Clinical Study Report Synopsis **GE Healthcare**

PDT409

Title: A MULTICENTER, RANDOMIZED, OPEN-LABEL, COMPARATIVE PHASE 4 TRIAL TO ASSESS CHANGES IN CLINICAL MANAGEMENT AFTER DaTscan™ IMAGING OF SUBJECTS WITH CLINICALLY UNCERTAIN PARKINSONISM

This is an exact copy of the synopsis from the final clinical study report for the study PDT409. The final clinical study report (document-identifier: PDT409 CREP) was authorized for use by the Head of Global Medical on 18-Oct-2011 (Version 1.0).

<table>
<tr><td>Name of Sponsor/Company:
GE Healthcare Ltd and its Affiliates</td><td rowspan="3">Individual Study Table Referring to Part of Dossier in Which the Individual Study or Study Table is Presented:

Volume:

Reference:</td><td rowspan="3">(For National Authority Use Only)</td></tr>
<tr><td>Name of Finished Product:
DaTscan™ in the US FDA-approved label, and DaTSCAN™ in the EMA-approved leaflet used by 32 countries in Europe.</td></tr>
<tr><td>Name of Active Ingredient:
[^{123}I]Ioflupane</td></tr>
<tr><td colspan="3">Title of Study: A multicenter, randomized, open-label, comparative Phase 4 trial to assess changes in clinical management after DaTscan™ imaging of subjects with clinically uncertain parkinsonism.</td></tr>
<tr><td colspan="3">Investigators and Study Centers: A total of 19 study centers in Europe and the USA.</td></tr>
<tr><td colspan="3">Publication (Reference): None.</td></tr>
<tr><td colspan="2">Study Period: 02 October 2006 to 03 January 2011</td><td>Phase of Development: Phase 4</td></tr>
<tr><td colspan="3">Objectives:
Primary Objective:
• To assess the influence of DaTscan™ imaging on the clinical management of subjects with clinically uncertain parkinsonism.
Secondary Objectives:
• To assess the influence of DaTscan™ imaging on the diagnosis of subjects with clinically uncertain parkinsonism.
• To assess changes in diagnostic confidence after DaTscan™ imaging.
• To describe healthcare resource use (HRU) from baseline to follow up.
• To explore the influence of DaTscan™ imaging on the quality of life (QoL) from baseline to follow up.</td></tr>
<tr><td colspan="3">Study Design: This was a multicenter, Phase 4, open-label, randomized, single-dose, comparative clinical trial to assess the impact of DaTscan™ single-photon emission computed tomography (SPECT) imaging on the clinical management of subjects with clinically uncertain parkinsonism. Subjects were randomized to either the DaTscan™ imaging group or no-imaging control group. All subjects in this study participated on an outpatient basis.
Within the planned study duration of 52 ± 4 weeks, all subjects in both study groups were required to attend 4 visits at the study site (from the baseline visit [Visit 1] to the 1-year follow-up visit [Visit 4]). After informed consent was obtained, all subjects attended Visit 1, where they were screened for study entry criteria. The investigators established a clinical diagnosis, including their confidence of diagnosis (COD) and reasons for uncertainty in the diagnosis. Main diagnoses (Parkinsonian syndrome [PS], non-PS, or inconclusive) and</td></tr>
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subdiagnoses (PS subdiagnoses: PS—precise diagnosis not available, Parkinson's disease [PD], vascular parkinsonism, drug-induced parkinsonism, other PS, and non-PS subdiagnoses: non-PS—precise diagnosis not available, essential tremor, other non-PS) were recorded. Baseline assessments regarding QoL, HRU, and planned clinical management were recorded.

Subjects randomized to the DaTscan™ imaging group attended the nuclear medicine department visit between 1 and 4 weeks after Visit 1. During this visit, a single intravenous (i.v.) dose of DaTscan™ was administered to the subjects in the DaTscan™ imaging group, and SPECT scanning was performed 3 to 6 hours after DaTscan™ DaTscan. Thyroid blocking was performed according to the hospital routines. Visual assessment of the images was performed by the nuclear physician investigator.

At Visit 2, which took place for all subjects 4 weeks (± 1 week) after Visit 1, the investigators re-evaluated the diagnosis, COD, and the clinical management plan. For subjects in the DaTscan™ group, the DaTscan™ imaging results were included in this assessment.

