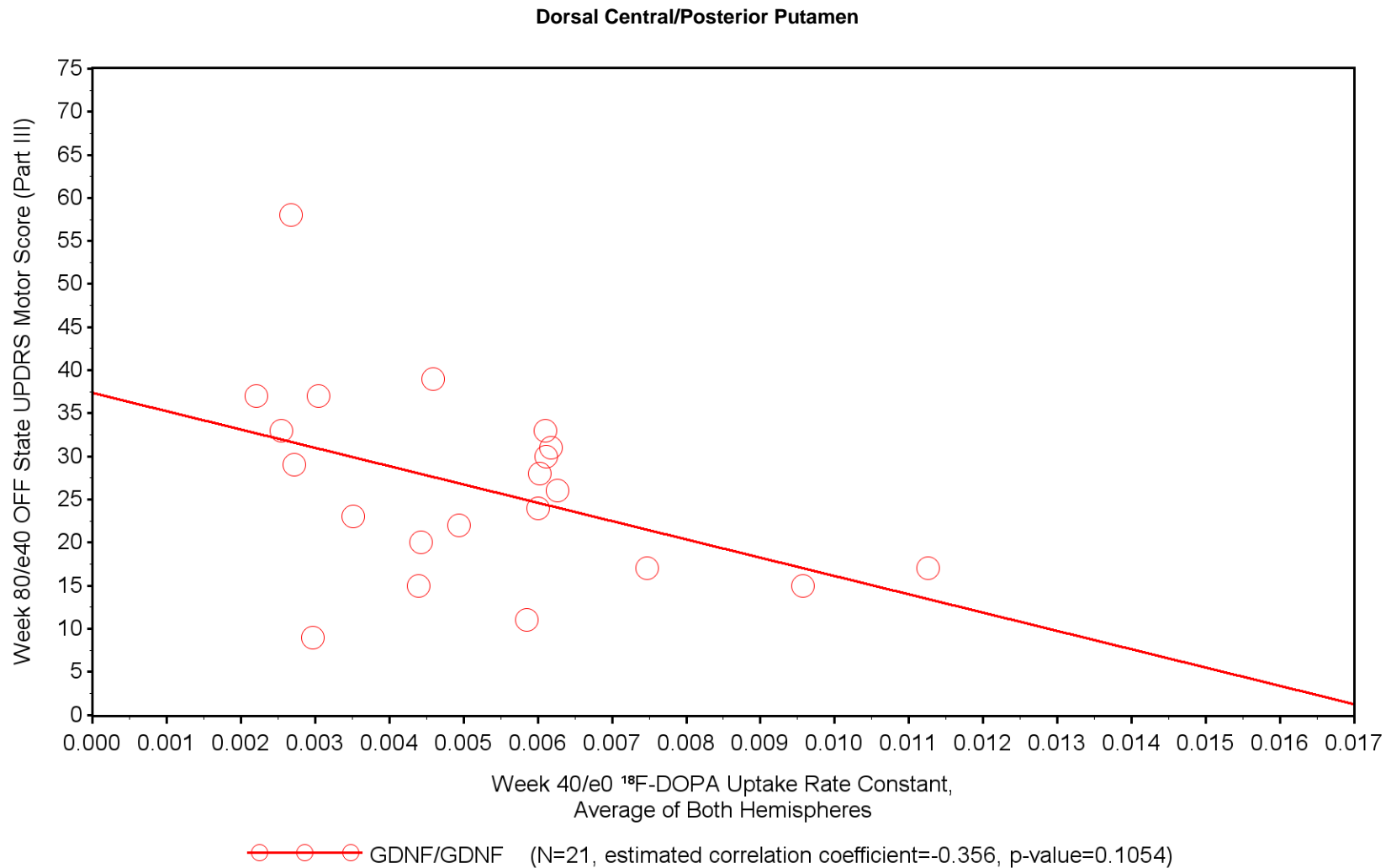
Figure 16.5.5.12 Correlation Analysis of Week 80/e40 OFF State UPDRS Motor Score (Part III) to Week 40/e0 ^{18}F-DOPA Uptake as Determined by PET Scan for GDNF/GDNF Subjects - ITT Overall Population

Dorsal Anterior Putamen

Note: Analysis uses non-parametric Spearman rank correlation. For subject 45, items 22, 27, 28, 29 and 30 are excluded from the score.
Source: Listing 17.2.2.1, Dataset: ADPR, ADQUPDRS, Program: f_correl3.sas, Output: f_16-5-5-12-correl.rtf, Generated on: 28JUL2017 06:58
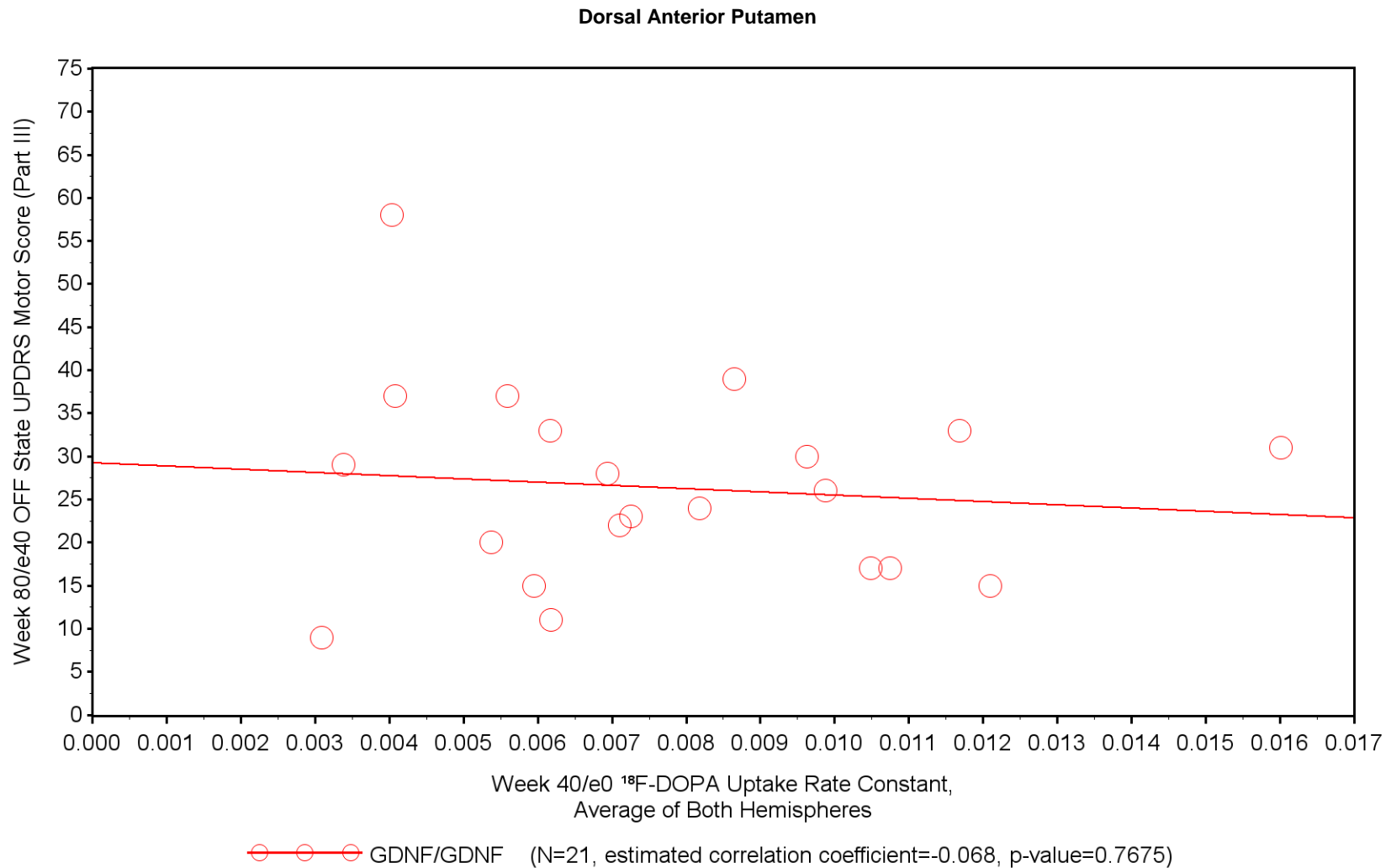
Figure 16.5.5.13 Correlation Analysis of Week 80/e40 OFF State UPDRS Motor Score (Part III) to Week 40/e0 ^{18}F-DOPA Uptake as Determined by PET Scan for Placebo/GDNF Subjects - ITT Overall Population

Dorsal Central/Posterior Putamen

Note: Analysis uses non-parametric Spearman rank correlation.
Source: Listing 17.2.2.1, Dataset: ADPR, ADQUPDRS, Program: f_correl3.sas, Output: f_16-5-5-13-correl.rtf, Generated on: 28JUL2017 06:58
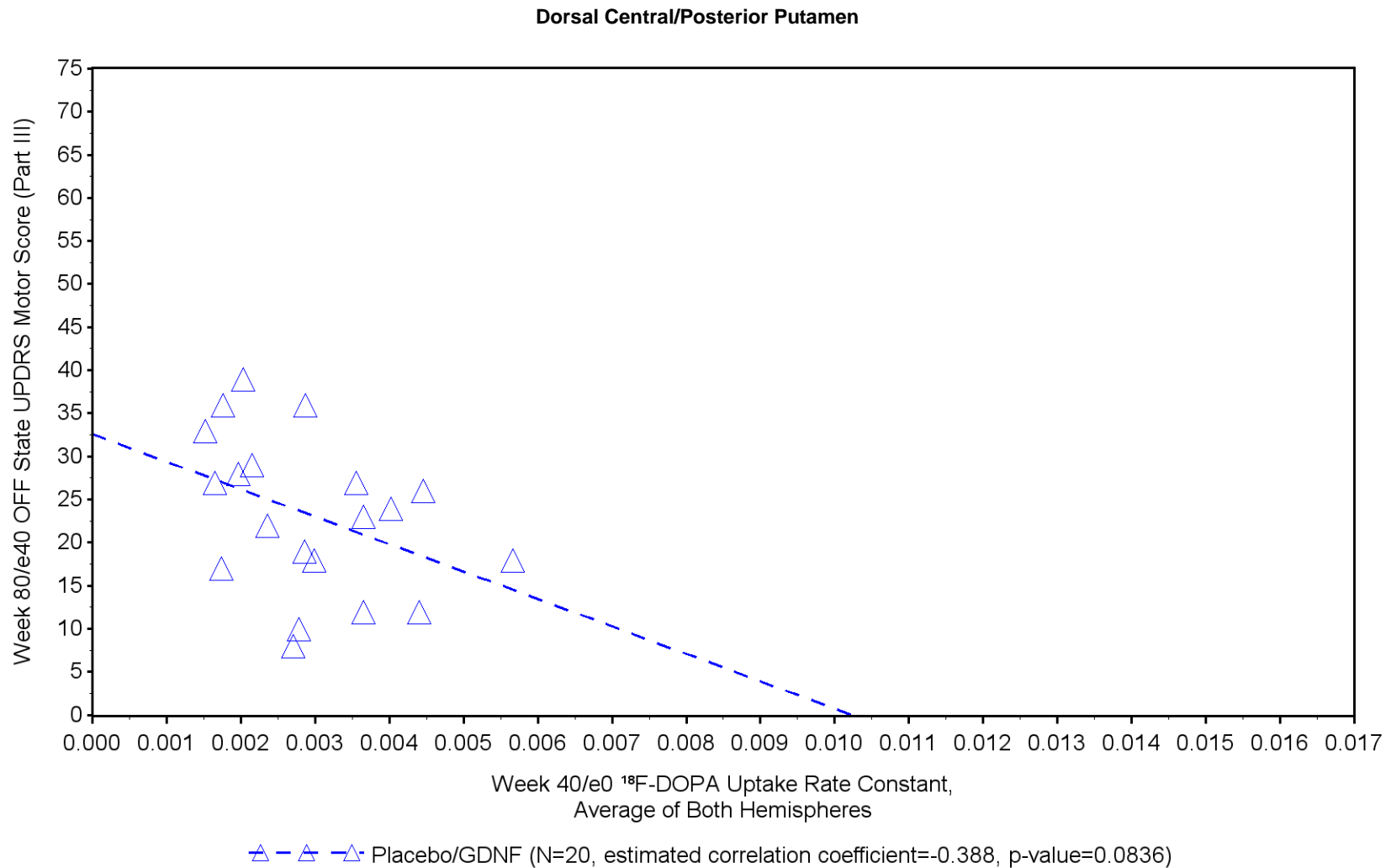
Figure 16.5.5.13 Correlation Analysis of Week 80/e40 OFF State UPDRS Motor Score (Part III) to Week 40/e0 ^{18}F-DOPA Uptake as Determined by PET Scan for Placebo/GDNF Subjects - ITT Overall Population

