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RESEARCH**

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MEDICAL REVIEW(S)

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Reviewer Name Leonard P. Kapcala, M.D.
Review Completion Date 2/7/17

Established Name SAFINAMIDE
(Proposed) Trade Name XADAGO
Therapeutic Class Monoamine Oxidase B
Inhibitor
Applicant Newron

Formulation(s) Tablet
Dosing Regimen Once daily orally
Indication(s) Treatment of signs and
symptoms of Parkinson's
disease
Intended Population(s) Patients with early and
advanced Parkinson's disease

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

- I recommend approval of this NDA for adjunctive treatment with levodopa/carbidopa in patients with Parkinson's disease to reduce "off" episodes.

1.2 Risk Benefit Assessment

- It is my opinion that this risk benefit assessment for safinamide supports the approval of safinamide for treatment of signs and symptoms of patients experiencing "off" episodes and taking concomitant levodopa/carbidopa (i.e., patients with advanced Parkinson's disease). The two pivotal trials (Studies 16 and SETTLE) conducted for advanced Parkinson's disease were positive and demonstrated adequate efficacy of safinamide. The safety profile of safinamide for treating this population was acceptable. My previous review (entered in DARRTS on 3/27/16) includes my detailed assessment risk benefit assessment of the efficacy and safety of safinamide.
- After completing my review of the sponsor's Safety Update, I find the information did not suggest any, new or significant adverse reactions that would change my impression of the safety profile for safinamide or my recommendation to approve safinamide as a safe and effective drug.
- I do, however, recommend that a new safety finding discovered in my review of this Safety Update be described in the label. Based upon my review of postmarket case 201600064DEU, I believe that hypersensitivity to safinamide should be described in the label as a Contraindication. The adverse reaction of hypersensitivity has the potential being a medically serious event, with potentially a fatal outcome. I conclude that there is a quite reasonable probability that safinamide caused this hypersensitivity reaction and that this hypersensitivity reaction recurred upon rechallenge with safinamide.
- I also recommend that the safinamide label should include additional information regarding taking safinamide with two drugs (i.e., linezolid and isoniazid-INH) with monoamine oxidase (MAO) inhibitory activity. During our review of the sponsor's Complete Response re-submission, we became aware that two antimicrobial drugs (i.e., linezolid and isoniazid) have MAO inhibitory activity. Linezolid is a reversible, nonselective MAO inhibitor which is indicated in adults and children for the treatment of the following infections caused by susceptible Gram-positive bacteria: Nosocomial pneumonia ; Community-acquired pneumonia; Complicated skin and skin structure infections, including diabetic foot infections, without concomitant osteomyelitis; Uncomplicated skin and skin structure infections; and Vancomycin-resistant *Enterococcus faecium* infections for a treatment period ranging between 10-28 days. Oral

tyramine challenge testing with linezolid has shown an increase in tyramine sensitivity but the label does not require dietary tyramine restriction. However, concomitant use of an MAO inhibitor is contraindicated in the linezolid label. The INH label notes that it has some MAO inhibiting activity, and that an interaction with tyramine-containing foods (cheese, red wine) may occur when taking INH. However, the INH label does not require dietary tyramine restriction nor does it contraindicate concomitant use of MAO inhibitors. A review of the published literature did not find results from any formal tyramine challenge testing.

In view of this new information, I recommend that the safinamide label contraindicate the use of linezolid because the linezolid label notes that it is an MAO inhibitor and the safinamide label contraindicates drugs (selective or nonselective) which are MAO inhibitors. Adding this contraindication in the safinamide label would make both labels consistent with each other relative to contraindicating concomitant MAO inhibitors with the use of safinamide or linezolid. I also recommend that safinamide label describes in the Drug Interactions section of the label that because INH has some MAO inhibitory activity, that patients taking safinamide together with INH could possibly experience a hypertensive reaction when ingesting tyramine containing food or drink. Patients taking safinamide and INH should be monitored for such a hypertensive reaction. Because the precise quantitative extent of MAO inhibition from INH is not clear, I do not believe that a contraindication for INH is necessary.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

- I do not have any recommendations for the postmarket risk evaluation and mitigation strategies for safinamide.

1.4 Recommendations for Postmarket Requirements and Commitments

- I do not have any recommendations for postmarket requirements or commitments for safinamide.

2 Introduction and Regulatory Background

2.1 Product Information (Based Upon Sponsor Summary)

Safinamide, an alpha-aminoamide derivative is structurally unrelated to any other drug for treatment of Parkinson's disease (PD), but is related to milacemide, a glycine prodrug. Safinamide may have multiple mechanisms of action. The sponsor describes properties such as state-dependently inhibits voltage-gated sodium channels (IC₅₀:1.6-4.9 μM for different subtypes), and at higher concentrations it inhibits calcium channels. The expected physiological

effect is the modulation of the hyper-active neurons and the consequent regulation of the neurotransmitter release: safinamide reduces the stimulated release of glutamate (~0.6 μM) without affecting basal glutamate levels. Safinamide is also a reversible and selective Monoamine Oxidase B (MAO-B) inhibitor (IC₅₀ 79-98nM: >1000-fold selective over MAO-A). It also binds at the WIN 35,428 site of the dopamine transporter (DAT) with IC₅₀ of 8.8 μM and displaces the serotonin transporter (SERT) ligand citalopram from its binding with IC₅₀ of 5.6 μM . leading to dopamine and the serotonin uptake inhibition in brain synaptosomes with IC₅₀s of 12.5 and 21 μM , respectively.

Safinamide enters the brain, and in animal models of PD has shown both dopaminergic benefits (increased brain dopamine content; extended efficacy of a given dose of L-dopa on motor symptoms) and non-dopaminergic effects (reduced L-dopa induced dyskinesia) associated with plasma safinamide levels corresponding to therapeutic doses in clinical trials. The sponsor also notes that results of some studies in preclinical models of PD and other CNS diseases suggest the possibility that safinamide may have a neuroprotective effect.

The initial non-clinical and clinical programs were performed by the Sponsor (Newron). In 2006 Merck-Serono acquired the exclusive worldwide rights to further develop, manufacture and commercialize safinamide. In October 2011, Merck-Serono announced their decision to discontinue the co-development agreement with Newron. Newron regained the full rights to safinamide from Merck-Serono in April 2012.

2.2 Other Relevant Background Information

The original NDA for safinamide for the treatment of Parkinson's disease (PD) was submitted on 27 May 2014. A 26 December 2014 Resubmission addressed organizational and navigational issues in the 28 July 2014 Refusal to File Letter.

On 29 March 2016 a Complete Response Letter was issued and outlined the various issues that the NDA Resubmission must comprehensively respond to and resolve in order to permit Approval. The CRL stated the necessity of providing a Safety Update and recommended conduct of additional clinical studies to evaluate (1) abuse liability of safinamide in experienced recreational drug users, and (2) potential withdrawal/discontinuation effects in Parkinson's disease patients.

An End of Review Conference (EoRC) was held on 21 July 2016. In the written Preliminary Response to the Sponsor's Questions submitted in the meeting briefing package, and during the meeting discussion, CSS revised its recommendations in the CRL, stating that the two additional clinical studies related to abuse potential were no longer recommended in light of review of recently submitted information. CSS also clarified recommendations concerning the structure and content of the Resubmission's revised "8-Factor Analysis" assessment of safinamide's abuse liability. In addition, the meeting discussion clarified the CRL's discussion

of the structure and content of the required Safety Update in the present NDA Resubmission in light of the limited clinical data collected subsequent to the original NDA submission in 2014 (FDA Minutes, 18 August; Sponsor Minutes, 25 July, SN 072).

3 Safety Update

My review focuses on the sponsor's Safety Update.

Overview of the Safety Update

Currently, there are no ongoing open-label extension clinical studies reported in the original NDA, and all of the safety data from these studies have been submitted. As discussed and agreed during the 21 July 2016 EoRC (FDA Minutes, 18 August; Sponsor Minutes, 25 July, SN 072), the information to be included in the present NDA Safety Update will be limited to presentation and analysis of the human safety data collected subsequent to the original December 2014 NDA submission :

- Data from an EU clinical trial in healthy subjects – Final Study Report Z7219J01;
- Synopses of results from 2 healthy volunteer studies completed in Japan – ME2125-1 and ME2125-2;
- Available safety data from ongoing Japanese Phase III development studies – Synopses of protocols ME2125-3 and ME2125-4, and narratives of serious adverse events (see appendix-expanded narratives. pdf); and
- Post-marketing safety data (narratives for serious adverse events/medically significant cases) from European countries.

The above data have been provided in standalone tables (including cases that are “blinded” from ongoing Japanese trials) to expedite the Division’s review. As agreed during the 21 July EoRC meeting, these data refer to the last version of the ISS submitted, where appropriate. As agreed with the Division, the Sponsor has not integrated these new safety data with the ISS. The Sponsor has replicated the organization of the safety data similar to that in the previous submission, as requested by the Division.

Adverse event data from three completed studies in healthy volunteers are provided while reported SAEs from the ongoing studies (table and narratives) in Japan are included. Post marketing SAEs are presented with hyperlinks to their respective narratives in the “expanded narratives.pdf” file, included as an appendix to this safety update. An additional table is provided that shows all cases arranged by System Organ Class (SOC) and Preferred Term (PT) (as presented in the ISS, and requested by the Medical Reviewer).

Japanese Study 1 (Pharmacokinetics Study) – Study ME2125-1

Title

A phase I, randomized, single-center, double-blind, placebo-controlled study to evaluate the pharmacokinetics and safety of ME2125 (safinamide) following single and multiple oral doses.

Brief description

This was a phase I, double-blind, placebo-controlled study in Japanese, male, healthy volunteers ages 20-35 to evaluate the pharmacokinetics of 50, 100, and 200 mg single and repeated oral doses of ME2125 (safinamide) (ME2125).

Healthy male volunteers (n=60) were randomized (4:1) to receive either safinamide (n=48) or placebo (n=12). Dosing was performed in 6 sequential cohorts, with each subject being dosed in each cohort. Each cohort was given either safinamide 50, 100, or 200 mg or matching placebo. Cohorts 1-3 took a single dose, and cohorts 4-6 received study medication (safinamide 50, 100, or 200 mg or matching placebo once daily) for 7 days. Prior to dosing the subjects were hospitalized (one day prior to the single doses, and two days prior to repeated dosing) and remained hospitalized until day 5 or day 11, respectively. Whether or not the subject continued to the next cohort was dependent on the safety and tolerability findings from the previous cohort.

In Step (Cohort) 1, a single oral dose of 50 mg of safinamide or a placebo was administered; in Step (Cohort) 2, a single oral dose of 100 mg or a placebo was administered; and in Step (Cohort) 3, a single oral dose of 200 mg or placebo was administered. In Step (Cohort) 4, 50 mg of safinamide or a placebo was administered; in Step (Cohort) 5, 100 mg of safinamide or a placebo; in Step (Cohort) 6, 200 mg of safinamide or a placebo was administered. In each of Steps 4-6, a dose was administered orally once daily and repeated for 7 days.

Status

This study is complete.

Safety Findings

There were no serious adverse events or events that led to early discontinuation of the study medication. There were 6 mild AEs following single administration [1, erythema, in the 50 mg dose (12.5%); 3 events (1 subject) for 100 mg dose (12.5%); 3 gastritis and anxiety for 200 mg dose (12.5%); and 1, ALT increase, in the placebo group (16.7%)]. All were mild and recovered without treatment, or sequelae.

There were 6 mild AEs following repeated administration [2, diarrhea, in the 50 mg dose (25%); 2, ALT increase and protein-positive urine in the 200 mg dose group (25%); and 1, C-reactive protein increase, in the placebo group (16.7%)]. All were mild and recovered without treatment, or sequelae.

The effect of safinamide on the QT/QTc interval following repeated oral administration was determined by the comparison of the categorical analyses of change (from the baseline to measured value), QT/QTc intervals, and the plasma concentrations of ME2125 and its metabolites. No QT/QTc prolongation was found, but a slight reduction was observed.

Japanese Study 2 (Bioequivalence Study) - Study ME2125-2

Title

A randomized, single-center, open-label, two-period crossover (14-day washout) study to show the bioequivalence of two different oral tablets of 50 mg safinamide (ME2125 50 mg tablet and the ME2125 (b) (4) 50 mg tablet), utilizing different manufacturing processes, in healthy volunteers.

Brief description

A single dose of the ME2125 50 mg tablet or the ME2125 (b) (4) 50 mg tablet was administered orally to 24 healthy, adult male subjects, ages 20-35, while fasting, and blood was collected over time. The concentration of safinamide in plasma, which was obtained after centrifugation, was measured. The pharmacokinetic parameters were calculated, and the bioequivalence of both drugs was verified.

Status

This study is complete

Safety results

There were three adverse events in one subject following a single oral administration of 50 mg ME2125, and the incidence rate of adverse events was 4.3% (1 in 23 subjects). No adverse events occurred during single oral administrations of a 50 mg-ME2125 (b) (4) tablet.

The adverse events that were reported during the administration of ME2125 50 mg tablet were aspartic acid aminotransferase (AST) increase, blood creatine phosphokinase (CPK) increase and blood lactate dehydrogenase (LDH) increase. The Principal Investigator assessed that the relationship of all events to the study medication could not be denied.

All reported adverse events were not serious, but were of mild severity and recovered without treatment. No subject interrupted treatment with the study medication because of the adverse events.

Conclusion

The results from the comparative analysis of the pharmacokinetic parameters calculated from the plasma concentrations of safinamide after single oral administrations of ME2125 TABLET 50 mg or of ME2125 (b) (4) tablet 50 mg were demonstrated to satisfy the standards in “Guideline for bioequivalence studies of generic drugs”, and therefore, the two formulations were bioequivalent. Moreover, no particular concern for safety was raised from the studies of the single oral administrations of ME2125 tablet 50 mg or ME2125 (b) (4) tablet 50 mg.

Studies in Patients (Japan)

Japanese Study 3 (Double-blind) – Study ME2125-3

Title

A Phase II/III, Double-Blind, Placebo-Controlled Study of ME2125 (safinamide) in Patients with Parkinson's Disease with Wearing-Off Phenomenon, Who Are Currently Receiving Levodopa.

Brief description

This is a 24-week, multi-center study to evaluate the efficacy and safety of two doses of ME2125 (50 and 100 mg, once a day), compared to placebo, as add-on therapy in Japanese patients with Parkinson's disease with wearing-off phenomenon, who are currently receiving levodopa.

The primary efficacy variable is the change in mean daily "on" time from baseline, which will be used to verify the superiority of 50 mg ME2125 compared to placebo. In addition, the superiority of 100 mg ME2125 to placebo will be also verified. Secondary efficacy variables are being measured as change from baseline to 24 weeks and include: change in mean daily "off" time, change in mean daily "on" time from baseline to each evaluation time point, change in UPDRS (Unified Parkinson's Disease Rating Scale) Part I, Part II ("on" phase, "off" phase), Part III ("on" phase) and Part IV, change in PDQ-39 (39-item Parkinson's Disease Questionnaire) total score, and responder rate at 24 weeks of the treatment phase and each evaluation time point.

Safety evaluations include: adverse events, laboratory tests, physiological tests and electrocardiograms. Blood samples for pharmacokinetic evaluations are also being collected at regular intervals.

Status

As of 31 July 2016 132 patients have been enrolled, and the study is currently ongoing.

Safety

Table 1 shows the serious adverse events that have been reported for this ongoing double-blind Japanese study.

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Table 1 Serious Adverse Events in Ongoing Double-Blind Japanese Study ME2125-3

Case Nr./ Age/ Sex/ Treatment	AE Start/ Stop	Time to onset (days)	Adverse Event (PT)	Relationship Reporter/ Manufact.	Relationship Sponsor	Outcome	Nar- rative link (page)
ME2125JP3- 0001/74/ M/ Placebo/saf	06 Apr 2016 / 17 May 2016	15	Cervical Vertebral Fracture (due to a fall)	Not related	Possible	Recovered	2
ME2125JP3- 0002/61/F/ Placebo/saf	11 May 2016 / ongoing	70	Fall	Not related	Not related	Recovering	4
ME2125JP3- 0003/83/F/ Placebo/saf	10 Jun 2016 / ongoing	129	Rib Fracture (due to a fall), Pneumo-thorax traumatic	Not related	Possible	Ongoing	6

Japanese Study 4 (Open-Label) Study ME2125-4

Title

A Phase III, Long-Term Treatment Study of ME2125 in Patients with Parkinson’s Disease with Wearing-Off Phenomenon.

Brief description

This is an open-label, 52-week study to evaluate the safety and efficacy of two doses of ME2125 (50 and 100mg, once a day) as add-on therapy in Japanese patients with Parkinson’s disease with wearing-off phenomenon, who are currently receiving levodopa. Patients will undergo standard safety evaluations, including assessment of adverse events, laboratory tests, physiological tests and electrocardiograms. Efficacy evaluations include change from baseline in mean daily “on” time, change in mean daily “off” time, change in mean daily “on” time from the baseline to each evaluation time point, change in UPDRS Part I, Part II (“on” phase, “off” phase), Part III (“on” phase) and Part IV, change in PDQ-39 total score, and responder rate at 52 weeks of the treatment phase, and at each evaluation time point. Pharmacokinetic evaluations are also being performed at regular intervals.

Status

As of 31 July 2016, 113 patients have been enrolled. This study is currently ongoing. Seven serious adverse events have been reported to date.

Summary of Safety events (Japanese Trials)

Ten SAEs were reported from 245 patients included in the trials in Japan performed in patients with Parkinson’s disease. Three cases are from the ongoing double-blind study (Study ME2125-3), that currently has 132 patients randomized (i.e. approx. 85 treated with safinamide), and seven cases are from an open-label, long-term treatment study (Study ME2125-4; safinamide 50mg or 100mg), that currently has 113 patients randomized.

In the double blind study ME2125-3, three patients experienced falls that led to fractures and their associated complications; in none of the 3 cases was the blind broken (patients could be on safinamide 50 or 100 mg, or on placebo), and treatment with the study medication was continued in 2 of the 3 patients. A contribution of study medication to the falls and their consequences is considered possible in patients ME2125JP3-0001, and ME2125JP3-0003. A history of falls preceded initiation of study medication in ME2125JP3-0002, and therefore the event is considered unrelated.

A fall also occurred in patient (ME2125JP4-0004), who fell after taking safinamide 50 mg for 57 days. The patient experienced a fracture of the femur. It is possible that safinamide contributed to the fall.

A death due to drowning (body found on the beach) occurred in a 77-year-old male patient (ME2125JP4-0007) who went swimming alone. Patient ME2125JP4-0005 was hospitalized for treatment of a upper respiratory tract inflammation with high fever while continuing treatment with safinamide, and no causal relationship is inferred between treatment with safinamide 50mg/day and the events in either of these cases. Parkinson's disease (aggravated) worsened in a patient (ME2125JP4-0001) on 50mg, followed by 100mg of safinamide for 24 and 8 days, respectively, and led to her hospitalization. The worsening of motor fluctuations was not controlled by the increase in dose of safinamide, which was discontinued. A contribution of safinamide to these events is considered possible. No relationship of safinamide is suspected in the causation of intestinal obstruction (ME2125JP4-0003), or the diagnosis of prostate cancer (diagnosis 4 days after starting 50mg of safinamide) in patient ME2125JP4-0002. Safinamide is considered unrelated to the occurrence of Neuroleptic Malignant Syndrome/ renal failure in patient ME2125JP4-0006, who was suffering from multiple illnesses and taking over 10 different medications. This syndrome presentation appears to have been precipitated by the use of ferrous sulphate that was initiated 110 days after starting safinamide. The patient was hospitalized for renal failure but recovered eventually.

Table 2 shows the events that have been reported for the ongoing open-label, long-term Japanese study.

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Table 2 Serious Adverse Events in an Ongoing Open-label, Long-term, Japanese study – ME2125-4

Case Nr./ Age/Sex/Dose	AE Start/ Stop	Time to onset (days)	Adverse Event (PT)	Relationship Reporter/ Manufact.	Relationship Sponsor	Outcome	Narrative link (page)
ME2125JP4-0001/52/F/ 50-100 mg/day	(b) (4) ongoing		Parkinson's Disease Aggravated	Possible	Possible	Recovering	8
ME2125JP4-0002/74/M/ 50 mg/day	07 Apr 2016/ ongoing	35	Prostate Cancer	Not related	Not related	Recovering	10
ME2125JP4-0003/81/M/ 50 mg/day	10 May 2016 / 25 May 2016	97	Sigmoid Volvulus	Not related	Not related	Recovered	12
ME2125JP4-0004/64/F/ 50 mg/day	25 May 2016 / ongoing	57	Femur Fracture (due to a fall)	Not related	Possible	Not Recovered	14
ME2125JP4-005/75/M/ 50 mg/day	26 Jun 2016 / 28 Jun 2016	40	Upper Respiratory Tract Inflammation, Pyrexia	Not related	Not related	Recovered	16
ME2125JP4-0006/77/M/ 50 mg/day	15 Jul 2016 / ongoing	176	Neuroleptic Malignant Syndrome, Renal Failure	Not related	Not related	Ongoing	17
ME2125JP4-0007/77/M/ 50 mg/day	25 Jul 2016 / 25 Jul 2016	19	Drowning	Not related	Not related	Death	20

Post Marketing Events from Europe

Safinamide was approved in Europe (EU) on February 24, 2015 and in Switzerland on November 12, 2015, and was first marketed in Germany in May 2015. It has been marketed in Germany for approx. one year, and in all other countries (Belgium, Italy, Spain, Denmark, Netherlands, Sweden, United Kingdom and Switzerland) only a few months have elapsed since it was launched. Based on this brief period it has been on the market, systematic data on the number of prescriptions is currently unavailable.

Projections of Number of Patients Receiving Safinamide based on Early Sales Data

A preliminary estimate of the number of patients who have been treated with safinamide was derived based on ex-factory sales data that are currently available on a monthly basis.

Safinamide is authorized as 50 mg and 100 mg film-coated tablets for oral administration. Treatment with safinamide is started at 50 mg per day, and this dose may be increased to 100

mg/day on the basis of therapeutic response, and individual clinical need. The Defined Daily Dose proposed by the WHO (i.e. 75 mg daily) has been used for the patient exposure calculation (PSUR final assessment report received in March 2016).

Table 3 presents, by country, the number of 50 and 100 mg blister packs of safinamide, for 30 and 100 days. The total number of milligrams sold were determined, and the total number of patient years of exposure was calculated during the period of 24 February 2015 through 31 July 2016, assuming that patients were treated chronically. This calculation estimates approx. 10490 patient-years of exposure, indicating a minimum of 10,490 patients have received treatment with a least one dose of safinamide.

Table 3 Estimation of Patients Treated with Xadago in EU Countries Based on Volume of Blister Pack Sales



(b) (4)

Spontaneously Reported-Post Marketing Serious Adverse Events

The list below (Table 4) includes all 36 post-marketing spontaneously reported cases of serious/medically important adverse events (by main reason) received by the Sponsor, that have been reported to the Drug Safety Unit at Zambon S.p.A. (Marketing Authorization Holder of Xadago in Europe) from the countries where safinamide is currently marketed (Belgium, Germany, Italy, Spain, and Switzerland); the Data Lock Point (DLP) for these cases is 31 July 2016. No cases were reported from Denmark, Netherlands, Sweden, and United Kingdom where Xadago (safinamide) is also marketed.

Four cases were reported that met with a fatal outcome (201601304DEU, 201601153DEU, 201600256DEU, 201501439COR). Two of the 4 deaths were associated with myocardial infarction or suspected myocardial infarction (201601304DEU, 201501439COR).

Table 4 Listing of Spontaneously Reported Post-Marketing Serious Adverse Events

Case Nr./Age/Sex/Dose (mg)	AE Start/ Stop	Time to onset (approx. days)	Adverse Event (PT)	Relationship: Reporter/ Manufacturer	Relationship: Sponsor	Outcome (b)	Narrative link (page)
201600931COR/71/M/50-100	04 Apr 2016/ Jun 2016	35	Acute Coronary Syndrome	Possible/Possible	Unlikely	Recovered	62
201601331CHE/ UNK/M/UNK	UNK/ UNK	UNK	Angina Pectoris	Not reported/Possible	Related	Recovered	81
201601123DEU/79/M/100	26 May 2016/ 02 Jun 2016	121	Atrial Fibrillation	Not related/Not related	Not Related	Recovered	69
201600479DEU/81/M/50-100	22 Mar 2016/ 27 Apr 2016	45	Bundle Branch Block Right Atrial Fibrillation	Related/Possible	Unlikely	Recovered	58
201601304DEU/70/F/50	04 Jul 2016/ 04 Jul 2016	132	Myocardial Infarction	Possible/Possible	Not Related	Fatal	76
201601055CHE/75/F/50	UNK / UNK	UNK	Visual Impairment Glaucoma	Not reported/Not assessable	Not Related	Unknown	66
201601311COR/53/M/50	27 Jun 2016/ 30 Jun 2016	7	Ophthalmoplegia	Not reported/Possible	Not Related	Recovered	79
201600942COR/59/M/50	04 Apr 2016/ UNK	4	Visual Acuity Reduced Glaucoma	Not reported/Possible	Unlikely	Recovered	64
201601217DEU/79/F/100	17 Jun 2016/ 30 Jun 2016	29	Visual Impairment	Related/Possible	Possible	Recovered	73

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Table 4 Listing of Spontaneously Reported Post-Marketing Serious Adverse Events (Continued)

Case Nr./Age/Sex/Dose (mg)	AE Start/ Stop	Time to onset (approx. days)	Adverse Event (PT)	Relationship: Reporter/ Manufacturer	Relationship: Sponsor	Outcome (b)	Narrative link (page)
201501151DEU/71/F/100	Aug 2015/ UNK	60	Visual Impairment	Not available/Unassessable	Possible	Not Recovered	24
201600064DEU/76/M/50	Oct 2015/ 30 Dec 2015	20	Swollen Tongue	Related/Probable	Probable	Recovered	40
201600253DEU/72/F/50	22 Feb 2016/ ongoing	UNK	Condition Aggravated	Related/Unlikely	Not Related	Ongoing	48
201601153DEU/UNK/M/UNK (a)	UNK/ UNK	UNK	Death	Not related/ Unassessable	Not Related	Fatal	72
201600256DEU/71/M/ 50-100	UNK/ UNK	120	Sudden Cardiac Death	Not related/Not related	Not Related	Fatal	50
201501421DEU/63/M/50	31 Oct 2015/ ongoing	97	Herpes Zoster	Related/Unlikely	Not related	Not Recovered	33
201501581DEU/76/M/50	30 Nov 2015/ 03 Dec 2015	7	Accidental Exposure to Product Blood Pressure Increased	Possible/Possible	Likely	Recovering	38
201501435DEU/UNK/M/UNK	UNK/ UNK	UNK	Contraindicated Drug Administered Paralysis	Not available/ Unassessable	Related	Unknown	35
201601096DEU/71/M/100	22 Mar 2016/ 11 Apr 2016	134	Freezing Phenomenon	Not related/Not related	Not Related	Resolved with sequelae	67
201501439COR/77/M/100	27 Oct 2015/ 02 Dec 2015	12	Drug Prescribing Error Silent Myocardial Infarction	Not available/Not related	Not Related	Death	36
201601136CHE/65/M/UNK	Jun 2016/ UNK	7	Fall Gait Disturbance	Possible/ Unassessable	Possible	Unknown	71
201600143DEU/UNK/M/ 100 (a)	08 Jan 2016/ UNK	60	Fall	Not related/ Unassessable	Possible	Unknown	44
201600199DEU/53/M/100	Jan 2016/ UNK	30	Fall	Not related/Unlikely	Possible	Resolved with sequelae	45
201600228DEU/65/M/50	10 Jan 2016/ UNK	30	Fall	Unassessable/Possible	Possible	Recovering	47
201600129DEU/65/F/50	16 Jan 2016/ 25 Jan 2016	1	Medication Error Dizziness	Related/Possible	Possible	Recovered	42
201600403DEU/54/F/50	22 Feb 2016/ ongoing	27	Off Label Use Dyskinesia	Related/Unassessable	Unlikely	Not resolved	57
201600289DEU/77/M/50	24 Feb 2016/ 26 Feb 2016	77	Blood Pressure Increased	Related/Possible	Likely Related	Recovered	52
201501289DEU/70/F/50	02 Sep 2015/ 09 Sep 2015	9	Hyponatremia	Possible/ Possible	Possible	Recovered	30
201501157DEU/77/M/UNK	UNK/ UNK	UNK	Mobility Decreased	Related/Unassessable	Not Related	UNK	26
201600291DEU/59/M/50	Jan 2016/ ongoing	180	Pathological Fracture	Unlikely/Unlikely	Not Related	Recovering	54

Table 4 Listing of Spontaneously Reported Post-Marketing Serious Adverse Events (Continued)

Case Nr./Age/Sex/Dose (mg)	AE Start/ Stop	Time to onset (approx. days)	Adverse Event (PT)	Relationship: Reporter/ Manufacturer	Relationship: Sponsor	Outcome (b)	Narrative link (page)
201500972DEU/77/M/50	02 Aug 2015/ UNK	3	Aphasia	Not available/ Unassessable	Likely	Recovered	23
201601245ESP/UNK/F/100mg	02 Jul 2016/ ongoing	60	Parkinsonism Hyperpyrexia Syndrome	Not related/ Unassessable	Not Related	Recovering	75
201600925DEU/58/M/100	17 Dec 2015/ UNK	UNK	Parkinson's Disease	Not related/Unlikely	Not Related	Recovered	60
201600303DEU/69/F/50	Jan 2016/ UNK	60	Device Damage	Not assessable/Not assessable	Not Assessable	Recovered with sequelae	56
201500754COR/72/F/50	07 Jun 2015/ UNK	7	Restlessness Hallucination, Visual	Related/Unlikely	Possible	Recovered	21
201501227DEU/51/F/100	Sep 2015/ 11 Oct 2015	35	Rapid Eye Movements Sleep Abnormal	Related/Possible	Possible	Recovered	28
201501345DEU/70/M/50	03 Oct 2015/ 27 Oct 2015	6	Micturition Urgency	Possible/Possible	Possible	Recovered	32

(a) 201601153DEU and 201600143DEU same subject; (b) at the time of reporting; UNK Unknown; PT Preferred Term (MedDRA Version 19.0)

The following postmarketing adverse event report of angioedema supports adding a description of angioedema in labeling.

Case number: 201600064DEU

Study Number Post marketing surveillance report (PMS)

Country of Origin: GERMANY

Product: Xadago (safinamide) 50 mg/day

Preferred Term(s): SWOLLEN TONGUE; DYSPNOEA; ORAL MUCOSAL ERYTHEMA; GINGIVAL SWELLING; RASH; RESTLESSNESS; ERYTHEMA; PRURITUS; HYPERHIDROSIS; DRY MOUTH; DYSPHONIA; APPETITE DISORDER; MALAISE

Reported Term: Swollen tongue; Dyspnea; Redness in mouth; Gum swelling; Rash body; Inner restlessness; Redness Head; Pruritus; Sweating attack; Dry mouth; Hoarseness; Appetite lost and increased appetite for sweets; Malaise

This 76-year-old male subject with Parkinson's disease since 2010 experienced medically significant serious adverse events of a swollen tongue, dyspnea, oral mucosal erythema, gingival swelling, rash, restlessness, erythema in the face, pruritus hyperhidrosis, dry mouth, dysphonia, appetite disorder and malaise.

Clinical Summary

This subject received oral Xadago (safinamide) 50 mg/day for Parkinson's disease starting at the beginning of October 2015.

In October 2015, approximately 20 days after start of Xadago, the subject developed a swollen tongue with dyspnea, redness in mouth, gingival swelling, rash on the trunk, appetite disorder with decreased appetite and increased appetite for sweets, inner restlessness, redness of face, pruritus, hyperhidrosis, dry mouth, hoarseness and malaise. No treatment information was reported. Xadago was withdrawn 2-3 days later on 26-OCT-2015 and the subject recovered fully within 4 days.

Based on the benefits of Xadago on the subject's condition, the drug was restarted in mid-NOV-2015 and at the same time, the dosage of L-dopa+benserazide was reduced to 3 times daily. However, approximately 27 days after the re-start of Xadago, the subject again developed a swollen tongue with dyspnea, redness in mouth, gingival swelling, severe hyperhidrosis, redness and pruritus on the body as well as inner restlessness and malaise. The adverse reactions were less pronounced than during the first cycle of Xadago administration. Two to three days later, Xadago was again discontinued on 28-DEC-2015 and the subject recovered within two days.

All events were reported as recovered. The subject did not report any previous history of these events.

Medical History and Concomitant Medication

The subject's relevant medical history includes Parkinson's disease since 2010.

Concomitant medications reported included L-dopa+benserazide 125 mg, 5 times daily for Parkinson's disease, fentanyl transdermal patch 200 µg / 2 days for treatment of pain, prophylactic aspirin 100 mg once daily, prednisolone 5 mg once daily, pantoprazole 20 mg once daily and DuoResp (budesonide+formoterol), as needed, for unknown indications, and Neupro transdermal patch for Parkinson's disease, which was discontinued due to hallucinations.

Reporter and Manufacturer Assessment

The reporter considered the events as related to Xadago, and the manufacturer considered the event as probably related.

Pertinent Positives and Negatives

This case is considered as serious (medically significant). Swollen tongue, gingival swelling and rash are not expected according to the current SmPC of Xadago 50 mg (version FEB-2015), whereas dyspnea, restlessness, hyperhidrosis, erythema, pruritus, dry mouth, dysphonia, malaise as well as decreased and increased appetite, represent expected undesirable effects. In consideration of the close temporal relationship between initiation of Xadago and onset of the events, and of a positive de-challenge and re-challenge, the Sponsor considers the relationship of Xadago to these events as probable.

Reviewer Comment

- It is not clear precisely what this adverse reaction experience represents as a syndrome for all these events. However, the syndrome described might suggest some type of “hypersensitivity” reaction/syndrome, although “hypersensitivity” syndrome can be a vague, “catch-all” description. At the very least, the swollen tongue and gingival swelling seem to suggest the occurrence of a serious medical adverse reaction of angioedema. The dyspnea could potentially have been related to laryngeal edema. The adverse reaction does not seem to have been serious enough to require a visit to an emergency room and thus does not likely seem to be anaphylaxis. Angioedema (allergic type) caused by food, insect bites, and drugs (as opposed to non-allergic angioedema caused by drugs inhibiting the renin-angiotensin system, e.g., angiotensin converting enzyme inhibitors or angiotensin receptor blockers) is also frequently accompanied by urticaria. Although urticaria were not explicitly described in this patient, the patient did have pruritus and perhaps may have had urticaria which may not have been specified in the report. Angioedema from a drug can occur within days to weeks and thus the onset of swollen tongue and gingiva seems possible having developed within a few weeks (i.e., 20 days) after starting safinamide treatment.
- The resolution of all these adverse clinical features within a few days after stopping safinamide is consistent with a positive dechallenge “response.” Of more importance perhaps is the suggestion of a positive rechallenge “response” whereby it appears that the same clinical signs and symptoms which developed 20 days after starting safinamide recurred 27 days after restarting safinamide. After this recurrence of the host of these adverse reactions, they resolved after stopping safinamide (i.e., within 2 days) for a second time (i.e., positive dechallenge).
- Although the past medical history does not specify any history of a pulmonary problem, it would seem that the patient may have had asthma and chronic obstructive pulmonary disease (COPD) because the patient was taking budesonide-formoterol, which is used for that indication and also prednisolone, perhaps for asthma/COPD. These drugs do not seem to have a risk for the adverse reactions experienced by this patient.
- The patient was also taking concomitant pantoprazole. The labeling for pantoprazole included a statement in the of Adverse Reaction section which describes allergic reaction, facial edema, pruritus, urticaria, and rash in adult and pediatric patients for relatively low incidence adverse reactions (without description relative to the incidence in placebo patients). Thus, it is possible this drug could have caused the adverse reactions described in this patient but there is no mention of this drug being started or stopped relative to these adverse reactions. Consequently, there is no suggestion of a positive dechallenge or rechallenge response with pantoprazole as seemed apparent with respect to safinamide.
- The details provided do not seem to fit the syndrome of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS).
- My previous detailed review of the safety of safinamide in the clinical development program (3/27/16) did not find any serious cases of similar clinical manifestations as experienced by this patient. Nor were there any adverse events (neither serious nor non-serious) described as angioedema. However, there were 2 patients who had an adverse event described as facial edema. Each of these patients was taking 100 mg safinamide daily and both patients were in

an extension trial (i.e., Study 18 and Study Motion Extension). I did not find any detailed narrative descriptions of these events both of which were not serious. However, I suspect the possibility that these events in these 2 patients may have been related to angioedema.

- I am unable to conclude about a single syndrome description of all of these adverse reactions in this patient short of “hypersensitivity.” However, I do think that the descriptions of tongue and gingival swelling seem to represent angioedema at the very least. I cannot conclude definitively that the adverse reactions experienced by this patient developed because of safinamide. But I do think that the temporal relationship of these adverse reactions starting within a few weeks after starting safinamide, resolving soon after safinamide was stopped (on two occasions), and seeming to recur with a rechallenge with safinamide could possibly suggest that safinamide was causal for these adverse reactions developing. Both the reporter and the sponsor consider that these adverse reactions were probably caused by safinamide. Although I think that safinamide might be a probable cause for these adverse reactions, at the very least, I think that it is clearly possible that safinamide played a causal role. The potentially serious nature of these adverse reactions, particularly if they were angioedema, make me think that it would be important to describe hypersensitivity in the safinamide label and to contraindicate safinamide in patients experiencing hypersensitivity to safinamide.

Post marketing Experience

In addition to the adverse experiences reported during clinical testing of XADAGO, the following adverse experience has been reported worldwide in patients receiving XADAGO post-approval.

This adverse experience, which has not been listed above and for which data are insufficient to support an estimate of its incidence or to establish causation, is angioedema.

Sponsor’s Conclusions and Recommendations

This safety update includes all SAEs reported from studies in Japan, where approx. 270 subjects have received at least one dose of safinamide. The maximum exposure to safinamide in these patients is 6 months. Ten SAEs were reported in Parkinson’s disease patients in the Japanese studies; three cases are from the ongoing double-blind study (Study ME2125-3), that currently has 132 patients randomized (i.e., approx. 85 treated with safinamide), and seven cases are from an open-label, long-term treatment study (Study ME2125-4; safinamide 50mg or 100mg), that currently has 113 patients randomized.

There was one death in the Japanese studies that occurred in a patient on safinamide; the death was due to drowning. No precipitating factors were identified that suggested a relationship to treatment with safinamide.

Four subjects experienced falls that led to hospitalization; the blind has not been broken in 3 of these patients whereas the 4th patient received safinamide 50mg in the open-label safety study. No meaningful pattern of relationship with safinamide was noted for any of the other events. Thirty-six post-marketing spontaneously reported cases of serious/medically important adverse events (by main reason) were reported to the Manufacturer (Drug Safety Unit at Zambon S.p.A; Marketing Authorization Holder of Xadago in Europe) up to 31 July 2016. It is estimated that a minimum of 10,490 patients have received treatment with safinamide

Four cases were reported that met with a **fatal outcome**. All four deaths (3 myocardial infarctions, or suspected MI, and one where the cause is not known), appear to be unrelated to treatment with Xadago.

Based on the data presented in this safety update, and previously submitted in the ISS, the contraindications, precautions and warnings in the proposed package insert appear to be adequate to capture the risks associated with Xadago treatment.

Reviewer Comment

- My review of the sponsor's Safety Update did not suggest any, new, significant adverse reactions that would change my impression of the safety profile for safinamide nor affect our ability to approve safinamide as a safe and effective drug and my recommendation to approve safinamide. The overall safety profile for safinamide is similar to the safety profile which I reviewed previously and was characterized previously in my review.
- I am not convinced that the one postmarket case (Case Number: 201600064DEU) of possibly angioedema and some type of hypersensitivity syndrome was definitely caused by safinamide. However, I do think that the specific circumstances associated with this case suggests that safinamide probably caused the hypersensitivity reaction and a recurrence of a similar reaction upon rechallenge with safinamide. We would need to watch for similar post marketing cases in the future as the use of safinamide increases globally. I do recommend that we describe this hypersensitivity reaction in the label and recommend that we consider contraindicating safinamide in patients who appear to experience a hypersensitivity reaction to safinamide.

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/s/

LEONARD P KAPCALA

03/17/2017

Dave, my review is ready for your signature. Thanx.

GERALD D PODSKALNY

03/19/2017

Deputy Office Director Decisional Memo

Date	(electronic stamp)
From	Robert Temple, MD
Subject	Deputy Division Director Summary Review
NDA/BLA #	207,145
Applicant Name	Newron Pharmaceuticals S.p.A.
Date of Submission	Dec 29, 2014
PDUFA Goal Date	March 29, 2016
Proprietary Name / Established (USAN) Name	Xadago /safinamide
Dosage Forms / Strength	Tablet 50 mg, 100 mg
Proposed Indication(s)	1. Add-on therapy to a single dopamine agonist at a stable dose in early stage, (b) (4) Parkinson's disease (PD) patients. 2. Add-on therapy to (b) (4) L-dopa alone or in combination with other PD drugs in mid to late-stage (b) (4) PD patients.
Action/Recommended Action for NME:	Complete Response

Material Reviewed/Consulted	Names of discipline reviewers
OND Action Package, including:	
Deputy Division Director Review	Eric Bastings
Regulatory Health Project Manager	Stacy Metz
Medical Officer Review	Leonard Kapcala
Statistical Review	Xiangmin Zhang
Pharmacology Toxicology Review	LuAnn McKinney
Clinical Pharmacology Review	Histrina Dimova
OPDP	Aline Moukhtara
OSI	Antoine El-Hage
CDTL Review	Gerald D. Podskalny
OSE/DMEPA	Justine Harris
OSE/DRISK	Erin Hachey
OPQ/Drug Substance	Sharon Kelly
OPQ/Drug Product	Sherita McLamore
OPQ/Process/Microbiology	Mark Johnson
OPQ/Facility	Tracie Sharp and Franck Wackes
OPQ/Biopharmaceutics	Okpo Eradiri
OPQ/Project/Business Process Manager	Dahlia A. Woody
OPQ/Application Technical Lead	Martha R. Heimann
OPQ/ Environmental Assessment	James Laurenson
Ophthalmology	Wiley Chambers
Controlled Substance Staff	Alicja Lerner
QT Study Review	Huifang Chen

OND=Office of New Drugs
 OSE= Office of Surveillance and Epidemiology
 DMEPA=Division of Medication Error Prevention and Analysis
 OSI=Office of Scientific Investigations
 DRISK=Division of Risk Management
 CDTL=Cross-Discipline Team Leader
 OPQ=Office of Pharmaceutical Quality

I. Background

Safinamide is a selective monoamine oxidase Type B (MAO-B) inhibitor, pharmacologically similar to selegiline and rasagiline. These drugs are used in patients with Parkinson's Disease (PD) to improve movement. They block catabolism (breakdown) of dopamine, increasing dopamine levels and dopamine activity in the brain. There were two uses proposed by the applicant: 1) use as add-on to a single dopamine agonist (b) (4) in early stage PD, and 2) use in combination with (b) (4) levodopa, alone or in combination with other PD drugs, in mid-to-late-stage (b) (4) PD patients. For the latter proposed use the aim is to increase the total daily "ON" time, i.e., total "ON" time without dyskinesia plus on time with non-troublesome dyskinesia over the 18 hour diary recording period, and to reduce total "OFF" time, periods in which PD patients revert to the immobility characteristic of the disease. In the early PD use, effects were measured using the Unified Parkinson's Disease Rating Scale (UPDRS), items II (Activities of Daily Living) and III (Motor Examination).

As described fully in reviews by Drs. Kapcala, Zhang, Podskalny, and Bastings, the 3 studies intended to support early use did not really do so, and all recommend that this claim not be approved. All, however, support the effectiveness of add-on treatment for patients with mid- to late-stage PD on (b) (4) of levodopa.

There are no product quality or clinical microbiology issues and these areas will not be discussed. PD is extremely rare in the pediatric population and pediatric studies are not feasible. A pediatric waiver will therefore be issued.

Not critical at this point, but of interest, and described in detail by Dr. Podskalny, the review of NDA 207145 was challenging even after the applicant's response to the initial refusal to file letter of July 28, 2014 and needed to overcome missing or unusable data, leading to many requests for data during review. A metabolite of safinamide (NW-1689) inhibits BCRP (Breast Cancer Resistance Protein), which metabolizes many potentially toxic drugs (see Safety Section IV below).

II. Clinical Pharmacology

As discussed by Dr. Bastings, safinamide is metabolized primarily by hepatic non-microsomal enzymes, cytosolic amidates (e.g., MAO-A) and only minimally by cytochrome P450 enzymes, with the multiple metabolic pathways leaving little potential for important drug-drug interactions. The > 95% metabolic transformation to non-active metabolites also obviates the need for adjustment for renal impairment.

III. Clinical/Statistical

A. Early Disease – Use as an add-on to a dopamine agonist.

All reviewers (Kapcala, Podskalny, Zhang) and Dr. Bastings agree that the 3 studies do not provide substantial evidence of effectiveness, but there are clearly some "trends," and Dr. Bastings has noted and assessed these. All 3 studies comparing safinamide to placebo in early PD used the UPDRS III scale as the primary endpoint, comparing average score as the endpoint in 2 studies and the rate of 30% improvement in one study. In the studies safinamide was added to a single dopamine agonist (Studies 015 and 27918 and many patients in Study 009) or to no other therapy (some patients in Study 009). The studies were of 12 (Study 009) or 24 (Studies 015, 27918) weeks in duration. All 3 studies compared 2 doses to placebo. Study 27918 evaluated the same 2 doses as the mid-to-late disease studies, 50 and 100 mg, and did not show statistically significant improvement compared to placebo on UPDRS Section III, although the p-value of 0.07 at the 100 mg dose was close to significant (p = 0.2 at the 50 mg dose). Study 015 studied doses 100 mg 200 mg, showing essentially no effect (p = 0.65) at the higher dose, blocking further statistical analysis (but the lower dose suggested effectiveness, with a

nominal $p = 0.04$). Thus both studies provided some suggestion of an effect, but not convincing evidence. The first study, 009, used mg/kg dosing, averaging 39 and 78 mg/day, which would still be informative, had the study been successful, and its primary endpoint was the rate of 30% reduction (improvement) in UPDRS Part III, called a “response,” which allowed calculation of responder rates. The responder rate evaluation (not used previously in this condition) was statistically significant with 21/56 on the higher dose vs 12/56 on placebo, i.e., 37.5% vs 21.4%, ($p = 0.006$). The mean change in UPDRS score (the endpoint measure used in the other 2 studies), however, was not statistically significant; $p = 0.19$.

Dr. Bastings thus finds Study 009 at least somewhat supportive of effectiveness, but on the responder rate endpoint, not previously used and of at least debatable clinical meaning. As noted, analysis of UPDRS scores was not close to significant in Study 009 using the planned Kruskal-Wallis test, although a later ANCOVA analysis did give statistical significance. The fact that the two substantially larger studies, 015 and 27918, did not really confirm a suggested effect, weakens the 009 finding, although, again, they were not wholly negative. The overall data led him to conclude that there was not sufficient evidence to support approval of safinamide in the early PD population, and I concur. The full data are considered in Dr. Bastings’s review, and they are summarized in Table 1 below, taken from various reviews.

Table I - Early Disease

Study	Low Dose	High Dose	Placebo
Study 009 (Podskalny, p 30)	n = 55 0.5 mg/kg	n = 56 1.0 mg/kg	n = 56
Baseline UPDRS III	16.4	16.5	17.3
Final Visit (mean)	13.8	13.2	16.7
Change from baseline	- 2.6	- 3.3	- 0.6
p-value		0.19	
Study 015 (Podskalny, p 32)	n = 86 100 mg/d	n = 81 200 mg/d	n = 87
Baseline UPDRS III	22.0	19.3	20.7
Final Visit (mean)	16.3	15.6	17.1
Change from baseline	- 6.0	- 3.9	- 3.6
p - value	0.04	0.65	
MOTION Study 27918 (Kapcala, p 56)	n = 227 50 mg/d	n = 227 100 mg/d	n = 225
Baseline UPDRS III	21.0	18.9	19.8
Week 24	19.0	16.9	18.0
Change from baseline	1.60	-1.98	-0.95
Change vs placebo	-0.65	-1.04	
p-value	0.259	0.073	

B. Late Disease – Mid-to-Late-State PD as add-on to L-dopa

This claim is supported by 2 studies of substantial size, studies 016 and 27919 (SETTLE), with 669 and 549 patients, respectively. Both studies utilized a 10-day screening period to optimize background PD treatments to minimize motor symptoms, followed by a 4-week levodopa stabilization phase. Patients were then randomized to 50 or 100 mg of safinamide or placebo (Study 016), or to safinamide 100 mg or to placebo (SETTLE), and followed for 24 weeks. The primary endpoint was “ON” time without troublesome dyskinesia (referred to later in this memo as “ON” time) measured in an 18 hour diary, the Parkinson’s Disease Patient Diary. Secondary endpoints included total daily OFF time and UPDRS III. UPDRS II (activities of daily living) was also examined.

Results of the 2 studies are shown in Table 2. There was a strongly significant difference of about 0.5 (Study 016) to 1 (Study 27919) hour in ON time and a similar increase in OFF time. The UPDRS III was also improved. There was no suggestion of a greater response of ON time with the higher dose but a small indication of increased response of UPDRS III. Whether to include the higher dose as a possibility in labeling will depend on the safety consequences.

Table 2

Study 016	Low Dose n = 217 50 mg	High Dose n = 216 100mg	Plbo n = 212
Baseline ON	9.41	9.66	9.29
Final ON	10.88	11.01	10.32
Change in ON	1.37	1.37	0.97
LS Difference from placebo	0.50	0.53	
p-value	0.0356	0.0238	
LS Diff from placebo in OFF	-0.55	-0.57	
p-value	0.0049	0.0037	
LS Difference from placebo in UPDRS III	-1.75	-2.48	
p-value	0.0212	0.0011	

SETTLE Study 27919	Safinamide n = 268 50-100 mg	Placebo n = 273
Baseline ON	9.30	9.09
Final ON	10.72	9.63
Change in ON	1.44	0.53
LS Difference from placebo in ON	0.99	
p-value	< 0.001	
Change from Baseline in OFF	-1.58	-0.52
LS Difference from placebo OFF	-1.06	
p-value	<0.001	
UPDRS III		
Change from baseline	-3.50	-2.05
LS Difference from placebo	-1.70	
p-value	<0.005	

The time course of improvement was similar in both studies (figures 1, 2 from Dr. Zhang's review). There was no suggestion of an earlier or larger response at the higher dose.

Figure 1. Study 016 mean (\pm standard error) of change from Baseline in total daily "on" time by week and treatment

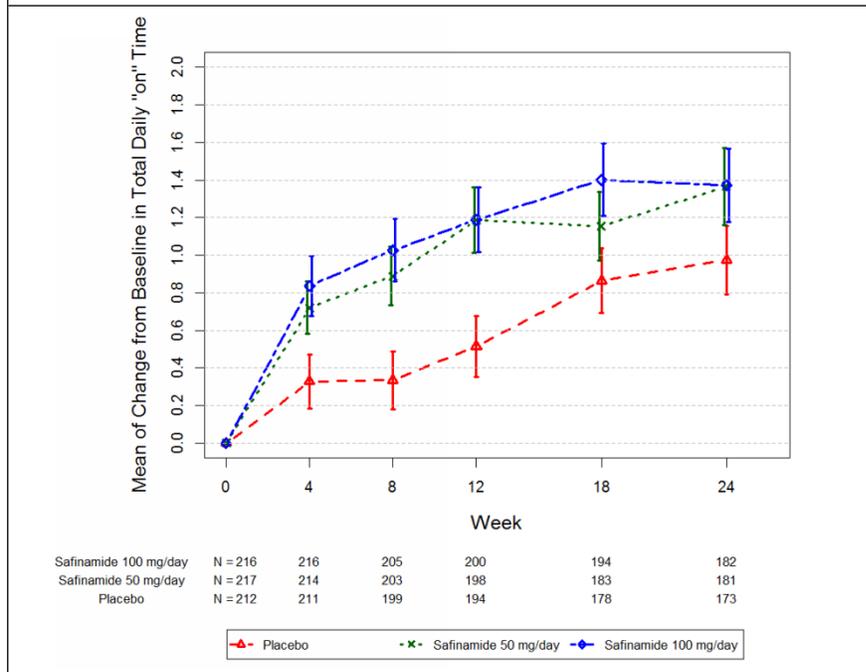
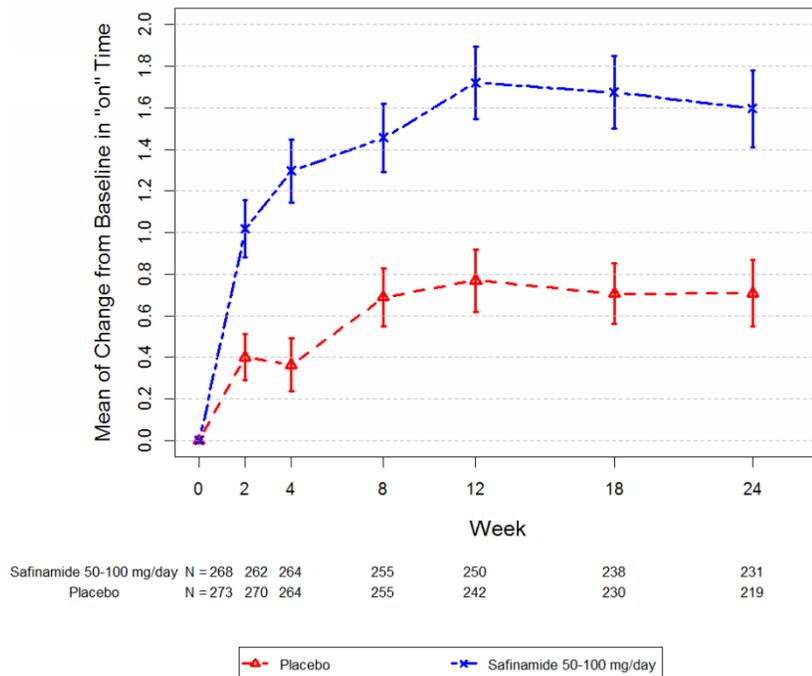


Figure 2. Study 27919 mean (\pm standard error) of change from Baseline in total daily "on" time by week and treatment



The cumulative distribution curves for Study 016 show the roughly half-hour difference between treatments (figure 3) with little sign of a subgroup with a larger response. The curve for Study 27919 shows the somewhat larger mean response in that study with perhaps a suggestion of some stronger responders.

Figure 3. Study 016 empirical cumulative distribution functions for the change from Baseline to Week 24 in total daily “on” time

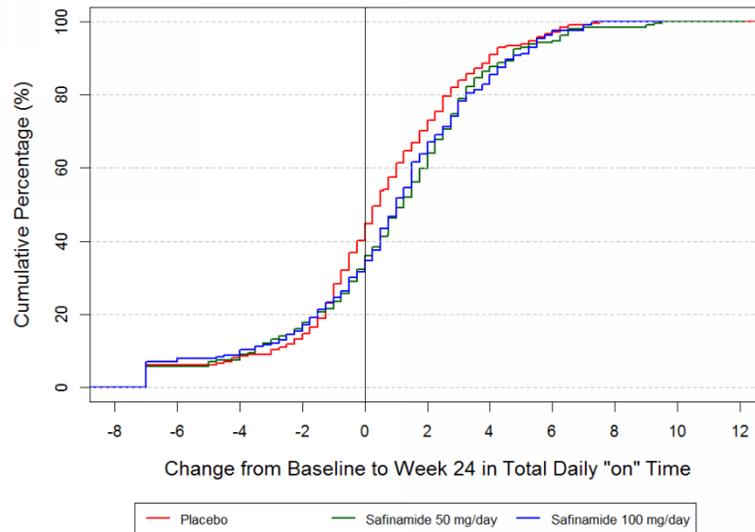
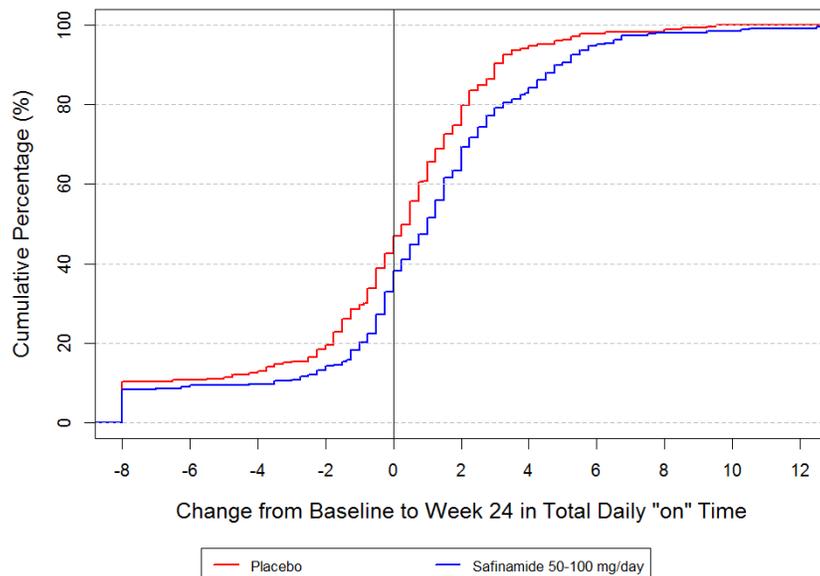


Figure 4. Study 27919 empirical cumulative distribution functions for the change from Baseline to Week 24 in total daily "on" time



The study populations in Study 016 and SETTLE were largely outside the United States (some N. America in SETTLE), were primarily Asian in Study 016, about 80% and about 67% Caucasian in SETTLE. About 35% of patients were over 65 in the 2 studies and about 35% were female. Analysis of results by age, race, gender, and geographic region by Dr. Zhang (p 24-30) did not find persuasive evidence of subgroup differences.

IV. Safety

The clinical safety database is well-described by Drs. Bastings, Podskalny, and Kapcala, and I have little to add. There was adequate patient exposure (1949 with some exposure, 744 in open label studies for ≥ 12 months and almost 500 patients for > 2 years. In the controlled trials of late PD, discontinuations for adverse events were about 5% on drug and placebo and death rates were low and similar, 5/721 on safinamide and 3/497 on placebo. Open-label extensions did not identify unexpected deaths.

Serious adverse effects in controlled trials were largely balanced in safinamide and placebo groups. The adverse reaction most clearly increased in rate on safinamide in controlled trials was dyskinesia (21% and 17% on 50 mg and 100 mg respectively, vs 9% on placebo. Falls, nausea and insomnia were slightly more common than placebo on 100 mg but not on 50 mg.

Retinal degeneration (atrophy of the outer nuclear layer) was observed in toxicology studies of up to 2-years' duration in rats and in a 2-year study in mice, but not in monkeys. In the 2-year study in rats, retinal scarring and cataracts were also observed. These findings led to close ophthalmological monitoring of patients in clinical trials. Although no signal of eye damage was observed and efforts were made to mask the reader of Optical Coherence Tomography (OCT) and electroretinography (ERG), the data, as assessed by Dr. Chambers, our ophthalmology consult, are limited by missing data and limited numbers of examinations. The conclusion is that the available data neither rule out nor confirm the retinal degeneration observed in non-clinical studies. It is also noted that use of other PD medications, retinal disease associated with PD, and lack of good baseline data all confound interpretation. The animal data will be described in labeling in Warnings and Precautions, with a recommendation to monitor patients who have any history of retinal disease.

A metabolite of safinamide (NW 1689) inhibits BCRP (Breast Cancer Resistance Protein), an intestinal protein metabolizer of many potentially toxic (if concentrations were materially increased) drugs, including methotrexate, mitoxantrone, imatinib, and others. The IC₅₀ of NW 1689 is 3.7 μ M, a concentration achieved in PD patients given 100 mg/day. There will be, as suggested by the Office of Clinical Pharmacology, a post-marketing requirement (PMR) for the applicant to complete an interaction study, evaluating the effect of NW 1639 on blood levels of BCRP metabolized drugs. Labeling will note the need to monitor patients receiving safinamide with these drugs.

Safinamide causes embryofetal developmental toxicity when given to pregnant rats and rabbits. In both species, toxicity was more severe when safinamide was given with levodopa/carbidopa; in rabbits, unique fetal abnormalities were observed with the combination. Labeling will caution against use in pregnancy, obviously very unusual in patients with PD.

V. Advisory Committee Meeting

Safinamide is the third selective MAO-B inhibitor approved in the US (after rasagiline and selegiline) for an identical population. No safety or effectiveness concerns needed advisory committee input.

VI. Drug Abuse Potential

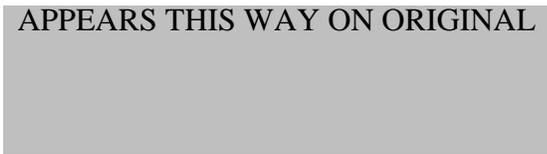
The Controlled Substance Staff has important reservations about the non-clinical studies intended to show absence of stimulatory or sedative effects; specifically, results of a comparison with midazolam have not been submitted. The lack of those data alone would keep us from making a scheduling determination, which is a basis for a complete response. CSS also has concluded, based on observed clinical results, that a human abuse potential study is needed, a further basis for a complete response.

VII. Conclusion/Risk-Benefit/Action

The applicant has demonstrated the effectiveness of safinamide in increasing “ON” time in patients with mid-to-late-stage PD on levodopa in two well-controlled studies using 50 or 100 mg/day. There was also a statistically significant decrease in “OFF” time and improvement in the UPDRS Part III score (assessing motor symptoms). The effect was generally similar to previously approved selective monoamine oxidase type B inhibitors and adverse effects were also similar with the most frequent being dyskinesia. Labeling will also warn of typical MAO-B inhibitor effects (hypertension, serotonin syndrome, abrupt sleepiness, impulse control problems, and compulsive behavior). There is only weak evidence that the 100 mg dose is better than 50 mg but there was a numerically greater effect of the higher dose on UPDRS Part III. As noted above, non-clinical data have raised a concern about retinal effects, but human data did not confirm the concern. It will be noted in labeling.

As described by Dr. Bastings, the Controlled Substance Staff has recommended a complete response (CR) because abuse potential has not been adequately assessed, and a CR is the action that will be taken.

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/s/

ROBERT TEMPLE
03/28/2016

Clinical Review
Leonard P. Kapcala, M.D.
NDA 207145 Safinamide (XADAGO)
Safinamide (XADAGO)

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	207145
Priority or Standard	Standard
Submit Date(s)	12/26/14
Received Date(s)	12/29/14
PDUFA Goal Date	3/29/16 (Including 3 Month Extension)
Division / Office	DNP/ODE I
Reviewer Name(s)	Leonard P. Kapcala, M.D.
Review Completion Date	1/11/16
Established Name	Safinamide
(Proposed) Trade Name	XADAGO
Therapeutic Class	Monoamine Oxidase Inhibitor B
Applicant	Newron
Formulation(s)	Tablet
Dosing Regimen	Once daily orally
Indication(s)	Treatment of early and mid-to-late stage Parkinson's disease (PD)
Intended Population(s)	Early stage, (b) (4) PD patients receiving dopamine agonist monotherapy AND Mid-to-late-stage (b) (4) PD patients receiving L-dopa alone, or in combination with other PD medications

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Based upon my review of NDA 207145, I recommend approval of XADAGO (safinamide), a reversible, relatively selective MAO-B inhibitor, for adjunctive treatment of Parkinson's disease patients experiencing "off" episodes while receiving concomitant levodopa with or without other dopaminergic medications.

1.2 Risk Benefit Assessment

Two phase 3 pivotal trials (Studies 16 and SETTLE) demonstrated efficacy of 50 mg and 100 mg safinamide (XADAGO) daily for increasing "ON" time without troublesome dyskinesia and decreasing "OFF" time in patients with late/advanced stage Parkinson's disease (LSPD; patients experiencing "OFF" episodes while on concomitant levodopa with or without other dopaminergic medications). Detailed evidence of safinamide efficacy in this population is presented in this review. In brief summary, the treatment difference (safinamide - placebo) for the primary efficacy endpoint (change from baseline in "ON" without troublesome dyskinesia) ranged between 0.5-1 hour. This treatment difference benefit was 0.5 hour for both doses (50 mg and 100 mg) in one pivotal trial (Study 16) suggesting no dose-related effect, and 1.0 hour for another pivotal trial (Study SETTLE). The magnitude of the safinamide treatment difference for decreasing "OFF" time (change from baseline as important secondary efficacy endpoint) in each trial was similar to the respective magnitude of the safinamide treatment difference for increasing "ON" without troublesome dyskinesia. This safinamide-related therapeutic benefit of increasing "ON" without troublesome dyskinesia and of decreasing "OFF" time was relatively similar to the range for rasagiline/Azilect (0.8 – 1 hour), a recently approved MAO-B inhibitor. However, the safinamide benefit was somewhat less than that for a single dose (2.5 mg daily) of Zydys selegiline/Zelapar (~ 1.6 hours), another more recently approved MAO-B inhibitor. It is not possible to compare the therapeutic benefit of safinamide to swallowed selegiline (i.e., Eldepryl), the first MAO-B inhibitor approved by the Agency in 1996, for these key efficacy endpoints because swallowed selegiline results for these endpoints are not known. Furthermore, because my summary of efficacy results for safinamide compared to these other MAO-B inhibitors (e.g., rasagiline, Zydys selegiline) are across study comparisons, conclusions about comparative efficacy should not be drawn.

Overall, the safety profile of safinamide did suggest any unique safety concerns compared to those shown by other dopaminergic drugs for Parkinson's disease and particularly other relatively selective MAO-B inhibitors. The most prominent safety signal for the LSPD population was for safinamide-induced dyskinesia. Other most common treatment-emergent adverse events (TEAEs) caused by safinamide are hypertension/increased blood pressure, blood glucose increased/hyperglycemia, fall, contusion, nausea, insomnia, chest pain, and eosinophil

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count increased. Safinamide treatment was also associated with other Parkinson's disease class adverse reactions including sleep attacks/sudden onset of sleep, hypotension/orthostatic hypotension, hallucinations/psychotic behavior, and impulsive/compulsive behavior. There were also rare cases of hypertensive crisis associated with safinamide treatment. The safety profile of ESPD patients treated with safinamide did not suggest any additional safety/toxicity issues that had not be observed in the LSPD population during safinamide treatment, There was no conclusive evidence of ocular toxicity from safinamide in ESPD and LSPD.

Although safinamide demonstrated a relatively small, but distinct increase in tyramine sensitivity for increasing blood pressure at the highest recommended dose (100 mg), this increased sensitivity was similar to the increased tyramine sensitivity of recommended dosing of rasagiline and somewhat less than the increased tyramine sensitivity of recommended dosing of swallowed selegiline. The label should describe the potential for significant blood pressure increases associated particularly with high tyramine ingestion

In summary, I believe that the data provided in the NDA show that safinamide (at 50 mg and 100 mg daily doses) can produce reasonable efficacy in LSPD and that this efficacy is relatively similar to that of other drugs approved for advanced Parkinson's disease (including other relatively selective MAO-B inhibitors). I also believe that the safety profile of safinamide in Parkinson's disease (especially LSPD) is acceptable and not associated with any safety/toxicity risks that are unique to safinamide nor notably greater for safinamide than for other drugs approved for LSPD. Considering these assessments, I believe that the therapeutic benefits of safinamide outweighs the safety/toxicity risks of safinamide and therefore supports a reasonably adequate assessment of therapeutic benefit relative to risk to support the approval of safinamide for LSPD.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

There are no recommendations for clinical postmarketing studies.

1.4 Recommendations for Postmarket Requirements and Commitments

Although I do not recommend Postmarketing Requirements or Commitments, based upon my clinical review of this NDA, I support the recommendation of the Office of Clinical Pharmacology for a Postmarketing Requirement (PMR) to conduct a clinical study to characterize drug-drug interaction of safinamide and BCRP substrates in healthy volunteers

2 Introduction and Regulatory Background

2.1 Product Information (Sponsor Summary)

Saffinamide, an alpha-aminoamide derivative is structurally unrelated to any other drug for treatment of Parkinson's disease (PD), but is related to milacemide, a glycine prodrug. Saffinamide acts through multiple mechanisms of action: it state-dependently inhibits voltage-gated sodium channels (IC₅₀:1.6-4.9 μM for different subtypes), and at higher concentrations it inhibits calcium channels. The expected physiological effect is the modulation of the hyperactive neurons and the consequent regulation of the neurotransmitter release: saffinamide reduces the stimulated release of glutamate (~0.6 μM) without affecting basal glutamate levels. Saffinamide is also a reversible and selective Monoamine Oxidase B (MAO-B) inhibitor (IC₅₀ 79-98nM: >1000-fold selective over MAO-A). It also binds at the WIN 35,428 site of the dopamine transporter (DAT) with IC₅₀ of 8.8 μM and displaces the serotonin transporter (SERT) ligand citalopram from its binding with IC₅₀ of 5.6 μM. leading to dopamine and the serotonin uptake inhibition in brain synaptosomes with IC₅₀s of 12.5 and 21 μM, respectively.

Saffinamide readily enters the brain, and in animal models of PD has shown both dopaminergic benefits (increased brain dopamine content; extended efficacy of a given dose of L-dopa on motor symptoms) and non-dopaminergic effects (reduced L-dopa induced dyskinesia) associated with plasma saffinamide levels corresponding to therapeutic doses in clinical trials. In addition, saffinamide has shown neuroprotective activity in preclinical models of PD and other CNS diseases, which is thought to result from non-dopaminergic mechanisms due to the partial inhibition of voltage-gated sodium channels and consequent normalization of excessive glutamate release.

The initial non-clinical and clinical programs were performed by the Sponsor (Newron). In 2006 Merck-Serono acquired the exclusive worldwide rights to further develop, manufacture and commercialize saffinamide. In October 2011, Merck-Serono announced their decision to discontinue the co-development agreement with Newron. Newron regained the full rights to saffinamide from Merck-Serono in April 2012.

The clinical development program for saffinamide aimed to demonstrate that saffinamide is effective and safe for treating patients with early stage Parkinson's disease (**ESPD** = patients taking a dopaminergic agonist but not experiencing motor fluctuations) and with late/advanced stage Parkinson's disease (**LSPD** = patients taking a dopaminergic agonist and levodopa and experiencing motor fluctuations).

References to early stage Parkinson's disease and ESPD and advanced stage Parkinson's disease and LSPD are used interchangeably throughout out this review.

2.2 Currently Available Treatments for Proposed Indications

Drugs approved in the U.S. for treating patients with ESPD/early Parkinson's disease include immediate and extended release formulations of levodopa/carbidopa, ropinirole, ropinirole XL, pramipexole, pramipexole XL, rotigotine, rasagiline, and amantadine. Drugs approved in the U.S. for treating patients with LSPD/advanced Parkinson's disease include levodopa/carbidopa (oral formulations and intestinal gel), ropinirole, ropinirole XL, pramipexole, pramipexole XL, rotigotine, rasagiline, selegiline, Zydys selegiline, apomorphine, entacapone, tolcapone, and amantadine.

2.3 Availability of Proposed Active Ingredient in the United States

Safinamide is new molecular entity (NME), thus is not approved for use in the U.S.

2.4 Important Safety Issues With Consideration to Related Drugs

The following adverse reactions are considered class safety issues for drugs that increase central dopaminergic tone : somnolence/sleep attacks/sudden onset of sleep, hypotension/orthostatic hypotension, impulse control disorders, dyskinesia, psychotic behavior, hallucinations, and withdrawal-emergent hyperpyrexia and confusion. Specific safety issues of concern for a relatively specific monoamine oxidase inhibitor B (MAO-B), such as hypertension/increased blood pressure and serious increases in blood pressure (e.g., hypertensive crisis/urgency/emergency) from exposure to high dietary tyramine or certain sympathomimetic amines. High dosing of a “selective” MAO-B inhibitor above the recommended dosing is associated with loss of selective MAO-B inhibition and increasing significant inhibition of MAO-A that increases the risk for serious/severe hypertensive adverse reactions.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Two meetings with FDA were held in 2013 to discuss Pre-NDA issues. The sponsor met with the Division of Neurological Products (DNP) on 16 September 2013 to discuss nonclinical, clinical pharmacology, and clinical issues. Subsequently there were additional submissions, e-mail correspondence, and a teleconference to clarify issues related to plans for the Integrated Summaries of the NDA.

DNP recommended that safety analyses of all studies (9, 15,17, 27918 [MOTION], 27938 MOTION EXT, 16, 18, and 27919 [SETTLE]) should be presented using “targeted” doses, as well as “All” doses. In addition, pooled analyses should be performed considering each of the following studies as a single trial: 015/017, 27918 (MOTION)/ 27938 (MOTION EXT.), and 016/018. The Division also asked for pooled analyses of Studies 015 and 27918 (MOTION), and 016 and 27919 (SETTLE). Notably, the Division indicated that Studies 009 and 024 should be excluded from the pooled safety analyses. The Division agreed that analyses based on modal dose and pooling of the 150-200 mg/day dose in the “All” safinamide grouping were not

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required. Analyses for “persistent” AEs (i.e., those continuing from the titration period into the maintenance period and lasting for >7 days in the maintenance period) will be limited to Studies 15 and 27919 (SETTLE), as these are the only studies that used dose titration.

DNP recommended that safety analyses be limited to the following subgroups: North America vs non-North America, North America vs Western Europe vs all other regions, males vs females, patients ≥ 65 years of age vs <65 years, patients on a dopamine (DA) agonist vs not taking a DA-agonist, patients on blood pressure (BP) lowering drugs vs. not taking BP lowering drugs, and Caucasian vs Asian, as well as patients of any race where they accounted for >5% of patients. The Division requested that the results for each of the subgroup analyses be presented in the same table, if possible.