Visit 3 was scheduled 12 weeks (± 2 weeks) after Visit 1. All subjects attended this visit where actual clinical management during the 3-month follow-up period was recorded and compared against the original management plan. Implementation of the clinical management plan was reviewed, and possible deviations were recorded. The diagnosis and COD were re-evaluated, and QoL at Visit 3 as well as HRU from Visit 1 until Visit 3 were recorded.

The investigator or designated study personnel contacted each subject by telephone approximately every 2 months between Visit 3 and Visit 4 to collect information about visits to healthcare professionals, overall clinical status, modifications of anti-parkinsonian and concomitant medications, and new diagnostic tests carried out since the prior visit or telephone contact. The investigator completed the phone interview page in the case report form (CRF).

At Visit 3, each subject was provided with a diary in which the subject recorded visits to healthcare professionals, any diagnostic procedure performed, or any change in anti-parkinsonian and concomitant medications that occurred between Visit 3 and Visit 4. The subjects used the diary to report the changes during the telephone contacts.

Visit 4 was scheduled 52 weeks (± 4 weeks) after Visit 1 to assess efficacy parameters after a 1-year follow-up period. All subjects were to attend this visit, where actual clinical management during the follow-up period was recorded. Implementation of the clinical management plan was reviewed, and deviations were recorded. The diagnosis and COD were re-evaluated, and QoL at Visit 4 as well as HRU from Visit 3 until Visit 4 were recorded. The subject diary was reviewed, and information from the telephone contacts was verified. The diary was retained at the site after this visit. The subjects in the no-imaging control group were offered the option of DaTscan™ imaging after completion of Visit 4.

Selection of Subjects:

Inclusion Criteria:

(1) Subjects with clinically uncertain PS or monosymptomatic, atypical or incomplete presentation of tremor, rigidity, bradykinesia or postural instability. The reasons for uncertainty were to be specified in the CRF.
(2) Onset of clinical manifestations within the last 5 years.
(3) The subject was able and willing to comply with study procedures, and signed and dated informed consent was obtained.
(4) The subject was at least 18 years old.
(5) The subject was able to cooperate with the protocol, and involvement would not adversely affect subject care, in the opinion of the investigator.
(6) Women who were surgically sterile (have had documented oophorectomy and/or documented

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hysterectomy) or were postmenopausal (cessation of menses for more than 1 year) were allowed to enroll in the study without a pregnancy test at screening.

Exclusion Criteria:

(1) Differential diagnosis between PD and progressive supranuclear palsy or PD and multiple system atrophy.
(2) Subjects with an established/certain movement disorder clinical diagnosis.
(3) Presence of known causes of tremor (e.g., hyperthyroidism).
(4) Subjects with a significant cognitive impairment as confirmed by a Mini-Mental State Examination score <24.
(5) Use of any concomitant medication that was known or suspected to interact with striatal uptake through direct competition with binding of DaTscan™ to the dopamine transporter that were not discontinued for at least 5 half-lives (these included amphetamine, benztropine, buproprion, cocaine, mazindol, methylphenidate, phentermine and sertraline).
(6) Presence of moderate to severe renal or hepatic impairment.
(7) Occupational exposure to radiation equal to, or above, 15 millisieverts (mSv) per year.
(8) History of abuse, or current abuse of drugs.
(9) History of alcohol abuse where period of abstinence was less than 3 years.
(10) Subjects with hypersensitivity to iodide or to any of the DaTscan™ excipients.
(11) The subject was previously included in this study.
(12) Female subjects who were pregnant or breast-feeding or planning a pregnancy during the course of this study or within 3 cycles of completing the study. Women of childbearing potential had to provide a negative beta human chorionic gonadotropin (β-HCG) pregnancy test (by urine dipstick method) at screening and also prior to investigational medicinal product (IMP) administration.
(13) Participation in a clinical study involving an unlicensed pharmaceutical product within 30 days prior to screening, and/or an unlicensed/licensed radiopharmaceutical within 5 radioactive half-lives prior to screening, or already planned within the subject's participation in this study including the follow-up period.
(14) The subject had a life-threatening disease state with a life expectancy of less than 1 year or history of significant medical disease trauma or surgical intervention that in the judgment of the investigators made the subject unsuitable for the study.
(15) The subject had already had DaTscan™ SPECT imaging or any other similar functional imaging test of the presynaptic dopaminergic system (e.g., [^{18}F]Dopa PET, [^{123}I]iodobenzamide).