Dorsal Anterior Putamen

Placebo/GDNF (N=20, estimated correlation coefficient=-0.528, p-value=0.0132)

Note: Analysis uses non-parametric Spearman rank correlation.
Source: Listing 17.2.2.1, Dataset: ADPR, ADQUPDRS, Program: f_correl3.sas, Output: f_16-5-5-13-correl.rtf, Generated on: 28JUL2017 06:58

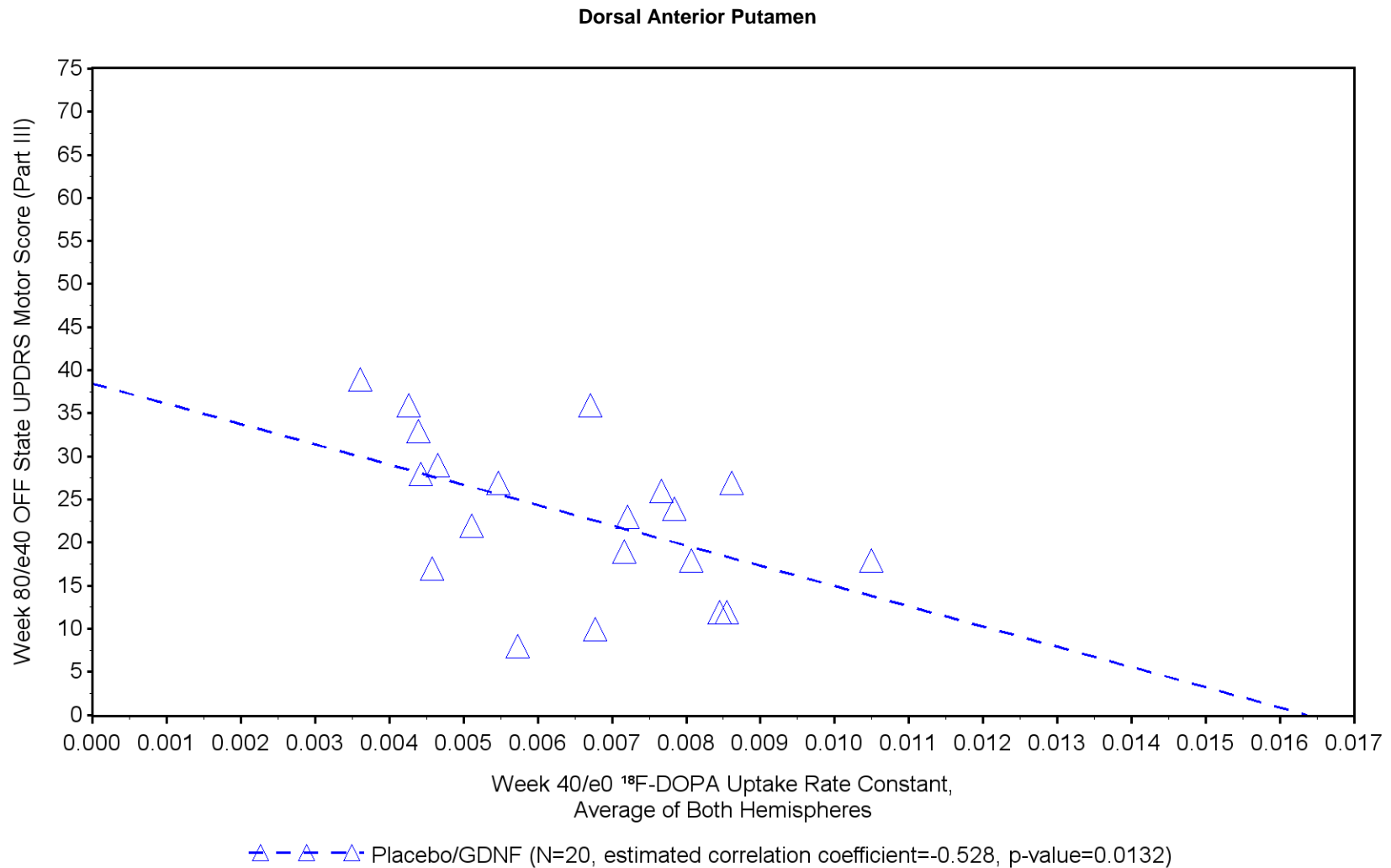**Figure 16.5.5.14 Correlation Analysis of Week 80/e40 OFF State UPDRS ADL Score (Part II) to Week 40/e0 ^{18}F-DOPA Uptake as Determined by PET Scan for GDNF/GDNF Subjects - ITT Overall Population**

Dorsal Central/Posterior Putamen

Note: Analysis uses non-parametric Spearman rank correlation. Data for Subject 45 are excluded from analysis.
Source: Listing 17.2.2.1, Dataset: ADPR, ADQUPDRS, Program: f_correl3.sas, Output: f_16-5-5-14-correl.rtf, Generated on: 28JUL2017 06:58
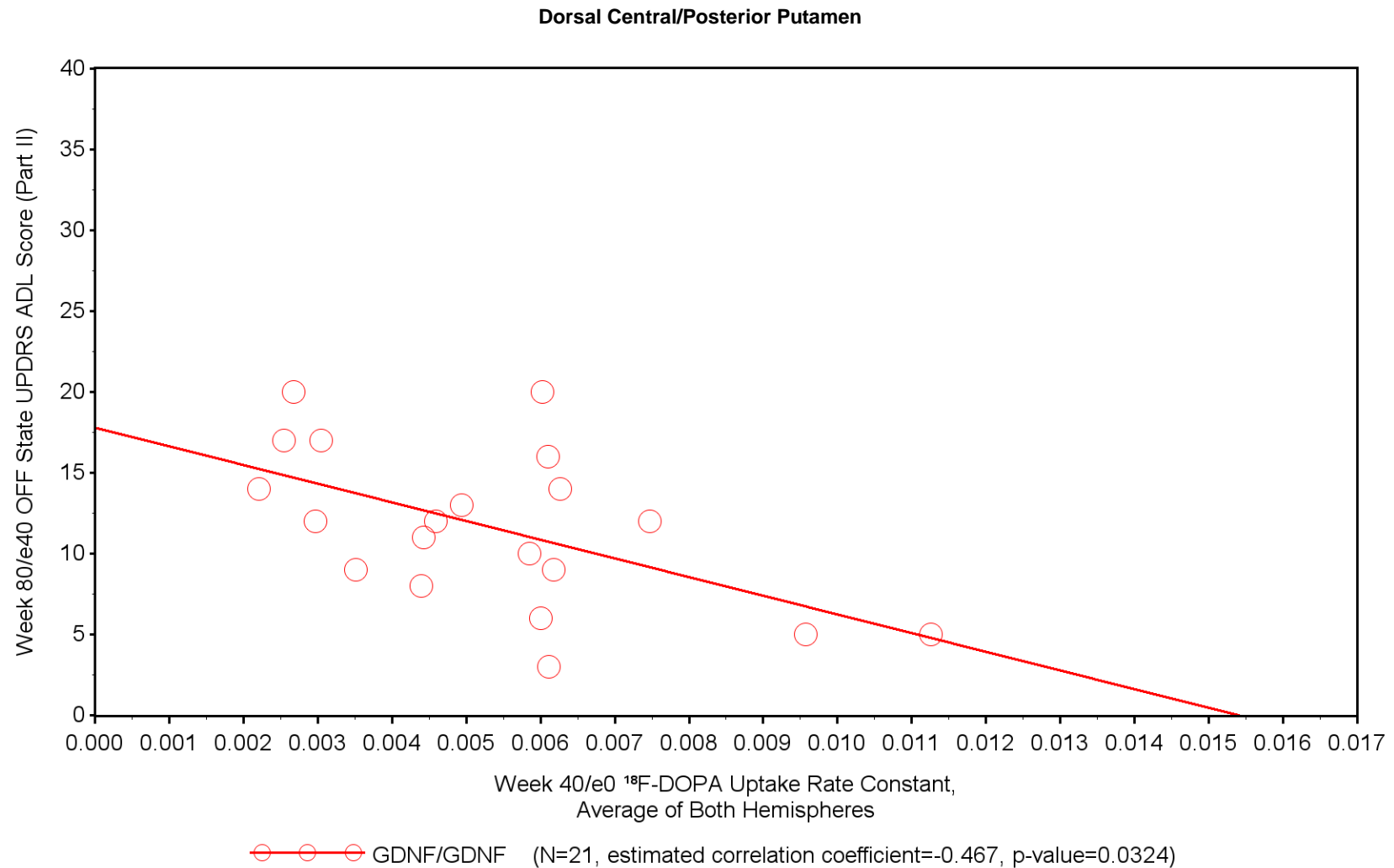
Figure 16.5.5.14 Correlation Analysis of Week 80/e40 OFF State UPDRS ADL Score (Part II) to Week 40/e0 ^{18}F-DOPA Uptake as Determined by PET Scan for GDNF/GDNF Subjects - ITT Overall Population