The Division agreed that narratives be provided for patients who experienced serious adverse events (SAEs), discontinued from the study due to AEs (ADOs), or experienced “AEs of special interest” that required therapeutic intervention. The Division specified certain categories of information that must be presented in each narrative. The Division requested that analyses be performed for all clinical laboratory data and vital signs (e.g., orthostatic vital signs in accordance with “DNP Recommended Shells for Vital Signs Analyses”) for individual studies and the pooled studies using the Division’s new recommended threshold for markedly abnormal values. It was agreed that these analyses be presented in the ISS only, and would not require updating of previously issued clinical study reports that used cut-off values that had been presented in the protocols and previously agreed upon with IRBs and Health Authorities, including FDA. The Division also agreed that outlier analyses for laboratory analytes, vital signs, and ECG be analyzed from a “time perspective,” comparing data from a 4-week initial period for “titration” vs the subsequent “maintenance” period.

The safinamide NDA (# 207,145) was submitted to the FDA on 29 May 2014. On 28 July, a Refusal to File (RTF) letter was received that indicated that organization and navigation issues needed to be improved to allow an efficient review of the submission. The specific requests involved the sponsor ensuring that appendices were named logically to describe contents, as well as including a comprehensive table of contents for all tables produced for the Integrated Summary of Safety (ISS) and Integrated Summary of Efficacy (ISE), and adding the page numbers to indicate the location of each table. The Division also requested that the order of the tables should be concordant with the ISE,ISS, and Statistical Analysis Plan (SAP) table of contents and the actual order of tables in the PDFs.

The Sponsor submitted a Meeting Request and Briefing package on 8 August 2014 and met with the Division’s reviewers on 3 Sept 2014, to provide a live demonstration of the changes made in accordance with the Division’s specific request to improve organization and navigation issues. The meeting was successful in ensuring agreement on the approaches to be taken in the NDA Resubmission as reflected in the Division’s Meeting Minutes (26 September 2014) and the Sponsor’s minutes (11 September 2014). The Sponsor agreed to provide a revised submission relating to the modules that were modified for a Reviewer’s Orientation meeting that was

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scheduled for December 2nd 2014, to discuss the revised NDA in advance of its formal resubmission.

As a result of the Division's continuing advice and discussions of the issues, this ISS reflects agreements reached on a variety of issues.

The overall clinical database for registration of safinamide, comprising >2400 unique exposures, including >500 patients treated for 2 years or more, >1100 treated for >1 year, and >1400 treated for >6 months, was accepted as meeting current ICH requirements. In addition, a total of 1180 patients treated with safinamide will have had ophthalmological examinations, including a Baseline (pre-treatment) assessment and at least one post-Baseline assessment, with 405 of these patient having OCT and 20 having electroretinography (ERG) evaluations.

2.6 Other Relevant Background Information

The development of safinamide for the treatment of idiopathic PD was guided by extensive regulatory interactions, during which Newron presented its perspective and sought regulatory input and concurrence on key issues across all disciplines (toxicology, DMPK [i.e., drug-drug interactions and population PK strategy], indications, pivotal study design, efficacy and safety measures, dose-finding strategy, titration schedule, etc.).

The unique indication of "add-on to a single dopamine (DA)-agonist" was agreed upon with the US Food and Drug Administration (FDA) at a pre-IND meeting held 16 January 2003, and subsequently with other health authorities. Scientific Advice (SA) meetings in 2004 and 2005 with the UK, France, Germany, Sweden, and Canada were conducted prior to finalizing the Phase 3 program. Subsequent SA meetings with EMA/CHMP (16 November 2006) and an End of Phase 2 meeting with the FDA (8 November 2005) confirmed key assumptions, including the plans for filing for registration based on single adequate and well-controlled studies evaluating safinamide in 2 idiopathic PD subpopulations for the following indications :

- Early stage (b) (4) patients, as add-on therapy to a single DA-agonist at a stable dose.
- Mid- to late-stage (b) (4) patients, as add-on therapy to (b) (4) L-dopa alone or in combination with other PD medications.

In addition, the meetings confirmed the choice of the primary efficacy variables [i.e., mean change in total Unified Parkinson's Disease Rating Scale – Section III (UPDRS III) for ESPD (non-fluctuators), and change in 'ON time without troublesome dyskinesia' for LSPD (fluctuators) studies], comprehensive ocular monitoring, and the Sponsor's rationale for not performing comparator trials for the 2 indications.

In 2006, Merck-Serono acquired the exclusive worldwide rights to further develop, manufacture, and commercialize safinamide. A "clinical hold" was imposed by the FDA on 18 December 2008 due to concerns arising from an incorrect assessment of retinal degeneration in a non-human primate toxicology study. This clinical hold was removed after an independent review of

the study, as well as the availability of ocular data from a placebo-controlled study in PD patients. The FDA requested further changes in the ocular monitoring program included in all trials, and required submission of ocular coherence tomography (OCT) data from 405 patients on sildenafil, including Baseline and post-Baseline assessments at 6 months and 1 year (extension trials). The FDA also requested the following changes to individual tests on the planned ophthalmological examination:

- Visual acuity – Change from Snellen chart to ETDRS best corrected visual acuity at 4 meters;
- Color vision – Change from Ishihara pseudo-isochromatic color plates to Farnsworth-Munsell 24, 40 or 100 hue tests;
- Fundus – Dilated fundus examinations, including fundus photography, were required, rather than being optional;
- Slit lamp – Slit lamp examination was added to examination.

In 2011, Merck-Serono terminated the co-development agreement for sildenafil and Newron assumed responsibility for its further development up to the present time.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

Two sites were selected for inspection by Division of Clinical Compliance and Evaluation in the Office of Scientific Investigations and Office of Compliance because both of these sites had a large enrollment and treatment of patients in the most important pivotal, dose-response trial for advanced Parkinson's disease (Study 16, also known as Study 1015/016) and also enrolled patients in the long-term extension phase of Study 16 (i.e., Study 18, also known as Study 1015/018).

Inspection of Site for Josef Szaz, M.D., Principal Investigator (Turgu Mures, Romania)

The following is an abstracted quotation from the inspection.

“For Study 1015/016: At this site, a total of 45 subjects were screened, seven subjects were reported as screen failures, 37 subjects were enrolled, and 37 subjects completed the study; all 37 subjects continued on the extension phase of Study 1015/018. Two subjects withdrew from the extension phase of the study, and thirty five subjects completed Study 1015/018. Review of the Informed Consent Documents, for all records reviewed, verified that subjects signed prior to enrollment.

The medical records/source data for 10 subjects from Study 1015/016, and 16 subjects from Study 1015/018 were reviewed in depth, including drug accountability records, vital signs, laboratory results, IRB records, patients’ diaries for inclusion/exclusion criteria, concomitant medications, and source documents were compared to data listings and adverse

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events reporting.

At the conclusion of the inspection, no Form 483 was issued to Dr. Szasz. The ORA investigators found minor protocol deviations and inadequate record keeping. The inspectional observations included, but were not limited to protocol violations and inadequate record keeping.”

The following is a summary quotation from the inspection report.

“The medical records reviewed disclosed no adverse findings that would impact the reliability of the data. In general, the records reviewed were found to be in order except for the above noted findings. There were no limitations to this inspection. Although minor deviations were noted, the data from Dr. Szasz’s site are considered reliable and appear acceptable in support of the pending application.”

Inspection of Site for Rupam Borgohain, D.M. (Punjagutta, Hyderabad, India)

The following is an abstracted quotation from the inspection.

“For Study 1015/016: At this site, a total of 51 subjects were screened, 12 subjects were reported as screen failures, 39 subjects were enrolled, and 34 subjects completed the study. For Study 1015/018 a total of 33 subjects continued on the extension phase of Study 1015/018, and 28 subjects completed the study. Review of the Informed Consent Documents, for all records reviewed, verified that subjects signed prior to enrollment.

A review of the medical records/source documents was conducted. The medical records/source data for 14 subjects from Study 1015/016, and 13 subjects from Study 1015/018 were reviewed, including drug accountability records, vital signs, laboratory results, IRB records, patients’ diaries for inclusion/exclusion criteria, financial disclosures, and concomitant medications. Source documents were compared to data listings for primary efficacy endpoints and adverse events reporting.

At the conclusion of the inspection, no Form 483 was issued to Dr. Borgohain. The ORA investigator found minor record keeping violations in terms of “documents were not filed properly in the regulatory binders such as training certification, signed financial disclosure forms” by study staff, and one subject experienced color vision in both eyes which was not reported.”

The following is a summary quotation from the inspection report.

“The medical records reviewed disclosed no adverse findings that would impact the reliability of the data. In general, the data reviewed were found to be verifiable except for the above noted findings. There were no limitations to this inspection. Although minor deviations were noted, the data from Dr. Borgohain’s site are considered reliable and appear acceptable in support of the pending application.”

Reviewer Comment

- I conclude that there were no significant inspection concerns identified with the conduct of these investigators at these important sites for the most important, pivotal trial in advanced Parkinson's disease.

3.2 Compliance with Good Clinical Practices

Protocols noted that the trials were to be conducted according to the Declaration of Helsinki ethical principles and also Good Clinical Practices (GCP) outlined in the ICH Guidance or Tripartite Guideline for GCP.

Reviewer Comment

The conduct of the clinical trials and the Clinical Development program for sildenafil appeared to comply with ethical principles and GCP.

3.3 Financial Disclosures

At the time of the NDA 207145 submission, a review of financial disclosure information indicated that the required information was not provided for all potentially pivotal trials. The Agency asked the sponsor to provide financial disclosure information for all pivotal trials.

The sponsor summarized financial disclosure information for all the clinical trials (in early stage Parkinson's disease-ESPD, and late or advanced stage Parkinson's disease-LSPD) that were considered to be potentially "pivotal" by their study design. Financial disclosure information for "investigators" included many study personnel involved in the trial in addition to the Principal Investigator at each study site. **Information for investigators in each pivotal trial was categorized into one of three categories : 1) Section 1 (without disclosable interest and arrangements); 2) Section 2 (possible disclosable interest or arrangement); and 3) Section 3 (due diligence but complete documentation not obtained).** This information is summarized in Table 1 for all pivotal trials in ESPD and LSPD.

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Table 1 Sponsor Summary of Categories for Financial Disclosure Information for All Types of Investigators for Pivotal Trials in ESPD and LSPD

This table provides a comprehensive overview of the financial disclosure information submitted for safinamide efficacy trials and the Sponsorship of these studies, with links to the Section 1, 2, and 3 Investigator Lists submitted in previous as well as the present submission.

Indication	Trial	Sponsor	Section 1	Section 2	Section 3
LSPD					
	016	Newron	104	0	210
	018	Newron	107	0	207
	SETTLE	MerckSerono	496	6	521
ESPD					
	009	Newron	75	0	33
	015	Newron	40	0	89
	017	Newron	41	0	80
	MOTION	MerckSerono	438	7	562

As part of the due diligence process, the Sponsor and/or its agents made numerous attempts to contact the Investigators listed in Section 3. These Investigators have been categorized into two broad categories :

- The term “non-responsive” has been used to identify those Investigators who could not be reached despite multiple phone attempts or emails; no reply was received relating to the Sponsors request to provide a post study financial disclosure form.
- The term “unreachable” is used to describe Investigators who met the following criteria:
 - Site staff confirmed the individual was no longer employed/present at the site, and no further information on their location was available.
 - Searches for alternate contact details using other sources (internet, etc.) were not successful.

The sponsor noted that due to the unanticipated early termination of the Phase III program and change in Sponsorship of the IND, timely collection of financial interest and arrangement information was not feasible. However, the current Sponsor diligently pursued collecting the required post study financial disclosure information whenever possible.

Although the section 2 column in Table 1 shows 13 individuals, the sponsor subsequently clarified that ultimately there was only one Investigator who had a disclosable financial interest, (b) (6) a Sub-Investigator who participated in both MOTION an SETTLE; he was compensated \$ 90,000 by the prior Sponsor, Merck Serono, for activities related to training for the trials. His (b) (6) site only enrolled (b) (6) patients, less than (b) (6) of subjects enrolled. The other Investigators listed in the Section 2 Tables had initial documentation that was erroneous or ambiguous regarding disclosable financial interests; follow-up investigations clarified that these Investigators did not have disclosable financial interests, as described in the Tables.

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Financial disclosure information was also sought from Principal Investigators and Clinical Investigators directly involved in the treatment or evaluation of research subjects who are not Principal Investigators. This group is limited to site employees who were integral to the conduct and outcome of the study; i.e., MDs/PhDs who performed key efficacy rating, took decisions on dose, continuation of patient in the study, etc. This group excludes some site personnel included in the comprehensive overview and summary table previously submitted in SN 031: ancillary medical specialists (ophthalmologists, dermatologists, & cardiologists who were contractors who performed limited evaluations), and Study Nurses and Study Coordinators (as they did not take any key decisions). Table 2 shows the breakdown of these 2 large groups (Principal Investigators, and Clinical Investigators who were not Principal Investigators) for the different categories regarding financial disclosure information.

Table 2 Sponsor Separate Summaries of Categories for Financial Disclosure Information for Principal Investigators and for Clinical Investigators Who Were Not Principal Investigators for Pivotal Trials in ESPD and LSPD

Principal Investigators

Indication	Trial	Sponsor	Section 1	Section 2	Section 3
ESPD	009	Newron	25	-	4
	015	Newron	14	-	12
	017	Newron	15	-	11
	MOTION	MerckSerono	112	6	11
LSPD	016	Newron	24	-	29
	018	Newron	24	-	31
	SETTLE	MerckSerono	124	4	7

Clinical Investigators, excluding Principal Investigators

Indication	Trial	Sponsor	Section 1	Section 2	Section 3
ESPD	009	Newron	42	-	24
	015	Newron	24	-	71
	017	Newron	26	-	63
	MOTION	MerckSerono	178	1	365
LSPD	016	Newron	65	-	155
	018	Newron	67	-	151
	SETTLE	MerckSerono	215	1	318

Reviewer Comment

- Overall, based upon known information, I did not have significant concerns about potential conflicts of interest regarding financial disclosures. Only one investigator, (b) (6) who participated in both MOTION and SETTLE, had a clear financial arrangement that could have represented a conflict of interest. However, (b) (6) was a Subinvestigator and the small enrollment of patients at his site accounted for < (b) (6) of all patients enrolled in the trials in which he was involved.

- Although the initial summary table of financial disclosure information for personnel involved with the pivotal trials (Table 1) showed potentially 13 individuals with possible conflicts of interest. The sponsor subsequently noted that upon additional clarification, that there was only one individual (b) (6) who had a potential conflict of interest regarding financial arrangements received.
- Table 2 shows a more detailed breakdown of numbers of individual in the 3 categories defined by the sponsor. One part of the overall table provides a breakdown for Principal Investigators and the other part of the table provides a breakdown for Clinical Investigators when Principal Investigators were excluded. (b) (6) is represented in section 2 for this table for Studies MOTION and SETTLE. The sponsor also had noted that there are more individuals in section 2 because that was the initial impression of the sponsor. but that ultimately the sponsor's conclusion was that there was only one individual (b) (6) who had a potential, financial conflict.
- It is noteworthy that each of these tables includes significant numbers of individuals in section 3 for which financial disclosure information was not able to be obtained despite the sponsor's most recent attempts. The sponsor also commented that one contributing factor to this noteworthy number of individuals in section 3 is due to the unanticipated early termination of the Phase III program and change in Sponsorship of the IND from the previous sponsor to the current sponsor, timely collection of financial interest and arrangement information had not been conducted.
- In summary, because I have no known reason to have specific concerns regarding financial arrangements with the many individuals involved in the relatively large clinical development program for Parkinson's disease without financial disclosure information. However, because of that perspective and the current sponsor's due diligence to collect missing information, I would not recommend withholding approval of XADAGO (safinamide) because of the missing information.

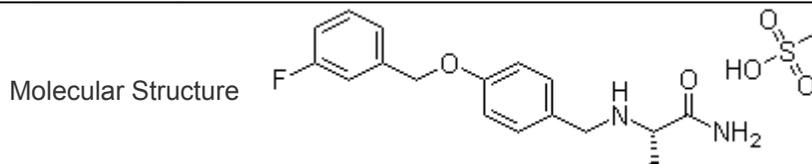
4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls (CMC)

The following shows the molecular formula, structure, weight, and names for safinamide.

Synonyms (S)-2-[[4-[(3-Fluorobenzyl)oxy]benzyl]amino]propanamide
methanesulfonate

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Molecular Formula C₁₇H₁₉FN₂O₂·CH₄O₃S
Molecular Weight 398.45
CAS Registry Number 202825-46-5

XADAGO 50 mg immediate release Tablets: Orange to copper with metallic gloss, round, biconcave shaped embossed with “50” on one side

XADAGO 100 mg immediate release Tablets: Orange to copper with metallic gloss, round, biconcave shaped embossed with “100” on one side.

The CMC team consists of many members from different disciplines reviewing different CMC aspects and components of this NDA. The CMC team includes : Drs. Sharon Kelly (Drug Substance), Sherita McLamore (Drug Product), Mark Johnson ((Process and Microbiology), Tracie Sharp replaced by Franck Wackes (Facility), Okpo Eradiri (Biopharmaceuticals), Dahlia Woody (Project/Business Process Manager), and Martha Heimann (Application Technical Lead).

The following is abstracted quote from the Executive Summary of the CMC draft review :

I. Recommendations

A. Recommendation and Conclusion on Approvability

From a product quality perspective, NDA 207145 is recommended for approval. The applicant has satisfactorily addressed all deficiencies identified during the review process. As the review team concurs with the expiration dating period proposed by the applicant, there are no comments to be conveyed in the action letter.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

Not Applicable”

Reviewer Comment

- There does not appear to be any significant concerns about the CMC aspects/components of this NDA.

4.2 Clinical Microbiology

Not applicable

4.3 Preclinical Pharmacology/Toxicology

The following is abstracted from the nonclinical review of Dr. Luann Mckinney, the primary nonclinical reviewer, for this NDA.

“1 Executive Summary

1.1 Recommendations

1.1.1 Approvability: From a pharmacologic/toxicologic perspective, sildenafil at 100 mg/day is approvable for therapy in Parkinson’s disease

1.1.2 Additional Non Clinical Recommendations

- 1) The safety margin for sporadic CNS signs is low (3-fold) and clinical monitoring may be warranted.
- 2) Adverse effects on fertility, on fetal development, and on neonatal health should be taken into consideration when administering sildenafil to women of child bearing age.
- 3) Clinical monitoring for adverse retinal changes may be advised when pramipexole and sildenafil are co-administered.”

Reviewer Comment

- The primary nonclinical reviewer’s recommendations can be addressed in labeling.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Sildenafil (XADAGO) is believed to act through enhancement of dopaminergic transmission through the selective, reversible inhibition of the Monoamine Oxidase B (MAO-B) enzyme, control of the neuronal excitability through state-dependent blockade of the voltage-gated sodium channels (VGSC), and reduction of glutamate release.

4.4.2 Pharmacodynamics

XADAGO reversibly and selectively inhibits Monoamine Oxidase B (MAO-B) (IC₅₀ of 79 nM in human brain mitochondrial fraction and 9.3 nM in human platelet-rich plasma; > 1000-fold selective over MAO-A). In clinical studies complete inhibition (>90%) of MAO-B was measured at doses > 20 mg. In addition XADAGO inhibited the voltage-gated sodium channels (VGSC) in a state-dependent manner (IC₅₀ values in the range of 1.6 to 4.9 μM for the different VGSC subtypes); this inhibition led to reduction of glutamate release as demonstrated in preclinical studies.

4.4.3 Pharmacokinetics

The following summary information of pharmacokinetics (PK) of sildenafil was obtained from the sponsor's proposed label.

Absorption:

[REDACTED] (b) (4)

Distribution

The volume of distribution (V_{ss}) is approximately 165 L, [REDACTED] (b) (4)

Metabolism:

In humans, sildenafil is almost exclusively eliminated via metabolism (~5% of the drug is eliminated unchanged, mainly in urine). [REDACTED] (b) (4)

[REDACTED] One pathway involves hydrolytic oxidation of the amide moiety leading to the primary metabolite 'sildenafil acid' (NW-1153). Another pathway is oxidative cleavage of the ether bond forming 'O-debenzylated sildenafil' (NW-1199). Finally the 'N-dealkylated acid' (NW-1689) is formed by oxidative cleavage of the amine bond of either XADAGO or the primary sildenafil acid metabolite (NW-1153). The 'N-dealkylated acid' (NW-1689) undergoes further conjugation with glucuronic acid yielding its acyl glucuronide.

[REDACTED] (b) (4)

[REDACTED] Dedicated drug-drug interactions studies [REDACTED] (b) (4) with ketoconazole, levodopa, and CYP1A2 and CYP3A4 substrates (caffeine and midazolam) did not demonstrate any clinically significant effects on the pharmacokinetic profile of sildenafil, or on the pharmacokinetic profile of co-administered levodopa or CYP 1A2 and CYP3A4 substrates.

[REDACTED] (b) (4)

Excretion:

[REDACTED] (b) (4)

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[REDACTED] (b) (4)

[REDACTED] (b) (4)

[REDACTED] (b) (4)

Hepatic Impairment:

The disposition of sildenafil was [REDACTED] (b) (4) in subjects with mild and moderate hepatic impairment and compared with subjects with normal hepatic function. [REDACTED] (b) (4)

[REDACTED]

Renal Impairment:

[REDACTED] (b) (4)

[REDACTED] (b) (4)

There are limited clinical data on the use of sildenafil in the elderly (>75 years). These data [REDACTED] (b) (4) that the pharmacokinetics of [REDACTED] (b) (4)

[REDACTED] (b) (4)

The following summary recommendation is abstracted from the review of Dr. Kristina Dimova, the primary Clinical Pharmacology reviewer.

“1.1 RECOMMENDATION

The Office of Clinical Pharmacology (OCP/DCP I) has reviewed the clinical Pharmacology and Biopharmaceutics sections of NDA 207145. The submission is acceptable from a Clinical Pharmacology and Biopharmaceutics point of view provided the sponsor agrees with the Agency’s labeling recommendations.

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Post-Marketing Commitments:

1. A clinical study to characterize drug-drug interaction of sildenafil and BCRP substrates in healthy volunteers

NW-1689 is a major metabolite of sildenafil found in plasma at the concentration of approximately 160% of parent compound, sildenafil. NW-1689 inhibited BCRP with an IC₅₀ of 3.7 ± 0.5 μM. The average maximal plasma concentration of Sildenafil was approximately 4 μM in Parkinson's disease patients treated with the highest dose of 100 mg/day. Based on this information from in vitro evaluation, there is a need for further in vivo drug interaction study at post-approval stage.

Substrates of BCRP include methotrexate, mitoxantrone, imatinib, irinotecan, lapatinib, rosuvastatin, sulfasalazine, topotecan.”

Reviewer Comment

- The Clinical Pharmacology recommendation for above described Post Marketing Commitment (PMC) can be communicated to the sponsor and included in an approval letter if the sponsor agrees to this PMC.

5 Sources of Clinical Data

The sponsor's clinical data were submitted to the Agency's electronic document room (EDR) location : \\CDSESUB1\evsprod\NDA207145\207145.enx .

5.1 Tables of Studies/Clinical Trials

Table 3 summarizes information about the pivotal trials for sildenafil. Table 4 summarizes information about special safety trials for sildenafil.

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Table 3 Pivotal Clinical Trials for Investigating Efficacy and Safety of Safinamide

Ph	Type of study	Study ID/Study Title/Status	Loc	Study Design Duration of treatment	Dosing regimen	Study pop	FPFV	Subjects Exposed	Countries
II/III a	Safety and Efficacy	NW-1015/009/II/2001 A Dose Finding, DB, PL-Controlled Study to Investigate the Efficacy and Safety of Saf, an MAO-B Inhibitor, in Pts Affected by Idiopathic Early PD COMPLETED	5.3.5.1	DB, PL controlled, add-on to Single DA. 3 parallel groups 12 wks duration Primary efficacy endpoint: proportion of "responders" (≥ 30% improvement in UPDRS III).	Saf: 0.5 mg/kg/day mg/day 1.0 mg/kg/day mg/day PL	Early PD, non-fluct.	FPI: 09/10/2001 LPO: 17/10/2002	Saf: 0.5 mg/kg/day = 55 1.0 mg/kg/day = 56 PL=56 Total=172 DA cohort: 0.5 mg/kg/day = 33 1.0 mg/kg/day = 34 PL=34 Total=101	Belgium, France, Germany, Italy and Poland
III	Safety and Efficacy	NW-1015/015/III/2003 [EudraCT Nr: 2004-000833-12] A Ph III, DB, PL-Controlled Study to Determine the Efficacy and Safety of a Low (50-100 mg/day) and High (150-200 mg/day) Dose Range of Saf, as "Add-On" Therapy, in Pts with Early Idiopathic PD Treated with a Stable Dose of a Single DA COMPLETED	5.3.5.1	DB, PL controlled, add-on to DA 3 parallel group 24 wks duration Primary efficacy endpoint: UPDRS III change from baseline	Saf: 50-100 mg/day 150-200 mg/day PL	Early PD, non-fluct.	FPI: 27/08/2004 LPO: 19/06/2006	Planned=270 Saf: 50-100 mg/day = 90 150-200 mg/day= 89 PL=90 Total=269	Argentina, Chile, Colombia, India, Italy, Spain and United Kingdom
III	Safety and Efficacy	NW-1015/017/III/2003 [EudraCT Nr: 2004-000835-27] A Ph III, DB, PL-Controlled, 12-Month Extension Study to Investigate the Efficacy and Safety of a Dose Range of Saf of 50-200 mg/day as Add-On Therapy in Pts with Early Idiopathic PD Treated with a Stable Dose of a Single Dopamine Agonist. COMPLETED	5.3.5.1	DB, PL controlled, Extension to study 015 3 parallel group 48 wks duration Primary efficacy endpoint: Time to intervention [Landmark analysis: 240-540 days]	Saf: 50-100 mg/day 150-200 mg/day PL	Early PD, non-fluct.	FPI: 17/03/2005 LPO: 07/02/2007	Patient completing 015 Saf: 50-100 mg/day = 80 150-200 mg/day= 69 PL=78 Total=227	Argentina, Chile, Colombia, India, Italy, Spain and United Kingdom
III	Safety and Efficacy	NW-1015/016/III/2006 [EudraCT Nr: 2006-005860-14] A Ph III, DB, PL-Controlled Study to	5.3.5.1	DB, PL controlled, add-on to L-dopa 24 wks duration	3 parallel groups Saf: 50 mg/day	PD Pts fluct.	FPI: 05/03/2007 LPO: 28/10/2008	Randomized 50 mg/day = 223 100 mg/day=	India, Italy, Romania

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Table 3 Pivotal Clinical Trials for Investigating Efficacy and Safety of Safinamide (Continued)

Ph	Type of study	Study ID/Study Title/Status	Loc	Study Design Duration of treatment	Dosing regimen	Study pop	FPFV	Subjects Exposed	Countries
		Determine the Efficacy and Safety of a Low (50 mg/day) and High (100 mg/day) Dose of Saf as Add-On Therapy in Pts with Idiopathic PD with Motor Fluctuations, Treated with a Stable Dose of L-dopa and Who May be Receiving Concomitant Treatment with Stable Doses of a Dopamine Agonist and/or an Anticholinergic COMPLETED		Primary efficacy endpoint: Daily 'on' time, change from baseline	100 mg/day PL			224 PL=222 Total=669 Completed 50 mg/day = 201 100 mg/day= 196 PL=197 Total=594	
III	Safety and Efficacy	NW-1015/018/III/2006 [EudraCT Nr: 2006-005861-21] A Ph III, DB, PL-Controlled, 18-month Extension Study to Investigate the Long-Term Efficacy and Safety of a Low (50 mg/day) and High (100 mg/day) Dose of Saf as Add-On Therapy, in Pts with Idiopathic PD with Motor Fluctuations, Treated with a Stable Dose of L-dopa and Who May be Receiving Concomitant Treatment with Stable Doses of a Dopamine Agonist and/or an Anticholinergic. COMPLETED	5.3.5.1	DB, PL controlled, extension to study 016 18 months duration Primary efficacy endpoint: Change in DRS during 'on' time	3 parallel groups Saf: 50 mg/day 100 mg/day PL	PD Pts fluct.	FPI: 24/08/2007 LPO: 29/04/2010	Patient who completed 016 Entered 50 mg/day = 189 100 mg/day= 180 PL=175 Total=544 Completed 50 mg/day = 148 100 mg/day= 150 PL=142 Total=440	India, Italy, and Romania
III	Safety and efficacy	27918 MOTION [EudraCT Nr: 2007-002963-28] A Ph III, DB, PL-controlled randomised trial to determine the efficacy and safety of a low (50 mg/day) and high (100 mg/day) dose of Saf, as add-on therapy, in subjects with early idiopathic Parkinson's Disease treated with a stable dose of a single dopamine agonist.	5.3.5.1	DB, PL-controlled randomised trial as add-on therapy. 3 parallel group 24 wks duration Primary efficacy endpoint: UPDRS III change from baseline	Saf 50 mg/day 100 mg/day PL stable dose of a single dopamine agonist.	Idiopathic early PD Pts on stable dose of a single dopamine agonist	FPI: 06/12/2007 LPO: 08/02/2012	Entered = 679 50 mg/day = 227 100 mg/day = 227 PL = 225	Argentina, Brazil, Bulgaria, Canada, Chile, Colombia, Croatia, Czech Republic, Finland, Germany, India, Italy, Mexico, Peru, Poland, Portugal, South

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Table 3 Pivotal Clinical Trials for Investigating Efficacy and Safety of Safinamide (Continued)

Ph	Type of study	Study ID/Study Title/Status	Loc	Study Design Duration of treatment	Dosing regimen	Study pop	FPFV	Subjects Exposed	Countries
		COMPLETED		[DA monotherapy sub-population, n=666]					Africa, Slovakia, Spain and USA
III	Safety and Efficacy	27938 MOTION Extension [EudraCT Nr: 2008-004146-88] A Ph III, DB, PL-controlled extension trial to investigate the long-term efficacy and safety of low (50 mg/day) and high (100 mg/day) dose Saf, as add-on therapy in subjects with early idiopathic PD treated with a stable dose of a single dopamine agonist TERMINATED EARLY DUE TO CHANGE IN SPONSOR. CSR SAFETY ONLY	5.3.5.1	DB, PL-controlled extension trial as add-on therapy 3 parallel group 78 wks duration	Saf: 50 mg/day 100 mg/day PL stable dose of a single dopamine agonist	Idiopathic early PD Pts on stable dose of a single dopamine agonist The trial population for the present trial 27938 will consist of subjects from trial 27918	FPI: 13/04/2009 LPO: 28/05/2012	Entered = 507 50 mg/day = 179 100 mg/day = 174 PL = 154	Argentina, Brazil, Bulgaria, Canada, Chile, Colombia, Croatia, Czech Republic, Finland, Germany, India, Italy, Mexico, Peru, Poland, Portugal, South Africa, Slovakia, Spain and USA
III	Safety and Efficacy	27919 SETTLE [EudraCT Nr: 2007-002964-90] A Ph III, DB, PL-controlled randomised trial to determine the efficacy and safety of a dose range of 50 to 100 mg/day of Saf, as add-on therapy, in subjects with idiopathic PD with motor fluctuations, treated with a stable dose of L-dopa and who may be receiving concomitant treatment with stable doses of a dopamine agonist, an anticholinergic and/or amantadine. COMPLETED	5.3.5.1	Double -blind, PL-controlled, Randomised Trial, as add-on therapy 2 parallel group 24 wks duration Primary efficacy endpoint: Daily 'on' time, change from baseline	Saf: 50-100 mg/day PL	Idiopathic PD Pts (>3 years' dur) with motor fluctuations (>1.5 hours of daily "OFF" Time) and a Hoehn and Yahr stage of 1-4	FPI: 30/03/2009 LPO: 23/02/2012	Entered = 549 50-100mg/day = 274 PL= 275	Australia, Austria, Belgium, Canada, Estonia, France, Germany, Hungary, India, Israel, KOREA, Malaysia, Netherlands, New Zealand, Slovakia, Spain, Switzerland, Taiwan, Thailand, UK and USA

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Table 4 Special Safety Trials (Tyramine Challenge and QTc Evaluation) for Safinamide

Ph	Type of study	Study ID/Study Title/Status	Loc	Study Design Duration of treatment	Dosing regimen	Study pop	FPFV	Subjects Exposed	Countries
I	Tyr	28558 Tyramine Pressor effects of Oral Tyramine in Saf Treatment, a DB, PL-controlled study COMPLETED	5.3.2.2	DB, active-, comparator- and PL controlled, randomized	5 parallel groups: Saf 100 mg/day, Saf 350 mg/day, Phenelzine 30 mg/day, Selegiline 10 mg/day, PL for up to 16 days Tyr as challenging agent: escalating, daily single doses from 100 mg to 700 mg at screening 6.25 to 200 mg (phenelzine group), 25 mg to 700 mg (saf, selegiline and PL groups) during the study	HV 18-70	FPI: 27/04/2010 LPO: 24/01/2011	89	France
I	Tyr	CRO-PK-03-101 (NW-1015-Tyr-I-2003) Pressor Effects of Oral Tyramine in Saf Treatment, an OL Study COMPLETED	5.3.2.2	OL, one sequence, study	Repeated admin of 300mg saf for up to 7 days. Oral tyramine challenges with doses of 200mg then 100mg or 400mg at screening, and 50mg up to 200mg under saf treatment	HV 45-65	FPI: 10/09/2003 LPO: 04/11/2003	20	Switzerland
I	Tyr	(b) (4) NW 1015/TYR-268-00 : Pressor Effects of I.V. Tyramine After Single Dose of Saf COMPLETED	5.3.2.2	OL, two treatment, two sequence, two period, PL-controlled study	2mg/kg Saf and PL Two single-doses separated by 3 days wash-out	HV 18-45	FPI: 15/02/2001 LPO: 28/03/2001	8	Switzerland
I	PD	Study 28559 Effect of Saf on the QT/QTc interval in HV	5.3.4.1	DB, PL controlled, multiple-dose parallel groups study with an OL, single-dose positive control (moxifloxacin 400 mg)	Four parallel groups: Saf 100 and 350mg/day for 6 days; Moxifloxacin 400 mg single dose; PL	HV 18-45	FPI: 08/09/2009 LPO: 07/04/2010	240	Germany

Study 28850 (OPEN LABEL)

Study 28850 was an open-label trial to determine the long-term safety of safinamide in Parkinson's disease patients. The study duration was planned to last up to 3 years however, the study was terminated early due to change in sponsorship on October 23, 2011. The study opened on April 22, 2009 the last patient visit was completed on June 5, 2012.

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Study 28850 was a Phase III, single arm, open-label, multi-center, extension study, evaluating the long-term safety and tolerability of safinamide (50 mg/day to 100 mg/day) in eligible patients treated for early or late stage PD. Patients who completed a previous safinamide clinical study in PD and met all the inclusion and exclusion criteria were offered enrollment. **Patients from the following studies were offered the opportunity to participate in study 28850 :**

- Study 018,
- MOTION extension (27938),
- SETTLE (27919),
- Cognition Study (EMR 701165-024),
- Levodopa-Induced Dyskinesia (LID) Study (701165-023) or
- Study 28780

Patients were initially dosed with 50 mg of safinamide daily, which was increased to 100 mg) daily, the targeted dose for all patients. Investigators were permitted to adjust the dose of safinamide, or any concomitant medications, at any time according based on their clinical judgment.

Study 28850 was conducted in the following countries : Argentina, Australia, Austria, Belgium, Bulgaria, Canada, Chile, Czech Republic, Estonia, Finland, France, Germany, Hungary, India, Israel, Italy, Korea, Malaysia, Mexico, Netherlands, New Zealand, Peru, Poland, Portugal, Romania, Slovakia, Spain, Switzerland, Taiwan, Thailand, UK and USA.

In total, 964 were enrolled in study 28850 of which 706 patients completed the study. Data for all 964 patients were included in the sponsor's safety analyses and datasets.

5.2 Review Strategy

My strategy for analyzing efficacy included reviewing the primary analysis for the primary efficacy endpoint according to each Statistical Analysis Plan (SAP) for each pivotal trial (one Phase 2 trial and two Phase 3 trials in early Parkinson's disease; two Phase 3 trials in advanced Parkinson's disease). My strategy also focused on reviewing important, supporting analyses for the primary efficacy endpoint and key secondary efficacy endpoint(s) in the modified Intent-to-Treat population (mITT), defined as : patients with baseline data and post-baseline/treatment efficacy data) using a Mixed Model Repeat Measures (MMRM) analysis including terms specified in the respective SAP for each trial. The NDA includes two 6 month trials (Studies 15 and 16) which incorporated long-term extensions (Study 17 for Study 15, 1 year; Study 18 for Study 16, 1.5 years) in which patients continued taking the same randomized treatments (including placebo) under double-blinded conditions. However, because concomitant medications for Parkinson's disease did not appear to be rigorously controlled at a stable level as at baseline in Studies 15 and 16, I did not focus on results of these extension phase trials as much as I did for all the 6 month trials. Of additional relevance, my review for efficacy primarily focused on looking at information and data from the ISE and individual study reports.

For Studies 9, and 15, the sponsor identified many secondary efficacy endpoints for statistical analyses in the Statistical Analysis Plans (SAPs) but there was no statistical adjustment for multiplicity/multiple comparisons. Consequently, I did not pay attention to these many secondary efficacy endpoints, many of which were not of clinical interest and all of which were analyzed without an adjustment for multiple comparison (e.g., there was no hierarchical sequence for conducting this testing).

For Studies MOTION (27918), 16, and SETTLE (27919), the sponsor not only identified many secondary efficacy endpoints for statistical analyses in the respective SAPs but also specified a hierarchical sequence for testing to adjust for multiple comparisons. When the primary analysis of a primary efficacy endpoint in these trials was statistically significant, that observation permitted statistical testing of secondary efficacy endpoints according to the prespecified hierarchical sequence. My review focused on presenting results of these secondary efficacy endpoints which were statistically significant up to and including the prespecified secondary efficacy endpoint which was not statistically significant.

My review strategy for the analysis of safety data included reviewing pooled study results in the Integrated Summary of Safety (ISS) and data in individual study reports. I focused on data from phase 3 pivotal trials (Studies 15 and MOTION in ESPD and Studies 16 and SETTLE in LSPD) and in some instances pools of phase 3 trial data : 1) Studies 15 and MOTION; 2) Studies 15 and 17 (1 year blinded extension phase of Study 15); 3) Studies 16 and SETTLE; and 4) Studies 16 and 18 (1.5 year blinded extension phase of Study 16). Although I reviewed safety data from the “catch-all” open-label extension trial (Study 28850), I focused more on safety data from long-term, double-blinded, placebo-controlled extension trials (Studies 17 and 18) in which patients continued on the same treatment (safinamide or placebo) to which they were randomized in

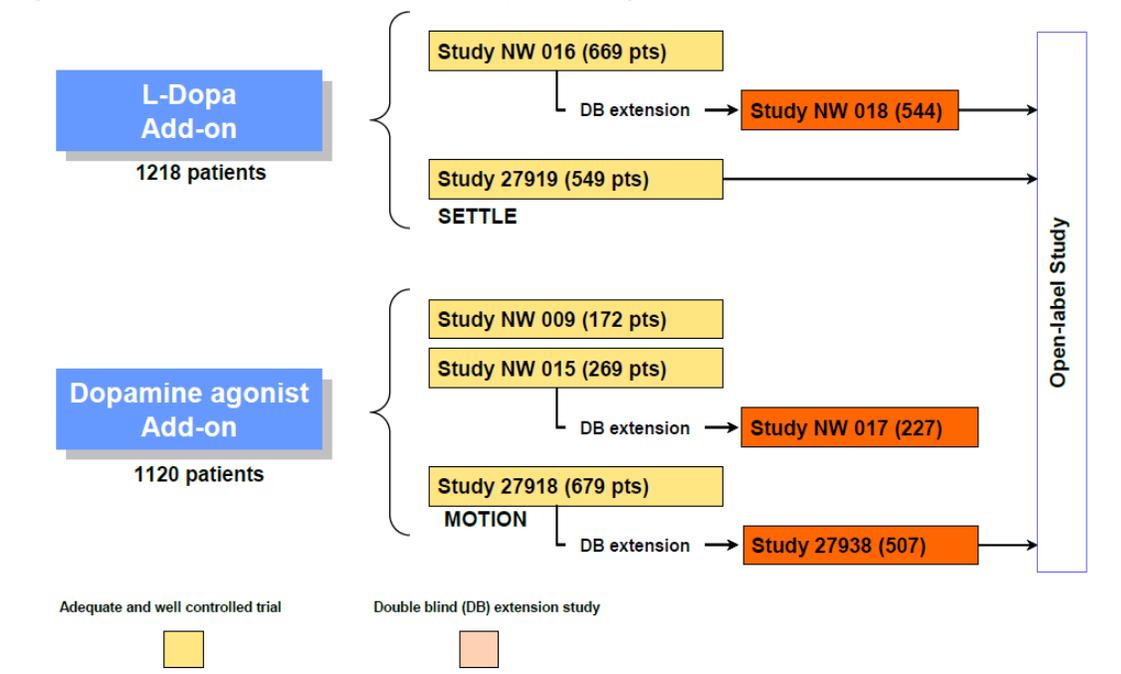
respective studies 15 and 16 under double-blinded conditions. Patients who completed long-term extension trials 17 and 18 could have been treated for up to 1.5 and 2 years, respectively under double-blinded, placebo-controlled conditions. Such long-term treatment under blinded, placebo-controlled conditions is unique in my experience (and perhaps in the experience of the DNP) because I have never seen any sponsor conduct such long-term, extension treatment. I considered this long-term treatment experience potentially more important and useful than the open-label treatment in Study 28850. Neither did I focus results of the extension phase of Study MOTION (Study 27938) because this trial was discontinued prematurely by the sponsor. I also placed a higher priority on safety results from studies in patients with advanced Parkinson's disease (than to safety results for patients with early Parkinson's disease) because efficacy was demonstrated in the advanced Parkinson's disease studies but was not demonstrated for patients with early Parkinson's disease based upon my review and that of the Agency Statistical team.

The presentation of safety results/analyses in my review largely reflects my review strategy for safety data.

5.3 Discussion of Individual Studies/Clinical Trials

Figure 1 depicts the safinamide clinical trials program for safinamide showing the sequence of pivotal trials for Parkinson's disease.

Figure 1 Safinamide Clinical Development Programs for Pivotal Trials for Parkinson's disease



Early Stage Parkinson's disease (ESPD)

Study 9

Study 9 (also referred to as Study 009) was a 12-week, double-blind, placebo-controlled, randomized, 3-arm, parallel-group, **phase 2**, multi-nation, multi-center, dose finding study to compare two doses (0.5 mg/kg/day and 1.0 mg/kg/day) of safinamide as add-on therapy to Parkinson's disease patients who were either *de novo* (i.e. currently untreated) or receiving a single dopamine agonist at a stable dose. A total of 150 patients were planned to be randomized in a 1:1:1 ratio to safinamide 0.5 mg/kg/day, safinamide 1.0 mg/kg/day or placebo. A total of 196 patients were screened in 24 centers in Belgium, France, Germany, Italy, and Poland. One hundred seventy-two patients were randomized. The median doses were 39.0 mg/day and 78.1 mg/day for the 0.5mg/kg/day group and 1.0 mg/kg/day group, respectively.

Study 15

Study 15 (also referred to as Study 015) was a 24-week, double-blind, placebo-controlled, randomized, 3-arm, parallel-group, phase 3, multi-nation, multi-center study to evaluate the safety and efficacy of safinamide as add-on therapy to early Parkinson's disease patients who were receiving a single dopamine agonist at a stable dose.

A total of 240 patients were planned to be randomized in a 1:1:1 ratio to safinamide 100 mg/day, safinamide 200 mg/day or placebo. **Patients underwent a titration to the randomized dose.** A total of 293 patients were screened in 25 centers in 7 countries (Argentina, Chile, Columbia, India, Italy, Spain, and United Kingdom). A total of 270 patients were actually randomized, of which 269 patients were treated. After randomization, screened patients returned for evaluations at Weeks 2, 4, 8, 12, 18 and 24, or at early discontinuation.

Study 17

Study 17 (also referred to as Study 017) was a double-blind extension trial (up to 48 weeks or nearly one additional year of treatment) of Study 15. Patients enrolled in Study 17 could have completed 24 weeks treatment in Study 15 or could have discontinued prematurely from Study 15 or could have discontinued treatment prematurely in Study 15. Safinamide treated patients in Study 17 were permitted any type of change (including increases) in concomitant Parkinson's disease drug doses and/or the addition of a new medication for Parkinson's disease. **Because many safinamide-treated patients in Study 17 had increases in the concomitant medications for Parkinson's disease, this fact confounded the ability to draw efficacy conclusions from this long-term study.**

Study MOTION (27918)

Study MOTION (27918) was a 24-week, double-blind, placebo-controlled, randomized, 3-arm, parallel-group, phase 3, multi-nation, multi-center study to evaluate the safety and efficacy of safinamide as add-on therapy to early Parkinson's disease patients who were receiving a single dopamine agonist at a stable dose.

A total of 666 patients were planned to be randomized in a 1:1:1 ratio to safinamide 50 mg/day, safinamide 100 mg/day or placebo. A total of 871 patients were screened in 25 centers in 19 countries in Asia, Eastern Europe, Western Europe, Latin America, and North America. A total of 679 patients were actually randomized.

Study MOTION Extension (27938)

Study MOTION Extension (27938) was an extension to the antecedent trial (Study MOTION/27918) and was a double-blind, placebo-controlled, multi-center, multi-national, 78-week, Phase III trial, conducted to evaluate the long-term efficacy and safety of a low (50 mg/day) and high (100 mg/day) dose safinamide, compared to placebo, as add-on therapy to a stable single dose of DA-agonist in early PD.

No direct enrollment into this trial occurred. Only subjects who successfully completed the previous trial (27918) were eligible to enroll in this long-term trial (27938).

Upon entry into this trial, subjects continued in the same treatment group and dose level of safinamide or placebo that they received in protocol MOTION/27918, along with the same dose of DA-agonist. Subjects returned for scheduled evaluations at 12, 24, 36, 48, 60 and 78 weeks after the first dose of Investigational Medicinal Product (IMP). Subjects who completed the 78-week extension trial either entered a 1-week taper phase before discontinuing from treatment or entered open-label treatment with safinamide (50-100 mg/day) in a separate open label trial (28850).

Subjects who entered the 1-week taper phase were followed for safety events for 4 weeks after the last administration of safinamide. The total duration of participation from the beginning of Study MOTION/27918 to the completion of Study MOTION Extension/27938 was expected to be 108.5 weeks.

Of the 610 subjects who were included in the Completer population of Study MOTION/27918, 507 enrolled in this extension trial. Of the 507 subjects enrolled in the trial, 174 (34 %) were assigned to the safinamide 50 mg/day group, 179 (35 %) to the safinamide 100 mg/day group, and 154 (30.4%) to the placebo group. A total of 216 (43 %) subjects had a Week 78 follow-up, and therefore completed the study. There were 80 (46 %), 73 (41 %), and 63 (41 %) subjects who completed the study in the safinamide 50 mg/day, safinamide 100 mg/day, and placebo groups, respectively. The mean duration of exposure of all patients (safinamide and placebo) was 406 days. The majority of patients who discontinued from the study did so due to “Other” reasons (i.e., 261 of a total of 291 discontinuations), the overwhelming majority of discontinuation were associated with the premature termination of the study.

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- My understanding of the reason that the sponsor terminated this extension trial was that the sponsor was planning to terminate its ownership of this sildenafil product and had planned to sell this product to another sponsor.
- **Because this trial was terminated prematurely, I did not present results of this trial in my review but rather focused on results of trials which were completed and which were not terminated prematurely (i.e., Studies 17 and 18). There were no findings in this trial which suggested that the safety profile of sildenafil was different than the safety profile characterized in the completed trials.**

Late/Advanced Stage Parkinson's disease (LSPD)

Study 16 (also referred to as Study 016) was a 24-week, double-blind, placebo-controlled, randomized, 3-arm, parallel-group, phase 3, multi-nation, multi-center study to evaluate the safety and efficacy of two fixed doses (50 mg/day and 100 mg/day) of sildenafil as add-on therapy to a stable dose of levodopa in Parkinson's disease patients with motor fluctuations. A total of 660 patients were planned to be randomized in a 1:1:1 ratio to placebo, sildenafil 50 mg/day, and sildenafil 100 mg/day. A total of 900 patients were screened in 52 study centers in India, Italy, and Romania. A total of 669 patients were actually randomized.

Interim Analyses and Data Monitoring

No interim analysis for efficacy was planned for the study; however, **a blinded assessment of the magnitude of the variance of the primary efficacy variable was planned** and conducted when one-third of patients (220 patients) completed Visit 7 (Week 18). The magnitude of the variance was calculated for Visits 4, 5, 6, and 7 and for the change from Baseline to Visit 7. Using the highest SD of 2.44 (at Visit 4), it was determined that 561 patients would need to complete the study to ensure 87% power. Therefore, 568 patients would be adequate and there was no change in planned enrollment.

An unplanned interim analysis for safety (ophthalmology data only) was also performed per protocol Amendment 4. This unblinded interim safety analysis of the first 350 randomized patients included 301 patients who completed 24 weeks of treatment. Of the 49 (14%) patients who withdrew from the study, 18 (5.1%) patients discontinued due to a nonserious AE and 3 (0.9%) patients discontinued due to an SAE. No patient withdrew because of an ocular AE. Overall, the interim analysis did not demonstrate a specific ocular toxicity for sildenafil. No evidence for clinically significant retinal dysfunction was detected. **The analysis did not detect a safety signal of clinical concern. As such, the data supported the continued clinical testing of sildenafil, conducted with vigilant ocular monitoring.**

Database Corrections

The study database was originally locked on 31 December 2008 with 6 queries outstanding. These queries comprised a variety of domains and included clarification of 2 CGI ratings, 1 levodopa dose, 1 AE, 1 SAE, and 1 concomitant medication. After receiving the randomization from the IVRS vendor and during the statistical analysis, minor issues

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with the drug kit numbers, AE stop and start dates, and discontinuation reasons needed clarification. The database was unlocked on 13 January 2009, updated, and then relocked on 15 January, 2009. Statistical analyses, as per the study SAP, were performed on the relocked database.

At the time of the study database lock, there was an ongoing extension study, Study 018. As a result of the clinical monitoring and data validation checks for the extension study, additional domains were found that needed to be changed in the study database, to be consistent with the extension study database. The issues in these domains were mainly related to clarification of dosages, start and stop dates of the PD treatments, and other concomitant medications that were incorrectly captured, as well as start and stop dates of AEs and laboratory AEs. Resolution of the queries and the resultant data followed conventions established in the Data Management Plan. The discrepant items were kept in an errata list with the intention of updating the study database prior to the extension study database lock.

The study database was unlocked on 31 July 2010, updated, and then relocked on 20 August 2010. The update to the database contained all the issues outlined in the errata list and documented in the relock documentation.

Issues emerged when the core and extension study databases were combined prior to the analysis of the long-term data. These issues included discrepancies in the start and end dates for AEs and laboratory AEs (e.g., events with a start date during the core study were found to be continuing into the extension study). The AEs registered in the extension study were found to have started in the core study, etc. The changes made to the database clarified whether these events belonged in the core, extension, or both databases.

The core study database was unlocked on 13 September 2010 and then relocked on 16 September 2010 to correct AE and laboratory AE discrepancies. The final statistical tables, including the ad-hoc tables, were produced based on the 16 September 2010 version of the study database. The changes from the original analyses on the 15 January 2009 database were described.

All database changes, locks, and relocks were conducted according to CliniRx SOPs, including verification that all the necessary changes were made accurately and no additional changes were inadvertently made. All data clarifications were verified and were completed appropriately. **The changes that were made had minimal impact on clinical values, efficacy of the patient's reported outcome; and, moreover, the repeat analyses did not show a material impact of the changes on the primary or key secondary measures and did not identify any new risks associated with the study drug.**

Study 18

Study 18 (also referred to as Study 018) was a double-blind extension trial (up to 1.5 years of additional year of treatment) of Study 16. Patients enrolled in Study 18 could have completed 24 weeks treatment in Study 16 or could have discontinued prematurely from Study 16 or could have discontinued treatment prematurely in Study 16. Safinamide treated patients in Study 18 were permitted any type of change (including increases) in concomitant Parkinson's disease drug doses and/or the addition of a new medication for Parkinson's disease. **Because many**

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sildenafil-treated patients in Study 18 had increases in the concomitant medications for Parkinson's disease, this fact confounded the ability to draw efficacy conclusions from this long-term study.

Study SETTLE (27919)

Study SETTLE (27919) was a 24-week double-blind, placebo-controlled, randomized, 2-arm, parallel-group, phase 3, multi-nation, multi-center study to evaluate the safety and efficacy of 100 mg of sildenafil as add-on therapy to a stable dose of levodopa in Parkinson's disease patients with motor fluctuations. A total of 484 patients were planned to be randomized in a 1:1 ratio to placebo and sildenafil 100 mg/day. **Patients underwent a titration to the randomized dose.** A total of 851 patients were screened in 126 study centers in Asia, Eastern Europe, Latin America, North America, and Western Europe and enrolled in 119 study centers. A total of 549 patients were actually randomized.

A blinded, interim analyses of variance was planned to assess whether the planned sample size estimation had been appropriate. It had been planned that at least 540 subjects would need to be screened to identify at least 484 randomized subjects (i.e., 242 subjects in each treatment group). Assuming a 14% dropout rate, it was anticipated that a total of 416 subjects would complete the study (i.e., 208 subjects in each treatment group), providing at least 90% power to detect a clinically meaningful difference of 0.75 hours in the primary parameter, daily *on* time as measured by diary cards, between the sildenafil and placebo treatment groups. These calculations were performed using a two-sided, two-sample t-test assuming the following: a common standard deviation (of change from baseline to Week 24 in daily *on* time) of 2.35 hours; a Type I error rate of 5%; and a 14% dropout rate. The treatment difference and standard deviation estimates used in these sample size computations considered previous results obtained in the PRESTO study. Subjects were randomized in a 1:1 ratio to sildenafil 50-100 mg/day or to placebo. Randomization was stratified by country/region (i.e., Asia, Eastern Europe, Western Europe, Latin America, and North America). Both randomization and allocation of treatment were performed by an interactive voice response system (IVRS).

Reviewer Comments

- The pivotal trials in ESPD (Studies 9, 15, and MOTION) had similar inclusion and exclusion criteria and overall study design.
- The pivotal trials in LSPD (Studies 16 and SETTLE) had similar inclusion and exclusion criteria and overall study design.
- Most pivotal trials (15, MOTION, 16, SETTLE) included a 24 week treatment. The phase 2 pivotal trial (Study 9) included a 12 week treatment.

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- All pivotal trials investigated safinamide via a fixed-dose study design. The ESPD trials investigated dosing of 0.5 mg/kg/day and 1.0 mg/kg/day and 50 mg, 100 mg, and 200 mg. The LSPD trials investigated dosing of 50 mg, and 100 mg.
- Studies 15 and SETTLE included short titration periods and permitted time-dependent safety analyses.
- Although Studies MOTION and SETTLE were the only pivotal trials enrolling patients from North America (but enrolled relatively small percentages of patients from North America), these trials permitted comparison of safety results for patients in North America to those outside of North America.
- The primary efficacy endpoint for ESPD in phase 3 pivotal trials (15 and MOTION) was the change from baseline in part III of UPDRS (motor subscale). The primary efficacy endpoint for ESPD in the phase 2 pivotal trial (Study 9) was the responder rate for a 30 % or greater improvement (i.e., reduction from baseline) in UPDRS Part III.
- The primary efficacy endpoint for LSPD in phase 3 pivotal trials (16 and SETTLE) was the change from baseline in “ON” time without troublesome dyskinesia (i.e., “ON” time without dyskinesia plus “ON” time with non-troublesome dyskinesia) based upon diary data.
- The combined trials in ESPD (15 and 17) and in LSPD (16 and 18) in which patients may have been treated continuously under double-blinded, placebo-controlled conditions for up to 1.5 and 2 years permitted placebo-controlled long-term safety analyses, a unique experience that we have never seen previously in Parkinson's disease. However, these combined trials were not conducive to investigating long-term efficacy because many patients (especially in the extension phase had increases in their dopaminergic treatment of Parkinson's disease(i.e., increase in total daily levodopa and/or addition of new dopaminergic medication for Parkinson's disease).
- **Blinded**, interim analyses of variance of pooled data had been prospectively planned in Studies 16 and SETTLE (27919) in each respective SAP to determine if the planned sample size was appropriate or if additional patients needed to be enrolled. Each interim analysis suggested that sample size was reasonably appropriate and that neither trial needed to enroll additional patients. However, it is not possible to exclude the possibility that a blinded review of the variance of pooled data of secondary efficacy endpoint by the sponsor did not have any impact on the sponsor’s protocol revisions of the prespecified, hierarchical sequence of statistical analyses of secondary efficacy endpoints prior to finalizing the Statistical Analysis Plan (SAP).

- The sponsor conducted an unblinded analysis of ocular safety data in Study 16. Although I have no specific reason to suspect that there was any unblinding of efficacy data, I cannot exclude that possibility.
- The sponsor noted that the database for Study 16 was re-opened on a few occasions after it had been locked. This conduct is undesirable and ostensibly as described by the sponsor does not seem to be problematic. However, it is not possible to exclude the possibility that inappropriate conduct by the sponsor occurred during these unlocking of the “locked” database. Nevertheless, I do not think that the sponsor inappropriately manipulated the efficacy data, especially regarding the results for the primary efficacy endpoint.

6 Review of Efficacy

Efficacy Summary

6.1 Indication

The sponsor’s proposed indication for safinamide is :

Safinamide is indicated for the treatment of patients with idiopathic Parkinson’s disease (PD) as add-on therapy to :

- A single DA-agonist at a stable dose in early stage (b) (4) patients, and
- (b) (4) L-dopa alone or in combination with other PD medications in mid- to late-stage (w) (4) patients

6.1.1 Methods

The key inclusion criteria for patients enrolled in the ESPD pivotal trials (15 and MOTION) were a diagnosis of idiopathic Parkinson's disease and a stable dose treatment with a concomitant dopaminergic for at least 4 weeks. Patients enrolled in Study 9 were required to have idiopathic Parkinson's disease and may not have been taking any treatment for Parkinson's disease or may have been receiving treatment with a dopaminergic agonist.

The key inclusion criteria for patients enrolled in the LSPD pivotal trials (16 and SETTLE) were a diagnosis of idiopathic Parkinson's disease, motor fluctuations of more than 1.5 hours daily and concomitant treatment with a stable dose of levodopa.

The sponsor submitted efficacy analyses (i.e., primary and secondary analyses) requested by the DNP (at Pre-NDA meeting) for the primary efficacy endpoint and key/important secondary efficacy endpoints (for the mITT population in individual pivotal trials (Studies 9, 15, 15 and 17 combined, MOTION in ESPD and Studies 16,16 and 18 combined, and SETTLE in LSPD). My

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review focused on efficacy results of individual pivotal trials and not on efficacy results of pooled trials that the sponsor also included in the Integrated Summary of Efficacy (ISE).

6.1.2 Demographics

The following tables show demographic information and baseline characteristics for the early stage and late/advanced stage populations of patients with Parkinson's disease.

Table 5 Demographic and Other Baseline Characteristics by Treatment Group of ESPD Patients from Pooled Studies 015 and MOTION (Safety Population)

	Safinamide			Placebo (N=315)
	50 mg/day (N=226)	100 mg/day (N=317)	Pooled 50/100 mg/day (N=543)	
Age (years)				
N	226	317	543	315
Mean	60.6	59.3	59.8	60.1
SD	10.26	10.36	10.33	10.57
Median	62.5	59.0	61.0	61.0
Min, Max	34.0, 80.0	30.0, 80.0	30.0, 80.0	33.0, 79.0
Age Category, n (%)				
<65	132 (58.4)	213 (67.2)	345 (63.5)	188 (59.7)
≥65	94 (41.6)	104 (32.8)	198 (36.5)	127 (40.3)
Gender, n (%)				
Male	136 (60.2)	214 (67.5)	350 (64.5)	189 (60.0)
Female	90 (39.8)	103 (32.5)	193 (35.5)	126 (40.0)
Race, n (%)				
Caucasian	179 (79.2)	226 (71.3)	405 (74.6)	221 (70.2)
Asian	26 (11.5)	59 (18.6)	85 (15.7)	60 (19.0)
Other	21 (9.3)	32 (10.1)	53 (9.8)	34 (10.8)
Ethnicity, n (%)				
Hispanic/Latin American	70 (31.0)	106 (33.4)	176 (32.4)	110 (34.9)
[Non-]Hispanic/Latin American	156 (69.0)	211 (66.6)	367 (67.6)	205 (65.1)
Weight (kg)				
N	225	316	541	314
Mean	74.1	75.5	75.0	74.2
SD	15.50	15.35	15.41	15.80
Median	74.0	75.0	75.0	72.8
Min, Max	38.8, 120.2	34.0, 133.5	34.0, 133.5	35.0, 131.0
Weight Category, n (%)				
<Median of Patients	107 (47.3)	138 (43.5)	245 (45.1)	157 (49.8)
≥Median of Patients	118 (52.2)	178 (56.2)	296 (54.5)	157 (49.8)
Region, n (%)				
North America	31 (13.7)	32 (10.1)	63 (11.6)	31 (9.8)
Non-NA	195 (86.3)	285 (89.9)	480 (88.4)	284 (90.2)
Western Europe	56 (24.8)	85 (26.8)	141 (26.0)	86 (27.3)
Other (All except NA, WE)	139 (61.5)	200 (63.1)	339 (62.4)	198 (62.9)

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Table 5 Demographic and Other Baseline Characteristics by Treatment Group of ESPD Patients from Pooled Studies 015 and MOTION (Safety Population) (Continued)

BMI (kg/m ²)				
N	225	315	540	314
Mean	26.4	26.8	26.7	26.7
SD	4.49	4.31	4.39	4.57
Median	26.3	26.4	26.3	26.3
Min, Max	16.3, 42.6	15.7, 44.1	15.7, 44.1	16.0, 42.3
BMI Category, n (%)				
< Median of Patients	110 (48.7)	148 (46.7)	258 (47.5)	152 (48.3)
≥ Median of Patients	115 (50.9)	167 (52.7)	282 (51.9)	162 (51.4)
PD Disease Duration (years)				
N	226	317	543	315
Mean	2.0	2.1	2.0	1.9
SD	1.44	1.48	1.46	1.42
Median	1.7	1.7	1.7	1.5
Min, Max	0.0, 5.1	0.0, 5.5	0.0, 5.5	0.1, 5.6
PD Disease Duration Category, n (%)				
< Mean of Patients	112 (49.6)	158 (49.8)	270 (49.7)	173 (54.9)
≥ Mean of Patients	114 (50.4)	159 (50.2)	273 (50.3)	142 (45.1)
Dopamine Agonist Concomitant Medication, n (%)				
Present	225 (99.6)	317 (100.0)	542 (99.8)	314 (99.7)
Absent	1 (0.4)	0 (0.0)	1 (0.2)	1 (0.3)
Blood Pressure Lowering Concomitant Medication, n (%)				
Present	91 (40.3)	108 (34.1)	199 (36.6)	134 (42.5)
Absent	135 (59.7)	209 (65.9)	344 (63.4)	181 (57.5)
UPDRS Section III (total score)				
N	226	314	540	314
Mean	21.0	19.7	20.3	20.1
SD	9.54	9.05	9.27	9.15
Median	20.0	18.0	19.0	19.0
Min, Max	5.0, 61.0	2.0, 59.0	2.0, 61.0	1.0, 61.0
Hoehn and Yahr Staging				
N	226	317	543	315
Mean	1.8	1.8	1.8	1.8
SD	0.59	0.55	0.57	0.54
Median	2.0	2.0	2.0	2.0
Min, Max	1.0, 3.0	1.0, 3.0	1.0, 3.0	1.0, 3.0

BMI=body mass index; Max=maximum; Min=minimum; NA=North America; PD=Parkinson's disease; SD=standard deviation.
(a) Regions are not mutually exclusive.
Source: ISS Table 13.2.1

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Table 6 Demographics and Other Baseline Characteristics by Treatment Group of LSPD Patients from Pooled Studies 16 and SETTLE (Safety Population)

	Safinamide			Placebo (N=497)
	50 mg/day (N=223)	100 mg/day (N=498)	All (N=721)	
Age (years)				
N	223	498	721	497
Mean	60.1	61.0	60.7	60.9
SD	9.66	9.10	9.28	9.25
Median	61.0	61.0	61.0	61.0
Min, Max	35.0, 78.0	35.0, 80.0	35.0, 80.0	30.0, 79.0
Age Category, n (%)				
<65	145 (65.0)	309 (62.0)	454 (63.0)	307 (61.8)
≥65	78 (35.0)	189 (38.0)	267 (37.0)	190 (38.2)
Gender, n (%)				
Male	157 (70.4)	334 (67.1)	491 (68.1)	323 (65.0)
Female	66 (29.6)	164 (32.9)	230 (31.9)	174 (35.0)
Race, n (%)				
Caucasian	43 (19.3)	228 (45.8)	271 (37.6)	230 (46.3)
Asian	180 (80.7)	267 (53.6)	447 (62.0)	265 (53.3)
Other	0	3 (0.6)	3 (0.4)	2 (0.4)
Ethnicity, n (%)				
Hispanic/Latin American	2 (0.9)	10 (2.0)	12 (1.7)	9 (1.8)
Non-Hispanic/Latin American	221 (99.1)	488 (98.0)	709 (98.3)	488 (98.2)
Weight (kg)				
N	223	496	719	496
Mean	63.1	68.3	66.7	67.9
SD	12.40	15.97	15.14	15.13
Median	61.0	66.8	65.0	66.0
Min, Max	38.5, 97.6	34.0, 125.0	34.0, 125.0	34.0, 124.5
Weight Category, n (%)				
< Median of Late Stage PD Patients	131 (58.7)	224 (45.0)	355 (49.2)	230 (46.3)
≥ Median of Early Late PD Patients	92 (41.3)	272 (54.6)	364 (50.5)	266 (53.5)
BMI (kg/m ²)				
N	223	495	718	496
Mean	23.9	24.8	24.5	24.8
SD	4.11	4.62	4.49	4.22
Median	23.7	24.4	24.1	24.4
Min, Max	15.0, 38.7	14.5, 43.0	14.5, 43.0	15.1, 43.1
BMI Category, n (%)				
< Median of Late Stage PD Patients	128 (57.4)	243 (48.8)	371 (51.5)	236 (47.5)
≥ Median of Late Stage PD Patients	95 (42.6)	252 (50.6)	347 (48.1)	260 (52.3)

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Table 6 Demographics and Other Baseline Characteristics by Treatment Group of LSPD Patients from Pooled Studies 16 and SETTLE (Safety Population) (Continued)

	Safinamide			Placebo (N=497)
	50 mg/day (N=223)	100 mg/day (N=498)	All (N=721)	
Geographic Region, n (%)^a				
NA	0	51 (10.2)	51 (7.1)	51 (10.3)
Non-NA	223 (100)	447 (89.8)	670 (92.9)	446 (89.7)
Western Europe	9 (4.0)	117 (23.5)	126 (17.5)	117 (23.5)
All other except NA and Western Europe	214 (96.0)	330 (66.3)	544 (75.5)	329 (66.2)
Disease Duration (years)				
N	223	498	721	497
Mean	7.9	8.6	8.4	8.7
SD	3.91	4.11	4.05	4.39
Median	6.6	7.4	7.1	7.3
Min, Max	-0.2, 25.3	-0.1, 28.4	-0.2, 28.4	0.2, 30.6
Disease Duration Category, n (%)				
< Mean of Late Stage PD Patients	135 (60.5)	233 (46.8)	368 (51.0)	241 (48.5)
≥ Mean of Late Stage PD Patients	88 (39.5)	265 (53.2)	353 (49.0)	256 (51.5)
UPDRS Section III (total score)				
N	222	494	716	494
Mean	27.3	25.0	25.7	25.6
SD	12.67	12.82	12.81	12.72
Median	26.0	24.0	25.0	24.0
Min, Max	2.0, 64.0	2.0, 73.0	2.0, 73.0	0.0, 74.0
Hoehn and Yahr Staging				
N	223	498	721	497
Mean	2.8	2.6	2.7	2.6
SD	0.62	0.63	0.63	0.65
Median	3.0	2.5	2.5	2.5
Min, Max	1.0, 4.0	1.0, 4.0	1.0, 4.0	1.0, 4.0
Dopamine Agonist, n (%)				
Present	140 (62.8)	334 (67.1)	474 (65.7)	337 (67.8)
Absent	83 (37.2)	164 (32.9)	247 (34.3)	160 (32.2)
Blood Pressure Lowering Concomitant Medication				
Present	91 (40.8)	184 (36.9)	275 (38.1)	176 (35.4)
Absent	132 (59.2)	314 (63.1)	446 (61.9)	321 (64.6)

BMI=body mass index; Max=maximum; Min=minimum; NA=North America; PD=Parkinson's disease; SD=standard deviation.

(a) Regions are not mutually exclusive.

Note: Patients 00010150160290018 and 0010150160460016 in Study 016 had negative study level PD Duration values.

Source: ISS Table 14.2.1

Reviewer Comment

- Demographic characteristics were reasonably similar for respective treatment groups in phase 3 pivotal trials for ESPD and LSPD.

6.1.3 Subject Disposition

The following information describes results for patient disposition in the pivotal trials.

Early Parkinson's disease (Early Stage Parkinson's disease – ESPD)

Table 7 Disposition by Treatment Group of ESPD Patients from Study 9

	Safinamide (mg/kg/day)			Placebo (N=58)
	0.5 (N=57)	1.0 (N=57)	All (N=114)	
	n (%)	n (%)	n (%)	n (%)
Safety Population[1]	56 (98.2)	56 (98.2)	112 (98.2)	56 (96.6)
Subjects who discontinued[2]	4 (7.1)	7 (12.5)	11 (9.8)	7 (12.5)
Reason for discontinuation				
Adverse Event	4 (7.1)	2 (3.6)	6 (5.4)	2 (3.6)
Death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Lost to Follow-Up	0 (0.0)	1 (1.8)	1 (0.9)	0 (0.0)
Lack of Efficacy	0 (0.0)	3 (5.4)	3 (2.7)	2 (3.6)
Non-Compliance	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Withdrew Consent	0 (0.0)	1 (1.8)	1 (0.9)	3 (5.4)
Termination by Investigator	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Termination by Sponsor	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Reviewer Comment

- The percentage of trial drop-outs for either safinamide dose was not greater than that for placebo. Neither was the specific reason for study drop-outs associated with safinamide treatment notably increased for either safinamide dose vs placebo.

Table 8 Disposition by Treatment Group of ESPD Patients from Study 15 (Safety Population in Trial Treated up to 6 Months)

	Safinamide (mg/day)			Placebo (N=90)
	100 (N=90)	200 (N=89)	All (N=179)	
	n (%)	n (%)	n (%)	n (%)
Safety Population[1]	90 (100.0)	89 (100.0)	179 (100.0)	90 (100.0)
Subjects who discontinued[2]	9 (10.0)	19 (21.3)	28 (15.6)	9 (10.0)
Reason for discontinuation				
Adverse Event	3 (3.3)	5 (5.6)	8 (4.5)	2 (2.2)
Death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Lost to Follow-Up	1 (1.1)	1 (1.1)	2 (1.1)	0 (0.0)
Lack of Efficacy	0 (0.0)	2 (2.2)	2 (1.1)	0 (0.0)
Non-Compliance	0 (0.0)	1 (1.1)	1 (0.6)	0 (0.0)
Withdrew Consent	3 (3.3)	7 (7.9)	10 (5.6)	7 (7.8)
Termination by Investigator	2 (2.2)	3 (3.4)	5 (2.8)	0 (0.0)
Termination by Sponsor	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Reviewer Comment

- The drop-out incidence for any reason for 200 mg safinamide was dose-related and approximately twice that of placebo. Discontinuation for adverse events was notably greater for 200 mg safinamide vs placebo.

Table 9 Disposition by Treatment Group of ESPD Patients from Pooled Studies 15 and 17 (Safety Population in Trial Treated up to 2 Years)

	Safinamide (mg/day)			Placebo (N=90)
	100 (N=90)	200 (N=89)	All (N=179)	
	n (%)	n (%)	n (%)	n (%)
Safety Population[1]	90 (100.0)	89 (100.0)	179 (100.0)	90 (100.0)
Subjects who discontinued[2]	25 (27.8)	27 (30.3)	52 (29.1)	25 (27.8)
Reason for discontinuation				
Adverse Event	6 (6.7)	6 (6.7)	12 (6.7)	5 (5.6)
Death	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)
Lost to Follow-Up	4 (4.4)	1 (1.1)	5 (2.8)	1 (1.1)
Lack of Efficacy	2 (2.2)	6 (6.7)	8 (4.5)	5 (5.6)
Non-Compliance	0 (0.0)	1 (1.1)	1 (0.6)	0 (0.0)
Withdrew Consent	11 (12.2)	10 (11.2)	21 (11.7)	12 (13.3)
Termination by Investigator	2 (2.2)	3 (3.4)	5 (2.8)	1 (1.1)
Termination by Sponsor	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Reviewer Comment

- The incidence of drop-outs for any reason was not notably different for any treatment group for the combined Studies 15 and 17 (placebo-controlled extension). Although the incidence of drop-out for lost-to-follow-up was notably greater for 100 mg safinamide compared to 200 mg safinamide and placebo, this difference did not appear to be of any rationale significance. No other differences were considered notable.