Number of Subjects (Planned and Analyzed):
Planned: Up to 250 subjects
Enrolled: 273
Randomized: 135 to the DaTscan™ imaging group; 138 to the no-imaging control group
Received IMP: 122
Efficacy population: 244 (116 in the DaTscan™ imaging group; 128 in the no-imaging control group)
Safety population: 259 (122 in the DaTscan™ imaging group; 137 in the no-imaging control group)
Per-protocol population: 215 (102 in the DaTscan™ imaging group; 113 in the no-imaging control group)

Treatment of Subjects:
Investigational Medicinal Product: DaTscan™ ([^{123}I]Ioflupane) isotonic solution (sterile, non-pyrogenic, aqueous 5% (v/v) ethanolic solution and sodium acetate buffer) of 185 Megabecquerels (MBq) (5 millicuries [mCi]) of [^{123}I]Ioflupane in 2.5 mL of solution. All dosed subjects received a single i.v. injection of DaTscan™

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(slow injection, not less than 15-20 seconds), followed by a saline flush, within the dose range of 111 to 185 MBq (3-5 mCi).

Standard of Truth, Control, or Comparator: No standard of truth was assessed in this study. The no-imaging control group followed the same procedures except that DaTscan™ SPECT imaging was offered to this group only after the completion of Visit 4.

Imaging: For all subjects in the DaTscan™ group, DaTscan™ imaging was conducted 1 to 4 weeks after Visit 1. Three to 6 hours after DaTscan™ injection, SPECT scanning was to be performed. Thyroid blocking was to be performed according to the hospital routines.

Duration of Study and Treatment: The study duration was 52 ± 4 weeks. Eligibility criteria were assessed at Visit 1 (baseline visit). Between 1 and 4 weeks after Visit 1, DaTscan™ imaging was performed. A single i.v. dose of DaTscan™ was administered to the subjects in the DaTscan™ group, and SPECT imaging was performed 3 to 6 hours after DaTscan™ injection. All subjects returned at 52 ± 4 weeks after Visit 1 to attend the 1-year follow-up visit (Visit 4).

Endpoints:

Primary Endpoint:

- Proportion of subjects with 1 or more changes in clinical management from Visit 1 to Visit 3.

Secondary Endpoints:

- Proportion of subjects with 1 or more changes in clinical management from Visit 1 to Visit 4.
- Proportion of subjects with change in diagnosis from baseline to Visit 2, Visit 3, and Visit 4.
- Change in COD from baseline (Visit 1) to Visit 2, Visit 3, and Visit 4.
- QoL assessment at Visit 1, Visit 3, and Visit 4.
- HRU from Visit 1 to Visit 3, from Visit 3 to Visit 4, and from Visit 1 to Visit 4.

Statistical Analyses:

Analysis Populations:

The efficacy population consisted of all subjects who had a clinical management plan at Visit 1 and who completed Visit 3. This population was used for the primary efficacy analysis and 1 secondary analysis (same parameter as the primary analysis, but at Visit 4).

The per-protocol population consisted of all subjects who completed all 4 study visits. The per-protocol population was used for the secondary efficacy analyses.

The safety population consisted of all DaTscan™ subjects who received DaTscan™ and all control subjects who had evaluations at Visit 1. This population was used for all demographic, baseline, and prior/concomitant medication summaries. Safety data were analyzed for the DaTscan™ subjects in the safety population.

Efficacy and Safety Variables:

Efficacy:

Primary Efficacy Analysis:

The primary efficacy analysis was the proportion of subjects with 1 or more significant changes in clinical management from Visit 1 to Visit 3. The efficacy population was used for the primary efficacy analysis.

