Clinical Study Report

Study Title:	A Phase 3, Double-Blind, Placebo-Controlled, 18-Month Extension Study to Determine the Efficacy and Safety of a Low (50 mg/day) and High (100 mg/day) Dose of Safinamide, as Add-on Therapy, in Patients with Idiopathic Parkinson's Disease with Motor Fluctuations, Treated with a Stable Dose of Levodopa and Who May Be Receiving Concomitant Treatment with Stable Doses of a Dopamine Agonist, and/or an Anticholinergic
Name of the Test Drug/Investigational Product:	Safinamide
EUDRACT Number:	2006-005861-21
Indication:	Parkinson's Disease
Study Design	Double-blind, placebo-controlled, parallel-group, multicenter, multinational
Name of the Sponsor:	Newron Pharmaceuticals SpA.
Protocol Number:	NW-1015/018/III/2006
Development Phase of Study:	Phase 3
Study Initiation Date (Date First Patient Screened):	13-January-07 (First Screening date for Study 016 patients who entered Study 018) 24-August-07 (First Screening date for Study 018)
Study Completion Date (Date Last Patient Completed Last Observation):	29-April-2010
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Good Clinical Practice (GCP) Statement:	This study was conducted in accordance with good clinical practices.
Date of Report:	11 January 2013

2. SYNOPSIS

Name of Sponsor/Company: Newron Pharmaceuticals SpA.		*(For National Authority Use Only)*
Name of Finished Product: Safinamide		
Name of Active Ingredient: Safinamide		
Title of Study: A Phase 3, Double-Blind, Placebo-Controlled, 18-Month Extension Study to Determine the Long-term Efficacy and Safety of a Low (50 mg/day) and High (100 mg/day) Dose of Safinamide, as Add-on Therapy, in Patients with Idiopathic Parkinson's Disease with Motor Fluctuations, Treated with a Stable Dose of Levodopa and Who May Be Receiving Concomitant Treatment with Stable Doses of a Dopamine Agonist, and/or an Anticholinergic		
Study Number: NW-1015/018/III/2006		
Investigators: See Appendix 16.1.3.		
Study Centers: The study was conducted at 52 study centers: 35 in India, 10 in Romania, and 7 in Italy.		
Publication (Reference): There were no publications based on this study.		
Study Period (Date First Patient Screened—Date Last Patient Completed Last Observation): 13-January-07 (First Screening data for Study 016 patients who entered Study 018) and 24-August-07 (First Screening data for Study 018)—29-April-2010	**Study Phase of Development:** 3	
Objectives: The objective of this study was to determine the long-term efficacy and safety of 2 oral (PO) doses of safinamide (50 and 100 mg/day) compared with placebo, as add-on therapy in patients with early idiopathic Parkinson's Disease with motor fluctuations, who were currently receiving a stable dose of levodopa.		

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Methods:

This study was a Phase 3, multicenter, multinational, double-blind, placebo-controlled, parallel-group study. Two oral doses of safinamide (50 and 100 mg/day) versus placebo as add-on therapy to a stable dose of levodopa were evaluated in patients with idiopathic PD with motor fluctuations. The total duration of the study, which was an extension to Study 016, was approximately 78 weeks (Studies 016 and 018 combined was 102 weeks). All randomized patients completing their participation in the double-blind treatment period in Study 016 could enter into this study. Upon entry into this study, patients continued to take the same treatment and dose they were receiving in Study 016 (safinamide 50 mg/day, safinamide 100 mg/day, or placebo), along with the same dose of levodopa (increases in the dose of the patient's levodopa or addition of any other antiparkinsonian treatments, excluding other MAO inhibitors, were permitted, if needed).

As in Study 016, patients who were unable to tolerate the high dose of 100 mg/day of safinamide could have had their dose decreased to 50 mg/day. Patients receiving this drop-back dose at the time of their completion of Study 016 were allowed to enroll in Study 018 if they met all other entry criteria. The initial screening evaluation for this study (Visit 1) included the final (Week 24) evaluations from Study 016. Patients who met eligibility criteria entered this study and received their first dose of study drug on the day on which their Week 24 visit was performed. Patients returned for scheduled evaluations at 12, 24, 36, 52, 64, and 78 weeks (or at early discontinuation), at which time efficacy and safety evaluations were performed. Patients who completed 78 weeks of treatment, and if possible, those who discontinued treatment prematurely, entered a 1-week taper phase, during which their dose of study medication was reduced and then discontinued. For those patients who completed Study 018, there was the possibility of continuing into an open-label extension (OLE) trial (Protocol Number 28850), run by Merck Serono. For patients entering the OLE study, the last visit of Study 018 was the End of Study visit at Week 78. No taper phase (Week 79) was to be performed for patients entering the OLE study.

Number of Patients (Planned and Analyzed):

Assuming an attrition rate of about 14% in Study 016, it was estimated that approximately 550 patients would be eligible for participation in this trial. Of the 669 patients who were randomized into Study 016 (222 to placebo, 223 to safinamide 50 mg/day, and 224 to safinamide 100 mg/day) and who comprised the ITT population, 544 (175 in the placebo group, 189 in the safinamide 50 mg/day group, and 180 in the safinamide 100 mg/day group) were enrolled into Study 018 and comprised the safety population.

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Diagnosis and Main Criteria for Inclusion:
Patients who completed 24 weeks of treatment in Study 016 (or if patients discontinued prematurely, they returned for all scheduled efficacy evaluations at Weeks 12 and 24 as part of the Retrieved Dropout [RDO] population), were compliant with taking study drug in Study 016, were not experiencing clinically significant AEs that would put them at risk for participating in this study, had not shown clinically significant deterioration during participation in Study 016, and signed an approved informed consent form for Study 018 were eligible for this study. For Study 016, eligible patients were men and women, 30 to 80 years, with a diagnosis of idiopathic PD of more than 5 years duration (patients who had PD for at least 3 years or who were older than 80 could have been enrolled upon approval of the Clinical Research Organization [CRO] Medical Monitor or Newron Medical Expert, respectively), a Hoehn and Yahr stage of 1–4 during an *off* phase, and motor fluctuations with > 1.5 hours *off* time during the day. Patients in a late stage of PD who were experiencing severe, disabling peak dose or biphasic dyskinesia or unpredictable or widely swinging fluctuations in their symptoms were excluded. Patients had to be receiving a stable dose of levodopa and could have been receiving a stable dose of a dopamine (DA) agonist or anticholinergic. Additionally, patients with a history of albinism, family history of hereditary retinal disease, progressive or severe diminution of visual acuity (ie, 20/70), retinitis pigmentosa, retinal pigmentation due to any cause, any active retinopathy or ocular inflammation (uveitis), or progressive, severe diabetic retinopathy were excluded from participating in the study.

Test Product, Dose and Mode of Administration, Batch Numbers:

Test product: safinamide

Route and mode of administration: oral

Dose and dosage schedule:
Safinamide 50/mg/day: 2 tablets once daily (one 50-mg tablet and 1 placebo tablet) for 78 weeks during the treatment phase; 2 tablets once daily (2 placebo tablets) during the optional 1-week taper phase
Safinamide 100 mg/day: 2 tablets once daily (two 50-mg tablets) for 78 weeks during the treatment phase; 2 tablets once daily (one 50 mg tablet and 1 placebo tablet) during the optional 1-week taper phase

Batch Numbers: 0010511, 00060610

Duration of Treatment:

24 weeks (Study 016) plus 78 weeks (Study 018) for a total of 102 weeks plus an optional 1-week taper phase

Reference Products, Dose, Mode of Administration, Batch Numbers:

Reference product: placebo

Route and mode of administration: oral

Dose and dosage schedule: 2 placebo tablets once daily for 78 weeks during the treatment phase; 2 placebo tablets once daily during the optional 1-week taper phase

Batch Numbers: 0000511, 000A0606, 00C0606

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Criteria for Evaluation:

Efficacy: The primary efficacy variable was the mean change in the Dyskinesia Rating Scale (DRS) during *on* time from Baseline (Study 016) to endpoint (last visit in Study 018), calculated as the sum of the severities across all items collected at a particular time point.

The secondary efficacy variables, which were analyzed in a hierarchical fashion, as listed below, included the following: 1) change in *on* time (*on* + *on* with minor dyskinesia); 2) diary responder rate at 12 months (primary) and 18 and 24 months (secondary), which included improvement in *on* time + *on* time with minor dyskinesia, with no increase in troublesome dyskinesia and lack of worsening (≤ 30 minutes) in *on* time + *on* time with minor dyskinesia, with no increase in troublesome dyskinesia; 3) UPDRS Section 4 total score (primary) and, if significant, items 32 through 35 and 32 through 34 taken individually and as subgroups (secondary); 4) time to develop troublesome dyskinesia; 5) time to develop any (minor and/or troublesome) dyskinesia; 6) change in ADL during *on* time compared with placebo (UPDRS Section 2); 7) maintenance of effect in UPDRS Section 2 responders (responder defined as ≥ 20% improvement from Baseline to Study 016 endpoint in ADL); 8) percentage change in levodopa dose; 9) percentage change in any PD drug (except levodopa) dose; 10) change in motor symptoms (UPDRS Section 3) from the Study 016 Baseline; 11) Clinical Global Impression–change from Baseline (CGI–C) in the mean score throughout the course of the study; 12) Clinical Global Impression–severity of illness (CGI–S) mean change from Baseline to endpoint; 13) change in individual diary categories as defined in Study 016 (*on*, *off*, *on* with minor dyskinesia, *on* with troublesome dyskinesia, asleep) compared with Baseline; and 14) UPDRS Section 1. Changes for all variables are calculated with respect to the Study 016 Baseline values.