Table 10 Disposition by Treatment Group of ESPD Patients from Study MOTION (Safety Population in Trial Treated up to 6 Months)

	Safinamide (mg/day)			Placebo (N=225)
	50 (N=227)	100 (N=227)	All (N=454)	
	n (%)	n (%)	n (%)	n (%)
Safety Population[1]	226 (99.6)	227 (100.0)	453 (99.8)	225 (100.0)
Subjects who discontinued[2]	28 (12.4)	18 (7.9)	46 (10.2)	27 (12.0)
Reason for discontinuation				
Adverse Event	4 (1.8)	4 (1.8)	8 (1.8)	13 (5.8)
Death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Lost to Follow-Up	4 (1.8)	6 (2.6)	10 (2.2)	6 (2.7)
Lack of Efficacy	12 (5.3)	3 (1.3)	15 (3.3)	1 (0.4)
Non-Compliance	2 (0.9)	2 (0.9)	4 (0.9)	0 (0.0)
Withdrew Consent	3 (1.3)	3 (1.3)	6 (1.3)	4 (1.8)
Termination by Investigator	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.3)
Termination by Sponsor	2 (0.9)	0 (0.0)	2 (0.4)	0 (0.0)
Other	1 (0.4)	0 (0.0)	1 (0.2)	0 (0.0)

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- The incidence of drop-outs for any reason was not notably different for either safinamide treatment group (vs placebo) for Study MOTION. Neither were any differences in the incidence of specific causes for study discontinuation of the different treatment groups considered to be notable.

Advanced Parkinson's disease (Late Stage Parkinson's disease – LSPD)

Table 11 Disposition by Treatment Group of LSPD Patients from Study 16 (Safety Population in Trial Treated up to 6 Months)

	Safinamide (mg/day)			Placebo (N=222)
	50 (N=223)	100 (N=224)	All (N=447)	
	n (%)	n (%)	n (%)	n (%)
Safety Population[1]	223 (100.0)	224 (100.0)	447 (100.0)	222 (100.0)
Subjects who discontinued[2]	21 (9.4)	29 (12.9)	50 (11.2)	25 (11.3)
Reason for discontinuation				
Adverse Event	11 (4.9)	13 (5.8)	24 (5.4)	11 (5.0)
Death	0 (0.0)	4 (1.8)	4 (0.9)	1 (0.5)
Lost to Follow-Up	4 (1.8)	4 (1.8)	8 (1.8)	5 (2.3)
Lack of Efficacy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Non-Compliance	1 (0.4)	2 (0.9)	3 (0.7)	1 (0.5)
Withdrew Consent	5 (2.2)	6 (2.7)	11 (2.5)	7 (3.2)
Termination by Investigator	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Termination by Sponsor	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Reviewer Comment

- The incidence of drop-outs for any reason was slightly higher for 100 mg safinamide treatment group (vs placebo) for Study 16. The incidence of discontinuation for adverse event was slightly higher for 100 mg safinamide (vs placebo) and the incidence of death was also slightly higher for this dose (Please refer to 7.3.1 Deaths and my review of this topic).

Table 12 Disposition by Treatment Group of LSPD Patients from Pooled Studies 16 and 18 (Safety Population in Trial Treated up to 2 Years)

	Safinamide (mg/day)			Placebo (N=222)
	50 (N=223)	100 (N=224)	All (N=447)	
	n (%)	n (%)	n (%)	n (%)
Safety Population[1]	223 (100.0)	224 (100.0)	447 (100.0)	222 (100.0)
Subjects who discontinued[2]	62 (27.8)	59 (26.3)	121 (27.1)	58 (26.1)
Reason for discontinuation				
Adverse Event	17 (7.6)	21 (9.4)	38 (8.5)	15 (6.8)
Death	3 (1.3)	9 (4.0)	12 (2.7)	7 (3.2)
Lost to Follow-Up	11 (4.9)	11 (4.9)	22 (4.9)	9 (4.1)
Lack of Efficacy	2 (0.9)	1 (0.4)	3 (0.7)	4 (1.8)
Non-Compliance	2 (0.9)	2 (0.9)	4 (0.9)	3 (1.4)
Withdrew Consent	27 (12.1)	15 (6.7)	42 (9.4)	20 (9.0)
Termination by Investigator	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Termination by Sponsor	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

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Reviewer Comment

- The incidence of drop-outs for any reason was similar amongst all treatment groups for combined Studies 16 and 18. However, the incidence of discontinuation for adverse event was slightly higher for 100 mg safinamide (vs placebo) and the incidence of death was also notably greater for this dose (Please refer to 7.3.1 Deaths and my review of this topic).

Table 13 Disposition by Treatment Group of LSPD Patients from Study SETTLE (Safety Population in Trial Treated up to 6 Months)

	Safinamide 100 (mg/day) (N=274)	Placebo (N=275)
	n (%)	n (%)
Safety Population[1]	274 (100.0)	275 (100.0)
Subjects who discontinued[2]	30 (10.9)	35 (12.7)
Reason for discontinuation		
Adverse Event	13 (4.7)	12 (4.4)
Death	1 (0.4)	2 (0.7)
Lost to Follow-Up	8 (2.9)	5 (1.8)
Lack of Efficacy	1 (0.4)	3 (1.1)
Non-Compliance	0 (0.0)	1 (0.4)
Withdrew Consent	3 (1.1)	10 (3.6)
Termination by Investigator	4 (1.5)	0 (0.0)
Termination by Sponsor	0 (0.0)	0 (0.0)
Other	0 (0.0)	2 (0.7)

Reviewer Comment

- The incidence of study discontinuation was not notably greater for 100 mg safinamide (vs placebo) for any reason nor for any specific cause.

6.1.4 Analysis of Primary Endpoint(s)

Sponsor’s Analytical Approaches for Handling Efficacy Data

The sponsor followed two approaches on how the post-baseline efficacy data were to be analyzed :

- **On-Treatment Approach:** In this approach, only the “On-Treatment” efficacy data were to be used for analysis. The On-Treatment efficacy data are all the post-baseline efficacy data that were collected up to either an increase of anti-Parkinsonian treatment, or Premature Treatment Discontinuation, or end of treatment, whichever occurs first.
- **Observed Case Approach** (also known as On-and-Off Treatment): In this approach, all the post-baseline efficacy data that were collected up to either study discontinuation or end of study were to be used for analysis, which include both On-Treatment and Off-Treatment efficacy data.

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A subject who permanently discontinued the treatment may or may not have discontinued from the study and was considered a “treatment drop-out.” A subject who permanently discontinued the treatment and continued on study until either discontinuation of study or end of study was considered a “retrieved treatment drop-out” (RDO) as a subset of treatment drop-outs. A subject who permanently discontinued the study was considered a “study drop-out.”

The Off-Treatment efficacy data were all the post-baseline efficacy data that were collected at the regularly scheduled visits after a subject is considered as Off-Treatment, which is triggered by either an increase of anti-Parkinsonian treatment (but a subject might remain on treatment), or Premature Treatment Discontinuation (but a subject might remain on study as noted in a protocol), whichever occurs first.

The “ON” treatment approach was applied as the primary analysis and censored data at the time of “rescue medication.” Rescue medication was defined as increase of total daily dose of levodopa or dopaminergic agonist or other Parkinson's disease drug of at least 20 % (or more) OR addition of new Parkinson's disease drug in Study 16. However, the definition of rescue medication and/or requirement for censoring efficacy in other pivotal protocols was not so precise as in Study 16 but was more vague in the other pivotal trials. When the sponsor was asked about this issue, the sponsor provided these additional clarifications shown below here in italics :

“The decision to increase the dose of concomitant PD medication or to add an additional PD medication (i.e., rescue medication) was based on the clinical judgment of the Investigator that the patient was not benefiting from study medication, and was at risk of worsening. This conclusion was based on discussions with the patient and caregiver. No specific guidelines or criteria for making these decisions were provided to the Investigators. There were no specific measurements, or scores on any measure, that were used for making this judgment.”

“No specific guidelines or criteria for administering “rescue medication” were provided. The decision by the Investigator to increase the dose of concomitant PD medication or add another PD medication could be made at any time and was not influenced by the stage of the trial. Investigators added “rescue medication” when they reached a conclusion that the patient was not benefiting from study medication, and was at risk of worsening. This conclusion could be reached at any point in the trial, and was not contingent on the patient staying on study medication for a certain length of time.”

“The definition of “rescue medication” used in each of the safinamide pivotal trials (9, 15, MOTION, 016 and SETTLE) and double-blind extension studies (17, 18 and MOTION Extension) for censoring efficacy data in the primary analysis are summarized in Table 3. It should be noted that the term “rescue medication” was not used in all studies, but the principle of censoring efficacy data following an increase in dose of concomitant PD medication or addition of another PD medication was implemented consistently across studies.”

The “ON” and “OFF” treatment/observed case approach included all data analyzed regardless of rescue medication or RDO data.

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- After the statistical reviewer looked at the sponsor's efficacy data, it appeared that the sponsor did not always conduct analyses according to all of the specific terms prespecified in each respective SAP. Consequently, repeat analyses were requested on multiple occasions before the statistical team was satisfied that appropriate analyses had been conducted and submitted along with appropriate efficacy datasets.
- Because the sponsor's "completer" analyses could have included patients who had discontinued treatment but had not discontinued from the trial (i.e., RDO patients), I did not focus much attention of the sponsor's completer analyses for efficacy.
- Although the sponsor censored patients and their efficacy data if they had received "rescue medication." (i.e., an increase in concomitant medication for Parkinson's disease or addition of a new drug for this disorder), the sponsor did not analogously censor patients who had experienced a "significant" or some threshold decrease in concomitant Parkinson's disease medications. I believe that such censoring should have also been conducted because such decreases in Parkinson's disease medications could have potentially impacted efficacy results.
- There was a specific definition of when the patient had received "rescue medication" (e.g., increase of total daily dose of concomitant Parkinson's disease medications of at least 20 % or addition of a new drug; and therefore when censoring of efficacy data was required) only for Study 16. In contrast, however, the protocols and/or Statistical Plans (SAPs) for the other pivotal trials did not provide a specific definition of a threshold increase for total daily dose of concomitant Parkinson's disease medication that would be considered "rescue medication and prompt censoring of efficacy data) but only referred vaguely to an "increase" in dose of concomitant medication.

In response to a request for clarification on this issue, the sponsor commented :” It should be noted that the term “rescue medication” was not used in all studies, but the principle of censoring efficacy data following an increase in dose of concomitant PD medication or addition of another PD medication was implemented consistently across studies.”

Early Parkinson's disease (ESPD)

Study 9

There were no RDO patients who discontinued treatment but continued in the trial for any treatment group nor any patients whose efficacy data were censored.

Table 14 shows results for the primary efficacy endpoint in Study 9.

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Table 14 Study 9 : Responder Rates (Improvement in UPDRS Part III from Baseline at Least 30 % as Primary Efficacy Endpoint) at Week 12 in the ITT Population (n=167) and Subpopulations Defined Based on Current PD Treatment

Responder Rates(a) (n/% of Patients)	Safinamide 0.5 mg/kg/day		Safinamide 1.0 mg/kg/day		Placebo		P-value vs. Placebo Group (Logistic regression analysis)	
	n/N	%	n/N	%	n/N	%	Saf 0.5 mg/kg	Saf 1.0 mg/kg
Population								
Total population	17/55	30.9	21/56	37.5	12/56	21.4	0.143	0.018
Single DA-agonist (n=101)	12/33	36.4	16/34	47.1	7/34	20.6	0.195	0.006
De novo (n=66)	5/22	22.7	5/22	22.7	5/22	22.7	0.874	0.925

ANCOVA=analysis of covariance; DA=dopamine; de novo=currently untreated with any PD medication; n=number of responders; N=total number in group; Saf=safinamide; UPDRS III=Unified Parkinson's Disease Rating Scale - Section III (Motor Examination). Endpoint=Week 12 or early discontinuation. a. Responder was defined as ≥30% improvement from baseline in UPDRS III total score. Source: CSR Study 009.

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- High dose safinamide (1.0 mg/kg/day) produced a statistically significant responder rate for UPDRS part III/motor subscale of at least a 30 % (or higher) improvement (i.e., decrease of UPDRS part III) vs placebo for the whole population and also for the subgroup on a dopaminergic agonist as shown in Table 14. Low dose safinamide (0.5 mg/kg/day) did not produce a statistically significant improvement vs placebo for either population. Based upon average weight in this trial, low dose patients received ~ 35-40 mg safinamide and high dose patients received about ~ 70-80 mg safinamide.
- Because this efficacy endpoint is not an acceptable primary efficacy endpoint for the Division of Neurology Products (DNP) for demonstrating efficacy in patients with early Parkinson's disease, we had informed the sponsor that our primary interest for demonstrating efficacy in this trial would be based upon results for the efficacy endpoint of a change from baseline in UPDRS part III/motor subscale. However, safinamide did not produce a statistically significant benefit (vs placebo) for this critically important efficacy endpoint (see 6.1.5 Analysis of Secondary Endpoints(s) and Secondary Analyses).
- In addition to my concern about the utility of the responder result for demonstrating efficacy, I have several additional concerns regarding efficacy results from this trial. First, this phase 2 trial was relatively small and did not enroll a homogenous population of patients without motor fluctuations but enrolled some patients who were using a concomitant dopaminergic agonist and others who were not. Second, efficacy based upon the primary endpoint, was only suggested in patients using a concomitant dopaminergic agonist and was not suggested in patients not using such treatment. This result is highly unusual because I am not aware of any FDA drug approved for advanced Parkinson's disease (i.e., ropinirole, pramipexole, rotigotine, rasagiline) which does not have an approval for patients with early Parkinson's disease without motor fluctuations and without any concomitant dopaminergic treatment when one or more pivotal trials were conducted by the sponsor and submitted to the Agency for this indication. Third, the formulation (capsules) and daily dosing investigated (0.5 and 1 mg/kg) in this trial was

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not the same formulation (tablets) and same daily dosing (i.e., 50 mg, 100 mg, 200 mg) which the sponsor investigated in the phase 3 pivotal trial program and which the sponsor would like to market. Fourth, safinamide did not produce a statistically significant benefit on the change from baseline in UPDRS part III/motor subscale (see 6.1.5 Analysis of Secondary Endpoints(s) and Secondary Analyses), an important efficacy endpoint of interest to the DNP. In summary, results from Study 9 did not provide support for the approval of 50 mg or 100 mg tablets of safinamide for treatment of patients with early Parkinson's disease (b) (4) who are taking a concomitant dopaminergic agonist.

Study 15

Study 15 results for the primary efficacy endpoint (change from baseline in UPDRS part III/motor subscale) are presented in Table 15. The primary efficacy analysis was performed on the mITT population using a mixed effect model with treatment, visit, and treatment-by-visit interaction as the fixed effects, country as the random effect, and baseline UPDRS III score as the covariate. The unstructured covariance matrix and “on treatment” approach were used. The planned multiple testing procedure was to sequentially test safinamide 200 mg/day versus placebo then safinamide 100 mg/day versus placebo if safinamide 200 mg/day is statistically significantly better than placebo. Each test was to be conducted at the two sided significance level $\alpha = 0.05$.

The number of RDO patients in Study 15 was quite small (placebo – 4, 50 mg – 2, 100 mg -1) in each treatment group. The number of patients with efficacy data censored was also small (placebo – 2, 50 mg – 3, 100 mg -1).

Table 15 Study 15 : Primary Efficacy Endpoint : Change from Baseline for UPDRS Part III at Endpoint/Week 24 for the ITT Population (No Imputation of Missing Data) (But also for mITT Population Because Baseline Data Required)

Visit	Statistic	Treatment					
		Safinamide				Placebo	
		High dose		Low dose		Value	Change
	Value	Change	Value	Change	Value	Change	
Endpoint	N	81	81	86	86	87	87
	Mean	15.6	-3.9	16.3	-6.0	17.1	-3.6
	SD	9.61	6.01	8.97	7.18	8.85	7.08
	Min	2	-18	1	-26	3	-24
	Median	14.0	-4.0	15.0	-5.0	16.0	-3.0
	Max	51	13	46	8	44	18
	95% CI	[-2.3, 1.4]		[-3.7, -0.1]			
	Point Estimate	-0.4		-1.9			
	p-value	0.6504		0.0419			

Randomized Low dose = 100 mg and Randomized High dose = 200 mg

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- This trial (Study 15) does not support efficacy for ESPD patients using a concomitant dopaminergic agonist because high dose safinamide (200 mg) was not statistically superior to placebo for the primary efficacy endpoint (and was only minimally different than placebo) and the SAP provided for a hierarchical statistical comparison of high dose safinamide vs placebo before comparing the effect of low dose safinamide (100 mg) vs placebo (Table 15). Thus, according to the prespecified SAP, statistical testing could not formally be conducted when the high dose failed showing statistically significant superiority to placebo. The p value of 0.0419 for the treatment difference of low dose safinamide vs placebo is a nominal p value that does not take into account multiple comparisons. Furthermore, a statistically significant benefit of low dose safinamide (that is only 50 % lower than high dose safinamide is not scientifically plausible when a 2 fold higher dose did not demonstrate nor suggest any efficacy for this endpoint.
- There are also concerns with the conduct of this trial because significant numbers of placebo patients were found to have measureable levels of safinamide at different visits in this trial. The precise explanation for this phenomenon was not clear.

Study 17 (Analysis Reflects Pooled Results of Studies 15 and 17)

The number of RDO patients in combined Studies 15 and 17 was quite small (placebo – 0, 50 mg - 2, 100 mg - 1) in each treatment group. However, the number of patients with efficacy data censored was quite large (placebo – 28, 50 mg - 21, 100 mg -23).

Table 16 shows results for the primary efficacy endpoint in Study 17.

Table 16 Study 17 : Primary Efficacy Variable: Time from Baseline (Start of Study 15) to “Intervention” or Last Follow-up (Days) in Study 17 (All Randomized Patients in Study 15)

Test	Statistic	Treatment	
		Pooled Safinamide	Placebo
	N	179	90
	Mean	349.1	347.2
	SD	196.36	182.03
Log-rank	p-value	0.3342	--
	Median (Time to ‘Intervention’ only)	559.0	466.0

N=Number of patients; SD=Standard deviation.

Baseline (Study 015), defined as the last observation before first administration of study medication in Study 015.

Time to ‘Intervention’ or follow-up (days) = First date of event – first date of study medication administration in Study 015 + 1.

Log-rank test was used to determine p-value for differences in event-free survival curves.

Source: CSR Study 017.

Reviewer Comments

- There was no statistically significant difference in the time to “intervention” for safinamide-treated vs placebo-treated patients who required a pharmacological “intervention” for their Parkinson's disease because their condition worsened.

Study MOTION (27918)

The analysis results of the primary efficacy endpoint (change from Baseline to Week 24 in the UPDRS Part III score) are presented in Table 17. The primary efficacy analysis was performed on the ITT population using an ANCOVA model with treatment and region effects and baseline value of the UPDRS Section III score as the covariate. The “on treatment” approach and the LOCF method were used for the analysis. The planned multiple testing procedure was to sequentially test safinamide 100 mg/day versus placebo then safinamide 50 mg/day versus placebo if safinamide 100 mg/day is statistically significantly superior to placebo. Each test was to be conducted at the two-sided significance level $\alpha = 0.05$.

The number of RDO patients in Study MOTION was quite small (placebo – 3, 50 mg -1, 100 mg -1) in each treatment group. The number of patients with efficacy data censored was notable (placebo - 9, 50 mg - 7, 100 mg -6) but relatively small compared to the total number of patients randomized for each treatment group.

Table 17 show results for the primary efficacy endpoint for Study MOTION.

Table 17 Study 27918 (MOTION): Primary Efficacy Endpoint : Change from Baseline in UPDRS Part III at Week 24 Baseline for ITT Population (ANCOVA [LOCF])

Visit Statistic	Treatment					
	Safinamide 50 mg/day		Safinamide 100 mg/day		Placebo	
	Value	Change	Value	Change	Value	Change
Baseline						
n (missing)	227 (0)	---	227 (0)	---	225 (0)	---
Mean (SD)	21.0 (9.52)	---	18.9 (8.40)	---	19.8 (8.95)	---
Week 24						
n (missing)	227 (0)	227 (0)	227 (0)	227 (0)	225 (0)	225 (0)
Mean (SD)	19.0 (10.3)	-1.95 (7.35)	16.9 (8.84)	-1.96 (5.53)	18.7 (9.76)	-1.10 (6.17)
LS Mean (SE)	---	-1.60 (0.42)	---	-1.98 (0.42)	---	-0.95 (0.42)
LS Diff vs Placebo (SE)	---	-0.65 (0.58)	---	-1.04 (0.58)	---	---
95% CI of LS Diff	---	-1.79, 0.48	---	-2.17, 0.10	---	---
p-value vs. Placebo	---	0.259	---	0.073	---	---

ANCOVA=Analysis of Covariance; CI=Confidence interval; Diff=Difference; ITT=Intent to Treat; LOCF=Last Observation Carried Forward; LS=Least squares; n=Number of patients with an evaluation; SD=Standard deviation; SE=Standard error; UPDRS III=Unified Parkinson's Disease Rating Scale – Section III.

Note: Parametric ANCOVA model is based on the change from baseline to endpoint with fixed effects for treatment and region and baseline value as covariate. All p-values, LS means and confidence intervals are calculated from the ANCOVA model.

Source: CSR Study 27918 (MOTION).

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- Because the SAP specified a hierarchical statistical approach in which formal statistical testing should cease if the 100 mg dose is not statistically superior ($p = 0.073$ and not < 0.05) to placebo for the primary efficacy endpoint, formal testing with a p value should not have been conducted for the 50 mg when the 100 mg dose failed the test for superiority as shown in Table 17. Regardless, the 50 mg dose group also failed to be superior to the placebo group according to the nominal p value shown.
- The magnitude of the treatment difference (safinamide – placebo) for the primary efficacy endpoint was relatively small for the 50 mg dose (- 0.65) and 100 mg dose (-1.04) particularly compared to the effect (~ -4 to -5) of dopaminergic agonists (e.g., ropinirole, pramipexole, rotigotine) on that same endpoint and was also smaller than the magnitude of the benefit (~ -2) of 1 mg rasagiline on that same endpoint.
- Considering that none of these three trials (Studies 9, 15, MOTION) in early Parkinson's disease can be considered positive, I am unable to conclude that safinamide is an effective treatment of Parkinson's disease patients without motor fluctuations (i.e., ESPD) but who are using a concomitant dopaminergic agonist. The statistical review by the primary reviewer, Dr. Xiangmin Zhang also fails to conclude that safinamide is effective for this population. Finally, it is also noteworthy that despite the fact the European Medicines Agency (EMA) concluded that safinamide was effective in Parkinson's disease patients with motor fluctuations and adjunctive levodopa (and approved safinamide for treating this population), EMA did not approve safinamide for early Parkinson's disease. The EMA summary review noted that it was able to conclude that safinamide is effective for this population after it reviewed the same efficacy results which I have reviewed.

Advanced Parkinson's disease (LSPD)

Study 16

The primary endpoint was change from Baseline to Week 24 in total daily “on” time (i.e., “on” time without troublesome dyskinesia = “on” time without dyskinesia + “on” time with non-troublesome dyskinesia) during 18-hour diary recording period.

The primary efficacy analysis was performed on the modified intent-to-treat (mITT) population using a mixed effect model repeated measure (MMRM), with treatment, center, visit, and treatment by visit interaction as the fixed effects and baseline as the covariate. The mITT population is defined as all patients randomized, treated, having baseline measurement, and having at least one post-baseline measurement. The unstructured variance-covariance matrix, Kenward-Roger approximation, and “on treatment” approach (i.e. patient’s data were censored at the time of rescue medication intake or retrieved drop-outs occurrence) were used for the analysis.

There were no RDO patients in Study 16. However, the number of patients with efficacy data censored was quite large (placebo – 21, 50 mg - 22, 100 mg -15).

Table 18 shows results for the primary efficacy endpoint for Study 16.

Table 18 Study 16 : Change from Baseline for Treatment Difference (Safinamide – Placebo) for Primary Efficacy Endpoint (“ON” without Troublesome Dyskinesia) for ITT Population According to Safinamide Treatment for MMRM and ANCOVA Analyses

Study 016: Change from Baseline at Endpoint (“ON treatment” approach)					
Efficacy Parameter	Statistic (a)	mITT Population			
		MMRM Analysis (b)		ANCOVA (LOCF) Analysis (c)	
		50 mg/day (n=217)	100 mg/day (n=216)	50 mg/day (n=217)	100 mg/day (n=216)
ON without T Dysk (h)	LS Diff vs Pbo	0.50	0.53	0.46	0.55
	p-value	0.0356	0.0238	0.0387	0.0134

Figure 2 shows the time course of the increase in “ON” time without troublesome dyskinesia for all treatments in Study 16 for each treatment group and the number of patients in each treatment group at each visit.

Figure 2 Study 16 : Mean (± Standard Error) Change from Baseline in Total Daily “On” Time Over Time and According to Treatment

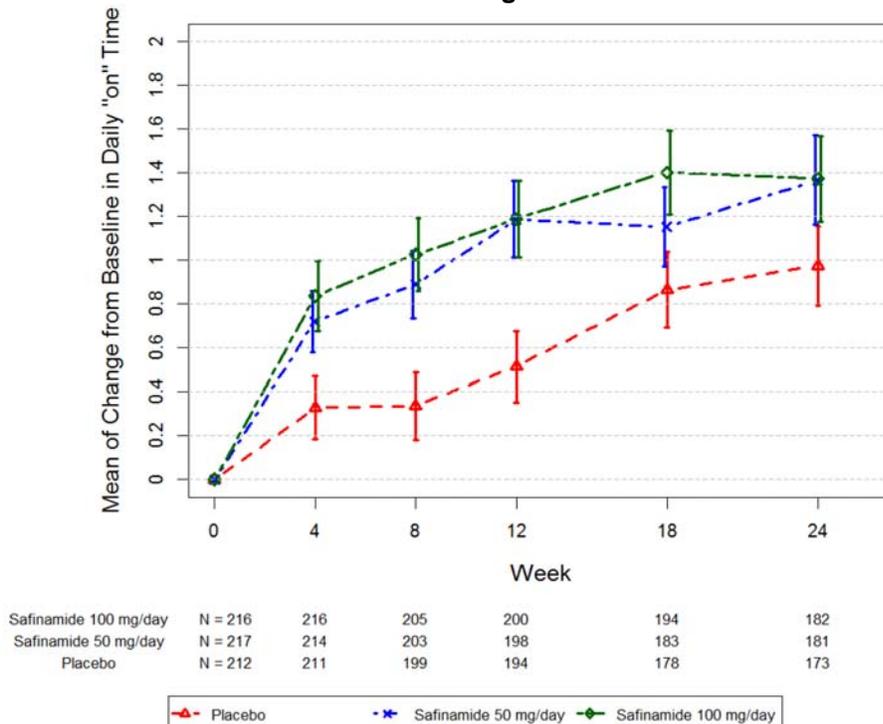
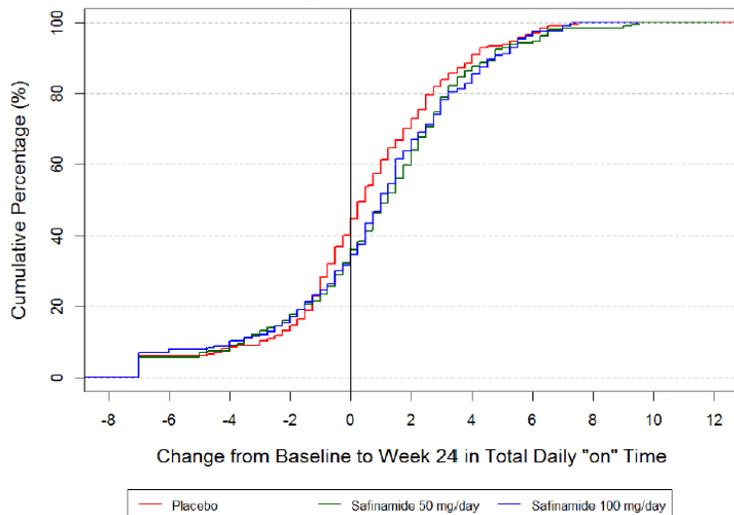


Figure 3 shows the cumulative distribution function (CDFs) for the cumulative percentage of patients with different changes from baseline in “ON” time without troublesome dyskinesia for each treatment group.

Figure 3 Study 16 : Empirical Cumulative Distribution Function for the Change from Baseline to Week 24 in Total daily “ON” Time Without Troublesome Dyskinesia According to Treatment



Source : Statistical Reviewer, Dr. Zhang

Reviewer Comments

- Table 18 shows the effect of safinamide (50 mg and 100 mg) on the primary efficacy endpoint, “ON” without troublesome dyskinesia (i.e., “ON” without dyskinesia + “ON” with non-troublesome dyskinesia) based upon 18 hour diary results. Both doses produced a similar treatment difference (safinamide-placebo) of approximately a 0.5 hour increase for this endpoint that can also be considered “good ON” time. Although the primary analysis with MMRM did not suggest any dose-response for this benefit, the ANCOVA-LOCF analysis suggested a slightly greater benefit for the higher dose. Overall, the benefit was quite similar for both analyses.
- The number of patients whose efficacy data were censored was lowest in the 100 mg safinamide treatment. Conceivably, this could have occurred because the 100 mg safinamide dose was most effective. However, the fact that the efficacy was similar for the 50 mg and 100 mg doses for the primary efficacy endpoint does not support this potential explanation.
- Based upon this trial, the magnitude of this benefit is relatively small and similar to the benefit shown for low dose rasagiline (0.5 mg daily), and notably lower than the benefit (increase of good “ON” time ranging from 0.8-1 hour) of high dose rasagiline (1 mg) and that of other drugs approved for LSPD for this same endpoint.
- Figure 2 shows that the increase in “ON” time without troublesome dyskinesia progressively increases over 24 weeks for each treatment and that the difference between

each safinamide dose and placebo appeared to be maximal at week 8 and relatively stable from weeks 8 to 24. The increase for each safinamide dose was relatively similar over the 24 week treatment period. This figure also shows the number of patients at baseline and the number who contributed to efficacy data at each visit. These numbers progressively decrease over time, to a relatively similar degree for each treatment because patients discontinued from the trial or from taking randomized study medication, or had their data censored because of “rescue medication.”

- Figure 3 shows that the cumulative distribution function curves for safinamide demonstrate a clear separation from placebo for a decrease in “ON” time without troublesome dyskinesia of approximately 1 hour for ~ 25 % of all patients up to an increase in “ON” time without troublesome dyskinesia of approximately 5 hours for ~ 90 % of all patients. The shift of both safinamide curves for 50 mg and 100 mg safinamide to the right of the placebo curve between 25 % and 90 % of patients demonstrates efficacy for these safinamide doses.
- Altogether, results of these analyses clearly show that safinamide is an effective treatment in this population but the average benefit appears to be relatively small.

Study 18 (Analysis Reflects Pooled Results of Studies 16 and 18)

There were no RDO patients in combined Studies 16 and 18. However, the number of patients with efficacy data censored was very large (placebo - 85, 50 mg - 95, 100 mg - 94).

Table 19 shows results for the primary efficacy endpoint (dyskinesia rating scale-DRS) for patients treated in pooled Studies 16 and 18 (i.e., patients starting in Study 16 and continuing treatment in Study 18).

Table 19 Study 18: DRS Scores for Treatment Difference (Safinamide – Placebo) During ON Time in Study 18 (ITT Population- MMRM)

DRS Change from baseline	Safinamide 50 mg/day			Safinamide 100 mg/day		
	N	LS Diff vs Placebo (95% CI)	P-value	N	LS Diff vs Placebo (95% CI)	P-value
ITT population	223	-0.51(-1.32, 0.29)	NS	223	-0.59 (-1.40, 0.21)	NS
DRS > 4 population	86	-0.73 (-1.84, 0.39)	NS	80	-1.22 (-2.33, -0.11)	0.0317

DRS=Dyskinesia Rating Scale; ITT=intent to treat; LS Diff=least squares difference; MMRM=mixed model repeated measures; NS=not significant;

Source: CSR Study 018 EOT Tables 44.2 and Ad Hoc 2.2.

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Table 20 Summary of Mean Change in the DRS During *On Time* in Studies 16 AND 18 —ITT Population

Study/ Week	Statistic	DRS During <i>On Time</i> ^a					
		Placebo (N = 222)		Safinamide 50 mg/day (N = 223)		Safinamide 100 mg/day (N = 224)	
		Value	Change	Value	Change	Value	Change
Study 016/ Baseline ^b	n	222	—	223	—	223	—
	Mean (SD)	3.4 (3.93)	—	3.9 (3.89)	—	3.7 (4.07)	—
	Median	2	—	4	—	3	—
	Min, Max	0, 17	—	0, 16	—	0, 20	—
Study 016/ Week 12	n	201	201	198	198	204	203
	Mean (SD)	3.1 (3.48)	-0.2 (2.25)	3.5 (3.61)	-0.4 (2.30)	3.4 (3.83)	-0.4 (2.62)
	Median	2	0	3	0	3	0
	Min, Max	0, 16	-13, 9	0, 16	-8, 7	0, 20	-12, 13
Study 018/ (Baseline)	n	179	179	184	184	184	183
	Mean (SD)	3.0 (3.40)	-0.3 (2.11)	3.6 (3.77)	-0.2 (2.58)	3.4 (3.79)	-0.4 (3.20)
	Median	2	0	3	0	2	0
	Min, Max	0, 16	-13, 9	0, 17	-9, 9	0, 20	-12, 13
Study 018/ (Week 24)	n	100	100	97	97	97	97
	Mean (SD)	3.2 (3.39)	-0.2 (2.56)	3.3 (3.54)	-0.5 (3.02)	3.1 (3.49)	-0.8 (3.34)
	Median	2	0	3	0	2	0
	Min, Max	0, 12	-13, 8	0, 17	-8, 11	0, 16	-12, 10
Study 018/ (Week 52)	n	78	78	79	79	84	84
	Mean (SD)	2.9 (3.33)	-0.2 (2.74)	2.8 (3.16)	-1.0 (2.65)	3.0 (3.33)	-0.9 (3.42)
	Median	1	0	2	0	3	0
	Min, Max	0, 10	-13, 8	0, 13	-8, 4	0, 11	-12, 11
Study 018/ (Week 78) ^c	n	64	64	69	69	70	70
	Mean (SD)	3.3 (3.47)	0 (3.02)	2.7 (2.96)	-1.2 (2.88)	2.8 (3.43)	-1.1 (4.06)
	Median	2	0	2	0	2	0
	Min, Max	0, 12	-14, 7	0, 13	-9, 5	0, 18	-12, 12
LS difference vs placebo	LS mean	—	0.32	—	-0.19	—	-0.28
	95% CI	—	—	—	-0.51	—	-0.59
	95% CI	—	—	—	(-1.32, 0.29)	—	(-1.40, 0.21)
	<i>P</i> value ^d	—	—	—	0.2125	—	0.1469

Abbreviations: CI, confidence interval; LS, least squares; SD, standard deviation.

^a *On time* was defined as *on time* without dyskinesia plus *on time* with minor dyskinesia.

^b Baseline or last nonmissing value before study drug was taken.

^c Study 018 (Week 78) or last available observation (LOCF).

^d Treatments were compared using a repeated measures model, based upon the change from Baseline, with terms for Baseline, treatment, pooled center, visit, and treatment*visit interaction, using the unstructured covariance structure. *P* values for the overall treatment effect were 0.5443 for treatment, < 0.0001 for pooled center, 0.2310 for visit, and 0.7149 for treatment*visit.

Source: EOT Table 44.2.

Reviewer Comment

- Table 19 shows that there was no statistically significant effect of either safinamide dose on the primary efficacy endpoint of a change from baseline in DRS for the ITT population in combined Studies 16 and 18. Although the sponsor showed a statistically significant change for the 100 mg dose group for the subgroup with DRS > 4, I cannot attach any significance to this finding in this arbitrary subgroup analysis.
- Table 20 shows results for the mean change from baseline in DRS over time and including the final study visit in combined Studies 16 and 18. There was not statistically significant benefit at the final study visit.

Study SETTLE

The primary efficacy analysis of the primary efficacy endpoint (i.e., change from Baseline to Week 24 in total daily “on” time without troublesome dyskinesia over 18 hours as measured by diary cards) was performed on the mITT population using an ANCOVA model, with treatment and region effects and baseline value of the total daily “on” time as the covariate. The “on treatment” approach and LOCF method were used for the analysis.

The number of RDO patients in Study SETTLE was very small (placebo - 1, 100 mg - 1) in each treatment group. However, the number of patients with efficacy data censored was very large (placebo - 54, 100 mg - 39).

Table 21 shows results for the primary analysis of the primary efficacy endpoint for 100 mg safinamide vs placebo. The dose is noted as 50 mg- 100 mg in this table because some patients may not have tolerated the 100 mg dose and had to have their dose decreased to 50 mg daily.

Table 21 Study SETTLE (27919): Change from Baseline for Primary Efficacy Endpoint (“ON” without Troublesome Dyskinesia) to Endpoint/Week 24 (On-Treatment, ANCOVA [LOCF], ITT Population)

Visit Statistic	Safinamide 50-100 mg/day		Placebo	
	Value	Change	Value	Change
Baseline				
n (N)	274 (274)	---	275 (275)	---
Mean (SD)	9.30 (2.41)	---	9.06 (2.50)	---
Median	9.50	---	9.25	---
Min; Max	0.8; 16.5	---	0.0; 15.5	---
Endpoint				
n (N)	274 (274)	274 (274)	275 (275)	275 (275)
Mean (SD)	10.73 (2.75)	1.42 (2.80)	9.63 (2.77)	0.57 (2.47)
Median	10.75	1.25	9.75	0.50
Min; Max	1.3; 17.3	-7.0; 13.8	0.0; 17.0	-6.5; 9.5
LS Mean (SE)	---	1.52 (0.15)	---	0.56 (0.15)
LS Difference vs. Placebo (SE)	---	0.96 (0.21)	---	-
95% Confidence Interval	---	0.56, 1.37	---	---
p-value vs. Placebo	---	<0.001	---	---

ITT=Intent to Treat; LOCF=Last observation carried forward; LS=Least squares; Max= Maximum; Min=Minimum; n=Number of patients with an evaluation; N=Number of patients in the ITT population; SD=Standard deviation; SE=Standard error.

Baseline: Visit 3; Endpoint: Visit 9 (Week 24 or early discontinuation).

The parametric ANCOVA Model was based on change from baseline to endpoint, with fixed effects for treatment and region, and baseline value as covariate. All p-values (2-sided), LS means, and confidence intervals are calculated from the ANCOVA model.

Source: CSR Study 27919 (SETTLE).

Figure 4 shows the time course of the increase in “ON” time without troublesome dyskinesia for all treatments in Study 16 for each treatment group.

Figure 4 Study SETTLE (27919) : Mean (± Standard Error) Change from Baseline in Total Daily "On" Time Over Time and According to Treatment

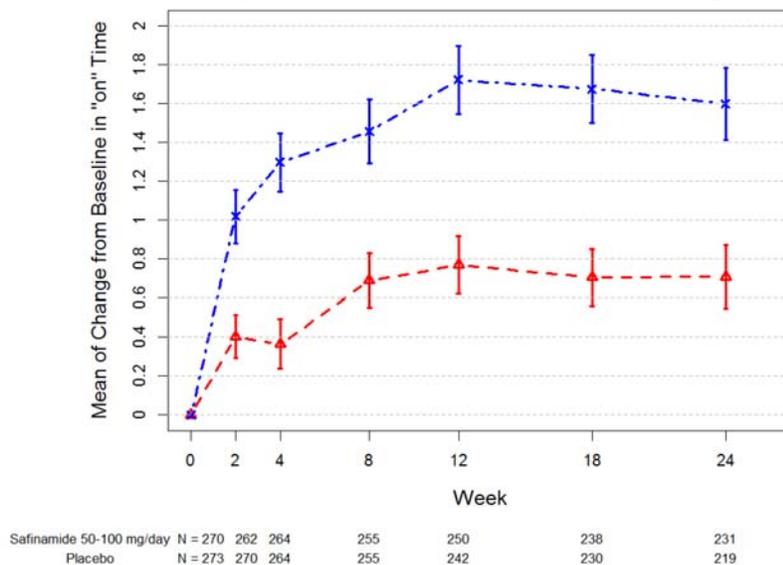
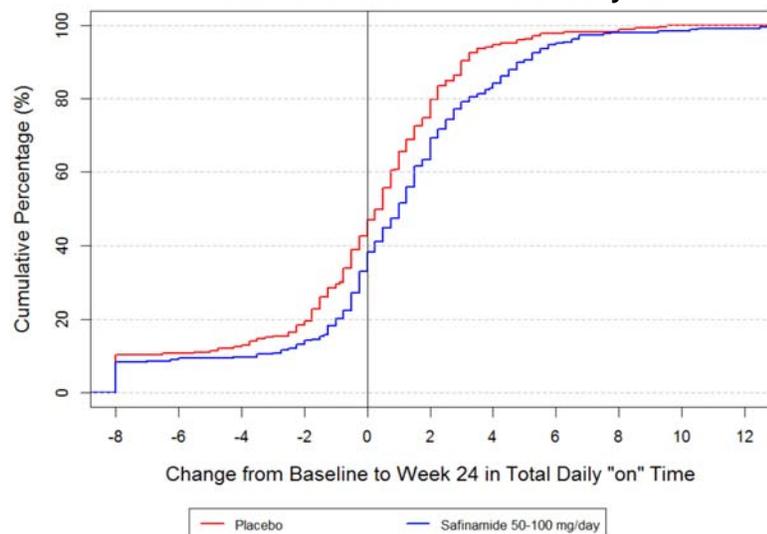


Figure 5 shows the cumulative distribution functions (CDFs) for the cumulative percentage of patients with different changes from baseline in “ON” time without troublesome dyskinesia for each treatment group.

Figure 5 Study SETTLE Empirical Cumulative Distribution Functions for the Change from Baseline to Week 24 in Total daily “ON” Time Without Troublesome Dyskinesia



Source : Statistical Reviewer, Dr. Zhang

Reviewer Comment

- Table 21 shows the effect of 100 mg safinamide on the primary efficacy endpoint, “ON” without troublesome dyskinesia based upon 18 hour diary results. Saffinamide produced a statistically significant treatment difference (saffinamide-placebo) benefit of approximately a 1 hour increase for this endpoint.
- The magnitude of this benefit to increase “good ON” is much larger (i.e., 2 fold) in this trial for the 100 mg dose was substantially greater than the same outcome observed for the same dose (~ 0.5 hours) in Study 16. The magnitude of this benefit in this trial compares more favorably to the magnitude of the same benefit with other drugs, especially relative to rasagiline, another selective MAO-B inhibitor and supports the approval of this higher dose that did not appear to produce a notably different outcome from the lower dose in Study 16.
- Figure 4 shows that the increase in “ON” time without troublesome dyskinesia progressively increased over 12 weeks for each treatment and that the difference between each safinamide dose and placebo appeared to be maximal at week 12 and relatively stable from weeks 12 to 24. This figure also shows the number of patients at baseline and the number who contributed to efficacy data at each visit. These numbers progressive decrease over time, to a relatively similar degree for each treatment because patients

discontinued from the trial or from taking randomized study medication, or had their data censored because of “rescue medication.”

- Figure 5 shows that the cumulative distribution curve for 100 mg sildenafil separates with a relatively constant separation from the placebo curve (with a relatively constant separation) for a decrease in “ON” time without troublesome dyskinesia of approximately 5 hours for ~ 15 % of all patients up to an increase in “ON” time without troublesome dyskinesia of nearly 5 hours for ~ 90 % of all patients. This shift of sildenafil curve for 100 mg to the right of the placebo curve between 15 % and 90 % of patients demonstrates efficacy for this sildenafil dose.
- Altogether, results of these analyses clearly show that sildenafil is an effective treatment in this population and supports the approval of the 100 mg strength of sildenafil.

6.1.5 Analysis of Secondary Endpoints(s) and Secondary Analyses

The following data represent results of secondary analyses of primary efficacy endpoints and primary and secondary analyses of secondary efficacy endpoints including some key secondary efficacy endpoints. For each trial, I have presented results for secondary endpoint and secondary analyses of most interest to DNP including desired analyses (e.g., MMRM) and desired population (e.g., mITT) which we requested be conducted and submitted. Following each of these presentations for each trial, I have outlined the sponsor’s prespecified secondary efficacy endpoints for key pivotal trials (Studies 9, 15, MOTION/27918, 16, and SETTLE/27919).

Early Parkinson's disease (ESPD)

Study 9

The DNP had informed the sponsor at the Pre-NDA meeting that the change from baseline of UPDRS Part III/motor subscale is an important efficacy endpoint of interest to the Agency for this population. Mean and median changes in UPDRS section III between baseline (Visit 2) and Visit 5, Visit 7 and the end of the study (Visit 9 or early study termination) included in the original final study report are presented in Table 22.

Table 22 Study 9 : Actual values and changes in UPDRS section III score between baseline and further visits (ITT cohort, N = 167)

	Placebo (N = 56)			Safinamide 0.5 mg/kg (N = 55)			Safinamide 1.0 mg/kg (N = 56)		
	Mean	SD	Median	Mean	SD	Median	Mean	SD	Median
Baseline (Visit 2) (N = 167)	17.3	7.8	16.0	16.4	7.7	15.0	16.5	7.4	15.5
Visit 5 (N = 157)	16.3	8.2	15.0	14.8	7.9	13.0	14.2	7.2	15.0
Visit 2 to Visit 5	-1.0	2.8	-1.0	-1.4	4.9	-1.0	-2.1	3.3	-1.5
Visit 7 (N = 151)	16.7	9.2	16.0	14.8	8.0	15.0	12.9	6.8	12.0
Visit 2 to Visit 7	-0.8	5.0	-1.0	-1.6	5.8	-2.0	-3.3	4.2	-2.5
Final¹ visit (N = 167)	16.7	8.9	16.0	13.8	7.8	12.0	13.2	7.1	13.0
Visit 2 to final ¹ visit	-0.6	5.4	-1.0	-2.6	5.5	-2.0	-3.3	5.5	-1.0

Source: Appendix B-1.2.1, Table 8

SD = standard deviation

¹ Final visit = Visit 9 or early study termination

The following description of the results presented in Table 22 was included in the sponsor’s original final report for Study 9. “As seen for changes in UPDRS section II scores, UPDRS section III scores did not change substantially in any of the three treatment groups during the study. The small changes in UPDRS section III score were comparable in all treatment groups between between baseline (Visit 2) and Visit 5, baseline and Visit 7 as well as baseline and the final visit (Visit 9 or early study termination) ($p \geq 0.05$, Kruskal-Wallis test).”

However, the sponsor revised the final study report regarding the statistical analysis of this endpoint and noted at the Pre-NDA meeting that re-analyses with different statistical models (ANCOVA) were “more appropriate” for results in this trial. The following shows how the final study report was revised.

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~~As seen for changes in UPDRS section II scores, UPDRS section III scores did not change substantially in any of the three treatment groups during the study.~~ **When data were analyzed using the Kruskal-Wallis test, the small** changes in UPDRS section III score were comparable (**$p \geq 0.05$**) in all treatment groups between baseline (Visit 2) and Visit 5, baseline and Visit 7, as well as baseline and the final visit (Visit 9 or early study termination) (**$p \geq 0.05$, Kruskal-Wallis test, (Appendix B-1.2.1, Table 8, Appendix B-2.2.1, Tests 18, 20 and 22).** **However, when the data were re-analyzed using the more appropriate ANCOVA models, statistically significant differences between safinamide 1.0 mg/kg and placebo ($p=0.005$), and between safinamide 0.5 mg/kg and placebo ($p=0.030$) were noted (Appendix B-3, Section 3).** **In addition, at Visit 7 a significant difference, compared to placebo, was measured for the safinamide 1.0 mg/kg group ($p=0.008$), but not for the 0.5 mg/kg group. No significant differences were noted at Visit 5.**

Table 23 presents results of this **post-hoc re- analysis** with a different statistical analysis (not previously specified analysis in the statistical analysis plan-SAP), an ANCOVA model.

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Table 23 Study 9: Mean change from Baseline in the UPDRS III Total Score at Endpoint (Secondary Efficacy Endpoint) in the Total Population (ITT; n=167) and Subpopulations Defined Based on Current PD Treatment

UPDRS III: Change from Baseline	Safinamide 0.5 mg/kg/day		Safinamide 1.0 mg/kg/day		Placebo		P-value vs. Placebo group (ANCOVA analysis)	
	Mean	SD	Mean	SD	Mean	SD	Saf 0.5 mg/kg	Saf 1.0 mg/kg
Total population	-2.6	5.5	-3.3	5.5	-0.6	5.4	0.030	0.005
Single DA-agonist (n=101)	-4.0	5.9	-4.7	5.7	-1.4	4.5	0.045	0.006
De novo (n=66)	-0.5	4.2	-1.0	4.5	0.6	6.6	0.485	0.303

ANCOVA=analysis of covariance; DA=dopamine; de novo=currently untreated with any PD medication; n=number of responders; N=total number in group; Saf=safinamide; UPDRS III=Unified Parkinson's Disease Rating Scale - Section III (Motor Examination). Endpoint=Week 12 or early discontinuation.

a. Responder was defined as $\geq 30\%$ improvement from baseline in UPDRS III total score.

Source: CSR Study 009.

In addition, the sponsor submitted statistical analyses of an Agency requested analysis (mITT population, MMRM) for this trial. Table 24 shows these results.

Table 24 Study 9: Analysis per FDA Request for Treatment Difference (Safinamide – Placebo) for the Key Secondary Efficacy Endpoints (UPDRS Sections II and III) for ESPD Patients (mITT Population)

Group 1 Study 009: UPDRS Sections II and III (a)							
Efficacy Parameter	Statistic p-value (b)	mITT Population					
		MMRM Analysis (c)			ANCOVA (LOCF) Analysis(d)		
		0.5 mg/kg/day (n=55)	1.0 mg/kg/day (n=55)	All Saf (n=110)	0.5 mg/kg/day (n=55)	1.0 mg/kg/day (n=55)	All Saf (n=110)
UPDRS II	LS Diff vs Pbo	-0.5	-0.3	-0.4	-1.2	-0.5	-0.8
	p-value	0.1937	0.4990	0.2551	0.0169	0.2909	0.0476
UPDRS III	LS Diff vs Pbo	-1.2	-2.1	-1.7	-2.2	-2.9	-2.5
	p-value	0.1331	0.0072	0.0161	0.0327	0.0050	0.0044
UPDRS II + III	LS Diff vs Pbo	-1.6	-2.3	-1.9	-3.3	-3.3	-3.3
	p-value	0.1350	0.0330	0.0367	0.0156	0.0146	0.0051

ANCOVA=Analysis of Covariance; ESPD=Early-Stage Parkinson's Disease; LOCF=Last Observation Carried Forward; LS Diff vs Pbo=Least Squares Mean Difference vs. Placebo; mITT=modified Intent-to-Treat; MMRM=Mixed Model Repeated Measures; UPDRS=Unified Parkinson's Disease Rating Scale (Section I – Mentation, Behavior and Mood ; Section II - Activities of Daily Living; Section III – Motor Examination); All Saf=safinamide 0.5 mg/kg/day and 1.0 mg/kg/day.

a. UPDRS I was not analyzed for Study 009 as UPDRS I was performed only at baseline.

b. P-value for comparison between safinamide and placebo; significant effects ($p < 0.05$) are in **bold** text.

c. MMRM model for change from Baseline to Endpoint includes treatment, region, and visit as fixed effects, and baseline value as a covariate.

d. ANCOVA model is based on change from Baseline to Endpoint with fixed effects for treatment, study, and baseline value as a covariate.

Source: ISE Tables 1.3.1.1; 1.3.1.3; 1.3.1.4.

Reviewer Comments

- Although the arithmetic treatment difference (safinamide – placebo) for the change from baseline to endpoint for UPDRS Part III was - 2.0 for 0.5 mg/kg/day and was - 2.7 for 1 mg/kg/day, these results (Table 22) were not statistically significant according to the prespecified analysis plan with the Kruskal-Wallis test.
- In contrast, Table 23 shows statistically significant differences ($p < 0.05$) for each safinamide dose compared to placebo for the whole study population and for patients on a

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concomitant dopaminergic but no statistically significant difference in “de novo” patients who were not taking a concomitant when an **post-hoc** ANCOVA analysis (not previously specific in the SAP) was applied for statistical testing.

- I am unable to consider this revised ANCOVA analysis as an appropriate one. The statistical analysis plan (SAP) noted that statistical significance would be tested with the Kruskal Wallis test. It also noted that if the data were distributed normally, that an ANCOVA would be used for statistical testing with baseline UPDRS as a covariate. However, the SAP did not specify any details nor the criteria for determining whether the data met (or did not meet) the criterion for normality. Furthermore, despite the fact that the sponsor suggested that the ANCOVA analysis was a more “appropriate” test, the sponsor did not explicitly justify and explain why the ANCOVA was more appropriate test (than the Kruskal-Wallis test) nor did the sponsor explicitly note that the data were normally distributed and possibly more appropriate for an ANCOVA analysis. Regardless of the sponsor’s post hoc revisions of the summary and conclusions of the efficacy of safinamide (on UPDRS Part III) described in the original final study report and the sponsor’s unjustified application of a different statistical analysis (i.e., ANCOVA), I remain unconvinced that Study 9 can be considered as a “positive” trial supporting efficacy of safinamide in this population.
- Table 24 shows results of FDA requested analyses (mITT population and MMRM) for change from baseline in UPDRS Part II (Activities of Daily Living-ADL), UPDRS Part III motor subscale, and UPDRS Parts II + III. The high safinamide dose was statistically significant ($p < 0.05$) for the MMRM analysis for Part III, and for Parts II+III. The magnitude of the treatment difference for each of these endpoints for the whole study population was relatively small (i.e., -1.2 for Part III, and - 1.6 for Part II+III). The magnitude of the treatment difference was greater for the subgroup population of patients taking a concomitant dopaminergic agonist (i.e., -2.3 for Part III, and - 2.7 for Part II+III) with high dose safinamide. In addition, ANCOVA analyses of the mITT population showed statistically significant changes for all outcomes for low dose safinamide and for UPDRS Part III and UPDRS Part II+III for high dose safinamide.
- Despite results of all of these post-hoc, exploratory statistical analyses and final study report revisions, I am still not able to conclude that Study 9 is a “positive” trial for demonstrating efficacy for patients with early Parkinson’s disease based upon an important, acceptable efficacy endpoint to the DNP. When I discussed these post-hoc analyses with Dr. Zhang, primary statistical reviewer, she noted that it is not appropriate to draw conclusions on these post-hoc, unjustified analyses when the prespecified analysis was “negative” because statistical significance for change from baseline of UPDRS Part III (a prime outcome of interest to us) was not demonstrated according to the prespecified analysis in the protocol.
- My previous comments about the design of Study 9 which are presented immediately after Table 14 further outline my concerns about why I am unable to conclude that results

of Study 9 support a conclusion that safinamide is an effective treatment for patients with early Parkinson's disease.

Sponsor Statistical Analysis Plan for Secondary Efficacy Endpoints/Analyses (Study 9)

The following language describes the analyses for secondary efficacy endpoints specified in the final SAP (7/8/02).

All secondary efficacy analyses will be performed two-sided with an α of 0.05 for the ITT cohort only. All secondary analyses will be interpreted in a descriptive manner.

The secondary efficacy variables are:

4.4.1 Percentage of subjects with an improvement of at least 30% in the UPDRS section III score between baseline (Visit 2) and Visit 5/Visit 7

The proportion of patient's achieving at least 30% improvement at visits 5 and visit 7 will be analysed using the same methods as for the primary efficacy variable.

4.4.2 Changes in the UPDRS sections II and III from baseline (Visit 2) to Visit 5, Visit 7 and the end of the study (Visit 9 or early termination).

The change from visits 5, 7 and Final (visit 9 or last visit) will be calculated for both sections II and III of the UPDRS assessment.

These endpoints will be assessed for between-group comparisons using the Kruskal-Wallis procedure. The following SAS® code will be used

```
proc npar1way wilcoxon;  
class treatment;  
var UPDRS_change;  
run;
```

The summaries of the changes from baseline will be presented along with the p-value obtained from the Kruskal-Wallis test. If the Kruskal-Wallis test is significant, pairwise comparisons will be presented.

The normality of the data distribution will be assessed. If the data is found to be sufficiently normal an Analysis of Covariance will be performed including the baseline UPDRS score as covariate.

4.4.3 CGI in the course of the study.

CGI is measured in two parts – part 1 assesses the severity of the patients' illness on a scale from 'Normal, not ill' to 'Extremely ill'. Part 1 is assessed at every visit and the change from baseline will be summarised at each assessment and tested for difference between treatment groups using a chi-square test.

Part 2 assesses global improvement on a scale from 'Markedly deteriorated' to 'Much improved' and is consequently not assessed at baseline. This measure will be summarised at each visit by treatment group and overall. Treatment differences will be assessed using a chi-square test.

4.4.4 Change in HAMD from screening (Visit 1) to the end of the study (Visit 9 or early termination).

The change in HAMD score will be calculated between the final visit (Visit 9 or last visit available) and summarised descriptively. A Kruskal-Wallis test will be performed to test for differences between groups, as described in section 4.4.2, and the p-value also presented. If the Kruskal-Wallis test is significant, pairwise comparisons will be presented.

The normality of the data distribution will be assessed. If the data is found to be sufficiently normal an Analysis of Covariance will be performed including the baseline HAMD score as covariate.

Reviewer Comment

- I have presented Study 9 results for secondary efficacy endpoints (i.e., UPDRS change from baseline for part III, and change from baseline in UPDRS part II) of interest to us earlier in this section for the originally planned analysis and also for the post-hoc, unjustified re-analysis.
- I have not presented the many secondary efficacy endpoints described in the sponsor's SAP because there was no plan for analyzing the many secondary efficacy endpoints with any planned adjustment for multiplicity.

Study 15

Table 25 shows results for the change from baseline for several individual UPDRS subscales and combinations of subscales for the DNP requested MMRM analysis of the mITT population for Study 15.

Table 25 Study 15 : Change from Baseline to Endpoint/Week 24 in UPDRS Subscales and Combined Subscales for the mITT Population (No Imputation of Missing Data)

Study 015: Change from Baseline at Endpoint							
Efficacy Parameter	Statistic p-value (a)	mITT Population					
		MMRM Analysis (b)			ANCOVA (LOCF) Analysis (c)		
		100 mg/day (n=87)	200 mg/day (n=87)	All Saf (n=174)	100 mg/kg/day (n=87)	200 mg/kg/day (n=87)	All Saf (n=174)
UPDRS I	LS Diff vs Pbo	-0.11	-0.18	-0.15	-0.09	-0.06	-0.08
	p-value	0.4267	0.2132	0.2366	0.5149	0.6952	0.5418
UPDRS II	LS Diff vs Pbo	-1.05	-0.63	-0.85	-1.00	-0.32	-0.65
	p-value	0.0213	0.1779	0.0328	0.0211	0.4575	0.0792
UPDRS III	LS Diff vs Pbo	-2.04	-0.53	-1.31	-1.53	-0.38	-0.94
	p-value	0.0266	0.5709	0.1005	0.0720	0.6540	0.1969
UPDRS II + III	LS Diff vs Pbo	-3.09	-1.12	-2.14	-2.59	-0.65	-1.61
	p-value	0.0124	0.3729	0.0466	0.0233	0.5671	0.1029
UPDRS I + II + III	LS Diff vs Pbo	-3.19	-1.45	-2.36	-2.84	-0.84	-1.86
	p-value	0.0117	0.2611	0.0311	0.0234	0.5034	0.0863

ANCOVA=Analysis of Covariance; ESPD=Early-Stage Parkinson's Disease; LOCF=Last Observation Carried Forward; LS Diff vs Pbo=Least Squares Mean Difference vs. Placebo; mITT=modified Intent-to-Treat; MMRM=Mixed Model Repeated Measures; UPDRS=Unified Parkinson's Disease Rating Scale (Section I – Mentation, Behavior and Mood; Section II - Activities of Daily Living; Section III – Motor Examination); All Saf=100 mg/day and 200 mg/day.

(a) p-value for comparison between safinamide and placebo; significant effects (p<0.05) are in **bold text**.

(b) MMRM model for change from Baseline to Endpoint includes treatment, visit, and treatment by-visit as fixed effects, center as a random effect, and baseline value as a covariate, using an unstructured variance-covariance matrix.

(c) ANCOVA model is based on change from Baseline to Endpoint with treatment and center as main effects, and baseline value as a covariate.

Source: ISE Tables 2.3.1.1; 2.3.1.2; 2.3.1.3, 2.3.1.4, 2.3.1.5.

Reviewer Comments

- In the MMRM analysis of the mITT population (the desired analysis by DNP), none of the various UPDRS endpoints are statistically significant (i.e., $p > 0.05$) for high dose safinamide (200 mg). In contrast, the results for low dose safinamide (100 mg) show that this treatment produced statistically significant effects (i.e., **nominal** $p < 0.05$) on the change for UPDRS Part II, Part III, Part II+III, and also Part I+II+III scales. ANCOVA LOCF analyses showed similar results for each dose with the exception that the change for Part III was not statistically significant but trending toward statistical significance ($p=0.0720$).
- Nevertheless, it is not possible to rely on results of low dose safinamide when the hierarchical, prespecified statistical analysis plan provided that statistical testing of the 100 mg dose was not formally possible if the 200 mg dose did not produce statistically significant results. These post-hoc results with nominal p values that seem to suggest efficacy for the lower dose cannot be explained in view of the negative results of the higher dose.
- My previous comments about efficacy results of Study 15, which are presented immediately after Table 15, further outline my concerns about why I am unable to conclude that results of Study 15 support a conclusion that safinamide is an effective

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treatment for patients with early Parkinson's disease taking a concomitant dopaminergic agonist. The primary statistical reviewer, Dr. Xiangmin Zhang, agrees with my conclusion on efficacy results of this trial.

Sponsor Statistical Analysis Plan for Secondary Efficacy Endpoints/Analyses (Study 15)

The following secondary analyses will be performed:

- Mean change from Baseline at Endpoint for each item on the UPDRS Section III (Motor examination) for the ITT population.
 - Variable: UPDRS Section III for the following items at Baseline and Visit 8 (Week 24) or LOCF:
 - 18. Speech.
 - 19. Facial expression.
 - 20. Tremor at rest.
 - 21. Action or postural tremor of hands.
 - 22. Rigidity.
 - 23. Finger taps.
 - 24. Hand movements.
 - 25. Rapid alternating movements of hands
 - 26. Leg agility.
 - 27. Arising from chair.
 - 28. Posture.
 - 29. Gait.
 - 30. Postural stability.
 - 31. Body bradykinesia and hypokinesia.
 - Calculation: The absolute change from Baseline at Endpoint which can be defined as either Visit 8 (Week 24) or LOCF, if applicable.
 - Statistics: Summary statistics at Baseline, Endpoint, and Change from Baseline at Endpoint.
- Analyses using the imputation schemes as discussed in Section 7.7 (LOCF, OC, RDO, OC and RDO):
 - Change from Baseline at Endpoint for UPDRS Section III Total Score.
 - Variable: UPDRS Section III Total Score at Baseline and Visit 8 (Week 24) or LOCF, if applicable.
 - Calculation: The absolute change from Baseline at Endpoint, which can be defined as either Visit 8 (Week 24) value or LOCF, if applicable.
 - Statistics: ANCOVA will be done on the change from Baseline at Endpoint using the Baseline value as covariate and treatment group and center as factors. A point estimate (PE) and 95% confidence interval (CI) for the difference between active treatment group and Placebo will also be calculated.
 - For the ANCOVA the SAS[®] code as above will be used:

```
PROC GLM data = <sas-dataset> alpha =0.05;
CLASS Trt Center;
MODEL ChangeUPDRS III = Trt Center BaselineUPDRS III;
ESTIMATE 'High Dose - Placebo' Trt 1 0 -1;
ESTIMATE 'Low Dose - Placebo' Trt 0 1 -1;
```

```
LSMEANS Trt / CL
STDERR PDIFF = CONTROL ('3' <Placebo>)
OUT = <adjustmean>;
RUN;
```

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- CGI: Change from Baseline for the ITT population.
 - Variable: CGI - Change from Baseline Score for Visit 8 (Week 24) or LOCF if applicable.
 - Calculation: The CGI - Change from Baseline Score will be categorized as either 'Improvement' (score of 1, 2 or 3) or 'No change or Worsening' (score of 4, 5, 6 or 7).
 - Statistic: The Cochran Mantel-Haenszel method weighted by center will be used to compare the proportion of patients showing 'Improvement' versus 'No change or Worsening'. A weighted PE and 95% CI will also be calculated. The homogeneity of the odds ratio across centers will be tested using the Breslow-Day test.
- Change from Baseline at Endpoint for UPDRS Section III Total Score by DA subgroup for the ITT population:
 - Subgroups:
 - Pramipexole.
 - Ropinirole.
 - Cabergoline.
 - Other DA's.
 - Variable: UPDRS Section III Total Score at Baseline and Visit 8 (Week 24) or LOCF, if applicable.
 - Calculation: The absolute change from Baseline at Endpoint, which can be defined as either Visit 8 (Week 24) value or LOCF, if applicable.
 - Statistic: ANCOVA will be done on the change from Baseline at Endpoint using the Baseline value as covariate and treatment group and center as factors. A point estimate (PE) and 95% confidence interval (CI) for the difference between active treatment group and Placebo will also be calculated.
 - For the ANCOVA the SAS[®] code as above will be used:
- Responder Rate: Patients with at least a 20% improvement of their UPDRS Section III Total Score from Baseline to Endpoint and no worsening of their UPDRS Section II and UPDRS Section IV Total Score for the ITT population.
 - Variable: UPDRS Section II, III and IV Total Score for each of the sections at Baseline and Visit 8 (Week 24) or LOCF, if applicable.
 - Calculation:
 - (UPDRS Section II Total Score at Baseline) - (UPDRS Section II Total Score at Visit 8 [Week 24] or LOCF).
 - (UPDRS Section IV Total Score at Baseline) - (UPDRS Section IV Total Score at Visit 8 [Week 24] or LOCF).
 - $\frac{([\text{UPDRS Section III Total Score at Baseline}] - [\text{UPDRS Section III Total Score for Visit 8 \{Week 24\} or LOCF}])}{\text{UPDRS Section III Total Score at Baseline}} * 100$.
 - For each patient, if the changes in the UPDRS Section II, and IV is ≥ 0 and the improvement on the UPDRS Section III is $\geq 20\%$ then the patient's response will be categorized as a 'Success', or else the response will be categorized as a 'Failure'.
 - Statistic: The Cochran Mantel-Haenszel method weighted by center will be used to compare the proportion of patients with 'Success'. A weighted PE and 95% CI will also be calculated. The homogeneity of the odds ratio across centers will be tested using the Breslow-Day test.
- Responder Rate: Patients with at least a 30% improvement of their UPDRS Section III
 - **Total Score from Baseline to Endpoint and no worsening of their UPDRS Section II and UPDRS section IV Total Score for the ITT population**

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- Variable: UPDRS Section II, III and IV Total Score for each of the sections at Baseline and Visit 8 (Week 24) or LOCF, if applicable.
- Calculation:
 - (UPDRS Section II Total Score at Baseline) - (UPDRS Section II Total Score at Visit 8 [Week 24] or LOCF).
 - (UPDRS Section IV Total Score at Baseline) - (UPDRS Section IV Total Score at Visit 8 [Week 24] or LOCF).
 - $\left(\frac{[\text{UPDRS Section III Total Score at Baseline}] - [\text{UPDRS Section III Total Score for Visit 8 \{Week 24\} or LOCF}]}{[\text{UPDRS Section III Total Score at Baseline}]} \right) * 100$.

For each patient, if the changes in the UPDRS Section II, and IV is ≥ 0 and the improvement on the UPDRS Section III is $\geq 30\%$ then the patient's response will be categorized as a 'Success', or else the response will be categorized as a 'Failure'.

- Statistic: The Cochran Mantel-Haenszel method weighted by center will be used to compare the proportion of patients with 'Success'. A weighted PE and 95% CI will also be calculated. The homogeneity of the odds ratio across centers will be tested using the Breslow-Day test.
- Mean change from Baseline at Endpoint for each item on the UPDRS Section II (Activities of daily living) for the ITT population.
 - Variable: UPDRS Section II for the following items at Baseline and Visit 8 (Week 24) or LOCF:
 - 5. Speech.
 - 6. Salivation.
 - 7. Swallowing.
 - 8. Handwriting.
 - 9. Cutting food and handling utensils.
 - 10. Dressing.
 - 11. Hygiene.
 - 12. Turning in bed and adjusting bed clothes.
 - 13. Falling.
 - 14. Freezing when walking.
 - 15. Walking.
 - 16. Tremor.
 - 17. Sensory complaint related to PD.
 - Calculation: The absolute change from Baseline at Endpoint which can be defined as either Visit 8 (Week 24) or LOCF, if applicable.
 - Statistics: Summary statistics at Baseline, Endpoint, and Change from Baseline at Endpoint.
- CGI: Change from Baseline score for the ITT population.
 - Variable: CGI: Change from Baseline Score for each of the visits.
 - Calculation: No calculation will be done, the score as an absolute value will be used.
 - Statistic: Treatments will be compared by means of the Cochran Mantel-Haenszel test stratified by center.
- Change from Baseline to Endpoint - UPDRS II for the ITT population.
 - Variable: UPDRS Section II Total Score at Baseline and Visit 8 (Week 24) or LOCF, if applicable.

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- Calculation: The absolute change from Baseline to Endpoint .
- Statistic: ANCOVA will be done on the change from Baseline using the Baseline value as covariate and treatment group and center as main effects. A point estimate and 95% CI for the difference between active treatment group and Placebo will also be calculated.
The same PROC GLM SAS® code will be used as described above for ANCOVA, adjusted for the change in UPDRS Section II Total Score.
- Change from Baseline to Endpoint - CGI: Severity of Illness for the ITT population.
 - Variable: CGI I - Severity of illness Score at Visit 2 (Baseline) and Visit 8 (Week 24) or LOCF, if applicable.
 - Calculation: The absolute change from Baseline to Endpoint .
 - Statistic: ANCOVA will be done on the change from Baseline using the Baseline value as covariate and treatment group and center as main effects. A point estimate and 95% CI for the difference between active treatment group and Placebo will also be calculated.
The same PROC GLM SAS® code will be used as described above for ANCOVA, adjusted for the change in CGI - Severity of Illness Score.
- Hoehn and Yahr staging for the ITT population.
 - Variable: Hoehn and Yahr staging for Visit 1 (Screening) and Visit 8 (Week 24).
 - Calculation: No calculation will be done, only Hoehn and Yahr Stage as documented on the CRF.
 - Treatments will be compared by means of Wilcoxon Rank Sum test.

Reviewer Comment

- I have presented Study 15 results for some secondary efficacy endpoints of potential interest to us earlier in this section.
- I have not presented results for the many secondary efficacy endpoints described in the sponsor's SAP because : 1) the primary statistically analysis of the primary efficacy endpoint was not "positive" for the high dose (200 mg daily) as appropriate for the prespecified SAP analysis; and 2) there was no plan for analyzing the many secondary efficacy endpoints with any planned adjustment for multiplicity.

Study 17 (Analysis Reflects Pooled Results of Studies 15 AND 17)

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Table 26 Studies 15 and 17 : Safinamide Treatment Difference (Safinamide – Placebo)UPDRS Subscales

Group 4 Combined Studies 015/017: Change from Baseline at Endpoint ("ON treatment" Approach)							
mITT Population							
Efficacy Parameter	Statistic p-value(a)	MMRM Analysis(b)			ANCOVA (LOCF) Analysis(c)		
		100 mg/day (n=87)	200 mg/day (n=87)	All Saf (n=174)	100 mg/day (n=87)	200 mg/day (n=87)	All Saf (n=174)
UPDRS I	LS Diff vs Pbo	0.02	-0.05	-0.01	0.17	0.14	0.16
	p-value	0.9009	0.8057	0.9486	0.3412	0.4466	0.3176
UPDRS II	LS Diff vs Pbo	-0.34	-0.37	-0.35	-0.52	-0.13	-0.32
	p-value	0.5677	0.5343	0.4926	0.3376	0.8119	0.4895
UPDRS III	LS Diff vs Pbo	-1.85	0.05	-0.93	-1.38	0.28	-0.54
	p-value	0.1565	0.9704	0.4139	0.2118	0.7990	0.5724
UPDRS II + III	LS Diff vs Pbo	-2.20	-0.45	-1.34	-1.99	0.21	-1.88
	p-value	0.1990	0.7939	0.3672	0.1802	0.8861	0.4940
UPDRS I + II + III	LS Diff vs Pbo	-2.61	-0.71	-1.69	-2.37	0.54	-0.94
	p-value	0.1277	0.6823	0.2557	0.1369	0.7351	0.4971

ANCOVA=Analysis of Covariance; ESPD=Early-Stage Parkinson's Disease; LOCF=Last Observation Carried Forward; LS Diff vs Pbo=Least Squares Mean Difference vs. Placebo; mITT=modified Intent-to-Treat; MMRM=Mixed Model Repeated Measures; UPDRS=Unified Parkinson's Disease Rating Scale (Section I – Mentation, Behavior and Mood; Section II - Activities of Daily Living; Section III – Motor Examination); All Saf=100 mg/day and 200 mg/day.

(a) p-value for comparison between safinamide and placebo; significant effects (p<0.05) are in bold text.

(b) MMRM model for change from Baseline to Endpoint includes treatment, visit, and treatment by-visit as fixed effects, center as a random effect, and baseline value as a covariate, using an unstructured variance-covariance matrix.

(c) ANCOVA model is based on change from Baseline to Endpoint with treatment and center as main effects, and baseline value as a covariate.

Source: ISE Tables 4.3.1.1; 4.3.1.2; 4.3.1.3, 4.3.1.4, 4.3.1.5.