Dorsal Anterior Putamen

Note: Analysis uses non-parametric Spearman rank correlation. Data for Subject 45 are excluded from analysis.
Source: Listing 17.2.2.1, Dataset: ADPR, ADQUPDRS, Program: f_correl3.sas, Output: f_16-5-5-14-correl.rtf, Generated on: 28JUL2017 06:58
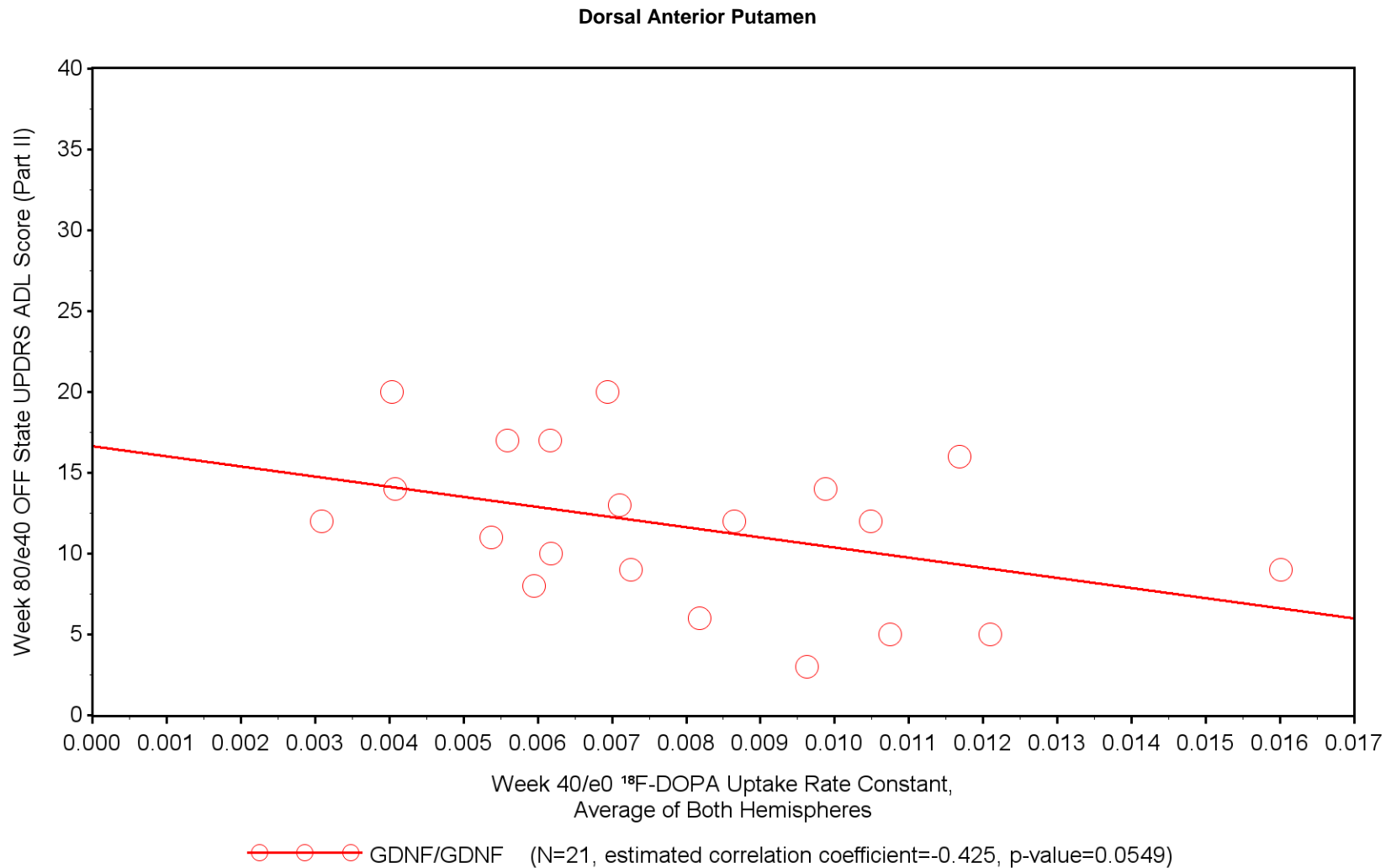
Figure 16.5.5.15 Correlation Analysis of Week 80/e40 OFF State UPDRS ADL Score (Part II) to Week 40/e0 ^{18}F-DOPA Uptake as Determined by PET Scan for Placebo/GDNF Subjects - ITT Overall Population

Dorsal Central/Posterior Putamen

Note: Analysis uses non-parametric Spearman rank correlation.
Source: Listing 17.2.2.1, Dataset: ADPR, ADQUPDRS, Program: f_correl3.sas, Output: f_16-5-5-15-correl.rtf, Generated on: 28JUL2017 06:58
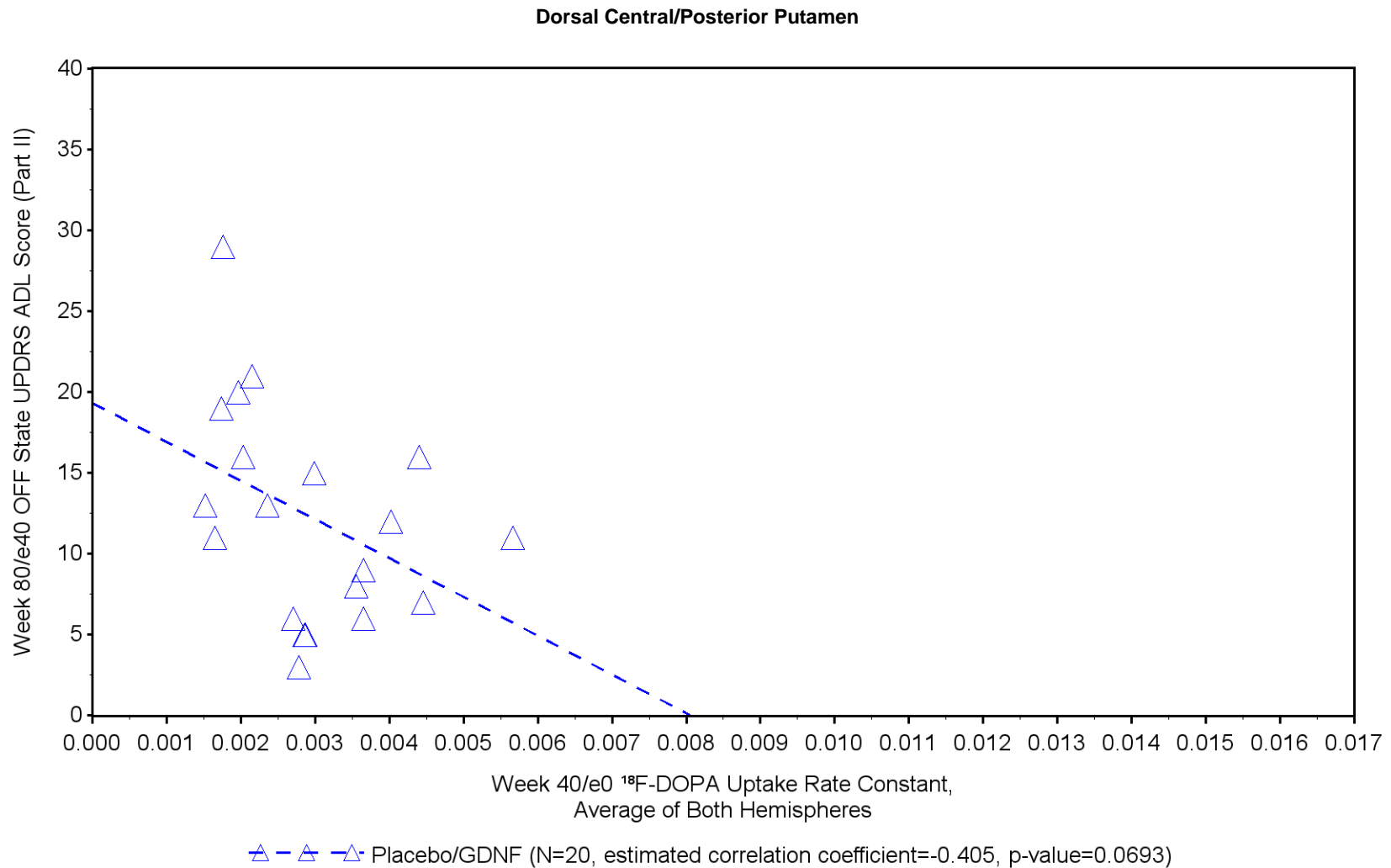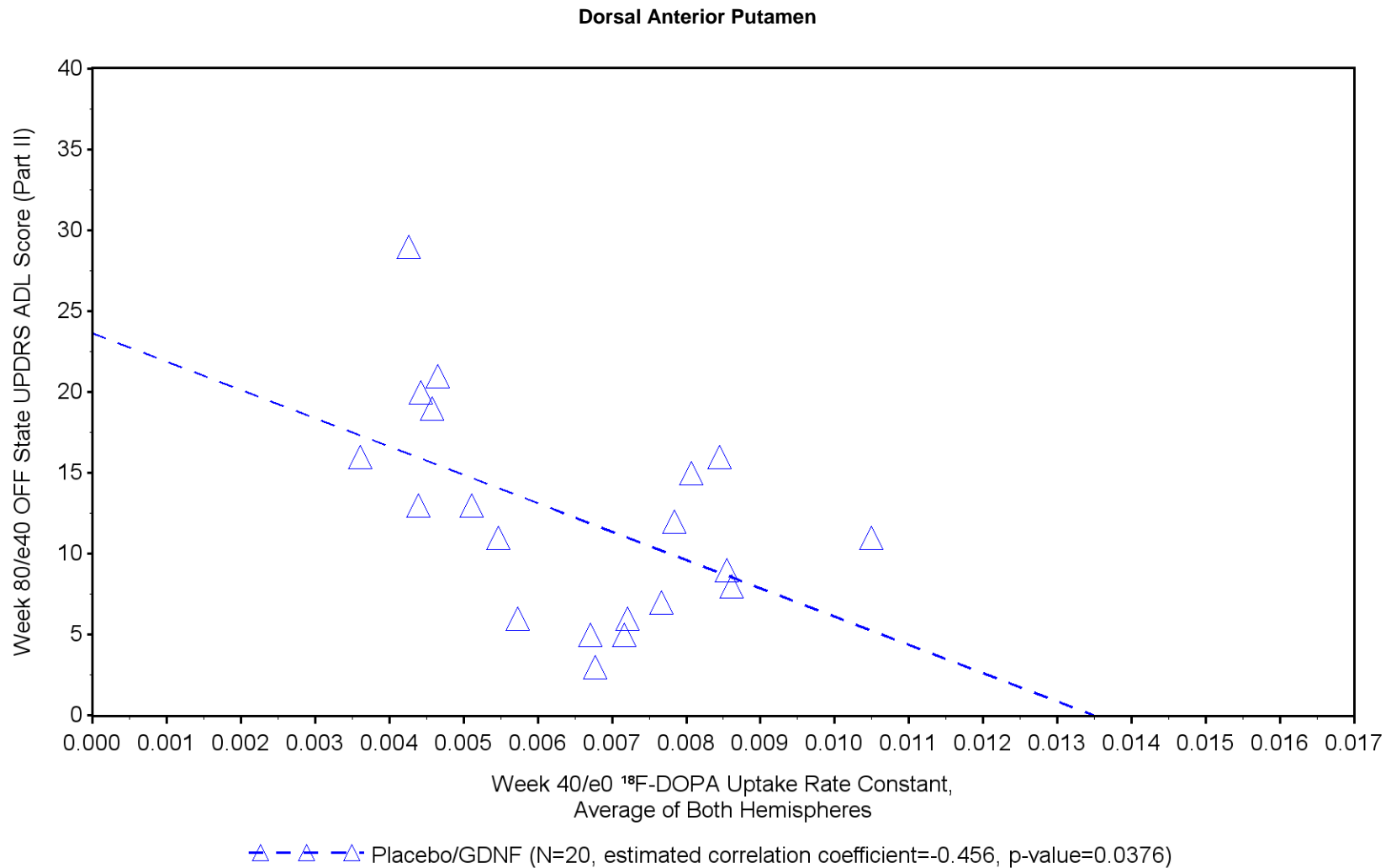
Figure 16.5.5.15 Correlation Analysis of Week 80/e40 OFF State UPDRS ADL Score (Part II) to Week 40/e0 ^{18}F-DOPA Uptake as Determined by PET Scan for Placebo/GDNF Subjects - ITT Overall Population

Dorsal Anterior Putamen

Note: Analysis uses non-parametric Spearman rank correlation.