The tertiary efficacy variables included the following: Hoehn and Yahr staging, grid version of Hamilton rating scale for depression–17-item scale (GRID-HAMD-17), Mini-Mental State Examination (MMSE), Parkinson's Disease Questionnaire (PDQ-39), and the Cogtest® battery.

Criteria for Evaluation:

Safety**:**

Safety variables included adverse events (AEs); clinical laboratory tests results (hematology, biochemistry, and urinalysis); vital sign measurements; 12-lead electrocardiogram (ECG) findings; physical, neurological, dermatological, and ophthalmological examination findings; and Epworth Sleepiness Scale (ESS) scores. Adverse events were presented as newly emergent and re-emergent for Study 018 and as treatment-emergent for Studies 016 and 018 combined.

Statistical Methods:

Demographic and Other Patient Characteristics: The demographic characteristics (age, sex, weight, height, race, and ethnicity) of patients were summarized by treatment group. Continuous data were summarized by descriptive statistics (n, mean, median, SD, and minimum and maximum), while absolute (n) and relative frequencies (%) were provided for categorical data.

The results of the following assessments pertaining to PD and concomitant neuropsychiatric disturbances at Visit 1 (Entry into Long-term Treatment) were presented for the ITT and mITT populations using appropriate descriptive statistics: summary statistics at Visit 1 for the Hoehn and Yahr staging, MMSE total score, UPDRS Section 1 total score, UPDRS Sections 2 through 4 total score. HAMD Total Score, and absolute (n) and relative (%) frequencies for CGI-S.

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Absolute (n) and relative (%) frequencies for the following 12 categories of findings on the neurological examination were provided: tremor at rest, bradykinesia, rigidity, gait abnormalities, balance impairment, handwriting impairment, end-of-dose wearing off phenomena, on-off phenomena, dyskinesias, motor fluctuations, facial expression hypomimic, and other neurological signs. Only findings that were present (n) were shown relative to the total number of patients with data at Visit 1.

Medical history and concomitant illnesses and conditions were coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 8.1, and were summarized based on the data collected from Study 016 for the patients who entered Study 018.

Medical history was presented as absolute (n) and relative (%) frequencies by preferred term (PT) within each system organ class (SOC). The difference in the proportion of patients with at least 1 medical history finding was calculated using the Cochran Mantel-Haenszel test stratified by center.

Concomitant illnesses and conditions were summarized for the following variables: severity (mild, moderate, or severe), frequency (single episode, intermittent, or continuous), and side effect of concomitant medication (yes or no), action taken (no action taken, dose of concomitant medication reduced, concomitant medication temporarily interrupted, concomitant medication discontinued due to AE, another concomitant medication taken, nondrug therapy given, or hospitalization or prolonged hospitalization).

Concomitant illnesses and conditions were presented by absolute (n) and relative (%) frequencies by PT within each SOC. The difference in the proportion of patients with at least 1 concomitant illness and condition finding were calculated using the Cochran Mantel-Haenszel test stratified by center. Patient data listings of all concurrent conditions and medical history were presented with coding details.

Prior and concomitant medications were summarized based on the data collected from Study 016 for the patients who entered Study 018. Prior medication (excluding PD medication) or prior PD medication was defined as any medication, other than the study medication, which started and ended before the first administration of the study drug. Concomitant medication (excluding PD medication) or concomitant medication for PD was defined as any medication, other than the study drug, that was started on or after the first administration of study drug for Study 016 and included those medications that were started before the first administration of the study drug, but use continued after the first dose of study drug. All medications were coded using the World Health Organization (WHO) Drug Dictionary (WHO-DD), version dated March 1, 2007, by drug class sorted by Anatomical Therapeutic Chemical (ATC) classification system. Concomitant medications were summarized separately for medication for PD and for medication for indications other than PD.

Medications were classified in the following 3 ways: 1) Newly emergent: any medication not recorded in Study 016 but recorded for the first time in Study 018. 2) Re-emergent: any medication that was started and stopped during Study 016 but was also recorded with a start date in Study 018. For PD medications, this was determined by the PT. If all medications have the same PT, then the medication would not be considered re-emergent. A window of 7 days was used to determine if a PD medication was re-emergent. That is, if a PD medication stopped within the last few days of Study 016 but started again within 7 days then it was not considered re-emergent but a continuation of the same medication. 3) All concomitant medications: all medications taken during Studies 016 and 018 after the first dose of study drug in Study 016.

Patient data listings of prior medication, prior medication for PD, concomitant medication other than for PD, and concomitant medication for PD were presented with the coding detail.

Treatment compliance was summarized by visit and by treatment group for the ITT population by absolute (n) and relative (%) frequencies. Treatment compliance was calculated using the following formula:
Compliance = (total number of tablets taken/treatment duration x 2) x 100, where total number of tablets taken = tablets dispensed at the previous visit – tablets returned – tablets lost.

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Drug dispensed, duration of treatment, and compliance by visit, as indicated in the CRF, was provided in the patient data listings.

Efficacy Evaluations:

Primary Efficacy Analysis: The primary efficacy variable, mean change in total DRS severity score from Baseline to endpoint, was analyzed using a Mixed Linear Model REML repeated measures model (MRRM) with treatment, center, visit and the treatment by visit interaction as fixed effects and the baseline value (from Study 016) as a covariate and using the ESTIMATE statement to compute the treatment mean difference together with the associated 2-sided 95% CI and 2-sided *P* value at the Final Visit. For the denominator degrees of freedom the KENWARDROGER option was used. The variance-covariance matrix of unstructured form was used to model the correlation within each patient between the postbaseline repeated measurements. Restricted maximum likelihood estimates of the above mixed model parameters were obtained by resorting to the iterative Newton-Raphson algorithm implemented in the SAS Mixed Procedure.

Two mixed linear model analyses were performed on the ITT population as follows: 1) On-treatment analysis. In this approach, patients' data were censored at the time of rescue medication intake or occurrence of retrieved dropouts; 2) On-and-off-treatment analysis. In this approach, all available data were analyzed regardless of the intake of rescue medication and included retrieved drop-out data.

Rescue medication was defined as an increase in the total daily dose of the PD therapy (ie, levodopa, DA agonist, or any other antiparkinsonian treatment) of at least 20% or the addition of a new antiparkinsonian drug to the patient treatment schedule.

The on-treatment mixed linear model analysis was considered the primary one, while the on-and-off-treatment mixed linear model analysis was performed for sensitivity purposes. The mixed linear model analyses included the data collected from all available time points in Study 016, as well as Study 018.

A supportive analysis was performed in addition to the primary analysis using both the on-treatment and on-and-off-treatment ITT and mITT populations with missing efficacy time points imputed by last observation carried forward (LOCF), and using an analysis of covariance (ANCOVA) model with the Baseline value as a covariate and treatment regimen and center as main effects.

The most disabling dyskinesias were summarized (n and percentage) by treatment and visit.

Secondary Efficacy Analyses: The secondary efficacy variables were evaluated in a hierarchical manner. Each of the variables was analyzed sequentially as long as a significant difference between the safinamide 100 mg/day group versus the placebo group was detected. In addition, if a significant difference was detected between the placebo group and the safinamide 100 mg/day group, the analysis proceeded to compare the placebo group with the safinamide 50 mg/day group. This approach avoided the need for correcting the *P* values due to multiplicity of testing over endpoints and over treatment groups.

Analyses were performed on the ITT and mITT populations, using the on-treatment approach and with LOCF imputation of missing data.

The secondary efficacy analysis included the following parameters, ordered according to the hierarchical analysis approach: 1) Change in *on* time (*on* + *on* with minor dyskinesia) compared with the Study 016 Baseline; 2) Diary responder rate at 12 months (primary) and 18 and 24 months (secondary) on the ITT and mITT populations and on the subset of patients who completed the 2-year treatment period; a) Improvement in *on* time + *on* time with minor dyskinesia, with no increase in troublesome dyskinesia with respect to the Study 016 Baseline; and b) Lack of worsening (≤ 30 minutes) in *on* time + *on* time with minor dyskinesia, with no increase in troublesome dyskinesia with respect to the Study 016 Baseline; 3) UPDRS Section 4 total score (primary) and, if significant, items 32 through 35 and 32 through 34 taken individually and as subgroups (secondary), change

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from the Study 016 Baseline; 4) Time to develop troublesome dyskinesia (> 30-minute increase of troublesome dyskinesia compared with the Study 016 Baseline); 5) Time to develop any (minor and/or troublesome) dyskinesia (> 30-minute increase of dyskinesia compared with the Study 016 Baseline); 6) Change in ADL during *on* time compared with placebo (UPDRS Section 2); 7) Maintenance of effect in UPDRS Section 2 responders (responder defined as ≥ 20% improvement from Baseline to Study 016 endpoint in ADL); 8) Percentage change in levodopa dose – change from the Study 016 Baseline to endpoint; 9) Percentage change in any PD drug (except levodopa) dose – change from the Study 016 Baseline to endpoint; 10) Change in motor symptoms (UPDRS Section 3) from the Study 016 Baseline; 11) CGI–C—assessment of the change from the Study 016 Baseline: mean score throughout the course of the study; 12) CGI–S—mean change from the Study 016 Baseline to endpoint; 13) Change in individual diary categories as defined in Study 016 (*on*, *off*, *on* with minor dyskinesia, *on* with troublesome dyskinesia, asleep) compared with Baseline; 14) UPDRS 1. Descriptive statistics were provided for individual diary categories.