Reviewer Comments

- Table 26 shows that there was no statistically significant improvement in any of these UPDRS subscales (individual subscales and combinations of subscales) for the 200 mg dose with the MMRM analysis in combined Studies 15 and 17. Because the statistical analysis plan provided for the 200 mg dose to be analyzed prior to the 100 mg dose, formal statistical testing must cease when the 200 mg dose fails to be statistically significant vs placebo. Thus, one cannot pay any attention to the results of the 100 mg dose which are also shown but are also not statistically significant vs placebo. Neither were there any statistically significant results for either safinamide dose (vs placebo) for the UPDRS subscales (individual subscales and combinations of subscales) in the ANCOVA (LOCF) analyses.

Study MOTION (27918)

Table 27 shows efficacy results for the primary efficacy endpoint (change from baseline for UPDRS Part III) and a secondary efficacy endpoint (change from baseline in UPDRS Part II-ADL subscale) according to the primary analysis in a **post-hoc subgroup of patients of the ITT population who were excluded because of a certain protocol violation**. This subgroup excludes patients (N=13) including one patient who was randomized to 100 mg safinamide but who did not receive any study treatment and discontinued from the trial in 4 days and others who were considered major protocol violators for the inclusion criterion of taking monotherapy

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for Parkinson's disease consisting only of a stable dose of only one concomitant dopaminergic agonist (Table 28). Eleven of these major protocol violators were not taking a concomitant dopaminergic agonist at baseline and another patient was taking 2 concomitant dopaminergic agonists with stable dosing. Table 29 shows specific treatments taken by patients considered to be major protocol violators for the inclusion criterion of monotherapy with a stable dose of a dopaminergic agonist. Results of this **post-hoc exploratory analysis** are compared to results of the primary analysis of the ITT population.

Table 27 Study MOTION : Comparison of Safinamide Treatment Difference (Safinamide – Placebo) for Key Efficacy Results between the Dopaminergic Agonist Monotherapy and ITT Populations

Statistic		DA-agonist Monotherapy Population (n=666)		ITT Population (n=679)	
		Safinamide		Safinamide	
		50 mg/day	100 mg/day	50 mg/day	100 mg/day
UPDRS III (On treatment)	N	223	221	227	227
	LS Mean Difference (SE)	-0.70 (0.58)	-1.20 (0.58)	-0.65 (0.58)	-1.04 (0.58)
	[95% CI]	[-1.85, 0.44]	[-2.35, -0.06]	[-1.79, 0.48]	[-2.17, 0.10]
	P-value	0.2280	0.0396	0.259	0.073
UPDRS II (ADL)	N	223	221	227	227
	LS Mean Difference (SE)	-0.41 (0.26)	-0.51 (0.26)	-0.38 (0.26)	-0.45 (0.26)
	[95% CI]	[-0.93, 0.10]	[-1.02, 0.01]	[-0.89, 0.13]	[-0.96, 0.06]
	P-value	0.1183	0.0546	0.142	0.085

DA=Dopamine; UPDRS=Unified Parkinson's Disease Rating Scale; PDQ-39=Parkinson's Disease Questionnaire. Parametric ANCOVA model is based on the change from baseline to endpoint with fixed effects for treatment, region and baseline value as a covariate. All p-values, Least Square (LS) means, and 95% confidence intervals (CI) are calculated from the ANCOVA model. (a) vs Placebo. Source: CSR Study 27918(MOTION) : EOT Table 15.2.1, Ad Hoc Table 17, EOT Table 15.2.8 and Ad Hoc Tables 19, 27, Appendix 16.5.2 (Report - PRO Analysis of MOTION Trial for Safinamide).

Table 28 Study MOTION Patients Sponsor Excluded from Efficacy Analyses (POST-HOC) Because Patients Were Protocol Violators Who Did Not Meet Inclusion Criterion for "Stable" Dopaminergic Agonist"

Subject ID Number	Region	Reason for Violating Dopamine Agonist Monotherapy Requirement at Baseline
Safinamide 50 mg/day		
003-0001	North America	Receiving carbidopa and levodopa
023-0006	Asia	Receiving trihexyphenidyl
092-0008	Eastern Europe	Receiving amantadine
Safinamide 100 mg/day		
023-0009	Asia	Receiving trihexyphenidyl
044-0001	Latin America	Receiving amantadine
045-0005	Latin America	Receiving biperiden
080-0001	Eastern Europe	Receiving biperiden
092-0010	Eastern Europe	Receiving biperiden
179-0008	Eastern Europe	Receiving amantadine
Placebo		
023-0007	Asia	Receiving trihexyphenidyl
023-0008	Asia	Receiving trihexyphenidyl
058-0003	Eastern Europe	Not receiving single dopamine agonist/not at stable dose
Note: An additional subject (Subject No. 159-0003 [North America]) was randomized to treatment (safinamide 100 mg/day) but did not receive any study medication and was discontinued after four days; therefore, this subject was also excluded from the analysis.		
Source: Appendix 16.2.12.4.		

Table 29 Study MOTION Concomitant Medications for Patients Excluded From the Sponsor's Analysis of the ITT Population (Source : CDTL)

Usubjid (Study ID/Sub ID)	Trt01a	Amantadine	Biperiden	*Pramipexole	Ropinirole	Rotigotine	Sinemet	*Trihexyphenidyl
0000027918 0230007	Placebo	0	0	0	1	0	0	1
0000027918 0230008	Placebo	0	0	0	1	0	0	1
0000027918 0580003	Placebo	0	0	0	0	0	0	0
0000027918 0230009	Safinamide 100 mg/day	0	0	0	1	0	0	1
0000027918 0440001	Safinamide 100 mg/day	1	0	1	0	0	0	0
0000027918 0450005	Safinamide 100 mg/day	0	1	1	0	0	0	0
0000027918 0800001	Safinamide 100 mg/day	0	1	1	0	0	0	0
0000027918 0920010	Safinamide 100 mg/day	0	1	1	0	0	0	0
0000027918 1790008	Safinamide 100 mg/day	1	0	0	0	1	0	0
0000027918 0030001	Safinamide 50 mg/day	0	0	0	0	0	1	0
0000027918 0230006	Safinamide 50 mg/day	0	0	0	1	0	0	1
0000027918 0920008	Safinamide 50 mg/day	1	0	1	0	0	0	0

*Combined with Pramipexole HCL or Trihexyphenidyl HCL. Highlighted medications are FDA approved dopamine agonists

Table 30 shows results for individual and combined UPDRS subscales for the DNP requested MMRM analyses of the mITT population and also an ANCOVA (LOCF) analysis of the mITT population.

Table 30 Study MOTION : Change from Baseline of Safinamide Treatment Difference (Safinamide – Placebo) for UPDRS Individual Subscales and Combined Subscales for mITT Population According to MMRM and ANCOVA (LOCF) Analyses

Group 3 Study 27918 (MOTION): UPDRS Sections I, II, and III							
Efficacy Parameter	Statistic p-value (a)	mITT Population					
		MMRM Analysis (b)			ANCOVA (LOCF) Analysis (c)		
		50 mg/day (n=225)	100 mg/day (n=227)	All Saf (n=452)	50 mg/day (n=225)	100 mg/day (n=225)	All Saf (n=452)
UPDRS I	LS Diff vs Pbo	-0.1	-0.1	-0.1	-0.1	-0.1	-0.1
	p-value	0.5378	0.5080	0.4610	0.5378	0.5080	0.4610
UPDRS II	LS Diff vs Pbo	-0.3	-0.3	-0.3	-0.4	-0.5	-0.5
	p-value	0.0598	0.0769	0.0351	0.1294	0.0462	0.0426
UPDRS III	LS Diff vs Pbo	-0.8	-0.8	-0.8	-0.6	-1.0	-0.8
	p-value	0.0357	0.0374	0.0156	0.3060	0.0742	0.1042
UPDRS II + III	LS Diff vs Pbo	-1.2	-1.1	-1.2	-1.0	-1.5	-1.3
	p-value	0.0192	0.0286	0.0088	0.1695	0.0421	0.0490
UPDRS I + II + III	LS Diff vs Pbo	-1.5	-1.4	-1.5	-1.5	-1.4	-1.5
	p-value	0.0675	0.0695	0.0355	0.0675	0.0695	0.0355

ANCOVA=Analysis of Covariance; ESPD=Early-Stage Parkinson's Disease; LOCF=Last Observation Carried Forward; LS Diff vs Pbo=Least Squares Mean Difference vs. Placebo; mITT=modified Intent-to-Treat; MMRM=Mixed Model Repeated Measures; UPDRS=Unified Parkinson's Disease Rating Scale (Section I – Mentation, Behavior and Mood; Section II - Activities of Daily Living; Section III – Motor Examination); All Saf=Safinamide 50 mg/day and 100 mg/day.

(a) p-value for comparison between safinamide and placebo; significant effects (p<0.05) are in bold text.

(b) MMRM model for change from Baseline to Endpoint includes treatment, region, and visit as fixed effects, and baseline value as a covariate.

(c) ANCOVA model is based on change from Baseline to Endpoint with fixed effects for treatment, study, and baseline value as a covariate.

Source: ISE Tables 3.3.1.1; 3.5.1.2, 3.5.1.4, 3.5.1.5.

Reviewer Comments

- Table 27 shows that the post-hoc subgroup analysis of patients who were not protocol violators for the inclusion criterion of taking monotherapy consisting of a stable dose of a concomitant dopaminergic agonist (and the patient who did not receive study treatment and discontinued) was statistically significant (p= 0.0396) for the 100 mg safinamide (vs placebo) for the primary efficacy endpoint (change of UPDRS Part III). This subgroup analysis was not statistically significant (p > 0,05) for change of UPDRS Part III or Part II for 50 mg safinamide nor for change for UPDRS Part II for 100 mg safinamide. For comparison, results of the ITT population is also shown.
- Table 28 shows patients who were considered major protocol violators and who were excluded from the sponsor's post-hoc re-analysis of the primary efficacy endpoint for patients who violated the requirement to be only on a stable dose of a dopaminergic agonist. Although the sponsor's presentation of this issue seemed to suggest that many of these patients were not taking a dopaminergic agonist, the issue for most of these patients was that they were taking more than a single treatment for Parkinson's disease (e.g., several of these patients were taking an anticholinergic treatment of Parkinson's disease in addition to a dopaminergic agonist. Table 29, which shows the specific Parkinson's disease medications for each patient, shows that most of these patient were taking a dopaminergic agonist and also an anticholinergic agent. Ordinarily, the pivotal trials that we see for treatment of early Parkinson's disease are considered as “monotherapy” because they are only taking the investigational agent or the investigational agent with or without an anticholinergic agent. The “monotherapy” terms refers to the fact that no other dopaminergic agent is being used. Consequently, I would

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not even consider that most of these patients were major protocol violators because I do not consider the concomitant treatment with an anticholinergic agent to be of significant importance. It is also interest and noteworthy that many of the patients (especially in the 100 mg safinamide dose group) who were excluded in the post-hoc revised analysis did not show any substantial improvement in their UPDRS part III motor score at the end of treatment or showed a worsening of this score.

- In comparison, Table 30 shows statistically significant results ($p < 0.05$) for 100 mg safinamide (vs placebo) for the change from baseline for UPDRS Part III and UPDRS Part II+III for this subgroup analysis for the mITT population with an MMRM analysis. There is some discordance relative to statistically significant results for the different endpoints shown based upon MMRM and ANCOVA (LOCF) analyses. It is also noteworthy that the magnitude of these statistically significant changes for the mITT population and MMRM analysis are not only small in absolute terms, but they are also smaller than the magnitude of effects of all other FDA approved drugs for early Parkinson's disease.
- These specific post-hoc analyses were not prespecified in the SAP as a primary nor secondary analysis and therefore, they must be considered as exploratory analyses. Considering that the prespecified, primary analysis of the primary efficacy endpoint was not statistically significant for either safinamide dose (vs placebo), I cannot conclude that Study MOTION demonstrates efficacy of safinamide in early Parkinson's disease.

Sponsor Statistical Analysis Plan for Secondary Efficacy Endpoints/Analyses (Study MOTION)

The sponsor SAP outlined the following hierarchical sequence for statistical testing to address multiplicity (i.e., multiple statistical comparisons...

A hierarchical procedure will be used in the inferential analysis for the comparison of the primary endpoint between each of the two safinamide doses to the placebo. This approach of conducting sequential tests preserves the pre-specified family-wise type I error rate without further adjustment.

First the safinamide 100 mg/day dose will be compared to the placebo at the significance level of 0.05 (High Dose Comparison). **If the High Dose Comparison is not statistically significant, neither of two safinamide doses meets the primary endpoint.** If the High Dose Comparison is statistically significant, then the safinamide 100 mg/day dose meets the primary endpoint. Then, the safinamide 50 mg/day dose will be compared to the placebo at the significance level of 0.05 (Low Dose Comparison). **If the Low Dose Comparison is not statistically significant, then the safinamide 50 mg/day dose does not meet the primary endpoint. According to the hierarchical procedure, all the confirmatory testing of the key secondary efficacy endpoints will be halted.** If the Low Dose Comparison is statistically significant, then the safinamide 50 mg/day dose also meets the primary endpoint. Then, the key secondary efficacy endpoints will be compared as specified.

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Key Secondary Endpoint Analyses

The confirmatory testing for the key secondary efficacy endpoints will only be performed if both safinamide doses meet the primary endpoint.

A hierarchical procedure will be performed for the key secondary endpoints according to the following pre-specified priority order.

- UPDRS Section II (ADL) score change from baseline to WK-24, safinamide 100 mg/day dose vs. placebo
- Proportion of subjects with scores 1,2,3 (showing improvement) on the CGI change scale at WK-24, safinamide 100 mg/day dose vs. placebo
- PDQ-39 score change from baseline to WK-24, safinamide 100 mg/day dose vs. placebo
- UPDRS Section II (ADL) score change from baseline to WK-24, safinamide 50 mg/day dose vs. placebo
- Proportion of subjects with scores 1,2,3 (showing improvement) on the CGI change scale at WK-24, safinamide 50 mg/day dose vs. placebo
- PDQ-39 score change from baseline to WK-24, safinamide 50 mg/day dose vs. placebo
- Cogtest PD Battery test – strategic target detection test (STDT) score change from baseline to WK-24, safinamide 100 mg/day dose vs. placebo
- Cogtest PD Battery test – auditory number sequencing test (ANS) score change from baseline to WK-24, safinamide 100 mg/day dose vs. placebo
- Cogtest PD Battery test – strategic target detection test (STDT) score change from baseline to WK-24, safinamide 50 mg/day dose vs. placebo
- Cogtest PD Battery test – auditory number sequencing test (ANS) score change from baseline to WK-24, safinamide 50 mg/day dose vs. placebo

The rule of hierarchical procedure testing is that only if the preceding hypothesis testing achieves the statistical significance of 0.05, the confirmatory testing will proceed to the next hypothesis testing. Otherwise, the confirmatory testing will be halted once a hypothesis testing did not meet the statistical significance. Any remaining endpoints yet to be tested are to be investigated on an exploratory basis only.

For the purpose of confirmatory testing, the primary analysis for each of the key secondary endpoints will be conducted in the ITT population using the On-Treatment Approach. The missing Endpoint at Week 24 will be imputed by a LOCF approach using the last post-baseline On-Treatment value.

Table 31 UPDRS Section II Score and Change from Baseline by Timepoint and Treatment Group – On-Treatment (ANCOVA [LOCF]), ITT Population

Timepoint	Statistics	Safinamide 50 mg/day (n = 227)		Safinamide 100 mg/day (n = 227)		Placebo (n = 225)	
		Value	Change	Value	Change	Value	Change
Baseline	n (missing)	227 (0)		227 (0)		225 (0)	
	Mean ± SD	7.38 ± 4.36		6.74 ± 3.79		6.88 ± 4.27	
	Median	7.00		6.00		6.00	
	Min; Max	1.0; 24.0		0.0; 18.0		0.0; 22.0	
Week 24	n (missing)	227 (0)	227 (0)	227 (0)	227 (0)	225 (0)	225 (0)
	Mean ± SD	6.83 ± 4.76	-0.55 ± 3.21	6.25 ± 3.73	-0.48 ± 2.47	6.82 ± 4.46	-0.07 ± 2.93
	Median	6.00	-0.52	6.00	0.00	6.00	0.00
	Min; Max	0.0; 24.0	-12.0; 14.0	0.0; 18.0	-8.0; 9.0	0.0; 27.0	-10.0; 13.0
	LS Mean (SE)		-0.44 (0.19)		-0.50 (0.19)		-0.05 (0.19)
	LS Diff vs. Placebo (SE)		-0.38 (0.26)		-0.45 (0.26)		
	95% CI of LS Diff		(-0.89, 0.13)		(-0.96, 0.06)		
p-value vs. Placebo ^a		0.142		0.085			

Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; ITT, intent to treat; LS, least squares; LOCF, last observation carried forward; SD, standard deviation; SE, standard error; UPDRS, Unified Parkinson's Disease Rating Scale. The parametric ANCOVA model is based on the change from Baseline to endpoint with fixed effects for treatment, region and Baseline value as a covariate.
^aAll p-values, LS means, and confidence intervals are calculated from the ANCOVA model.
Source: EOT Table 15.2.8.

Reviewer Comment

- I have presented Study MOTION results for some secondary efficacy endpoints of most interest to us earlier in this section.
- I have not presented results for the many secondary efficacy endpoints described in the sponsor's SAP because the primary statistical analysis of the primary efficacy endpoint was not "positive" for the primary analysis of the primary efficacy as appropriate for the prespecified SAP. Nevertheless, for completeness sake, I have presented above in Table 31 the sponsor's planned results of the first secondary efficacy endpoint (change from baseline in UPDRS part II-activities of daily living-ADL) in the hierarchical sequence for testing. If this testing was considered formally appropriate (but it is not because the primary efficacy endpoint for both safinamide doses was not statistically superior to placebo), formal testing of the prespecified hierarchical sequence of secondary efficacy endpoints would cease because the 100 mg dose of safinamide was not statistically superior to placebo for UPDRS part II-ADL (neither was the 50 mg safinamide dose statistically superior to placebo).

Advanced Parkinson's disease

Study 16

Table 32 shows results for all diary categories and for individual UPDRS Subscales and Combined Subscales for the mITT population for MMRM and ANCOVA (LOCF) analyses.

Table 32 Study 16 : Change from Baseline for Treatment Difference (Safinamide – Placebo) for Primary Efficacy Endpoint (“ON” without Troublesome Dyskinesia) and Other Efficacy Endpoints for mITT Population According to Safinamide Treatment for MMRM and ANCOVA Analyses

Study 016: Change from Baseline at Endpoint ("ON treatment" approach)					
Efficacy Parameter	Statistic (a)	mITT Population			
		MMRM Analysis (b)		ANCOVA (LOCF) Analysis (c)	
		50 mg/day (n=217)	100 mg/day (n=216)	50 mg/day (n=217)	100 mg/day (n=216)
ON without T Dysk (h)	LS Diff vs Pbo	0.50	0.53	0.46	0.55
	p-value	0.0356	0.0238	0.0387	0.0134
ON without Dysk (h)	LS Diff vs Pbo	0.41	0.56	0.46	0.64
	p-value	0.1463	0.0470	0.0710	0.0122
ON with NT Dysk (h)	LS Diff vs Pbo	0.08	-0.04	-0.03	-0.14
	p-value	0.6834	0.8360	0.8641	0.4349
ON with T Dysk (h)	LS Diff vs Pbo	0.11	0.06	0.11	0.06
	p-value	0.4080	0.6669	0.3488	0.6438
OFF Time (h)	LS Diff vs Pbo	-0.54	-0.53	-0.55	-0.57
	p-value	0.0088	0.0110	0.0049	0.0037
Asleep Time (h)	LS Diff vs Pbo	-0.07	-0.05	-0.03	-0.03
	p-value	0.4565	0.5909	0.7622	0.7174
UPDRS I	LS Diff vs Pbo	0.02	-0.02	0.02	0.00
	p-value	0.8460	0.8968	0.8484	0.9920
UPDRS II	LS Diff vs Pbo	-0.38	-0.75	-0.49	-0.91
	p-value	0.3253	0.0523	0.1718	0.0121
UPDRS III	LS Diff vs Pbo	-1.71	-2.24	-1.75	-2.48
	p-value	0.0373	0.0065	0.0212	0.0011
UPDRS II + III	LS Diff vs Pbo	-2.06	-3.00	-2.19	-3.37
	p-value	0.0654	0.0075	0.0334	0.0010
UPDRS I +II +III	LS Diff vs Pbo	-2.47	-3.23	-2.57	-3.25
	p-value	0.0269	0.0040	0.0203	0.0036

ANCOVA=Analysis of Covariance; Dysk=Dyskinesia; h= hours; LOCF=Last Observation Carried Forward; LS Diff vs Pbo=Least Squares Mean Difference vs. Placebo; LSPD=Late-Stage Parkinson's Disease; MMRM=Mixed Model Repeated Measures; mITT=modified Intent-to-Treat; NT=Non-troublesome; ON=ON Time; T=Troublesome; UPDRS=Unified Parkinson's Disease Rating Scale (Section I – Mentation, Behavior and Mood ; Section II - Activities of Daily Living; Section III – Motor Examination).

- p-value for comparison between safinamide and placebo; significant effects (p<0.05) are in **bold text**.
- MMRM model for change from Baseline to Endpoint includes treatment, center, and visit and treatment-by-visit as fixed effects, and baseline value as a covariate, using an unstructured variance-covariance matrix.
- ANCOVA model is based on change from Baseline to Endpoint with treatment and center as main effects and baseline value as a covariate.

NOTE: gray shading indicates values that have changed to non-significant upon re-analysis.

Source: ISE Tables 12.3.1.1, 12.3.1.2, 12.3.1.3, 12.3.1.4, 12.3.1.5, 12.3.1.6, 12.3.1.7, 12.3.1.8, 12.3.1.9, 12.3.1.10, 12.3.1.11.

Reviewer Comment

- Based upon the MMRM analyses of the mITT population (Table 32), there was a statistically significant decrease in the treatment difference of “OFF” time (~ 0.5 hours) for each dose that was similar in magnitude to the increase in “ON” time without troublesome dyskinesia indicating that the increase in “good ON” (i.e., “ON” time without troublesome dyskinesia) was primarily responsible for the decrease in “OFF.” There was no dose-response for the change in “OFF” just as there was no dose-response for the change in “good ON.” A statistically significant increase in “ON” time without any dyskinesia for 100 mg safinamide was also similar in magnitude to the increase in “ON” time without troublesome dyskinesia indicating that the change in this primary efficacy endpoint was not also related to an increase in “ON” with non-troublesome dyskinesia. Low dose (50 mg) safinamide also resulted in a noteworthy numerical increase in “ON” time without dyskinesia (~ 0.4 hours) that accounted for approximately 80 % of the increase in “ON” time without troublesome dyskinesia also associated with that dose. The p value was trending toward statistical significance (p = 0.1463). There did not appear to be any noteworthy change in any other diary category (i.e., “ON” with troublesome dyskinesia, or sleep time). In general, results for the ANCOVA (LOCF) analyses were similar to those for the MMRM analyses.
- Statistically significant decreases were evident for a decrease of UPDRS part III, and part I + II + III for both safinamide doses, and for a decrease of part II + III only for 100 mg safinamide. However, there were also noteworthy numerical improvements in UPDRS part II for the high dose and in UPDRS part II + III for the low dose that were slightly above the minimal requirement for statistical significance. The changes in UPDRS part II, part III, part II + III, and part I + II + III clearly suggested a dose-response for 100 mg safinamide because results for this dose showed larger beneficial changes than those for 50 mg safinamide.
- All these results clearly support beneficial effects of safinamide (for both 50 and 100 mg daily doses) in patients with advanced Parkinson's disease taking concomitant levodopa.

Sponsor Statistical Analysis Plan for Secondary Efficacy Endpoints/Analyses (Study 16)

The following language describes the sponsor’s plan outlined in the final SAP (dated 12/19/08, a few days before the database was locked on 12/31/08) for analyzing secondary analyses/endpoints.

“The secondary efficacy measures will be evaluated in a hierarchical fashion. Each of the below variables will be analyzed sequentially as long as a significant difference between the 100 mg/day group vs. placebo group is detected. In addition, if a significant difference is detected between the placebo group and the 100 mg/day group , the analysis will proceed to compare the placebo group to the 50 mg/day group . This approach should avoid the need for correcting the p-value due to multiplicity of testing over endpoints and over treatment groups.

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Below analyses will be performed on the ITT population, following the “ON Treatment” approach and with LOCF imputation of missing data.

The secondary efficacy analysis will include the following parameters ordered according to the hierarchical analysis approach:

- Decrease in total daily “off” time, as measured by diary cards – change from baseline to endpoint
- UPDRS Section III during “on” phase (based on diary) - mean change from baseline to endpoint
- CGI - Change from baseline - mean score in the course of the study
- Change in cognition (cognitive test battery) (analysis is beyond the scope of this document) mean change from baseline to endpoint (and to each evaluation done)
- Decrease in mean “off” time following first morning dose of levodopa – change from baseline to endpoint
- Improvement in the Dyskinesias Rating Scale during “on” phase – change from baseline to endpoint
- UPDRS Section II during “on” phase (based on diary) - mean change from baseline to endpoint
- CGI - Severity of illness – mean change from baseline to endpoint
- Mean percentage reduction in levodopa dose – change from baseline to endpoint

For the decrease in total daily “off” time, decrease in mean “off” time following the first morning dose of levodopa, UPDRS - Sections II and III, and CGI-Severity, change from Baseline to Endpoint will be analyzed using analysis of covariance (ANCOVA) with baseline values as a covariate and treatment regimen and center as main effects. The Dyskinesias Rating Scale (DRS) and the percentage reduction in levodopa dose, will be analyzed using the Wilcoxon Rank Sum Test. PROC NPAR1WAY with options WILCOXON and CLASS TREATMENT will be used. For DRS the changes from baseline will be considered irrespective of the most disabling dyskinesia. The normal approximation z two-sided p-value will be used to determine statistical significance of the reduction in levodopa dose in 100 mg/day and 50 mg/day treatment groups, as compared to placebo. For analyzing CGI - Change score, the Cochran-Mantel-Haenszel test (CMH3 for General Association Statistic) blocking on center, will be used to compare the proportion of patients showing improvements (score of 1, 2, or 3) versus no change or worsening (scores of 4, 5, 6 or 7). PROC FREQ using center as stratification factor will be employed. Summary statistics for all secondary parameters will be presented.

Sponsor Results from Final Study Report of Study 16

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Table 33 Study 16 : Summary of Change from Baseline in Total Daily Off Time —ITT Population

Week (Visit)	Statistic	Total Daily Off Time (hours)					
		Placebo (N = 222)		Safinamide 50 mg/day (N = 223)		Safinamide 100 mg/day (N = 224)	
		Value	Change	Value	Change	Value	Change
Visit 3 (Baseline) ^a	n	221	—	223	—	224	—
	Mean (SD)	5.3 (2.06)	—	5.2 (2.08)	—	5.2 (2.16)	—
	Median	5.0	—	4.8	—	4.8	—
	Min, Max	1, 12	—	2, 13	—	0, 13	—
Visit 8 (Week 24) ^b	n	214	213	215	215	217	217
	Mean (SD)	4.5 (2.66)	-0.8 (2.19)	3.9 (2.58)	-1.3 (2.28)	3.9 (2.48)	-1.3 (2.16)
	Median	4.4	-0.8	3.3	-1.3	3.8	-1.3
	Min, Max	0, 13	-8, 6	0, 13	-11, 6	0, 11	-7, 7
LS mean ^c		—	-0.7	—	-1.3	—	-1.3
LS difference vs placebo		—	—	—	-0.6	—	-0.6
95% CI		—	—	—	(-0.9, -0.2)	—	(-1.0, -0.2)
P value ^d		—	—	—	0.0043	—	0.0034

Abbreviation: CI, confidence interval; LS, least squares; SD, standard deviation.
^a Visit 3 (Baseline) or last nonmissing value before study drug was taken.
^b Visit 8 (Week 24) or last available observation (LOCF).
^c LS mean change from Baseline to Visit 8 (Week 24).
^d Treatments were compared using an ANCOVA with terms for treatment and center and Baseline as a covariate. P values for the overall treatment effect were 0.0038 for treatment and < 0.0001 for center.
Source: EOT Table 33.

Table 34 Study 16 : Summary of the UPDRS Section 3 (Motor Examination)—ITT Population

Week (Visit)	Statistic	Placebo (N = 222)		Safinamide 50 mg/day (N = 223)		Safinamide 100 mg/day (N = 224)	
		Value	Change	Value	Change	Value	Change
		Visit 3 (Baseline) ^a	n	222	—	223	—
Mean (SD)	28.7 (12.02)		—	27.3 (12.66)	—	28.3 (13.30)	—
Median	28.0		—	26.0	—	27.0	—
Min, Max	1, 60		—	2, 64	—	3, 73	—
Visit 8 (Week 24) ^b	n	217	217	214	214	217	217
	Mean (SD)	23.9 (12.60)	-4.8 (9.37)	21.1 (12.04)	-6.1 (9.61)	21.3 (12.53)	-7.1 (10.53)
	Median	23.0	-3.0	19.5	-5.0	20.0	-4.0
	Min, Max	2, 65	-39, 28	2, 60	-41, 23	1, 72	-35, 30
LS mean ^c		—	-4.3	—	-6.1	—	-6.9
LS difference vs placebo		—	—	—	-1.8	—	-2.6
95% CI		—	—	—	(-3.3, -0.4)	—	(-4.1, -1.1)
P value ^d		—	—	—	0.0138	—	0.0006

Abbreviation: CI, confidence interval; LS, least squares; SD, standard deviation.
^a Visit 3 (Baseline) or last nonmissing value before study drug was taken.
^b Visit 8 (Week 24) or last available observation (LOCF).
^c LS mean change from Baseline to Visit 8 (Week 24).
^d Treatments were compared using an ANCOVA with Baseline as a covariate and treatment and center as main effects. P values for overall treatment effect were 0.0018 for treatment and < 0.0001 for center.
Source: EOT Table 25.3.

**Table 35 Summary of the Clinical Global Impression—Change Scale (CGI-C)
—ITT Population**

Week (Visit)	Response	Placebo (N = 222) n (%)	Sildenafil 50 mg/day (N = 223) n (%)	Sildenafil 100 mg/day (N = 224) n (%)
Visit 8 (Week 24) ^c	Improvement ^a	123 (55.4)	148 (66.4)	144 (64.3)
	No change or worsening ^b	94 (42.3)	66 (29.6)	73 (32.6)
	Missing	5 (2.3)	9 (4.0)	7 (3.1)
	P value ^d	—	0.0010	0.0089

^a Includes patients with scores of 1 (very much improved), 2 (much improved), or 3 (minimally improved).
^b Includes patients with scores of 4 (no change), 5 (minimally worse), 6 (much worse), or 7 (very much worse).
^c Visit 8 (Week 24) or last available observation (LOCF).
^d Treatments were compared using Cochran-Mantel-Haenszel test stratified by center.
Source: EOT Table 27.2.

The sponsor noted that the complex results of the fourth prespecified secondary efficacy endpoint (i.e., change in cognition) was not statistically superior for sildenafil vs placebo. The sponsor described this result with the following language : “However primary interest involved differences between each of the doses (high or low dose sildenafil) when compared to placebo within the subgroup categories themselves and these were summarized in the matrix summary table (Table 1). Throughout all Cogtest assessments performed, neither of the two treatment doses showed any consistent significant differences within any of the subgroups assessed. In fact there were only two statistically significant differences, one each within the ‘Responders’ and ‘Freezing’ subgroups, with the high dose group. However, given the number of statistical tests performed this is most likely a chance event and is unlikely to be clinically relevant.” Thus, results of this analysis were extremely complex and were not reflected in a single table because the sponsor had conducted complex analyses which had not been clearly prespecified and which were presented a separate report for “cognition” in which many cognitive domains had been tested and analyzed for “cognition.” More specifically, cognitive function had been assessed with a computerized test battery (Cogtest Inc., www.cogtest.com) incorporating the following tests from the Cogtest Library: 1. Auditory Number Sequencing (ANS), 2. Spatial Working Memory (SWM), 3. Strategic Target Detection Test (STDT), 4. Verbal Memory – Selective reminding (and delay), 5. Digit Symbol and 6. Tower of London.

Reviewer Comment

- Formal testing of the prespecified hierarchical testing sequence (in the SAP) for secondary efficacy endpoints showed statistical superiority of both doses of sildenafil (vs placebo) for decrease in “off” time, decrease in UPDRS part III, and CGI-C Table 33, Table 34, and Table 35 respectively.
- My earlier review of these secondary efficacy endpoints of most interest to us according to the DNP recommended analyses (mITT population and MMRM) showed the

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“positive” results of safinamide treatment (vs placebo) for decrease of “off” time and UPDRS part III motor score.

- Formal testing of secondary efficacy endpoints was supposed to cease at the endpoint of change in cognition because this endpoint was not statistically superior for safinamide vs placebo.

Study 18 (Analysis Reflects Pooled Results of Treatment in Studies 16 AND 18)

APPEARS THIS WAY ON ORIGINAL

Table 36 Studies 16 and 18 (Pooled Analysis) : Change from Baseline at Endpoint for Safinamide Treatment Difference (Safinamide – Placebo) for Many Secondary Efficacy Endpoints

Combined Studies 016/018; Change from Baseline at Endpoint ("ON treatment" Approach)					
		mITT Population			
Efficacy Parameter	Statistic (a)	MMRM Analysis (b)		ANCOVA (LOCF) Analysis (c)	
		50 mg/day (n=217)	100 mg/day (n=216)	50 mg/day (n=217)	100 mg/day (n=216)
ON without T Dysk (h)	LS Diff vs Pbo	1.03	1.18	0.66	0.80
	p-value	0.0033	0.0007	0.0037	0.0005
ON without Dysk (h)	LS Diff vs Pbo	0.77	0.69	0.63	0.68
	p-value	0.0628	0.0930	0.0181	0.0103
ON with NT Dysk (h)	LS Diff vs Pbo	0.25	0.47	0.00	0.07
	p-value	0.3238	0.0654	0.9903	0.6879
ON with T Dysk (h)	LS Diff vs Pbo	-0.20	-0.30	0.02	0.02
	p-value	0.3854	0.1833	0.8705	0.9060
OFF Time (h)	LS Diff vs Pbo	-0.70	-0.90	-0.60	-0.73
	p-value	0.0153	0.0016	0.0014	0.0001
Asleep Time (h)	LS Diff vs Pbo	-0.25	-0.08	-0.08	-0.07
	p-value	0.1785	0.6626	0.4309	0.4654
UPDRS I	LS Diff vs Pbo	-0.10	-0.15	-0.09	0.00
	p-value	0.6035	0.4513	0.4800	0.9694
UPDRS II	LS Diff vs Pbo	-0.59	-0.79	-0.52	-0.98
	p-value	0.4224	0.2840	0.1924	0.0131
UPDRS III	LS Diff vs Pbo	-0.47	-1.34	-0.96	-2.12
	p-value	0.6987	0.2711	0.2172	0.0062
UPDRS II + III	LS Diff vs Pbo	-1.41	-2.28	-1.41	-3.08
	p-value	0.3393	0.1203	0.1870	0.0038
UPDRS I + II + III	LS Diff vs Pbo	-1.89	-2.52	-1.92	-2.90
	p-value	0.2082	0.0919	0.0971	0.0131

ANCOVA=Analysis of Covariance; Dysk=Dyskinesia; LOCF=Last Observation Carried Forward; LS Diff vs Pbo=Least Squares Mean Difference vs. Placebo; LSPD=Late-Stage Parkinson's Disease; MMRM=Mixed Model Repeated Measures; mITT=modified Intent-to-Treat; NT=Non-troublesome; ON=ON Time; T=Troublesome; UPDRS=Unified Parkinson's Disease Rating Scale (Section I – Mentation, Behavior and Mood; Section II - Activities of Daily Living; Section III – Motor Examination).

(a)p-value for comparison between safinamide and placebo; significant effects (p<0.05) are in **bold** text.

(b)MMRM model for change from Baseline to Endpoint includes treatment, center, visit, and treatment-by-visit as fixed effects, and baseline value as a covariate. An unstructured variance-covariance matrix was used except for UPDRSII+III and UPDRS I+II+III where model would not converge and the Toeplitz matrix was used.

(c)ANCOVA model is based on change from Baseline to Endpoint with treatment and center as main effects, and baseline value as a covariate.

NOTE: gray shading indicates values that have changed to non-significant upon re-analysis.

NOTE: For UPDRS I+II+III and UPDRSII+III endpoints, the MMRM model would not converge with an unstructured covariance matrix, therefore, the Toeplitz covariance matrix was used.

Source: ISE Tables 13.3.1.1, 13.3.1.2, 13.3.1.3, 13.3.1.4, 13.3.1.5, 13.3.1.6, 13.3.1.7, 13.3.1.8, 13.3.1.9, 13.3.1.10, 13.3.1.11.

Reviewer Comments

- Table 36 shows the results for the various efficacy endpoints for the change from baseline in each safinamide treatment group (50 mg and 100 mg separately vs placebo) in MMRM analysis and also ANCOVA (LOCF) analysis in combined Studies 16 and 18. **I do not believe that these results are necessarily reliable. Therefore, I believe that these results should be interpreted with caution because patients could have experienced significant changes (increase or decrease) in doses of concomitant dopaminergic drugs or even the addition of a new concomitant dopaminergic drug in extension Study 18.**
- In the MMRM analyses, nominal p-values show statistically significant benefits for “ON” without troublesome dyskinesia (both safinamide doses), and “OFF” time (both doses) but no statistically significant benefits on the various UPDRS subscales and combinations of subscales.
- In the ANCOVA (LOCF) analyses, nominal p-values show statistically significant benefits for “ON” without troublesome dyskinesia (both safinamide doses), and “OFF” time (both doses) and also statistically significant benefits on individual UPDRS subscales (UPDRS part II, UPDRS part III) and combinations of subscales (UPDRS parts I+II+III, and parts II+III) for the 100 mg dose.

Study SETTLE (27919)

Table 37 and Table 38 show results for the various perspectives on every diary category including change from baseline in absolute hours, percentage change from baseline, and change of percentage of diary category for the MMRM and ANCOVA (LOCF) analyses for the mITT and completer populations. Table 39 shows results for UPDRS subscales and combinations of subscales for MMRM and ANCOVA (LOCF) analyses of the mITT and completer populations.

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Table 37 Study SETTLE (27919) : Change from Baseline to Endpoint/Week 24 for Safinamide Treatment Difference (Safinamide – Placebo) in Diary Categories (MMRM and ANCOVA-LOCF Analyses for mITT and Completer Populations)

Group 7 Study 27919 (SETTLE): Patient Diary Categories, Part 1					
Efficacy Parameter	Statistic (a)	mITT Population		Completer Population	
		MMRM Analysis (b)	ANCOVA (LOCF) Analysis (c)	MMRM Analysis (b)	ANCOVA (OC-Completers) Analysis (c)
		Safinamide 100 mg/day (n=270)	Safinamide 100 mg/day (n=270)	Safinamide 100 mg/day (n=241)	Safinamide 100 mg/day (n=241)
ON without T Dysk (h)	LS Diff vs Pbo	0.9	1.0	0.8	1.0
	p-value	<0.0001	<0.0001	<0.0001	<0.0001
ON without Dysk (h)	LS Diff vs Pbo	0.5	0.7	0.5	0.6
	p-value	0.0026	0.0051	0.0047	0.0145
ON with NT Dysk (h)	LS Diff vs Pbo	0.3	0.3	0.3	0.3
	p-value	0.0320	0.1197	0.0359	0.1138
ON with T Dysk (h)	LS Diff vs Pbo	0.1	0.1	0.1	0.0
	p-value	0.4226	0.4923	0.5229	0.7683
OFF Time (h)	LS Diff vs Pbo	-1.0	-1.0	-1.0	-1.0
	p-value	<0.0001	<0.0001	<0.0001	<0.0001
Asleep Time (h)	LS Diff vs Pbo	0.1	0.0	0.1	0.1
	p-value	0.2265	0.8941	0.1994	0.5309
%ON without T Dysk	LS Diff vs Pbo	20.0	24.2	19.8	22.7
	p-value(d)	0.0008	0.0021	0.0021	0.0093
%ON without Dysk	LS Diff vs Pbo	22.8	26.8	23.1	26.4
	p-value	0.0075	0.0057	0.0143	0.0145
%ON with NT Dysk	LS Diff vs Pbo	17.2	25.6	17.4	27.8
	p-value	0.0591	0.0193	0.0761	0.0218
%ON with T Dysk	LS Diff vs Pbo	2.0	-2.3	-3.4	-11.0
	p-value	0.7446	0.8178	0.4442	0.1856
%OFF Time	LS Diff vs Pbo	-20.2	-25.3	-17.6	-19.8
	p-value	<0.0001	<0.0001	<0.0001	<0.0001
%Asleep Time	LS Diff vs Pbo	5.4	2.8	6.2	5.6
	p-value	0.1419	0.5904	0.0956	0.2842

LSPD=Late-Stage Parkinson's Disease; ANCOVA=Analysis of Covariance; Dysk=Dyskinesia; LOCF=Last Observation Carried Forward; LS Diff vs Pbo=Least Squares Mean Difference vs. Placebo; mITT=modified Intent-to-Treat; MMRM=Mixed Model Repeated Measures; NT=Non-troublesome; OC=Observed Cases; ON=ON Time; Saf=Safinamide; T=Troublesome; %ON=change in ON Time as a percentage of the total ON Time at Baseline.

a. p-value for comparison between safinamide and placebo; significant effects (p<0.05) are in bold text.

b. MMRM model for change from Baseline to Endpoint includes treatment, region, and visit as fixed effects, and baseline value as a covariate.

c. ANCOVA model is based on change from Baseline to Endpoint with fixed effects for treatment, study, and baseline value as a covariate.

Source: ISE Tables 7.3.1.6, 7.3.1.7, 7.3.1.8, 7.3.1.9, 7.3.1.10, 7.3.1.11; 7.3.2.6, 7.3.2.7, 7.3.2.8, 7.3.2.9, 7.3.2.10, 7.3.2.11, 7.3.1.12, 7.3.1.13, 7.3.1.14, 7.3.1.15, 7.3.1.16, 7.3.1.17; 7.3.2.12, 7.3.2.13, 7.3.2.14, 7.3.2.15, 7.3.2.16, 7.3.2.17.

Table 38 Study SETTLE (27919) : Change from Baseline to Endpoint/Week 24 for Treatment Difference (Safinamide – Placebo) in Diary Categories (MMRM and ANCOVA-LOCF Analyses for mITT and Completer Populations)

Group 7 Study 27919 (SETTLE): Patient Diary Categories, Part 2					
Efficacy Parameter	Statistic (a)	mITT Population		Completer Population	
		MMRM Analysis (b)	ANCOVA (LOCF) Analysis (c)	MMRM Analysis (b)	ANCOVA (OC-Completers) Analysis (c)
		Safinamide 100 mg/day (n=270)	Safinamide 100 mg/day (n=270)	Safinamide 100 mg/day (n=241)	Safinamide 100 mg/day (n=241)
Change of %ON without T Dysk	LS Diff vs Pbo	4.9	5.6	4.7	5.3
	p-value	<0.0001	<0.0001	<0.0001	<0.0001
Change of %ON without Dysk	LS Diff vs Pbo	4.8	5.5	4.7	5.3
	p-value	<0.0001	<0.0001	<0.0001	<0.0001
Change of %ON with NT Dysk	LS Diff vs Pbo	1.7	1.7	1.7	1.8
	p-value	0.0320	0.1197	0.0359	0.1138
Change of %ON with T Dysk	LS Diff vs Pbo	0.4	0.4	0.3	0.2
	p-value	0.4226	0.4923	0.5229	0.7683
Change of %OFF Time	LS Diff vs Pbo	-5.5	-5.8	-5.3	-5.7
	p-value	<0.0001	<0.0001	<0.0001	<0.0001
Change of %Asleep Time	LS Diff vs Pbo	0.4	0.1	0.4	0.3
	p-value	0.2265	0.8941	0.1994	0.5309

ANCOVA=Analysis of Covariance; Dysk=Dyskinesia; LOCF=Last Observation Carried Forward; LS Diff vs Pbo=Least Squares Mean Difference vs. Placebo; LSPD=Late-Stage Parkinson's Disease; mITT=modified Intent-to-Treat; MMRM=Mixed Model Repeated Measures; NT=Non-troublesome; OC=Observed Cases; ON=ON Time; Saf=Safinamide; T=Troublesome; %ON=change in ON Time as a percentage of the total ON Time at Baseline.

a. p-value for comparison between safinamide and placebo; significant effects (p<0.05) are in bold text.

b. MMRM model for change from Baseline to Endpoint includes treatment, region, and visit as fixed effects, and baseline value as a covariate.

c. ANCOVA model is based on change from Baseline to Endpoint with fixed effects for treatment, study, and baseline value as a covariate.

Source: ISE Tables 7.3.1.18, 7.3.1.19, 7.3.1.20, 7.3.1.21, 7.3.1.22, 7.3.1.23, 7.3.2.18, 7.3.2.19, 7.3.2.20, 7.3.2.21, 7.3.2.22, 7.3.2.23.

Table 39 Study SETTLE (27919) : Change from Baseline to Endpoint/Week 24 for Treatment Difference (Safinamide – Placebo) for UPDRS Individual and Combined Subscales (MMRM and ANCOVA-LOCF Analyses for mITT and Completer Populations)

Group 7 Study 27919 (SETTLE): UPDRS Sections I, II, and III					
Efficacy Parameter	Statistic (a)	mITT Population		Completer Population	
		MMRM Analysis (b)	ANCOVA (LOCF) Analysis (c)	MMRM Analysis (b)	ANCOVA (OC-Completers) Analysis (c)
		Safinamide 100 mg/day (n=270)	Safinamide 100 mg/day (n=270)	Safinamide 100 mg/day (n=241)	Safinamide 100 mg/day (n=241)
UPDRS I	LS Diff vs Pbo	-0.0	0.0	-0.0	0.0
	p-value	0.8593	0.8593	0.9483	0.9483
UPDRS II	LS Diff vs Pbo	-0.4	-0.5	-0.4	-0.4
	p-value	0.0564	0.1175	0.1255	0.1392
UPDRS III	LS Diff vs Pbo	-0.9	-1.7	-0.6	-1.3
	p-value	0.0514	0.0060	0.2247	0.0436
UPDRS II + III	LS Diff vs Pbo	-1.4	-2.2	-1.0	-1.8
	p-value	0.0218	0.0049	0.0987	0.0263
UPDRS I + II + III	LS Diff vs Pbo	-1.9	-1.9	-1.8	-1.8
	p-value	0.0197	0.0197	0.0303	0.0303

ANCOVA=Analysis of Covariance; LOCF=Last Observation Carried Forward; LS Diff vs Pbo=Least Squares Mean Difference vs. Placebo; LSPD=Late-Stage Parkinson’s Disease; mITT=modified Intent-to-Treat; MMRM=Mixed Model Repeated Measures; OC=Observed Cases; UPDRS=Unified Parkinson’s Disease Rating Scale (Section I – Mentation, Behavior and Mood; Section II - Activities of Daily Living; Section III – Motor Examination).

- a. p-value for comparison between safinamide and placebo; significant effects (p<0.05) are in bold text.
- b. MMRM model for change from Baseline to Endpoint includes treatment, region, and visit as fixed effects, and baseline value as a covariate.
- c. ANCOVA model is based on change from Baseline to Endpoint with fixed effects for treatment, study, and baseline value as a covariate.

Source: ISE Tables 7.3.1.1, 7.3.1.2, 7.3.1.3, 7.3.1.4, 7.3.1.5, 7.3.2.1, 7.3.2.2, 7.3.2.3, 7.3.2.4, 7.3.2.5.

Reviewer Comments

- My comments on Study SETTLE efficacy results shown in Table 37, Table 38, and Table 39 focus on the mITT population and MMRM analyses and do not address the Completer population because the sponsor’s Completer population includes patients in the RDO subpopulation who have discontinued study treatment but are coming to visits for efficacy data collection. I do not think that this population is of great interest because these results include patients who are not receiving randomized study medication.
- Table 37 and Table 38 show treatment difference results for all possible diary categories. In Table 37, there were statistically significant changes in absolute hours and percentage change for “ON” without troublesome dyskinesia, “ON” without dyskinesia, and “OFF” for the mITT population with MMRM analyses. The change in “OFF” was a decrease in the opposite direction of the change in the two categories of “ON” and the magnitude of the decrease in “OFF” was similar to the increase in “ON” without troublesome dyskinesia. “ON” with non-troublesome dyskinesia was statistically significant for absolute increase and close to being statistically significant for percentage change in same category. The increase in “ON” without dyskinesia was nearly 60 % of the increase in “ON” without troublesome dyskinesia suggesting that most of the improvement in the primary endpoint was the best type of improvement of “ON” time without any dyskinesia. Of importance, there were no statistically significant increases in “ON” with troublesome dyskinesia nor with sleep time. Overall, the ANCOVA (LOCF) analyses were quite concordant with the MMRM analyses.

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- Table 38 which presents the change in the treatment difference of the percentage of different diary categories for MMRM analyses, showed that safinamide produced a statistically significant increase in percentage of “ON” without troublesome dyskinesia, “ON” without any dyskinesia, and “ON” with non-troublesome dyskinesia, and also a statistically significant decrease in percentage of “OFF” time. There were no statistically significant changes in the percentage of “ON” with troublesome dyskinesia, or with sleep time. Overall, the ANCOVA (LOCF) analyses were quite concordant with the MMRM analyses.
- Table 39 which presents the treatment difference for the change in UPDRS subscales and combinations of subscales, showed statistically significant decreases in UPDRS part II + III, and I + II + III in the MMRM analyses. The decrease in UPDRS was relatively small (0.9) and slightly above the level of statistical significance ($p = 0.514$) as was also the decrease in UPDRS part II (-0.4; $p = 0.564$). In general, the results of the ANCOVA (LOCF) analyses were somewhat similar. Statistically significant improvement were observed for the changes of UPDRS part III, and UPDRS part II + III, and part I + II + III. However, the magnitude of the changes were numerically, substantially greater for changes of UPDRS part III, and UPDRS art II + III.

Sponsor Statistical Analysis Plan for Secondary Efficacy Endpoints/Analyses (Study SETTLE)

Key Secondary Endpoint Analyses

The key secondary efficacy endpoints will be evaluated in a hierarchical fashion. Each of the below key efficacy endpoints will be analyzed sequentially as long as a significant difference between the safinamide group versus placebo group is concluded.

This approach (conducting sequential tests) can preserve the pre-specified family-wise type I error rate (α) without further adjustment.

- Daily “off” time as measured by diary cards, change from baseline to WK-24
- UPDRS Section III score during the “on” phase change from baseline to WK-24
- UPDRS Section II (ADL) score during the “on” phase change from baseline to WK-24
- Proportion of subjects with scores 1,2,3 (showing improvement) on the CGI change scale at WK-24
- PDQ-39 summary index score change from baseline to WK-24

In addition to the inferential analyses described below, each secondary endpoint will be presented descriptively by treatment group and visit.

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Table 40 Study SETTLE : Summary of Total Daily Off Time and Change from Baseline by Timepoint and Treatment Group – On-Treatment (ANCOVA [LOCF]), ITT Population

Timepoint	Statistics	Safinamide (n=274)		Placebo (n=275)	
		Value	Change	Value	Change
Baseline	n (missing)	274 (0)		275 (0)	
	Mean ±SD	5.34 ± 1.97		5.38 ± 2.01	
	Median	5.25		5.25	
	Min; Max	0.0; 12.5		0.3; 12.0	
Week 24	n (missing)	274 (0)	274 (0)	275 (0)	275 (0)
	Mean ±SD	3.77 ±2.56	-1.56 ±2.35	4.84 ±2.59	-0.54 ±2.21
	Median	3.88	-1.38	5.00	-0.50
	Min; Max	0.0; 16.3	-9.0; 6.5	0.0; 13.0	-8.5; 5.8
	LS Mean (SE)		-1.65 (0.14)		-0.62 (0.14)
	LS Diff vs. Placebo (SE)		-1.03 (0.19)		
	95% CI of LS Diff		(-1.40, -0.67)		
	p-value vs. Placebo		<0.001		

Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; ITT, intent to treat; LOCF, last observation carried forward; LS, least squares; SD, standard deviation; SE, standard error.
Parametric ANCOVA model is based on the change from baseline to endpoint with fixed effects for treatment, region, and baseline value as a covariate.
All p-values, LS means, and confidence intervals are calculated from the ANCOVA model.
Source: [EOT Table 15.2.8](#)

Table 41 Study SETTLE : UPDRS Section III During On Phase and Change from Baseline by Timepoint and Treatment Group – On-Treatment (ANCOVA [LOCF]), ITT Population

Timepoint	Statistics	Safinamide (n=274)		Placebo (n=275)	
		Value	Change	Value	Change
Baseline	n (missing)	274 (0)		275 (0)	
	Mean ±SD	22.26 ± 11.66		23.05 ± 12.65	
	Median	22.00		22.72	
	Min; Max	2.0; 72.0		0.0; 74.0	
Week 24	n (missing)	274 (0)	274 (0)	275 (0)	275 (0)
	Mean ±SD	18.83 ±10.87	-3.43 ±7.72	21.22 ±11.78	-1.83 ±8.23
	Median	17.00	-3.00	19.00	-1.00
	Min; Max	1.0; 53.0	-43.0; 27.0	1.0; 64.0	-28.0; 35.0
	LS Mean (SE)		-3.52 (0.46)		-1.70 (0.46)
	LS Diff vs. Placebo (SE)		-1.82 (0.61)		
	95% CI of LS Diff		(-3.01, -0.62)		
	p-value vs. Placebo		0.003		

Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; ITT, intent to treat; LOCF, last observation carried forward; LS, least squares; SD, standard deviation; SE, standard error; UPDRS, Unified Parkinson's Disease Rating Scale.
Parametric ANCOVA model is based on the change from baseline to endpoint with fixed effects for treatment, region, and baseline value as a covariate.
All p-values, LS means, and confidence intervals are calculated from the ANCOVA model.
Source: [EOT Table 15.2.15](#)

Table 42 Study SETTLE : UPDRS Section II During On Phase and Change from Baseline by Timepoint and Treatment Group – On-Treatment (ANCOVA [LOCF]), ITT Population

Timepoint	Statistics	Safinamide (n = 274)		Placebo (n = 275)	
		Value	Change	Value	Change
Baseline	n (missing)	274 (0)		275 (0)	
	Mean ±SD	9.97 ±5.53		10.43 ±6.29	
	Median	10.00		10.00	
	Min; Max	0.0; 28.0		0.0; 35.0	
Week 24	n (missing)	274 (0)	274 (0)	275 (0)	275 (0)
	Mean ±SD	8.90 ±5.44	-1.07 ±3.63	9.68 ±5.94	-0.75 ±3.95
	Median	9.00	-1.00	9.00	0.00
	Min; Max	0.0; 26.0	-16.2; 9.0	0.0; 28.0	-20.2; 13.0
	LS Mean (SE)		-1.22 (0.23)		-0.79 (0.23)
	LS Diff vs. Placebo (SE)		-0.43 (0.30)		
	95% CI of LS Diff		(-1.02, 0.16)		
	p-value vs. Placebo		0.149		

Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; ITT, intent to treat; LOCF, last observation carried forward; LS, least squares; SD, standard deviation; SE, standard error; UPDRS, Unified Parkinson's Disease Rating Scale.
Parametric ANCOVA model is based on the change from baseline to endpoint with fixed effects for treatment, region and baseline value as a covariate.
All p-values, LS means, and confidence intervals are calculated from the ANCOVA model.
Source: EOT Table 15.2.22

Reviewer Comment

- My earlier review of these secondary efficacy endpoints of most interest to us according to the DNP recommended analyses (mITT population and MMRM) showed the “positive” results of safinamide treatment (vs placebo) for decrease of “off” time and UPDRS part III motor score.
- Based upon the sponsor’s prespecified hierarchical sequence for analyzing secondary efficacy endpoints, Table 40 shows that safinamide was superior to placebo for the first secondary efficacy endpoint for decreasing “OFF” time. Table 41 shows that safinamide was superior to placebo for the first next prespecified secondary efficacy endpoint for decreasing UPDRS part III. However, Table 42 shows that safinamide was not statistically superior to placebo for the next secondary efficacy endpoint in the hierarchical sequence designated. In consideration of the sponsor’s “formal,” prespecified hierarchical analysis (in SAP) of secondary efficacy endpoints, testing should cease after testing for a secondary efficacy endpoint which was not statistically superior for safinamide vs placebo. Thus, formal testing stopped after analyzing UPDRS part II-ADL.

6.1.6 Other Endpoints

Not applicable. Efficacy endpoints of interest/relevance have been presented in Sections 6.1.4 and 6.1.5.

6.1.7 Subpopulations

Results for the primary efficacy endpoint for all patients vs subpopulations are shown for patients with advanced stage Parkinson's disease in Studies 16 and SETTLE (the only “positive” pivotal trials demonstrating efficacy of safinamide) in Table 43.

Table 43 Primary Efficacy Endpoint (Change from Baseline of “ON without Troublesome Dyskinesia) for Subpopulations vs All Patients in LSPD Studies 16 and SETTLE

Populati on	Study 16**						Study SETTLE***				
	Place bo	Safinamide 50 mg			Safinamide 100 mg			Place bo	Safinamide 100 mg		
	N	N	Treatme nt Differenc e*	P Valu e	N	Treatme nt Differenc e*	P Valu e	N	N	Treatme nt Differenc e*	P Value Pr
All Patients	212	21 7	0.50	0.035 6	21 6	0.53	0.023 8	273	26 8	0.99	< 0.001
Gender											
Male	152	15 2	0.70	0.013 2	15 7	0.59	0.033 9	162	16 8	0.71	0.0087
Female	60	65	0.32	0.486 3	59	0.45	0.329 3	111	10 0	1.39	< 0.0001
Age											
< 65 yo	143	14 2	0.60	0.037 6	14 4	0.53	0.067 4	156	15 7	0.96	0.0005
≥ 65 yo	69	75	0.49	0.268 4	72	0.50	0.253 5	117	11 1	1.08	0.0010
Race											
Asian	171	17 6	0.64	0.011 7	17 3	0.54	0.032 6	85	87	0.83	0.0112
Caucasia n	41	41	0.15	0.801 5	43	0.53	0.390 2	186	17 8	1.10	< 0.0001

Source : Primary Statistical Reviewer : Dr. Zhang
*Treatment Difference (Safinamide – Placebo)

Reviewer Comment

- All subgroups show statistically significant results ($p < 0.05$) for the primary efficacy endpoint for each of these subgroups for Study SETTLE. For Study 16 results of at least one subgroup showed such statistically sign cant results for the primary efficacy endpoint. The subgroup, which did not demonstrate such a statistically significant result, always consisted of a markedly/notably lower number of patients compared to the corresponding, respective subgroup showing a statistically significant result in Study 16. I believe that the main reason that these subgroups did not show statistically significant results for the primary efficacy endpoint was related to the fact there was a much smaller number of patients in each respective subgroup and that the number of patients studied in these subgroups was underpowered to show a statistically significant result. My conclusions about the efficacy of safinamide for LSPD remain unaltered given the subgroup comments which I have noted.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Reviewer Comment

- Efficacy results from Studies 16 and SETTLE indicate that daily safinamide doses of 50 mg and 100 mg are effective treatment in LSPD. Although results for both doses of safinamide in Study 16 showed a similar benefit for increase from baseline in “ON” time without troublesome dyskinesia (0.5 hrs), Study SETTLE showed a 1 hour improvement in this efficacy outcome. Thus, results of both of these trials support a recommendation for approval of both doses of safinamide.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Analyses of combined Studies 16 and 18 in LSPD suggested that safinamide may have been effective for treatment up to 2 years.

Reviewer Comment

- It is difficult to draw conclusions about the persistence of long-term efficacy (up to 2 years) of safinamide for increasing “ON” time without troublesome dyskinesia and decreasing “OFF” time because the majority of patients did not complete 2 years of treatment and many of these patients had received “rescue” medication from the perspective that the total daily dose of levodopa or a concomitant dopaminergic medication increased during treatment and/or a new dopaminergic medication was added.

6.1.10 Additional Efficacy Issues/Analyses

Secondary analyses and secondary efficacy endpoints of interest are presented in section 6.1.5 Analysis of Secondary Endpoints(s) and Secondary Analyses.

7 Review of Safety

Safety Summary

The sponsor submitted safety analyses requested by the DNP (at Pre-NDA meeting) for treatment-emergent adverse events (TEAEs), clinical laboratory analytes, orthostatic vital signs, and ECG parameters in individual pivotal trials and in some pools of individual trials (Studies 9, 15, 17, 15 and 17 combined, MOTION, 15 and MOTION in ESPD and Studies 16, 18, 16 and 18 combined, SETTLE, 16 and SETTLE in LSPD). My review focused on these safety analyses of individual pivotal trials and of pooled trials that the sponsor included in the Integrated Summary of Safety (ISS).

GENERAL ANALYSIS AND CONSIDERATIONS OF THE SPONSOR’S APPROACH TO CONDUCTING AND PRESENTING SAFETY ANALYSES

All safety analyses for the Integrated Summary of Safety (ISS) were performed using the Safety Population data. The Safety Population, for the ISS data analyses, was defined as all patients who received at least one dose of trial medication and had a subsequent safety assessment. The sponsor clarified that reporting of a patient's adverse event was considered as a safety assessment and that it was not necessary that a patient was required to have attended a planned trial visit for a safety assessment. The statistical analyses and outputs including tables, listings, and figures were programmed using SAS® for Windows (Version 9.3 or higher for PC [SAS Institute, Cary, North Carolina, USA]).

Continuous variables are summarized by descriptive statistics (number of patients, mean, standard deviation (SD), minimum, median and maximum). For categorical variables, the number (n) and the percentage (%) of patients with values in each category are presented. Data from sildenafil trials were converted into Clinical Data Interchange Standards Consortium (CDISC) compliant datasets.

Summary tables were generated for the following safety data:

- Treatment-Emergent Adverse Events (TEAEs) were analyzed with descriptive statistics summarized by TEAE System Organ Class-SOC, preferred term-PT, severity, relationship, and randomized treatment (including dose group) according to MedDRA 13.0. Time perspective analyses were conducted only for Studies 015 and SETTLE, as well as Studies 015 and 017 combined.
- Deaths (descriptive statistics summarized by TEAE SOC, PT, and randomized treatment group for those TEAEs with fatal outcome or whose seriousness criterion is “Results in Death” or have death as the preferred term)
- Serious Adverse Events-SAEs (descriptive statistics and time perspective analyses summarized by TEAE SOC, PT, and randomized treatment)
- TEAEs leading to treatment discontinuation (descriptive statistics summarized by TEAE SOC, PT, and randomized treatment)
- Laboratory evaluations (descriptive statistics, change from baseline to last visit, clinically significant values summarized by randomized treatment for chemistry, hematology, and urinalysis parameters)
- Vital Signs (descriptive statistics, change from baseline at each visit, shift tables of subjects who went from being normal at Baseline to abnormal post-Baseline, clinically significant outliers by randomized treatment for Systolic Blood Pressure-SBP, Diastolic Blood Pressure-DBP, pulse, weight, and temperature parameters)
- ECG data (descriptive statistics, change from baseline at each visit, shift tables of subjects who went from being normal at Baseline to abnormal post-Baseline, outlier analyses by randomized treatment for heart rate-HR, QRS, QTc [both Fridericia and Bazett corrections], RR interval, and PR interval parameters) .
Table 44 summarizes the list of individual studies and pools analyzed for safety.

Table 44 Summary List of Individual Studies and Pools of Studies Analyzed for Safety

Study Group	Studies included
1	Individual Study 009 (ESPD)
2	Individual Study 015 (ESPD)
3	Individual Study 017 (extension of Study 015 - ESPD)
4	Individual Study 024 (ESPD)
5	Individual Study 27918 (MOTION - ESPD)
6	Individual Study 27938 (MOTION extension - ESPD)
7	Individual Study 016 (LSPD)
8	Individual Study 018 (extension of Study 016 - LSPD)
9	Individual Study 27919 (SETTLE - LSPD)
10	Combined Studies 015/017 (ESPD)
11	Combined Studies 27918 (MOTION)/MOTION extension (ESPD)
12	Combined Studies 016/018 (LSPD)
13	Pooled Studies 015/27918 (MOTION - ESPD)
14	Pooled Studies 016/27919 (SETTLE - LSPD)
15	Pooled Open-label studies (ESPD and LSPD)

Analysis of TEAEs were performed for each of the 15 Study Groups. However, the primary focus of the summary data for TEAEs is presented for the 3 pooled study groups, as follows:

- **Patients with Early-Stage Parkinson’s Disease (ESPD); Pooled Group 13:** patients with ESPD in pooled completed controlled therapeutic trials. These data are for patients in pooled Studies 015/27918 (MOTION). Other individual (Study 009, Study 015, Study 017 [extension of Study 015], Study 024, Study 27918 [MOTION], and Study 27938 [the MOTION extension study]) and combined (Studies 015/017 and Studies 27918 [MOTION]/27938 [MOTION extension]) ESPD study TEAE summaries are also generally reviewed.
- **Patients with Late-Stage Parkinson’s Disease (LSPD); Pooled Group 14:** patients with LSPD in pooled completed controlled therapeutic trials. These data are for patients in pooled Studies 016/27919 (SETTLE). Other individual (Study 016, Study 018 [extension of Study 016], and Study 27919 [SETTLE]) and combined (Studies 016/018) LSPD study TEAE summaries are also generally reviewed.
- **Patients in Open-label (OL) trials; Pooled Group 15:** PD patients in pooled open-label trials.

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Summaries of the TEAEs occurring during each of the 3 groups of pooled trials showing the number and percent of each treatment group's subjects reporting TEAEs are presented overall, by severity, and by relationship to treatment.

For each pooled treatment group, the number and percentage of the treatment group's subjects who had TEAEs and the incidence rate are displayed by MedDRA SOC and PT. Further, TEAEs are presented :

□ in descending order of incidence within the **pooled 50 mg/100mg safinamide treatment groups** for Pooled Group 13; there was a 200 mg/day treatment group, however, the focus was on the 50 mg/day and 100 mg/day treatment groups, as well as the pooling of these treatment groups.

□ in descending order of incidence within the **“All Safinamide” treatment group** for Pooled Groups 14 and 15. Only safinamide 50 mg/day and 100 mg/day doses were received. No doses exceeded 100 mg/day.

Analysis of TEAEs was performed for each of the 15 Study Groups. However, the primary focus of the summary data for TEAEs is presented for the 3 pooled study groups, as follows:

□ **Patients with Early-Stage Parkinson's Disease (ESPD); Pooled Group 13:** patients with ESPD in pooled completed controlled therapeutic trials. These data are for patients in pooled Studies 015/27918 (MOTION). Other individual (Study 009, Study 015, Study 017 [extension of Study 015], Study 024, Study 27918 [MOTION], and Study 27938 [the MOTION extension study]) and combined (Studies 015/017 and Studies 27918 [MOTION]/27938 [MOTION extension]) ESPD study AE summaries are also generally reviewed.

□ **Patients with Late-Stage Parkinson's Disease (LSPD); Pooled Group 14:** patients with LSPD in pooled completed controlled therapeutic trials. These data are for patients in pooled Studies 016/27919 (SETTLE). Other individual (Study 016, Study 018 [extension of Study 016], and Study 27919 [SETTLE]) and combined (Studies 016/018) LSPD study TEAE summaries are also generally reviewed.

□ **Patients in Open-label (OL) trials; Pooled Group 15:** PD patients in pooled open-label trials.

Summaries of the TEAEs occurring during each of the 3 groups of pooled trials showing the number and percent of each treatment group's subjects reporting TEAEs are presented overall, by severity, and by relationship to treatment.

For each pooled treatment group, the number and percentage of the treatment group's subjects who had TEAEs and the incidence rate are displayed by MedDRA SOC and PT. Further, TEAEs are presented:

□ in descending order of incidence within the **pooled 50 mg/100mg safinamide treatment groups** for Pooled Group 13; there was a 200 mg/day treatment group, however, the focus was on the 50 mg/day and 100 mg/day treatment groups, as well as the pooling of these treatment groups.

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□ in descending order of incidence within the “**All Sildenafil**” treatment group for Pooled Groups 14 and 15. Only sildenafil 50 mg/day and 100 mg/day doses were received. No doses exceeded 100 mg/day.

Reviewer Comment

- I concurred with the sponsor’s safety analyses conducted and overall, the sponsor’s presentation of safety analyses. After the NDA was not filed because of difficulties of navigating the NDA, the sponsor revised the NDA in conjunction with Agency feedback and markedly improved the NDA that was finally submitted.
- The Agency’s JUMPSTART program helped this reviewer by conducting various analyses of the sponsor’s safety data for Studies 15, MOTION, 16, SETTLE, and pool of Studies 16 and 18 (the long-term extension trial of Study 16). Overall, these JUMPSTART analyses appeared to be quite similar to those of the sponsor. Consequently, my review focuses on presenting data from the sponsor’s analyses.

7.1 Methods

Incidence data presented that are not copies of sponsor tables are shown as rounded off percentages based upon this reviewer’s review of sponsor’s data.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Table 44 shows the specific trials and pools of trial analyzed to evaluate safety.

7.1.2 Categorization of Adverse Events

Overall treatment-emergent adverse events (TEAEs)

TEAEs were defined as an adverse event which started after the first administration of placebo or sildenafil in a sildenafil trial, or which started before the first administration of placebo or sildenafil, but worsened after the start of trial treatment.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Table 44 shows the pools of trials analyzed to evaluate safety,

Reviewer Comment

- The pools this reviewer consider of most interest for analysis and/or presentation of results were the pools of Studies 15 and 17 for TEAEs, Studies 15 and MOTION for all safety parameters, Studies 16 and 18 for TEAEs, and Studies 16 and SETTLE for all safety parameters.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Table 45 summarizes total numbers of patients exposed to any safinamide or placebo treatment in all trials, all trials for ESPD, and all trials for LSPD,

Table 45 Summary of Exposure to Safinamide and Placebo in All Clinical Trials

Exposure	Any	>6 months	>1 yr	>2 yrs	>3 yrs	>4 yrs
Number of All PD patients exposed to safinamide	1949 (a)	1440	1180	533	222	169
Number of Early PD patients exposed to safinamide	879	542	428	110	0	0
Number of Late PD patients exposed to safinamide	1036	876	734	414	222	169
Number of All PD patients exposed to placebo	919	438	359	64	0	0
Number of Early PD patients exposed to placebo	422	240	192	17	0	0
Number of Late PD patients exposed to placebo	497	198	167	47	0	0

Source: ISS Appendix 16, Table Ex-adhoc4

(a) excluding 64 patients who received safinamide in the “not pooled” studies: 004, 012, 0023, 28780 and 28849 (DAT), and did not enter the Open Label Phase.

Table 46 shows dose and duration data for the mean daily safinamide dose for patients with ESPD, LSPD, and all Parkinson's disease patients combined, These data are presented as mutually exclusive data such that patients are presented in only a single cell according to their mean daily safinamide dose and duration of treatment,

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Table 46 Exposure to Safinamide According to Dose (Mean Daily) and Duration of Treatment and Parkinson's disease Population

Duration (weeks)	0 < Dose ≤ 5mg	5 < Dose ≤ 10mg	10 < Dose ≤ 20mg	20 < Dose ≤ 30mg	30 < Dose ≤ 50mg	50 < Dose	Total (Any Dose)	Percent
Early Stage PD								
0 < Dur ≤ 1	0	0	0	0	1	0	1	0.1%
1 < Dur ≤ 2	0	0	0	0	2	3	5	0.6%
2 < Dur ≤ 4	0	0	0	2	3	7	12	1.4%
4 < Dur ≤ 12	0	0	3	15	34	62	114	13.7%
12 < Dur ≤ 24	0	0	1	2	31	88	122	14.6%
24 < Dur ≤ 48	0	0	0	0	36	97	133	15.9%
48 < Dur ≤ 96	0	0	0	0	66	218	284	34.0%
Dur >96	0	0	0	0	31	133	164	19.6%
Total (Any Duration)	0	0	4	19	204	608	835	100.0%
Percent	0.0%	0.0%	0.5%	2.3%	24.4%	72.8%	100.0%	
Late Stage PD								
0 < Dur ≤ 1	0	0	0	0	2	3	5	0.5%
1 < Dur ≤ 2	0	0	0	0	3	1	4	0.4%
2 < Dur ≤ 4	0	0	0	0	8	6	14	1.4%
4 < Dur ≤ 12	0	0	0	1	8	25	34	3.3%
12 < Dur ≤ 24	0	0	0	0	16	42	58	5.6%
24 < Dur ≤ 48	0	0	0	0	32	129	161	15.6%
48 < Dur ≤ 96	0	0	0	0	17	254	271	26.3%
Dur >96	0	0	0	0	35	447	482	46.8%
Total (Any Duration)	0	0	0	1	121	907	1029	100.0%
Percent	0.0%	0.0%	0.0%	0.1%	11.8%	88.1%	100.0%	
Combined, All PD Subjects								
0 < Dur ≤ 1	0	0	0	0	3	3	6	0.3%
1 < Dur ≤ 2	0	0	0	1	5	4	10	0.5%
2 < Dur ≤ 4	0	0	0	3	11	13	27	1.4%
4 < Dur ≤ 12	0	0	3	16	42	89	150	7.9%
12 < Dur ≤ 24	0	0	1	2	47	135	185	9.7%
24 < Dur ≤ 48	0	0	0	0	68	233	301	15.9%
48 < Dur ≤ 96	0	0	0	0	83	477	560	29.5%
Dur >96	0	0	0	0	66	593	659	34.7%
Total (Any Duration)	0	0	4	22	325	1547	1898	100.0%
Percent	0.0%	0.0%	0.2%	1.2%	17.1%	81.5%	100.0%	

Reviewer Comment

- It is important to recognize that the sponsor's presentation of dose duration results considers the mean daily dose that includes a titration period in some patients (Studies 15, and SETTLE). Consequently, the mean daily safinamide dose could be less than the category for the modal daily dose, particularly for most of the safinamide exposure,

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- Overall, relatively few Parkinson's disease patients of any stage (and presumably no LSPD patients because 100 mg daily was the maximal targeted dose for LSPD) were treated with safinamide daily dosing greater than 100 mg, thus the columns showing the patients treated with a modal dose of 50 mg daily ($30 < \text{Dose} \leq 50 \text{ mg}$) and a modal dose of 100 mg daily represent the overall dose-duration exposure in all the pivotal trials.
- Considering the comments noted above, for LSPD (and that categorical presentations are mutually exclusive), it would appear that a majority of patients (472) received a modal daily dose of 100 mg of safinamide daily for more than 96 months (i.e., more than 8 years), and that 872 patients received a modal daily dose of 100 mg of safinamide for more than 12 months. These data clearly show an adequate dose-duration exposure of patients for the 100 mg safinamide dose in LSPD.
- Given these same considerations, 1438 of all Parkinson's disease patients (ESPD and LSPD) appear to have been treated with a daily modal dose of at least 100 mg (or greater) for more than 12 months and approximately 40 % of these patients were treated with a modal dose of 100 mg for more than 8 years.
- In summary, I interpret these data as indicating that the long-term exposure of adequate numbers of Parkinson's disease patients to a daily safinamide dose of up to 100 mg (and also a significant proportion of these patients to a daily dose of 100 mg) along with collection of safety data to be adequate for potentially supporting the approval of safinamide (XADAGO) for daily dosing up to 100 mg.