Figure 16.5.5.16 Correlation Analysis of Baseline (Week 0) OFF State UPDRS Motor Score (Part III) to Baseline (Week 0) ^{18}F-DOPA Uptake as Determined by PET Scan for All Subjects - ITT Overall Population

Dorsal Central/Posterior Putamen

All Subjects (N=41, estimated correlation coefficient=-0.115, p-value=0.4714)

Note: Analysis uses non-parametric Spearman rank correlation. For subject 45, items 22, 27, 28, 29 and 30 are excluded from the score.
Source: Listing 17.2.2.1, Dataset: ADPR, ADQUPDRS, Program: f_correl3.sas, Output: f_16-5-5-16-correl.rtf, Generated on: 28JUL2017 06:58

Figure 16.5.5.16 Correlation Analysis of Baseline (Week 0) OFF State UPDRS Motor Score (Part III) to Baseline (Week 0) ^{18}F-DOPA Uptake as Determined by PET Scan for All Subjects - ITT Overall Population

Dorsal Anterior Putamen

All Subjects (N=41, estimated correlation coefficient=-0.194, p-value=0.2210)

Note: Analysis uses non-parametric Spearman rank correlation. For subject 45, items 22, 27, 28, 29 and 30 are excluded from the score.
Source: Listing 17.2.2.1, Dataset: ADPR, ADQUPDRS, Program: f_correl3.sas, Output: f_16-5-5-16-correl.rtf, Generated on: 28JUL2017 06:58
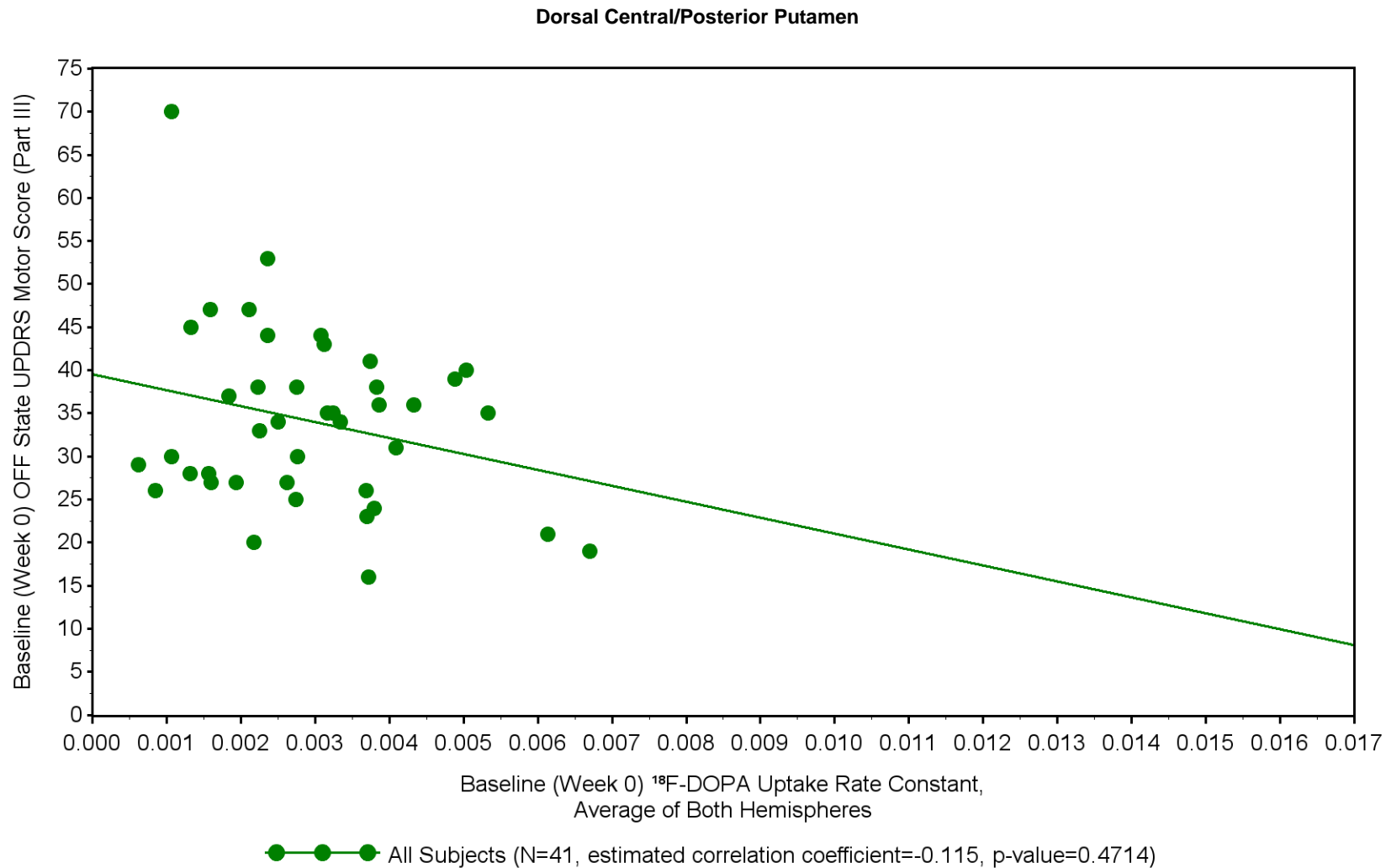
Figure 16.5.5.17 Correlation Analysis of Baseline (Week 0) OFF State UPDRS ADL Score (Part II) to Baseline (Week 0) ^{18}F-DOPA Uptake as Determined by PET Scan for All Subjects - ITT Overall Population

Dorsal Central/Posterior Putamen

All Subjects (N=41, estimated correlation coefficient=-0.370, p-value=0.0167)

Note: Analysis uses non-parametric Spearman rank correlation. Data for Subject 45 are excluded from analysis.
Source: Listing 17.2.2.1, Dataset: ADPR, ADQUPDRS, Program: f_correl3.sas, Output: f_16-5-5-17-correl.rtf, Generated on: 28JUL2017 06:58
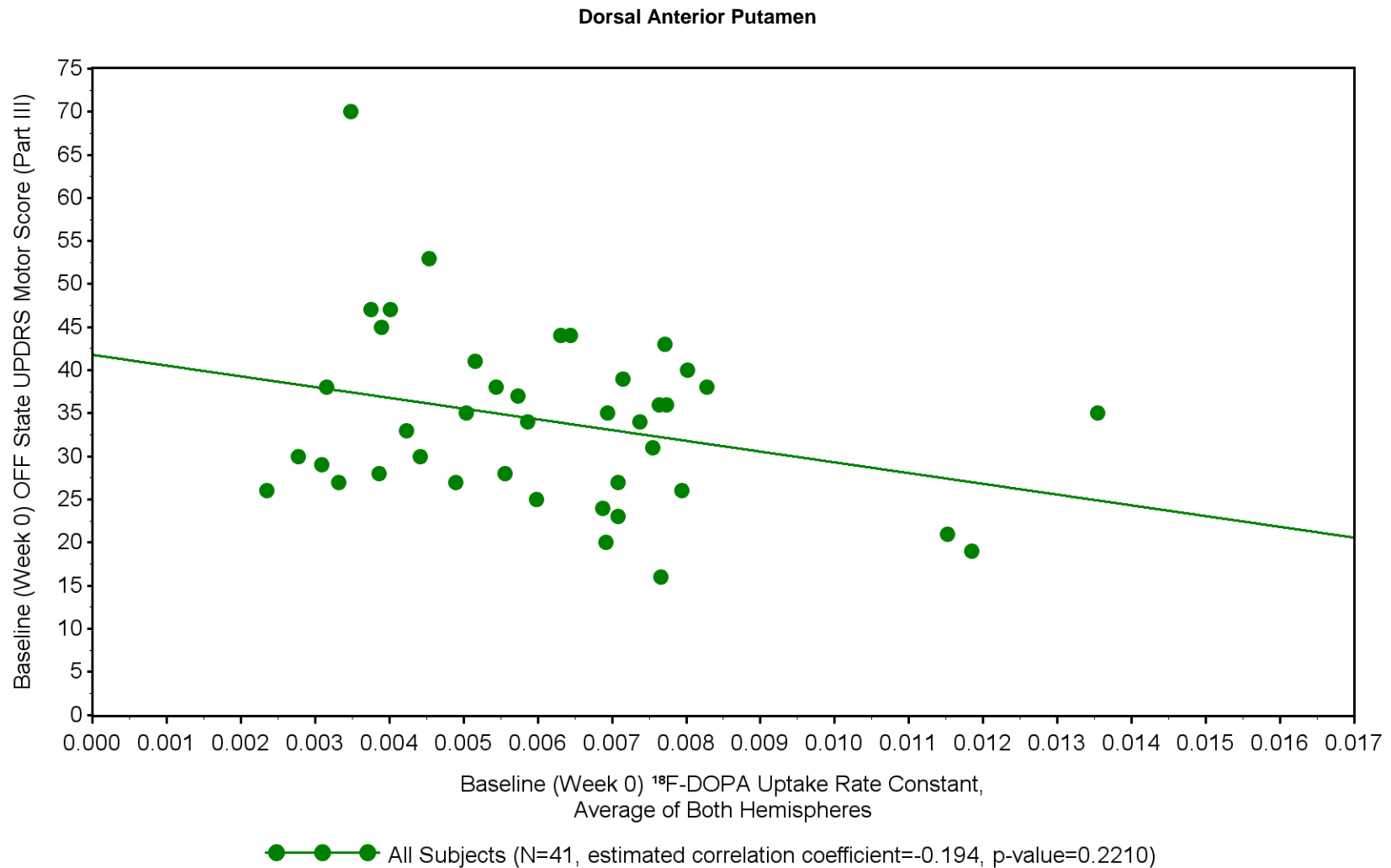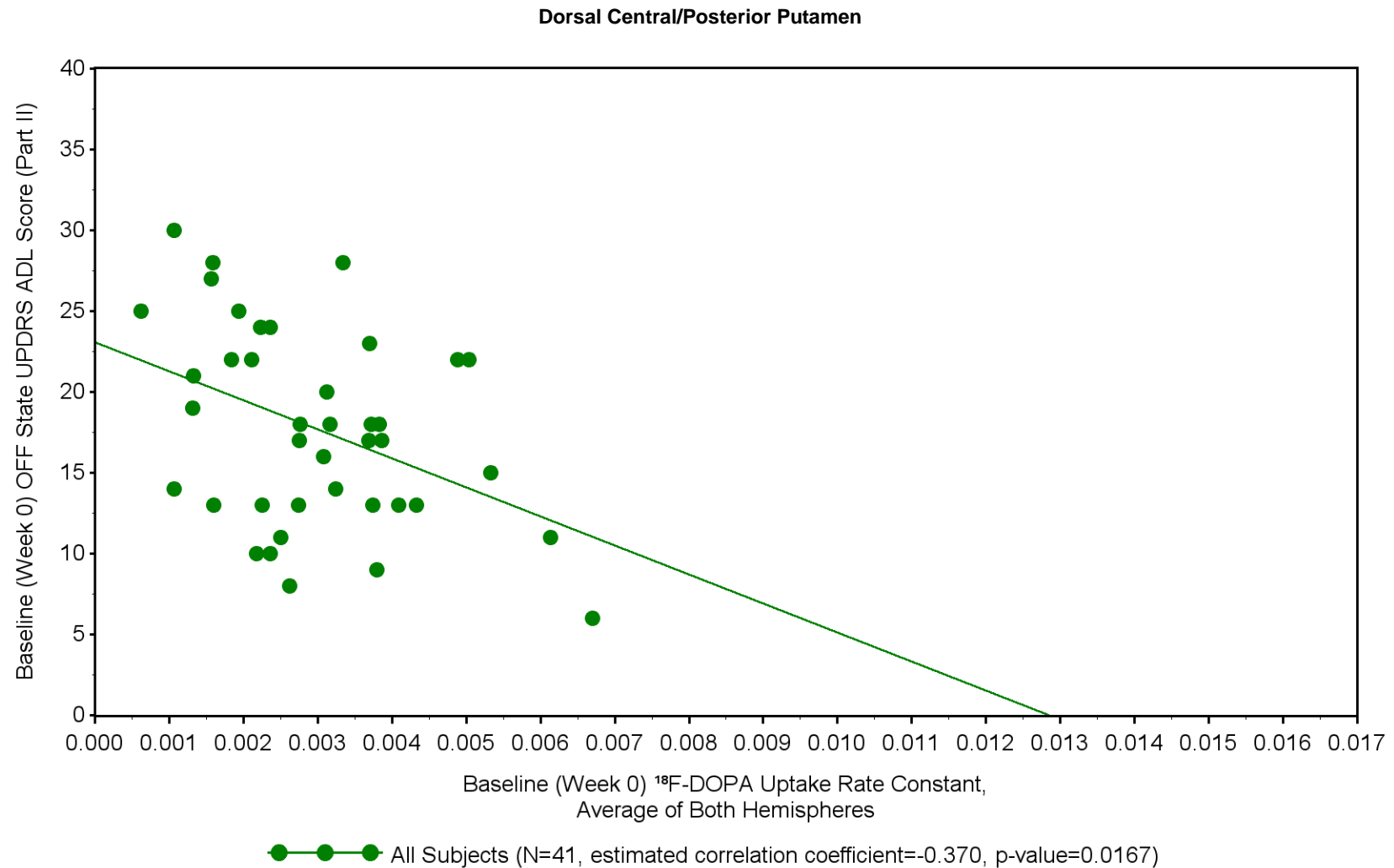
Figure 16.5.5.17 Correlation Analysis of Baseline (Week 0) OFF State UPDRS ADL Score (Part II) to Baseline (Week 0) ^{18}F-DOPA Uptake as Determined by PET Scan for All Subjects - ITT Overall Population