If a significant difference at the 0.05 level was detected between the placebo group and the 100 mg/day group, the analysis proceeded to compare the placebo group to the 50 mg/day group. This hierarchical approach voided the need for correcting the *P* value due to multiplicity of testing over endpoints and over treatment groups.

Summary statistics for all visits in both Studies 016 and 018 were presented for an overall picture of the patients over time but all testing procedures evaluated the change from Baseline of Study 016 to the endpoint of Study 018 only.

Mean change in ADL (UPDRS Section 2), change in diary times, change in UPDRS Sections 3 and 4, and CGI-S from Baseline to endpoint were analyzed using an analysis of covariance (ANCOVA) on the ITT and mITT populations with missing efficacy time points imputed by LOCF using the Study 016 Baseline value as a covariate and treatment regimen and center as main effects.

Changes in diary times were measured by diary cards from the time of awakening to the time when the patient falls asleep (06.00 to 24.00). Diary information was collected for the 5 days preceding the scheduled visits, and the last 2 days of recording were used for data analysis purposes.

The responder rate for the diary data were analyzed using a Cochran Mantel Haenszel (CMH) test with center as the stratification factor at each time point (12, 18, and 24 months). This analysis was performed using the whole ITT and mITT populations and also on the subset of those patients who completed the 2-year treatment period.

The time to develop troublesome dyskinesia (> 1 hour increase compared with Baseline) was analyzed using Kaplan Meier methodology. Testing using the log-rank test was performed to compare active treatment with placebo.

Maintenance of effect in UPDRS 2 responders and CGI–C score was analyzed using the CMH test (CMH3 for General Association Statistic) of PROC FREQ with center as the stratification factor.

CGI–C score was summarized as the proportion of patients showing improvements (score of 1, 2, or 3) versus no change or worsening (scores of 4, 5, 6 or 7).

A Wilcoxon rank sum test was used to determine statistical significance of the percent change from Baseline in levodopa dose in the safinamide 100 mg/day and safinamide 50 mg/day treatment groups, compared with the placebo group and the percent change in PD medications (collectively and by preferred term). The number of patients with any reduction in levodopa dose in each active treatment group was compared with placebo using the CMH test with center as a stratification factor.

Tertiary Efficacy Analysis: Summary statistics for all visits in both Studies 016 and 018 were presented. The Hoehn and Yahr staging change from Baseline was compared between treatments using the Wilcoxon rank sum test. All other tertiary efficacy variables were analyzed using ANCOVA on the change from Baseline to endpoint

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value using the Baseline value as a covariate and treatment regimen and center as main effects.

Additional Ad-hoc Analyses: Additional analyses were performed on the ITT population to emphasize the importance of parallel changes in different clinical characteristics, ie, clinically meaningful improvement in motor symptoms, as rated by the investigator, and *on* and *off* time, as reported by the patient in the diary, after 2 years of treatment (responder rates). The additional analysis of UPDRS Section 3 and UPDRS Section 2 combined in the ITT population was run to support the results of the changes obtained in the UPDRS Sections 2 and UPDRS Section 3 analyses done separately. To further evaluate the effect of safinamide on dyskinesia, additional analyses also were performed on those patients who presented with moderate-to-severe dyskinesia at baseline of Study 016 (ie, DRS total score > 4).

Safety Evaluations:

Adverse Events: AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 8.1, and were summarized overall and by treatment group. The summaries were presented by MedDRA System Organ Class (SOC) and Preferred Term (PT). Analyses were performed for 3 sets of AEs: newly emergent, re-emergent, and all treatment emergent (Studies 016 and 018 combined). A treatment-emergent AE (TEAE) was defined as an AE that started on or after the first administration of study drug, or AEs that started before administration of study drug but worsened after administration of study drug. A newly emergent AE was defined as any event not recorded in Study 016 or any AE recorded in Study 016 but reported in Study 018 with a higher intensity. Re-emergent AEs were defined as AEs that started and stopped during Study 016 and were also recorded with a start date in Study 018, but with the same or lower intensity as recorded in Study 016. TEAEs were summarized by intensity and relationship to study drug. Serious AEs (SAEs) and AEs leading to study discontinuation were summarized separately. TEAEs were compared across treatment groups using Cochran Mantel Haenszel test stratified by center.

Clinical Laboratory Evaluation: Summary statistics were presented for all laboratory assessments, separated by hematology, biochemistry, and urinalysis parameters, for each scheduled visit, as well as the absolute change from Baseline to each of the visits. Absolute and relative frequencies were presented for categorical urinalysis values for each visit. Shift table analysis (below, within, and above the reference range) were provided. Incidences of clinically notable results were presented, showing the notable value relative to the safety population and percentage of nonmissing values for a specific parameter at each visit. Clinically notable results were presented by showing the notable value relative to the Safety population and percentage of nonmissing values for a specific parameter at each visit.

Vital Signs: For the safety population, each vital sign measurement was summarized at Baseline (before study drug administration in Study 018) and absolute change from Baseline (Study 016) to endpoint with descriptive statistics (n, mean, SD, median, minimum, and maximum). Clinically notable vital sign changes from Baseline (Study 016) (before first dose of study drug) to each of the visits were summarized using the appropriate absolute and relative frequencies. Number and percentage of patients with a clinically notable vital sign value were presented per treatment group.

Other Safety Parameters: Descriptive statistics were provided for the physical, neurological, and dermatological examinations and the Epworth Sleepiness Scale using the Safety population. Patient data listings were provided for all dermatological, neurological, and physical findings. The ECG data were analyzed separately. Refer to Appendix 16.5.1 for the ECG report.

All ophthalmology data were reviewed by a central reviewer (expert ophthalmologist) who was blinded to the treatment. The central ophthalmologist reviewed the source data; when source data were unavailable, the site ophthalmology evaluation based on the data contained in the ophthalmology form was reviewed. The central ophthalmologist provided ratings for each evaluation (both eyes). The central ophthalmologist also provided an

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assessment of plausibility of the findings. The battery of tests performed was designed to include all aspects of a general ophthalmology examination (visual acuity, color vision, visual fields, and fundoscopy). All ophthalmological analyses were presented using LOCF, and patient counts were presented for the left eye, right eye, either eye, and both eyes, as applicable. All comparisons for changes were versus the Study 016 Baseline.

Visual acuity was determined as a 20/20 equivalent and was summarized categorically for each fractional equivalent. LogMAR values (logarithm of the minimum angle of resolution [base 10 logarithm transformation of the reciprocal of visual acuity]) were summarized as a continuous variable (n, mean, median, standard deviation [SD], minimum, and maximum). Change from Baseline to the subsequent visit was calculated for LogMAR and was presented as the number and percent of patients. This change was summarized categorically (worsened, no change, and improvement). Further, worsened (increase in LogMar value) was distinguished by grade based on the following criteria: mild, change > 0 to < 0.15; moderate, 0.15 ≤ change ≤ 0.30; severe, change > 0.30. Summaries were presented by visit and treatment group for right eye, left eye, either eye, and both eyes. Color vision was determined using Ishihara pseudoisochromatic tables (in most cases). Color vision responses (number correct, when available) were summarized categorically by visit and treatment. The percentage of patients with worsening (defined as ≥ 2 plates change from Baseline) color vision were summarized.

Visual field was charted for both eyes using the Humphrey 24-2 apparatus (or similar equivalent) and findings expressed as normal, abnormal, or unassessable. Mean deviation (MD; the average of all differences between measures and their normal values, weighted by the variance observed in the general population) and pattern standard deviation (PSD; a normalized distance, standardized with reference to the general population, calculated for each point) were derived and summarized as continuous variables (n, mean, median, SD, minimum, and maximum) by visit and treatment group for patients tested using the Humphrey 24-2. Those patients assessed with an alternative testing procedure (ie, Humphrey 30-2 or Octopus) had data summarized in shift tables only. Further, visual field mapping assessments were classified by the specific abnormalities like hemianopia, quadrantanopia, bitemporal defect, arcuate defect, peripheral defect, central defect, and other defects and summarized.

A fundoscopy examination was performed. Each eye was assessed as normal or abnormal and any abnormality was noted. Photographs taken for the fundoscopy assessment were summarized by treatment and visit. Further fundoscopy assessments were classified by the specific abnormality (ie, macular, peripheral, vascular, optic disc) and summarized.