7.2.2 Explorations for Dose Response

Refer to section 7.5.1 for explorations of dose-dependent TEAEs and dose response. Results of safety analyses of other parameters (i.e., clinical laboratory analytes, vital signs, and ECGs) were also presented according to randomized treatment (including dose). Thus, explorations of all safety analyses considered the demonstration of a dose response. This reviewer's comments note safinamide dose response for safety parameters whenever dose response is considered to have been demonstrated or possibly demonstrated.

7.2.3 Special Animal and/or In Vitro Testing

Reviewer Comment

- I am not aware of any special animal nor in vitro testing conducted by the sponsor to address potential TEAEs or clinical findings of interest.

7.2.4 Routine Clinical Testing

Reviewer Comment

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- Overall, I believe that routine clinical safety testing conducted in the pivotal trials was adequate.

7.2.5 Metabolic, Clearance, and Interaction Workup

Reviewer Comment

- The primary Clinical Pharmacology reviewer, Dr. Dimova, considered the sponsor's metabolic, clearance, and interaction workup to be adequate and acceptable with the exception of the interaction study recommended as a postmarket commitment regarding sildenafil and BCRP substrates in healthy volunteers.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The sponsor evaluated many potential adverse events for similar drugs in the class of sildenafil by conducted analyses using many varied preferred terms of treatment-emergent adverse events (TEAEs) possibly reflecting the adverse event of interest. In addition, I presented additional analyses of some adverse events of special interest. These additional compliment the various analyses of the sponsor All these analyses are presented in section 7.3.5 Submission Specific Primary Safety Concern.

7.3 Major Safety Results

7.3.1 Deaths

Sponsor's Summary of Deaths

Analyses were performed for patients in the ESPD studies (N=1217), the LSPD studies (N=1218), the combined placebo-controlled studies (ESPD and LSPD patients; N= 2435), and the open-label studies (Study 28850 [OLE] and open-label phase of Study 024; N=1025) in which all patients received sildenafil. The Sponsor has performed analyses for all 61 deaths, as well as for the 59 deaths that occurred within 30 days of the last dose of study medication, as defined in the study protocols. Mortality was analyzed in terms of crude incidence rate (i.e., number of deaths divided by the number of patients at risk) and by exposure (expressed as number of deaths per 100 patient years of exposure). In light of the extensive treatment duration for both sildenafil and placebo, mortality was analyzed overall and in terms of mutually exclusive (non-overlapping) epochs of time – 6-month and 12-month intervals for the first two years (i.e., 0-6 months, >6-12 months, >12-18 months, >18-24 months), a 12-month interval between years 2 and 3 (>2-3 years), and greater than 3 years.

Two patients ([#00000279180480009](#) and [#00010150160330001](#)) died outside of the 30-day window, and analyses were performed excluding these two patients.

In LSPD patients there was no evidence of increased mortality with sildenafil compared to placebo with an exposure adjusted rate of 2.2/100 patient years for both treatment groups;

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excluding the 1 patient who died >30 days after last dose, the safinamide rate was 2.1/100 patient years. In ESPD patients there were very few deaths; the mortality rates were 0.5/100 patient years versus 0.2/100 patient years for safinamide and placebo, respectively; excluding the 1 patient who died >30 days after last dose, the safinamide rate was 0.4/100 patient years. In open-label studies the mortality rate was 1.3/100 patient years – the exposure adjusted rates in the first and second year of exposure were similar (1/100 patient years) with an increase to 2/100 patient years in the third year, with no increase subsequently.

There were 61 deaths in the safinamide program conducted over 10 years including two on safinamide that occurred more than 30 days after the last dose of safinamide. The crude incidence rate was higher in the safinamide group compared with placebo (2.6% versus 1.2%) as the period of observation was much longer for safinamide treated patients. A large number of safinamide patients were treated for periods exceeding six years, whereas a much smaller number of patients received placebo for up to only two years. Limiting the analyses to patients who died within 30 days of the last dose of study medication indicated that the crude incidence of mortality was 2.5% on safinamide and 1.2% on placebo. This difference in mortality may be explained by the much longer duration of treatment in safinamide-treated patients (>6 years) compared to placebo-treated patients (2 years).

In LSPD patients, for exposure-adjusted mortality rate, whether assessed for all deaths (n=28), or for those that occurred within 30 days of the last dose, over 2 years or for a 6-month period, no difference could be detected between safinamide and placebo. Mortality rates with long-term open-label treatment with safinamide were 1.3/100 patient years.

In ESPD trials there were very few deaths, with an exposure-adjusted mortality rate of 0.5 versus 0.2/100 years of exposure (safinamide versus placebo) when all deaths (n=5) were included. Restricting the analysis to patients who died within 30 days of the last dose of study medication provided incidence rates of 0.4 and 0.2/100 years of exposure for safinamide and placebo, respectively. The imbalance is likely the result of small numbers, since over the 18 months for Group 10 (Studies 015/017) the exposure-adjusted mortality rate was the same for safinamide and placebo (both 0.9), whereas over the 24 months for Group 11 (Studies MOTION/MOTION Extension), there were two deaths on safinamide and none on placebo (mortality rates of 0.3 versus 0).

Analyses of double-blind, placebo-controlled studies and in the open-label trial indicated that the rate adjusted for time at risk did not detect any pattern of increasing mortality in safinamide treated patients compared with placebo.

The mortality rate for safinamide in these trials that included a large number of patients on treatment as usual, and were exposed to safinamide, is lower than the Standardized Mortality Rate (SMR) for Parkinson's disease patients 1.35 – 2.01 (Elbaz A et al, 2003; Herlofson K et al, 2004). No pattern of association could be detected for deaths on safinamide and any specific SOC, including cardiac disorder.

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The sildenafil program was monitored by an independent safety monitoring board (ISMB) that reviewed notable events on a timely basis, with all other safety data periodically. The ISMB reviewed unblinded data during every scheduled meeting and determined if there were any signals of potential risk for patients involved in the program. Summary conclusions of the final review of the ISMB meeting indicated that no signal of increased safety risk was identified by the ISMB.

Table 47 is a listing of all deaths in the clinical development program including deaths in 48 patients treated with sildenafil in the double-blinded, placebo-controlled phase and open-label phase, in 11 placebo-treated patients (00010150150190008, 00010150160080010, 00010150160160006, 00010150160280005, 00010150160280022, 00010150160290035, 00010150160410002, 00010150160500012, 00010150160770001, 00000279193120003, 00000279195010002,) and in two sildenafil-treated patients (00000279180480009 and #00010150160330001) who died outside of the 30 day window after sildenafil had been discontinued.

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Table 47 Sponsor Summary List of Causes of Death in Individual Patients
Tabular summary of patients who died - by cause of death

Term (cause of death)	Patient ID (hyperlink to Narrative)	Patient ID (hyperlink to CRFs)
Accident – road traffic	00010150160770001	00010150160770001
Arrhythmia	00000279193250003	00000279193250003
Aspiration	00010150160280022	00010150160280022
Cardiac arrest	00010150160160006	00010150160160006
	00000279193550001	00000279193550001
Cardiac failure	00000279193840003	00000279193840003
Cardiac tamponade	0000288506420017	0000288506420017
Cerebellar infarction	00010150160330001	00010150160330001
Cerebral haemorrhage due to trauma	00010150160080010	00010150160080010
Chikungunya virus infection	00010150150190008	00010150150190008
Colon cancer	00000279193760001	00000279193760001
Colonic pseudo-obstruction	00010150160440005	00010150160440005
Death	00010150160190001	00010150160190001
	00010150160200009	00010150160200009
	00010150160160007	00010150160160007
	00010150160200007	00010150160200007
	00010150160220002	00010150160220002
Death - sudden	00010150160270009	00010150160270009
	00010150160280019	00010150160280019
	00010150160290022	00010150160290022
	00010150160290035	00010150160290035
	00010150160010021	00010150160010021
	00010150160220011	00010150160220011
	00010150160380014	00010150160380014
	00010150160390008	00010150160390008
	00010150160390014	00010150160390014
Death – sudden cardiac	00010150160410002	00010150160410002
Dehydration	00010150150210012	00010150150210012
Gun shot wound	00010150150260005	00010150150260005
Hepatic encephalopathy	00010150160400001	00010150160400001
Hepatitis viral	00010150160400001	00010150160400001
Leptospirosis	00010150160130008	00010150160130008
Leukaemia - acute	00010150160440015	00010150160440015
Leukaemia – acute lymphocytic	00000279195010002	00000279195010002
Metastases to lung	00010150160710016	00010150160710016
Myocardial infarction	00010150160290019	00010150160290019
	00010150160330007	00010150160330007
	00010150160330013	00010150160330013
	00000279181790003	00000279181790003
Myocardial infarction - acute	00010150160280010	00010150160280010
	00010150160610002	00010150160610002
	00000279180480009	00000279180480009
Myocardial infarction – possible	00010150160370004	00010150160370004
Myocardial infarction - silent	00010150160200004	00010150160200004
Myocardial ischaemia	00000279193120003	00000279193120003
Neoplasm malignant	00000279194060004	00000279194060004
Pancreatic carcinoma metastatic	00010150160050003	00010150160050003
Pancytopenia	00010150160440004	00010150160440004
	00000279195010002	00000279195010002
Parkinson’s disease	00000279192300002	00000279192300002
Pneumonia	00010150160100007	00010150160100007
Pneumonia aspiration	00010150160280005	00010150160280005
	00010150160280009	00010150160280009
	00010150160290012	00010150160290012
	00010150160330018	00010150160330018
Pulmonary embolism	00010150160710028	00010150160710028
	00000279193860001	00000279193860001
Renal failure	00010150150210012	00010150150210012
Renal failure (with complications)	00010150160140005	00010150160140005
Respiratory failure - acute	00010150160920004	00010150160920004
Sepsis	00010150160500012	00010150160500012
	00010150160050010	00010150160050010
Septic shock	00010150160080004	00010150160080004
Suicide - completed	00000279194140001	00000279194140001

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Table 48 Incidence of Deaths According to Treatment in ESPD Studies

Dose (mg/day)	Safinamide (mg/day)			Overall	Placebo
	50	100	150-200		
N (exposed)	282	424	89	795	422
Deaths	1	2	1	4	1
%	0.35%	0.47%	1.12%	0.50%	0.24%
Excluding 1 patient who died >30 days after last dose					
Deaths	1	1	1	3	1
%	0.35%	0.24%	1.12%	0.38%	0.24%

Source: [ISS-appendix-17-death listing](#)

Table 49 Summary of Death Rates (# Deaths/100 Patient Years Treatment) by Treatment and Different Treatment Periods in ESPD Studies

Treatment	Deaths (n)	Patients (n)	Incidence Rate (%)	Person Time (years)	Mortality Rate per 100 person years
Placebo - Overall	1	422	0.2	402.7	0.2
Placebo 0 to 6 months	0	422	0.0	170.0	0.0
Placebo >6 - 12 months	1	240	0.4	106.4	0.9
Placebo >12 - 18 months	0	192	0.0	87.7	0.0
Placebo >18 months - 2 years	0	122	0.0	38.1	0.0
Placebo >2 - 3 years	0	17	0.0	0.5	0.0
Placebo >3 years	.	0	.	.	.
Safinamide - Overall	4	795	0.5	848.7	0.5
Safinamide 0 to 6 months	1	795	0.1	331.9	0.3
Safinamide >6 - 12 months	1	513	0.2	235.8	0.4
Safinamide >12 - 18 months	1	428	0.2	191.6	0.5
Safinamide >18 months - 2 years	1	258	0.4	87.9	1.1
Safinamide >2 - 3 years	0	40	0.0	1.4	0.0
Safinamide >3 years	.	0	.	.	.

Source: [Appendix 16, MORT Ad Hoc Analysis – Table 3](#)

Table 50 Incidence of Deaths According to Treatment in LSPD Studies

Dose (mg/day)	Safinamide (mg/day)			Placebo
	50	100	Overall	
N (exposed)	243	478	721	497
Deaths	5	13	18	10
%	2.06%	2.72%	2.50%	2.01%
Excluding 1 patient who died >30 days after last dose				
Deaths	5	12	17	10
%	2.06%	2.51%	2.36%	2.01%

Source: [ISS-appendix-17-death listing](#)

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Table 51 Summary of Death Rates (# Deaths/100 Patient Years Treatment) by Treatment and Different Treatment Periods in LSPD Studies

Treatment	Deaths (n)	Patients (n)	Incidence Rate (%)	Person Time (years)	Mortality Rate per 100 person years
Placebo - Overall	10	497	2.0	460.5	2.2
Placebo 0 to 6 months	4	497	0.8	221.5	1.8
Placebo >6 - 12 months	0	198	0.0	85.5	0.0
Placebo >12 - 18 months	4	167	2.4	80.2	5.0
Placebo >18 months - 2 years	2	152	1.3	71.1	2.8
Placebo >2 - 3 years	0	47	0.0	2.2	0.0
Placebo >3 years	.	0	.	.	.
Safinamide - Overall	18	721	2.5	816.8	2.2
Safinamide 0 to 6 months	6	721	0.8	327.2	1.8
Safinamide >6 - 12 months	5	395	1.3	175.5	2.8
Safinamide >12 - 18 months	1	336	0.3	162.8	0.6
Safinamide >18 months - 2 years	5	315	1.6	146.3	3.4
Safinamide >2 - 3 years	1	97	1.0	4.9	20.5
Safinamide >3 years	.	0	.	.	.

Source: [Appendix 16, MORT Ad Hoc Analysis – Table 2](#)

Table 52 Incidence of Deaths According to Treatment in All Placebo-Controlled Trials of Parkinson's disease

Dose (mg/day)	Safinamide (mg/day)				Placebo
	50	100	200	Overall	
N (exposed)	525	902	89	1516	919
Deaths*	6	15	1	22	11
%	1.14%	1.66%	1.12%	1.45%	1.20%
Excluding 2 patients who died >30 days after last dose					
Deaths	6	13	1	20	11
%	1.14%	1.44 %	1.12%	1.32%	1.20%

*Deaths are summarized in [ISS Appendix 17 – Listing of deaths](#)

Table 53 Summary of Death Rates (# Deaths/100 Patient Years Treatment according to Overall Unique Exposure) By Treatment in All Trials (Controlled and Open-Label) Parkinson's disease

Treatment	Deaths (n)	Subjects (n)	Incidence Rate (%)	Person Time (years)	Mortality Rate per 100 person years
Placebo	11	919	1.2	863.2	1.3
Safinamide	50	1949	2.6	3021.6	1.7
Excluding 2 patients who died >30 days after last dose					
Safinamide	48	1949	2.5	3021.6	1.6

Source: Appendix 16, MORT Ad Hoc Analysis – Table 10 and Table 20

Table 54 Summary of Death Rates (# Deaths/100 Patient Years Treatment) by Treatment and Different Treatment Periods in All Placebo-Controlled Studies

Treatment	Deaths (n)	Patients at Risk (n)	Incidence Rate (%)	Person Time (years)	Mortality Rate per 100 person years
Placebo - Overall	11	919	1.2	863.2	1.3
Placebo 0 to 6 months	4	919	0.4	391.6	1.0
Placebo >6 - 12 months	1	438	0.2	191.8	0.5
Placebo >12 - 18 months	4	359	1.1	167.9	2.4
Placebo >18 months - 2 years	2	274	0.7	109.2	1.8
Placebo >2 - 3 years	0	64	0.0	2.6	0.0
Placebo >3 years	.	0	.	.	.
Safinamide - Overall	50	1949	2.6	3021.6	1.7
Safinamide 0 to 6 months	9	1949	0.5	862.7	1.0
Safinamide >6 - 12 months	13	1440	0.9	656.5	2.0
Safinamide >12 - 18 months	4	1180	0.3	533.8	0.7
Safinamide >18 months - 2 years	10	851	1.2	353.3	2.8
Safinamide >2 - 3 years	8	533	1.5	330.3	2.4
Safinamide >3 years	6	222	2.7	285.0	2.1

Source: Appendix 16, MORT Ad Hoc Analysis – Table 10

Mortality in Open-Label Studies

The mortality rate in the open-label studies (Study 28850 and open-label phase of Study 024 – i.e., Group 15), in which all patients received safinamide, was 2.7% (28 of 1025) patients, and when adjusted for treatment exposure was 1.3 per 100 patient years (Table 55), proportions of patients that died due to respiratory, cardiac, psychiatric and neoplastic conditions were higher than in the placebo-controlled studies, possibly reflecting the increasing age of the patients, longer duration of PD and increasing severity of PD; these factors have been associated with increased mortality in PD (Guttman et al., 2001, Morens et al., 1996, de Lau et al., 2005; Morgante et al., 2000). In addition, the vast majority of these patients had at least one concomitant illness at baseline. The exposure adjusted mortality rates in the first and second year

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of exposure to open-label sildenafil were the same (both 1.0/100 patient years). In the third year the mortality rate increased to 2.1/100 patient years, but did not increase subsequently.

Table 55 Summary of Deaths by Treatment - Open-Label Extension Study

Treatment	Deaths (n)	Patients (n)	Incidence Rate (%)	Person Time (years)	Mortality Rate per 100 person years
Sildenafil - Overall	28	1025	2.7	2122.5	1.3
Sildenafil 0 to 6 months	2	1025	0.2	482.5	0.4
Sildenafil >6 - 12 months	7	881	0.8	409.7	1.7
Sildenafil 0 - 12 months	9	1025	0.9	892.2	1.0
Sildenafil >12 - 18 months	2	744	0.3	343.4	0.6
Sildenafil >18 months - 2 years	4	606	0.7	274.7	1.5
Sildenafil >12 months - 2 years	6	744	0.8	618.1	1.0
Sildenafil >2 - 3 years	7	479	1.5	327.3	2.1
Sildenafil >3 years	6	222	2.7	285.0	2.1

Source: Appendix 16, MORT Ad Hoc Analysis – Table 4

Reviewer Comment

- Although the incidence of death was higher in some placebo-controlled trials, the sponsor also focused analyzing deaths (sildenafil and placebo treatment) in individual trials, in pools of individual, placebo-controlled trials and in open-label treatment experience according to death rates (i.e., number of deaths/patient-years of treatment). I agree with the sponsor’s approach to focus analyses on death rates that takes into consideration the duration of specific treatments.
- Narratives of sildenafil treated patients who died did not suggest specific reasons for believing that sildenafil had contributed to the death. Thus, there were no specific causes of death associated with sildenafil treatment that seemed to stand out. Review of narrative descriptions of death cases also indicated that : 1) the use of the term “cardiorespiratory” was non-specific (e.g., everyone who dies has cardiorespiratory arrest at the time of death) and used for cases that seemed like sudden death without a clearly specific, known cause; and 2) many cases identified with some term suggesting myocardial infarction (usually based upon an investigator’s subjective assessment without corresponding objective data) did not have any pre-mortem nor post-mortem autopsy evidence indicating myocardial infarction. Typically, some term suggesting myocardial infarction was a speculative term designated by the investigator for a case that for practical purposes could have been designated as “sudden death.”
- I do not believe that the 2 cases (00000279180480009 and #00010150160330001) in which death occurred after the 30 day post-treatment window ended should be counted

in any analyses because that is the typical standard in which analyses of TEAEs are considered (up to 30 days after the last treatment).

- I agree with the sponsor that results of death rates do not suggest a concern for safinamide as a cause for increased mortality. In particular, Table 53 shows that the death rate for all safinamide treatment similar (1.6 deaths/100 patient years) was similar to the rate for placebo (1.3 deaths/100 patient years). Although the rate was minimally higher for safinamide compared to placebo, I do not consider this marginal difference to be noteworthy. It is also worthy to note that the death rate for the open label experience with safinamide treatment (as shown in Table 55) was identical to the death rate (1.3) of placebo treatment (Table 53).

7.3.2 Nonfatal Serious Adverse Events (SAEs)

Early Stage Parkinson's disease (ESPD)

Study 15

The overall incidence of patients with at least one SAE was increased for patients treated with 100 mg safinamide (4%) vs placebo (2%) but was not increased for 200 mg safinamide (2%). There were no specific SAEs occurring in two or more patients.

Study MOTION (27918)

The overall incidence of patients with at least one SAE was increased for patients treated with 50 mg (4 %) and 100 mg safinamide (4 %) vs placebo (2 %). There were no specific SAEs occurring in two or more patients. In several instances, one patient in the placebo group had the same specific SAE as a patient in a safinamide dose group.

Pool of Studies 15 and 17

The combined analysis of Study 15 along with its extension phase (Study 17), in which patients could have been treated up to 1.5 years, showed that the incidence of any SAE was increased for 100 mg (10 %), 200 mg (8 %), and any safinamide/combined 50 mg and 100 mg (9 % %) compared to placebo (3 %). However, almost all specific SAEs in a safinamide treatment group only occurred in a single patient. The only specific SAE occurring in 2 (or more) patients was coronary artery disease which had an incidence of 2 % for 100 mg and 0 % for placebo and 200 mg treatment groups.

Pool of Studies 15 and MOTION (27918)

The overall incidence of patients with at least one SAE was increased for patients treated with 50 mg (4%), 100 mg safinamide (4 %), and all safinamide doses combined (4 %) vs placebo (2 %), but was not increased for the 200 mg dose group (2%) (Table 56). There were no specific SAEs

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occurring in two or more patients and for which the incidence of a specific TEAE was numerically greater for any safinamide dose group than for placebo treatment.

Table 56 Treatment-Emergent Serious Adverse Events (SAEs) by Treatment Group (Randomized Assignment) in Pooled ESPD Studies 15 and MOTION

System Organ Class/ Preferred term[1]	Safinamide (mg/day)					
	50 (N=226)	100 (N=317)	Pooled 50/100 (N=543)	200 (N=89)	All (N=632)	Placebo (N=315)
Subjects with at least one serious event	9 (4.0)	12 (3.8)	21 (3.9)	2 (2.2)	23 (3.6)	7 (2.2)
CARDIAC DISORDERS	2 (0.9)	2 (0.6)	4 (0.7)	0 (0.0)	4 (0.6)	1 (0.3)
ANGINA PECTORIS	0 (0.0)	1 (0.3)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
ATRIAL FIBRILLATION	1 (0.4)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)	1 (0.3)
ATRIAL FLUTTER	0 (0.0)	1 (0.3)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
CORONARY ARTERY STENOSIS	0 (0.0)	1 (0.3)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
MYOCARDIAL INFARCTION	1 (0.4)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
VENTRICULAR TACHYCARDIA	1 (0.4)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
EYE DISORDERS	0 (0.0)	3 (0.9)	3 (0.6)	0 (0.0)	3 (0.5)	0 (0.0)
CATARACT	0 (0.0)	1 (0.3)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
GLAUCOMA	0 (0.0)	1 (0.3)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
MACULAR OEDEMA	0 (0.0)	1 (0.3)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
MACULOPATHY	0 (0.0)	1 (0.3)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
OCULAR VASCULAR DISORDER	0 (0.0)	1 (0.3)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
PAPILLOEDEMA	0 (0.0)	1 (0.3)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
RETINAL VEIN OCCLUSION	0 (0.0)	1 (0.3)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
GASTROINTESTINAL DISORDERS	2 (0.9)	1 (0.3)	3 (0.6)	0 (0.0)	3 (0.5)	1 (0.3)
DUODENAL POLYP	1 (0.4)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
GASTROINTESTINAL HAEMORRHAGE	0 (0.0)	1 (0.3)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
INGUINAL HERNIA	1 (0.4)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
NECROTISING COLITIS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
PERITONITIS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	1 (0.4)	2 (0.6)	3 (0.6)	1 (1.1)	4 (0.6)	0 (0.0)
CONCUSSION	1 (0.4)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
HUMERUS FRACTURE	0 (0.0)	1 (0.3)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
JOINT INJURY	0 (0.0)	1 (0.3)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
GUN SHOT WOUND	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)	1 (0.2)	0 (0.0)
INVESTIGATIONS	1 (0.4)	1 (0.3)	2 (0.4)	0 (0.0)	2 (0.3)	0 (0.0)
ELECTROCARDIOGRAM CHANGE	0 (0.0)	1 (0.3)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
ELECTROCARDIOGRAM QT PROLONGED	1 (0.4)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
NERVOUS SYSTEM DISORDERS	2 (0.9)	0 (0.0)	2 (0.4)	1 (1.1)	3 (0.5)	1 (0.3)
DIZZINESS	1 (0.4)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
PRESYNCOPE	1 (0.4)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
QUADRIPLEGIA	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)	1 (0.2)	0 (0.0)
SYNCOPE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	0 (0.0)	1 (0.3)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
IRON DEFICIENCY ANAEMIA	0 (0.0)	1 (0.3)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
EAR AND LABYRINTH DISORDERS	0 (0.0)	1 (0.3)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
MENIERE'S DISEASE	0 (0.0)	1 (0.3)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	1 (0.4)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
GAIT DISTURBANCE	1 (0.4)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
INFECTIONS AND INFESTATIONS	1 (0.4)	0 (0.0)	1 (0.2)	1 (1.1)	2 (0.3)	0 (0.0)
TRACHEOBRONCHITIS	1 (0.4)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
GASTROENTERITIS	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)	1 (0.2)	0 (0.0)
METABOLISM AND NUTRITION DISORDERS	0 (0.0)	1 (0.3)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
MALNUTRITION	0 (0.0)	1 (0.3)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	1 (0.4)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)	1 (0.3)
OSTEOARTHRITIS	1 (0.4)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
ARTHRITIS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	0 (0.0)	1 (0.3)	1 (0.2)	0 (0.0)	1 (0.2)	1 (0.3)
SKIN CANCER	0 (0.0)	1 (0.3)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
PROSTATE CANCER	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	0 (0.0)	1 (0.3)	1 (0.2)	1 (1.1)	2 (0.3)	0 (0.0)
DYSPNOEA	0 (0.0)	1 (0.3)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
RESPIRATORY FAILURE	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)	1 (0.2)	0 (0.0)
HEPATOBIILIARY DISORDERS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
CHOLECYSTITIS ACUTE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
PSYCHIATRIC DISORDERS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
SUICIDE ATTEMPT	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)

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- Separate analyses of Studies 15 and MOTION suggest a numerically increased risk for 100 mg safinamide vs placebo. It is not clear if the increased risk for any SAE observed for 100 mg safinamide in Study 15 was real because it was not observed with the 200 mg dose. The increased risk observed in MOTION for 100 mg was also similar for the low dose (50 mg). However, analyses of specific SAEs in these different trials do not suggest a clearly increased risk.
- The analysis of patients in Studies 15 and 17 (up to 1.5 years of treatment) suggested an increased risk for 100 mg or 200 mg safinamide (vs placebo) but there was no specific SAE for which there appeared to be an increased risk. The risk for any SAE with long-term safinamide treatment (in Study 17) did not substantially increase over the increased risk for a shorter treatment period (in Study 15). However, because patients (especially in Study 17) could have received an increase in the dose of the concomitant medication for Parkinson's disease or addition of a new drug for Parkinson's disease, it is not possible to exclude this overall increased risk of an SAE as perhaps being related to increased concomitant medication for Parkinson's disease.
- Although overall results for safinamide vs placebo in 6 month pivotal trials (separate analyses of 15 and MOTION and pooled analyses of 15 and MOTION) suggest an increased risk for SAEs in ESPD for 50 mg and/or 100 mg safinamide (vs placebo), there does not appear to be a clearly increased risk for any specific SAE in this population.

Late/Advanced Stage Parkinson's disease (LSPD)

Study 16

The overall incidence of patients with at least one SAE was increased for patients treated with 100 mg safinamide (10 %) vs placebo (8 %) but not for patients treated with 50 mg safinamide (4 %). The only specific SAEs occurring in two or more patients and for which the incidence of a specific TEAE was numerically greater for safinamide treatment than for placebo treatment were for falls (2 % vs 1 %) and femur fracture (2 % vs 1 %) and this higher incidence was only associated with the high dose group (100 mg). All other specific SAEs in 50 mg or 100 mg safinamide groups (or placebo) occurred in only one patient.

Pool of Studies 16 and 18

The combined analysis of Study 16 along with its extension phase (Study 18), in which patients could have been treated up to 2 years, showed that the incidence of any SAE was increased for 100 mg (19 %) and any safinamide dose (17 %) compared to placebo (14 %) or 50 mg safinamide (14 %). Although there were several specific SAEs that occurred in 2 or more safinamide-treated patients, only some of these specific SAEs had a incidence greater than the placebo incidence. For most of these specific SAEs (i.e., freezing phenomenon, femur fracture, myocardial infarction, cardiac failure, pneumonitis, insomnia, acute renal failure, anemia, cataract), the treatment difference for any safinamide group (vs placebo) was only 1 %.

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However, the incidence of fall as a specific SAE was notably increased for 100 mg sildenafil (4 %) compared to placebo (1 %), 50 mg sildenafil (1 %) and any sildenafil/combined 50 mg and 100 mg (2 %).

Study SETTLE (27919)

The overall incidence of patients with at least one SAE was not increased for patients treated with 100 mg sildenafil (7 %) vs placebo (9 %). The only specific SAEs occurring in two or more patients and for which the incidence of a specific TEAE was numerically greater for sildenafil treatment than for placebo treatment were for visual hallucination (1 % vs 0 %) and breast cancer (1 % vs 0 %). All other specific SAEs in the sildenafil group (or placebo) occurred in only one patient.

Pool of Studies 16 and SETTLE

The overall incidence of patients with at least one SAE was not increased for patients treated with 50 mg (4%) or 100 mg sildenafil (8 %) vs placebo (9 %) (Table 57). There were no specific SAEs occurring in two or more patients and for which the incidence of a specific TEAE was numerically greater for sildenafil treatment than for placebo treatment. Most specific SAE occurred in only one patient in a sildenafil group and in the rare instances in which a specific SAE occurred in two patients in a sildenafil dose group, the incidence was not notably higher than that for placebo.

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Table 57 Treatment-Emergent Serious Adverse Events (SAEs) by Treatment Group (Randomized Assignment) Pooled LSPD Studies 16 and SETTLE

	Safinamide (mg/day)			
	50 (N=223) n (%)	100 (N=498) n (%)	All Safinamide (N=721) n (%)	Placebo (N=497) n (%)
Patients with at least one serious adverse event	9 (4.0)	42 (8.4)	51 (7.1)	42 (8.5)
Preferred term*				
Fall	0	5 (1.0)	5 (0.7)	4 (0.8)
Cataract operation	1 (0.4)	2 (0.4)	3 (0.4)	2 (0.4)
Diarrhea	1 (0.4)	0	1 (0.1)	3 (0.6)
Depression	0	1 (0.2)	1 (0.1)	3 (0.6)
Dyskinesia	0	1 (0.2)	1 (0.1)	2 (0.4)
Abdominal pain	1 (0.4)	1 (0.2)	2 (0.3)	1 (0.2)
Dyspnea	1 (0.4)	1 (0.2)	2 (0.3)	1 (0.2)
Urinary tract infection	1 (0.4)	1 (0.2)	2 (0.3)	1 (0.2)
Death	0	2 (0.4)	2 (0.3)	0
Parkinson's Disease (worsening)	0	2 (0.4)	2 (0.3)	0
Femur fracture	2 (0.9)	0	2 (0.3)	0
Hallucination, visual	0	2 (0.4)	2 (0.3)	0
Breast cancer	0	2 (0.4)	2 (0.3)	0
Pleural effusion	0	1 (0.2)	1 (0.1)	1 (0.2)
Pneumonia	0	1 (0.2)	1 (0.1)	1 (0.2)
Chest pain	1 (0.4)	0	1 (0.1)	1 (0.2)
Non-cardiac chest pain	1 (0.4)	0	1 (0.1)	1 (0.2)
Gamma-glutamyltransferase increased	0	1 (0.2)	1 (0.1)	1 (0.2)
Road traffic accident	1 (0.4)	0	1 (0.1)	1 (0.2)
Hallucination	0	0	0	3 (0.6)
Cellulitis	0	0	0	2 (0.4)
Pyrexia	0	0	0	2 (0.4)
Myocardial ischemia	0	0	0	2 (0.4)

Source: ISS Table 14.6.1.4

*SAEs reported more than once across all treatment groups for Pooled Group 14 patients with LSPD (Studies 016 and SETTLE)

Reviewer Comment

- Study 16 showed that the incidence of any SAE was numerically increased in the 100 mg safinamide dose group compared to the incidence in the 50 mg or placebo treatment groups. Two specific SAEs, which were numerically increased for the high dose 100 mg dose group, were fall and femur fracture. Thus, the risk for SAEs in general and for this specific SAEs appeared to be dose-dependent. The occurrence of an increased risk for specific SAEs such as fall and fracture (femur) is quite plausible considering that the risk for a fall (and possible fracture) is a serious complication of patients with advanced Parkinson's disease. This risk could be related to Parkinson's disease itself and the associated postural instability, and possible hypotension/orthostatic hypotension related

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to age, concomitant Parkinson's disease medications, and/or Parkinson's disease itself. My review of the section on TEAEs of special interest (i.e., 7.3.5 Submission Specific Primary Safety Concern) presents other analyses supportive of this increased risk for falls and fractures.

- The combined analysis of Studies 16 and 18 (up to 2 years of treatment) showed a dose-dependent increased risk for any SAE for the 100 mg safinamide dose (vs placebo and 50 mg dose). Although the risk for any SAE was greater for 50 mg and 100 mg safinamide relative to placebo with long-term safinamide treatment in Study 18 (up to 18 months) compared to the risk with shorter exposure in Study 16 (up to 6 months), this risk did not seem to be substantially greater with much longer exposure. The only specific SAE for which there appeared to be an increased risk in this analysis was for fall for which there was also an increased risk in Study 16 (up to 6 months treatment). However, because patients (especially in Study 18) could have received an increase in the dose of any concomitant medication for Parkinson's disease or addition of a new drug for Parkinson's disease, it is not possible to exclude this overall increased risk of an SAE as possibly being related to increased concomitant medication for Parkinson's disease.

The risk for any SAE with long-term safinamide treatment (in Study 17) did not substantially increase over the increased risk for a shorter treatment period (in Study 15).

- Results of Study SETTLE suggested the possibility of an increased risk for visual hallucinations as an SAE for 100 mg (vs placebo). This possibility is highly plausible considering that hallucinations are a class concern for drugs increasing dopaminergic tone, especially in patients with advanced Parkinson's disease.
- There was no suggestion of an increased risk for all types of SAEs or for any specific SAEs for 100 mg safinamide (vs placebo) in Study SETTLE.
- The pooled analyses of Studies 16 and SETTLE for patients with advanced Parkinson's disease did not suggest a risk for the incidence of any SAE for safinamide (50 mg or 100 mg) treatment compared to the incidence for placebo (Table 57).

Open Label Safety Experience (Study 28850)

Table 58 show the incidence of the most frequently occurring SAEs in the pooled open-label trials.

Table 58 Summary of Most Frequently-Reported Treatment-Emergent Serious Adverse Events for Sildenafil Pooled Open-label Trials

	Sildenafil (100 mg/day) (N=1025) n (%)
Patients with at least one serious adverse event	153 (14.9)
Preferred term*	
Inguinal hernia	9 (0.9)
Pneumonia aspiration	6 (0.6)
Sudden death	5 (0.5)
Femoral neck fracture	5 (0.5)
Osteoarthritis	5 (0.5)
Femur fracture	4 (0.4)
Dyskinesia	4 (0.4)
Parkinson's disease (worsening)	4 (0.4)
Cellulitis	4 (0.4)
Hallucination	4 (0.4)
Cardiac failure	4 (0.4)
Hyponatremia	4 (0.4)
Cataract	4 (0.4)
Benign prostatic hyperplasia	4 (0.4)
Fall	3 (0.3)
Abdominal pain	3 (0.3)
Diarrhea	3 (0.3)
Cerebrovascular accident	3 (0.3)
Convulsion	3 (0.3)
Pulmonary embolism	3 (0.3)
Acute myocardial infarction	3 (0.3)
Prostate cancer	3 (0.3)
Hypoglycemia	3 (0.3)
Urinary retention	3 (0.3)

Source: ISS Table 15.6.1.4

*SAEs with 3 or more reports in Sildenafil-treated Pooled Group 15 (Open-label) patients

Reviewer Comment

- Table 58 shows the incidence of the most frequent SAEs in the open-label trial (Study 28850) for sildenafil. The incidence of all specific SAEs in the open-label treatment experience was < 1%. There were no specific SAEs that suggested a serious or significant treatment risk for sildenafil treatment.

7.3.3 Dropouts and/or Discontinuations

Early Stage Parkinson's disease (ESPD)

Study 15

The overall incidence of patients with at least one TEAE causing study discontinuation was not increased for patients treated with 100 mg (2 %) or 200 mg safinamide (3%) vs placebo (4%).

Almost all specific TEAEs in any safinamide dose group occurred in only one patient and in the only instance in which there were two patients with a specific TEAE (i.e., nausea), the incidence of nausea was not greater than that for placebo.

Pool of Studies 15 and 17

The overall incidence of patients with at least one TEAE causing study discontinuation showed a slightly increased for patients treated with 100 mg (2 %) or 200 mg safinamide (2%) vs placebo (1 %).

Almost all specific TEAEs in any safinamide dose group occurred in only one patient and in the only instance in which there were two patients with a specific TEAE (i.e., nausea), the incidence of nausea was not greater than that for placebo.

Study MOTION (27918)

The overall incidence of patients with at least one TEAE causing study discontinuation was not increased for patients treated with 50 mg (2 %) or 100 mg safinamide (4 %) vs placebo (6%). Almost all specific TEAEs in a safinamide dose group occurred in only one patient. In the single instance in which a specific TEAE (i.e., QT prolongation) occurred in two safinamide (50 mg) treated patients, there were no patients with that specific TEAE in the 100 mg safinamide dose (0 %) group or placebo group (0 %).

Pool of Studies 15 and MOTION (27918)

The overall incidence of patients with at least one TEAE was not increased for patients treated with 50 mg (2%), 100 mg (4 %), or 200 mg safinamide (3 %) vs placebo (6 %) (Table 59). There were no specific TEAEs occurring in two or more patients and for which the incidence of a specific TEAE was numerically greater for safinamide treatment than for placebo treatment. The vast majority of specific SAEs occurred in only one patient in a safinamide group. There was only one instance when a specific TEAE (QT prolongation) occurred in more than one patient (i.e., 2 patients) and the incidence (1 %) of this TEAE was numerically greater than that for placebo (0%).

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Table 59 Treatment-Emergent Adverse Events (TEAEs) Leading to Treatment Discontinuation by Treatment Group (Randomized Assignment) in ESPD Pooled Studies 15 and MOTION (Safety Population)

System Organ Class/ Preferred term[1]	Safinamide (mg/day)					Placebo (N=315)
	50 (N=226)	100 (N=317)	Pooled 50/100 (N=543)	200 (N=89)	All (N=632)	
Subjects with at least one event leading to discontinuation	4 (1.8)	12 (3.8)	16 (2.9)	3 (3.4)	19 (3.0)	18 (5.7)
CARDIAC DISORDERS	2 (0.9)	3 (0.9)	5 (0.9)	0 (0.0)	5 (0.8)	0 (0.0)
ANGINA PECTORIS	0 (0.0)	1 (0.3)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
AORTIC VALVE INCOMPETENCE	0 (0.0)	1 (0.3)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
ATRIAL FLUTTER	0 (0.0)	1 (0.3)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
MYOCARDIAL INFARCTION	1 (0.4)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
PALPITATIONS	1 (0.4)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
VENTRICULAR TACHYCARDIA	1 (0.4)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
INVESTIGATIONS	3 (1.3)	1 (0.3)	4 (0.7)	0 (0.0)	4 (0.6)	4 (1.3)
ELECTROCARDIOGRAM QT PROLONGED	2 (0.9)	0 (0.0)	2 (0.4)	0 (0.0)	2 (0.3)	0 (0.0)
BLOOD CREATINE PHOSPHOKINASE INCREASED	0 (0.0)	1 (0.3)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
BLOOD GLUCOSE INCREASED	1 (0.4)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
ANTI-THYROID ANTIBODY POSITIVE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
BLOOD ALKALINE PHOSPHATASE INCREASED	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
BLOOD THYROID STIMULATING HORMONE INCREASED	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
GAMMA-GLUTAMYLTRANSFERASE INCREASED	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.6)
VISUAL FIELD TESTS ABNORMAL	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
EAR AND LABYRINTH DISORDERS	1 (0.4)	1 (0.3)	2 (0.4)	0 (0.0)	2 (0.3)	0 (0.0)
VERTIGO	1 (0.4)	1 (0.3)	2 (0.4)	0 (0.0)	2 (0.3)	0 (0.0)
EYE DISORDERS	0 (0.0)	2 (0.6)	2 (0.4)	0 (0.0)	2 (0.3)	2 (0.6)
CATARACT	0 (0.0)	1 (0.3)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
LACRIMATION INCREASED	0 (0.0)	1 (0.3)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
MACULAR OEDEMA	0 (0.0)	1 (0.3)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
MACULOPATHY	0 (0.0)	1 (0.3)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
OCULAR VASCULAR DISORDER	0 (0.0)	1 (0.3)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
PAPILLOEDEMA	0 (0.0)	1 (0.3)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
DIPLOPIA	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
VISION BLURRED	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
INFECTIONS AND INFESTATIONS	0 (0.0)	2 (0.6)	2 (0.4)	0 (0.0)	2 (0.3)	0 (0.0)
GASTROENTERITIS	0 (0.0)	1 (0.3)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
RHINITIS	0 (0.0)	1 (0.3)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	1 (0.4)	1 (0.3)	2 (0.4)	0 (0.0)	2 (0.3)	3 (1.0)
MUSCLE SPASMS	1 (0.4)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
MUSCULOSKELETAL STIFFNESS	0 (0.0)	1 (0.3)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
ARTHRITIS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
FIBROMYALGIA	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
JOINT SWELLING	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)

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Table 59 Treatment-Emergent Adverse Events (TEAEs) Leading to Treatment Discontinuation by Treatment Group (Randomized Assignment) in ESPD Pooled Studies 15 and MOTION (Safety Population) (Continued)

System Organ Class/ Preferred term[1]	Safinamide (mg/day)					Placebo (N=315)
	50 (N=226)	100 (N=317)	Pooled 50/100 (N=543)	200 (N=89)	All (N=632)	
NERVOUS SYSTEM DISORDERS	1 (0.4)	1 (0.3)	2 (0.4)	1 (1.1)	3 (0.5)	3 (1.0)
PARAESTHESIA	0 (0.0)	1 (0.3)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
TREMOR	1 (0.4)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)	1 (0.3)
DIZZINESS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
DYSTONIA	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
HEAD TITUBATION	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)	1 (0.2)	0 (0.0)
HEADACHE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	0 (0.0)	2 (0.6)	2 (0.4)	0 (0.0)	2 (0.3)	0 (0.0)
PAIN OF SKIN	0 (0.0)	1 (0.3)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
RASH ERYTHEMATOUS	0 (0.0)	1 (0.3)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	0 (0.0)	1 (0.3)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
IRON DEFICIENCY ANAEMIA	0 (0.0)	1 (0.3)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
GASTROINTESTINAL DISORDERS	1 (0.4)	0 (0.0)	1 (0.2)	3 (3.4)	4 (0.6)	4 (1.3)
NAUSEA	1 (0.4)	0 (0.0)	1 (0.2)	2 (2.2)	3 (0.5)	2 (0.6)
ABDOMINAL PAIN UPPER	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
DIARRHOEA	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)	1 (0.2)	0 (0.0)
GASTROESOPHAGEAL REFLUX DISEASE	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)	1 (0.2)	0 (0.0)
NECROTISING COLITIS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
VOMITING	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)	1 (0.2)	0 (0.0)
PSYCHIATRIC DISORDERS	0 (0.0)	1 (0.3)	1 (0.2)	1 (1.1)	2 (0.3)	7 (2.2)
DEPRESSED MOOD	0 (0.0)	1 (0.3)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
ANXIETY	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)	1 (0.2)	1 (0.3)
COMPULSIVE SEXUAL BEHAVIOUR	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
HALLUCINATION	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
IMPULSE-CONTROL DISORDER	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
INSOMNIA	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
LIBIDO DECREASED	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
NERVOUSNESS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
NIGHTMARE	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)	1 (0.2)	0 (0.0)
SUICIDE ATTEMPT	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	0 (0.0)	1 (0.3)	1 (0.2)	0 (0.0)	1 (0.2)	2 (0.6)
BRONCHOSPASM	0 (0.0)	1 (0.3)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
COUGH	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
DYSPHONIA	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
DYSPNOEA	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
FATIGUE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
METABOLISM AND NUTRITION DISORDERS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
HYPONATRAEMIA	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
VASCULAR DISORDERS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
HYPERTENSION	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)

[1] System organ classes and Preferred terms are coded using the MedDRA dictionary (Version 13.0). System organ classes and Preferred terms are listed in descending order of frequency within the Pooled 50/100 Safinamide group. A subject with multiple occurrences of an AE is counted only once in the System Organ Class and Preferred term category.

Reviewer Comment

- In ESPD, there was no clear suggestion that the risk for TEAEs causing study discontinuation in general nor any specific TEAEs was increased with safinamide treatment (50 mg, 100 mg, or 200 mg) vs placebo.

Late/Advanced Stage Parkinson's disease (LSPD)

Study 16

The overall incidence of patients with at least one TEAE causing study discontinuation was slightly increased for patients treated with 100 mg safinamide (6 %) vs placebo (5 %) but not for patients treated with 50 mg safinamide (4 %). The only specific TEAE causing study discontinuation and occurring in at least two patients and for which the incidence of the TEAE was numerically greater for safinamide treatment than for placebo treatment was for dyspnea (1 % vs 0 %) and this higher incidence was only associated with the 50 mg dose group. All other specific TEAEs in 50 mg or 100 mg safinamide groups occurred in only one patient.

Pool of Studies 16 and 18

The overall incidence of patients with at least one TEAE causing study discontinuation was increased for patients treated with 50 mg (7 %), 100 mg (9 %), and any safinamide/combined 50 mg and 100 mg (8 %) vs placebo (6 %). Several safinamide-treated specific TEAEs causing study discontinuation occurred in at least 2 patients. However, in this subgroup, the only specific TEAEs with an incidence greater than placebo were dyskinesia and dyspnea. This incidence for dyskinesia was 2 % for 50 mg and for 100 mg safinamide and 1 % for placebo. For dyspnea, the incidence was 1 % for 50 mg safinamide and 0 % for placebo and the 100 mg dose group. However, because patients (especially in Study 18) could have received an increase in the dose of any concomitant medication for Parkinson's disease or addition of a new drug for Parkinson's disease, it is not possible to exclude this overall increased risk of a TEAE causing study discontinuation as possibly being related to increased concomitant medication for Parkinson's disease.

Study SETTLE (27919)

The overall incidence of patients with at least one TEAE causing study discontinuation was increased for patients treated with 100 mg safinamide (7 %) vs placebo (4 %). The only specific TEAEs causing study discontinuation and occurring in at least two patients and for which the incidence of the TEAE was numerically greater for safinamide treatment than for placebo treatment was for dyskinesia (1% vs 0 %), for Parkinson's disease (1 % vs 0 %), and visual hallucination (1 % vs 0%). and this higher incidence was only associated with the 50 mg dose group. All other specific TEAEs in the safinamide group occurred in only one patient.

Studies 16 and SETTLE (27919)

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The overall incidence of patients with at least one TEAE causing study discontinuation was increased for patients treated with 50 mg (5%), 100 mg safinamide (6%), and any safinamide dose (6%) vs placebo (4%) (Table 60). Almost all specific TEAEs in a safinamide dose group occurred in only one patient. Only two specific TEAEs (i.e., dyskinesia and dyspnea) occurred in two or more safinamide treated patients and were associated with an incidence greater than placebo. The incidence of dyskinesia was 1% for 50 mg, 100 mg, and any safinamide dose and 0% for placebo. The incidence of dyspnea was 1% for 50 mg, and 0% for 100 mg, any safinamide dose and 0% for placebo.

Table 60 Treatment-Emergent Adverse Events (TEAEs) Leading to Treatment Discontinuation by Treatment Group (Randomized Assignment) in LSPD Pooled Studies 16 and SETTLE (Safety Population)

System Organ Class/ Preferred term[1]	Safinamide (mg/day)			Placebo (N=497)
	50 (N=223)	100 (N=498)	All (N=721)	
Subjects with at least one event leading to discontinuation	11 (4.9)	31 (6.2)	42 (5.8)	21 (4.2)
NERVOUS SYSTEM DISORDERS	6 (2.7)	14 (2.8)	20 (2.8)	7 (1.4)
DYSKINESIA	3 (1.3)	7 (1.4)	10 (1.4)	2 (0.4)
PARKINSON'S DISEASE	0 (0.0)	3 (0.6)	3 (0.4)	0 (0.0)
DIZZINESS	1 (0.4)	1 (0.2)	2 (0.3)	1 (0.2)
PARAESTHESIA	1 (0.4)	1 (0.2)	2 (0.3)	0 (0.0)
BALANCE DISORDER	1 (0.4)	0 (0.0)	1 (0.1)	0 (0.0)
COGNITIVE DISORDER	0 (0.0)	1 (0.2)	1 (0.1)	0 (0.0)
PRESYNCOPE	0 (0.0)	1 (0.2)	1 (0.1)	0 (0.0)
TREMOR	1 (0.4)	0 (0.0)	1 (0.1)	1 (0.2)
AKATHISIA	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
MEMORY IMPAIRMENT	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
SOMNOLENCE	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
GASTROINTESTINAL DISORDERS	3 (1.3)	2 (0.4)	5 (0.7)	1 (0.2)
ABDOMINAL PAIN	1 (0.4)	1 (0.2)	2 (0.3)	0 (0.0)
VOMITING	1 (0.4)	1 (0.2)	2 (0.3)	0 (0.0)
APHTHOUS STOMATITIS	1 (0.4)	0 (0.0)	1 (0.1)	0 (0.0)
CONSTIPATION	1 (0.4)	0 (0.0)	1 (0.1)	0 (0.0)
NAUSEA	1 (0.4)	0 (0.0)	1 (0.1)	0 (0.0)
HAEMATEMESIS	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
PSYCHIATRIC DISORDERS	0 (0.0)	5 (1.0)	5 (0.7)	6 (1.2)
HALLUCINATION, VISUAL	0 (0.0)	3 (0.6)	3 (0.4)	0 (0.0)
HALLUCINATION	0 (0.0)	1 (0.2)	1 (0.1)	3 (0.6)
SLEEP TERROR	0 (0.0)	1 (0.2)	1 (0.1)	0 (0.0)
BRADYPHRENIA	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
DEPRESSION	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
PSYCHOTIC DISORDER	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	2 (0.9)	1 (0.2)	3 (0.4)	1 (0.2)
ASTHENIA	1 (0.4)	1 (0.2)	2 (0.3)	0 (0.0)
CHEST DISCOMFORT	1 (0.4)	0 (0.0)	1 (0.1)	0 (0.0)
FATIGUE	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
OEDEMA PERIPHERAL	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	1 (0.4)	2 (0.4)	3 (0.4)	4 (0.8)
MUSCLE SPASMS	0 (0.0)	2 (0.4)	2 (0.3)	0 (0.0)
MUSCLE RIGIDITY	1 (0.4)	0 (0.0)	1 (0.1)	1 (0.2)
BACK PAIN	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)
MUSCULOSKELETAL STIFFNESS	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
PAIN IN EXTREMITY	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	0 (0.0)	3 (0.6)	3 (0.4)	1 (0.2)
BASAL CELL CARCINOMA	0 (0.0)	1 (0.2)	1 (0.1)	0 (0.0)
BREAST CANCER	0 (0.0)	1 (0.2)	1 (0.1)	0 (0.0)
NON-HODGKIN'S LYMPHOMA	0 (0.0)	1 (0.2)	1 (0.1)	0 (0.0)
ACUTE LYMPHOCYTIC LEUKAEMIA	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)

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Table 60 Treatment-Emergent Adverse Events (TEAEs) Leading to Treatment Discontinuation by Treatment Group (Randomized Assignment) in LSPD Pooled Studies 16 and SETTLE (Safety Population) (Continued)

System Organ Class/ Preferred term[1]	Sildenafil (mg/day)			
	50 (N=223)	100 (N=498)	All (N=721)	Placebo (N=497)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	3 (1.3)	0 (0.0)	3 (0.4)	1 (0.2)
DYSPONOEA	2 (0.9)	0 (0.0)	2 (0.3)	0 (0.0)
PNEUMONITIS	1 (0.4)	0 (0.0)	1 (0.1)	0 (0.0)
DYSPONOEA EXERTIONAL	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
CARDIAC DISORDERS	1 (0.4)	1 (0.2)	2 (0.3)	0 (0.0)
ARRHYTHMIA	0 (0.0)	1 (0.2)	1 (0.1)	0 (0.0)
PALPITATIONS	1 (0.4)	0 (0.0)	1 (0.1)	0 (0.0)
VENTRICULAR TACHYCARDIA	0 (0.0)	1 (0.2)	1 (0.1)	0 (0.0)
EYE DISORDERS	0 (0.0)	2 (0.4)	2 (0.3)	2 (0.4)
CATARACT SUBCAPSULAR	0 (0.0)	1 (0.2)	1 (0.1)	0 (0.0)
VISION BLURRED	0 (0.0)	1 (0.2)	1 (0.1)	1 (0.2)
DRY EYE	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
INVESTIGATIONS	0 (0.0)	2 (0.4)	2 (0.3)	1 (0.2)
ELECTROCARDIOGRAM CHANGE	0 (0.0)	1 (0.2)	1 (0.1)	0 (0.0)
ELECTROCARDIOGRAM QT PROLONGED	0 (0.0)	1 (0.2)	1 (0.1)	1 (0.2)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	0 (0.0)	2 (0.4)	2 (0.3)	2 (0.4)
BLISTER	0 (0.0)	1 (0.2)	1 (0.1)	0 (0.0)
HYPERHIDROSIS	0 (0.0)	1 (0.2)	1 (0.1)	0 (0.0)
LICHEN PLANUS	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
PSORIASIS	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
INFECTIONS AND INFESTATIONS	1 (0.4)	0 (0.0)	1 (0.1)	0 (0.0)
URINARY TRACT INFECTION	1 (0.4)	0 (0.0)	1 (0.1)	0 (0.0)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	0 (0.0)	1 (0.2)	1 (0.1)	1 (0.2)
FALL	0 (0.0)	1 (0.2)	1 (0.1)	1 (0.2)
SUBDURAL HAEMATOMA	0 (0.0)	1 (0.2)	1 (0.1)	0 (0.0)
METABOLISM AND NUTRITION DISORDERS	0 (0.0)	1 (0.2)	1 (0.1)	0 (0.0)
CACHEXIA	0 (0.0)	1 (0.2)	1 (0.1)	0 (0.0)
VASCULAR DISORDERS	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
ORTHOSTATIC HYPOTENSION	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)

[1] System organ classes and Preferred terms are coded using the MedDRA dictionary (Version 13.0). System organ classes and Preferred terms are listed in descending order of frequency within the Overall Sildenafil group. A subject with multiple occurrences of an AE is counted only once in the System Organ Class and Preferred term category.

Reviewer Comment

- Each of the trials (Studies 16 and SETTLE) in LSPD showed an increased risk for the incidence of any TEAE causing study discontinuation for both sildenafil doses vs placebo when evaluated individually and also in a pooled analysis of these trials. Not surprisingly, dyskinesia causing study discontinuation had an increased incidence for each sildenafil dose vs the placebo incidence. Analyses of each of the pools (Studies 16 and SETTLE; Studies 16 and 18) also supported an increased risk for dyskinesia as a TEAE causing study discontinuation. There was no clearly increased risk for any other specific TEAE for study discontinuation.

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7.3.4 Significant Adverse Events

“Significant adverse events” are presented in the next section (7.3.5 Submission Specific Primary Safety Concern) addressing adverse events of special interest for sildenafil and some adverse events of interest for the class of Parkinson's disease drugs that increase central dopaminergic tone.

7.3.5 Submission Specific Primary Safety Concern

Overview of Treatment Emergent Adverse Events of Special Interest (TEAOSI)

The sponsor identified the following treatment-emergent adverse events as adverse events of special interest (TEAOSI) :

- Hepatotoxicity Adverse Events
- Skin Melanoma Adverse Events
- Phototoxicity Adverse Events
- Serotonin Syndrome Adverse Event
- Hypertensive Crisis Adverse Events
- Fractures and Falls Adverse Events
- Ocular Adverse Events
- Neuropsychiatric Adverse Events
- Cardiovascular Adverse Events
- Dyskinesia Adverse Events
- Drug Abuse, Dependence, and Withdrawal Adverse Events
- Suicidality Adverse Events

The sponsor analyzed various specific preferred terms (and also Standardized MedDRA Queries-SMQs) that it had identified in its ISS Statistical Analysis Plan (SAP) to suggest the possibility of the above outlined TEAOSI.

In addition, I considered the following TEAEs to be TEAOSI :

- TEAEs Suggestive of Fall (Integrated and Presented with Sponsor Analysis of Fractures and Falls Adverse Events)
- TEAEs Suggestive of Hypotension/Orthostatic hypotension
- Impulsive/Compulsive Disorders
- Sleep Attacks/Sudden Onset of Sleep/Excessive Sleepiness or Somnolence

My presentation will focus on showing “positive” results suggesting an effect (i.e., potentially increased risk) of sildenafil.

Hepatotoxicity Adverse Events

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Hepatotoxicity adverse events of interest were based on hepatic failure, fibrosis and cirrhosis, and several other liver damage-related conditions and SMQs. The sponsor noted that TEAEs suggesting hepatotoxicity were rare and that there was no suggestion of hepatotoxicity secondary to sildenafil. In addition, there were no cases of Hy's Law.

Reviewer Comment

- I concur with the sponsor that there was no suggestion of sildenafil-induced hepatotoxicity.

Skin Melanoma Adverse Events

Skin melanoma adverse events of interest were based on high-level terms of Skin melanomas. There was one case of melanoma in a sildenafil-treated patient during open-label treatment. The sponsor concluded

APPEARS THIS WAY ON ORIGINAL

Reviewer Comment

- I concur with the sponsor that there was no suggestion of sildenafil-induced melanoma.

Phototoxicity Adverse Events

Adverse events suggestive of phototoxicity, or that were coded to this term, were reported in a total of 8 patients on sildenafil (in two patients the same TEAEs were reported in the randomized and in the open-label phases). None of these phototoxicity adverse events was considered serious, or led to patient discontinuation. The sponsor did not conclude that the relatively few TEAEs of phototoxicity were related to sildenafil treatment.

Reviewer Comment

- I concur with the sponsor that there was no suggestion of sildenafil-induced phototoxicity.

Serotonin Syndrome Adverse Event

One case of serotonin syndrome was observed in a sildenafil treated patient. The following is a summary of this case.

“This 61-year-old female patient (Patient No. 900445/45003), with a known case of PD, entered into the extension study (Study 018) after completion of the core study (Study 16).

The patient was hospitalized with complaints of sudden onset of uneasiness and tremulous movements involving all four limbs, along with shivering, palpitations, and sweating. On examination, the patient was hyperthermia, mentally confused, and rigid with flushed face; BP was 150/100 mmHg; deep tendon reflexes were brisk; tone was increased; and myoclonus was present. EEG was normal and laboratory test were clinically not significant. The patient was

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diagnosed with serotonin syndrome for which the concomitant drug fluoxetine was implicated and was thus withdrawn. The study drug was also permanently stopped. The patient was started with IV fluids, and anti-Parkinson's treatment was continued. This SAE resolved without sequelae and the patient was discharged and also discontinued from the study.

Although the investigator implicated fluoxetine for the event, the investigator maintained the study drug relationship with the event as possible.

Sponsor Assessment

*The patient developed serotonin syndrome 1.5 years after the start of the study drug. The patient was on concomitant medication fluoxetine (selective serotonin reuptake inhibitor) for depression. There was a possibility of drug interaction between the study drug and the selective serotonin reuptake inhibitor that could have led to serotonin syndrome in the patient. Although the concomitant drug fluoxetine was implicated for the event, the study drug relationship with the event could not be ruled out as the study drug was also withdrawn, along with fluoxetine after which the patient improved. **In view of the above, the event was considered to be possibly related to the study drug.***

Reviewer Comment

- I believe that this case appears to represent a case of serotonin syndrome and that it is possible that it may have developed because of an interaction between sildenafil and an SSRI (i.e., fluoxetine). I believe that the label should note that serotonin syndrome has been observed in the sildenafil clinical development program when sildenafil was used along with a concomitant SSRI.

Hypertensive Crisis Adverse Events

The incidence of these events were very low. *The Sponsor has provided the overall incidence by the indications, ESPD and LSPD, and for the open-label studies. In addition, the incidence in the ISS study groupings of interest is also presented.* Hypertensive crisis adverse events of interest were based on the preferred terms Accelerated hypertension, Hypertensive crisis, Hypertensive emergency, Malignant hypertension, Malignant hypertensive heart disease, and Malignant renal hypertension.

The sponsor summarized that there were 3 cases of “hypertensive crisis” (2 cases for sildenafil : one patient while on 100 mg sildenafil in Study MOTION and one patient while on 50 mg sildenafil); one patient while on placebo in Study MOTION extension) coded to that term based upon the investigator’s assessment (including verbatim terms of “hypertensive crisis”). All patients had a history of hypertension and had been taking anti-hypertensive medication, There were no details regarding the specific presentation nor basis upon which the investigator considered these patients to have experienced a TEAE of hypertensive crisis. None of the cases were coded as a serious adverse event and none discontinued from the trial nor experienced a change in study medication.

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- I believe that it is possible that the 2 sildenafil-treated patients experienced some significant increase in blood pressure (potentially consistent with an undefined term of “hypertensive crisis”) in the absence of detailed information about each event which argues against the plausibility of such an event. Although it is not possible to know precisely what the investigators who had designated these patients as having hypertensive crisis had observed, I think that one would have to consider that what was observed must have been a significant hypertensive response to have been labeled by these investigators as a TEAE with a verbatim term of hypertensive crisis. I further believe that the label should mention that hypertensive crisis was observed in the clinical development program associated with sildenafil treatment.

Neuropsychiatric Adverse Events

Neuropsychiatric adverse events of interest were based on psychosis and psychotic disorders SMQ. Across pooled groups (Studies 15 and MOTION in ESPD, Studies 16 and SETTLE in LSPD, open-label patients), the frequently-reported neuropsychiatric adverse events of interest were insomnia, hallucination, anxiety, depression, and visual hallucination. The sponsor interpreted results to suggest that the pooled results respectively for neuropsychiatric events were comparable in placebo-treated and sildenafil-treated patients.

Reviewer Comment

- In the ESPD pool, the 50 mg sildenafil dose showed an increased incidence of insomnia (5 % vs 4 % for placebo) and depression (4 % vs 3 % for placebo). In this pool, the high sildenafil dose (200 mg) showed an increased incidence of anxiety (6 % vs 3 % for placebo).
- In the LSPD pool, the 100 mg sildenafil dose showed an increased incidence of insomnia (4 % vs 2 % for placebo) and anxiety (2 % vs 1 % for placebo). The incidence of anxiety was also increased for the 50 mg dose (2 %).
- In Study SETTLE, the incidence of visual hallucination was increased vs placebo (i.e., 1 % vs 0 %) as an SAE and also as a TEAE causing study discontinuation.

Dyskinesia Adverse Events

The sponsor provided the following summary about dyskinesia adverse events, In the LSPD patients, dyskinesia was reported with a higher incidence in the pooled sildenafil group (18.6%) compared with placebo (8.9%). In these patients, dyskinesia was considered mild or moderate in most patients, and was rated as severe in 1.5% of sildenafil and 1.2% of placebo patients. The incidence of dyskinesia considered related was 16.1% on sildenafil and 7.4% on placebo. No ESPD patient discontinued prematurely due to dyskinesia; 10 LSPD patients on sildenafil (1.4%) and two patients on placebo (0.4%) discontinued treatment due to dyskinesia,

while only two patients (0.2%) on sildenafil discontinued prematurely in the open-label study due to dyskinesia.

Based upon this reviewer's review of results, there was no suggestion of a safety signal for dyskinesia in ESPD based upon results of the pivotal trials (Studies 9, 15, MOTION, and pool of 15 and MOTION).

There was a clear safety signal for an increased risk of dyskinesia with sildenafil treatment in patients with LSPD. Table 75, Table 76, and Table 77 show this increased risk for TEAEs of dyskinesia in Study 16 (and pool of 16 and 18), Study SETTLE, and pools 16 and SETTLE, respectively.

Reviewer Comment

- Dyskinesia was the most common TEAE caused by sildenafil in patients with LSPD. This was not surprising considering that dyskinesia is typically one of the most common (if not most common) TEAEs caused by dopaminergic medications in patients with LSPD.

Fractures and Falls Adverse Events

The sponsor conducted various analyses of the incidence of falls and fractures for the individual pivotal trials and some pivotal trial pools. The sponsor noted that review of falls related to fractures revealed that most falls did not lead to a fracture event in the pools of pivotal trials for ESPD, LSPD, and pools of open-label trials for ESPD and LSPD. When comparing and separating the fall and fracture events for pools of pivotal trials for ESPD and LSPD, sildenafil-treated subjects and placebo subjects were generally similar. The open-label experienced a somewhat higher percentage of fractures, especially patients experiencing a fracture not related to a fall.

In addition, in response to our request, the sponsor conducted "worst case" analyses that show the incidence of adverse events possibly suggestive of falls for the controlled trials according to treatment. For example, TEAEs of fall, abrasion, laceration, fracture, hematoma (any type), ecchymosis, joint sprain, head injury, and limb injury NOS, and crush injury to a limb could be considered suggesting a fall. In these analyses, the occurrence of any of these such events would indicate the incidence of a TEAE possibly suggestive of a fall.

There was no suggestion of an increased risk for fractures and falls or TEAEs suggestive of a fall in the analyses of individual pivotal trials for ESPD or the pool of Studies 15 and MOTION for ESPD.

However, these analyses for patients with LSPD suggested a signal for sildenafil treatment. The following tables show the incidence of falls and/or fractures and of TEAEs suggestive of a fall.

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Table 61 Study 16 : Incidence of Falls and/or Fractures

System Organ Class/ Preferred term[1]	Safinamide (mg/day)			Placebo (N=222)
	50 (N=223)	100 (N=224)	All (N=447)	
Subjects with at least one fractures and falls event of interest [2]	12 (5.4)	11 (4.9)	23 (5.1)	10 (4.5)
Subjects with at least one Fracture event	4 (1.8)	2 (0.9)	6 (1.3)	2 (0.9)
Subjects with both a Fall and a Fracture event (at least one)	1 (0.4)	1 (0.4)	2 (0.4)	1 (0.5)
Subjects with only a Fracture event (at least one) and no Fall events	3 (1.3)	1 (0.4)	4 (0.9)	1 (0.5)
Subjects with only a Fall event (at least one) and no Fracture events	7 (3.1)	9 (4.0)	16 (3.6)	8 (3.6)

Table 62 Study 16 : Incidence of TEAEs Possibly Suggesting a Fall

System Organ Class/ Preferred term[1]	Safinamide (mg/day)			Placebo (N=222)
	50 (N=223)	100 (N=224)	All (N=447)	
Subjects with at least one event suggestive of a fall [2]	8 (3.6)	12 (5.4)	20 (4.5)	9 (4.1)

Table 63 Study SETTLE (27919) : Incidence of TEAEs for Fall and/or Fracture

System Organ Class/ Preferred term[1]	Safinamide 100 (mg/day) (N=274)	Placebo (N=275)
	Subjects with at least one fractures and falls event of interest [2]	
Subjects with at least one Fracture event	5 (1.8)	1 (0.4)
Subjects with both a Fall and a Fracture event (at least one)	4 (1.5)	0 (0.0)
Subjects with only a Fracture event (at least one) and no Fall events	1 (0.4)	1 (0.4)
Subjects with only a Fall event (at least one) and no Fracture events	17 (6.2)	10 (3.6)

Table 64 Study SETTLE (27919) : Incidence of TEAEs Possible Suggestive of a Fall

System Organ Class/ Preferred term[1]	Safinamide 100 (mg/day) (N=274)	Placebo (N=275)
	Subjects with at least one event suggestive of a fall [2]	

Table 65 Pooled Studies 16 and SETTLE (27919) : Incidence of TEAEs for Fall and/or Fracture

System Organ Class/ Preferred term[1]	Safinamide (mg/day)			Placebo (N=497)
	50 (N=223)	100 (N=498)	All (N=721)	
Subjects with at least one fractures and falls event of interest [2]	12 (5.4)	33 (6.6)	45 (6.2)	21 (4.2)
Subjects with at least one Fracture event	4 (1.8)	7 (1.4)	11 (1.5)	3 (0.6)
Subjects with both a Fall and a Fracture event (at least one)	1 (0.4)	5 (1.0)	6 (0.8)	1 (0.2)
Subjects with only a Fracture event (at least one) and no Fall events	3 (1.3)	2 (0.4)	5 (0.7)	2 (0.4)
Subjects with only a Fall event (at least one) and no Fracture events	7 (3.1)	26 (5.2)	33 (4.6)	18 (3.6)

Table 66 Pooled Studies 16 and SETTLE (27919) : Incidence of TEAEs Possible Suggestive of a Fall

System Organ Class/ Preferred term[1]	Safinamide (mg/day)			Placebo (N=497)
	50 (N=223)	100 (N=498)	All (N=721)	
Subjects with at least one event suggestive of a fall [2]	8 (3.6)	36 (7.2)	44 (6.1)	19 (3.8)

Reviewer Comment

- Altogether these analyses show an increased risk for fractures and falls for sildenafil treatment. In particular, fall was shown to be TEAE for which there was an increased risk in the pool of Studies 16 and SETTLE(Table 77).

TEAEs Suggestive of Hypotension/Orthostatic Hypotension

In response to our request, the sponsor conducted “worst case” analyses that show the incidence of TEAEs possibly possibly suggestive of hypotension/orthostatic hypotension to treatment. For example, TEAEs of blood pressure orthostatic decreased, dizziness postural, orthostatic hypotension, blood pressure ambulatory decreased, blood pressure decreased, blood pressure diastolic decreased, blood pressure systolic decreased, mean arterial pressure decreased, diastolic hypotension, systolic hypotension, hypotension, dizziness, vertigo, light-headedness, postural lightheadedness, impaired balance, and feeling drunk could be considered suggesting hypotension/orthostatic hypotension.. In these analyses, the occurrence of any of these such events would indicate the incidence of a TEAE possibly suggestive of hypotension/orthostatic hypotension.

Table 67 and Table 68 show the increased risk for at least one sildenafil dose group (vs placebo) for TEAEs suggestive of hypotension/orthostatic hypotension in the ESPD and LSPD pools.

Table 67 Pooled Studies 15 and MOTION (27918) : Incidence of TEAEs Possible Suggestive of Hypotension/Orthostatic Hypotension

System Organ Class/ Preferred term[1]	Sildenafil (mg/day)					Placebo (N=315)
	50 (N=226)	100 (N=317)	Pooled 50/100 (N=543)	200 (N=89)	All (N=632)	
Subjects with at least one event suggestive of hypotension/orthostatic hypotension [2]	28 (12.4)	29 (9.1)	57 (10.5)	9 (10.1)	66 (10.4)	27 (8.6)

Table 68 Pooled Studies 16 and SETTLE (27919) : Incidence of TEAEs Possible Suggestive of Hypotension/Orthostatic Hypotension

System Organ Class/ Preferred term[1]	Sildenafil (mg/day)			
	50 (N=223)	100 (N=498)	All (N=721)	Placebo (N=497)
Subjects with at least one event suggestive of hypotension/orthostatic hypotension [2]	20 (9.0)	38 (7.6)	58 (8.0)	38 (7.6)

Reviewer Comment

- Each of the pool analyses for ESPD and for LSPD suggest a slightly increased risk for TEAEs suggestive of hypotension/orthostatic hypotension for at least one sildenafil dose group vs placebo. For ESPD, there was an increased sildenafil incidence of these type of TEAEs for 50 mg and 200 mg. For LSPD, there was an increased sildenafil incidence of these type of TEAEs for 50 mg.

Cardiovascular Adverse Events

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Cardiovascular TEAEs of interest were based on events related to bradyarrhythmias, conduction defects, tachyarrhythmias, ischemic heart disease, and blood pressure. Overall, cardiovascular TEAEs were relatively few. For pool of ESPD and LSPD, the sponsor noted that the overall incidence of these cardiovascular TEAEs in placebo-treated patients was generally comparable to that in sildenafil-treated patients.

Reviewer Comment

- I concur with the sponsor that there does not appear to be any clearly increased risk for sildenafil-induced cardiovascular TEAEs.