Dorsal Anterior Putamen

All Subjects (N=41, estimated correlation coefficient=-0.352, p-value=0.0236)

Note: Analysis uses non-parametric Spearman rank correlation. Data for Subject 45 are excluded from analysis.
Source: Listing 17.2.2.1, Dataset: ADPR, ADQUPDRS, Program: f_correl3.sas, Output: f_16-5-5-17-correl.rtf, Generated on: 28JUL2017 06:58

Figure 16.5.5.18 Correlation Analysis of Percentage Change from Baseline to Week 80/e40 in OFF State UPDRS Motor Score (Part III) to Change From Baseline to Week 40/e0 in ^{18}F-DOPA Uptake as Determined by PET Scan - ITT Overall Population

Dorsal Caudate Nucleus

GDNF/GDNF (N=21, estimated correlation coefficient=-0.202, p-value=0.3741)

Placebo/GDNF (N=20, estimated correlation coefficient=-0.373, p-value=0.0978)

Note: Analysis uses non-parametric Spearman rank correlation. For subject 45, items 22, 27, 28, 29 and 30 are excluded from the score.
Source: Listing 17.2.2.1, Dataset: ADPR, ADQUPDRS, Program: f_correl2.sas, Output: f_16-5-5-18-correl.rtf, Generated on: 28JUL2017 06:57
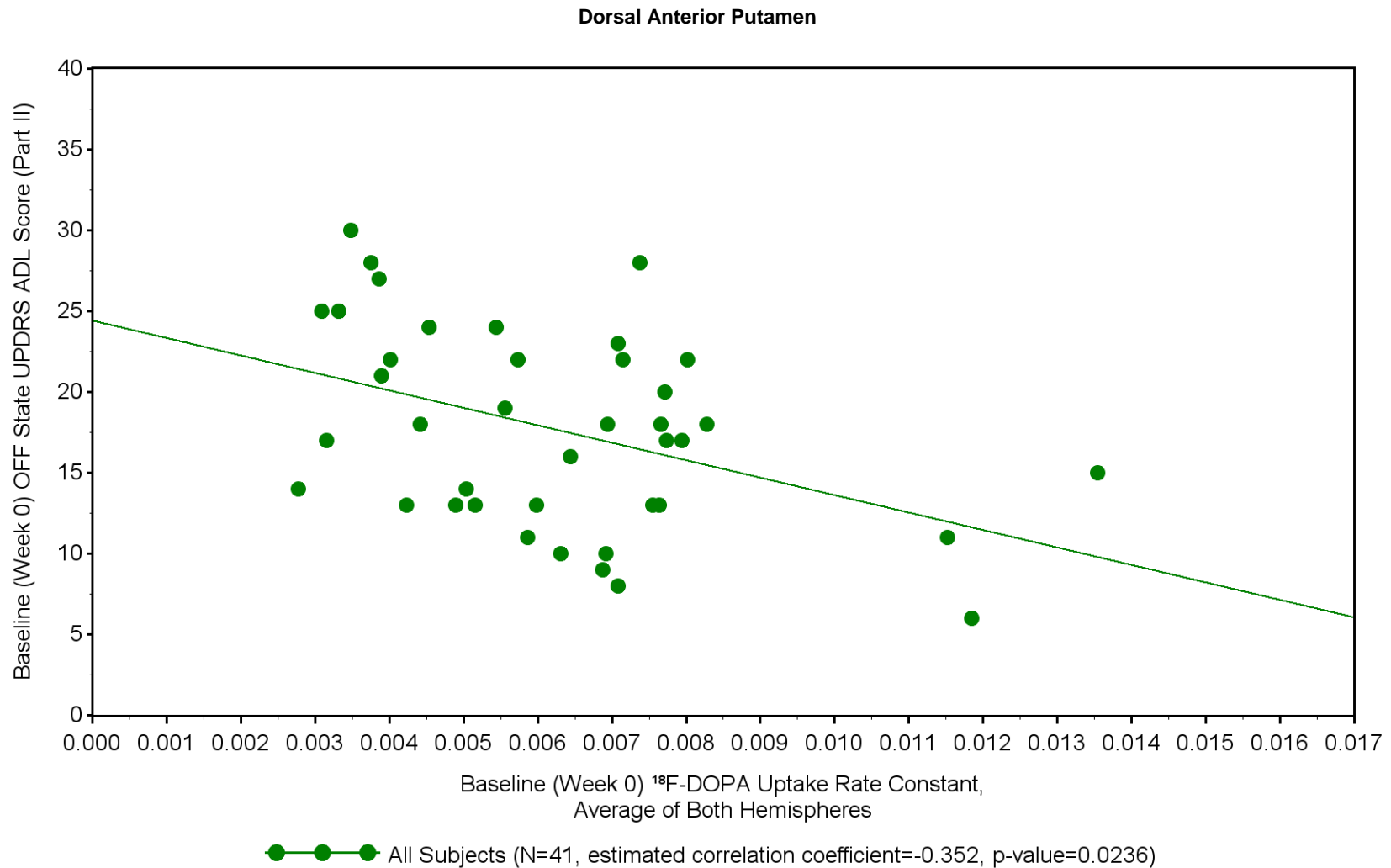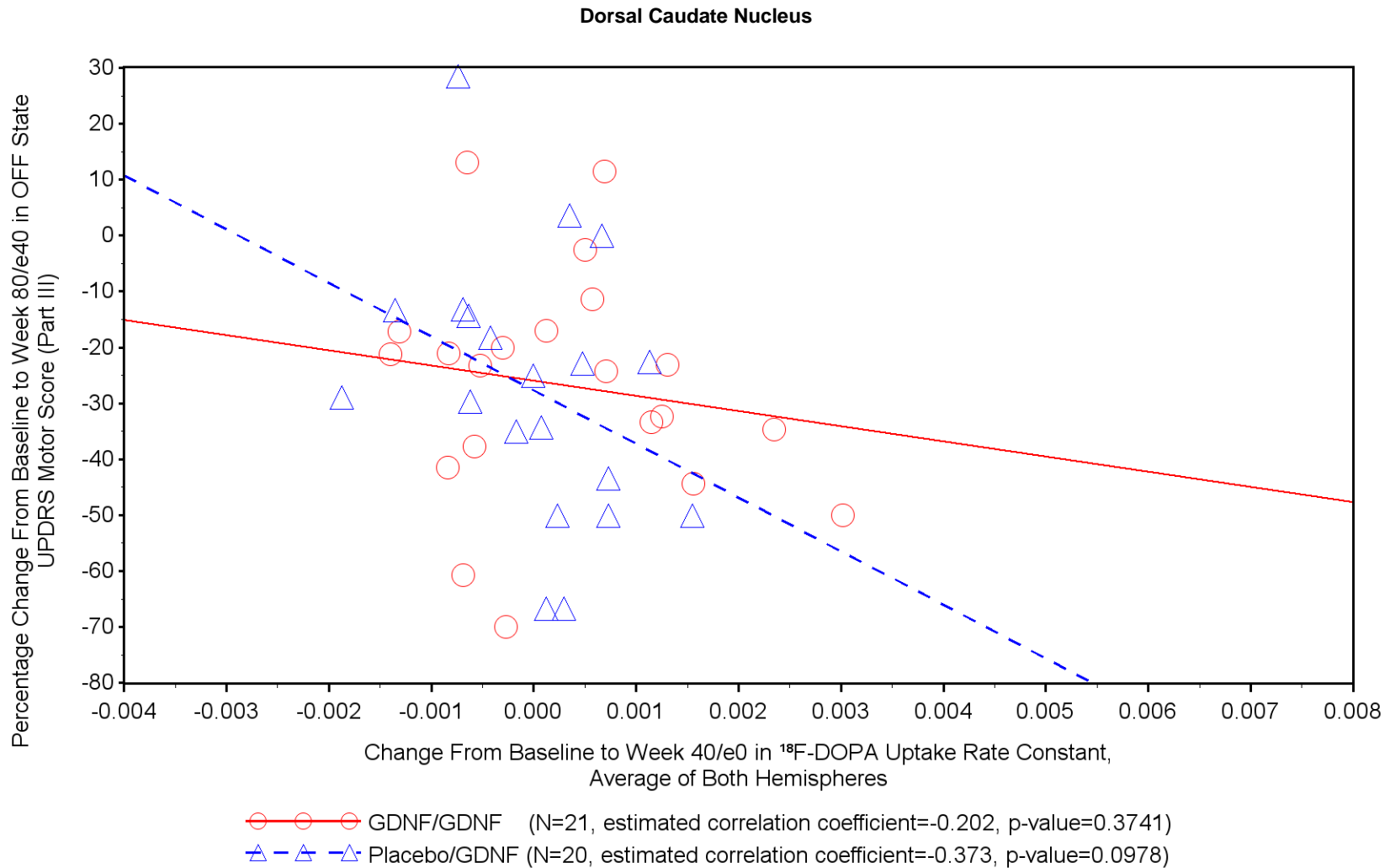
Figure 16.5.5.18 Correlation Analysis of Percentage Change from Baseline to Week 80/e40 in OFF State UPDRS Motor Score (Part III) to Change From Baseline to Week 40/e0 in ^{18}F-DOPA Uptake as Determined by PET Scan - ITT Overall Population

Dorsal Anterior Putamen

GDNF/GDNF (N=21, estimated correlation coefficient=-0.065, p-value=0.7784)

Placebo/GDNF (N=20, estimated correlation coefficient=0.269, p-value=0.2429)

Note: Analysis uses non-parametric Spearman rank correlation. For subject 45, items 22, 27, 28, 29 and 30 are excluded from the score.