The primary ocular endpoint was the Central Reader Global Impression Score. It was analyzed as a binary response (ie, whether the patient had worsened to a clinically significant degree from Baseline to Week 78), and performed on the worst eye assessment for each individual patient. The primary analysis of this endpoint was analyzed using a 2-sided Fisher's exact test (unadjusted analysis) to test the treatment difference between each of the active arms versus the placebo group. If any of the comparisons were significant, then an appropriate adjusted analysis was performed (eg, logistic regression). The test was adjusted for one or more stratification variables (eg, concomitant illnesses) that were decided post hoc.

No formal hypothesis testing was done for secondary ocular endpoints (visual acuity, color vision, visual fields, and fundoscopy) except for the central reader's evaluation of worsening. Only descriptive statistics were performed on these parameters. In addition, the incidence of patients who worsened on each endpoint, and worsened on more than one endpoint, based on the central rater's evaluation compared with the Study 016 Baseline was calculated and a Fisher's exact test was performed to evaluate treatment differences.

SUMMARY—CONCLUSIONS

EFFICACY RESULTS

The ITT population was used as the primary population for all efficacy analyses and included all 669 patients

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randomized to treatment in Study 016. Data from the mITT population, comprising the 527 patients enrolled in Study 018 that had a postbaseline efficacy evaluation in Study 018, were also analyzed for each efficacy variable.

Primary Efficacy Endpoint: Mean Change in the DRS During On Time

The primary efficacy endpoint was the mean change in the DRS during *on* time from Baseline (Study 016) to endpoint (last visit in Study 018), calculated as the sum of the severities across all items collected at a particular time point. At Baseline (Study 016), the mean (SD) DRS scores for the placebo, safinamide 50 mg/day, and safinamide 100 mg/day groups were 3.4 (3.93), 3.9 (3.89), and 3.7 (4.07), respectively. Although there was little change in the placebo group with regard to DRS scores over the course of the study, a steady decrease in DRS scores from Baseline (Study 016) to Week 78 in Study 018 occurred in the active treatment groups: in the safinamide 50 mg/day group, the mean (SD) DRS score was 2.7 (2.96) at Week 78 (a 31% reduction) and in the safinamide 100 mg/day group, the mean (SD) DRS score was 2.8 (3.43) at Week 78 (a 27% reduction). The changes in DRS scores from Baseline to Week 78 for the active treatment groups were not statistically significantly different from placebo ($P = 0.2125$ for the safinamide 50 mg/day group and $P = 0.1469$ for the safinamide 100 mg/day group).

Similar results were observed for the mITT population. The changes in DRS scores from Baseline to Week 78 were not statistically significantly different from placebo (LS mean was –0.28 [$P = 0.2358$] for the safinamide 50 mg/day group and –0.43 [$P = 0.1141$] for the safinamide 100 mg/day group).

For both the ITT and mITT populations, chorea was reported as the most disabling dyskinesia in most patients with dyskinesia at all study visits. In a smaller percentage of patients, dystonia was reported as the most disabling dyskinesia. Approximately one-third of patients at each visit had no dyskinesias.

Secondary Efficacy Endpoints

Change in *On* Time (*On* + *On* With Minor Dyskinesia): For the ITT population, analysis of the change in mean *on* time (*on* + *on* with minor dyskinesia) from Baseline (Study 016, Week 0) to Study 018 Week 78 indicated that the safinamide treatment groups had a statistically significantly greater mean increase from Baseline (1.01 hours for the safinamide 50 mg/day group [$P = 0.0031$] and 1.18 hours for the safinamide 100 mg/day group [$P = 0.0002$]) compared with the placebo group (0.34 hours). Similar results were observed for the mITT population.

Diary Responder Rate: For the ITT population, at 12, 18, and 24 months, statistically significantly higher percentages of patients in the safinamide 50 mg/day group (52.0%, $P = 0.0073$; 50.7%, $P = 0.0138$; and 52.5%, $P = 0.0288$, respectively) and the safinamide 100 mg/day group (51.3%, $P = 0.0159$; 52.2%, $P = 0.0111$; and 52.7%, $P = 0.0179$, respectively) had an improvement (> 30-minute) in *on* time (*on* + *on* with minor dyskinesia) compared with the placebo group (38.7%, 39.6%, and 41.0%, respectively). For the mITT population, a statistically significantly higher percentage of patients in the safinamide 100 mg/day group had an improvement in *on* time at 12 months (56.5%, $P = 0.0421$) and 18 months (57.6%, $P = 0.0290$) compared with the placebo group (44.4% and 45.6%, respectively).

UPDRS Section 4: The reduction (improvement) in mean UPDRS Section 4 total scores from Baseline to Week 78 for the ITT population was statistically significantly greater in the safinamide 100 mg/day group (LS mean, –0.90 [$P = 0.0003$]), but not in the safinamide 50 mg/day group (LS mean, –0.35 [$P = 0.5100$]), compared with the placebo group (LS mean, –0.22). Similar results were seen for the mITT population.

Additionally, the changes from Baseline to Week 78 in UPDRS Section 4 (complications of therapy) items 32 (proportion of the waking day dyskinesias are present), 33 (how disabling are the dyskinesias), 34 (how painful are the dyskinesias), and 35 (presence of early morning dystonia) total score were not statistically significantly

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different between the active treatment groups and the placebo group for the ITT population. Similar results were found for the mITT population.

Further, the change from Baseline to Week 78 in UPDRS Section 4 items 32 through 34 total score was not statistically significantly different between the active treatment groups and the placebo group. Similar results were found for the mITT population.

With regard to individual item scores, for the ITT population, the changes from Baseline to Week 78 in UPDRS Section 4 in items 32, 33, and 34 were not statistically significantly different between the active treatment groups and the placebo group. For item 35, there was a statistically significantly greater decrease ($P = 0.0222$) in the mean scores from Baseline to Week 78 for the safinamide 100 mg/day group (LS mean, –0.09) compared with the placebo group (LS mean, 0), but not for the safinamide 50 mg/day group (LS mean, –0.04; $P = 0.3525$) compared with the placebo group. Similar results were observed for the mITT population.

Time to Develop Troublesome Dyskinesia: For the ITT population, the time to develop troublesome dyskinesia was longest in the safinamide 100 mg/day group (563.13 minutes) followed by the placebo (537.32 minutes) and safinamide 50 mg/day (506.42 minutes) groups. There were no statistically significant differences among the treatment groups. Similar results were observed for the mITT population.

Time to Develop Any (Minor and/or Troublesome Dyskinesia): The time to develop any dyskinesia was longest in the placebo group (427.14 minutes) followed by the safinamide 100 mg/day group (409.86 minutes) and safinamide 50 mg/day (306.96 minutes) group. There were no statistically significant differences among the treatment groups for the ITT and mITT populations.

Change in ADL During *On* Time (UPDRS Section 2): For the ITT population, reductions in mean UPDRS Section 2 scores from Baseline were observed at all visits for all 3 treatment groups. Analysis of the change in UPDRS Section 2 scores from Baseline to Week 78 revealed that the safinamide 100 mg/day group had a statistically significantly greater LS mean decrease from Baseline (–1.97 [$P = 0.0068$]) compared with the placebo group (–0.91), whereas the safinamide 50 mg/day group (–1.43 [$P = 0.1857$]) was not statistically significantly different from the placebo group. Similar results were seen for the mITT population.

Maintenance of Effect in UPDRS Section 2 Responders: For the ITT population, the safinamide 50 mg/day and 100 mg/day groups had a higher percentage of patients with ≥20% improvement in UPDRS Section 2 scores at the end of Study 016 (42.2% and 48.2% versus 37.4%, respectively), which was maintained in Study 018 (86.2% and 89.8% versus 81.9%, respectively); however, the groups were not statistically significantly different. Similar results were observed for the mITT population.

Percentage Change in Levodopa Dose: In the placebo group, 11.3% of patients had any reduction in their levodopa dose, whereas 17.0% and 18.3% of patients in the safinamide 50 and 100 mg/day groups, respectively, had reductions in their levodopa dose. The 5.7% absolute difference between the placebo and the safinamide 50 mg/day groups was not statistically significant, when compared using the Cochran-Mantel-Haenszel test; however, the 7.0% absolute difference between the placebo and the safinamide 100 mg/day groups was statistically significant ($P = 0.0317$). For the mITT population, the 7.3% absolute difference in the percentage of patients with any reduction in their levodopa dose between the placebo and the safinamide 50 mg/day groups was statistically significant ($P = 0.0260$), as was the 7.5% absolute difference between the placebo and the safinamide 100 mg/day groups ($P = 0.0256$).

The placebo group had a 17.67% mean increase in levodopa dose during the study, compared with a 9.92% increase in the safinamide 50 mg/day group and a 4.99% increase in the safinamide 100 mg/day group. Because the median value for all 3 treatment groups was zero, a comparison using a Wilcoxon rank-sum test was performed; the results revealed that the mean percent increase in levodopa dose was statistically significantly different from placebo for the safinamide 100 mg/day group ($P = 0.0044$), but not for the safinamide 50 mg/day

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group ($P = 0.2024$). Similar results were observed for the mITT population.