Secondary Efficacy Analysis:

The same analysis as the primary efficacy analysis was performed for the subjects in the efficacy population who had significant changes in clinical management from baseline to Visit 4. All other secondary efficacy analyses were done on the per-protocol population. At Visits 2, 3, and 4, the proportion of subjects with changes in diagnosis and in COD since Visit 1 were compared between groups. Changes in QoL from Visit 1 to Visit 3 and from Visit 1 to Visit 4 were assessed using the 8 dimensions of the 39-Item Parkinson's Disease Questionnaire (PDQ-39) questionnaire as well as the European Quality of Life-5 Dimensions (EQ-5D)

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questionnaire. HRU for the periods from Visit 1 to Visit 3, from Visit 3 to Visit 4, and from Visit 1 to Visit 4 were described for each group.

Safety:

The safety variable was the proportion of subjects in the DaTscan™ group with 1 or more treatment-emergent adverse events (TEAEs). The number and percent of subjects with 1 or more adverse events (AEs) are summarized. AEs were collected for the DaTscan™ group from the DaTscan™ visit through Visit 4; thus AE data were summarized only for this group in the safety population. Subjects in the DaTscan™ group who terminated the study prior to administration of DaTscan™ were not included in the safety population summaries, but their data were included in the listings. The no-imaging control group did not receive treatment; therefore, TEAEs were not recorded.

Methodology:

Assuming that the probability of change in management was 60% for subjects in the DaTscan™ imaging group and 40% for subjects in the no-imaging control group, 108 subjects in each study group would yield 80% power to detect a 20% difference between the groups with a 5% level of significance. Proportions were estimated with exact 95% confidence intervals (CIs).

Tabulations of summary statistics and statistical analyses were performed using SAS® software, Version 9.0 or higher. All tables and listings were separated by subject group (DaTscan™ imaging or no-imaging control). Summary measures for continuous variables included, but were not limited to, the number of observations, mean, standard deviation (SD), median, minimum, and maximum. Summary measures for categorical variables were performed using frequency counts and percentages. Statistical tests used a 0.05 significance level and were 2-sided unless noted otherwise. One-sided tests used a 0.025 significance level. CIs, both individual and simultaneous, were at a 95% confidence level unless stated otherwise.

Fisher's exact test was used to evaluate the association between study group (DaTscan™ imaging or no-imaging control) and significant change in subject management from Visit 1 to Visit 3. The primary endpoint was assessed with a 1-sided Fisher's exact test using a 0.025 level of significance. For both study groups, the proportion of subjects with a significant change in subject management was estimated with exact 95% CIs.

At Visits 2, 3, and 4, the proportion of subjects with changes in suspected clinical diagnosis from Visit 1 was compared between groups using a 2-sided Fisher's exact test, and the percent mean change in COD since Visit 1 was compared using a 1-sided t-test. Changes in QoL from Visit 1 to Visit 3 and from Visit 1 to Visit 4 were assessed using the 8 subscales of PDQ-39 as well as changes in the EQ-5D and EQ Visual Analogue Scale (VAS) (my health status today). The scores of the 8 dimensions of the PDQ-39 and the EQ VAS scores were assessed for association with treatment group by analysis of covariance, using baseline QoL, baseline diagnosis, and other relevant demographic baseline variables as covariates. Scores from the 5 sections of the EQ-5D were summarized, and the change in total score was analyzed using the Wilcoxon-Mann-Whitney test. HRU for the periods from Visit 1 to Visit 3, Visit 3 to Visit 4, and from Visit 1 to Visit 4 was summarized for each group and compared between groups using a 1-sided Fisher's exact test.

Summaries of AEs were done by system organ class and preferred term for the safety population. A listing that includes intensity, degree of seriousness, cause of event, action taken, and outcome is also provided.

Summary of Results

Efficacy:

Changes in actual clinical management were analyzed for the efficacy population, which included 244 subjects (116 subjects in the DaTscan™ imaging group and 128 subjects in the no-imaging control group). A statistically significant difference in the proportion of subjects with at least 1 change in actual clinical management at Visit 3 (12 weeks) compared to Visit 1 (baseline) was noted in the DaTscan™ imaging group

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(50%) versus the no-imaging control group (31%) (p = 0.002). These changes included the initiation of new medications, the withdrawal of medications, and performing unplanned diagnostic tests. Similar results were observed at the 1-year follow-up; 41% of subjects in the DaTscan™ group had at least 1 change in their actual clinical management compared to 22% of subjects in the no-imaging control group (p <0.001).