Figure 16.5.5.18 Correlation Analysis of Percentage Change from Baseline to Week 80/e40 in OFF State UPDRS Motor Score (Part III) to Change From Baseline to Week 40/e0 in ^{18}F-DOPA Uptake as Determined by PET Scan - ITT Overall Population

Dorsal Central/Posterior Putamen

Note: Analysis uses non-parametric Spearman rank correlation. For subject 45, items 22, 27, 28, 29 and 30 are excluded from the score.
Source: Listing 17.2.2.1, Dataset: ADPR, ADQUPDRS, Program: f_correl2.sas, Output: f_16-5-5-18-correl.rtf, Generated on: 28JUL2017 06:57
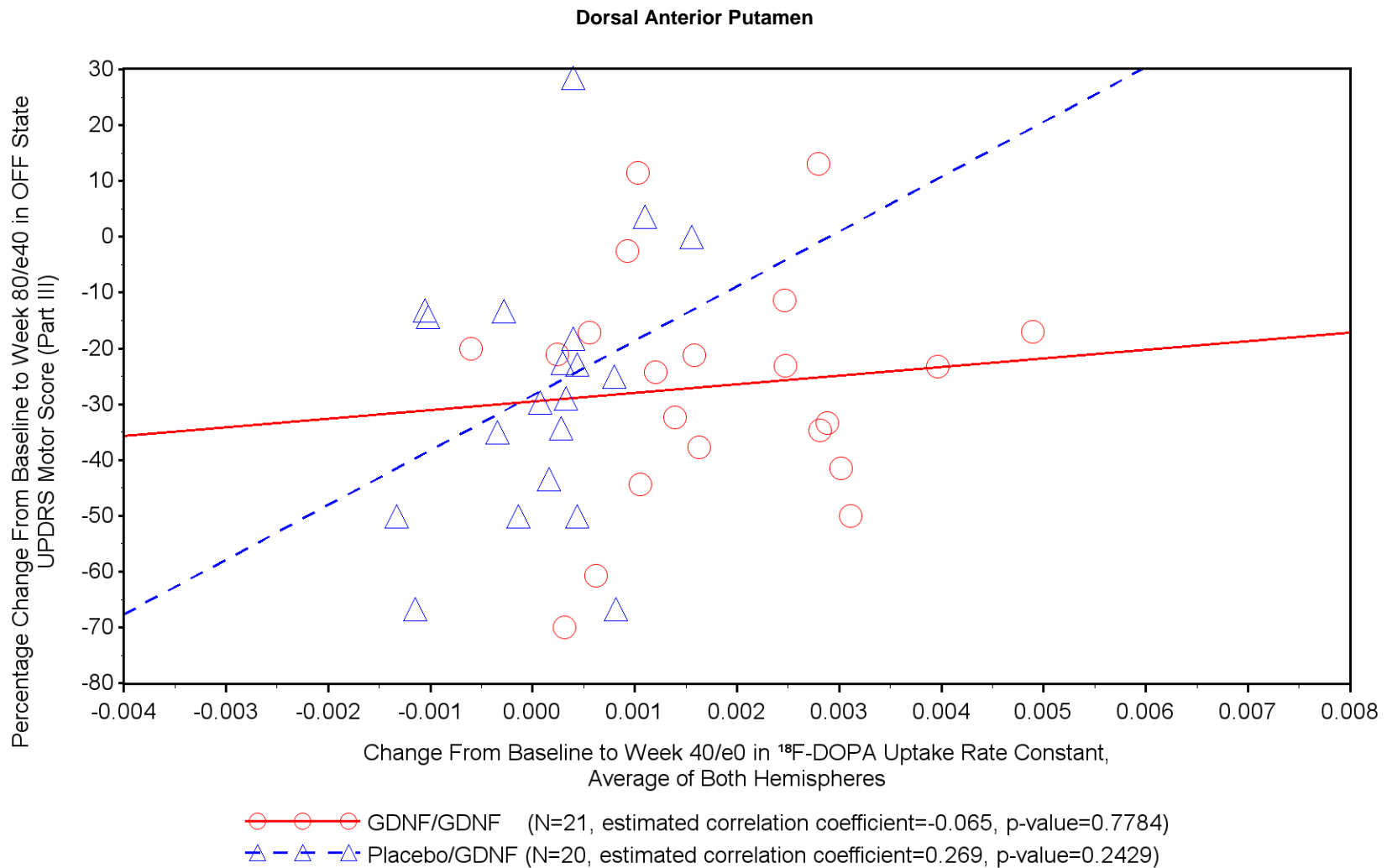
Figure 16.5.5.18 Correlation Analysis of Percentage Change from Baseline to Week 80/e40 in OFF State UPDRS Motor Score (Part III) to Change From Baseline to Week 40/e0 in ^{18}F-DOPA Uptake as Determined by PET Scan - ITT Overall Population

Ventral Striatum

Note: Analysis uses non-parametric Spearman rank correlation. For subject 45, items 22, 27, 28, 29 and 30 are excluded from the score.
Source: Listing 17.2.2.1, Dataset: ADPR, ADQUPDRS, Program: f_correl2.sas, Output: f_16-5-5-18-correl.rtf, Generated on: 28JUL2017 06:57
Page 4 of 5   Page 610
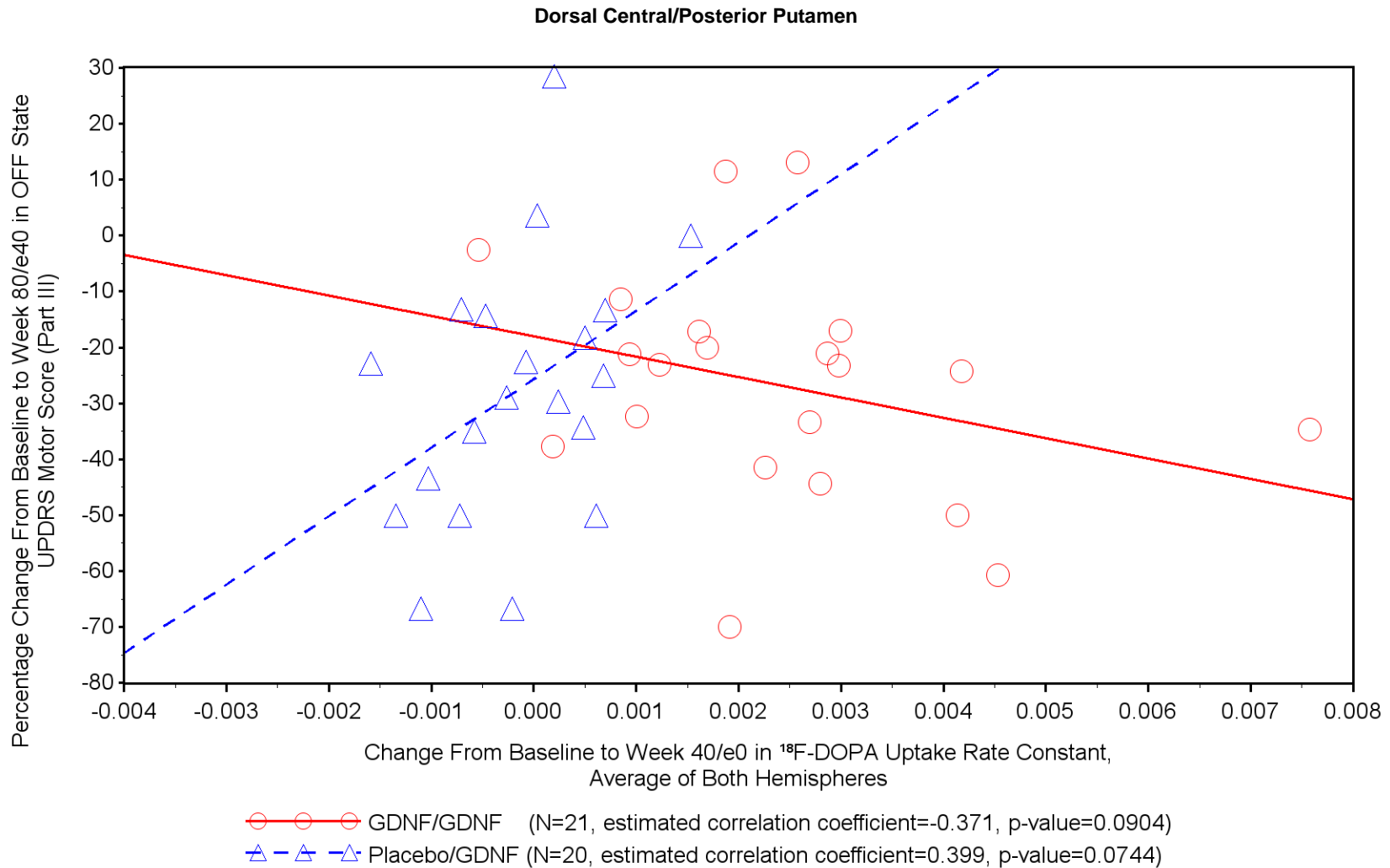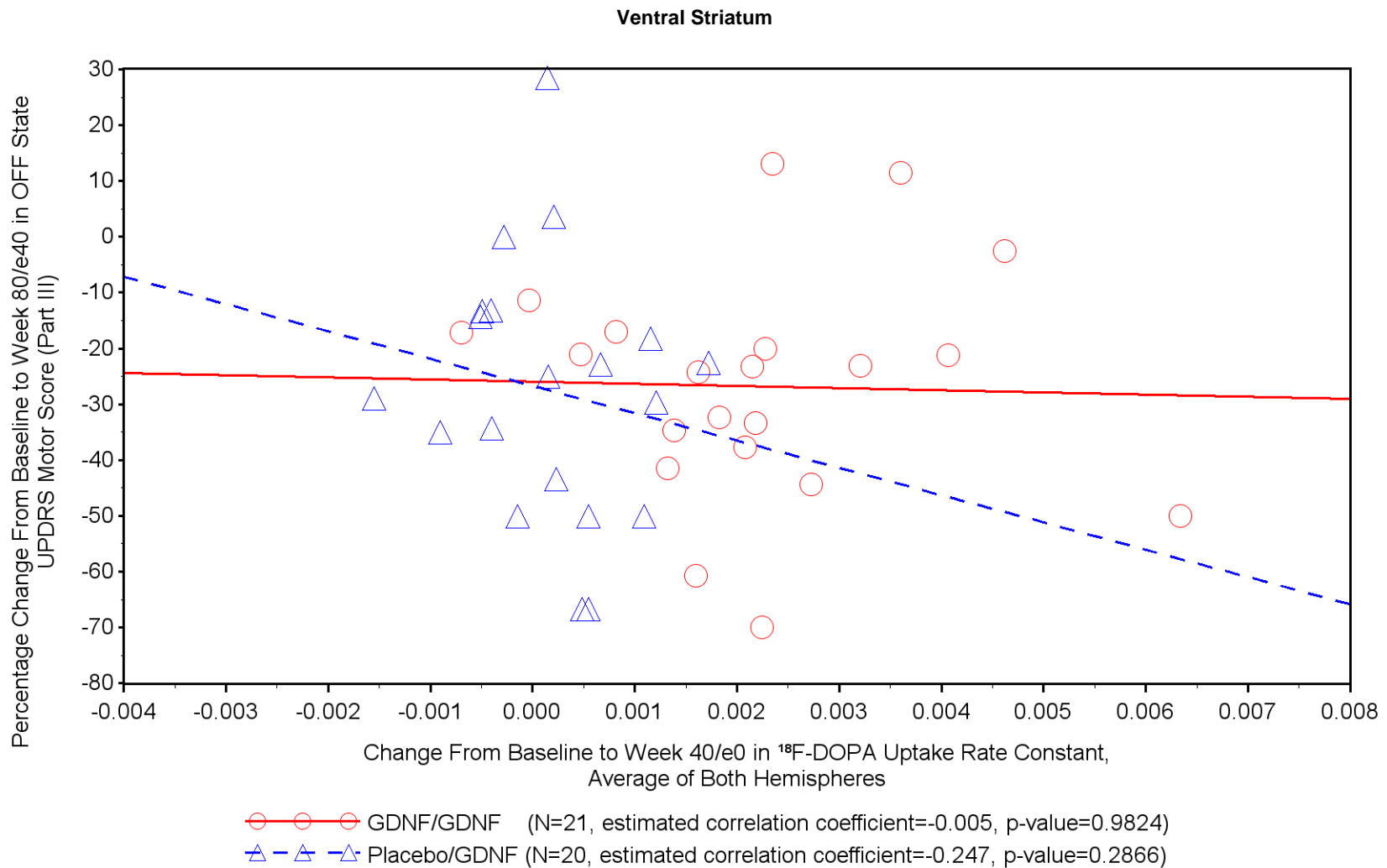
Figure 16.5.5.18 Correlation Analysis of Percentage Change from Baseline to Week 80/e40 in OFF State UPDRS Motor Score (Part III) to Change From Baseline to Week 40/e0 in ^{18}F-DOPA Uptake as Determined by PET Scan - ITT Overall Population