Percentage Change in Any PD Drug (Other Than Levodopa): For the other PD concomitant medications, there were no statistically significant differences among the treatment groups with regard to the number of patients with any reduction in the PD medication dose and the percentage change in dose, except for ropinirole. An analysis using the 2-sample *t* test revealed a statistically significant difference in the percentage change in ropinirole dose for both the safinamide 50 mg/day (–16.34%; $P = 0.0494$) and safinamide 100 mg/day (–17.27%; $P = 0.0439$) groups compared with the placebo group, which had an 8.53% increase. Similarly, an analysis of the mITT population, using the 2 sample *t* test, revealed a statistically significant difference in the percentage change in ropinirole dose for both the safinamide 50 mg/day (–4.41%; $P = 0.0024$) and safinamide 100 mg/day (2.28%; $P = 0.0132$) groups compared with the placebo group (34.84% increase). A further analysis of the mITT population, using a Wilcoxon rank-sum test, showed a statistically significant difference between the safinamide 50 mg/day group ($P = 0.0334$), but not the safinamide 100 mg/day group ($P = 0.0707$), compared with the placebo group.

Change in Motor Symptoms (UPDRS Section 3): For the ITT population, a reduction in mean UPDRS Section 3 total scores from Baseline was observed at all visits for all 3 treatment groups. At Week 78, the mean (SD) change from Baseline in UPDRS Section 3 scores was –4.7 (9.40) for the placebo group, –5.1 (10.27) for the safinamide 50 mg/day group, and –6.4 (10.96) for the safinamide 100 mg/day group. An analysis of the change in mean UPDRS Section 3 scores from Baseline to Week 78 revealed that the safinamide 100 mg/day group had a statistically significantly greater mean reduction from Baseline (LS mean, –6.06; $P = 0.0063$) compared with the placebo group (LS mean, –3.94); however, the safinamide 50 mg/day group (LS mean, –4.98; $P = 0.1791$) was not statistically significantly different from the placebo group. An analysis of the mITT population showed no statistically significant difference between the safinamide 50 mg/day (LS mean, –5.79; $P = 0.2873$) and safinamide 100 mg/day (LS mean, –6.48; $P = 0.0610$) groups versus placebo (LS mean, –4.87) in the mean change from Baseline in UPDRS Section 3 scores.

Clinical Global Impression–Change Scale (CGI-C): At all visits from Week 4 (Study 016) to Week 78 (Study 018), the percentage of patients showing improvement was greater in each of the safinamide groups than in the placebo group for the ITT population. From Week 4 (Study 016) to Week 78 (Study 018), the placebo, safinamide 50 mg/day, and safinamide 100 mg/day groups had a 10.4%, 8.5%, and 0.4% absolute increase in the percentage of patients with improvement and a –0.5%, –8.6%, and –0.4% absolute decrease in the percentage of patients with no change or worsening in their clinical status, respectively. The difference between the treatment groups was statistically significant for the safinamide 50 mg/day group ($P = 0.0085$) but not for the safinamide 100 mg/day group ($P = 0.0625$). Likewise, for the mITT population, the difference between the treatment groups was statistically significant for the safinamide 50 mg/day group ($P = 0.0455$), but not for the safinamide 100 mg/day group ($P = 0.1458$).

Clinical Global Impression–Severity of Illness (CGI-S): The mean CGI-S scores were reduced from Baseline at all visits for all 3 treatment groups. At Week 78, the mean (SD) change from Baseline in CGI-S scores was –0.3 (0.67) for the placebo group, –0.4 (0.66) for the safinamide 50 mg/day group, and –0.4 (0.73) for the safinamide 100 mg/day group. Analysis of the change in mean CGI-S scores from Baseline to Week 78 indicated that the safinamide 50 mg/day and the safinamide 100 mg/day groups had a statistically significantly greater mean reduction from Baseline (LS mean, –0.40 for the safinamide 50 mg/day group [$P = 0.0068$] and –0.38 for the safinamide 100 mg/day group [$P = 0.0147$]) compared with the placebo group (LS mean, –0.24). For the mITT population, an analysis of the change in mean CGI-S scores from Baseline to Week 78 showed that, compared with the placebo group (LS mean, –0.33), the mean reduction from Baseline was statistically significantly greater for the safinamide 50 mg/day group (LS mean, –0.49 [$P = 0.0085$]), but not for the safinamide 100 mg/day group [LS mean, –0.43 [$P = 0.1063$]).

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Change in Individual Diary Categories:

Total Daily On Time: For the ITT population, the mean total daily *on* time increased over time for each of the 3 treatment groups. At Week 78, the mean (SD) change from Baseline in total daily *on* time was 0.495 (3.072) hours for the placebo group, 1.046 (3.416) hours for the safinamide 50 mg/day group, and 1.081 (2.957) hours for the safinamide 100 mg/day group. An analysis of the change in mean total daily *on* time from Baseline to Week 78 revealed that the safinamide groups had a statistically significantly greater mean increase from Baseline (LS mean, 0.82 hours for the safinamide 50 mg/day group [$P = 0.0194$] and 0.92 hours for the safinamide 100 mg/day group [$P = 0.0071$]) than the placebo group (LS mean, 0.20 hours). Similar results were seen for the mITT population.

Total Daily Off Time: The mean total daily *off* time decreased over time for each of the 3 treatment groups; however, the mean reduction in the score was greater in each of the safinamide groups than in the placebo group at each postbaseline time point. At Week 78, the mean (SD) change from Baseline in total daily *off* time was –0.775 (2.325) hours for the placebo group, –1.297 (2.065) hours for the safinamide 50 mg/day group, and –1.412 (2.097) hours for the safinamide 100 mg/day group. An analysis of the change in mean total daily *off* time from Baseline to Week 78 revealed that the safinamide 50 mg/day and the safinamide 100 mg/day groups had a statistically significantly greater mean reduction from Baseline (LS mean, –1.36 hours for the safinamide 50 mg/day group [$P = 0.0011$] and –1.49 hours for the safinamide 100 mg/day group [$P < 0.0001$]) compared with the placebo group (LS mean, –0.74 hours). Similar results were seen for the mITT population.

Total Daily On Time with Minor Dyskinesia: For the ITT population, an analysis of the change from Baseline to Week 78 in the mean diary *on* time with minor dyskinesia, using ANCOVA, revealed no statistically significant differences between the safinamide 50 mg/day group ($P = 0.9583$) and the safinamide 100 mg/day group ($P = 0.7445$) compared with the placebo group. Similar results were observed for the mITT population.

Total Daily On Time with Troublesome Dyskinesia: For the ITT population, an analysis of the change from Baseline to Week 78 in the mean diary *on* time with troublesome dyskinesia, using ANCOVA, revealed no statistically significant differences between the safinamide 50 mg/day group ($P = 0.7776$) and the safinamide 100 mg/day group ($P = 0.8995$) compared with the placebo group. Similar results were observed for the mITT population.

Total Daily Asleep Time: For the ITT population, an analysis of the change from Baseline to Week 78 in the mean total daily asleep time, using ANCOVA, revealed no statistically significant differences between the safinamide 50 mg/day group ($P = 0.4131$) and the safinamide 100 mg/day group ($P = 0.4525$) compared with the placebo group. Similar results were observed for the mITT population.

UPDRS Section 1: For the ITT population, the mean reductions in UPDRS Section 1 total scores from Baseline to Week 78 were not statistically significantly greater in the safinamide 50 mg/day group (–0.22 [$P = 0.6026$]) or in the safinamide 100 mg/day group (–0.18 [$P = 0.8592$]) compared with the placebo group (–0.16). Similar results were observed for the mITT population.

Tertiary Efficacy Endpoints

Hoehn and Yahr Staging: For the ITT population, at Baseline (Study 016), the median Hoehn and Yahr stage was 3 (which was defined as moderately severe bilateral disease, significant slowing of body movements, and impairment of equilibrium) for all 3 treatment groups. At Week 78, the median Hoehn and Yahr stage was 2.5 (which was defined as bilateral involvement and posture, gait, and balance were affected but symptoms caused minimal disability) for all 3 treatment groups. There was no statistically significant difference in the mean change from Baseline to Week 78 in the Hoehn and Yahr stage between the placebo and safinamide 50 mg/day ($P = 0.3408$) and safinamide 100 mg/day ($P = 0.4416$) treatment groups. Similar results were observed for the mITT population.

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GRID-HAMD-17: Small reductions in mean GRID-HAMD-17 scores from Baseline were observed at all visits for all 3 treatment groups for the ITT population. At Week 78, the mean (SD) change from Baseline in GRID-HAMD-17 total score was –0.3 (3.58) for the placebo group, –0.5 (3.43) for the safinamide 50 mg/day group, and –0.8 (2.92) for the safinamide 100 mg/day group. An analysis of the GRID-HAMD-17 scores from Baseline to Week 78 revealed that the safinamide 100 mg/day group had a statistically significantly greater mean reduction from Baseline (LS mean, –0.88 [$P = 0.0475$]) compared with the placebo group (LS mean, –0.31), while the safinamide 50 mg/day group (LS mean, –0.46 [$P = 0.6018$]) was not statistically significantly different from placebo. For the mITT population, the analysis showed no statistically significant differences between the active treatment groups and placebo in the changes from Baseline to Week 78 in the GRID-HAMD-17 total score.

An analysis, using ANCOVA, of the mean change from Baseline to Week 78 for the individual item scores for the GRID-HAMD-17 (ITT population), showed statistically significant differences ($P < 0.05$), indicating greater improvement with safinamide treatment, compared with placebo, for the following items: guilt (safinamide 50 mg/day; $P = 0.0231$); psychomotor agitation (safinamide 100 mg/day; $P = 0.0471$); and sexual interest (safinamide 50 mg/day, $P = 0.0445$).