All other efficacy endpoints were analyzed for the per-protocol population. In the DaTscan™ imaging group, half of the subjects (51 of 102 [50%]) had changes made in their planned clinical management at Visit 2 (4 weeks) compared to 24 of 113 (21%) subjects in the no-imaging control group.

Compared to the diagnoses at Visit 1, 31 of 102 (30%) subjects in the DaTscan™ imaging group had changes in their diagnoses (change in main diagnosis of PS, non-PS, or inconclusive) at each of Visits 2, 3, and 4. In the no-imaging control group, 6 of 113 (5%) subjects had changes in their diagnoses from Visit 1 to Visit 2 and Visit 1 to Visit 3, and 15 of 113 (13%) subjects had changes from Visit 1 to Visit 4.

The proportion of subjects with a change in the diagnosis (change in main diagnosis or subdiagnosis) at Visit 2 (4 weeks), Visit 3 (12 weeks), and Visit 4 (1 year) compared to Visit 1 (baseline) was significantly higher in the DaTscan™ imaging group (46 [45%], 47 [46%], and 55 [54%], respectively), than in the no-imaging control group (10 [9%], 13 [12%], and 26 [23%], respectively). The difference between treatment groups was statistically significant (all p-values were <0.001).

In 31 of 102 (30%) subjects, the main diagnoses were changed from Visit 1 after DaTscan™ imaging at Visit 2. Of these, the diagnoses were changed from PS in 17 subjects to either non-PS (15 subjects) or inconclusive (2 subjects) due to normal scans; changed from non-PS in 4 subjects to PS (3 subjects) and inconclusive (1 subject), due to abnormal, Type 1 and Type 2 scans; and 10 subjects from inconclusive to either PS (3 [27%]), due to abnormal, Type 1 and Type 2 scans, or non-PS (7 [64%]), due to normal scans.

Compared to the mean COD at Visit 1, the mean percent change in the COD of PS and non-PS at Visit 2, Visit 3, and Visit 4 was greater in the DaTscan™ imaging group than in the no-imaging control group. This difference between groups was statistically significant at each visit (all p-values were <0.001).

At Visit 1, a total of 69 (68%) subjects in the DaTscan™ imaging group and 76 (67%) subjects in the no-imaging control group were diagnosed with PS; the mean COD was 72.6% in each treatment group. The mean confidence of the subdiagnoses within PS ranged from 66.0% to 80.0% in the DaTscan™ imaging group and from 70.0% to 80.0% in the no-imaging control group. A total of 22 (22%) subjects in the DaTscan™ imaging group and 24 (21%) subjects in the no-imaging control group were diagnosed with non-PS; the mean COD was 79.1% in the DaTscan™ imaging group and 78.1% in the no-imaging control group. The mean confidence of the subdiagnoses within non-PS ranged from 60.0% to 81.0% in the DaTscan™ imaging group and from 78.1% to 78.2% in the no-imaging control group.

After DaTscan™ imaging, at Visit 2, a total of 58 (57%) subjects in the DaTscan™ imaging group and 73 (65%) subjects in the no-imaging control group were diagnosed with PS; the mean COD was higher (87.9%) than at Visit 1 in the DaTscan™ imaging group, whereas the mean COD was about the same (73.9%) as at Visit 1 in the no-imaging control group. The mean COD values of the subdiagnoses within PS were higher than at Visit 1, ranging from 77.7% to 95.0%, in the DaTscan™ imaging group, and were about the same as at Visit 1, ranging from 72.3% to 82.0%, in the no-imaging control group. A total of 41 (40%) subjects in the DaTscan™ imaging group and 24 (21%) subjects in the no-imaging control group were diagnosed with non-PS; the mean COD was higher (90.6%) than at Visit 1 in the DaTscan™ imaging group and about the same (78.5%) as at Visit 1 in the no-imaging control group. The mean confidence of the subdiagnoses within non-PS ranged from 82.1% to 95.5% in the DaTscan™ imaging group and from 77.3% to 90.0% in the no-imaging control group. At Visits 3 (12 weeks) and 4 (1 year), the number of subjects diagnosed with PS and non-PS were

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approximately the same as at Visit 2 (4 weeks) in each treatment group, but the mean COD remained higher in the DaTscan™ imaging group than in the no-imaging control group for PS, non-PS, and all subdiagnoses, except for vascular parkinsonism.