Drug Abuse, Dependence, and Withdrawal Adverse Events

Drug abuse, dependence, and withdrawal TEAEs of interest were based on Drug abuse and dependence SMQ and Drug withdrawal SMQ. These could be a mix of intentional overdose of other drugs in some cases and sildenafil in others. The sponsor did not conclude an increased sildenafil risk for these type of TEAEs.

Reviewer Comment

- I concur with the sponsor that there does not appear to be an increased risk for drug abuse, dependence, or withdrawal TEAEs associated with sildenafil treatment. In particular, I did not observe any TEAEs which appeared to suggest withdrawal-emergent hyperpyrexia and confusion.

Suicidality Adverse Events

Suicide TEAEs of interest were based on Suicide/self-injury SMQ. For the ESPD pool, there was one suicidal ideation in the sildenafil 100 mg/day treatment group and one in the placebo group, and also one suicide attempt in the placebo group. For the LSPA pool, there were no suicidality TEAEs. In the open-label treatment experience, there was one completed suicide, 2 suicide attempts, and one intentional self-injury TEAE. Thus, in the placebo-controlled treatment experience, there was no suggestion of an increased risk for suicidality TEAEs with sildenafil treatment.

Reviewer Comment

- There does not appear to be an increased sildenafil risk for suicidality TEAEs.

Ocular Adverse Events

Sponsor's Overall Discussion and Conclusions About Special Ophthalmological Safety Data Collection

The ocular safety of sildenafil in the Phase 3 program was based on an assessment of visual function, including visual acuity, color vision, visual field, fundus examination, OCT (in over 400 patients) and ERG (in a single center; n=20) in approximately 2000 patients in placebo-

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controlled trials, with over 1000 patients contributing data for up to 2 years in these trials. In addition, evaluations using slit lamp, measurements of intraocular pressure, and external eye examinations were performed in some of the studies.

Based on the complexity of the program that involved trials in over 300 centers, 5 continents and countries, there was significant heterogeneity in the approach to ocular safety monitoring, as well as the measures used in the studies, as described above. This heterogeneity was noted within studies, as well as between studies, and constrains the pooling of data for most of the individual measures mentioned above. However, for Studies 016/018, MOTION/MOTION Extension and SETTLE an independent experienced neuro-ophthalmologist, unaware of the treatment the patients were receiving, reviewed the data that was submitted from the sites that used a trained local ophthalmologist. The central reviewer provided an assessment of the status of the patient's ocular function, i.e. normal/abnormal, as well as change from baseline in terms of worsening (clinically significant/not clinically significant), no change, or improved.

In summary, a detailed review of the data from individual tests on the ophthalmological examination, including visual acuity, color vision, visual field, fundus, cataract, OCT (in selected patients), and ERG (from one center) did not indicate any adverse ocular effects for sildenafil compared with placebo in any of the studies. Adverse events relating to the Eye Disorders SOC were equally distributed in the sildenafil and placebo groups in each of the studies. The incidence of individual ocular TEAEs was low and did not show any meaningful differences between treatment groups. Overall in the above analyses, there was no difference in the effects among sildenafil doses, and no difference between sildenafil and placebo was noted in the overall change in ocular function, as rated by the expert neuro-ophthalmologist, over the 2-year treatment period in early-stage and mid-late-stage PD patients.

FDA Consult to Division of Transplant and Ophthalmology Products (DTOP) Regarding Review of Sponsor Special Ophthalmological Monitoring and Collection of Prospective Data

We consulted the DTOP to assess NDA results regarding ocular adverse events and particularly the results of the specific prospective ophthalmological data collection. The consult was conducted by Dr. Wiley Chambers. His assessment and conclusions of this review can best be understood by his following responses to specific questions posed in the consult.

DTOP Consult Responses to Questions :

1. Would you please review the special ophthalmological report (iss-appendix-21-ocularsafety-report.pdf) and data/information related to this report and tell us whether results suggest or indicate that sildenafil treatment results in any ophthalmological adverse reactions? If yes, please comment on this adverse reaction.

Reviewer's Response: *It has not been possible to distinguish between impaired vision due to the underlying condition, the inability to perform ocular assessment testing, and adverse*

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events related to the use of the drug product.

2. Would you please tell us if you have any reservations or concerns about the conduct of ophthalmological testing/monitoring in the sildenafil clinical development program?

Reviewer's Response: *It has not been possible to distinguish between impaired vision due to the underlying condition, the inability to perform ocular assessment testing, and adverse events related to the use of the drug product.*

3. Would you please tell us if you have any reservations or concerns about the presentation and/or analyses of results of ophthalmological testing/monitoring in the sildenafil clinical development program?

Reviewer's Response: *None, beyond that already explained above.*

4. Would you please let us know if you have any information requests for the sponsor?

Reviewer's Response: *No.*

5. Would you please tell us if the label should describe any adverse ophthalmological effects? If yes, please summarize the information that should be described in the label.

Reviewer's Response: *Consideration should be given to describing in the labeling that ocular parameters were difficult to evaluate because approximately a third of all patients (including placebo) experienced decreased ocular function during the clinical trials.*

6. Would you please tell us if you have any other comments or recommendations regarding sildenafil and ophthalmological issues?

Reviewer's Response: *No.*

Reviewer Comment

- Based upon the DTOP consult of Dr. Chambers, it appears that we cannot draw a definitive conclusion about an ophthalmological risk for sildenafil treatment. However, it seems like we should insert some caution in the label regarding the limitation of the ophthalmological testing recommended by the consult.

Sleep Attacks/Sudden Onset of Sleep/Excessive Sleepiness or Somnolence

There was a distinct increased risk for sleep attacks/sudden onset of sleep with sildenafil treatment. There was one TEAE for sleep attacks and two TEAEs of sudden onset of sleep for the 100 mg dose in Studies 15 and 17 and no such TEAEs for placebo.

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There was a signal for somnolence (including similar PTs) as a TEAE in many pivotal trials. In Study 15, the incidence of somnolence was 3 % for 100 mg, 7 % for 200 mg and 4 % for placebo. In pool of Studies 15 and MOTION, the incidence of somnolence was 8 % for 50 mg, 4 % for 100 mg, and 4 % for placebo. In Study 16, the incidence of somnolence was 4 % for 50 mg, 2 % for 100 mg and 3 % for placebo. In Study SETTLE, the incidence of somnolence was 4 % for 100 mg, and 3 % for placebo.

The effect of safinamide on sedation was assessed by the Epworth Sleepiness Scale (ESS) in studies MOTION, MOTION Extension, 16, 16 and 18, and SETTLE. The ESS total score was defined as the sum of the eight-item scores assessing the subject's level of daytime sleepiness. The propensity of the subject to fall asleep during normal daytime activities (sitting and reading, watching television, being a passenger in or driving a motor vehicle, etc.) is rated on a four-point scale. A score of 0 indicates that the subject would never doze or sleep during the activity, while scores of 1, 2, or 3 indicate a slight, moderate, or high chance of dozing or sleeping, respectively. A total score of < 10 is considered 'normal', a total score of ≥ 10 is considered 'sleepy', while a score of 18 or more is considered 'very sleepy'.

Overall ESS evaluation across all studies showed mean total ESS score values <10 in all treatment groups. There were no meaningful differences in the mean change from baseline in the total ESS score compared to baseline, at Endpoint in the single studies. The proportions of subjects in each ESS total score category ("normal", "sleepy", "very sleepy") were similar among groups and time points. The sponsor's overall conclusion was that safinamide did not produce any clear increase in excessive daytime sleepiness based upon analyses of ESS.

Reviewer Comment

- Three patients with sleep attack/sudden onset of sleep associated with 100 mg safinamide and no such TEAEs for placebo in the clinical development program not unexpectedly indicates a safinamide-related risk for sleep attack/sudden onset of sleep.
- Not surprisingly, there was also a signal for somnolence (a common class event for dopaminergic drugs for Parkinson's disease as a TEAE) associated with safinamide treatment in the pivotal trials.
- These safinamide-related risks for sleep attack/sudden onset of sleep and somnolence should be described in the label.
- There did not appear to be any clear effect of safinamide on excessive daytime sleepiness based upon ESS testing.

Impulsive/Compulsive Behavior

The sponsor noted that safinamide was not associated with an increase in impulsive/compulsive behavior, as assessed by the QUIP (Parkinson's Disease Impulsive-Compulsive Disorders Questionnaire, a self-

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administered questionnaire specifically designed to assess the severity of symptoms of impulse control disorders (e.g. pathological gambling, buying, eating, and sexual behavior) in patients with PD. The QUIP was performed in the Studies MOTION and SETTLE. The following summarizes the sponsor’s interpretation of QUIP results. Data analyses from MOTION and SETTLE did not detect any difference in the magnitude of change from baseline in the QUIP scale, between safinamide and placebo groups. The total scores for the QUIP were analyzed based on the change of the presence or absence of abnormal behaviors. The distribution of the patients in the different categories did not change from the baseline to the worst post baseline and was similar in the safinamide and placebo groups. Post-baseline evaluations indicated no noteworthy differences in the change from baseline between the various categories in safinamide and placebo groups.

During our review, we requested that the sponsor conduct focused analyses of many TEAE preferred terms (PTs) related to impulsive and compulsive behaviors because there were many such TEAEs in the pivotal trials. Table 69 and Table 70 show results of these analyses in the pools of ESPD and LSPD.

Table 69 Summary of FDA-defined Impulse Control Disorder Events for Safinamide Pooled Group 13 (Studies 15 and MOTION/27918) Patients with ESPD

	Safinamide				Placebo (N=315) n (%)
	50 mg/day (N=226) n (%)	100 mg/day (N=317) n (%)	200 mg/day (N=89) n (%)	All (N=632) n (%)	
Patients with at least one FDA-defined Impulse Control Disorder event	2 (0.9)	4 (1.3)	0	6 (0.9)	3 (1.0)
Compulsions	0	1 (0.3)	0	1 (0.2)	0
Libido increased	0	1 (0.3)	0	1 (0.2)	0
Mental disorder	1 (0.4)	0	0	1 (0.2)	1 (0.3)
Psychotic disorder	0	1 (0.3)	0	1 (0.2)	0
Hyperphagia	0	1 (0.3)	0	1 (0.2)	0
Gambling	1 (0.4)	0	0	1 (0.2)	0
Impulse control disorder	0	0	0	0	1 (0.3)
Obsessive-compulsive disorder	0	0	0	0	1 (0.3)

Source: ISS Table 13.6.1.73

Table 70 Summary of FDA-defined Impulse Control Disorder Events for Safinamide Pooled Group 14 (Studies 16 and SETTLE/27919) Patients with LSPD

	Safinamide			Placebo (N=497) n (%)
	50 mg/day (N=223) n (%)	100 mg/day (N=498) n (%)	All (N=721) n (%)	
Patients with at least one FDA-defined Impulse Control Disorder event	0	10 (2.0)	10 (1.4)	2 (0.4)
Libido increased	0	2 (0.4)	2 (0.3)	0
Psychotic disorder	0	2 (0.4)	2 (0.3)	2 (0.4)
Emotional disorder	0	1 (0.2)	1 (0.1)	0
Hypersensitivity	0	1 (0.2)	1 (0.1)	0
Hypomania	0	1 (0.2)	1 (0.1)	0
Obsessive thoughts	0	1 (0.2)	1 (0.1)	0
Restlessness	0	1 (0.2)	1 (0.1)	0
Thinking abnormal	0	1 (0.2)	1 (0.1)	0

Source: ISS Table 14.6.1.73

Reviewer Comment

- Table 70 shows that when one combines many various PTs indicating some type of impulsive/compulsive behavior that there is an increased risk for these behaviors in LSPD patients treated with 100 mg safinamide vs placebo or 50 mg safinamide. There was no similarly increased risk in the ESPD population.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The following tables show the incidence (rounded off) of TEAEs in individual, pivotal phase 3 trials and pools of trials for ESPD or LSPD. These tables were created by the reviewer are based upon sponsor tables in ISS appendices. Each table shows “common TEAEs” (in bold font and yellow highlight) when the incidence of a specific preferred term TEAE of a safinamide treatment group was $\geq 3\%$ greater than the incidence for placebo.

In some instances, the sponsor had categorized many similar TEAEs with different preferred terms. A request was sent to the sponsor to combine similar preferred terms (based upon my review) and to show the incidence of the adverse event based upon these combined terms. One example was to combine the terms abdominal pain, abdominal pain upper, abdominal discomfort, and dyspepsia as “abdominal pain/discomfort.” An asterisk (*) denotes when the specific TEAE presented is based upon a combined analysis of multiple terms.

Early Stage Parkinson's disease (ESPD)

Table 71, Table 72, and Table 73 present the incidence of TEAEs in individual and pooled trials in early Parkinson's disease where the incidence for at least one safinamide dose was $\geq 2\%$ and numerically greater than the incidence for placebo.

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Table 71 COMPARISON of Incidence (Rounded Off %) of Treatment-Emergent Adverse Events (TEAEs) in Study 15 vs Studies 15 and 17 Pooled for Safinamide TEAEs at Least 2 % (i.e., ≥ 2 %) and Greater Than Placebo Incidence

Treatment-Emergent Adverse Events	Study 15 (Up to 6 Months)				Studies 15 and 17 Combined (Up to 1.5 Years)			
	Safinamide			Placebo N = 90	Safinamide			Placebo N = 90
	100 mg N= 90	200 mg N = 89	Any Dose N = 179		100 mg N= 90	200 mg N = 89	Any Dose N = 179	
Nervous System Disorders								
Dizziness	7	5	6	2	9	7	8	6
Somnolence	3	5	4	4				
Somnolence*	3	7	5	4	4	8	6	6
Hypersomnia	0	2	1	0				
Sudden onset sleep					2	0	1	0
Tremor	6	2	4	1	7	3	5	1
Visual field defect					3	2	3	2
Paresthesia					3	0	2	0
Psychiatric Disorders								
Anxiety	3	6	5	2	6	8	7	3
Sleep disorder	2	0	1	0	2	0	1	0
Sleep Attacks*					2	0	1	0
Delusion					0	2	1	0
Metabolism and Nutrition Disorders								
Hypercholesterolemia	3	0	2	1	3	0	2	1
Diabetes mellitus					1	2	2	0
Hypoglycemia					2	0	1	0
Gastrointestinal Disorders								
Nausea	9	9	9	8	11	10	11	9
Abdominal pain	2	0	1	1				
Abdominal pain upper	9	1	5	4	9	5	7	6
Abdominal pain/discomfort*	16	9	12	9	17	15	16	11
Gastritis	9	1	5	4	6	7	6	2
Dyspepsia					2	2	2	0
Constipation	1	2	2	1	3	5	4	2
Salivary hypersecretion					0	2	1	0
Infections and Infestations								
Bronchitis	3	0	2	2	3	1	2	2
Nasopharyngitis	4	6	5	1	4	6	5	1
Influenza	1	2	2	1				
Onychomycosis	2	0	1	0	2	0	1	0

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Treatment-Emergent Adverse Events	Study 15 (Up to 6 Months)				Studies 15 and 17 Combined (Up to 1.5 Years)			
	Safinamide			Placebo N = 90	Safinamide			Placebo N = 90
	100 mg N= 90	200 mg N = 89	Any Dose N = 179		100 mg N= 90	200 mg N = 89	Any Dose N = 179	
Upper respiratory tract infection	0	2	1	0	0	2	1	0
Viral infection					2	0	1	0
General Disorders and Administration Site Conditions								
Peripheral edema	6	3	5	4				
Chest pain	1	2	2	0	2	2	2	0
Asthenia	0	2	1	1				
Asthenic Conditions*	0	3	2	1	0	3	2	2
Influenza like illness					3	1	2	1
Musculoskeletal and Connective Tissue Disorders								
Back pain	6	3	5	3	13	5	9	6
Pain in extremity	1	3	2	0	3	5	4	1
Osteoarthritis	0	2	1	1	0	2	1	1
Myalgia					0	2	1	0
Arthralgia					6	5	5	3
Muscular rigidity					1	2	2	1
Eye disorders								
Vision blurred	6	2	4	1	8	2	5	1
Visual acuity reduced	2	0	1	1	4	2	3	2
Scotoma					8	3	6	7
Cataract					4	6	5	4
Macular degeneration					0	2	1	0
Retinal degeneration					0	2	1	0
Retinal exudates					2	0	1	1
Retinal pigment epitheliopathy					2	0	1	0
Retinal pigmentation					2	0	1	0
Respiratory Thoracic and Mediastinal Disorders								
Cough	7	6	6	6	7	8	7	6
Vascular disorders								
Hypertension	0	8	4	3	4	9	7	4
Hypertension/Increased blood pressure*	0	8	4	3	4	9	7	4
Orthostatic hypotension	1	3	2	0	2	5	3	0

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Treatment-Emergent Adverse Events	Study 15 (Up to 6 Months)				Studies 15 and 17 Combined (Up to 1.5 Years)			
	Safinamide			Placebo N = 90	Safinamide			Placebo N = 90
	100 mg N= 90	200 mg N = 89	Any Dose N = 179		100 mg N= 90	200 mg N = 89	Any Dose N = 179	
Hypotension/Orthostatic Hypotension*	1	5	3	2	2	6	4	3
Varicose vein	2	0	1	0	2	0	1	0
Investigations								
Blood glucose increased	4	1	3	2	6	2	4	2
Alanine aminotransferase increased	3	1	2	1	4	1	3	1
Blood triglycerides increased	3	1	2	2	3	1	2	2
Blood creatinine increased	2	1	2	0	3	1	2	0
Protein urine present	3	0	2	0	3	0	2	0
Protein urine	2	0	1	0	2	0	1	0
Urine Protein*	3	0	2	0	3	0	2	0
Glucose urine present	2	0	1	1	2	0	1	1
White blood cells urine positive					2	1	2	1
Blood Analyte								
Blood Glucose Increased/Hyperglycemia*	4	1	3	3	6	2	4	3
Blood Glucose decreased/Hypoglycemia*					2	1	2	1
Blood Cholesterol Increased/Hypercholesterolemia*	3	0	2	2	3	0	2	2
Blood Bilirubin Increased/Hyperbilirubinemia*					2	0	1	1
Blood Potassium Increased/ Hyperkalemia*					2	0	1	0
Blood and Lymphatic System Disorders								
Eosinophilia	2	0	1	0	2	0	1	1
Skin and Subcutaneous Tissue Disorders								
Pruritis	2	0	1	1	2	0	1	1
Injury, poisoning, and procedural complications								
Limb injury					2	0	1	0
Renal and urinary disorders								

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Treatment-Emergent Adverse Events	Study 15 (Up to 6 Months)				Studies 15 and 17 Combined (Up to 1.5 Years)			
	Sildenafil			Placebo N = 90	Sildenafil			Placebo N = 90
	100 mg N= 90	200 mg N = 89	Any Dose N = 179		100 mg N= 90	200 mg N = 89	Any Dose N = 179	
Pollakuria					2	2	2	1
Dysuria					0	2	1	1
Renal colic					2	0	1	0
Cardiac disorders								
Angina pectoris					2	2	2	0
Coronary artery disease					2	0	1	0
Coronary Artery Disease/ Angina*					2	0	1	0
Atrioventricular block first degree					1	2	2	0

Source : Created by Reviewer from Sponsor ISS Appendices 2 and 10, Tables 2. 6.1.1. and 10.6.1.1

* Similar preferred terms are combined

Bold and yellow highlight indicates treatment difference at least 3 % greater than placebo

Source : Created by Reviewer from Sponsor ISS Appendices 2 and 10, Tables 2. 6.1.1. and 10.6.1.1

Source : Created by Reviewer from Sponsor ISS Appendix 5, Table 5.6.1.1

Reviewer Comment

- Table 71 compares the incidence of TEAEs in the 6 month trial (Study 15) and in the same trial including a one year extension phase (Study 17) in which patients continued receiving the same randomized treatment assigned in Study 15 under randomized, double-blind, placebo-controlled conditions for up to 6 months. Thus, results included for Studies 15 and 17 combined represent patients who had been treated for various times in both studies up to a total of 1.5 years.
- For Study 15, the most common TEAEs (sildenafil incidence of any treatment group $\geq 3\%$ greater than placebo incidence) were dizziness, somnolence, tremor, anxiety, abdominal pain/discomfort, gastritis, bronchitis, nasopharyngitis, back pain, blurred vision, hypertension, and hypotension/orthostatic hypotension. Somnolence, anxiety, nasopharyngitis, hypertension, and hypotension/orthostatic hypotension appeared to be dose-related because the incidence was higher for 200 mg vs 100 mg. All these dose-related TEAEs (with the exception of nasopharyngitis) suggested an increased risk (vs placebo) only at the high sildenafil dose (200 mg). Considering that the highest sildenafil dose proposed for marketing is 100 mg, the most common

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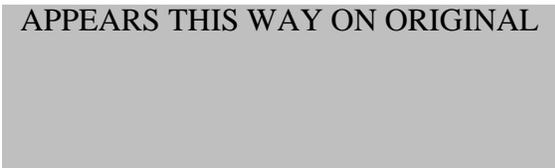
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TEAEs associated with this dose were dizziness, tremor, abdominal pain/discomfort, gastritis, nasopharyngitis, back pain, blurred vision, hypertension, and hypotension/orthostatic hypotension.

- For combined Studies 15 and 17, the most common TEAEs (safinamide incidence of any treatment group $\geq 3\%$ greater than placebo incidence) were dizziness, tremor, anxiety, abdominal pain/discomfort, gastritis, constipation, nasopharyngitis, back pain, pain in extremity, arthralgia, blurred vision, hypertension, hypotension/orthostatic hypotension, blood glucose increased/hyperglycemia, blood creatinine increased, and urine protein. Most of these “most common” TEAEs associated with much longer safinamide exposure (up to 1.5 years) were the same “most common” TEAEs observed in the early part of investigation (up to 6 months in Study 15) and the incidence of these events did not seem to substantially increase with long-term treatment. These common TEAEs which had a higher incidence at 200 mg (than 100 mg) were anxiety, constipation, gastritis, nasopharyngitis, hypertension, and hypotension/orthostatic hypotension
- The “most common” TEAEs that were unique to the longer safinamide exposure were constipation, pain in extremity, arthralgia, blood glucose increased/hyperglycemia, blood creatinine increased, and urine protein. There were many other TEAEs that had a greater incidence than placebo in this longer safinamide treatment period but these TEAEs did not suggest medically serious events that would raise concerns about long-term treatment with safinamide. Although it is possible that the suggestion of an increased risk for certain TEAEs with the long-term treatment might be related to longer safinamide exposure, the possibility cannot be excluded that these TEAEs developed because of an increase in dosing of concomitant drugs for Parkinson's disease or addition of a new drug for Parkinson's disease. Increased medication for Parkinson's disease was a distinct possibility permitted in the extension phase (Study 17).

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Table 72 Incidence (Rounded Off %) of Treatment-Emergent Adverse Events (TEAEs) in Study MOTION (27918) for Sildenafil TEAEs at Least 2 % (i.e., $\geq 2\%$) and Greater Than Placebo Incidence

Treatment-Emergent Adverse Events	Sildenafil			Placebo N = 225
	50 mg N = 226	100 mg N = 227	Any Dose N = 453	
Nervous System Disorders				
Dizziness	8	6	7	7
Paresthesia	3	1	2	2
Gastrointestinal Disorders				
Nausea	6	10	8	7
Abdominal pain	2	1	1	1
Infections and Infestations				
Urinary tract infection	5	3	4	3
Nasopharyngitis	6	2	4	3
Upper respiratory tract infection	3	2	2	2
Musculoskeletal and Connective Tissue Disorders				
Arthralgia	5	4	5	3
Muscle spasms	3	2	2	2
Musculoskeletal pain	1	2	2	0
Osteoarthritis	2	1	1	1
Myalgia	0	2	1	1
Psychiatric disorders				
Insomnia	5	4	4	4
Depression	4	1	2	3
Eye disorders				
Conjunctivitis	0	2	1	0
Respiratory Thoracic and Mediastinal Disorders				
Cough	4	2	3	2
Vascular disorders				
Hypertension	1	4	3	2
Hypertension/ Increased Blood Pressure*	1	4	3	2
Metabolism and Nutrition Disorders				
Decreased appetite	1	2	1	1
Ear and Labyrinth Disorders				
Vertigo	2	2	2	1
Vertigo*	3	2	2	1

Source : Created by Reviewer from Sponsor ISS Appendix 5, Table 5.6.1.1

* Similar preferred terms are combined

Bold and yellow highlight indicates treatment difference at least 3 % greater than placebo

Reviewer Comment

- For Study MOTION (Table 72), the most common TEAEs (sildenafil incidence of any treatment group $\geq 3\%$ greater than placebo incidence) were nausea and nasopharyngitis. The risk for nausea was dose-related and only observed at 100 mg sildenafil. Other TEAEs which were presumably caused by sildenafil (because of a greater incidence than placebo incidence) and

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which are frequently observed with other drugs for Parkinson's disease that increase central dopaminergic tone include dizziness, nausea, hypertension and vertigo.

- Nausea, hypertension, and decreased appetite appeared dose-related because the incidence of the 100 mg dose was greater than that of the 50 mg dose.

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Table 73 Incidence (Rounded Off %) of Treatment-Emergent Adverse Events (TEAEs) in the POOL of Studies 15 and MOTION (27918) for Safinamide TEAEs at Least 2 % (i.e., ≥ 2 %) and Greater Than Placebo Incidence

Treatment-Emergent Adverse Events	Safinamide					Placebo N=315
	50 mg N=226	100 mg N=317	Pool of 50/100 mg N=593	200 mg N=89	Any Dose N=632	
Nervous System Disorders						
Dizziness	8	6	7	5	7	6
Somnolence	8	4	6	5	7	7
Paresthesia	3	2	2	0	2	1
Psychiatric Disorders						
Insomnia	5	4	4	1	4	4
Anxiety	3	2	2	6	3	3
Depression	4	1	2	1	2	3
Metabolism and Nutrition Disorders						
Hypertriglyceridemia	1	1	1	2	1	1
Gastrointestinal Disorders						
Nausea	6	9	8	9	8	7
Abdominal pain upper	4	2	3	1	3	3
Abdominal Pain/Discomfort*	5	9	7	9	3	3
Gastritis	0	2	1	6	2	2
Diarrhea	4	2	3	1	3	3
Infections and Infestations						
Nasopharyngitis	6	3	4	6	4	3
Onychomycosis	1	2	1	0	1	1
Upper respiratory tract infection	3	1	2	2	2	1
Urinary tract infection	5	3	4	2	4	3
General Disorders and Administration Site Conditions						
Fatigue	3	2	3	1	2	2
Pyrexia	1	2	1	6	2	3
Musculoskeletal and Connective Tissue Disorders						
Arthralgia	5	4	4	3	4	3
Pain in extremity	3	2	4	3	3	2
Osteoarthritis	2	1	1	2	1	1
Eye disorders						
Cataract	1	2	2	0	1	1
Conjunctivitis	0	2	1	0	1	0
Vision blurred	0	2	1	2	1	1
Respiratory Thoracic and Mediastinal Disorders						
Cough	4	4	4	6	4	3
Vascular disorders						
Hypertension	1	3	2	8	3	3
Hypertension/Increased Blood Pressure*	1	3	2	8	3	3
Orthostatic hypotension	1	1	1	3	1	0
Hypotension/Orthostatic Hypotension*	2	1	2	5	2	2
Ear and Labyrinth Disorders						
Vertigo	2	1	2	1	2	1
Vertigo*	3	1	2	1	2	1
Investigations						
Alanine aminotransferase increased	0	2	1	1	1	1
Blood Analyte						
Blood Glucose Increased /	2	2	2	1	2	1

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Treatment-Emergent Adverse Events	Sildenafil					Placebo N=315
	50 mg N=226	100 mg N=317	Pool of 50/100 mg N=593	200 mg N=89	Any Dose N=632	
Hyperglycemia*						
Blood Triglycerides Increased / Hypertriglyceridemia*	1	2	2	3	2	2

Source : Created by Reviewer from Sponsor ISS Appendix 13, Table 13.6.1.1

* Similar preferred terms are combined

Bold and yellow highlight indicates treatment difference at least 3 % greater than placebo

Reviewer Comment

- For the pool of Study 15 and MOTION, the most common TEAEs (sildenafil incidence of any treatment group $\geq 3\%$ greater than placebo incidence) were anxiety, abdominal pain/discomfort, gastritis, pyrexia, cough, hypertension, and hypotension/orthostatic hypotension (Table 73). All of these TEAEs were dose-related (i.e., greater incidence at higher doses) and the majority of these TEAEs (i.e., anxiety, gastritis, pyrexia, hypertension, hypotension/orthostatic hypotension) suggested an increased risk only at the highest sildenafil dose (200 mg). There were many other TEAEs (most of which were not considered medically serious) which occurred with a small sildenafil treatment difference $\leq 2\%$ vs placebo.

Table 74 Summary of TEAEs (with at least a 2-fold higher incidence in sildenafil than in placebo) for Pool of Studies 15 and MOTION (27918)

	Sildenafil (mg/day)			Placebo (N=315) n (%)
	50 (N=226) n (%)	100 (N=317) n (%)	Pooled 50/100 (N=543) n (%)	
Patients with at least one adverse event	152 (67.3)	223 (70.3)	375 (69.1)	221 (70.2)
Preferred term*				
Vertigo	5 (2.2)	4 (1.3)	9 (1.7)	2 (0.6)
Orthostatic hypotension	2 (0.9)	3 (0.9)	5 (0.9)	1 (0.3)
Abnormal dreams	2 (0.9)	2 (0.6)	4 (0.7)	1 (0.3)
Electrocardiogram QT prolonged	2 (0.9)	2 (0.6)	4 (0.7)	1 (0.3)
Gastroenteritis	2 (0.9)	2 (0.6)	4 (0.7)	1 (0.3)
Pollakiuria	3 (1.3)	1 (0.3)	4 (0.7)	1 (0.3)
Restless legs syndrome	2 (0.9)	2 (0.6)	4 (0.7)	1 (0.3)
Tension headache	2 (0.9)	2 (0.6)	4 (0.7)	1 (0.3)
Varicose vein	1 (0.4)	3 (0.9)	4 (0.7)	1 (0.3)

Source: ISS Table 13.8.1

*Events sorted by descending incidence in Pooled 50/100 mg/day sildenafil group for Pooled Group 13 (Studies 015 and MOTION) ESPD patients

Reviewer Comment

- The sponsor presented Table 74 which shows TEAEs with at least a 2 fold higher incidence for the pooled 50 mg and 100 mg doses compared with the placebo incidence.

The absolute incidence of these TEAEs for any safinamide dose or the pool of doses was relatively small and in almost all instances (except for vertigo) less than 1 %.

Late/Advanced Stage Parkinson's disease (LSPD)

Table 75, Table 76, and Table 77 present the incidence of TEAEs in individual and pooled trials in advanced Parkinson's disease where the incidence for at least one safinamide dose was $\geq 2\%$ and numerically greater than the incidence for placebo.

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Table 75 **COMPARISON of Incidence (Rounded Off %) of Treatment-Emergent Adverse Events (TEAEs) in Study 16 vs Studies 16 and 18 Pooled for Safinamide TEAEs at Least 2 % (i.e., ≥ 2 %) and Greater Than Placebo Incidence**

Treatment-Emergent Adverse Events	Study 16 (Up to 6 Months)				Studies 16 and 18 Combined (Up to 2 Years)			
	Safinamide			Placebo N = 222	Safinamide			Placebo N = 222
	50 mg N = 223	100 mg N = 224	Any Dose N = 447		50 mg N = 223	100 mg N = 224	Any Dose N = 447	
Nervous System Disorders								
Dyskinesia	21	19	20	13	31	28	29	22
Dizziness	3	2	3	2				
Bradykinesia	0	2	1	1	2	3	3	2
Paresthesia	2	1	1	1	2	2	2	1
Hypoesthesia					1	2	2	1
Somnolence*	4	2	3	3	4	6	5	4
Headache					9	8	9	6
Head discomfort					3	1	2	0
Headache/Head Discomfort*	7	5	6	5	12	9	10	6
Freezing phenomenon					5	3	4	4
Dystonia					3	2	3	1
Balance disorder					2	2	2	1
Speech disorder					3	0	2	1
Amnesia					2	0	1	1
Investigations								
Weight increased	1	3	2	2	2	5	3	4
Weight decreased					8	7	8	6
Low density lipoprotein increased	2	1	1	1				
Very low density lipoprotein increased					2	2	2	1
Eosinophil count increased					3	0	2	2
Glucose urine present					2	2	2	1
Blood Analyte								
Blood Glucose Increased / Hyperglycemia*	4	3	4	3	7	8	7	6
Blood Cholesterol Increased / Hypercholesterolemia*					2	4	3	3
Blood Calcium Decreased / Hypocalcemia*					2	0	1	0
Retinal function test abnormal					1	2	2	0
Gastrointestinal Disorders								
Nausea	3	4	3	3	4	5	5	4
Hyperchlorhydria	0	3	2	1	1	5	3	2
Abdominal pain	2	1	2	1				
Abdominal pain upper					1	2	2	1
Abdominal discomfort					2	2	2	1
Abdominal Pain / Discomfort*					9	11	10	8
Constipation					9	8	8	6
Diarrhea					5	2	3	2
Vomiting					2	3	3	2
Salivary hypersecretion					2	2	2	1
General Disorders								

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Treatment- Emergent Adverse Events	Study 16 (Up to 6 Months)				Studies 16 and 18 Combined (Up to 2 Years)			
	Safinamide			Placebo N = 222	Safinamide			Placebo N = 222
	50 mg N = 223	100 mg N = 224	Any Dose N = 447		50 mg N = 223	100 mg N = 224	Any Dose N = 447	
and Administration Site Conditions								
Chest pain	3	1	2	1	5	2	3	3
Chest Pain / Discomfort (not Angina) *					4	2	3	3
Gait disturbance	0	2	1	1				
Edema peripheral					2	4	3	2
Discomfort					2	1	2	1
Infections and Infestations								
Nasopharyngitis	2	1	1	1				
Gastroenteritis					2	0	1	1
Musculoskeletal and Connective Tissue Disorders								
Arthralgia	4	1	3	2				
Muscle rigidity	2	3	2	2				
Muscle Stiffness / Rigidity	3	5	4	2	7	8	7	4
Musculoskeletal pain	2	1	1	1				
Musculoskeletal stiffness	0	2	1	0				
Back pain					8	11	10	10
Pain in extremity					7	4	6	5
Myalgia					2	0	1	1
Psychiatric disorders								
Insomnia	1	4	3	3	9	6	8	7
Anxiety	2	1	1	1	3	2	3	2
Psychotic Behavior*								
Eye disorders								
Scotoma	2	2	2	1				
Refraction disorder	0	2	1	1	0	3	2	1
Retinal degeneration					2	1	1	1
Respiratory Thoracic and Mediastinal Disorders								
Cough	2	1	1	1				
Oropharyngeal pain								
Vascular disorders					3	0	2	2
Hypertension	6	5	5	4	9	8	9	6
Hypertension/ Increased Blood Pressure*	7	5	6	4	10	9	9	6
Hypotension					3	1	2	2
Metabolism and Nutrition Disorders								
Decreased appetite	2	3	2	2				
Hyperglycemia	2	1	2	1	3	3	3	1
Hypercholesterolemia					1	2	2	1
Hypocalcemia					1	0	1	0
Ear and Labyrinth Disorders								
Vertigo	2	1	1	1	3	1	2	1
Vertigo*					3	2	2	1
Skin and subcutaneous tissue disorders								

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Treatment- Emergent Adverse Events	Study 16 (Up to 6 Months)				Studies 16 and 18 Combined (Up to 2 Years)			
	Safinamide			Placebo N = 222	Safinamide			Placebo N = 222
	50 mg N = 223	100 mg N = 224	Any Dose N = 447		50 mg N = 223	100 mg N = 224	Any Dose N = 447	
Pruritis					2	0	1	1
Eczema					2	0	1	1
Rash								
Renal and urinary disorders								
Dysuria					2	1	2	1
Blood and lymphatic system disorders								
Eosinophilia					1	3	2	2
Lymphopenia					0	4	2	2

Source : Created by Reviewer from Sponsor ISS Appendices 7 and 12, Tables 7.6.1,1 and 12.6.1.1

* Similar preferred terms are combined

Bold and yellow highlight indicates treatment difference at least 3 % greater than placebo

Reviewer Comment

- Table 75 compares the incidence of TEAEs in the 6 month trial (Study 16) and in the same trial including a one year extension phase (Study 18) in which patients continued receiving the same randomized treatment assigned in Study 16 under randomized, double-blind, placebo-controlled conditions. Thus, results included for Studies 16 and 18 combined represent some patients who had been treated for up to 2 years.
- For Study 16, the most common TEAEs (safinamide incidence of any treatment group \geq 3 % greater than placebo incidence) were dyskinesia, muscle stiffness/rigidity, and hypertension/increased blood pressure. Although an increased risk (vs placebo) was apparent at both the 50 mg and 100 mg doses, only muscle stiffness/rigidity appeared to be dose-related because the incidence for 100 mg was greater than that for 50 mg.
- For combined Studies 16 and 18, the most common TEAEs (safinamide incidence of any treatment group \geq 3 % greater than placebo incidence) were dyskinesia, headache/head discomfort, hyperchlorhydria, abdominal pain/discomfort, muscle stiffness/rigidity, and hypertension/increased blood pressure. Headache/head discomfort, hyperchlorhydria, and muscle stiffness/rigidity, appeared dose-related because the incidence for 100 mg was greater than that for 50 mg.
- TEAEs that were “most common” TEAEs (dyskinesia, muscle stiffness/rigidity, hypertension/increased blood pressure) in the shorter exposure (up to 6 months) and also in the much longer safinamide exposure (up to 2 years) showed noteworthy increases in the incidence with much longer treatment. However, this experience does not seem very surprising.

- TEAEs that met the “most common” threshold” ($\geq 3\%$ treatment difference) for the longer safinamide exposure (and were not most common in Study 16) were headache/head discomfort, hyperchlorhydria, and abdominal pain/discomfort. However, headache/head discomfort, and hyperchlohydria appeared to be TEAEs for which there was an increased risk from safinamide treatment for the shorter exposure period.
- It is also important to be mindful that despite the suggestion of an increased risk for certain TEAEs with the long-term treatment, this increased risk might not necessarily be related to longer safinamide exposure because one cannot exclude the possibility that these TEAEs developed due to an increase in dosing of concomitant drugs for Parkinson's disease or addition of a new drug for Parkinson's disease. Increased medication for Parkinson's disease was a distinct possibility permitted in the extension phase (Study 18).

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Safinamide (XADAGO)

Table 76 Incidence (Rounded Off %) of Treatment-Emergent Adverse Events (TEAEs) in Study SETTLE (27919) for Safinamide TEAEs at Least 2 % (i.e., ≥ 2 %) and Greater Than Placebo Incidence

Treatment-Emergent Adverse Events	Safinamide 100 mg N = 275	Placebo N = 275
Nervous System Disorders		
Dyskinesia	16	6
Somnolence	4	3
Somnolence*	4	3
Dizziness	4	3
Paresthesia	2	1
Hypoesthesia	3	1
Parkinson's disease	4	2
Gastrointestinal Disorders		
Nausea	7	6
Abdominal distention	2	0
Dyspepsia	3	1
Dry mouth	2	0
General Disorders and Administration Site Conditions		
Non cardiac chest pain	2	0
Infections and Infestations		
Urinary tract infection	7	4
Bronchitis	2	0
Musculoskeletal and Connective Tissue Disorders		
Pain in extremity	3	2
Psychiatric disorders		
Insomnia	4	2
Anxiety	3	2
Respiratory Thoracic and Mediastinal Disorders		
Cough	2	1
Vascular disorders		
Orthostatic hypotension	2	0
Metabolism and Nutrition Disorders		
Decreased appetite	2	1
Injury poisoning and procedural complications		
Fall	8	4
Contusion	3	0

Source : Created by Reviewer from Sponsor ISS Appendix 9, Table 9.6.1.1

* Similar preferred terms are combined

Bold and yellow highlight indicates treatment difference at least 3 % greater than placebo

Reviewer Comment

- For Study SETTLE (Table 76), the most common TEAEs (≥ 3 % treatment difference) were dyskinesia, urinary tract infection, fall, and contusion. Dyskinesia was the only TEAE that met this most common threshold in both 6 month trials (Studies 16 and SETTLE) in advanced Parkinson's disease.

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Table 77 Incidence (Rounded Off %) of Treatment-Emergent Adverse Events (TEAEs) in POOL of Studies 16 and SETTLE (27919) for Safinamide TEAEs at Least 2 % (i.e., ≥ 2 %) and Greater Than Placebo Incidence

Treatment-Emergent Adverse Events	Safinamide			Placebo N =497
	50 mg N = 223	100 mg N =498	Any Dose N =721	
Nervous System Disorders				
Dyskinesia	21	18	19	9
Paresthesia	2	1	1	1
Visual Field Defect	2	1	1	1
Headache / Head Discomfort*	7	5	6	6
Parkinson's disease	6	4	5	5
Investigations				
Weight decreased	4	2	2	3
Low density lipoprotein increased	2	0	1	1
Eosinophil count increased	2	0	1	0
Blood glucose increased	2	1	2	1
Blood Analyte				
Blood Glucose Increased / Hyperglycemia*	4	2	3	1
Gastrointestinal Disorders				
Nausea	3	6	5	4
Abdominal discomfort	2	1	1	1
Abdominal pain	2	1	1	1
General Disorders and Administration Site Conditions				
Pyrexia	4	1	2	3
Chest pain	3	1	1	1
Chest Pain / Discomfort (not Angina) *	3	1	1	1
Infections and Infestations				
Urinary tract infection	3	5	4	4
Musculoskeletal and Connective Tissue Disorders				
Pain in extremity	3	2	2	2
Arthralgia				
Muscle rigidity	2	1	1	1
Muscle Stiffness / Rigidity*	3	2	2	2
Psychiatric disorders				
Insomnia	1	4	3	2
Anxiety	2	2	2	1
Respiratory Thoracic and Mediastinal Disorders				
Cough	2	2	2	1
Vascular disorders				
Hypertension	6	3	4	3
Hypertension / Increased Blood Pressure*	7	3	4	3
Orthostatic hypotension	2	2	2	1
Hypotension / Orthostatic Hypotension*	4	2	3	3

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Treatment-Emergent Adverse Events	Sildenafil			Placebo N =497
	50 mg N = 223	100 mg N =498	Any Dose N =721	
Hypotension	2	0	1	1
Metabolism and Nutrition Disorders				
Dyslipidemia	2	1	1	1
Hyperglycemia	2	1	1	0
Ear and Labyrinth Disorders				
Vertigo	2	1	1	1
Vertigo*	2	1	1	1
Injury poisoning and procedural complications				
Fall	4	6	5	4
Contusion	0	2	1	0
Renal and Urinary Disorders				
Pyuria	3	1	2	1

Source : Created by Reviewer from Sponsor ISS Appendix 14, Table 14.6.1.1
Bold and yellow highlight indicates treatment difference at least 3 % greater than placebo

Reviewer Comment

- For the pool of Study 16 and SETTLE, the most common TEAEs (sildenafil incidence of any treatment group $\geq 3\%$ greater than placebo incidence) were dyskinesia, blood glucose increased/hyperglycemia, hyperchlorhydria, insomnia, and hypertension/increased blood pressure. Of this most common group, only insomnia appeared to be dose-related at the 100 mg dose.
- Some TEAEs, which did not meet the most common threshold and which appeared to be dose-related, were nausea and fall.

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Table 78 Summary of TEAEs (with at least a 2-fold higher incidence in sildenafil than in placebo) for Pool of Studies 16 and SETTLE (27919)

	Sildenafil (mg/day)			Placebo (N=497) n (%)
	50 (N=223) n (%)	100 (N=498) n (%)	All Sildenafil (N=721) n (%)	
Patients with at least one adverse event	160 (71.7)	363 (72.9)	523 (72.5)	359 (72.2)
Preferred term*				
Dyskinesia	47 (21.1)	87 (17.5)	134 (18.6)	44 (8.9)
Hypoesthesia	1 (0.4)	9 (1.8)	10 (1.4)	3 (0.6)
Contusion	0	8 (1.6)	8 (1.1)	1 (0.2)
Hyperchlorhydria	2 (0.9)	6 (1.2)	8 (1.1)	1 (0.2)
Hyperglycemia	5 (2.2)	3 (0.6)	8 (1.1)	2 (0.4)
Non-cardiac chest pain	1 (0.4)	6 (1.2)	7 (1.0)	1 (0.2)
Blood urea increased	2 (0.9)	2 (0.4)	4 (0.6)	1 (0.2)
Bronchitis	0	4 (0.8)	4 (0.6)	1 (0.2)
Cholelithiasis	0	4 (0.8)	4 (0.6)	1 (0.2)
Cystitis	0	4 (0.8)	4 (0.6)	1 (0.2)
Influenza	1 (0.4)	3 (0.6)	4 (0.6)	1 (0.2)

Source: ISS Table 14.8.1

Reviewer Comment

- The sponsor presented Table 74 which shows TEAEs with at least a 2 fold higher incidence for the pooled 50 mg and 100 mg doses compared with the placebo incidence. The absolute incidence of these TEAEs for any sildenafil dose or the pool of doses was relatively small and in almost all instances (except for dyskinesia) less than 2 % (rounded off).

Open-Label Study 28850

In open-label Study 28850, the only TEAE with an incidence of 10 % (or greater) was dyskinesia at 10 %. Table 89 shows the TEAEs with an incidence of at least 1 % but less than 10 %. The number and incidence of these events was relatively small. Overall the incidence of TEAEs was generally similar to those observed in Pooled Group 13 patients with ESPD and Pooled Group 14 patients with LSPD.

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Table 79 Incidence of TEAEs (> 1 % and < 10 %) in Two or More Patients in Open-Label Study 28850

System Organ Class/ Preferred term[1]	Safinamide 100 (mg/day) (N=1025)
Subjects with at least one event	749 (73.1)
NERVOUS SYSTEM DISORDERS	312 (30.4)
PARKINSON'S DISEASE	44 (4.3)
DIZZINESS	40 (3.9)
HEADACHE	37 (3.6)
ON AND OFF PHENOMENON	26 (2.5)
SOMNOLENCE	16 (1.6)
TREMOR	16 (1.6)
PARKINSONISM	14 (1.4)
PARAESTHESIA	12 (1.2)
INFECTIONS AND INFESTATIONS	218 (21.3)
URINARY TRACT INFECTION	55 (5.4)
NASOPHARYNGITIS	30 (2.9)
UPPER RESPIRATORY TRACT INFECTION	21 (2.0)
BRONCHITIS	11 (1.1)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	216 (21.1)
BACK PAIN	60 (5.9)
ARTHRALGIA	40 (3.9)
PAIN IN EXTREMITY	37 (3.6)
MUSCULOSKELETAL PAIN	19 (1.9)
MUSCLE SPASMS	13 (1.3)
OSTEOARTHRITIS	13 (1.3)
MUSCULOSKELETAL STIFFNESS	12 (1.2)
MUSCLE RIGIDITY	11 (1.1)
GASTROINTESTINAL DISORDERS	210 (20.5)
CONSTIPATION	51 (5.0)
NAUSEA	44 (4.3)
DIARRHOEA	34 (3.3)
ABDOMINAL PAIN UPPER	17 (1.7)
ABDOMINAL PAIN	15 (1.5)
VOMITING	15 (1.5)
DYSPEPSIA	12 (1.2)
INGUINAL HERNIA	12 (1.2)
PSYCHIATRIC DISORDERS	175 (17.1)
HALLUCINATION	35 (3.4)
INSOMNIA	33 (3.2)
DEPRESSION	25 (2.4)
ANXIETY	23 (2.2)
HALLUCINATION, VISUAL	17 (1.7)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	156 (15.2)
PYREXIA	35 (3.4)
OEDEMA PERIPHERAL	31 (3.0)
ASTHENIA	24 (2.3)
FATIGUE	15 (1.5)
PAIN	12 (1.2)
GAIT DISTURBANCE	11 (1.1)
INVESTIGATIONS	124 (12.1)
WEIGHT DECREASED	27 (2.6)
PLATELET COUNT DECREASED	15 (1.5)
BLOOD CREATINE PHOSPHOKINASE INCREASED	13 (1.3)
BLOOD GLUCOSE INCREASED	13 (1.3)
EOSINOPHIL COUNT INCREASED	12 (1.2)
GAMMA-GLUTAMYLTRANSFERASE INCREASED	12 (1.2)
WEIGHT INCREASED	11 (1.1)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	122 (11.9)
FALL	62 (6.0)
EYE DISORDERS	112 (10.9)
CATARACT	42 (4.1)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	69 (6.7)
COUGH	19 (1.9)
DYSPNOEA	15 (1.5)
VASCULAR DISORDERS	62 (6.0)
HYPERTENSION	20 (2.0)
ORTHOSTATIC HYPOTENSION	13 (1.3)
RENAL AND URINARY DISORDERS	57 (5.6)
DYSURIA	11 (1.1)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	44 (4.3)
BASAL CELL CARCINOMA	11 (1.1)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	42 (4.1)
ANAEMIA	21 (2.0)

Reviewer Comment

- The incidence of TEAEs in the open-label treatment experience did not suggest nor raise any new safety concerns relative to the safety profile shown in the 6 month placebo-controlled trials for ESPD and LSPD or in the long-term placebo-controlled, extension trials involving sildenafil treatment up to 1.5 years in ESPD (Studies 15 and 17) or up to 2 years in LSPD(Studies 16 and 18) .

7.4.2 Laboratory Findings

Central Tendency Analyses

The sponsor conducted central tendency analyses for hematology and chemistry laboratory analytes according to randomized treatment and showed the absolute mean absolute values (SD, median, range) at baseline and the mean change from baseline over the individual phase 2 and 3 trials or phase 3 trial pools.

The sponsor concluded that there no noteworthy changes in hematology and chemistry analytes from sildenafil treatment based upon the various central tendency analyses.

Reviewer Comment

- I am unable to conclude that there are any clear or noteworthy changes in the central tendency analyses for any analytes.

Outlier Analyses

The sponsor conducted outlier analyses for the percentage shift from baseline value to the worst post-baseline/treatment value for each hematology and chemistry clinical laboratory analyte and also for urinalysis parameters according to treatment. The sponsor also conducted analyses for the incidence of markedly abnormally/clinically notable low and high values (using DNP recommended thresholds. for hematology and chemistry analytes relative to the normal reference range. The sponsor concluded that there were no noteworthy changes of the various outlier analyses for any analytes.

I have focused attention on presenting outlier analyses because outlier analyses are generally more sensitive than central tendency analyses for showing drug effects.

Table 80 presents outlier results of shift analyses from baseline to the worst on treatment for hematology and chemistry analytes for the pool of Studies 15 and MOTION/27918 (ESPD) and pool of Studies 16 and SETTLE/27919 (LSPD).

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Table 80 Incidence (Rounded Off %) of Abnormal Shifts (from High/Normal Baseline to Low and from Low/Normal Baseline to High) to Worst On Treatment Value for Clinical Laboratory Analytes (Hematology and Chemistry) at Any Time in Pooled Pivotal Trials for Early Parkinson's Disease-ESPD and for Advanced Parkinson's Disease-LSPD
Bold Yellow Highlight % Indicates > 2 % Higher Than Placebo

Clinical Laboratory Analyte and Treatment Group	Early Parkinson's Disease Pool of Studies 15 & MOTION (27918)		Advanced Parkinson's Disease Pool of Studies 16 & SETTLE (27919)	
	Shift to Low	Shift to High	Shift to Low	Shift to High
Basophils				
Placebo	0	0	0	17
Saf 50	0	0	0	38
Saf 100	0	0	0	17
Pool 50/100	0	0	0	24
Saf 200	0	0		
Pool 50/100/200	0	0		
Eosinophils				
Placebo	4	3	10	5
Saf 50	0	2	19	7
Saf 100	5	4	8	5
Pool 50/100	3	3	11	6
Saf 200	26	3		
Pool 50/100/200	6	3		
Erythrocytes				
Placebo	8	2	14	0
Saf 50	5	1	15	0
Saf 100	5	2	15	0
Pool 50/100	5	2	15	0
Saf 200	3	2		
Pool 50/100/200	5	2		
Hematocrit				
Placebo	9	6	15	3
Saf 50	10	1	15	5
Saf 100	9	8	11	3
Pool 50/100	10	5	13	4
Saf 200	8	10		
Pool 50/100/200	9	6		
Hemoglobin				
Placebo	7	3	15	0
Saf 50	5	0	17	1
Saf 100	8	3	10	0
Pool 50/100	7	2	12	0
Saf 200	8	2		
Pool 50/100/200	7	2		
Leukocytes				
Placebo	5	5	11	4
Saf 50	10	1	11	3
Saf 100	4	2	9	5
Pool 50/100	6	2	10	4
Saf 200	1	13		
Pool 50/100/200	6	3		
Lymphocytes				
Placebo	8	2	15	2
Saf 50	9	3	21	3
Saf 100	8	3	17	1
Pool 50/100	8	3	18	1
Saf 200	6	1		
Pool 50/100/200	8	2		
Monocytes				
Placebo	18	1	5	9

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Clinical Laboratory Analyte and Treatment Group	Early Parkinson's Disease Pool of Studies 15 & MOTION (27918)		Advanced Parkinson's Disease Pool of Studies 16 & SETTLE (27919)	
	Shift to Low	Shift to High	Shift to Low	Shift to High
Saf 50	10	2	0	16
Saf 100	13	1	7	9
Pool 50/100	12	1	5	11
Saf 200	31	0		
Pool 50/100/200	15	1		
Neutrophils				
Placebo	3	5	2	10
Saf 50	5	2	0	14
Saf 100	3	5	3	11
Pool 50/100	4	4	2	12
Saf 200	2	7		
Pool 50/100/200	3	4		
Platelets				
Placebo	4	2	5	2
Saf 50	5	1	5	3
Saf 100	3	1	5	2
Pool 50/100	4	1	5	3
Saf 200	1	2		
Pool 50/100/200	3	1		
Alkaline Phosphatase				
Placebo	3	5	1	8
Saf 50	5	3	0	10
Saf 100	4	5	2	6
Pool 50/100	4	4	2	7
Saf 200	0	4		
Pool 50/100/200	4	4		
ALT				
Placebo	1	8	13	3
Saf 50	0	8	12	5
Saf 100	0	13	12	7
Pool 50/100	0	11	12	6
Saf 200	0	13		
Pool 50/100/200	0	11		
AST				
Placebo	1	4	5	3
Saf 50	1	7	6	7
Saf 100	1	9	4	6
Pool 50/100	1	8	5	6
Saf 200	0	3		
Pool 50/100/200	1	8		
Bicarbonate				
Placebo	15	16	13	12
Saf 50	14	17	7	5
Saf 100	17	13	13	9
Pool 50/100	15	15	11	8
Saf 200	0	0		
Pool 50/100/200	15	15		
Bilirubin				
Placebo	0	4	10	3
Saf 50	1	4	23	3
Saf 100	1	4	12	2
Pool 50/100	1	4	15	3
Saf 200	0	1		
Pool 50/100/200	1	4		
Calcium				
Placebo	1	1	3	1
Saf 50	2	2	0	0

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Clinical Laboratory Analyte and Treatment Group	Early Parkinson's Disease Pool of Studies 15 & MOTION (27918)		Advanced Parkinson's Disease Pool of Studies 16 & SETTLE (27919)	
	Shift to Low	Shift to High	Shift to Low	Shift to High
Saf 100	2	2	1	1
Pool 50/100	2	2	1	1
Saf 200	3	0		
Pool 50/100/200	2	2		
Chloride				
Placebo	2	3	1	15
Saf 50	2	3	3	26
Saf 100	1	5	2	13
Pool 50/100	1	4	2	17
Saf 200	0	0		
Pool 50/100/200	1	4		
Cholesterol				
Placebo	4	19	3	19
Saf 50	9	16	0	14
Saf 100	5	14	6	10
Pool 50/100	1	4	4	11
Saf 200	0	7		
Pool 50/100/200	6	14		
CPK				
Placebo	0	15	4	21
Saf 50	0	22	7	20
Saf 100	0	19	4	20
Pool 50/100	0	20	5	20
Saf 200	0	7		
Pool 50/100/200	0	18		
Creatinine				
Placebo	0	5	6	0
Saf 50	0	5	9	1
Saf 100	0	5	5	3
Pool 50/100	0	5	6	2
Saf 200	0	4		
Pool 50/100/200	0	5		
GGT				
Placebo	2	5	8	5
Saf 50	1	5	11	2
Saf 100	1	8	6	3
Pool 50/100	1	7	8	4
Saf 200	0	7		
Pool 50/100/200	1	7		
Glucose				
Placebo	2	12	2	16
Saf 50	1	11	0	17
Saf 100	3	11	1	17
Pool 50/100	3	11	1	17
Saf 200	8	15		
Pool 50/100/200	3	11		
LDH				
Placebo	1	7	3	7
Saf 50	0	7	5	10
Saf 100	0	4	2	9
Pool 50/100	0	5	3	9
Saf 200	0	0		
Pool 50/100/200	0	4		
Potassium				
Placebo	4	2	6	2
Saf 50	6	1	3	4
Saf 100	4	3	3	3
Pool 50/100	5	2	3	3

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Clinical Laboratory Analyte and Treatment Group	Early Parkinson's Disease Pool of Studies 15 & MOTION (27918)		Advanced Parkinson's Disease Pool of Studies 16 & SETTLE (27919)	
	Shift to Low	Shift to High	Shift to Low	Shift to High
Saf 200	1	4		
Pool 50/100/200	4	2		
Sodium				
Placebo	2	4	7	4
Saf 50	3	2	24	3
Saf 100	6	3	9	4
Pool 50/100	5	2	14	4
Saf 200	8	2		
Pool 50/100/200	5	2		
Triglycerides				
Placebo	2	16	4	18
Saf 50	4	8	0	24
Saf 100	2	15	3	17
Pool 50/100	3	12	2	19
Saf 200	0	22		
Pool 50/100/200	3	13		
HDL Cholesterol				
Placebo	10	2	13	6
Saf 50	12	3	18	9
Saf 100	14	2	17	4
Pool 50/100	13	2	27	6
Saf 200	10	0		
Pool 50/100/200	13	2		
LDL Cholesterol				
Placebo	0	15	0	13
Saf 50	0	15	0	10
Saf 100	0	10	0	11
Pool 50/100	0	12	0	10
Saf 200	0	4		
Pool 50/100/200	0	11		
VLDL Cholesterol				
Placebo	4	14	4	19
Saf 50	6	8	0	23
Saf 100	4	11	4	18
Pool 50/100	5	10	3	19
Saf 200	2	17		
Pool 50/100/200	4	11		
BUN				
Placebo	2	10	6	12
Saf 50	3	9	10	12
Saf 100	1	10	4	15
Pool 50/100	1	10	6	14
Saf 200	2	4		
Pool 50/100/200	2	9		

Source : Appendix 13, Tables 11.1.27, 11.1.28; Appendix 14 : Tables 11.1.27, 11.1.28

N (number of patients) for Early Parkinson's disease Pool According to Treatment : Placebo = 315, Saf 50 mg = 226, 100 mg =317, Pool 50/100 mg = 543, 200 mg = 89, Pool 50/100/200 mg = 632

N (number of patients) for Advanced Parkinson's disease Pool According to Treatment : Placebo=497, Saf 50 mg = 223, 100 mg = 498, Pool 50/100 mg = 721

Because shift analyses in Table 80 for pooled trials for early and advanced Parkinson's disease suggested an increased risk for increased serum ALT and AST and decreased serum sodium and HDL cholesterol during safinamide treatment, I reviewed the individual trials of each pool to see

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if one trial was driving these signals or if analysis of the individual trials for each pool similarly showed the same abnormalities.

Table 81 - Table 84 presents shift analyses results for the treatment difference (safinamide % - placebo %) for these analytes in each individual trial.

Table 81 Treatment Difference % (Safinamide % - Placebo %) for Shift from Baseline to Worst Value in Study 15 (ESPD)

Analyte Shifts	Safinamide 100 mg	Safinamide 200 mg	Any Safinamide Dose
ALT shift from normal or low to high	6	12	9
AST shift from normal or low to high	2	1	2
Sodium shift from normal or high to low	7	3	5
HDL Cholesterol shift from normal or high to low	16	9	12

Table 82 Treatment Difference % (Safinamide % - Placebo %) for Shift from Baseline to Worst Value in Study MOTION/27918 (ESPD)

Analyte Shifts	Safinamide 100 mg	Safinamide 200 mg	Any Safinamide Dose
ALT shift from normal or low to high	< 0	5	1
AST shift from normal or low to high	2	6	4
Sodium shift from normal or high to low	2	2	2
HDL Cholesterol shift from normal or high to low	0	1	1

Table 83 Treatment Difference % (Safinamide % - Placebo %) for Shift from Baseline to Worst Value in Study 16 (LSPD)

Analyte Shifts	Safinamide 50 mg	Safinamide 100 mg	Any Safinamide Dose
ALT shift from normal or low to high	1	4	2
AST shift from normal or low to high	3	2	3
Sodium shift from normal or high to low	11	5	8
HDL Cholesterol shift from normal or high to low	5	8	6

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Table 84 Treatment Difference % (Safinamide % - Placebo %) for Shift from Baseline to Worst Value in Study SETTLE/27919 (LSPD)

Analyte Shifts	Safinamide 100 mg
ALT shift from normal or low to high	4
AST shift from normal or low to high	4
Sodium shift from normal or high to low	0
HDL Cholesterol shift from normal or high to low	2

Reviewer Comment

- In Table 80, my review of outlier results (based upon shift analyses from baseline to the highest and lowest results for hematology and chemistry analytes) suggested noteworthy safinamide-induced shifts for only a few analytes of the many analytes evaluated. In many instances there were very small increases (1 %) in the incidence of a safinamide shift abnormality (vs placebo) or a larger incidence increase for an isolated single safinamide dose but these findings were typically only observed for one population (i.e., only early Parkinson's disease or only advanced Parkinson's disease). However, when my analysis focused on treatment differences (safinamide % - placebo %) ≥ 2 % for abnormal shifts and on observing similar abnormal shifts for both populations (analyzed as a pool of 2 pivotal trials), it appeared that safinamide induced shifts to an increased serum ALT and AST, and a decreased serum sodium and HDL cholesterol. My reasoning for focusing on similar abnormal shift results in both populations was that it seemed most likely that if safinamide was causing an abnormality, that the abnormality would be an objective finding that might be expected in both populations of patients.
- To clarify that these abnormal shifts were observed in individual trials of each population and were not driven by a single trial, I reviewed such shift results for serum ALT, AST, sodium, and HDL cholesterol in each of the individual trials.
- Table 81, Table 82, Table 83, and Table 84 showed that safinamide treatment (at least one dose) was associated with the same type of abnormal shift for all analytes (except for low sodium shift in Study SETTLE) in each of the trials for early Parkinson's disease and for advanced Parkinson's disease. The only shift that appeared to be dose-related because the incidence was higher for the higher safinamide dose was for the shifts for ALT.
- Analyses of these analytes for markedly abnormal values after treatment did not indicate that safinamide-induced increases in ALT and AST or decreases in sodium and HDL cholesterol were severely abnormal. Markedly abnormal thresholds applied for these analyses were : ≥ 3 x ULN for serum AST and ALT, < 30 mg/dL for serum HDL cholesterol, and ≤ 127 mEq/L for serum sodium.

Clinical Review

Leonard P. Kapcala, M.D.

NDA 207145 Safinamide (XADAGO)

Safinamide (XADAGO)

- I conclude that there is a distinct and real but relatively small/low risk for increases in serum ALT and AST (above the reference range) and for decreases in serum sodium and HDL cholesterol with safinamide treatment. I do not believe that there is any evidence suggesting that these changes are indicative of any medically serious problems. In particular, there were no cases of “Hy’s Law” in this NDA for markedly abnormally increased levels of AST or ALT suggesting potentially serious hepatic pathology. The decrease in HDL could potentially have some significance to patients with coronary disease because HDL cholesterol is believed to be cardioprotective for coronary artery disease and “low” or low normal levels are considered risk factors for coronary disease. **I recommend that these abnormalities in these 4 analytes be described in the safinamide label.**
- During my review of the incidence of markedly abnormal analytes (hematology and chemistry, initially, I looked at results from pools of early (Studies 15 and MOTION) and advanced Parkinson's disease (Studies 16 and SETTLE). Although there were some analytes with a safinamide dose incidence greater than the placebo incidence, there were no examples in which a safinamide incidence for a specific analyte was at least 2 % greater than placebo incidence and this finding was observed in both populations of patients. Because these results did not show a pattern of a safinamide dose treatment difference of at least 2 % in both populations for both populations, I did not think that these isolated findings were real and suggesting causality by safinamide. Consequently, I concluded that there was no clear nor noteworthy changes in the incidence of markedly abnormally low or high results for any of the hematology or chemistry analytes (including especially ALT, AST, Sodium, and HDL cholesterol) during safinamide treatment.
- There was no suggestion of any clear or noteworthy abnormalities for safinamide induced shifts in urinalysis analyses.

7.4.3 Vital Signs

Central Tendency Analyses of Orthostatic Vital Signs (Blood Pressure and Pulse) and Other Vital Sign Parameters (Body Weight, Temperature, and Ventilatory/Respiratory Rate)

The sponsor conducted central tendency analyses for orthostatic (supine, standing, change from supine to standing) vital signs (VS) for systolic blood pressure (SBP), diastolic blood pressure (DBP), and pulse and other VS parameters (body weight, temperature, and ventilatory/respiratory Rate) according to randomized treatment. In these analyses, the sponsor showed the mean absolute values at baseline and the mean change from baseline over time for the individual phase 2 and 3 trials and phase 3 trial pools.

Clinical Review
Leonard P. Kapcala, M.D.
NDA 207145 Sildenafil (XADAGO)
Sildenafil (XADAGO)

The sponsor concluded that there no noteworthy effects of sildenafil treatment on orthostatic VS nor on other VS (weight, temperature, ventilator/respiratory rate) from the various central tendency analyses.

Reviewer Comment

- I conclude that there are no clear nor noteworthy changes in the central tendency analyses for these various VS analyses.

Outlier Analyses

Other Vital Sign Parameters (Body Weight, Temperature, and Ventilatory/Respiratory Rate)

In addition to analyses of mean change from baseline to each time point, the number (percentage) of patients with clinically significant values at each time point was also analyzed. These clinically significant values were defined in the clinical trials as follows:

- Body weight (kg): $\geq 7\%$ increase or $\geq 7\%$ decrease from baseline;
- Temperature ($^{\circ}\text{C}$): Value ≥ 38.3 and ≥ 1.1 increase from baseline;
- Ventilatory/Respiratory rate (breaths/min): value < 10 or > 20

In the ISS, the sponsor noted that there were no noticeable trends for these VS values over the course of the study and that abnormal VS outliers, were comparable between the combined sildenafil and placebo groups, as well as between sildenafil dose groups, in the Pooled, Combined, and Individual study populations. However, in each individual final study report (for Studies 16 and SETTLE), there was recognition that there appeared to be an increased incidence of clinically significant/notable weight change (increase **OR** decrease)with 100 mg sildenafil treatment.

Reviewer Comment

- I conclude that there are no clear nor noteworthy changes in the outlier analyses for these “other” VS analyses for temperature and ventilator/respiratory rate.
- In separate analyses of LSPD patients (Study 16, and Study SETTLE), there appears to be a clinically significant/notable change in outliers for weight of at least 7 % (or greater) from baseline for an increase or decrease for 100 mg sildenafil vs placebo (and vs 50 mg in Study 16) at week 24. In Study 16, the incidence of such outliers for 100 mg was 12.1 % compared to an incidence of 8.6 % for placebo and 7.6 % for 50 mg. In Study SETTLE, the incidence of such outliers for 100 mg was 13.1 % compared to an incidence of 10.5 % for placebo. However, it is not clear if this increased incidence of weight is for an increase or decrease or neither because the sponsor did not analyze outliers for such a threshold increased weight and also for decrease weight. The sponsor should clarify if there is a sildenafil-related increased risk for decreased weight or increased weight by analyzing data separately for this threshold change in weight specifically for an increase and also a decrease in weight over time and according to randomized treatment.

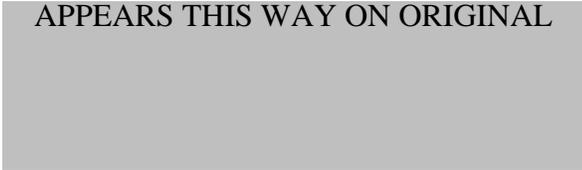
Clinical Review
Leonard P. Kapcala, M.D.
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Orthostatic Blood Pressure and Pulse

Because outlier analyses are generally more sensitive for detecting safety signals, including abnormalities for orthostatic VS, I have focused my presentation of results of DNP requested analyses on outlier analyses, particularly those showing the incidence of various threshold increases and decreases of SBP, DBP, and pulse according to randomized treatment and relative to measurements while supine, standing, and changing from supine to standing positions.