Substantia Nigra

GDNF/GDNF   (N=21, estimated correlation coefficient=-0.180, p-value=0.4287)
Placebo/GDNF (N=20, estimated correlation coefficient=-0.258, p-value=0.2641)

Note: Analysis uses non-parametric Spearman rank correlation. For subject 45, items 22, 27, 28, 29 and 30 are excluded from the score.
Source: Listing 17.2.2.1, Dataset: ADPR, ADQUPDRS, Program: f_correl2.sas, Output: f_16-5-5-18-correl.rtf, Generated on: 28JUL2017 06:57
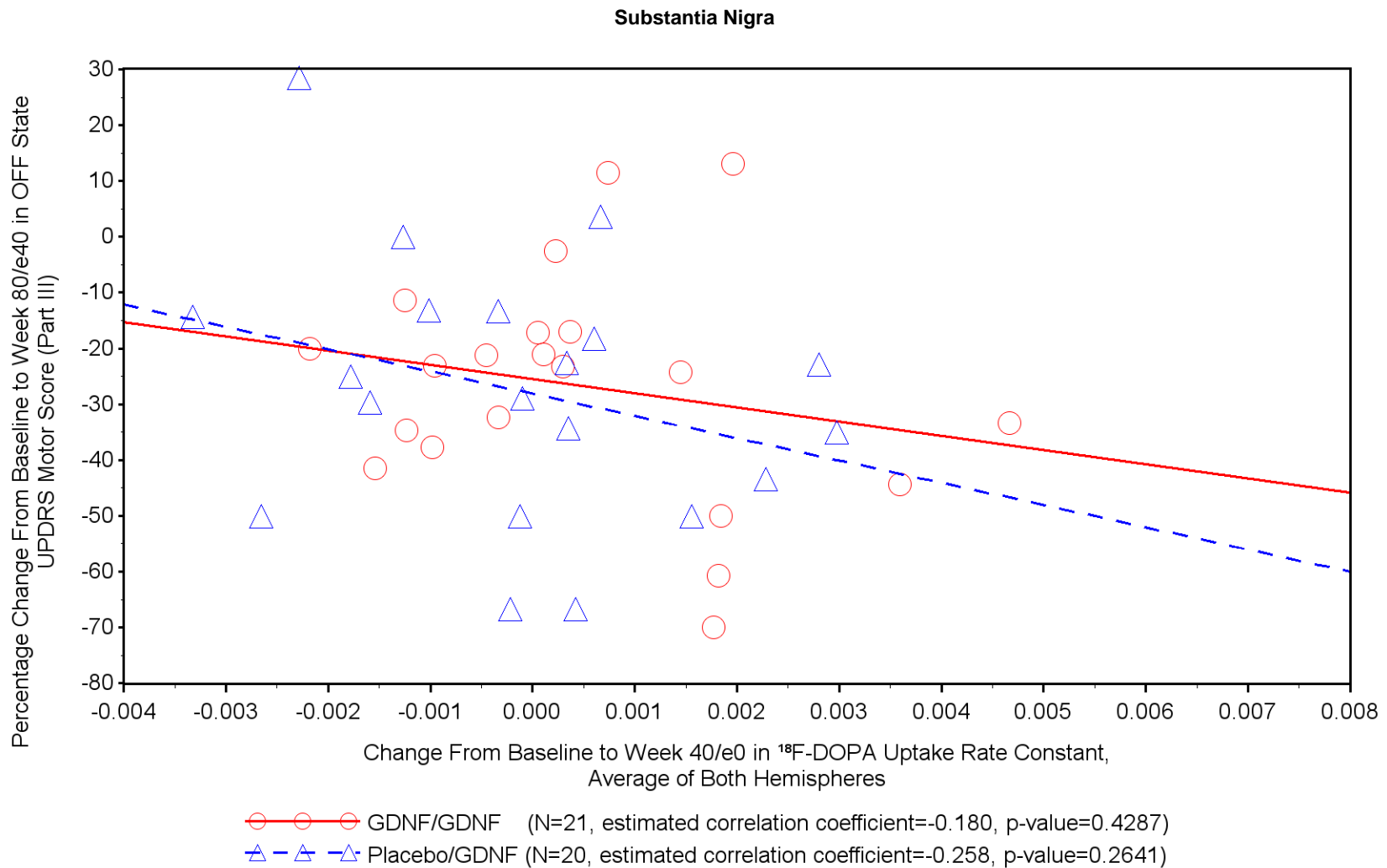
16.6 Subject Narratives

Subject narratives were written for all subjects with treatment-emergent serious AEs. The subject narratives are based on the clinical database that contains all data used in the analyses presented in this clinical study report, but also draw on relevant additional information taken from serious AE reports that has not been entered into the clinical database or reconciled with that database.

No subjects died. Two of the subjects with a treatment-emergent serious AE had to discontinue study medication during the Pilot Extension after explantation of their device.

Subject No.	Treatment group	Preferred term
PILOT STAGE		
04	GDNF/GDNF	Device occlusion
		Procedural complication
		Application site hypertrophy
		Device related infection[a]
		Psychosis postoperative
05	GDNF/GDNF	Device occlusion
		Application site infection[b]
		Application site infection
07	GDNF/GDNF	Application site inflammation
PRIMARY STAGE		
13	GDNF/GDNF	Muscle rupture
22	Placebo/GDNF	Dehydration
23	GDNF/GDNF	Menorrhagia
		Post procedural infection
24	Placebo/GDNF	Appendicitis
39	Placebo/GDNF	Osteoarthritis
45	GDNF/GDNF	Confusional state
47	GDNF/GDNF	Depression
		Paranoia

[a] AE leading to port explantation 8 days after Week e2-36.
[b] AE leading to port explantation 2 days after Week e2-32.

Subject Narrative

Subject No.: 04

Study stage / Treatment group:	Pilot Stage / GDNF/GDNF
Age (years) at screening in study 2553:	44
Sex:	Male
Time of first PD symptom:	1994
UPDRS motor score (part III) in OFF state at screening in study 2553:	45
Hoehn and Yahr stage in OFF state at screening in study 2553:	3
Serious adverse event(s): [preferred terms]	Device occlusion Procedural complication Application site hypertrophy Device related infection Psychosis postoperative

Description: Several months into the extension study, the subject's pump pressures began to rise during infusions, and catheters were ultimately blocked at the end of the Initial Extension. In order to proceed with the subsequent Pilot Extension and achieve satisfactory putamenal coverage, the subject eventually underwent surgery 9 months after the device occlusion initially occurred to replace the delivery system and port. The seriousness criterion specified by the investigator was "required hospitalization / prolongation". The intensity of the event was reported as moderate. The event was considered by the investigator to be unrelated to study drug but related to the device.

During the replacement surgery, presumably caused by the anesthetic tubing while in the prone position, the subject experienced significant trauma to the tongue, producing a postoperative procedural complication including tongue swelling as a serious AE and tongue ulceration as a nonserious AE. The tongue swelling further provoked dysphagia, dysphonia, and a subsequent chest infection, as well as a reduction in Parkinson's motor symptom control and a mood disorder. In the opinion of the investigator, these additional AEs did not individually reach the level of seriousness despite being significantly distressing in aggregate to the subject. The tongue swelling was managed with analgesics, intravenous steroids (hydrocortisone, dexamethasone), furosemide, promethazine, Benzydamine mouthwash, and nasogastric feeding. It resulted in prolongation of the subject's hospital stay, and hence the seriousness criterion specified by the

investigator was "required hospitalization / prolongation". The intensity of the event was reported as severe. The event ultimately resolved after approximately 10 weeks and was considered by the investigator to be unrelated to study drug but related to the device.

Starting approximately 3 months after the replacement surgery, the subject gradually developed hypertrophy of the skin surrounding the port site, with the result that the port was beneath the surface of the skin and could no longer be used to enable connection of an administration device for GDNF infusions. Approximately 5 months after the replacement surgery, the subject therefore underwent a brief surgical procedure to remodel the skin around the port site. Postoperatively, the subject was instructed to wear a silicone healing cap. The seriousness criterion specified by the investigator was "required hospitalization / prolongation". The intensity of the event was reported as mild. The event was considered by the investigator to be unrelated to study drug but related to the device.

Approximately 9.5 months after the replacement surgery, the subject noticed swelling and itching of the scalp, and the study neurosurgeon noted pus discharge from skin. Eight days after Week e2-36, the subject underwent surgical exploration of the port site which revealed an infection that was felt to have arisen along the outside course of the subcutaneous tubing. Granulation tissue was removed and the port was explanted together with the catheters on the right side. The explantation of the port led to permanent discontinuation of study medication. A wound swab isolated methicillin-sensitive Staphylococcus aureus, and the subject was treated with antibiotics (flucloxacillin, gentamicin, vancomycin, ceftriaxone, and rifampicin). When discharged approximately 2 weeks after admission, he was still on oral antibiotics (rifampicin, doxycycline). The subject was reviewed again on an outpatient basis another 2 weeks later. Since he was in a good overall condition, inflammatory markers were within normal limits, and MRI of the brain did not show any signs of intracerebral infection, the antibiotic treatment was stopped. The seriousness criterion specified by the investigator was "required hospitalization / prolongation". The intensity of the event was reported as severe. The event was considered by the investigator to be unrelated to study drug but related to the device.

Starting 3 days after the port explantation, the subject developed a mild to moderate postoperative psychosis, manifested as visual hallucinations, paranoid delusions, and anxiety. The subject's PD medication was adjusted, and he was started on a course of atypical neuroleptic (quetiapine) and sedative-hypnotic (zopiclone). Symptoms improved within a week and resolved fully within 3 days after discharge from hospital. The seriousness criterion specified by the investigator was "other (complicated hospitalization)". The intensity of the event was reported as moderate. The event was considered by the investigator to be unrelated to study drug but related to the device.

Subject Narrative

Subject No.:   05

Study stage / Treatment group:	Pilot Stage / GDNF/GDNF
Age (years) at screening in study 2553:	51
Sex:	Female
Time of first PD symptom:	2007
UPDRS motor score (part III) in OFF state at screening in study 2553:	27
Hoehn and Yahr stage in OFF state at screening in study 2553:	2
Serious adverse event(s): [preferred terms]	Device occlusion Application site infection Application site infection

Description: Several months into the extension study, the subject's pump pressures began to rise during infusions, and catheters were ultimately blocked at the end of the Initial Extension. In order to proceed with the subsequent Pilot Extension and achieve satisfactory putamenal coverage, the subject eventually underwent surgery 6 months after the device occlusion initially occurred to replace the delivery system and port. The seriousness criterion specified by the investigator was "required hospitalization / prolongation". The intensity of the event was reported as moderate. The event was considered by the investigator to be unrelated to study drug but related to the device.