For the safinamide 100 mg/day group, the GRID-HAMD-17 item depressed mood was reduced (–0.14) compared with the placebo group (–0.01; $P = 0.0516$). Additionally, for the safinamide 100 mg/day group, the GRID-HAMD-17 item anxiety, somatic was reduced (–0.09) compared with the placebo group (0; $P = 0.0708$); and the item loss of appetite was increased (0.07) compared with the placebo group (–0.05; $P = 0.0591$). For the safinamide 50 mg/day group, the GRID-HAMD-17 item insomnia early was increased (0.09) compared with the placebo group (–0.02; $P = 0.0598$).

For the mITT population, no statistically significant differences, indicating greater improvement with safinamide treatment, were noted, except for sexual interest (safinamide 50 mg/day; $P = 0.0080$) and loss of weight (on weekly rating) (safinamide 50 mg/day; $P = 0.0486$).

Mini-Mental State Examination (MMSE): For the ITT population, at Baseline (Study 016), patients in all 3 treatment groups exhibited good cognitive function, as indicated by median MMSE scores of 28, 29, and 29 for the placebo, safinamide 50 mg/day and safinamide 100 mg/day groups, respectively. At Week 78, there was little change in MMSE scores from Baseline for any treatment group. Similar results were observed for the mITT population.

PDQ-39: For the total score, decreases in mean scores from Baseline were observed at all visits for all 3 treatment groups for the ITT population. There was a statistically significantly greater mean decrease from Baseline in total scores in the safinamide 100 mg/day group (LS mean, –32.01 [$P = 0.0195$]) compared with the placebo group (–13.65) at Week 78. The mean reduction from Baseline in the total score for the safinamide 50 mg/day group (–24.12) was not statistically significantly different from the placebo group ($P = 0.1837$).

For the mobility dimension, decreases in mean scores from Baseline were observed at all visits for all 3 treatment groups. Although there was a larger mean decrease from Baseline in mobility scores in the safinamide 50 mg/day (LS mean, –5.72 [$P = 0.1009$]) and safinamide 100 mg/day (–5.73 [$P = 0.0990$]) groups compared with placebo (–3.20) at Week 78, the differences between the means were not statistically significant.

For the ADL dimension, decreases in mean scores from Baseline were observed at all visits for all 3 treatment groups. The mean decreases from Baseline in ADL scores for the safinamide 50 mg/day group (LS mean, –7.13 [$P = 0.0027$]) and the safinamide 100 mg/day group (–5.73 [$P = 0.0305$]) were statistically significantly greater than for the placebo group (–2.19) at Week 78.

For the emotional well being dimension, decreases in mean scores from Baseline were observed at all visits for all 3 treatment groups. At Week 78, the mean change from Baseline in emotional well being scores for the

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safinamide 100 mg/day group was statistically significantly greater (LS mean, –5.82 [$P = 0.0036$]) than for the placebo group (–2.06), while the safinamide 50 mg/day group (–3.89 [$P = 0.1577$]) was not statistically significantly different from placebo.

For the stigma dimension, decreases in mean scores from Baseline were observed at all visits for all 3 treatment groups. Although there was a larger mean decrease from Baseline in scores for the stigma dimension at Week 78 in the safinamide 50 mg/day (LS mean, –5.05 [$P = 0.4339$]) and safinamide 100 mg/day (–4.08 [$P = 0.8101$]) groups compared with the placebo group (–3.65), the differences between the means were not statistically significant.

For the social support dimension, the median changes from Baseline were zero at all time points for all 3 treatment groups. There were no observed trends in mean scores over time; and the safinamide 50 mg/day and safinamide 100 mg/day treatment groups were not statistically significantly different from the placebo group at Week 78.

For the cognition dimension, there were no observed trends in mean scores over time; and the safinamide 50 mg/day and safinamide 100 mg/day treatment groups were not statistically significantly different from the placebo group at Week 78.

For the communication dimension, decreases in mean scores from Baseline were observed at all visits for all 3 treatment groups. The mean decrease from Baseline in communication scores for the safinamide 100 mg/day group was statistically significantly greater (LS mean, –3.77 [$P = 0.0490$]) compared with the placebo group (–0.79) at Week 78, while the decrease for the safinamide 50 mg/day group (–3.57 [$P = 0.0668$]) was not statistically significantly different from placebo. Conversely, for the mITT population, the mean change from Baseline in communications scores for the safinamide 100 mg/day group was not statistically significantly different (–4.15 [$P = 0.1139$]) compared with the placebo group (–1.53) at Week 78, while the decrease for the safinamide 50 mg/day group (–5.47 [$P = 0.0179$]) was statistically significantly greater than for placebo.

For the bodily discomfort dimension, the safinamide 50 mg/day group had a small increase in mean scores at Week 78 (LS mean change, 0.66). In contrast, the safinamide 100 mg/day group (–4.89) and placebo (–1.23) groups had decreases in mean scores at Week 78; the decrease in the mean score for the safinamide 100 mg/day group was statistically significantly greater compared with the placebo group ($P = 0.0190$) at Week 78.

Except as noted for the communication dimension, similar results were seen for the PDQ-39 total score and individual dimension scores for the mITT population.

Cogtest Battery: Of the 20 separate cognition tests that were evaluated, mean results of the Strategic Target Detection Test Two Shape Duration test between the safinamide 100 mg/day group and placebo ($P = 0.0371$) and the Word List Memory Delay Delayed Recall Correct test between the safinamide 50 mg/day group and placebo ($P = 0.0379$) were statistically significantly different.

Additional Ad-hoc Efficacy Analyses

Improvement in Diary Responder Rate and UPDRS Section 3 Total Score: A statistically significantly higher percentage of patients in the safinamide 50 mg/day group (27.4%; $P = 0.0058$) and the safinamide 100 mg/day group (29.9%; $P = 0.0016$) had ≥ 20% improvement relative to the placebo group (18.5%) in the UPDRS Section 3 (motor examination) scores (as assessed by the investigator) and at least a 30-minute increase in *on* time plus a 30-minute decrease in *off* time (as reported by the patient) from Baseline (Study 016, Week 0) to endpoint (Study 018, Week 78, or last available observation) . Moreover, a statistically significantly higher percentage of patients in the safinamide 50 mg/day group (21.1%; $P = 0.0149$) and the safinamide 100 mg/day group (25.9%; $P = 0.0004$) had ≥ 30% improvement in the UPDRS Section 3 scores, along with the specified improvements in *on* and *off* time, compared with the placebo group (14.0%).

Combined UPDRS Sections 2 and Section 3 Total Score: A reduction (improvement) in mean combined

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UPDRS Sections 2 and 3 total scores from Baseline was observed at all visits for all 3 treatment groups; however, the mean reductions in total score for the safinamide 50 mg/day and 100 mg/day groups were greater than for the placebo group at all visits. At Week 78, the mean change from Baseline in the UPDRS Sections 2 and 3 scores was –5.8 for the placebo group, –6.6 for the safinamide 50 mg/day group, and –8.5 for the safinamide 100 mg/day group. An analysis of the change in mean UPDRS Sections 2 and 3 scores from Baseline to Week 78 revealed that the safinamide 100 mg/day group had a statistically significantly greater mean reduction from Baseline (LS mean, –8.08; $P = 0.0031$), compared with the placebo group (LS mean, –4.90); however, the change for the safinamide 50 mg/day group (LS mean, –6.40) was not different from the placebo group ($P = 0.1632$).

Subpopulation Analyses in Patients with DRS > 4: *Baseline Disease Characteristics and Antiparkinsonian Drug Doses*: For patients with a DRS score > 4, at Baseline (Week 0 of Study 016), there were no statistically significant differences among the 3 treatment groups with respect to the demographic variables (age, sex, handedness, ethnicity group, race, height, weight, and education). For this subpopulation, the 3 treatment groups were similar with regard to baseline disease characteristics. Overall, compared with patients with a DRS total score ≤ 4 at Baseline (Study 016), patients with a DRS total score > 4 at Baseline had a longer mean duration of PD (9.258 vs 7.754 years); a similar mean *on* time (9.384 vs 9.407 hours); a shorter *off* time (4.773 vs 5.473 hours); a shorter *off* time post morning dose (4.369 vs 4.912 hours); a shorter *on* time (individual category) (5.482 vs 7.937 hours); a longer *on* time with minor dyskinesia (3.901 vs 1.471 hours); a longer *on* time with troublesome dyskinesia (1.628 vs 0.455 hours); and a higher mean UPDRS Section 1 total score (2.2 vs 1.9), Section 2 total score (13.9 vs 11.0), Section 3 total score (31.2 vs 26.4), Section 4 total score (7.6 vs 4.5), Section 4 (items 32-35) subscale score (4.0 vs 1.2), and Section 4 (items 32-34) subscale score (3.6 vs 0.9). At Baseline, for patients with a DRS total score > 4, the mean DRS score was 8.1; and for patients with a DRS total score ≤ 4, the mean DRS score was 1.2.