The following tables show the incidence of various outlier thresholds according to position for orthostatic VS for each treatment in phase 3 trials when at least one sildenafil dose shows a higher incidence than placebo for a specific outlier threshold. An outlier increase or decrease during/on treatment is relative to the VS parameter at baseline/pre-treatment. **Incidence data are bolded and highlighted in yellow when a sildenafil dose incidence is at least 3 % (or more) greater than placebo incidence.**

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Clinical Review
Leonard P. Kapcala, M.D.
NDA 207145 Safinamide (XADAGO)
Safinamide (XADAGO)

Table 85 Incidence (Rounded Off) of “Abnormal” Thresholds for Orthostatic Vital Signs at ANY TIME in Study 15 (Early Parkinson's disease) When Safinamide Incidence was Greater than Placebo Incidence

Vital Sign Threshold	Supine				Standing 1 Min				Standing 3 Min				Standing Average of 1 and 3 Min				Change from Supine to Standing			
	100 mg	200 mg	Any Dose	Pla- cebo	100 mg	200 mg	Any Dose	Pla- cebo	100 mg	200 mg	Any Dose	Pla- cebo	100 mg	200 mg	Any Dose	Pla- cebo	100 mg	200 mg	Any Dose	Pla- cebo
SBP ≤ 90 mm Hg					1	3	2	2	2	2	2	1	1	2	2	1				
SBP ≥ 180 mm Hg																				
DBP ≤ 50 mm Hg																				
DBP ≥ 105 mm Hg	2	1	2	0	2	0	1	0					2	0	1	0				
Pulse ≤ 50 BPM									2	1	2	0								
Pulse ≥ 120 BPM																				
SBP Increase ≥ 20 mm Hg	13	17	15	6	10	14	12	9	8	12	10	4	7	10	8	4				
SBP Increase ≥ 40 mm Hg																				
SBP Decrease ≥ 20 mm Hg																				
SBP Decrease ≥ 40 mm Hg					1	2	2	1	1	2	2	1	1	2	2	1				
DBP Increase ≥ 10 mm Hg	29	26	27	13	20	28	24	12	18	23	20	16	18	23	20	10	11	15	13	13
DBP Increase ≥ 20 mm Hg	6	6	6	2	8	3	6	1	6	2	4	1	4	2	3	1	0	2	1	1
DBP Decrease ≥ 10 mm Hg									28	17	22	27					18	9	13	12
DBP Decrease ≥ 20 mm Hg																	2	1	2	0
Pulse Increase ≥ 15 BPM	10	20	15	9	10	18	14	6	9	19	14	4	8	18	13	6	3	2	3	1
Pulse Increase ≥ 30 BPM																				
Pulse Decrease ≥ 15 BPM																				
Pulse Decrease ≥ 30 BPM					2	0	1	1	2	0	1	0								

Source : Created by Reviewer from Sponsor ISS Appendix 5, Table 5.6.1.1
Safinamide 50 mg (N=90), Safinamide 100 mg (N=89), All Safinamide (N=179), Placebo (N=90)
Bold font and yellow highlight indicates treatment difference (safinamide % - placebo %) ≥ 3 %

Clinical Review
Leonard P. Kapcala, M.D.
NDA 207145 Safinamide (XADAGO)
Safinamide (XADAGO)

Table 86 Incidence (Rounded Off) of “Abnormal” Thresholds for Orthostatic Vital Signs at ANY TIME in Study MOTION (Early Parkinson's disease) When Safinamide Incidence was Greater than Placebo Incidence

Vital Sign Threshold	Supine				Standing 1 Min				Standing 3 Min				Standing Average of 1 and 3 Min				Change from Supine to Standing			
	50 mg	100 mg	Any Dose	Pla- cebo	50 mg	100 mg	Any Dose	Pla- cebo	50 mg	100 mg	Any Dose	Pla- cebo	50 mg	100 mg	Any Dose	Pla- cebo	50 mg	100 mg	Any Dose	Pla- cebo
SBP ≤ 90 mm Hg					5	2	4	4	2	2	4	2	4	1	3	2				
SBP ≥ 180 mm Hg																				
DBP ≤ 50 mm Hg																				
DBP ≥ 105 mm Hg	2	1	1	1																
Pulse ≤ 50 BPM	6	2	4	2	2	1	2	1	2	1	1	1	2	1	1	0				
Pulse ≥ 120 BPM																				
SBP Increase ≥ 20 mm Hg																				
SBP Increase ≥ 40 mm Hg									2	0	1	1								
SBP Decrease ≥ 20 mm Hg	19	20	20	26	26	16	21	20	23	17	20	16	19	15	17	15				
SBP Decrease ≥ 40 mm Hg					4	1	2	2	2	0	1	1	3	0	2	1				
DBP Increase ≥ 10 mm Hg																	21	15	18	18
DBP Increase ≥ 20 mm Hg									4	3	3	3	3	1	2	2				
DBP Decrease ≥ 10 mm Hg	39	34	37	30	39	31	35	29	36	31	34	32	34	27	31	25	13	19	16	15
DBP Decrease ≥ 20 mm Hg	9	2	6	4	8	7	8	6					7	3	5	4	1	2	2	1
Pulse Increase ≥ 15 BPM	12	16	14	11	17	15	16	12	13	15	14	14	12	14	13	10				
Pulse Increase ≥ 30 BPM																				
Pulse Decrease ≥ 15 BPM					12	10	11	10	12	10	11	11					8	4	6	1
Pulse Decrease ≥ 30 BPM																				

Source : Created by Reviewer from Sponsor ISS Appendix 5, Table 5.14.1 (Results for 200 mg in Study 15 not presented)
Safinamide 50 mg (N=226), Safinamide 100 mg (N=227), All Safinamide (N=453), Placebo (N=225)

Bold font and yellow highlight indicates treatment difference (safinamide % - placebo %) ≥ 3 %

Clinical Review
Leonard P. Kapcala, M.D.
NDA 207145 Safinamide (XADAGO)
Safinamide (XADAGO)

Table 87 Incidence (Rounded Off) of “Abnormal” Thresholds for Orthostatic Vital Signs at ANY TIME in Study 16 (Advanced Parkinson's disease) When Safinamide Incidence was Greater than Placebo Incidence

Vital Sign Threshold	Supine				Standing 1 Min				Standing 3 Min				Standing Average of 1 and 3 Min				Change from Supine to Standing			
	50 mg	100 mg	Any Dose	Pla-cebo	50 mg	100 mg	Any Dose	Pla-cebo	50 mg	100 mg	Any Dose	Pla-cebo	50 mg	100 mg	Any Dose	Pla-cebo	50 mg	100 mg	Any Dose	Pla-cebo
SBP ≤ 90 mm Hg	2	2	2	0	4	5	4	4	5	3	4	2	4	4	4	1				
SBP ≥ 180 mm Hg													0	1	1	0				
DBP ≤ 50 mm Hg	1	0	0	0																
DBP ≥ 105 mm Hg																				
Pulse ≤ 50 BPM																				
Pulse ≥ 120 BPM																				
SBP Increase ≥ 20 mm Hg																	2	2	2	1
SBP Increase ≥ 40 mm Hg	2	1	2	1	2	1	2	1					1	1	1	0				
SBP Decrease ≥ 20 mm Hg	17	20	19	18					20	18	19	19					6	5	5	5
SBP Decrease ≥ 40 mm Hg																				
DBP Increase ≥ 10 mm Hg	27	22	24	26					23	22	23	21					9	11	10	4
DBP Increase ≥ 20 mm Hg					4	3	3	3	5	4	4	3	3	2	3	1				
DBP Decrease ≥ 10 mm Hg	33	33	33	28	36	30	33	31	37	28	32	30	32	21	26	23				
DBP Decrease ≥ 20 mm Hg	6	7	6	5	6	9	7	5	6	5	6	5					2	1	1	1
Pulse Increase ≥ 15 BPM					15	13	14	13									1	2	1	1
Pulse Increase ≥ 30 BPM	1	0	0	0	1	0	1	0	1	0	1	0								
Pulse Decrease ≥ 15 BPM	8	10	9	7	9	11	10	6	9	8	8	6	7	9	8	5				
Pulse Decrease ≥ 30 BPM					1	2	1	0												

Source : Created by Reviewer from Sponsor ISS Appendix 7, Table 7.14.1
Safinamide 50 mg (N=223), Safinamide 100 mg (N=224), All Safinamide (N=447), Placebo (N=222)
Bold font and yellow highlight indicates treatment difference (safinamide % - placebo %) ≥ 3 %

Clinical Review
Leonard P. Kapcala, M.D.
NDA 207145 Safinamide (XADAGO)
Safinamide (XADAGO)

Table 88 Incidence (Rounded Off) of “Abnormal” Thresholds for Orthostatic Vital Signs at ANY TIME in Study SETTLE (Advanced Parkinson's disease) When Safinamide Incidence was Greater than Placebo Incidence

Vital Sign Threshold	Supine		Standing 1 Min		Standing 3 Min		Standing Average of 1 and 3 Min		Change from Supine to Standing	
	100 mg	Placebo	100 mg	Placebo	100 mg	Placebo	100 mg	Placebo	100 mg	Placebo
SBP ≤ 90 mm Hg	3	2	12	9			7	6		
SBP ≥ 180 mm Hg										
DBP ≤ 50 mm Hg			4	2	4	2	3	1		
DBP ≥ 105 mm Hg					2	1				
Pulse ≤ 50 BPM			2	1	3	0	2	1		
Pulse ≥ 120 BPM										
SBP Increase ≥ 20 mm Hg										
SBP Increase ≥ 40 mm Hg	2	1								
SBP Decrease ≥ 20 mm Hg	25	23	28	24			24	22	8	7
SBP Decrease ≥ 40 mm Hg										
DBP Increase ≥ 10 mm Hg	28	24	30	25	29	23	26	23		
DBP Increase ≥ 20 mm Hg									4	2
DBP Decrease ≥ 10 mm Hg	40	37	42	38	40	34	35	32	23	19
DBP Decrease ≥ 20 mm Hg			8	7						
Pulse Increase ≥ 15 BPM	15	13	16	13	16	12				
Pulse Increase ≥ 30 BPM					2	1				
Pulse Decrease ≥ 15 BPM					10	8				
Pulse Decrease ≥ 30 BPM	10	7								

Source : Created by Reviewer from Sponsor ISS Appendix 9, Table 9.14.1
Safinamide 100 mg (N=274), Placebo (N=275)

Bold font and yellow highlight indicates treatment difference (safinamide % - placebo %) ≥ 3 %

Clinical Review
Leonard P. Kapcala, M.D.
NDA 207145 Safinamide (XADAGO)
Safinamide (XADAGO)

The sponsor conducted analyses for the incidence of various threshold decrease of systolic blood pressure and diastolic blood pressure with orthostatic changes from supine to standing over time. Table 89 shows the incidence of orthostatic hypotension for diastolic blood pressure decrease of 10 mm Hg or greater over time in Study 16. **This specific outcome was selected for presentation because this was the only specific blood pressure outlier that showed a consistent abnormality over time.**

Table 89 Incidence of Orthostatic Hypotension (OH) Over Time for Diastolic Blood in Study 16 (Advanced Parkinson's disease) When Safinamide incidence is Greater than Placebo Incidence

Type of OH at Different Times	Safinamide 50 mg N = 223		Safinamide 100 mg N = 224		All Safinamide N = 447		Placebo N = 223	
	OH/Total Tested (%) [*]	OH/Baseline OH (%) ^{**}	OH/Total Tested (%) [*]	OH/Baseline OH (%) ^{**}	OH/Total Tested (%) [*]	OH/Baseline OH (%) ^{**}	OH/Total Tested (%) [*]	OH/Baseline OH (%) ^{**}
Baseline								
<i>SBP OH ≥ 20 mm Hg</i>	< 1 %		0 %		< 1 %		0 %	
<i>Severe SBP OH ≥ 40 mm Hg</i>	0 %		0 %		0 %		0 %	
<i>DBP ≥ 10 mm Hg</i>	< 1 %		< 1 %		< 1 %		< 1 %	
<i>DBP ≥ 20 mm Hg</i>	0 %		0 %		0 %		0 %	
<i>SBP OH and DBP OH</i>	< 1 %		0 %		< 1 %		0 %	
<i>Severe SBP OH and DBP OH</i>	0 %		0 %		0 %		0 %	
Week 4								
<i>DBP ≥ 10 mm Hg</i>	5 %	500 %	6 %	200 %	5 %	733 %	4 %	450 %
Week 8								
<i>DBP ≥ 10 mm Hg</i>	3 %	300 %	5 %	900 %	4 %	500 %	4 %	350 %
Week 12								
<i>DBP ≥ 10 mm Hg</i>	7 %	650 %	10 %	1000 %	6 %	767 %	5	500
Week 24								
<i>DBP ≥ 10 mm Hg</i>	2 %	200 %	2 %	300 %	7 %	233 %	4 %	400 %
Endpoint								
<i>DBP ≥ 10 mm Hg</i>	2 %	200 %	3 %	600 %	2 %	333 %	4 %	400 %

Bolded yellow highlight indicates safinamide result greater than placebo

^{*}OH/Total Tested (%) indicates incidence of patients with the outlier at a specific time.

^{**}OH/Baseline OH (%) indicates proportion of the incidence of patients with the outlier at a specific time after treatment over the incidence at baseline.

Reviewer Comment

Clinical Review

Leonard P. Kapcala, M.D.

NDA 207145 Sildenafil (XADAGO)

Sildenafil (XADAGO)

- Overall, the analyses of several phase 3 pivotal trials in ESPD and LSPD and appropriate pools of these trials showed an increased risk (based upon a numerically greater incidence for a sildenafil treatment compared to the incidence of the respective placebo) for numerous “abnormal thresholds” (as defined) and for various positional analyses (i.e., supine, standing, change from supine to standing).

- In Study 15, Table 85 shows results for various “abnormal” outliers for sildenafil vs placebo. I consider the following sildenafil outliers most worthy of notation :
 - low SBP (i.e., $SBP \leq 90$) upon standing and mostly for the high dose of 200 mg
 - high DBP ≥ 105 when supine and standing for both 100 mg and 200 mg
 - SBP increase ≥ 20 for both 100 mg and 200 mg when supine and standing and notable magnitude for sildenafil incidence data
 - SBP decrease ≥ 40 when standing only for 200 mg
 - DBP increase ≥ 10 when supine and standing for both doses and notable magnitude for sildenafil incidence data
 - DBP increase ≥ 20 when supine and standing for both doses and notable magnitude for sildenafil incidence data
 - orthostatic DBP decrease ≥ 10 for 100 mg
 - pulse increase ≥ 15 BPM when supine and standing for both doses and notable magnitude for sildenafil incidence data

- In Study MOTION, Table 86 shows results for various “abnormal” outliers for sildenafil vs placebo. I consider the following sildenafil outliers most worthy of notation :
 - low SBP (i.e., $SBP \leq 90$) upon standing and only for 50 dose
 - SBP decrease ≥ 20 for both 50 mg and 100 mg doses when supine and standing and notable magnitude for sildenafil incidence data
 - DBP decrease ≥ 10 when supine and standing for both doses and notable magnitude for sildenafil incidence data
 - DBP decrease ≥ 20 when supine and standing for both doses and notable magnitude for sildenafil incidence data
 - orthostatic DBP decrease ≥ 10 for 50 mg
 - pulse increase ≥ 15 BPM when supine and standing for both doses and notable magnitude for sildenafil incidence data

- In Study 16, Table 87 shows results for various “abnormal” outliers for sildenafil vs placebo. I consider the following sildenafil outliers most worthy of notation :
 - low SBP (i.e., $SBP \leq 90$) when supine and standing for both 50 mg and 100 mg doses and notable magnitude for standing sildenafil incidence data
 - SBP increase ≥ 40 for supine and standing for 50 mg
 - DBP decrease ≥ 10 when supine and standing for both doses and notable magnitude for sildenafil incidence data
 - DBP decrease ≥ 20 when supine and standing for both doses

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NDA 207145 Safinamide (XADAGO)

Safinamide (XADAGO)

- orthostatic DBP increase ≥ 10 for both doses and notable magnitude for safinamide incidence data
 - pulse decrease ≥ 15 BPM when supine and standing for both doses and notable magnitude for safinamide incidence data
- In Study SETTLE, Table 88 shows results for various “abnormal” outliers for safinamide vs placebo. I consider the following safinamide outliers most worthy of notation :
 - low SBP (i.e., $SBP \leq 90$) when supine and standing for 100 mg dose
 - SBP decrease ≥ 20 when supine and standing for 100 mg dose
 - DBP increase ≥ 10 when supine and standing for 100 mg dose and notable magnitude for safinamide incidence data
 - DBP decrease ≥ 10 when supine and standing for 100 mg dose and notable magnitude for safinamide incidence data
 - pulse increase ≥ 15 BPM when supine and standing for 100 mg dose and notable magnitude for safinamide incidence data
- Table 89 shows the incidence of orthostatic hypotension for Study 16 over time and indicated that the only consistent orthostatic hypotensive outlier was for a modest decrease in DBP (≥ 10 but not ≥ 20) when changing from supine to standing position. This increased risk that seemed apparent for both 50 mg and 10 mg doses was only evident in the early part of treatment (i.e., between weeks 4-12) and was not evidence at week 24 nor the end of treatment for completers at week 24 and patients who discontinued prematurely and had data collected at a final trial visit.
- Based upon review of all of these outlier analyses for pivotal trials in ESPD and LSPD, it appears that safinamide treatment has the potential to be associated with many complex changes in SBP and DBP (sometimes positional) and in some instances modest changes in heart rate pulse. The blood pressure changes include increases and decreases. Considering that I am only recommending approval of safinamide for treatment of LSPD, I recommend noting these increased risks for blood pressure increases and decreases that were observed in LSPD in the label. It is relevant to note that there was a noteworthy increased risk for hypertension/increased blood pressure in Studies 16 and SETTLE in LSPD based upon analyses of TEAEs. It is also relevant to recognize that labels for Parkinson's disease that increase dopaminergic tone have class labeling that describes an increased risk for hypotension/orthostatic hypotension. Several other labels for drugs indicated for LSPD (i.e., Azilect/rasagiline, Requip XL/extended release ropinirole, Neupro/rotigotine) also describe a risk for elevation of blood pressure or hypertension.
- Because the risk for pulse/heart rate changes were not consistent in both pivotal trials for LSPD and were relatively small/modest, I do not believe that it is important to describe this information in the safinamide label.

Ambulatory Blood Pressure Monitoring for MOTION and SETTLE Studies

Clinical Review

Leonard P. Kapcala, M.D.

NDA 207145 Sildenafil (XADAGO)

Sildenafil (XADAGO)

The following is the sponsor's summary of the evaluation of ambulatory blood pressure monitoring/data collection.

Ambulatory blood pressure monitoring (ABPM) was performed on a limited number of subjects (~10%). This procedure was performed in patients participating in the MOTION and SETTLE studies only.

Ambulatory BP values were collected in a subset of patients in the MOTION (n=77) and SETTLE (n=51) studies to assess the effect of sildenafil (50-100 mg/day) on dietary tyramine-induced blood pressure changes. These measurements were performed at Baseline, Week 6, and Week 20, prior to (0 min) and at various time points after meal consumption (60, 90, 120, 150, 180, 210, 240, and ≥ 270 min). The results of ABPM monitoring did not detect any systematic pattern of change in systolic and diastolic BP between sildenafil treatment and placebo in either of the two studies.

A pooled analysis was performed in 117 patients who participated in the ABPM monitoring in the two studies. Most subjects in the sildenafil (49 [92.5%] patients) and placebo (31 [96.9%] patients) groups had post-prandial SBP change ≥ 30 mmHg at baseline. A majority of subjects in the sildenafil and placebo groups had SBP change ≥ 30 mmHg at Week 6 (41 [77.4%] vs. 28 [87.5%], respectively) and Week 20 (42 [79.2%] vs. 25 [78.1%], respectively). Results were similar for the 50 and 100 mg/day sildenafil dose groups and placebo for outliers with a post-prandial increase of ≥ 20 or ≥ 30 mm Hg at weeks 6 and 20 during treatment.

Overall, the results of the ABPM assessments did not indicate any post-prandial effects of sildenafil on BP changes related to dietary tyramine consumption.

Reviewer Comment

- I agree with the sponsor's assessment that there did not appear to be an increased risk for sildenafil-induced increases in SBP related to eating.

7.4.4 Electrocardiograms (ECGs)

Central Tendency Analyses

The sponsor conducted central tendency analyses for ECG parameters (PR interval, QRS interval, QTcFridericia, QTc Bazett) showing mean results and mean change from baseline over time according to treatment for the pooled results from for each pivotal trial and the pool of Studies 15 and MOTION, and the pool of Studies 16 and SETTLE.

Reviewer Comment

- My review of the central tendency analyses for these pivotal trials and the pools of trials did not suggest any clear changes in ECG parameters that are noteworthy.

Outlier Analyses

The sponsor conducted outlier analyses for heart rate (< 50 or >120 BPM), PR Interval (> 200 msec), QRS interval (> 100 msec), QTcF (different thresholds ranging from 320-< 350 up to > 500 msec), QTcF change from baseline (> 30-60 msec increase, > 60 msec increase) according to randomized treatment for the individual, pivotal trials and pools of trials. The sponsor also conducted shift analyses of ECG interpretations from normal or abnormal at baseline to normal or abnormal on treatment according to randomized treatment for the individual, pivotal trials and pools of trials.

The sponsor conclude that there were no remarkable differences in outlier results for sildenafil vs placebo in the various analyses.

Reviewer Comment

- My review of the outlier analyses for these pivotal trials and the pools of trials did not suggest any clear changes in ECG parameters that are noteworthy.

7.4.5 Special Safety Studies/Clinical Trials

Thorough QT Trial (TQT)

The sponsor conducted a double-blinded, placebo-controlled TQT investigating the effects of an oral 100 mg dose and a suprathreshold dose (350 mg) along with a moxifloxacin positive control. The sponsor concluded that there was not significant QTc pro

The following summarizes the consult from the Interdisciplinary Review QT Team (IRQT) for the sponsor's TQT trial.

“OVERALL SUMMARY OF FINDINGS

No significant QTc prolongation effect of sildenafil (100 mg and 350 mg) was detected in this TQT study. The largest upper bounds of the 2-sided 90% CI for the mean difference between sildenafil (100 mg and 350 mg) and placebo were below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines. The largest lower bound of the two-sided 90% CI for the $\Delta\Delta$ QTcF for moxifloxacin was greater than 5 ms, and the moxifloxacin profile over time is adequately demonstrated in Figure 4, indicating that assay sensitivity was established.

In this randomized, blinded, four-arm parallel study, 240 healthy subjects received sildenafil 100 mg, sildenafil 350 mg, placebo, and a single oral dose of moxifloxacin 400 mg. Overall summary of findings is presented in Table 90.

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Table 90 Point Estimate and the 90 % Confidence Intervals (Cis) Corresponding to the Largest Upper Bounds for Safinamide (100 mg and 350 mg) and the Largest Lower Bound for Moxifloxacin (FDA Analysis)

Treatment	Time (hour)	$\Delta\Delta\text{QTcF}$ (ms)	90% CI (ms)
Safinamide 100 mg	0	-0.8	(-4.2, 2.6)
Safinamide 350 mg	0	-2.3	(-5.8, 1.1)
Moxifloxacin 400 mg*	2	11.5	(7.1, 16.0)

* Multiple endpoint adjustment of 3 time points was applied.

Reviewer Comment

- I agree with the conclusion of the sponsor and of the IRQT that there was no significant QTc prolongation with 100 mg or 350 mg of safinamide.

Tyramine Challenge Trial

The sponsor had conducted two tyramine challenge studies (TYR-268-00 with oral tyramine, and 03-101 with IV tyramine) to assess and characterize tyramine sensitivity to safinamide treatment because monoamine oxidase inhibition (supposedly “selective” for MAO-B inhibition) is a major pharmacodynamic effect of safinamide and possibly its main mechanism of action for treating Parkinson's disease. Because the Division of Neurology Products (DNP) did not consider that these trials were adequately designed to characterize tyramine sensitivity adequately, the DNP recommended that the sponsor conduct another trial to adequately characterize sensitivity to oral tyramine after safinamide treatment and gave the sponsor detailed recommendations for the study design of this trial. **The sponsor conducted Trial 28599 and incorporated DNP’s most important and key recommendations.** This trial was a randomized, double-blinded, placebo-controlled trial which included the highest recommended daily safinamide dose (100 mg), a supratherapeutic dose (350 mg), a “positive” control (phenelzine), and an FDA approved MAO-B inhibitor (oral selegiline) as a comparator. The following information presents the results from that trial.

Primary Objective

The primary objective of the trial was to evaluate the potentiation of the pressor effect of oral tyramine by safinamide 100 mg (therapeutic dose) at steady-state versus placebo.

Secondary Objectives

The secondary objectives of the trial were:

- To evaluate the potentiation of the pressor effect of oral tyramine by safinamide 350 mg (supratherapeutic dose) at steady-state versus placebo;
- To demonstrate the sensitivity of the trial via the potentiation of the pressor effect of oral tyramine by phenelzine 30 mg versus placebo;

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- To evaluate the potentiation of the pressor effect of oral tyramine by selegiline (comparator control) at steady-state versus placebo;
- To evaluate the safety of safinamide in a multiple-dose regimen, at the expected therapeutic dose as well as at a suprathreshold dose.

The following describes information regarding the study design of the sponsor's key tyramine challenge trial.

Figure 6 Schematic Diagram of Tyramine Challenge Trial Design

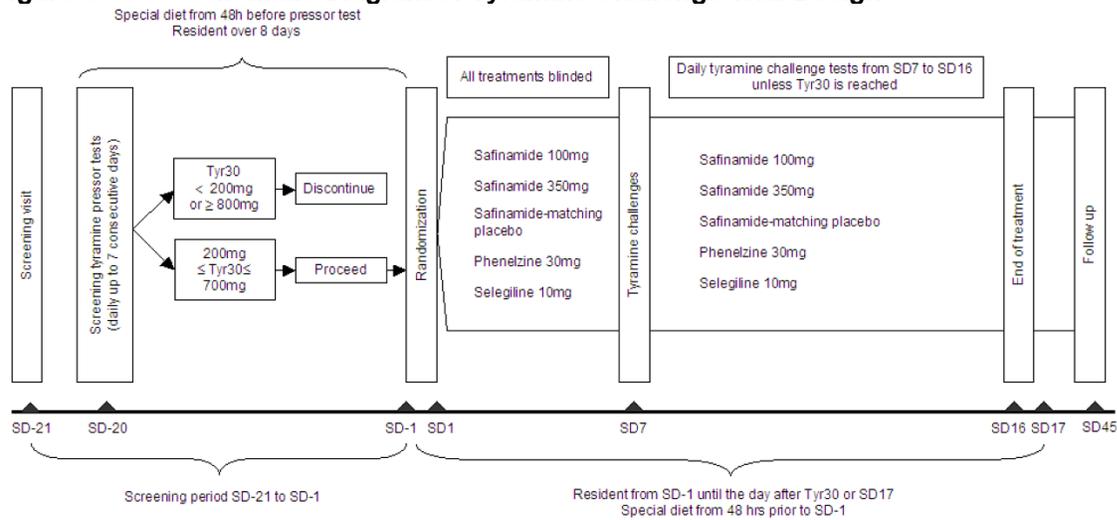


Table 91 Dosage and Administration Schedule of Tyramine during Screening Period

Study Day*	Tyramine (mg)
SD-7	100
SD-6	200
SD-5	300
SD-4	400
SD-3	500
SD-2	600
SD-1	700

* The Study Days mentioned in the table are for indication; tyramine challenges could be performed within 21 days prior to SD1, not necessarily from SD-7 to SD-1.

Table 92 Dosage and Administration Schedule of Tyramine during Treatment Period

Study Day	Tyramine (mg)	
	Phenelzine treatment group	Safinamide/placebo and selegiline treatment groups
SD7	6.25	25
SD8	12.5	50
SD9	25	100
SD10	37.5	150
SD11	50	200
SD12	75	300
SD 13	100	400
SD 14	125	500
SD 15	150	600
SD 16	200	700

Table 93 presents demographic characteristics of the healthy subjects in this trial.

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Table 93 Demographic Characteristics of Placebo-Controlled Tyramine Challenge Trial

Demographic characteristic	Statistics	Safinamide 100 mg (n=18)	Safinamide 350 mg (n=18)	Phenelzine 30 mg (n=17)	Selegiline 10 mg (n=18)	Placebo (n=18)	Total (n=89)
Age (yrs)	Mean (s.d.)	39.8 (14.9)	41.2 (11.5)	40.6 (11.1)	43.2 (13.5)	38.8 (10.9)	40.7 (12.3)
	Min ;Max	20 ;70	24 ;62	24 ;59	20 ;68	21 ;55	20 ;70
Age in class, n(%)	<=45 years old	10 (55.6)	11 (61.1)	11 (64.7)	9 (50.0)	12 (66.7)	53 (59.6)
	>45 years old	8 (44.4)	7 (38.9)	6 (35.3)	9 (50.0)	6 (33.3)	36 (40.4)
Sex, n(%)	Male	9 (50.0)	9 (50.0)	9 (52.9)	9 (50.0)	9 (50.0)	45 (50.6)
	Female	9 (50.0)	9 (50.0)	8 (47.1)	9 (50.0)	9 (50.0)	44 (49.4)
Race, n(%)	White	17 (94.4)	16 (88.9)	13 (76.5)	16 (88.9)	15 (83.3)	77 (86.5)
	Black	0 (0.0)	2 (11.1)	3 (17.6)	1 (5.6)	3 (16.7)	9 (10.1)
	Asian	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Other	1 (5.6)	0 (0.0)	1 (5.9)	1 (5.6)	0 (0.0)	3 (3.4)
Height (cm)	Mean (s.d.)	168.4 (9.1)	170.3 (8.5)	172.1 (8.7)	168.5 (10.2)	169.1 (9.5)	169.7 (9.1)
	Min ;Max	155 ;186	155 ;183	156 ;190	146 ;188	156 ;188	146 ;190
Weight (kg)	Mean (s.d.)	67.33 (12.55)	65.72 (12.90)	71.18 (11.13)	68.17 (11.63)	69.89 (14.39)	68.43 (12.45)
	Min ;Max	47.0 ;94.0	47.0 ;92.0	54.0 ;97.0	48.0 ;93.0	47.0 ;97.0	47.0 ;97.0
BMI (kg/m ²)	Mean (s.d.)	23.64 (3.40)	22.50 (3.03)	23.95 (2.62)	23.93 (2.95)	24.23 (3.44)	23.65 (3.10)
	Min ;Max	18.6 ;29.8	18.7 ;27.5	20.3 ;29.1	19.3 ;29.6	18.4 ;29.8	18.4 ;29.8

Source: [Table 15.1.2.1](#), [Listing 16.2.4.1](#)

Table 94 shows the percentage of subjects who achieve a TYR30 threshold (i.e., 3 consecutive increases of systolic blood pressure (SBP) of 30 mm Hg or higher above pre-treatment SBP after oral tyramine challenge according to tyramine dose .

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Table 94 Percentage (%) of Subjects with TYR30 Threshold Systolic Blood Pressure Increase Before (Pre-Rx) and After (Post-Rx) Treatment (Placebo, Safinamide, Selegiline or Phenzelzine) for Different Tyramine Challenge Doses

Tyramine Dose	Placebo N=18		Safinamide 100 mg N=18		Safinamide 350 mg N=18		Selegiline 10 mg N=18		Phenelzine 30 mg N=17	
	Pre-Rx	Post-Rx	Pre-Rx	Post-Rx	Pre-Rx	Post-Rx	Pre-Rx	Post-Rx	Pre-Rx	Post-Rx
6.25 mg										6
12.5 mg										12
25 mg		6		6		18		11		24
37.5 mg										12
50 mg		0		6		18		6		18
100 mg		6		22		6		6		12
125 mg		0								12
150 mg		11		11		6		39		6
200 mg	6	11	22	11	0	6	0	22	12	
300 mg	6	11	6	17	28	0	28	17	29	
400 mg	28	17	22	11	50	41	39		24	
500 mg	44	11	17	11	22	6	11		29	
600 mg	6	11	28	0	0		11		0	
700 mg	11	17	6	6	0		11		6	
≤ 25 mg	0	6	0	6	0	17	0	11	0	41
≤ 50 mg	0	6	0	11	0	33	0	17	0	71
≤ 100 mg	0	11	0	33	0	39	0	22	0	94
≤ 150 mg	0	22	0	44	0	44	0	61	0	100
≤ 200 mg	6	33	22	56	0	50	0	83	12	

Results (%) are shown only when tyramine dose was administered; Yellow highlights indicate treatment-induced tyramine sensitivity vs placebo.

Table 95 describes statistics (arithmetic mean, geometric mean, median, minimum and maximum) for the tyramine sensitivity factor (pre-treatment tyramine dose for TYR30/post-treatment tyramine dose for TYR30; TSF) according to treatment. Table 96 summarizes ANOVA TSF results for the different treatments compared to placebo.

Table 97 shows effects of the various treatments on tyramine dose required to achieve a TYR30 threshold relative to the pre-treatment TYR30 dose.

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Table 95 Descriptive Statistics of Tyramine Sensitivity Factor (TSF)

Statistics	Safinamide 100 mg (n=18)	Safinamide 350 mg (n=18)	Phenelzine 30 mg (n=17)	Selegiline 10 mg (n=18)	Placebo (n=18)
n (missing)	18 (0)	17 (1)	17 (0)	18 (0)	18 (0)
Mean (s.d.)	2.994 (2.965)	4.775 (4.962)	13.843 (14.400)	3.861 (3.269)	2.459 (3.700)
Geometric Mean	2.152	2.740	9.977	3.115	1.515
Median	1.833	2.500	10.667	2.667	1.000
Min ;Max	0.80 ;12.00	0.75 ;16.00	3.33 ;64.00	1.67 ;12.00	0.71 ;16.00

Source: [Table 15.5.1.1.1](#) and [Listing 16.2.9.1](#)

Table 96 Summary of Back-transformed ANOVA Results for TSF in Original-Scale

Contrasts	Ratio (%)	90% CI of Ratio(L)	90% CI of Ratio(U)
Safinamide 100 mg vs. Placebo	155.9	102.5	237.0
Safinamide 350 mg vs. Placebo	175.3	114.9	267.6
Phenelzine 30 mg vs. Placebo	598.2	391.1	914.7
Selegiline 10 mg vs. Placebo	218.7	144.0	332.1

L: Lower limit of 90%CI

U: Upper Limit of 90%CI

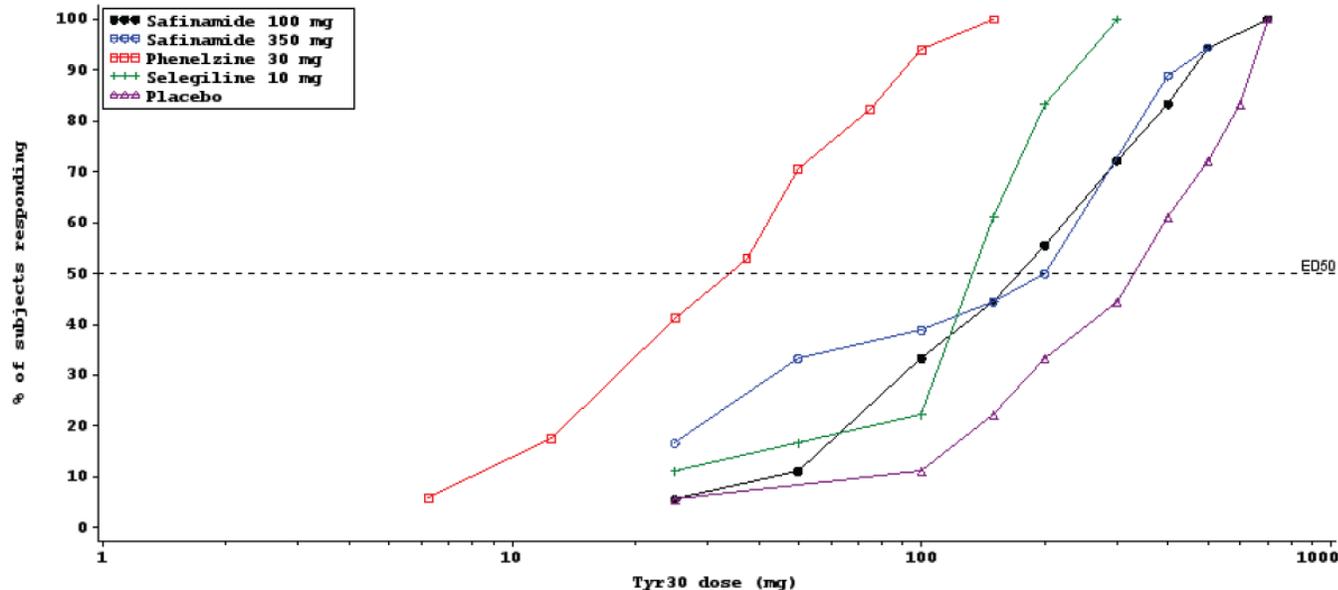
Source: [Table 15.5.1.3.1](#) and [Listing 16.1.9.2.1.1](#)

Table 97 Descriptive Statistics of Tyr30 and ED50 for Tyramine Dosing Before and After Treatment

Timepoint	Statistics	Safinamide 100 mg (n=18)	Safinamide 350 mg (n=18)	Phenelzine 30 mg (n=17)	Selegiline 10 mg (n=18)	Placebo (n=18)
Tyr30 Screening	n (missing)	18 (0)	18 (0)	17 (0)	18 (0)	18 (0)
	Mean (SD)	438.889 (164.992)	394.444 (72.536)	394.118 (129.762)	438.889 (133.456)	472.222 (122.741)
	Median	450.000	400.000	400.000	400.000	500.000
	Min ;Max	200.00 ;700.00	300.00 ;500.00	200.00 ;700.00	300.00 ;700.00	200.00 ;700.00
Tyr30 Under treatment	n (missing)	18 (0)	17 (1)	17 (0)	18 (0)	18 (0)
	Mean (SD)	254.167 (185.554)	233.824 (180.698)	50.368 (38.557)	163.889 (83.235)	384.722 (219.816)
	Median	200.000	200.000	37.500	150.000	400.000
	Min ;Max	25.00 ;700.00	25.00 ;500.00	6.25 ;150.00	25.00 ;300.00	25.00 ;700.00
Tyr30 Change from Baseline	n (missing)	18 (0)	17 (1)	17 (0)	18 (0)	18 (0)
	Mean (SD)	-184.722 (173.022)	-166.176 (171.833)	-343.750 (120.708)	-275.000 (93.934)	-87.500 (213.901)
	Median	-150.000	-250.000	-350.000	-250.000	0.000
	Min ;Max	-500.00 ;100.00	-450.00 ;100.00	-650.00 ;-150.00	-500.00 ;-150.00	-600.00 ;200.00
ED 50		200.000	200.000	37.500	150.000	400.000
ED 50 Ratio		2.00	2.00	10.67	2.67	

Figure 7 depicts the cumulative distribution of TYR30 doses for each treatment. Table 98 shows various central tendency results according to treatment for TYR30 threshold based upon a single SBP increase of TYR30,, or 2 or 3 consecutive increases of TYR30.

Figure 7 Cumulative Frequency Distribution of Tyr30 Values by Treatment Group



Source: Listing 16.2.9.2.1

Table 98 shows a comparison of central tendency presentations of TSF according to tyramine threshold dose determined from a single threshold increase of systolic blood pressure (> 30 mm hg), two consecutive threshold increases, or three consecutive threshold increases.

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Table 98 Comparison of Central Tendency Presentations of TSF According to Tyramine Threshold Dose Determined from a Single Threshold Increase of Systolic Blood Pressure (> 30 mm Hg), Two Consecutive Threshold Increases, or Three Consecutive Threshold Increases

Central Tendency Presentations (Geometric Mean, Arithmetic Mean, Median) of TSF for Different Criteria for Determining TYR30 Threshold Dose		Placebo	Safinamide (100 mg daily)	Safinamide (350 mg daily)	Selegiline (10 mg daily)	Phenelzine (30 mg daily)
N		18	18	18	18	17
n (missing)						
	TYR30 ₃ TSF	18 (0)	18 (0)	17 (1)	18 (0)	17 (0)
	TYR30 ₂ TSF	18 (0)	18 (0)	17 (1)	18 (0)	17 (0)
	TYR30 ₁ TSF	18 (0)	18 (0)	18 (0)	18 (0)	17 (0)
Geometric Mean						
	TYR30 ₃ TSF	1.574	2.152	2.740	3.065	9.977
	TYR30 ₂ TSF	1.605	2.233	3.273	2.734	9.492
	TYR30 ₁ TSF	1.651	2.538	3.462	3.255	10.31
Arithmetic Mean (SD)						
	TYR30 ₃ TSF	2.505 (3.683)	2.994 (2.965)	4.775 (4.962)	3.838 (3.287)	13.84 (14.40)
	TYR30 ₂ TSF	2.524 (3.669)	2.997 (2.869)	5.564 (5.445)	3.634 (3.405)	11.63 (7.867)
	TYR30 ₁ TSF	2.569 (3.657)	3.324 (2.891)	5.727 (5.464)	4.204 (3.59)	14.12 (14.74)
Median						
	TYR30 ₃ TSF	1.125	1.833	2.500	2.667	10.67
	TYR30 ₂ TSF	1.250	1.833	2.500	2.583	10.00
	TYR30 ₁ TSF	1.250	2.250	3.250	2.667	8.000
Range (Min-Max)						
	TYR30 ₃ TSF	0.71 - 16	0.80 - 12	0.75 - 16	1.25 - 12	3.33 - 64
	TYR30 ₂ TSF	0.57 - 16	0.80 - 12	0.75 - 16	1.00 - 12	3.33 - 32
	TYR30 ₁ TSF	0.57 - 16	1.00-12	0.75 - 16	1.33 - 12	4.00 - 64

TYR30₃ = Tyramine threshold dose based upon 3 consecutive increments (compared to mean pre-tyramine SBP) of supine SBP of ≥ 30 mm Hg when 3 consecutive SBP measurements meet that threshold within 4 hours of tyramine administration

TYR30₂ = Tyramine threshold dose based upon 2 consecutive increments (compared to mean pre-tyramine SBP) of supine SBP of ≥ 30 mm Hg when 3 consecutive SBP measurements meet that threshold within 4 hours of tyramine administration

TYR30₁ = Tyramine threshold dose based upon the first increment (compared to mean pre-tyramine SBP) of supine SBP of ≥ 30 mm Hg when a SBP measurement meets that threshold within 4 hours of tyramine administration

Source: Study 28558, advs.sas7bdat

Notes:

Subject 285580010045 (Safinamide 350 mg) completed the On Treatment Period on Day 12, without achieving either 2 or 3 consecutive SBP measurements ≥ 30 mm Hg compared to baseline. Therefore, only TSF30₁ could be derived for this subject.

Sponsor's Conclusions

The sponsor concluded that safinamide 100 mg (therapeutic dose) and 350 mg (supratherapeutic dose) induced a mild increase in tyramine sensitivity and that this effect was slightly dose-dependent. However, this increased tyramine sensitivity with safinamide was less than that of the comparator oral selegiline for which there is no dietary tyramine restriction in its label. The sponsor also thought that the risk for a hypertensive crisis with safinamide treatment was very low and that dietary tyramine restriction was not warranted for the safinamide label.

Reviewer Comment

- Table 94 clearly shows that each treatment increased the percentage of subjects who achieved TYR30 threshold at lower tyramine doses (25 mg-200 mg) compared to pre-treatment. The percentage of subjects with a TYR30 for each active drug (safinamide, selegiline, phenelzine) was notably greater at the lowest tyramine doses vs placebo. The increase in the percentage of subjects with lower TYR dose was significantly greater for

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the suprathreshold dose vs the therapeutic dose. However, the selegiline effect at most low doses (25 mg-200 mg) on these percentages was greater than the effect of 100 mg safinamide. The effect of phenelzine was markedly greater than effects of safinamide or selegiline.

- Table 95 showed that the TSF for each treatment (safinamide, selegiline, phenelzine) was notably greater than that for placebo with respect to geometric mean, arithmetic mean, and median) and indicated an increase in tyramine sensitivity. The TSF for the 350 mg dose was greater for each of the central tendency values than the respective values for 100 mg safinamide. The geometric mean and median TSF for both safinamide doses was less than the respective TSFs for selegiline and the arithmetic mean TSF for 100 mg safinamide was less than that for selegiline.
- Table 96 shows that the lower bound of the 90 % confidence intervals for each drug (vs placebo) was above 100 % of that of placebo.
- Table 97 shows that each treatment decreased the tyramine dose required to achieve the TYR30 threshold and the magnitude of the tyramine dose reduction for each treatment. The magnitude of the mean decrease in tyramine dose was smallest for placebo, larger for each safinamide dose, even larger for selegiline, and greatest for phenelzine. The reductions in tyramine dose for achieving TYR30 reflected the increased tyramine sensitivity with each treatment and the degree of increase in tyramine sensitivity.
- Figure 7 illustrates how the distribution of tyramine doses for achieving a TYR30 shift to the left (indicating increased tyramine sensitivity) for each treatment relative to placebo. The distribution of TSFs for safinamide was largely overlapping for both doses and generally similar to the distribution for selegiline. The distribution of TSFs for phenelzine, the positive control, was markedly shifted to the left of all other treatments.
- Table 98 shows the more reliable TSF results appear to be obtained when one applies a requirement of at least 2 or 3 successive results at or above the SBP threshold (> 30 mm Hg), compared to a single threshold result and that perhaps the most reliable results are suggested when one applies a requirement for 3 consecutive SBP increases at or above this minimal threshold.
- I conclude that there is a distinct increase (but relatively small or modest increase) in tyramine sensitivity for the highest safinamide dose (100 mg) proposed for marketing. Although the increase in tyramine sensitivity was even greater for the suprathreshold dose (350 mg), this dose-dependent increase was relatively small for a 3.5 fold increase in dose and suggested a shallow dose-response curve. Of significant relevance, overall, the increase in tyramine sensitivity of 100 mg safinamide was notably less than the increase in tyramine sensitivity for selegiline, an FDA approved, “selective” MAO-B inhibitor which does not have any dietary restriction for tyramine and which was also investigated as a comparator for safinamide. I also conclude : 1) that this safinamide-

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induced increase in tyramine sensitivity does not warrant dietary tyramine restriction; and 2) that this effect can be described in labeling as is a similar, small increase in tyramine sensitivity produced by rasagiline, another “selective” MAO-B inhibitor approved by the Agency for treatment of Parkinson's disease.

7.4.6 Immunogenicity

Not applicable

7.5 Other Safety Explorations

The sponsor conducted subgroup analyses all safety parameters. More specifically these subgroup analyses were for all types of adverse events (i.e., any TEAE, SAEs, TEAEs causing study discontinuation), laboratory findings, vital signs, and ECGs for various subgroups including geographic region, (North America, non-North America, Western Europe, All Other Regions excluding North America), gender, age (< 65 years, ≥ 65 years), presence or absence of dopaminergic agonist, and presence or absence of blood pressure lowering drug.

Results of specific subgroup analyses are only presented where there is a suggestion of a signal for a safinamide differential effect on a particular subgroup.

7.5.1 Dose Dependency for Adverse Events

The sponsor presented all adverse event analyses (for individual trials and pools of trials) including analyses of any TEAE, SAEs, and TEAEs causing study discontinuation according to randomized treatment and also for “any safinamide dose” in which all safinamide doses were combined.

Reviewer Comment

- My Reviewer Comments in section 7.4.1 Common Adverse Events describe dose-related/-dependent TEAEs. There were several instances in different trial analyses where the incidence of a specific TEAE for a higher safinamide dose was greater than the incidence for a lower dose and my comment suggested a dose-re
- Overall, it was difficult to conclude that the incidence of specific SAEs or specific TEAEs causing study discontinuation were dose-related because the incidence of most specific SAEs and specific TEAEs causing study discontinuation was based upon a single patient in a treatment group.

7.5.2 Time Dependency for Adverse Events

Two trials (Study 15 for ESPD and Study SETTLE for LSPD), both of which were 6 month trials) included a titration period in which they were titrated to the randomized treatment. In

response to DNP requests, the sponsor conducted specific time-dependent analyses for these trials in which all TEAEs, SAEs, and TEAEs causing study discontinuation were analyzed for : 1) their onset in the titration period; 2) their onset in the maintenance period (i.e., period after end of titration period until end of trial or treatment; and 3) their onset in the titration period and persisting into the maintenance period with a duration of at least 7 days in the maintenance period (i.e., considered as “persistent”).

Description of Dose Titration

The end of the titration period was longer than the time to reach the highest targeted dose according to the protocol-specified titration. The maintenance period started at the end of the titration period.

Study 15

Patients randomized to Low Dose (100 mg/day target dose) started at a dose of 50 mg/day on Day 0 and were to remain at that dose level for 2 weeks, before being titrated up to their target dose of 100 mg/day on Day 14, provided there were no dose-limiting side effects.

Patients randomized to High Dose (200 mg/day target dose) started at a dosage of 100 mg/day on Day 0. On Day 7, their dose was to be increased to 150 mg/day. They were titrated up to their target dose of 200 mg/day on Day 14, provided there were no dose-limiting side effects.

The total titration period was considered to be 4 weeks.

Study SETTLE

Subjects started on Day 0 at 50 mg and remained at that dose for two weeks before being titrated up to their target dose (100 mg) if the 50 mg dose was tolerated,

The total titration period was considered to be 4 weeks (2 weeks after titration to the highest dose).

My presentation of time-dependent TEAEs for which there appeared to be an increased risk focuses on specific TEAEs occurring with a sildenafil treatment difference (sildenafil dose % - placebo %) of ≥ 2 % based upon rounded off incidence data.

Study 15

Titration Period

There was an increased risk for the following TEAEs in the titration period : nausea, abdominal pain/discomfort, somnolence, hypertension/increased blood pressure, blood glucose

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increased/hyperglycemia, paresthesia, peripheral edema, influenza-like illness, influenza, nasopharyngitis, orthostatic hypotension, and cough.

There was no notably increased risk for any specific SAEs or TEAEs causing study discontinuation in the titration period.

Maintenance Period

There was an increased risk for the following TEAEs in the maintenance period : hypertension/increased blood pressure , urine protein, blood triglycerides increased/hypertriglyceridemia, dizziness, tremor, nasopharyngitis, bronchitis, upper respiratory tract infection ,back pain, arthralgia, pain in extremity, chest pain, pain, blood creatinine increased, vision blurred, anxiety, and sleep disorder.

There was no notably increased risk for any specific SAEs or TEAEs causing study discontinuation in the maintenance period.

Persistent

There was an increased risk for the following persistent TEAEs : abdominal pain/discomfort, blood glucose increased/hyperglycemia , back pain, and cough.

There was no notably increased risk for any specific SAEs or TEAEs as being persistent.

Study SETTLE

Titration Period

There was an increased risk for the following TEAEs in the titration period : dyskinesia and dyspepsia.

Maintenance period

There was an increased risk for the following TEAEs in the maintenance period : dyskinesia, dizziness, bronchitis, nausea, pain in extremity, insomnia, anxiety, fall, contusion, and decreased appetite.

There was no notably increased risk for any specific SAEs or TEAEs causing study discontinuation in the maintenance period.

Persistent

There was an increased risk for the following persistent TEAEs : dyskinesia and somnolence.

There was no notably increased risk for any specific SAEs or TEAEs causing study discontinuation as being persistent.

Reviewer Comment

- The results of the time-dependent analyses summarized above here indicated that certain TEAEs have an increased risk (i.e., with at least 2 % or higher treatment difference for a sildenafil dose incidence compared to placebo incidence) for occurring in the titration period, in the maintenance period, or developing in the titration period and persisting into the maintenance period and have a minimal duration of 7 days or longer.
- For Study 15, certain TEAEs appeared to have an increased risk for onset **only** in the titration period or **only** in the maintenance period. TEAEs that appeared to have an increased risk for onset **only** in the titration period were : nausea, abdominal pain/discomfort, somnolence, blood glucose increased/hyperglycemia, paresthesia, peripheral edema, influenza-like illness, influenza, orthostatic hypotension, and cough. TEAEs that appeared to have an increased risk for onset **only** in the maintenance period were : urine protein, blood triglycerides increased/hypertriglyceridemia, dizziness, tremor, bronchitis, upper respiratory tract infection ,back pain, arthralgia, pain in extremity, chest pain, pain, blood creatinine increased, vision blurred, anxiety, and sleep disorder.
- For Study 15, certain TEAEs appeared to have a relatively sustained duration based upon their onset in the titration period and persistence into the maintenance period and having a duration of at least 7 days or longer. Such TEAEs are : abdominal pain/discomfort, blood glucose increased/hyperglycemia , back pain, and cough.
- For Study 16, certain TEAEs appeared to have an increased risk for onset **only** in the titration period or **only** in the maintenance period. TEAEs that appeared to have an increased risk for onset **only** in the titration period were : dyspepsia. TEAEs that appeared to have an increased risk for onset **only** in the maintenance period were : dizziness, bronchitis, nausea, pain in extremity, insomnia, anxiety, fall, contusion, and decreased appetite.
- For Study 16, certain TEAEs appeared to have a relatively sustained duration based upon their onset in the titration period and persistence into the maintenance period and having a duration of at least 7 days or longer. Such TEAEs are : dyskinesia and somnolence.
- I believe that these time-dependent increased risks for certain TEAEs should be described in labeling only for the population (e.g., LSPD) for whom sildenafil would be approved (based upon this reviewer's assessment and belief).

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7.5.3 Drug-Demographic Interactions

My review focused on assessing drug-demographic interaction by specifically focusing on effects of gender, age (≥ 65 years old vs < 65 years old), race (Caucasian vs Asian), and geographic region (especially North America vs non-North America) particularly for the incidence of at least one TEAE (when all TEAEs are combined), TEAEs possibly suggestive of falls, and TEAEs possibly suggestive of hypotension/orthostatic hypotension. To assess possible differences, I focused on calculating the relative risk for each treatment for each subgroup (e.g., % with any TEAE for sildenafil 50 mg **for males**/ % with any TEAE for sildenafil 50 mg **for females**) and then compared the relative risk for the specific sildenafil doses compared to the relative risk for placebo for each of the respective demographic subgroups.

There were no clear, noteworthy differences in the overall incidence of **all** TEAEs combined for the pivotal trial analyses (i.e., Studies 15, MOTION, 15 and MOTION, 15 and 17, 16, SETTLE, 16 and SETTLE, 16 and 18) for any specific dose of sildenafil treatment vs placebo treatment for the respective analyses in each specific trial or trial pool based upon relative risk of the respective treatment groups for the demographic variables of gender, race, and age.

Comparison of the incidence of specific TEAEs in North America vs outside of North America was conducted because past experience has suggested that the incidence of all types of TEAEs in general is greater in North America than outside of North America. The following specific TEAEs had a notably more frequent treatment difference incidence (specific sildenafil dose % - placebo %) of at least 5 % (or higher) for North America (vs outside of North America) for terminal insomnia, GGT increased, cough, dysphonia, pollakiuria, and eczema in Study MOTION, and for dyskinesia, nausea, urinary tract infection, fall, contusion, and hypoesthesia in Study SETTLE. Study SETTLE and MOTION were the only pivotal trials enrolling patients from North America. Although each of these trials enrolled patients from North America, the percentage of patients from North America vs outside of North America was relatively small (14 % in MOTION and 19 % in SETTLE).

There appeared to be some noteworthy differences in the sildenafil-related risk for TEAEs possibly suggestive of falls and for TEAEs possibly suggestive of hypotension/orthostatic hypotension relative to race in Study MOTION. The relative risk appeared to be increased for sildenafil in Caucasians compared to Asians for TEAEs possibly suggestive of falls (i.e., TEAEs possibly suggesting falls in Caucasians/ TEAEs possibly suggesting falls in Asians). However, a specific relative risk could not be calculated in some instances for a sildenafil dose when the incidence for Asians was 0 %. When the relative risk cannot specifically be calculated, I present the incidence for each subgroup. The incidence of TEAEs possibly suggestive of falls was 5.6 % for Caucasians vs 0 % for Asians for 50 mg sildenafil, 2.3 % for Caucasians vs 0 % for Asians for 100 mg sildenafil, and the relative risk for Caucasians/Asians was 0.9 for placebo. In addition, there appeared to be an increased relative risk (1.7) for TEAEs possibly suggestive of hypotension/orthostatic hypotension in Caucasians vs Asians in Study SETTLE.

Reviewer Comment

Clinical Review

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- Overall, there were no major drug-demographic interactions for TEAEs in general and TEAEs possibly suggestive of falls or hypotension.
- Some of the drug-demographic interactions described above for race and geographic region are based upon a relatively small percentage of patients in one group (North America, Asians) vs the comparison groups (outside of North America, Caucasians). Consequently, I do not consider the results to be as clearly reliable as they might have been if the percentage of Asians and patients from North America was significantly larger. I do not believe that any drug-demographic interactions need to be described in the label.

7.5.4 Drug-Disease Interactions

There were no apparent drug-disease interactions.

7.5.5 Drug-Drug Interactions

My review for drug-drug interactions for sildenafil and other drugs (e.g., dopaminergic agonists and blood pressure lowering drugs) focused on the 6 month pivotal trials (Studies 15. MOTION, 16, SETTLE, and pools of Studies 15 and MOTION and of Studies 16 and SETTLE). More specifically, I evaluated the relative risk for the incidence of any TEAE, TEAEs possibly suggesting a fall, and TEAEs possibly suggesting hypotension/orthostatic hypotension for each treatment (i.e., each sildenafil dose vs placebo) in patients taking a dopaminergic agonist or blood pressure lowering drug and in patients not taking either of those groups of drugs. Each relative risk was calculated as : incidence of IEAE of interest in patients taking dopaminergic or blood pressure lowering drug/ incidence of IEAE of interest in patients **NOT** taking a respective dopaminergic or blood pressure lowering drug.

The following information describes relative risk when it appeared to be notably increased for a sildenafil dose compared to the relative risk for placebo.

Study 15

There was an increased relative risk (3.5 for 100 mg, 1.0 for 200 mg, 0.8 for placebo) for TEAEs possibly suggestive of hypotension/orthostatic hypotension with 100 mg sildenafil treatment in patients taking a concomitant blood pressure lowering drug.

Study 16

There was an increased relative risk (4.2 for 50 mg, 3.7 for 100 mg, 0.8 for placebo) for TEAEs possibly suggestive of falls with both sildenafil doses in patients taking a concomitant dopaminergic agonist.

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There was an increased relative risk (0.6 for 50 mg, 2.7 for 100 mg, 1.2 for placebo) for TEAEs possibly suggestive of hypotension/orthostatic hypotension with 100 mg safinamide treatment in patients taking a concomitant blood pressure lowering drug.

Pool of Studies 16 and SETTLE

There was an increased relative risk (4.2 for 50 mg, 1.7 for 100 mg, 0.7 for placebo) for TEAEs possibly suggestive of falls with both safinamide doses in patients taking a concomitant dopaminergic agonist.

Reviewer Comment

- There appeared to be a noteworthy increased risk (based upon relative risk assessments) for TEAEs possibly suggestive of a fall associated with the concomitant treatment of a dopaminergic agonist in patients with LSPD. Analysis of the relative risk for the specific TEAE of fall in Study 16 similarly showed an increased risk for each safinamide dose compared to the relative risk for placebo. I believe that this increased risk suggesting a drug-drug interaction between safinamide and a dopaminergic agonist should be described in labeling.
- There appeared to be a noteworthy increased risk (based upon relative risk assessments) for TEAEs possibly blood pressure lowering drug in patients with ESPD and LSPD. I believe that this increased risk suggesting a drug-drug interaction between safinamide and a blood pressure lowering drug should be described in labeling.
- The sponsor assessed the potential of safinamide to alter the pharmacokinetic profile of levodopa and this evaluated did not show an pharmacokinetic interaction. However, the sponsor did not conduct formal clinical pharmacology/pharmacokinetic trials assessing the potential for drug-drug interactions related to pharmacokinetic interactions between safinamide and the many various dopaminergic agonists used in these trials and the many blood pressure lowering drugs. Nevertheless, I believe that the above described drug-drug interactions are more likely to be pharmacodynamics interactions rather than pharmacokinetic interactions.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

There was no evidence nor suggestion of carcinogenicity from safinamide treatment based upon non clinical data and no suggestion of carcinogenic risk in the clinical trials.

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7.6.2 Human Reproduction and Pregnancy Data

The following information was summarized in the sponsor's proposed label regarding human reproduction and pregnancy data.

Pregnancy : Pregnancy Category C

(b) (4)

There are no adequate and well-controlled studies of XADAGO in pregnant women. (b) (4)

(b) (4)

(b) (4)

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Reviewer Comment

- I agree with the sponsor's summary of what information is known and not known regarding human reproduction and pregnancy data.

7.6.3 Pediatrics and Assessment of Effects on Growth

Because sildenafil is not intended for pediatric (patients less than 18 years old) use, no trials have been conducted in pediatric patients.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Overdose

The sponsor noted that there appeared to be one case of "overdose" and another suspicious case of "overdose" in patients with LSPD.

In the one case, the patient took double the sildenafil dose (e.g., 200 mg daily) for 11 days and the patient started experiencing nausea during this overdosage period. The patient's nausea was controlled after withholding the study drug, and it did not recur after the restart of the study drug. The patient also experienced repeated falls during, as well as before, this overdosage period. The repeated falls recurred even after stopping the study drug. Dyskinesia was present before as well as after the start of the study drug. In view of all these factors, the sponsor considered the event of nausea could possibly have been due to the study drug overdose but thought that the frequent falls and dyskinesia were unlikely to be due to the study drug.

In the case of suspected overdose, this suspicion was based upon the patient returning less pills than were supposed to be returned. The study drug accountability record showed discrepancies: the subject was dispensed 108 tablets of 100 mg on 5 Nov 2010 (Study day 337), 42 were returned on 23 Dec 2010 whereas 66 should have been returned. Eighteen tablets of 50 mg were dispensed on 17 Dec 2010 and 6 tablets were returned instead of 12 on 23 Dec 2010. Sildenafil was stopped permanently on 24 Dec 2010. The subject was seen for his final safety visit on 21 Jan 2011 and when asked, could not give a clear history to account for the missing tablets. It is unclear whether he ingested them or if they were misplaced or destroyed. On 21 Jan 2011 a urine drug screen was performed. It was negative for urinary ethanol and cannabinoids. It detected benzotropine and paracetamol. No other drug was detected in this specimen. Confusion, sleepiness, forgetfulness and dilated pupils were resolved on 21 Jan 2011, and the event 'overdose' was considered resolved.

Reviewer Comment

- I do not believe that there were any serious clear cases of sildenafil overdose with any medically serious outcomes.

Withdrawal and Rebound

Sponsor's Summary

Safinamide is associated with a long half-life (~24-26 hours) and thus it is unlikely that withdrawal symptoms would be noted immediately even after an abrupt discontinuation. Based on its long half-life, its CNS effects persist for a number of days. Analyses of the TEAE data did not detect any symptoms suggestive of withdrawal e.g. anxiety, panic attacks, depression, dysphoria, agitation, irritability, insomnia / increased sleeping, increased appetite, muscle pain, drug cravings, on immediate or tapered discontinuation. Treatment practice in Parkinson's disease includes addition of another Parkinson's disease medication when an existing medication is to be discontinued. This further masks the emergence of any withdrawal symptoms. There are no specific analyses available to assess rebound for the above reasons; review of the scores of the limited number of patients who were assessed after discontinuation did not detect any symptoms of rebound.

Analyses were performed to review the incidence of TEAEs suggestive of withdrawal symptoms following abrupt discontinuation of safinamide 015/017 and 016/018. TEAEs which occurred within 2 days of termination of treatment with safinamide were identified and if the symptoms included the following :

Worsening of Parkinson's disease (re-emergence of motor manifestations) : Parkinson's disease, Motor dysfunction, Parkinsonism, Hypokinesia, Bradykinesia, Ataxia, Muscle rigidity, Tremor, Gait disturbance, Coordination abnormal, Worsening On and off phenomenon, Freezing phenomenon, Balance disorder, Dystonia, Withdrawal dystonia, Muscle twitching, Chorea, Dopamine dysregulation syndrome, Restless legs syndrome, Seizures, Convulsions, Jerks.

Dependence-like (psychostimulant withdrawal) symptoms : Apathy, Insomnia, Anxiety, Depression, Asthenia, Fatigue, Nervousness, Affect lability, Agitation, Irritability, Restlessness, Panic attack, Agoraphobia, Dysphoria, Drug craving, Cognitive worsening.

Autonomic manifestations : Orthostatic hypotension, Autonomic nervous system imbalance, Dizziness, Photophobia, Hypotension, Dizziness postural, Vertigo, Vertigo postural, Hyperacusis, Drooling.

Only one patient (200 mg/day; orthostatic hypotension) in the ESPD and 3 patients (50 mg/day asthenia (n=1), and 100 mg/day asthenia (n=1) and orthostatic hypotension (n=1)) in the LSPD groupings were identified as having one of the above symptoms.

Based on the scarcity of data suggestive of withdrawal symptoms, the sponsor concluded that abrupt discontinuation of safinamide is not associated with withdrawal symptoms.

Reviewer Comment

- I do not consider that there is any clear risk for withdrawal or rebound TEAEs associated with discontinuation of safinamide. Neither did the review of section 7.3.5 Submission Specific Primary Safety Concern assessing the potential for TEAEs of drug abuse, dependence, and withdrawal TEAEs suggest a safety signal for safinamide.

Drug Abuse

Sponsor's Summary About Drug Abuse Potential of Safinamide

A range of comprehensive safety studies in rat and mice at single dose of 50- 1000 mg/kg/day conclusively demonstrated that safinamide was not associated with any psychostimulant effect but instead was associated with CNS depressant effects such as decrease in locomotion); this contrasts with the profile observed with psychostimulant drugs. On the contrary, in a combination study with cocaine, safinamide attenuated the hyperactivity induced by 20 mg/kg cocaine i.p. with an ED50 of 43.7 mg/kg (i.p.) achieving statistical significance at 100 mg/kg.

Similarly, no CNS stimulant effects were noted in repeated dose toxicity studies in rats (up to 26 weeks) or monkeys (up to 39 weeks) up to safinamide doses exceeding the maximum tolerated dose (MTD). In addition, there were no withdrawal symptoms after safinamide discontinuation during washout periods in any of the toxicology studies including up to 26 weeks in rats and 39 weeks in monkeys.

Safinamide was tested in a range of doses 0.32 to 10 mg/kg i.m., in four monkeys trained to discriminate the cocaine stimulus. Preliminary assessment indicated that the effects might suggest that safinamide (in the range 1 to 10 mg/kg i.m.) enhances the discriminative stimulus effects of cocaine, however, detailed review indicated that there were significant methodological and experimental limitations (low number of animals, unclear dosing schedule/wash out periods, variability of baseline effects, inconsistent responses sometimes even in opposite directions with increasing doses of safinamide) that these findings might be artefactual. No follow up studies were conducted based on mechanistic considerations, in particular for the lack of any effects of safinamide in the dopaminergic mesolimbic pathway as demonstrated in the monkey. This is further supported by the lack of any psychostimulant / withdrawal symptoms in acute to chronic studies in rodents and monkeys, and the absence of any findings suggestive of dependence liability of safinamide in humans, as described in the next sections.

Clinical data from > 2000 patients treated with safinamide for up to 2 years did not show any pattern of behavior that could be considered indicative of addiction liability. No neurological signs indicative of mood elevation, or "highs" have been reported in healthy human subjects that received multiple high doses of safinamide up to 350 mg/day and up to 7 days. The absence of euphoria, that is anticipated with the peak effect of psychostimulant drugs, indicates that safinamide is devoid of the potential to induce drug-seeking behaviors.

Conclusions of Animal Study Reports Submitted

Safinamide does not produce tolerance or sensitization after prolonged administration to female or male rats nor a syndrome of behavioral and/or physical dependence on abrupt withdrawal.

Safinamide does not evoke stimulant (d-amphetamine-like) psychoactive effects in rats.

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Controlled Substance Staff (CSS) Consult

After this NDA was submitted, a consult was made to the Controlled Substance Staff (CSS) at the Agency regarding sildenafil. When the CSS personnel reviewed studies that had been conducted to address the potential for sildenafil for abuse and the potential for scheduling sildenafil, they concluded that the sponsor had not conducted all the appropriate, desired studies in animals. The CSS specifically noted that additional studies were needed and this need was communicated to the sponsor which subsequently conducted studies to address the potential for sildenafil to : 1) induce tolerance in male and female rats; 2) produce discrimination relative to rats trained to discriminate d-amphetamine from saline; 3) produce discrimination relative to rats trained to discriminate midazolam from saline; and 4) stimulate abuse of rhesus monkey for intravenous self-administration relative to intravenous self-administration of cocaine.

Up to 2/10/15, the sponsor had submitted 3 final study reports for the studies assessing induction of tolerance (one in male rats and one in female rats) and discrimination assessment relative to d-amphetamine in rats. The reports of the other 2 outstanding studies assessing discrimination relative to midazolam and assessing abuse potential for self administration of cocaine are expected in February and March. In addition, the CSS has recently requested additional analyses from the sponsor relative to TEAEs occurring after stopping sildenafil in patients who completed treatment in the pivotal trials.

Reviewer Comment

- Considering the important caveat that we have not yet received the consult from the CSS on the abuse potential of sildenafil, I note **at this time** that I am unable to conclude that there is any clear indication nor suggestion of a significant or noteworthy potential for abuse in humans. My assessment on this topic could change once the CSS consult is complete.

7.7 Additional Submissions / Safety Issues

Not applicable

8 Postmarket Experience

Although this sildenafil (Xadago) was approved by EMA in 12/14, the marketing launch did not occur until much later in 2015. There is no known postmarketing experience at this time.

9 Appendices

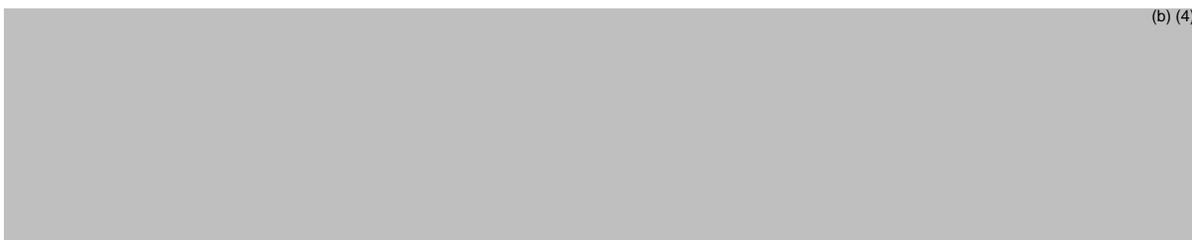
9.1 Literature Review/References

The sponsor did not provide a specific review with discussion of the published literature relative to safinamide, However, the sponsor did provide electronic copies of all publications referenced in the NDA.

9.2 Labeling Recommendations

The sponsor's original submission of a proposed label was considered to be grossly inadequate for multiple sections throughout the label.

Major recommendations for the label include :



- Insert the typical class labeling for dopaminergic drugs for Parkinson's disease for Warnings and Precautions (e.g., somnolence/suddenly falling asleep, hypotension/orthostatic hypotension, dyskinesia, hallucinations/psychotic behavior, melanoma, withdrawal hyperpyrexia and confusion)
- Use most recent Azilect/rasagiline label as a template for relatively selective MAO-B inhibitor label especially regarding issues of possible serotonin syndrome from interactions with certain drugs and MAO-inhibitor, hypertension and risk for hypertensive crisis from tyramine exposure, class contraindications for MAO-inhibitor

9.3 Advisory Committee Meeting

Not applicable

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/s/

LEONARD P KAPCALA

03/27/2016

Dave, Here is my updated review, which I had sent to Eric and you a few weeks ago, for your signature. Len

GERALD D PODSKALNY

03/27/2016

Cross-Discipline Team Leader Review

Date	3/22/2016
From	Gerald D. Podskalny, DO, MSPH
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	NDA 207-145
Supplement#	
Applicant	Newron
Date of Submission	12/29/2014
PDUFA Goal Date	03/29/2016 with 3 Month Extension
Proprietary Name / Established (USAN) names	Safinamide (Xadago)
Dosage forms / Strength	50 mg and 100 mg oral tablets
Proposed Indication(s)	1. Adjunctive treatment in patients with Parkinson's disease on (b) (4) levodopa
Recommended:	<i>Complete Response</i>

1. Introduction

The Sponsor of this application, Newron, submitted an original 505(b)(1) NDA for Safinamide (Xadago). The clinical development program was designed to support an indication, “as an add-on therapy for the treatment of early stage, (b) (4) PD patients receiving dopamine agonist monotherapy, and mid to late stage (b) (4) PD patients receiving L-dopa alone, or in combination with other PD medications”. The proposed indication divides PD into three arbitrary stages early, mid and late stage PD.

The European Commission approved Safinamide in February 2015. Germany was the first country to permit marketing of safinamide starting in May 2015. The Swiss regulatory agency (Regulator Swissmedic) approved safinamide in November 2015, and in January 2016, Newron began to market safinamide under the proprietary name Xadago in Switzerland.

2. Background

Safinamide is a new molecular entity (NME), however, it is the fourth product (3rd ME) in the drug class of selective monoamine oxidase type B (MAO-B) inhibitors. Inhibition of MAO-B is the primary mechanism of action in patients with PD. When an MAO-B inhibitor is administered chronically, it increases the availability of dopamine to striatal neurons by slowing the breakdown of dopamine making dopamine more available in the CNS. The sponsor included additional mechanisms of actions for safinamide based on in vitro electrophysiological studies that show safinamide is a state-dependent inhibitor of voltage-gated sodium channels, and in in vivo microdialysis studies in rats, showing safinamide decreases veratridine (sodium channel activator)-stimulated hippocampal glutamate release, without affecting basal glutamate release. The sponsor relates the secondary mechanisms of action to anti-dyskinetic effect observed in

nonclinical models of PD. However, the clinical data shows that safinamide increases the risk dyskinesia in patients treated for advanced PD.

There are several medication approved by the FDA to treat the motor symptoms of PD as monotherapy or as add-on therapy to levodopa or other PD medications. Safinamide does not address an unmet need for patients with PD.

Dr. Kapcala provided an in depth description of the approved drugs for the treatment of PD in his review. There are several class of medications are approved for the treatment of patients with PD, and each class (except for amantadine) has at least two members in the class. There are also several carbidopa/levodopa products approved for use in the US. There are four approved dopamine agonist medications, two MAO-B inhibitors, two catechol-O-methyl transferase inhibitors, amantadine and anticholinergic medication that are used less often because of their adverse effects.

Regulatory Background and Marketing History

The FDA imposed a “clinical hold” on the safinamide IND on December 18, 2008, due to concerns arising from observed retinal degeneration in a non-human primate toxicology study. The clinical hold was removed after independent review of the study, and after the sponsor included ocular monitoring in placebo-controlled studies of PD. The FDA requested further changes in the ocular monitoring program included in all trials, and required submission of ocular coherence tomography (OCT) data from 405 patients on safinamide, including Baseline and post-Baseline assessments at 6 months and 1 year (extension trials). The FDA also requested the following changes to individual tests on the planned ophthalmological examination:

The Agency Refused to File the original NDA (7/28/14) because the application was poorly organized and sections of the submission, tables and appendices were poorly labeled, making it difficult to navigate to important information in the application, such as case narratives for patients who died, and tables for required subgroup analyses. The files were arranged in listings without a table of contents or pagination. The title of appendices and tables did not reveal their contents. There were other deficiencies in the initial application that were not considered reasons to refuse to file the application but the sponsor needed to resolve the deficiencies.

After filing, there were numerous requests from the Clinical Team, Statistics, the Controlled Substance Staff, CMC, and Clinical Pharmacology. The information requests ranged from requesting missing datasets, missing SAS programs, needing to reanalyze clinical trials results because of errors in the protocol specified analysis, and more. The sponsor also submitted more than a thousand of pages of missing financial disclosure information from clinical investigators for their pivotal trials.

Review of the submitted safety datasets found the ADSL datasets in the ISS contained mix open label and placebo controlled data creating the need to sort multiple columns to select the appropriate population and study subsets. The organization of the ADLS datasets rendered them unusable with FDA analysis tools and safety analysis macros. The datasets also used variables with ADaM designated names however; the ADaM names were for sponsor-derived variables that

did not follow CDISC terminology. Several sponsor-derived variables were not decoded in the Define files for the ISS. The clinical team need to request a list of variables used to create the ISS tables to isolate study populations in the ADSL and AE datasets for independent review.

The sponsor's clinical trials datasets were review for data fitness by the JumpStart program analysts. They concluded the datasets were not fit for use with FDA review tools including JReview. The data fitness review concluded, "Recent FDA specific data requirements were ignored, and many issues in the data were not included or explained". Nonstandard (CDISC) terminology was used in several domains. The variable names were not consistent across datasets creating the need to manually subset datasets to perform analyses of efficacy and safety data. Reviewers need to use supplemental datasets to perform several safety analyses. The supplemental datasets provided little clarity.

The August 31, 2015, submission contained several thousand pages of financial disclosure information, and documentation of due diligence of attempts to obtain financial disclosures constituted a major amendment extending the review clock. The sponsor was notified of the review clock extension on September 16, 2015. Although this submission was as the reason for extension described in the Extension Letter, the totality of the data submitted after filing was very large, and it was not possible to detect these deficiencies until detailed the review teams began detailed review and analyses of the data.

Assessment of Abuse Potential and Related Labeling

Dr. Randall-Thompson concluded, the pre-clinical drug discrimination study (Study RS1414) using amphetamine as the training drug indicates that the interceptive cues produced by safinamide are weakly similar to the interceptive cues induced by the stimulant, amphetamine. There were other deficiencies in the design of the study that are discussed in Section 11 of this review. The results of Study RS1417, an intravenous self-administration cocaine study in Rhesus monkey also had significant methodological flaws discussed in section 11 of this review. Beyond the methodological concerns, two out of the 4 primates (50%) were shown to self-administer safinamide indicating an abuse signal. Study RS1426 included an assessment of the interceptive cues of safinamide in comparison to the interceptive cues of the sedative drug midazolam, which is a critical study in the opinion of the Controlled Substance Staff (CSS) nonclinical reviewer but the results of this study will not available until after the PDUFA deadline.

The CSS is recommending the sponsor conduct a Human Abuse Potential Study (HAPS) based on the signal for abuse potential found in the Studies RS1414 and RS1417. The sponsor would be unable to submit the results of a HAPS before the PDUFA deadline, which is the primary reason for the Complete Response Action.