Approximately 6.5 months after the replacement surgery, the subject was diagnosed with a Staphylococcus aureus infection of the port site. The subject was systemically well, and there were no clinical or biological markers of sepsis. CT of the brain ruled out an intracerebral spread of infection. The subject was treated with oral flucloxacillin and daily local cleaning and rinsing of the port site. However, the infection persisted. In order to avoid spread of infection, the port was removed by day-case surgery 2 days after Week e2-32, approximately 7 weeks after the initial diagnosis. All other parts of the delivery device were left in place. The removal of the port led to permanent discontinuation of study medication and effectively marked the end of the study for the subject. Postoperatively, a small pocket of pus extending from beneath the port site to the dura was found, but considered by the surgical team to be of no concern. Antibiotic treatment was continued for 7 days. At that time, wound healing was good and sutures were removed. The subject was clinically well, without signs of infection, and her PD was stable. The seriousness

criterion specified by the investigator was "required hospitalization / prolongation". The intensity of the event was reported as moderate. The event was considered by the investigator to be unrelated to study drug but related to the device.

Starting approximately 4.5 months after the port explantation, the subject reported pain and tenderness over the occipital vertex. A contrast-enhanced MRI scan of the brain performed another 2 months later did not show any signs of intracranial infection. A further 6 weeks later, local discharge of pus triggered a neurosurgical review; CT of the head did not reveal any unexpected findings. The subject was put on oral antibiotics. However, the situation did not improve and approximately 5 weeks later, the catheters and filter system (excluding the guide tubes) were removed due to chronic low grade infection with persisting discharge and pain. Intraoperative findings showed that the in-line filters were displaced and partially overlying each other; an infection in the subcutaneous space involving the catheters was present. After receiving intravenous antibiotics for 2 days, the subject was discharged home. The seriousness criterion specified by the investigator was "required hospitalization / prolongation". The intensity of the event was reported as moderate. The event was considered by the investigator to be unrelated to study drug but related to the device.

Subject Narrative

Subject No.:   07

Study stage / Treatment group:	Pilot Stage / GDNF/GDNF
Age (years) at screening in study 2553:	41
Sex:	Female
Time of first PD symptom:	2004
UPDRS motor score (part III) in OFF state at screening in study 2553:	27
Hoehn and Yahr stage in OFF state at screening in study 2553:	2
Serious adverse event(s): [preferred terms]	Application site inflammation

Description: Three days after receiving the seventh infusion of GDNF in the Initial Extension, the subject reported that the port behind her left ear was red and inflamed. The subject was admitted to hospital the next morning, a microbiology swab of the port site and blood cultures were taken, and treatment with flucloxacillin was commenced (first intravenous, then oral). White blood cell count was normal, C-reactive protein was minimally raised but normal 2 days later. Both the blood cultures and the swab came back negative, and the subject was discharged home 4 days later. One week after discharge, the event had resolved. As a preventive measure to avoid skin hypertrophy, the subject was instructed to wear the port site healing cap. The seriousness criterion specified by the investigator was "required hospitalization / prolongation". The intensity of the event was reported as moderate. The event was considered by the investigator to be unrelated to study drug but related to the device.

Subject Narrative

Subject No.:   13

Study stage / Treatment group:	Primary Stage / GDNF/GDNF
Age (years) at screening in study 2553:	61
Sex:	Female
Time of first PD symptom:	2002
UPDRS motor score (part III) in OFF state at screening in study 2553:	36
Hoehn and Yahr stage in OFF state at screening in study 2553:	2
Serious adverse event(s): [preferred terms]	Muscle rupture

Description: Approximately 7 months into the Initial Extension, the subject presented with ongoing pain, swelling, and bruising around the right hip. She was diagnosed with a right gluteus medius tear, presumably resulting from a skiing fall 9 months earlier where she had sustained an injury to her right hip. About 10 weeks post-diagnosis, after completion of the Initial Extension, the subject was hospitalized for repair surgery. The recovery was uneventful. The subject was discharged home after 4 days and was expected to mobilize normally within 2 months. The seriousness criterion specified by the investigator was "required hospitalization / prolongation". The intensity of the event was reported as moderate. The event was considered by the investigator to be unrelated to study drug or the device.

Subject Narrative

Subject No.:   22

Study stage / Treatment group:	Primary Stage / Placebo/GDNF
Age (years) at screening in study 2553:	41
Sex:	Male
Time of first PD symptom:	2007
UPDRS motor score (part III) in OFF state at screening in study 2553:	34
Hoehn and Yahr stage in OFF state at screening in study 2553:	2
Serious adverse event(s): [preferred terms]	Dehydration

Description: A few days prior to the first visit in the Supplemental Extension, the subject was admitted to hospital because she had developed acute diarrhea leading to dehydration after a holiday. The subject was treated with intravenous Ringer's lactate solution and saline, and was discharged home without sequelae on the next day. The seriousness criterion specified by the investigator was "required hospitalization / prolongation". The intensity of the event was reported as severe. The event was considered by the investigator to be unrelated to study drug or the device.

Subject Narrative

Subject No.:   23

Study stage / Treatment group:	Primary Stage / GDNF/GDNF
Age (years) at screening in study 2553:	45
Sex:	Female
Time of first PD symptom:	2009
UPDRS motor score (part III) in OFF state at screening in study 2553:	44
Hoehn and Yahr stage in OFF state at screening in study 2553:	2.5
Serious adverse event(s): [preferred terms]	Menorrhagia Post procedural infection

Description: Two weeks after the Week 72/e32 visit, the subject was admitted for vaginal hysterectomy and bilateral salpingo-oophorectomy as a definitive treatment for menorrhagia. She recovered and was discharged 4 days after surgery. The condition had been known prior to enrollment of the subject in study 2553, and anemia due to heavy periods was documented at screening. During the early phase of study 2553, the subject underwent preplanned endometrial ablation as a day-case procedure without resolution of the problem. The seriousness criterion specified by the investigator was "required hospitalization / prolongation". The intensity of the event was reported as moderate. The event was considered by the investigator to be unrelated to study drug or the device.

Five days after discharge, the subject was readmitted to hospital with a postoperative collection and infection. She received intravenous antibiotics (cefalexin, metronidazole), and the collection was drained. The subject felt much better and was discharged 3 days later. The seriousness criterion specified by the investigator was "required hospitalization / prolongation". The intensity of the event was reported as moderate. The event was considered by the investigator to be unrelated to study drug or the device.

Subject Narrative

Subject No.: 24

Study stage / Treatment group:	Primary Stage / Placebo/GDNF
Age (years) at screening in study 2553:	53
Sex:	Male
Time of first PD symptom:	2004
UPDRS motor score (part III) in OFF state at screening in study 2553:	38
Hoehn and Yahr stage in OFF state at screening in study 2553:	2.5
Serious adverse event(s): [preferred terms]	Appendicitis

Description: Nine days after his final visit (Week e3-8) in the Supplemental Extension, the subject presented at a hospital emergency department with abdominal pain. A diagnosis of acute appendicitis was suspected. Laparoscopic appendectomy was performed the next day. One day later, the subject was discharged home with a 5-day course of oral antibiotics. The seriousness criterion specified by the investigator was "required hospitalization / prolongation". The intensity of the event was reported as moderate. The event resolved and was considered by the investigator to be unrelated to study drug or the device.

Subject Narrative

Subject No.:   39

Study stage / Treatment group:	Primary Stage / Placebo/GDNF
Age (years) at screening in study 2553:	60
Sex:	Female
Time of first PD symptom:	2003
UPDRS motor score (part III) in OFF state at screening in study 2553:	29
Hoehn and Yahr stage in OFF state at screening in study 2553:	2
Serious adverse event(s): [preferred terms]	Osteoarthritis

Description: One day after the Week 76/e36 visit, the subject was admitted to a local hospital for elective left total hip replacement to treat the severe osteoarthritis diagnosed about 5 months earlier. The operation was completed successfully without immediate complication. The subject was discharged after 4 days and continued physiotherapy and a recovery plan at home. The seriousness criterion specified by the investigator was "required hospitalization / prolongation". The intensity of the event was reported as moderate. The event resolved and was considered by the investigator to be unrelated to study drug or the device.

Subject Narrative

Subject No.: 45

Study stage / Treatment group:	Primary Stage / GDNF/GDNF
Age (years) at screening in study 2553:	66
Sex:	Female
Time of first PD symptom:	2004
UPDRS motor score (part III) in OFF state at screening in study 2553:	43
Hoehn and Yahr stage in OFF state at screening in study 2553:	2
Serious adverse event(s): [preferred terms]	Confusional state

Description: Approximately half way through the Initial Extension, the subject was noted by caregivers and family to be suffering from episodes of confusion and fluctuating cognition. During study 2553, the subject was involved in a car accident and experienced a series of serious AEs that were unrelated to study drug or the device. She eventually became wheelchair-bound and institutionalized in a nursing home. While it was felt that this complex medical history may have contributed to her current condition, the subject was admitted to hospital for a short-term stay to establish a clearer picture. A Mini-Mental State Examination yielded a score of 24 which is at the low end of the normal range (24-30). The MoCA could not be performed since the subject did not have her prescription glasses with her. At admission, she was on a combination of oral medications including pramipexole, diazepam, and baclofen which was considered to be likely partly responsible for the confusional episodes. Undertreatment of the subject's hypothyroidism and a urinary tract infection were identified as additional contributing factors. Her PD medications were adjusted, and treatment with both rivastigmine and nitrofurantoin was started. Although no relationship with study drug was suspected, the Week 60/e20 infusion was omitted to derive a clean picture of the effect of the actions taken. When the subject was re-assessed after 4 weeks, she was found to be alert, fully oriented and back to her previous level of cognition, with no active neuropsychiatric symptoms. Therefore, study treatment was resumed at the Week 64/e24 visit. The seriousness criterion specified by the investigator was "required hospitalization / prolongation". The intensity of the event was reported as moderate. The event resolved and was considered by the investigator to be unrelated to study drug or the device.

Subject Narrative

Subject No.: 47

Study stage / Treatment group:	Primary Stage / GDNF/GDNF
Age (years) at screening in study 2553:	57
Sex:	Female
Time of first PD symptom:	2005
UPDRS motor score (part III) in OFF state at screening in study 2553:	37
Hoehn and Yahr stage in OFF state at screening in study 2553:	3
Serious adverse event(s): [preferred terms]	Depression Paranoia

Description: Approximately 1 week after the Week 68/e28 visit, the subject came in for an unscheduled trial visit because she felt that she was going through an episode of acute depression after she had been experiencing low mood, anxiety, and insomnia for the past week. It was known that the subject previously had 2 episodes of depression related to life events and that the past several months had been difficult for her due to social and personal reasons. The subject was therefore admitted to hospital and received a neuropsychiatric review. Her PD, depression, and sedative medications were adjusted. Within 1 week, her mood improved significantly, and her insomnia resolved. After 11 days, the acute depression was clinically assessed to be fully resolved, and the subject was discharged with a plan of care in the community. Two weeks later, at the next trial visit, the situation was confirmed to be stable. The seriousness criterion specified by the investigator was "required hospitalization / prolongation". The intensity of the event was reported as moderate. The event was considered by the investigator to be unrelated to study drug or the device.

Approximately 2 weeks after her final study visit (Week e3-4), the subject had paranoid thoughts, and her dose of pramipexole was reduced. A week later, she was hospitalized due to paranoid systemized persecutory delusion that she was at risk from her neighbor together with symptoms of hypomania including poor sleep and increased rate of speech. At the Week e3-4 visit, there were no indications of the subsequent problems, and the subject was very well in herself. Her motor and non-motor PD burden was low, and all safety assessments were within normal limits. At hospitalization, upon reducing her doses of pramipexole and amantadine and commencing low-dose neuroleptic treatment with quetiapine, the subject improved rapidly and

was discharged 3 weeks later when she had fully recovered. Based on detailed insight into the subject's history, the investigator concluded that the specific medical, social, and personal history was the most likely explanation for the genesis of the current episode. The seriousness criterion specified by the investigator was "required hospitalization / prolongation". The intensity of the event was reported as moderate. The event was considered by the investigator to be unrelated to study drug or the device.