With regard to antiparkinsonian drug doses at Baseline (Study 016), the mean levodopa dose was higher for patients with a DRS total score > 4 (658.8 mg) compared with patients with a DRS total score ≤ 4 (574.3 mg). Further, the mean amantadine and carbidopa doses were higher for patients with a DRS total score > 4 compared with patients with a DRS total score ≤ 4 (225.0 mg vs 202.1 mg; and 154.4 mg vs 136.4 mg, respectively) at Study 016 Baseline. However, the mean entacapone dose was lower for patients with a DRS total score > 4 (726.2 mg) compared with patients with a DRS total score ≤ 4 (795.5 mg). Mean doses of anticholinergics (eg, trihexyphenidyl) and dopamine agonists (eg, pramipexole, ropinirole) were comparable in the 2 subpopulations. Similarly, at Study 018 Baseline, the mean levodopa dose was higher for patients with a DRS total score > 4 (629.9 mg) compared with patients with a DRS total score ≤ 4 (553.4 mg). The mean amantadine, carbidopa, and entacapone doses were higher for patients with a DRS total score > 4 compared with patients with a DRS total score ≤ 4 (231.0 mg vs 197.5 mg; 149.3 mg vs 127.0 mg; and 769.7 mg vs 753.9 mg, respectively) at Study 018 Baseline. Mean doses of anticholinergics and dopamine agonists were comparable in the 2 subpopulations.

Change from Baseline in Disease Characteristics and Antiparkinsonian Drug Doses: For both subpopulations, the mean *off* time ($P \leq 0.0377$) and *off* time post morning dose ($P \leq 0.0209$) for the safinamide 50 mg/day and 100 mg/day groups were statistically significantly decreased from Baseline compared with the placebo group. The mean *on* time was statistically significantly increased, compared with the placebo group, for patients with a DRS total score > 4 at Baseline in the safinamide 50 mg/day group ($P = 0.0189$); and for patients with a DRS total score ≤ 4, in the safinamide 50 mg/day ($P = 0.0155$) and 100 mg/day ($P < 0.0001$) groups. Mean *on* time (individual category) was statistically significantly increased in patients with a DRS total score ≤ 4 in the safinamide 50 mg/day ($P = 0.0308$) and 100 mg/day ($P = 0.0044$) groups, relative to the placebo group. For patients with a DRS total score > 4 at Baseline, statistically significant decreases (improvements) were observed in the mean UPDRS Section 2 total score ($P = 0.0401$), Section 3 total score ($P = 0.0270$), Section 4 total score

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($P = 0.0027$), Section 4 (items 32-35) subscale score ($P = 0.0128$), Section 4 (items 32-34) subscale score ($P = 0.0139$), and DRS total score ($P = 0.0317$) in the safinamide 100 mg/day group compared with the placebo group. For patients with a DRS total score > 4, a statistically significant ($P = 0.0210$) reduction from Baseline in levodopa dose was observed in the safinamide 100 mg/day group compared with the placebo group. The change from Baseline in other antiparkinsonian drug doses were not significantly different in the safinamide groups compared with the placebo group for either subpopulation of patients (patients with a DRS total score > 4 and patients with a DRS total score ≤ 4).

Mean Change in the DRS for Subjects with DRS Total Score > 4: At Baseline (Study 016), the mean DRS scores for the placebo, safinamide 50 mg/day, and safinamide 100 mg/day groups were 7.9, 8.0, and 8.4, respectively, for patients with a DRS total score > 4. A decrease in DRS scores from Baseline (Study 016) was observed in all 3 treatment groups at all visits; however, the reductions were greater in the safinamide 50 mg/day and 100 mg/day groups compared with the placebo group. The mean (SD) reduction from Baseline (Study 016) to Week 78 in Study 018 was –1.4 (3.37), a decrease of 17.5%, in the safinamide 50 mg/day group, and –2.0 (4.73), a decrease of 23.8%, in the safinamide 100 mg/day group, compared with –0.8 (3.60) in the placebo group. The LS mean change in the DRS scores from Baseline to Week 78 for the safinamide 100 mg/day group (–1.50) was statistically significantly different ($P = 0.0317$) from the placebo group (–0.28). When the analysis was repeated, excluding those patients whose levodopa dose was reduced at the endpoint, similar results were observed: a reduction in DRS scores at all visits in all 3 treatment groups, with greater improvements in the safinamide groups compared with the placebo group; a decrease from Baseline (Study 016) to Week 78 of 17.5% (mean change of –1.3) in the safinamide 50 mg/day group and a decrease of 34.5% (mean change of –2.9) in the safinamide 100 mg/day group, compared with a mean change of –0.5 in the placebo group. The LS mean change in the DRS scores from Baseline to Week 78 for the safinamide 100 mg/day group (–1.97) was statistically significantly different ($P = 0.0010$) from the placebo group (0.06), but not for the 50 mg/day group (–1.01; $P = 0.1999$).

SAFETY RESULTS

A total of 435 of 544 (80.0%) patients experienced 1806 newly emergent TEAEs in Study 018. In the 3 treatment groups, the percentage of patients with 1 or more newly emergent TEAEs was statistically significantly different ($P = 0.0329$) among the groups (85.1% [149 of 175] of patients in the placebo group; 76.7% [145 of 189] of patients in the safinamide 50 mg/day group; and 78.3% [141 of 180] of patients in the safinamide 100 mg/day group). The most commonly reported newly emergent TEAEs that occurred in > 5.0% of patients in any treatment group were cataract, constipation, asthenia, pyrexia, fall, weight decreased, back pain, pain in extremity, arthralgia, worsening of PD, dyskinesia, insomnia, and hypertension.

A total of 58 of 544 (10.7%) patients experienced 96 re-emergent TEAEs in Study 018. In the 3 treatment groups, the percentage of patients with 1 or more newly emergent TEAEs was similar ($P = 0.6736$) among the groups (12.0% [21 of 175] of patients in the placebo group; 9.5% [18 of 189] of patients in the safinamide 50 mg/day group; and 10.6% [19 of 180] of patients in the safinamide 100 mg/day group). Of the re-emergent TEAEs, only dry mouth and dyskinesia were reported in more than 2.0% of patients in any treatment group.

A total of 491 of 544 (88.6%) patients experienced 2993 TEAEs in Studies 016 and 018 combined. In the 3 treatment groups, the percentage of patients with 1 or more TEAEs in Studies 016 and 018 combined was similar ($P = 0.4456$) among the treatment groups (91.4% [160 of 175] of patients in the placebo group; 88.9% [168 of 189] of patients in the safinamide 50 mg/day group; and 90.6% [163 of 180] of patients in the safinamide 100 mg/day group).

In Studies 016 and 018 combined, the most commonly reported TEAEs that occurred in > 5.0% of patients in any treatment group were anemia, cataract, visual acuity reduced, constipation, nausea, asthenia, cough,

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hypertension, arthralgia, pyrexia, pain, urinary tract infection, fall, weight decreased, weight increased, anorexia, back pain, pain in extremity, dyskinesia, worsening of PD, headache, somnolence, visual field defect, tremor, dizziness, insomnia, and depression. Only cataract, asthenia, pyrexia, fall, back pain, dyskinesia, worsening of PD, headache, and insomnia occurred in greater than 10% of patients.

A similar percentage of patients in the placebo (10.3% [18 of 175]), safinamide 50 mg/day group (9.0% [17 of 189]), and safinamide 100 mg/day group (9.4% [17 of 180]) experienced newly emergent severe TEAEs in Study 018.

A total of 76 patients experienced newly emergent SAEs in Study 018: 22 (12.6%) patients in the placebo group, 28 (14.8%) patients in the safinamide 50 mg/day group, and 26 (14.4%) patients in the safinamide 100 mg/day group. There were no re-emergent SAEs in Study 018. In Studies 016 and 018 combined, a total of 94 patients experienced SAEs: 28 (16.0%) patients in the placebo group, 32 (16.9%) patients in the safinamide 50 mg/day group, and 34 (18.9%) patients in the safinamide 100 mg/day group. No specific pattern of occurrence of SAEs was observed.

A similar percentage of patients discontinued from Study 018 due to TEAEs (5.7% in the placebo group, 5.3% in the safinamide 50 mg/day group, and 6.7% in the safinamide 100 mg/day group).

Twenty-five deaths were reported during the combined studies (8 in the placebo group, 5 in the safinamide 50 mg/day group, and 12 in the safinamide 100 mg/day group), none of which were considered to be related to the study drug.

Overall, there were 299 newly emergent laboratory TEAEs experienced by 142 patients . A higher percentage of patients in the placebo group (30.3% [53 of 175]) experienced laboratory TEAEs compared with the safinamide 50 mg/day (22.2% [42 of 189]) and safinamide 100 mg/day (26.1% [47 of 180]) groups, although this difference among the groups was not statistically significant ($P = 0.2045$). Only 4 patients experienced re-emergent laboratory TEAEs.

The 3 treatment groups were generally similar with regard to changes from Baseline in hematology parameters, renal and liver function tests, biochemistry analytes, and urinalysis parameters. The frequency of individual newly occurring abnormal clinical laboratory test results was similar among the treatment groups. Overall, 46.9% of patients in the placebo group, 50.8% of patients in the safinamide 50 mg/day group, and 47.2% of patients in the safinamide 100 mg/day group had at least 1 clinically notable laboratory value throughout the study.