For QoL parameters (PDQ-39, and EQ-5D,including the EQ VAS for health status), the proportion of responses to each of the categories at Visit 1, Visit 3, and Visit 4 in the DaTscan™ imaging and the no-imaging control groups was similar. A small proportion of subjects was unable to perform usual activities, had extreme pain or discomfort, or was extremely anxious or depressed at Visit 1, Visit 3, and Visit 4 across treatment groups.

From an analysis of covariance, the 8 dimensions of the PDQ-39 and the EQ VAS results were found to vary with demographic and baseline characteristics.

From baseline to Visit 3, around one-third of all subjects used at least 1 healthcare resource (33% in the DaTscan™ imaging group and 38% in the no-imaging control group); notably, 2 (2%) subjects in the DaTscan™ imaging group underwent hospitalization versus no subjects in the no-imaging control group. Also, fewer subjects in the DaTscan™ imaging group (16 [17%] subjects) reported a visit to a family doctor than in the no-imaging control group (27 [26%] subjects); however, the difference was not statistically significant ($p = 0.094$). From baseline to Visit 4 and from Visit 3 to Visit 4, HRU was reported by a similar proportion of subjects in each treatment group.

There were no notable differences between the DaTscan™ imaging group and the no-imaging control group in demographics (overall, 97% Caucasian, 54% male, mean age of 66.2 years), movement disorder history (overall, the mean time since onset of symptoms to study start was 2.32 years, with a predominantly unilateral onset [71%] and primary first symptom of tremor [71%]), and Hoehn and Yahr disease staging (overall, primarily Stage 1 [44%] or Stage 2 [31%]). In addition, the reasons for diagnosing clinically uncertain PS at baseline (Visit 1) were comparable between the 2 treatment groups.

Safety:

AEs were recorded from the DaTscan™ visit (after Visit 1) through Visit 4 for the subjects in the DaTscan™ imaging group. In the safety population (DaTscan™ imaging group only), 2 (2%) subjects experienced 1 pre-treatment AE each. One (1%) subject reported a post-treatment TEAE with a suspected relationship to the IMP, and 1 (1%) subject reported a post-treatment TEAE with no suspected relationship to the IMP. There were no serious AEs (SAEs), and 1 death not related to IMP reported during the study.

The pre-treatment AEs reported were influenza-like symptoms in 1 (1%) subject and a fall in 1 (1%) subject. The post-treatment TEAE with a suspected relationship to the IMP was a headache, and the post-treatment TEAE with no suspected relationship to the IMP was a sleep disorder.

These results support DaTscan™ as a safe and well-tolerated radiopharmaceutical agent.

Conclusions:

- Changes in the actual clinical management at 12 weeks were observed in a significantly greater number of subjects in the DaTscan™ imaging group (50%) than in the no-imaging control group (31%, $p= 0.002$). Similar statistically significant results were observed at the 1-year follow-up (41% versus 22%, $p<0.001$).
- Changes in the clinical diagnosis at 4 weeks, 12 weeks, and 1 year were observed in a significantly greater number of subjects in the DaTscan™ imaging group (45%, 46%, and 54%) than in the no-imaging control group (9%, 12%, and 23%; all $p<0.001$).
- The change from baseline in the COD of PS and non-PS at 4 weeks, 12 weeks, and 1 year was significantly greater at all visits in the DaTscan™ imaging group than in the no-imaging control group (all $p<0.001$).
- There was no major deterioration from baseline in the QoL in either treatment group at 12 weeks and 1 year.

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- From baseline to 12 weeks, from baseline to 1 year, and from 12 weeks to 1 year, HRU was reported by a similar proportion of subjects in each treatment group. Fewer subjects in the DaTscan™ imaging group compared to the no-imaging control group reported a visit to their family doctor between baseline and 12 weeks, but this difference did not reach statistical significance ($p = 0.094$).
- Single doses of DaTscan™ were safe and well-tolerated. No SAEs, or withdrawals due to AEs occurred during the study. There was 1 death not related to DaTscan™. Only 1 subject had an AE (headache) post-treatment with suspected relationship to DaTscan™.