In all 3 treatment groups, there were minimal mean changes from Baseline in vital signs data at Visit 7 (Week 78), with no meaningful differences among groups for any parameter. There were few clinically notable vital signs values at any visit, except for weight, and no meaningful differences among treatment groups. The percentage of patients with a clinically notable change in weight increased with each visit across the treatment groups: at Visit 7 (Week 78) or endpoint, 22.9% of patients in the placebo group, 23.8% of patients in the safinamide 50 mg/day group, and 26.1% of patients in the safinamide 100 mg/day group had a clinically notable change from Baseline in weight.

Physical and neurological examination results were similar across treatment groups at Baseline and at Visit 7 (Week 78). For all 3 treatment groups, there was a reduction in neurological findings (ie, tremor at rest, bradykinesia, rigidity, gait abnormalities, balance impairment, handwriting impairment, end-of-dose wearing off phenomenon, on-off phenomena, dyskinesia, motor fluctuations, hypomimic facial expression, and other signs) at Visit 7 (Week 78) compared with Baseline.

Safinamide treatment at doses of 50 mg/day and 100 mg/day does not seem to have an effect on QTc or other ECG parameters in the population of patients with PD that were enrolled in this study, all of whom were receiving concomitant treatment with levodopa, and in many cases other medication for PD.

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All 3 treatment groups were similar with regard to the results of the dermatological examination.

There were no observed trends in mean ESS total scores over time and no indication of effects of treatment on daytime sleepiness.

Ocular History, Ocular TEAEs, and Ophthalmological Examination Results

Patients with albinism, family history of hereditary retinal disease, progressive or severe diminution of visual acuity, retinitis pigmentosa, retinal pigmentation, retinopathy, ocular inflammation (uveitis), or progressive, severe diabetic retinopathy were excluded from the study. A past medical history of eye disorders was reported in less than 3.5% of patients overall; however, almost 34% of patients had a concomitant illness or condition related to the eye, primarily cataract and refraction disorders, at Screening. All patients were taking levodopa. Most patients (about 86%) were taking 1 or more concomitant medications besides PD medications, most commonly agents acting on the renin-angiotensin system, analgesics, beta-blocking agents, drugs for acid-related disorders, drugs used in diabetes, lipid-modifying agents, and vitamins. The DA agonists ropinirole and pramipexole, both of which are known to cause retinal degeneration in albino rats, were taken by more than 60% of patients; however, there has been no evidence to date that these drugs cause retinal degeneration in the PD population.

Overall, a total of 245 ocular TEAEs were reported in 147 of 516 (28.5%) patients. Ocular-related TEAEs were reported in a similar percentage of patients in the 3 treatment groups: 31.5% of patients in the placebo group, 25.7% of patients in the safinamide 50 mg/day group, and 28.5% of patients in the safinamide 100 mg/day group ($P = 0.3459$). Cataract (occurring in 10.9% of patients), visual field defect (occurring in 3.3% of patients), and visual acuity reduced (occurring in 2.5% of patients) were the most commonly reported ocular-related TEAEs. Additionally, there were 10 (1.9%) patients who were reported to have cataract nuclear and 2 (0.4%) patients who were reported to have cataract cortical. The remainder of the ocular-related TEAEs occurred in less than 3% of patients in any treatment group.

Global Impression: A central reviewer provided a Global Impression score (normal/abnormal/unassessable) and an assessment of worsening both for the overall results and for each of the individual tests that were part of the ophthalmological examination. The treatment groups were similar with regard to the percentage of patients who received a rating of normal (18.2%, 12.8%, and 18.0%, respectively) and abnormal (81.2%, 84.9%, and 82.0%, respectively) on the overall Global Impression. Of the abnormal findings, in the placebo, safinamide 50 mg/day, and safinamide 100 mg/day groups, respectively, 19.4%, 27.4%, and 18.6% of the findings were assessed as no change from Baseline; 11.5%, 14.5%, and 13.4% were assessed as improved; and 44.8%, 39.1%, and 40.7% were considered clinically significantly worsened. The treatment groups were similar with regard to the percentage of patients assessed as clinically significantly worsened. For findings assessed as worsened (both clinically significant and not clinically significant), the relationship to study drug was assessed as plausible in most instances.

Worsening in Ocular Endpoints: The percentage of patients in the placebo, safinamide 50 mg/day, and safinamide 100 mg/day groups, respectively, who experienced worsening in any endpoint (46.7%, 43.0%, and 47.1%) , worsening in visual acuity (29.7%, 25.1%, and 32.0%), worsening in color vision (2.4%, 3.4%, and 4.1%), worsening in visual fields (22.4%, 18.4%, and 23.3%), and worsening in fundoscopy (2.4%, 3.9%, and 0.6%), as assessed by the central reviewer, were similar among the placebo, safinamide 50 mg/day, and safinamide 100 mg/day groups.

Visual Acuity: At most study visits, the percentage of patients with visual acuity abnormalities (as assessed by the local reviewers and the central reviewer) for the right eye, left eye, either eye and both eyes, were similar among the 3 treatment groups. Within and among the treatment groups, there was little variation with regard to mean logMAR values for the right and left eye at all study visits. There was an overall increase in the percentage

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of patients with a worsening (assessed primarily as mild or moderate) of visual acuity throughout the study across all 3 treatment groups.

Color Vision: Most patients had normal color vision evaluations at Baseline and all subsequent examinations. The treatment groups were generally similar with regard to the percentage of patients who had worsened color vision at subsequent study visits for both the right and left eye, either eye, and both eyes.

Fundoscopy: Although the percentage of patients with abnormal fundoscopy assessments was relatively low and similar between the treatment groups by reviewer, there was a noticeable difference in the frequency of abnormal fundoscopies between the local reviewers and the central reviewer: the local reviewers assessed more fundoscopies as abnormal for all treatment groups and for all visits than did the central reviewer.

Visual Fields: No noticeable trends were observed in the percentage of patients with abnormal visual field mapping assessments or with regard to types of abnormalities across the study visits or among the study treatments.

MD and PSD: As expected because of the average age of this patient population, mean MD was mildly depressed and PSD was elevated at Baseline for both eyes in all 3 treatment groups. For the 3 treatment groups, the mean MD scores were slightly improved and the mean PSD scores showed little change over the study period. No meaningful differences among the 3 treatment groups were observed for mean MD or PSD.

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CONCLUSION:

- Safinamide at doses of 50 mg/day and 100 mg/day reduced dyskinesia (DRS) scores by 31% and 27%, respectively, from Baseline compared with placebo (3% reduction) over the 2-year (102 weeks), double-blind treatment period in combined Studies 016 and 018; these differences were not statistically significant. However, in patients with moderate-to-severe dyskinesia at Baseline (DRS total score > 4), DRS scores were statistically significantly reduced at endpoint by 23.8% in the safinamide 100 mg/day group compared with the placebo group. Further, in this subpopulation, excluding patients whose levodopa dose was reduced at the endpoint, a statistically significant reduction of 34.5% in DRS scores was observed in the safinamide 100 mg/day group relative to the placebo group.
- Over the 2-year studies, safinamide 100 mg/day, in patients with a DRS total score > 4 at Baseline, exhibited statistically significant improvements in *off* time, *on* time, UPDRS Sections 2, 3 and 4 scores, and percent reduction in levodopa dose at endpoint.
- Over the 2-year studies, safinamide 100 mg/day exhibited a statistically significant increase in mean total daily *on* time (*on* + *on* time with minor dyskinesia); improvement in *on* time; and reductions in total daily *off* time, UPDRS Section 2 (ADL) scores, UPDRS Section 3 (motor examination) scores, UPDRS Section 4 (complications of therapy) scores, CGI-S scores, levodopa dose, GRID-HAMD-17 total scores and psychomotor agitation scores, and total PDQ-39 and ADL, emotional well being, communications, and bodily discomfort dimension scores.
- Over the 2-year studies, safinamide 50 mg/day exhibited a statistically significant increase in mean total daily *on* time (*on* + *on* time with minor dyskinesia), improvement in *on* time; and reductions in CGI-C scores, levodopa dose, GRID-HAMD-17 guilt and sexual interest scores, and PDQ-39 ADL dimension scores.
- Safinamide at doses of 50 mg/day and 100 mg/day, improved symptoms of PD including ADL and motor symptoms (as measured by the UPDRS and global severity of illness [CGI-S]); patient's health status and QOL (as measured by the PDQ-39); and severity of depression symptoms (as measured by the GRID-HAMD-17).
- Safinamide at doses of 50 mg/day and 100 mg/day was safe and well tolerated in this population of patients with PD receiving levodopa and other PD medications.
- No major safety concerns have been identified. Apart from dyskinesia, which occurred more frequently in patients in both safinamide groups, the incidence of individual TEAEs was similar across treatment groups. There were no significant findings with regard to tolerability of safinamide in this study.
- Considering the benefits seen with safinamide across numerous variables in patients with PD with motor fluctuations being treated with levodopa and other antiparkinsonian medications, and the low number of observed AEs, the benefits of long-term use (102 weeks) of safinamide 50 mg/day and 100 mg/day outweigh the risks of treatment.

DATE OF THE REPORT:

11 January 2013