Table 1: FDA Reviews Included in This Review

Reviewer	FDA Office or Division
Leonard Kapcala, M.D. Clinical Reviewer	OND-1, Division of Neurology Products
Martha R. Heimann, Ph.D. Application Technical Lead Pharmacology/Toxicology (Primary reviewers listed in the CMC section)	Office of Pharmaceutical Quality Office of New Drug Products
Luann McKinney's, DVM Lois Freed, Ph.D. (Supervisory Memo)	OND-1, Division of Neurology Products
Xiangmin Zhang, Ph.D.	Office of Biostatistics
Hristina Dimova, Ph.D. Jagan Parepally, Ph.D. Atul Bhattaram, Ph.D.	Clinical Pharmacology/ Biopharmaceutics Review
Jovita Randall-Thompson, Ph.D. Alicja Lerner, MD	Controlled Substance Staff
Antoine El-Hage, Ph.D.	Office of Scientific Investigations
Wiley A. Chambers, MD Ophthalmology Consult	Office of Antimicrobial Division of Transplant and Ophthalmology Products
Interdisciplinary Review Team for QT Studies	OND-1, Division of Cardiovascular and Renal Products
Danielle Harris, Pharm D Irene Z. Chan, Pharm D	Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis
Erin Hachey, Phar.D.	Division of Risk Management (DRISK)

3. CMC/Device

Table 2: Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Sharon Kelly	ONDP/DNDAPI/NDBI
Drug Product	Sherita McLamore	ONDP/DNDPI/NDPBI
Process	Mark Johnson	OPF/DPAI/PABI
Microbiology	Mark Johnson	
Facility	Tracie Sharp replaced with Franck Wackes	OPF/DIA/IABII

Biopharmaceutics	Okpo Eradiri	ONDP/DB/BBI
Project/Business Process Manager	Dahlia A. Woody	OPRO/DRBPMI/RBPMBI
Application Technical Lead	Martha R. Heimann	ONDP/DNDPI/NDPBI
Laboratory (OTR)	N/A	
ORA Lead	N/A	
Environmental Assessment (EA)	James Laurenson	ONDP/EA Team

Drug Substance

The drug substance (DS) reviewer notes that Safinamide is a small molecule with one chiral center. The DS is manufactured by (b) (4) and supplied to the sponsor’s drug product manufacturer, (b) (4). The sponsor cross-referenced the (b) (4) (DMF (b) (4)), and identified this DMF as the primary source of information for the DS.

Safinamide Mesylate is made (b) (4)

The sponsor reported (b) (4)

The DS reviewer noted an error in the formula used by the tablet manufacturer, (b) (4). The correction is used for the weigh out of DS during commercial manufacture. The sponsor also noticed the error in the formula used by (b) (4). Dr. Kelly notes, the weigh out procedure for the registration batches was based on values calculated by the DS manufacturer using the correct formula.

Impurities

The analysis of impurities was provided in both the NDA and DMF. These analyses assessed actual and potential impurities including organic impurities (including possible routes of degradation), genotoxic impurities, inorganic impurities, and residual solvents

The DS acceptance specification was amended in response to an information request from the FDA (11/10/2015). The sponsor developed and validated a quantitative test to measure the (b) (4) using Ion Chromatography (IC). The quantitative test method, the specification and justification of the acceptance criterion (b) (4) was sufficient. The amendment allows for verification of the test parameters in the DS supplier’s certificate of analysis (COA) and the identification testing of the

(b) (4). Prior to drug product manufacture, (b) (4) repeats all the tests on safinamide except for the quantitative test for (b) (4) for which (b) (4) relies on the CoA of the drug substance supplier.

Drug Substance Reviewer's Assessment

“Setting of specification was based on data obtained from drug substance batches manufactured at (b) (4) the Holder of DMF (b) (4). The drug substance specifications of the drug substance manufacturer and drug product manufacturer, (b) (4) As incoming goods testing, (b) (4) accepts the quantitative test for (b) (4) based on the CoA of the drug substance supplier. However, the results can be verified following a test method used at (b) (4)

Stability

The only degradation product is (b) (4), which is observed during long-term and accelerated stability studies of drug substance as well as drug product. (b) (4) is also a major metabolite (b) (4) of safinamide.

Based on the stability data available a re-test period of (b) (4) months is assigned when packaged in the described container closure system¹ and stored at 25°C.

Post-approval stability protocol and stability commitment

The ongoing stability studies on the primary stability and process validation batches (commercial production scale) will continue throughout re-test period according to the protocol.

Post-approval, at least one commercial batch per year (unless none is produced that year) will be added to the long-term stability monitoring program, and is tested at least annually, or if less than one batch is manufactured per year the batch which will be produced at next will be added to the long-term stability monitoring program.

Drug Product (DP)

Sherita McLamore-Hines, Ph.D., is the Primary Drug Product Quality Reviewer for this application.

DP development progressed (b) (4) (b) (4) The clinical performance of the “to be marketed” drug product was assessed during clinical development in the sponsor’s Phase 3 trials; in patients with early and late stage PD.

Commercial manufacture of safinamide (b) (4) 50 mg and 100 mg tablets was initially developed and performed by (b) (4) Manufacture of commercial batches was transferred to (b) (4) The (b) (4) kg commercial batch size results in (b) (4) and (b) (4) units respectively, of the 50 and 100 mg drug products. The tablets will be packaged in three packaging configurations: 30 and 90 count (30 and 50 mL) HDPE bottles and in a 14

¹ The drug substance is (b) (4)

count [REDACTED] (b) (4) aluminum blister (physician sample), debossed with “50” and “100” on one side, respectively.

Excipients

Dr. McLamore-Hines noted, with the exception of the film coat, all excipients are compendial and comply with the current monographs. Except for the film coating, each of the compendial excipients are commonly used in the manufacture of solid oral dosage and are approved for use in the FDA Inactive Ingredient Guide (IIG). There are no novel excipients or excipients of human or animal origin used in the manufacture of the drug product.

Compendial references for the components of [REDACTED] (b) (4) were not included in the NDA. The applicant responded to a request from the Product Quality reviewer and provided specifications and analytical procedures for [REDACTED] (b) (4). The information provided was complete and adequate to support the approval of the drug product. Accordingly, the quality of all excipients is adequately controlled with satisfactory specifications.

Batch Analyses

Batch analyses were provided for 51 batches of the drug product (27 batches of the 50 mg tablet and 24 batches of the 100 mg tablet). Information provided included the batch number size and use, manufacturing dates and sites, drug substance batch and the process/formulation used. Of the batches include in this submission, 18 were manufactured at the proposed drug product manufacturing site [REDACTED] (b) (4) and 22 were manufactured [REDACTED] (b) (4).

Product Specifications (Table 2)

The DP quality reviewer concluded “The applicant has adequately justified the inclusion and exclusion) for each of the tests and the acceptance criteria in the drug product specification The proposed tests incorporate all critical quality attributes and the acceptance criteria are consistent with the results in the batch analyses. The drug product specification is acceptable as it is consistent with ICH Q6A, includes all critical quality attributes and ensures that the identity, strength, quality, purity, and potency, and bioavailability of the drug product remain consistent and comparable to the pivotal clinical trial.”

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Table 3: Drug Product Specification

Test	Method	Acceptance Criteria	Justification	Typical Ranges Observed	
				Pivotal Clinical Trial	Registration Stability
Description	Visual	<i>50 mg DP:</i> <i>orange to copper with metallic gloss, round film-coated tablets, biconcave with "50" embossed on one side; approx. 7 mm diameter</i>	Qualitative test which describes the visual appearance of the drug product. The proposed acceptance criterion is based on the appearance of the tablet and includes the shape, color, debossment and size	Complies	Complies
		<i>100 mg DP:</i> <i>orange to copper with metallic gloss, round film-coated tablets, biconcave with "100" embossed on one side; approx. 9 mm diameter</i>		Complies	Complies
Identification	RP-HPLC	<i>Retention time of sample corresponds to retention time of standard</i>	The identification is based on retention time of the drug substance relative to the reference standard. The identity is determined via two methods as per ICH Q6A and provides unambiguous identification of the active.	Complies	Complies
	FT-IR	<i>Spectrum of the sample corresponds to spectrum of standard</i>		Complies	Complies
Content Uniformity*	Ph. Eur/ USP	<i>Meets USP <905></i> (b) (4)	Based on USP <905> for uniformity of dosage units requirements is consistent with industry standard for this dosage form		(b) (4)
Assay (Label Claim)	RP-HPLC	(b) (4) % of Label Claim	Limit is supported by batch release and stability data and is tighter than the ICH Q6A recommendation for assay		(b) (4)
Impurities					
<i>Specified</i>					
(b) (4)	RP-HPLC	NMT (b) (4)	Proposed limit is based on the stability studies, chemical development studies and routine batch analyses. There were 20 potential drug substance impurities and 6 actually observed. Of those 6 only (b) (4) which is a (b) (4) (b) (4) degradation product, was observed in the drug product batches manufactured by the commercial process. Based on the MDD of 100 mg (b) (4) is equivalent to (b) (4) (b) (4) (b) (4) (b) (4) (b) (4)	(b) (4)	ND

				Typical Ranges Observed	
<i>Any Unspecified</i>		NMT (b) (4)	Proposed limit was set based on ICH Q3(R2)	(b) (4) %	(b) (4) %
<u>Total</u>		NMT (b) (4)	Proposed limit was set based on ICH Q3(R2)	(b) (4) %	(b) (4) %
Dissolution	Ph. Eur/ USP	$\geq \frac{(b)(4)}{(4)}\%$ ($Q = \frac{(b)(4)}{(4)}\%$) of labelled claim in 30 minutes	The proposed limit was set based on release, stability, clinical and bioavailability data. The test is performed in accordance with USP <711>. The single point measurement was selected based on ICH Q6A decision tree #7. The acceptability of the proposed specification will be determined by the ONDP biopharmaceutics reviewer.	(b) (4) %* (mean)	(b) (4) %* (mean)
(b) (4)					
Microbial limits¹	Ph. Eur/ USP				
Total Aerobic microbial count		$\leq \frac{(b)(4)}{(4)}\text{CFU/g}$	Based on USP <61> for microbial limit requirements is consistent with industry standard solid oral dosage forms	$\leq \frac{(b)(4)}{(4)}\text{CFU/g}$	$\leq \frac{(b)(4)}{(4)}\text{CFU/g}$
Total Combined yeast and mold		$\leq \frac{(b)(4)}{(4)}\text{CFU/g}$	See above	$\leq \frac{(b)(4)}{(4)}\text{CFU/g}$	$\leq \frac{(b)(4)}{(4)}\text{CFU/g}$
<i>E.coli</i>		(b) (4)	See above	absent	absent

¹Test performed at release, beginning and end of stability studies

*Results were collected for $Q = \frac{(b)(4)}{(4)}\%$ in 45 minutes

ND = not detected

Source: Newron Table

Compatibility

The results of the sponsor’s compatibility studies on binary mixtures of the drug substance and each of the excipients support excipient-drug substance compatibility.

Shelf-life

The sponsor submitted the results of stability studies and data to support the proposed (b) (4) month shelf life for the 50 and 100 mg drug products in the commercial container/closure systems. The Product Quality Review Team granted the proposed (b) (4) month expiration dating period for the product when stored at room temperature.

The post approval stability protocol includes placing one commercial batch of each strength of the drug product into the long term stability program annually. The post approval stability commitment is consistent with recommendations in ICH Q1A(R2) to included data from at least three production scale batches.

DP Quality Reviewer's Assessment:

The DP Quality reviewer concluded the information provided is adequate to support the approval of this application. The reviewer concluded there were "no scientific or regulatory concerns about the proposed composition of the drug product."

Inspectional results

The Facilities Assessment Reviewer's recommendation was to waive the facility inspections. This poses a low to moderate risk mitigated by the use of a common dose form, a process relatively straight forward, and the facilities named in this submission have recent and acceptable compliance history.

The process reviewer, Mark Johnson was contacted 2/3/2015 to determine if the process review for this NME raised any glaring risks that would warrant facility inspections. The process reviewer did not observe any potential issues from review of process-related CMC information in Module 3.2.P.2 or Module 3.2.P.3 that would suggest inspection(s) are needed.

Tracie H.Sharp 2/5/2015.

Facilities

(b) (4) is manufacturing the tablet drug product, completing release and stability testing, and performing packaging operations. Low facility risks have been identified in the NDA and based on the firm's last two NAI classified inspections, no pre-approval inspection was recommended. Any verbal recommendations made to the firm can be verified on subsequent surveillance inspections, if necessary.

(b) (4) will be completing microbial limits testing on the drug product. This facility was last inspected 06/06/2013 and was found to be acceptable for these testing operations. Safinamide pre-approval coverage is not required.

(b) (4) will be completing drug product (b) (4) This facility was last inspected 03/07/2014 and was found to be acceptable for these testing operations. Safinamide pre-approval coverage is not required.

(b) (4) will be completing stability testing for the Safinamide. This facility was last inspected 04/30/2013 and was found to be acceptable for these testing operations. Safinamide pre-approval coverage is not required.

Final Recommendation:
ACCEPTABLE.

Assessment of Biopharmaceutics Information

Okpo Eradiri, PhD, Acting Biopharmaceutics Lead, Division of Biopharmaceutics completed the Biopharmaceutics review for this application.

Two Biowaiver requests were submitted in the NDA however, they were no longer relevant at the time of review.

- The sponsor's proposed dissolution method is acceptable.
- The final To-be-Marketed formulation of safinamide tablets ((b) (4) Tablets) was adequately bridged to the clinical batch through demonstration of bioequivalence in an in-vivo pharmacokinetic study.
- The two Biowaiver requests in the submission were deemed irrelevant at the point of review of the NDA.
- The sponsor's proposed dissolution acceptance criterion ($Q = \frac{(b)(4)}{(4)}$) was permissive and therefore unacceptable. A dissolution specification of $Q = \frac{(b)(4)}{(4)}\%$ in 20 min was therefore recommended. The sponsor accepted the FDA's recommended dissolution acceptance criterion ($Q = \frac{(b)(4)}{(4)}\%$ in 20 min) on Friday September 4, 2015. The updated Specification tables for the 50 and 100 mg strengths of Safinamide tablets were sent to the RBPM via email and they will be formerly submitted as an amendment to the NDA via the electronic gateway.

The Division of Biopharmaceutics had assessed NDA 207145 for Safinamide Tablets, 50 & 100 mg, and recommends the Application for APPROVAL.

Quality Review Team Recommendation

From a product quality perspective, NDA 207145 is recommended for approval. The sponsor satisfactorily addressed all deficiencies identified during the review process. The review team concurred with the expiration dating period proposed by the sponsor, and there are no comments to be conveyed in the action letter.

4. Nonclinical Pharmacology/Toxicology

Dr. McKinney's review included results of in vitro and in vivo pharmacology studies submitted by the sponsor to show that safinamide is a selective, reversible MAO-B inhibitor. Safinamide was observed to inhibit the oxidation of the MOA-B substrate phenylethylamine in rat brain mitochondria (IC₅₀ of 98 nM) but it did not inhibit the oxidation of serotonin (an MAO-A substrate) at an IC₅₀ of 584 nM. The results was supported by studies using platelet-rich human plasma where the results indication that the inhibiting effects safinamide had on MAO-B found in human platelets was reversed completely by washing the platelets after drug exposure. A study in monkeys chronically treated with safinamide for 13 and 39 weeks, found that it increased dopamine levels in the brain.

The sponsor reported safinamide inhibits glutamate release induced by a depolarizing agent (KCl) in rat hippocampal synaptosomes. In in vivo microdialysis studies in rats, safinamide has been shown to decrease veratridine (sodium channel activator)-stimulated hippocampal glutamate release without affecting basal glutamate release. In nonclinical models, the levels of safinamide

in the brain, overlaps with plasma concentration found in humans after taking a 100 mg dose of safinamide. However, there is no direct or indirect evidence to show that either proposed mechanism of action is clinically relevant to treating patients with patients with PD.

Safinamide was not shown to have an effect on the D1 or D2 family of receptors. Although safinamide binds to the dopamine and serotonin transporters, the extracellular concentrations are low. Brain imaging studies with the ¹²⁵I-CIT SPECT scan studies in baboons, show no evidence that safinamide interacts with either transporter system, making it unlikely that a direct interaction with dopamine receptors, or the dopamine transporter contributes to clinical actions of safinamide.

Absorption

Safinamide was rapidly absorbed orally (Tmax ≤ 1-2 hr in rodent and 2-3 hr in monkey) and bioavailability was high in both rat (92%), monkey (80%) and in human (95%). The AUC consistently increased with increasing doses. The half-life was 1-2 hr in rat and mouse and 8-11 hr in monkey.

Distribution

Safinamide widely distributed to fatty tissues, kidney, liver, within 4 hours of oral dosing post-dose. Levels of safinamide in the brain were low at 1 hour, but safinamide was detectable at 4 hours post-dose but no longer detectable at 24 hours post dose. Safinamide is highly bound to plasma proteins in mouse (88%), monkey (85%), and human (89%). The rank order of plasma binding by safinamide and metabolites was NW-1689 > NW-1689 AG > safinamide > NW-1153. The volume of distribution is moderate and it is consistent with distribution into tissues.

Metabolites

The metabolism of safinamide largely relies on MAO-A, cytosolic amidases, and to a lesser extent by CYP3A4. The major human metabolites following a single dose of safinamide were NW-1689 (30%) and NW-1689 AG (18%). After repeat doses of safinamide, NW-1153 was also identified as a major metabolite (10-11%).

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Table 4: PK Properties of Safinamide and Its Metabolites Following 100 mg/day repeat dose in Rat, Monkey and Human

Species	Rat	Monkey	Human
Safinamide dose	50 mg/kg/d ^{a)}	50 mg/kg/d ^{b)}	100 mg/d ^{c)}
NW-1153			
C _{max} (µg/mL) AUC _{0-24h} (µg/mLxh) AUC ratio ^{e)}	0.942 11.3 5.6	0.65 7.45 3.7	0.123 2.03 -
NW-1689			
C _{max} (µg/mL) AUC _{0-24h} (µg/mLxh) AUC ratio	146 2860 106	34.2 599.4 22.1	1.31 27.1 -
NW-1689 AG			
C _{max} (µg/mL)	low exposure, ^d not quantifiable na	4.08 43.8 10.1	0.321 4.32 -

Values are means (male and females)

a) The overall NOAEL in rat was established at 45 mg/kg/day, however, metabolite exposure data are lacking for that study (8724). Therefore, data at the close dose of 50 mg/kg/day from study ONP005 (week 42) were taken instead.

b) The overall NOAEL in monkey was established at 50 mg/kg/day: however, metabolite exposure data are lacking for that study (30939TCP). Therefore, week 2 data from the repeat dose PK study RF2310 at the same dose were taken instead.

c) From QT/QTc study (IMP28559): 100 mg/d, 6d, po administration

d) From Study DMPK 09-08

e) ratio animal/human

NW-1689

NW-1689 is formed by metabolism of safinamide by MAO-A, with no effect on metabolism in the presence of MAO-B inhibitors. Level of NW-1689 is greater than safinamide in all animals studied in nonclinical development (mouse rat dog, rabbit, monkey and in human). In rat, NW-1689 was the major metabolite, and exposure (AUC) to NW-1689 was up to 27-fold greater than to safinamide, and after repeat doses, levels increased up to 60-fold that of the parent compound. In monkey, NW-1689 was the main metabolite and exceeded the level of safinamide by 3-fold. NW-1689 is also a major human metabolite in humans when measured in vivo. Dr. McKinney's review indicates there is adequate toxicology coverage for NW-1689 and it is adequately assessed in the sponsor's carcinogenicity studies in rat (Table 4).

NW-1689 Acyl Glucuronide (AG)

The sponsor identified the NE-1689 AG as a major circulating metabolite present at levels that are approximately 18% of the parent when measured in acidified plasma. NW-1689 is not detectable in mouse, and it is present at levels below the limit of detection (trace amounts) in rat. The absence of detectable levels of the AG metabolite in mouse and rat means it is not assessed by the sponsor's carcinogenicity studies. In monkey, the levels are 10 fold the human exposure (AUC).

NW-1689 AG was also present in rabbit, and there were no observed unique clinical or histopathological toxicities in female rabbits.

Some acyl glucuronides are known to be reactive towards cellular macromolecules, which may lead to idiosyncratic drug toxicity. The sponsor investigated the reactivity of NW-1689 AG towards proteins in vitro. The potential for hepatotoxicity is evaluated by in vitro methods that evaluate covalent binding of acyl glucuronides to tissue proteins assessed in human liver microsomes. The sponsor compared several methods to assess the potential for idiosyncratic drug reactions and concluded safinamide was “low risk” for potential idiosyncratic reactions. Dr. McKinney remarks that these methods are unreliable for predicting the potential for in vivo adverse reactions.

The toxicity of NW-1689 AG was assessed in monkey, and there were no reported changes besides increased liver weights (dose 70 mg/kg/day) that returned to normal during recovery (8-week recovery period), mild reversible elevations in transaminases but no relevant histopathological changes were reported in hepatocytes.

There is adequate toxicology information for NW-01689 AG from studies in monkey. Because NW-1689 AG is not produced in mice or rats, it was not assessed in sponsor’s carcinogenicity studies.

Dr. McKinney concurred that NW-1689 AG was not found to be mutagenic or clastogenic in the sponsor in vitro genotoxicology battery. However, she notes that acyl glucuronides can form DNA adducts, resulting in possible genotoxicity, and they can directly activate neutrophils and/or macrophages resulting in release of proinflammatory cytokines. However, there no reliable method to predict the possibility of DNA adducts. In Dr. McKinney’s opinion, information from a dedicated carcinogenicity study of NW-1689 AG would not better predict of the clinical risk.

NW-1153

NW-1153 is a major human metabolite (the level is approximately 10% of the parent) is derived from hydrolysis of the amide group in safinamide, and it is converted to metabolite NW-1689. The in vivo mechanism responsible for NW-1153 to NW-1689 conversion is unknown. NW-1153 is a main component in humans in vitro, was minor in all nonclinical species, except rabbit.

Minor Metabolite NW-1199

NW-1199 was minor in human and rat, minipig, and monkey. Distribution to the retina in pigmented (Lister hooded) and albino (Wistar) rats was assessed in a series of studies.

Elimination

Safinamide and its metabolites are primarily eliminated in the urine with only low levels found in feces. The pattern of elimination is consistent in all animal species tested including humans.

Safety pharmacology

Cardiovascular

The sponsor conducted a study to evaluate the cardiovascular effect of safinamide in conscious dogs dosed at 5 mg/kg and 15 mg/kg), the results showed no significant changes in heart rate blood pressure of O₂ levels. Dr. McKinney notes that similar results were reported for a separate study of R-safinamide.

In Study 9750238-N826X, Cynomolgus monkeys received safinamide in combinations of intra-duodenal (ID) doses of 120 or 240 mg/kg and/or intravenous (IV) doses ranging from 75 to 171 mg/kg. All doses exceeded the maximum tolerated dose and at levels above 113 mg/kg IV, animals were observed to have hypotension, resulting in death. In a separate arm of the study monkeys received intra-cisternal infusion of safinamide resulting in hypotension at lower plasma levels that had been given IV or ID. Hypotension was reversed by intravenous dobutamine infusion. The results led the sponsor to speculate that hypotension may stem from a central mechanism.

hERG Study

The sponsor conducted a GLP compliant hERG study. Dr. McKinney concurred with the sponsor's conclusion that the reported effect of safinamide on the potassium current was 28.3 mcM, which was generally considered to have a low potential for QTc prolongation. In the presence on a concurrent positive control terfenadine (60 nM), which inhibited the hERG potassium current by 82.4 ± 3.2%.

Respiratory

In a study performed in conscious rats, oral doses of safinamide up to 200 mg/kg PO had no effect on respiratory parameters. The R-enantiomer at a dose of 30 mg/kg also had no effect on respirations.

Toxicology

Table 5: Overview of oral repeated dose toxicity studies with safinamide

Study Type	Species/strain	Route	Duration	Dose (mg/kg/day)	Study No.
4-week mice	Mouse/Crl:CD-1	oral (gavage)	4 weeks	0, 50, 100, 300	ONP001
13-week mice	MouseCrl:CD-1	oral (gavage)	13 weeks	0, 100, 200, 375→250	ONP002
4-week rat	Rat/Crl:CD (SD*)	oral (gavage)	4 weeks	0, 50, 100, 200	N596-Q1354 (9550005)
4-week rat with 4-week recovery	Rat/Crl:CD (SD*)	oral (gavage)	4 weeks	0, 20, 60, 100, 500	N814-Q1505 (9750253)
13-week rat	Rat/Crl:CD (SD*)	oral gavage	13 weeks	0, 100, 200, 300→250	ONP003
13-week rat with 4-week recovery	Rat/Hsd:SD*	oral (gavage)	13 weeks	0, 15, 30, 80	7552 (7552/T/144/2000)
26-week rat with 8-week recovery	Rat/Hsd:SD*	oral (gavage)	26 weeks	0, 5, 15, 45	8724 (8724/T/390/2002)
26-week rat with 6-week recovery	Rat/Crl:CD (SD*)	oral (gavage)	26 weeks	0, 60, 120, 180	RE6230 (28452)
4-week monkey	Cynomolgus Monkey	rhinogastric gavage	4 weeks	0, 50, 100, 200	N636-Q1392 (9550237)

4-week monkey with 2-week recovery	Cynomolgus Monkey	rhinogastric gavage	4 weeks	0, 20, 40, 80, 120	N822-Q1509 (9750107)
13-week monkey with 6-week recovery	Cynomolgus Monkey	rhinogastric gavage	13 weeks	0, 10, 20, 50	991180
39-week monkey with 8-week recovery	Cynomolgus Monkey	oral (gavage)	39 weeks	0, 3.2, 8, 20	21893TCP
39-week monkey with interim sacrifice at week 26	Cynomolgus Monkey	oral (gavage)	26/39 weeks	0, 30, 50, 70	30939 TCP

*SD, (SD) =Sprague Dawley rat,

Key findings in single and repeat dose toxicology studies

Adverse CNS effects, including tremors, abnormal coordination, clonic contractions and convulsions leading to death were seen in rats (500 mg/kg/day), mice ($\geq 375/250$ mg/kg/day and in monkeys (≥ 70 mg/kg/day). CNS toxicity led to premature death in one female treated with 70 mg/kg/day.

The liver appeared to be a target organ in rats and in mice but not in monkeys. The findings in the liver included centrilobular hypertrophy and increased fatty change. At 4 weeks in rats, there was fatty change at ≥ 50 mg/kg/day, increased weight at ≥ 60 mg/kg/day, centrilobular hypertrophy and increased serum enzymes at ≥ 200 mg/kg/day. At 13 weeks, there was increased alkaline phosphatase at 80 mg/kg/day, increased liver weight was seen at ≥ 30 mg/kg/day.

In rat, foamy macrophages were observed in the lungs and in repeat dose toxicity studies at doses ≥ 60 mg/kg/day seen in the thymus, liver, uterus and vagina. In monkey, infiltration with foamy macrophage was seen in lymph nodes, thymus and spleen at doses of 80 and 120 mg/kg/day in a 4-week repeat dose toxicity study. No effects were seen in subsequent monkey studies up to 39 weeks of duration at doses up to 70 mg/kg/day. In the second 26-week rat study, EM examinations showed that the alveolar macrophages contained concentric multi-lamellar, myeloid body-like inclusions in the cytoplasm believed to be Phospholipidosis. Phospholipidosis can be drug induced most often in association with cationic amphiphilic drugs. The importance of phospholipidosis is unknown (Anderson & Borlak, 2006). Phospholipid appears to accumulate within the lysosome, and they may or may not be associated with clinical symptoms.

Adrenal gland enlargement was noted in monkeys and rats. Increased weight and adrenal cortical hypertrophy occurred in different studies in rats at doses ≥ 50 mg/kg/day. Similar effects were seen in the 4-week monkey studies at doses ≥ 40 mg/kg/day. Results of serum cortisol and ACTH level measurements performed in monkeys in two 4-week studies, and one 39-week study were inconclusive.

The gastric mucosa appeared "roughened" and dilated intestines were seen in rats that were found dead or euthanized, but similar changes were not observed in survivors at terminal necropsy or after recovery. There was no apparent histologic correlate for the GI signs. In monkeys, gastric erosion was seen on gross examination in monkeys dosed at 20 and 50 mg/kg/day.

Retinal Degeneration

Dr. McKinney summarized the retinal toxicity in her review. Retinal degeneration was found in the pivotal, 13-week toxicology studies. Retinal degeneration was detected in rats and mice but

not in monkeys. The lowest dose showing retinal degeneration was 15 mg/kg/day. The initial retinal degeneration in rats was characterized histopathologically by diffuse loss of nuclei from the outer nuclear layer (ONL). Retinal degeneration associated with safinamide increased in severity with increasing dose and duration of exposure from mild-to severe atrophy of the ONL. The ONL is where the nuclei of the rods and cones of the photo-receptor layer are located. The outer-most segments of the photo-receptor layer are embedded in the microvilli of the retinal pigmented epithelium (Kumar, Van Gerpen, Bower, & Ahlskog). The RPE is adjacent to the choroid and is part of the blood-retinal barrier. It functions to transport nutrients to the retina, secretes trophic substances and returns water, ions and metabolites to the systemic circulation.

In combination drug studies that included safinamide and pramipexole, at doses of pramipexole that did not cause retinal changes (25 mg/kg/day PO), the combination exacerbated the retinal lesions caused by 50 mg/kg/day safinamide PO in both pigmented and albino rats. No adverse effects were detected in retinas of pigmented rats treated with 50 mg/kg/day safinamide alone. Pramipexole is a dopamine agonist approved for the treatment of patients with Parkinson's disease. The combination treatment with levodopa/carbidopa and pramipexole did not exacerbate degeneration of the ONL.

Based on a lack of retinal changes in clinical studies, and the absence of change in monkeys, the sponsor concluded that retinal atrophy is a rodent phenomenon and that there was no increased risk for patients. The sponsor concluded that retinal degeneration was observed in rats exposed to safinamide does not predict retinal degeneration in humans. Published reports of other compounds, including marketed drugs have reported similar retinal changes. The sponsor notes that none of these compounds has been associated with retinal changes citing data from clinical trials. However, quality of the clinical trials data assessing retinal changes in patients taking safinamide or placebo is severely limited due to large amounts of missing data and baseline abnormalities. The clinical trials data is too limited conclude safinamide does not cause retinal degeneration in humans.

Toxicokinetics

Safinamide was rapidly absorbed orally ($T_{max} \leq 1-2$ hr in rodent and 2-3 hr in monkey) and bioavailability was high in both rat (92%), monkey (80%) and 95% in human. The AUC consistently increased with dose, but was less than dose-proportional in mouse with little accumulation, but greater than dose-proportional in rat and monkey and accumulated over time. The half-life was 1-2 hr in rat and mouse and 8-11 hr in monkey.

Exposure to metabolites NW-1153 was generally less the parent (safinamide). Levels ranged from 3 fold less in rat to 30% less in female rabbit. Exposure to NW-1689 greater than the parent ranging from 5 fold to 200 fold greater than safinamide in mouse, as high as 40 fold higher in rat and rabbit, and 4 fold higher in monkey.

NW-1689 Acyl glucuronides was only present in detectable levels in monkey. Exposure was less than the levels of safinamide and levels were approximately 4% of the total of NW-1689. NW-1689 AG exposure in monkeys was about 15 – 45% that of safinamide and was almost two times higher in females compared to males. NW-1689 Acyl glucuronides is discussed earlier in this review.

Impurities and Degradants

Dr. McKinney noted (b) (4) is a (b) (4) found in the drug substance and would normally be limited to (b) (4) mcg/day. However, the sponsor has proposed a validated process that eliminates (b) (4) from the drug product.

(b) (4) In the drug substance and the drug product (b) (4) has a specification limit of \leq (b) (4) % the MRHD (b) (4) mcg) this amount exceeds the recommended threshold by (b) (4). However, because (b) (4) is also a major human metabolite (10-11% at steady state) therefore, the daily exposure to (b) (4) as a degradant is not concern.

(b) (4)

Although a 90-day toxicity study would qualify (b) (4) for the intended purpose, the sponsor submitted results of a 28-day comparative toxicology study of the (b) (4) in rat, there were no toxicities unique to (b) (4) (b) (4)

(b) (4) was not mutagenic in the Ames test and the proposed level is acceptable.

Genotoxicity and Carcinogenicity

Genotoxicity

Dr. McKinney reviewed the results of the sponsor's valid ecotoxicology battery of tests. She concurred with the results of the sponsor's finding that (b) (4), NW-1153, NW-1689, and NW-1689 AG were neither clastogenic or mutagenic. Saffinamide was also not observed to and did not induce DNA repair in rat hepatocytes.

Carcinogenicity

The sponsor conducted two 104 week carcinogenicity studies one in mice and the other in rats. The mouse was an appropriate model to study the neoplastic potential of the test article. As described in the discussion of the metabolites, the major human metabolite NW-1689 AG is not detected in either species. The FDA CAC concurred that carcinogenicity studies were adequate.

Reproductive Toxicology

In the first embryofetal development study in pregnant rats, safinamide in doses of 200, 300 and 400 mg/kg/day exceeded the MTD and were associated with a higher incidence of intrauterine deaths, reduced fetal weight and cleft palates in all three dose groups tested. In a subsequent embryo-fetal toxicity study in combination with L-dopa/carbidopa the group receiving safinamide alone at 40 mg/kg/day showed an increased incidence of minor skeletal abnormalities.

In a third embryofetal development study, treatment with safinamide in doses of 25, 50 and 100 mg/kg/day in combination with levodopa/carbidopa at 80/20 mg/kg/day was associated with an increase of skeletal abnormalities in all safinamide dose groups with LD/CD and with safinamide 100 mg/kg alone. Major skeletal malformations including bent scapulae and short, bent and thickened humerus. Abnormalities in kidney included absent/rudimentary renal papilla, dilated ureter.

The results of a combination study in rabbit of oral safinamide 4, 12, and 40 mg/kg (including metabolites NW-1153 and NW1689) and LD/CD of 40/10 and 80/20 mg/kg showed increased fetal deaths compared to controls, misshapen heart/atrium/ventricle, and an increase of major cardiovascular abnormalities already observed with L-dopa/carbidopa alone.

All dose levels of safinamide in combination with 80/20 mg/kg/day levodopa/carbidopa resulted in an increased incidence of fetuses/litters with major abnormalities including membranous ventricular septal defect, dilated single vessel arising from the heart and enlarged/misshapen heart/atrium/ventricle. Similar cardiovascular abnormalities were found in fetuses/litters given 80/20 mg/kg/day levodopa/carbidopa alone. In litters exposed to safinamide alone at a dose of 40 mg/kg only minor skeletal abnormalities were reported. These results indicate safinamide in combination with levodopa/carbidopa increases the risk for fetal abnormality.

In a Pre- and Post-Natal Development studies that assessed oral gavage of safinamide in rat offspring from control group dams that were cross-fostered and reared by dams receiving 50 mg/kg/day. Offspring in this group showed the treatment-related clinical sign of orange skin color between days 3 and 9 of age and macro-pathology findings of offspring tinged yellow prior to weaning and orange tinged skull at weaning. Dr. McKinney notes these results indicating that the toxicity resulted from exposure both in utero and via milk. These results are not considered conclusive that safinamide contained in milk was responsible for change in tissue pigment.

Nonclinical Recommendation

1. From a pharmacologic/toxicologic perspective, safinamide at 100 mg/day is approvable for therapy in Parkinson's disease.
2. The safety margin for sporadic CNS signs is low (3-fold) and clinical monitoring may be warranted.
3. Adverse effects on fertility, on fetal development, and on neonatal health should be taken into consideration when administering safinamide to women of child bearing age.
4. Clinical monitoring for adverse retinal changes may be advised when pramipexole and safinamide are co-administered.

5. Clinical Pharmacology/Biopharmaceutics

The clinical program for safinamide included 37 trials: 20 Phase 1, 8 Phase 2, and 9 Phase 3 trials.

Bridging Strategy

The sponsor developed [REDACTED] (b) (4)

ONDQA determined that the Biowaiver criteria were not met and an in vivo BE bridging study was needed to bridge the capsules to the (b) (4) tablets. The sponsor did not conduct an in vivo BE study to bridge the capsule and the (b) (4) tablet. The capsule (10,mg, 50 mg and 100 mg) were used in 009, 015 and 017 in trials evaluating safinamide in patients with early PD as add-on therapy to patients on a stable dose of a dopamine agonist. Clinical trial 27918 (MOTION) was the only study in patients with early PD to use the (b) (4) tablet but provides support for this formulation in this population. Bridging studies to the capsule formulation were not considered necessary to support approval of the To Be Marketed tablet formulation.

The sponsor conducted a series of dissolution studies to bridge the (b) (4) tablet to the (b) (4) tablet manufactured by (b) (4) and the (b) (4) manufactured by (b) (4)

ADME

Absorption/Distribution.

The bioavailability of safinamide is approximately 95% following oral administration. It is highly soluble at low pH but at higher pH, solubility is reduced. In a dedicated food effect study, food delayed Tmax by approximately 0.75 hours but it did not significantly alter AUC (Table 6). Safinamide can be administered without regards to food. The increase in Cmax and AUC of are dose proportional with increasing doses of safinamide.

Safinamide has a high volume of distribution (165L), and 88% to 92% of safinamide is bound to plasma proteins. The predominant human metabolite is NW-1689 with levels that exceed the levels of the parent. Dr. Dimova notes NW-1689 is >99.5% protein bound.

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Table 6: Effect of Food ON the PK Parameters of Safinamide

PK Parameter	Treatment A (Fasted)	Treatment C* (IV Infusion)
C _{max} [ng/mL]	322.3 (17.9) 227.0 – 421.0	411.6 (18.8) 305.0 – 591.1
t _{max} [h]	2.5 2.0 – 5.0	0.5 0.25 – 5.0
AUC _{0-τ} [ng/mL*h]	9811 (25.4) 6584 – 16737	10340 (20.8) 7173 – 13815
AUC _{0-∞} [ng/mL*h]	10205 (26) 6779 – 17012	10785 (22.0) 7314 – 14801
t _{1/2} [h]	26.2 (19.2) 20.0 – 40.8	26.0 (11.3) 20.7 – 30.7
CL/f [L/h]	4.9 (26.0) 2.9 – 7.4	4.6 (22.0) 3.4 – 6.8
V _{z/f} [L]	185.0 (17.7) 142.9 – 260.5	174.1 (15.6) 146.6 – 222.7
F [%]	94.98 (9.25) 83.93 – 119.33	–

Source: Newron

Metabolism

The results of in vitro studies show that safinamide is primarily metabolized by hepatic nonmicrosomal enzymes, cytosolic amidases and MAO-A catalyzes the metabolism of safinamide. CYP3A4 plays a minor role in safinamide metabolism. Several aldehyde dehydrogenase (ALDH) and UGT isoenzymes are involved in the final stages of metabolism. Dr. Dimova notes that the potential for drug-drug interaction at the ALDH or UGT steps is limited because there are several isoenzymes in each system are involved in metabolism.

There are 3 major human metabolites (NW-1153, NW-1689 and NW-1689 acly glucuronide (AG)). There is one minor metabolites O-debenzylated safinamide (NW-1199). All of the metabolites are inactive.

NW-1153 is formed from safinamide by cytosolic amidases and human fatty acid amide hydrolase (FAAH). NW-1689 is formed from NW-1153 and the N-dealkylated amine. NW-1689 AG is formed from NW01689 by UGT1A isoenzymes andUTG2B15.

In her review, Dr. Dimova noted that in the human mass balance study (CRO-02-33), the main radioactive component in plasma was parent safinamide, the AUC₀₋₂₄ accounted for ~30% of the total radioactivity AUC₀₋₂₄ (AUCTR). The main circulating metabolite was identified as NW-1689, accounting for ~30% of AUCTR. NW-1689 AG was found to represent 10-20% of the AUC of parent compound in human clinical studies but only after plasma samples were stabilized to prevent degradation by glucuronide hydrolysis.

Dr. Dimova concluded that the PK parameters of safinamide and its metabolites do not change appreciably after multiple dose oral administration compared to single dose. The PK profile is the same in healthy subjects compared to patients with PD. At steady state, there is low inter- and intrasubject variability in PK parameters.

Elimination

Approximately 95% of safinamide is eliminated after metabolic transformation and only 5% is eliminated unchanged after 48 hours. Safinamide is renally eliminated with approximately 76% of the total dose of safinamide is found in urine mainly in the form of metabolites.

Intrinsic factors

The sponsor conducted population PK analyses performed in pivotal clinical trials, 016 and 27918 (advanced PD) and 27919 (early PD). The results did not show there was a need for dose adjustment based on age (< 65 years versus \geq 65 years), gender or race (Caucasian versus Non-Caucasian). Safinamide has not been studied for use in the pediatric population.

Renal Impairment

The sponsor conducted a study in patients with moderate to severe renal impairment. The PK profile of safinamide is not substantially changed (40% increases in plasma concentration) in patients with moderate or severe renal impairment. Exposure (C_{max} and AUC) to the major (inactive) metabolites of safinamide increase up to several fold (6X) AUC in subjects with moderate to severe renal impairment compared to subjects with normal renal function. Dr. Dimova requested additional analyses of adverse events in patients with renal impairment. The results provided by the sponsor only found a small increase in nausea in patients with moderate renal impairment. Dr. Dimova concurs with the sponsor's recommendation that patients with renal impairment do not require dose adjustment.

Hepatic Impairment

The sponsor conducted a single dose study in patients with moderate hepatic impairment (Child-Pugh A), and in patients with moderate hepatic impairment (Child-Pugh B). In patients with mild hepatic impairment, there was a 30% increase in AUC that is not large enough to warrant dose adjustment. In patients with moderate hepatic impairment, the AUC was observed to increase by approximately 80% following a 50 mg dose of safinamide. The recommendation for patients with moderate hepatic impairment is to limit the daily dose to 50 mg. Patients with severe hepatic impairment should not receive treatment with safinamide.

CDTL Comment:

I agree with the recommendations from the Office of Clinical Pharmacology to contraindicate safinamide in patients with severe hepatic impairment. The dose of safinamide in patients with moderate hepatic impairment should be limited to 50 mg daily. There is no change in dose recommended in patients with mild hepatic impairment or in patients with renal impairment even in those with severe renal impairment.

Potential for Drug-Drug Interactions

CYP Interactions

Dr. Dimova reviewed the sponsor studies that evaluate the potential for CYP enzyme inhibition. She concluded, there was no evidence of direct or Time Dependent Inhibition (TDI) of CYP2A6, CYP2C8, CYP2C9, CYP2E1, and CYP3A4/5 by safinamide at concentrations up to 100 μ M. There was no direct inhibition by safinamide metabolites NW-1153 or NW-1689 for any of the

CYP enzymes tested. There was evidence of TDI of CYP1A2, CYP2B6, CYP2C19, and CYP2D6 that was NADPH dependent, indicating that safinamide is a metabolism-dependent inhibitor of these enzymes. Dr. Dimova concluded there was some evidence that the TDI of CYP1A2 (36% at 100 μ M) and CYP2B6 (78% at 100 μ M) that may be caused by the safinamide metabolite NW-1153, but not NW-1689. The metabolism-dependent inhibition of CYP1A2 and CYP2B6 was unaffected by dilution of the incubate indicating that safinamide is an irreversible or quasi-irreversible inhibitor. Follow-up studies showed that NW-1153 caused weak metabolism-dependent (time-dependent and NADPH-dependent) inhibition of CYP1A2 that was partially reversible.

The results of an in vivo study of the effects of CYP3A4 inhibition with ketoconazole found safinamide levels were increased by 13%. Dr. Dimova concluded there were no relevant drug-drug interaction with CYP3A4 inhibitors is expected with safinamide, and safinamide can be co-administered with drugs known to inhibit the CYP3A4 iso-enzyme without dose adjustment.

In vitro studies demonstrated that safinamide is a weak competitive inhibitor of CYP1A2 and a weak inducer of CYP3A4. Dr. Dimova concluded that neither effect was likely to be clinically relevant and concurred with the sponsor's proposal to add the following statement to the product label, (b) (4)

Effect on Transporter Function

Safinamide and its metabolites did not inhibit other transporters OCT2, OATP1B1, OATP1B3, BSEP or OAT1/3/4 at clinically relevant concentrations. Safinamide is not a substrate or inhibitor of P-gp

In in vitro studies of human hepatocytes, there was no evidence of direct inhibition of MAO-A activity by NW-1153, NW-1689 or NW-1199 and the IC₅₀ values for this enzyme were >100 μ M. Safinamide, NW-1153 and NW-1689 have no inhibition potential on levodopa decarboxylase.

Based on the K_i and IC₅₀ values for inhibition, safinamide or its major metabolites are not inhibitors of CYP, ALDH, levodopa decarboxylase or MAO-A enzymes, at clinically relevant concentrations. Therefore, the inhibition potential of safinamide is low.

Dr. Dimova discovered NW-1689, the major metabolite of safinamide has potential to inhibit intestinal Breast Cancer Resistance Protein (BCRP) at a dose of 100 mg (the recommended high dose in labeling). Plasma levels of NW-1689 are 1.6 time the parent in humans.

Intestinal BCRP limits systemic exposure to substrates that include a growing list of drugs, such as chemotherapy agents and statins. Inhibition of BCRP could result in increased exposure to NW-1689, which is a BCRP substrate. This information was discussed with the sponsor at the Late Cycle Meeting. The sponsor offered to submit additional information to address the Office of Clinical Pharmacology's (OCP) concerns. The sponsor submitted (October 14, 2015) three study reports that were review by OCP however, completed studies did not adequately evaluate the potential of NW-1689 to inhibit BCRP. The sponsor studied the effect caused by weak BCRP substrates such as diclofenac and only assessed the effect of other safinamide metabolites (NW-

1153) but not of the effect of NW-1689. Lastly, the sponsor's study of the GI transit time for safinamide did not include an estimate of NW-1689.

In OCP's opinion, an in vivo study of NW01689 is needed to evaluate the potential for NW1689 to inhibit BCRP. This information was not included in the NDA submission or in the subsequent response to OCP's information request.

CYP Enzyme Inducers

Safinamide was studied in an open label Phase 2 study in patients taking antiepileptic drugs that are enzyme inducers. The study was performed as part of the sponsor's exploration of the antiepileptic properties of safinamide. Safinamide levels trended lower (approximately 30%) in patients taking a stable dose of an enzyme inducer. Based on these results and the primary route of metabolism (MAO-A and cytosolic amidases) in vivo studies were not required.

Interactions with Drugs Approved to Treat PD

In vivo drug-drug interaction studies performed with levodopa did not demonstrate significant effects on the pharmacokinetic profile of safinamide, or on the pharmacokinetic profile of co-administered levodopa. The sponsor did not evaluate the potential drug-drug interaction between ropinirole in a dedicated study however, DDI with ropinirole was investigated in clinical trial 27918 (in patients with early PD). Patients in the study were maintained on a stable dose of a dopamine agonist. The data suggest there was little potential for DDI between safinamide and ropinirole. There is no information regarding the potential interaction of safinamide with pramipexole. However, the potential for DDI with pramipexole was discussed with Dr. Dimova based on knowledge for the metabolism of pramipexole, the potential for DDI with safinamide appears to be low.

Safinamide is highly soluble at low (pH 1.2 and 4.5), it has low solubility at pH 6.8 and 7.5. The pharmacometrics reviewer conducted a population PK analysis for the potential interactions between proton pump inhibitors (PPI) and safinamide. Useful data was available for 98 patients taking a concomitant PPI during PK sampling. The data suggest that the interaction potential of safinamide with PPI is low. No data was presented to assess the potential DDI between pramipexole and safinamide. In a follow-up conversation with Dr. Dimova, she explained that a DDI between pramipexole and safinamide was unlikely given the differences in metabolism for the respective drugs.

Pharmacodynamic Interactions

There are several pharmacodynamic interactions between MAO-B inhibitors as a class, with analgesics, other MAO inhibitors, decongestants and several classes of antidepressants. These drug interactions are described in the rasagiline (Azilect) and selegiline (Eldepryl, Zydis and Emsam) labels. The safinamide label include the similar Contraindications or Warning statements (as class labeling language) regarding these potential adverse reactions because they may result in serious outcomes. The sponsor did not restrict the short-term use of dextromethorphan during in their clinical studies. A review of concomitant medication in the ISS datasets finds that only nine patients took concomitant dextromethorphan while participating in controlled or open label trials however, the daily dose was not provided in the (Conmed) dataset. There is insufficient clinical

experience to justify removing the information about the interaction between safinamide and dextromethorphan from Warnings and Precautions section of the product label.

DDI Information to Include in the Product Label

Contraindications

- For use with meperidine, tramadol, methadone, propoxyphene and MAO inhibitors (MAOIs), including other selective MAO-B inhibitors, because of risk of serotonin syndrome
- For use with dextromethorphan because of risk of episode of psychosis or abnormal behavior.
- Serotonin syndrome has been reported with concomitant use of antidepressant (e.g., selective serotonin reuptake inhibitors-SSRIs, serotonin-norepinephrine reuptake inhibitors-SNRIs, tricyclic antidepressants, tetracyclic antidepressants, triazolopyridine antidepressants) and a nonselective MAO-I (e.g., phenelzine, tranylcypromine) or selective MAO-B inhibitors

Warnings and Precautions

- Dopamine antagonists, such as antipsychotics or metoclopramide, could diminish the effectiveness of Safinamide
- Monitor for hypertension if XADAGO is prescribed concomitantly with any sympathomimetic medications including prescription or nonprescription nasal, oral, and ophthalmic decongestants and cold remedies.

Potential Drug-Dietary Interaction

Dietary Tyramine

Nonselective and selective MAO inhibitors have the potential for interaction with dietary tyramine. The loss of the protective effect of MAO-A in the GI tract and absorption of tyramine that is converted to norepinephrine can result in hypertension, including hypertensive crisis and tyramine syndrome (headache, nausea and hypertension). Safinamide, like other selective MAO-B inhibitors loses its selectivity for MAO-B at high doses.

The sponsor conducted 3 dedicated tyramine studies in healthy subjects. In the pivotal study, the primary endpoint was the Tyramine Sensitivity factor (TSF), was defined as the dose of oral tyramine that increased systolic blood pressure by 30 mm Hg (Tyr30) that is calculated as the subject-specific Tyr30 at screening, divided by the subject-specific Tyr30 on treatment. The study compared safinamide 100 mg (highest therapeutic dose), safinamide 350 mg (supratherapeutic dose), selegiline 10 mg (recommended dose) which is an approved MAO-B inhibitor, and phenelzine (a nonselective MAO inhibitor) as a positive control. The results showed safinamide, 100 mg and 350 mg, respectively, potentiated the pressor effect of tyramine by 1.6-fold and 1.8-fold versus placebo, compared to 2.2-fold for selegiline 10 mg and 6-fold for phenelzine 30 mg.

The results support the sponsor's proposed statement in labeling that safinamide can be taken without dietary tyramine restriction. However, in the sponsor's clinical trials program some patients developed hypertension including hypertensive crisis while taking safinamide in

recommended doses. In addition, rasagiline (Azilect) and selegiline (Eldepryl) are also selective MAO-B inhibitors approved for treating PD. These products have class language advising prescribers to inform patients that ingestion of foods or beverages with high levels (>150 mg) of tyramine could cause hypertension. The individual nature of the response to ingested tyramine and the potential variation of the amount of tyramine contained in food and beverages may lead to hypertension in an individual patient.

Thorough QT (TQT) Study

The Interdisciplinary Review Team for QT Studies was consulted to review the results of the sponsor's TQT study (IMPL 28559). Two hundred forty healthy subjects were enrolled into one of 4 arms: Safinamide 100 mg, Safinamide 350 mg, Placebo and Moxifloxacin 400 mg (active control). Safinamide 350 mg was considered to be an adequate supratherapeutic dose. The results showed that safinamide 100 mg and 350 mg dose caused dose dependent QT shortening. QT prolongation was not observed.

OCP Recommendation

The Office of Clinical Pharmacology (OCP/DCP I) concluded the information in the NDA submission was acceptable from a Clinical Pharmacology and Biopharmaceutics point of view. The information supports an approval action however, OCP recommended a Postmarketing Requirement to characterize drug-drug interaction of safinamide and BCRP substrates

Post-Marketing Requirement:

1. A clinical study to characterize drug-drug interaction of safinamide and BCRP substrates in healthy volunteers NW-1689 is a major metabolite of safinamide found in plasma at the concentration of approximately 160% of parent compound, safinamide. NW-1689 inhibited BCRP with an IC₅₀ of $3.7 \pm 0.5 \mu\text{M}$. The average maximal plasma concentration of Safinamide was approximately 4 μM in Parkinson's disease patients treated with the highest dose of 100 mg/day. Based on this information from in vitro evaluation, there is a need for further in vivo drug interaction study at post-approval stage. Substrates of BCRP include methotrexate, mitoxantrone, imatinib, irrinotecan, lapatinib, rosuvastatin, sulfasalazine, topotecan.

6. Clinical Microbiology

The specifications and the methods of assessment for microbial limits for the drug product for were included The OPQ review. The proposed limits and assessments are acceptable.

7. Clinical/Statistical- Efficacy

The sponsor's application relies upon the results of the five clinical trials listed in Table 7 to provide evidence of safety and effectiveness. Long-term safety is supported by three double blind extensions studies NW-017, NW-018 and 27938 and open label study 28850.

Table 7: Overview of Clinical Trial Supporting Effectiveness

Phase	Study ID/Title	Study Design and Population	Primary Endpoint/ Analysis	Secondary Endpoints	Doses	N	Duration Months
Add-on to a Dopamine Agonist							
II/I IIa	NW-1015/009/II/2001 - A Dose Finding, Double-Blind, Placebo-Controlled Study to Investigate the Efficacy and Safety of Safinamide, an MAO-B Inhibitor, in Patients Affected by	DB, placebo-controlled, dose finding study, add-on to DA, 3 parallel groups, 12 weeks duration. Early PD,	UPDRS III responders ($\geq 30\%$ improvement) ^{*(2)} <i>Primary Analysis (ITT):</i> Logistic regression <i>Subgroup Analyses:</i> -DA monotherapy patients ^{*(2)} - <i>De-novo</i> patients	UPDRS II UPDRS III mean change ^{*(1, 2)} CGI-C HAMD	0.5 mg/kg/day 1.0 mg/kg/day Placebo	55 (DA 33) 56 (DA 33) 56 (DA 34)	3
III	NW-1015/015/III/2003 [EudraCT Nr: 2004-000833-12] - A Phase III, Double-Blind, Placebo-Controlled Study to Determine the Efficacy and Safety of a Low (50 100 mg/day) and High (150 200 mg/day) Dose Range of Safinamide, as “Add-On” Therapy, in Patients with Early Idiopathic Parkinson's Disease Treated with a Stable Dose of a Single Dopamine Agonist.	DB, placebo-controlled, Add-on to DA, 3 parallel groups, 24 weeks duration. Early PD, non-fluctuators	UPDRS III change from baseline ^{*(1)} <i>Primary Analysis:</i> MMRM <i>Sensitivity Analyses:</i> ANCOVA – LOCF, OC and OC + RDO	CGI-C Responder Rate (UPDRS) ^{*(1)} CGI-S UPDRS II ^{*(1)} Cognition QoL	50-100 mg/day 150-200 mg/day Placebo	90 89 90	6

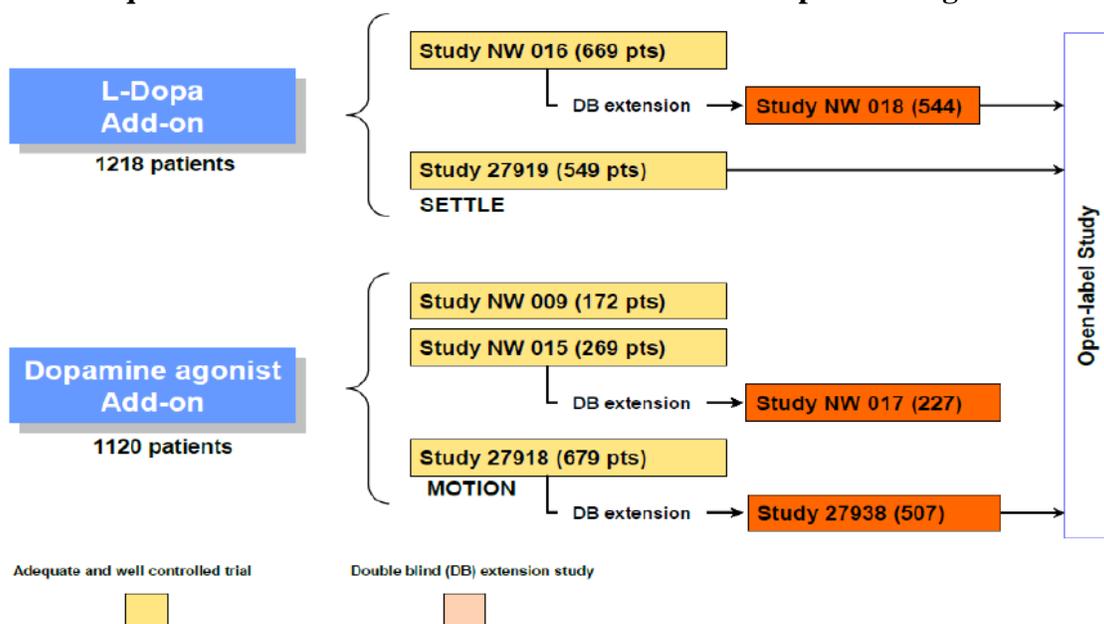
III	NW-1015/017/III /2003 2003 [EudraCT Nr: 2004-000835-27] A Phase III, Double-Blind, Placebo-Controlled, 12-Month Extension Study to Investigate the Efficacy and Safety of a Dose Range of Safinamide of 50-200 mg/day as Add-On Therapy in Patients with Early Idiopathic Parkinson's Disease Treated with a Stable Dose of a Single Dopamine Agonist.	Extension of Study 015; DB, placebo-controlled, 3 parallel groups, 48 weeks duration. Early PD, non-fluctuators	Time to intervention <i>Primary Analysis:</i> Cox proportional hazards model (assumptions not met) <i>Modified Primary Analysis:</i> Landmark analysis: 240-540 days ⁽¹⁾	CGI-C Responder Rate (UPDRS III) ^{*(1)} UPDRS III mean change CGI-S UPDRS II Cognition QoL	50-100 mg/day 150-200 mg/day Placebo	80 69 78	12
III	27918 (MOTION) [EudraCT Nr: 2007-002963-28] A phase III, double-blind, placebo-controlled randomized trial 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 subjects with early idiopathic Parkinson's Disease treated with a stable dose of a single dopamine agonist.	DB, placebo-controlled, add-on to DA, 3 parallel groups, 4 weeks duration. Early PD, non-fluctuators	UPDRS III change from baseline [DA monotherapy sub-population, n=666 ^{*(2)}] <i>Primary Analysis:</i> ANCOVA-LOCF <i>Sensitivity Analyses:</i> MMRM ANCOVA - OC	UPDRS II Cognition CGI-S CGI-C UPDRS III Responders QoL (EQ-5D; PDQ-39) ^{*(2)}	50 mg/day 100 mg/day Placebo	227 227 225	6
Add-on to Levodopa (alone or in combination with other PD medication)							

III	NW-1015/016/III/2006 [EudraCT Nr: 2006-005860-14] A Phase III, Double-Blind, Placebo-Controlled 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	DB, placebo-controlled, add-on to L-Dopa, 3 parallel groups, 24 weeks duration. Mid-to-late PD, fluctuators	Daily 'on' time, change from baseline ^{*(1,2)} <i>Primary Analysis:</i> MMRM; On-Treatment <i>Sensitivity Analyses:</i> - ANCOVA – LOCF and OC - On-and-Off-Treatment analyses	Decrease in daily 'off' time	50 mg/day	223	6 months
				Off' time after first morning L-dopa dose	100 mg/day	224	
				Cognition DRS in 'on' time UPDRS II in 'on' time ^{*(2)} UPDRS III in 'on' time UPDRS IV in 'on' time CGI-C CGI-S L-dopa dose reduction	Placebo	222	

Source Sponsor's Table

After completing Study NW-016, NW-015 or 27918 in early or late stage PD, patients were offered the opportunity to enter a long-term double blind extension study or a long-term open label study. Study 009 ended without a follow-on long-term controlled or open label study (Figure 1). Patients completing study 27919 or the long-term extension studies were offered the opportunity to enter the open label study 28850.

Fig 1: XX Sequence of Clinical Trials in the Safinamide Development Program



Source: Newron Figure

Study 28850 (Long-term, Open label Safety)

This was an open-label trial to determine the long-term safety of safinamide in Parkinson's disease patients. The study duration was planned to last up to 3 years however, the study was terminated early due to change in sponsorship on October 23, 2011. The study opened on April 22, 2009 the last patient visit was completed on June 5, 2012.

Study 28850 was a Phase III, single arm, open-label, multi-center, extension study, evaluating the long-term safety and tolerability of safinamide (50 mg/day to 100 mg/day) in eligible patients treated for early or late stage PD. Patients who completed a previous safinamide clinical study in PD and met all the inclusion and exclusion criteria were offered enrollment. Patients from the following studies were offered the opportunity to participate in study 28850:

- Study 018,
- MOTION extension (27938),
- SETTLE (27919),
- Cognition Study (EMR 701165-024),
- Levodopa-Induced Dyskinesia (LID) Study (701165-023) or
- Study 28780

Patients were initially dosed with 50 mg of safinamide daily, which was increased to 100 mg daily, the targeted dose for all patients. Investigators were permitted to adjust the dose of safinamide, or any concomitant medications, at any time according based on their clinical judgment.

In total, 964 were enrolled in study 28850 of which 706 patients completed the study. Data for all 964 patients was included in the sponsor's safety analyses and datasets.

Add-on Therapy in Patients Treated with a Stable Dose of a Dopamine Agonist (Early Stage PD (ESPD))

StudyNW-009

Study 009 was a double blind, placebo controlled, Phase 2 study in patients with early untreated (de novo) PD, or early patients taking a stable dose of a dopamine agonist (DA). The group treated with a stable dose of a DA was further divided into patients without prior treatment for PD or patients on treatment for PD at screening. The study was 12 weeks duration. Safinamide capsules were doses on a milligram per kilogram basis. Patients were randomized equally to safinamide 0.5 mg/kg, 1 mg/kg, or placebo. The patient dose in mg/kg was achieved by administering a combination of 10 mg and 50 mg safinamide capsules, or matching placebo. One hundred seventy two patients were randomized at study sites in France, Italy, Belgium, Germany and Poland. The first patient enrolled on October 9, 2001 and the last subject completed the study on October 17, 2002.

The primary endpoint for study 009 was the difference in the responder rates, defined as at least 30% improvement in UPDRS Part 3 scores from Baseline to Week 12, between the two safinamide groups and placebo. The primary analysis included all patients, those on a DA or de novo patients in the primary analysis. The sponsor conducted a secondary analysis (without multiplicity adjustment) of the subpopulation on a stable dose of a DA compared to de novo

patients. The mean baseline UPDRS (Part3) scores in each of the safinamide treatment groups was approximately 17. The primary analysis used a logistic regression model with Baseline UPDRS Part 3 scores, Country and Treatment Arm included in the model.

Table 8: Study 009 Analysis for Difference in Responder Rates UPDRS Part 3 Scores

Responder Rates(a) (n/% of Patients)	Safinamide 0.5 mg/kg/day		Safinamide 1.0 mg/kg/day		Placebo		P-value vs. Placebo Group (Logistic regression analysis)	
	n/N	%	n/N	%	n/N	%	Saf 0.5 mg/kg	Saf 1.0 mg/kg
Population								
Total population	17/55	30.9	21/56	37.5	12/56	21.4	0.143	0.018
Single DA-agonist (n=101)	12/33	36.4	16/34	47.1	7/34	20.6	0.195	0.006
De novo (n=66)	5/22	22.7	5/22	22.7	5/22	22.7	0.874	0.925

ANCOVA=analysis of covariance; DA=dopamine; de novo=currently untreated with any PD medication; n=number of responders; N=total number in group; Saf=safinamide; UPDRS III=Unified Parkinson's Disease Rating Scale - Section III (Motor Examination). Endpoint=Week 12 or early discontinuation. a. Responder was defined as ≥30% improvement from baseline in UPDRS III total score. Source: CSR Study 009. Source: Newron

The results of the primary analysis (Table 8) for the difference in the responder rate (the percentage of the patients who had a 30% improvement in UPDRS Part 3 scores) for the safinamide 1mg/day compared to placebo was statistically significant however, the comparison of the 0.5 mg/day dose to placebo was not significant. The subgroup analysis was nominally significant in the 1 mg/kg dose subgroup taking a DA but not for the de novo subgroup.

Table 9: Study 009 the Change from Baseline in UPDRS Part 3 Scores

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Table 8: Summary of UPDRS III Score
Intention-to-treat Analysis Set

Page 1 of 4

Overall		Treatment Group						Kruskal-Wallis p-value
		Safinamide 0.5 mg/kg N = 55		Safinamide 1.0 mg/kg N = 56		Placebo N = 56		
		Actual	Change	Actual	Change	Actual	Change	
Baseline	n	55		56		56		
	Missing	0		0		0		
	Mean (sd)	16.4 (7.7)		16.5 (7.4)		17.3 (7.8)		
	Median	15.0		15.5		16.0		
	Range	3 - 34		3 - 36		5 - 43		
Visit 5	n	53	53	52	52	52	52	0.3062
	Missing	2	2	4	4	4	4	
	Mean (sd)	14.8 (7.9)	-1.4 (4.9)	14.2 (7.2)	-2.1 (3.3)	16.3 (8.2)	-1.0 (2.8)	
	Median	13.0	-1.0	15.0	-1.5	15.0	-1.0	
	Range	1 - 34	-17 - 9	0 - 29	-8 - 5	0 - 41	-9 - 5	
Visit 7	n	51	51	50	50	50	50	0.1526
	Missing	4	4	6	6	6	6	
	Mean (sd)	14.8 (8.0)	-1.6 (5.8)	12.9 (6.8)	-3.3 (4.2)	16.7 (9.2)	-0.8 (5.0)	
	Median	15.0	-2.0	12.0	-2.5	16.0	-1.0	
	Range	0 - 30	-21 - 11	0 - 28	-16 - 3	0 - 40	-11 - 11	
Final Visit	n	55	55	56	56	56	56	0.1935
	Missing	0	0	0	0	0	0	
	Mean (sd)	13.8 (7.8)	-2.6 (5.5)	13.2 (7.1)	-3.3 (5.5)	16.7 (8.9)	-0.6 (5.4)	
	Median	12.0	-2.0	13.0	-1.0	16.0	-1.0	
	Range	0 - 33	-24 - 11	0 - 29	-19 - 8	1 - 43	-10 - 14	

N = Number of patients
n = Number of patients with data available
sd = standard deviation

Source: Newron

CDTL Comment:

The Part 3, motor subscale of the UPDRS has a maximum possible score of 108 for all items. A study of the clinometric properties of The UPDRS found the mean UPDRS, Part 3 scores in a cohort (n=404) of patients with early, untreated PD was 17.8 with a standard deviation of ± 8.4 (Siderowf et al., 2002). Several patients in study 009 who met responder criteria had very low baseline UPDRS Part 3 scores. The 1 mg/kg safinamide responder subgroup included six patients with a baseline UPDRS Part 3 score ≤ 10 , all of these patients had change scores at the final visit that were below eight, and three had change scores of four points or less however, small change (4/104 or 4% change in the maximum UPDRS Part 3 score) still qualified them as a 30% responder. The percent change in UPDRS Part 3 scores and the proportion of responders inflates the magnitude of the change in UPDRS Part 3 scores to make a small change in UPDRS Part 3 scores appear larger however, these small changes may not be clinically meaningful especially in very mildly or severely affected patients.

Dr. Kapcala points out in his review that the division has not approved treatments for PD based on the responder rate based for UPDRS Part 3 scores. Typically, the difference in UPDRS Part 3 scores from baseline to trial completion is has served as the primary endpoint in pivotal trials that support new treatments for PD. The results of protocol specified analysis (Kruskal-Wallis test) for the change in UPDRS Part 3 scores (Table 9) from baseline to Visit 9 (final visit) for either safinamide dose compared to placebo was not a statistically significant. The sponsor conducted a post hoc reanalysis of the data in 2004. The post hoc ANCOVA reanalysis shows a significant treatment benefit of safinamide 0.5 mg/kg and 1 mg/kg compared to placebo. The sponsor did not provide a justification as to why the protocol specified analysis was incorrect, or why the ANCOVA was the correct analysis.

CDTL Comment

The results of study 009 do not show that safinamide provides a clinical meaningful benefit to patients with early PD, whether safinamide is administered as monotherapy or as an adjunct treatment with a single DA. In addition, the mg/kg dosing scheme used in study 009 does not support the 50 mg to 100 mg per day regimen proposed in draft labeling. The formulation and dosing regimen are not the same as the To Be Marketed formulation or the proposed dosing recommendations.

Study NW-015

This was a randomized, double blind, placebo-controlled, parallel-group, Phase III study, comparing two oral dose ranges of safinamide (High Dose: 150 to 200 mg/day and Low Dose: 50 to 100 mg/day) versus Placebo, as add-on therapy to a stable dose of a single DA. The trial was conducted in 26 study centers in Argentina (2), Chile (2), Colombia (3), India (5), Italy (8), Spain (3) and the United Kingdom (2). The first patients enrolled on December 21, 2004 and the last patients completed the study on January 23, 2006.

The primary efficacy endpoint was the UPDRS Part 3 score at the 6 post-baseline visit for the ITT population. The primary analysis model was a mixed model ANCOVA with Baseline UPDRS Section III total score as covariate, Treatment, visit and the treatment*visit interaction as fixed effects and Country treated as a random effect. The plan to control for multiple comparisons placed the high dose first followed by the low dose group in a testing order. Missing clinical outcomes data were not imputed for the primary analysis.

The results of the primary analysis (Table 10) did not show a significant benefit for the high dose group compared to placebo (P=0.6504). Testing of the low dose was not permitted under the gatekeeping procedure. The sponsor’s analysis of the low dose group reported a nominally significant improvement for the mean UPDRS Part 3 score for the low dose group compared to placebo. Sensitivity analyses using several different methods of imputation did not change the results for the primary analysis. The CGI-C was included as a secondary endpoint. The result of the CGI-C was not significant for the high dose or the low dose (Table 11).

Table 10: Primary Efficacy Parameter: UPDRS Section III (Motor) Total Score at Each Visit, Endpoint and Change from Baseline for the ITT Population (No Imputation for Missing Data)

Visit Statistic	Treatment					
	High Dose Safinamide		Low Dose Safinamide		Placebo	
	Value	Change	Value	Change	Value	Change
Baseline						
n (N)	89 (89)		90 (90)		90 (90)	
Mean (SD)	19.3 (9.80)		22.0 (10.15)		20.7 (9.63)	
Median	18.0		21.5		18.5	
Min; Max	6; 45		3; 59		3; 53	
Visit 3						
n (N)	86 (89)	86 (89)	87 (90)	87 (90)	88 (90)	88 (90)
Mean (SD)	16.5 (8.61)	-2.8 (4.70)	19.0 (9.05)	-3.5 (4.93)	18.2 (9.28)	-2.1 (3.67)
Median	15.0	-1.5	17.0	-2.0	16.0	-1.0
Min; Max	3; 39	-15; 14	4; 46	-19; 8	4; 55	-15; 6
Visit 4						
n (N)	80 (89)	80 (89)	86 (90)	86 (90)	86 (90)	86 (90)
Mean (SD)	15.5 (8.66)	-4.2 (4.72)	18.0 (9.55)	-4.5 (5.64)	17.4 (9.15)	-3.1 (4.72)
Median	14.0	-4.0	16.5	-4.0	16.0	-3.0
Min; Max	2; 36	-21; 5	2; 58	-20; 10	3; 42	-13; 17
Visit 5						
n (N)	78 (89)	78 (89)	85 (90)	85 (90)	85 (90)	85 (90)
Mean (SD)	15.4 (9.06)	-4.4 (5.13)	16.9 (8.39)	-5.7 (6.43)	16.3 (9.06)	-4.2 (5.42)
Median	13.5	-4.0	16.0	-5.0	15.0	-4.0
Min; Max	2; 41	-14; 14	3; 42	-22; 12	3; 45	-16; 17
Visit 6						
n (N)	79 (89)	79 (89)	85 (90)	85 (90)	87 (90)	87 (90)
Mean (SD)	14.6 (9.20)	-4.5 (5.57)	16.1 (9.18)	-6.4 (6.98)	16.2 (9.20)	-4.5 (6.11)
Median	12.0	-4.0	15.0	-5.0	14.0	-4.0
Min; Max	2; 42	-15; 15	2; 49	-28; 8	3; 45	-23; 17
Visit 7						
n (N)	74 (89)	74 (89)	82 (90)	82 (90)	84 (90)	84 (90)
Mean (SD)	14.9 (9.07)	-4.8 (5.55)	16.1 (8.63)	-6.6 (7.23)	16.5 (9.43)	-4.2 (5.94)
Median	12.5	-4.0	15.0	-7.0	14.0	-3.0
Min; Max	2; 38	-22; 10	1; 40	-24; 18	2; 49	-22; 17
Endpoint						
N (n)	81 (89)	81 (89)	86 (90)	86 (90)	87 (90)	87 (90)
Mean (SD)	15.6 (9.61)	-3.9 (6.01)	16.3 (8.97)	-6.0 (7.18)	17.1 (8.85)	-3.6 (7.08)
Median	14.0	-4.0	15.0	-5.0	16.0	-3.0
Min; Max	2; 51	-18; 13	1; 46	-26; 8	3; 44	-24; 18
95% Confidence interval		[-2.3, 1.4]		[-3.7, -0.1]		
Point estimate		-0.4		-1.9		
p-value		0.6504		0.0419		

n: Number of patients with an evaluation; N: Number of patients in the ITT population; ITT: Intention to Treat;

ME: Motor examination; SD: Standard deviation; UPDRS: Unified Parkinson's Disease Rating Scale.

Baseline: Visit 2.

Endpoint: Visit 8 (Week 24) or Visit 8 (Early Discontinuation), depending on last date of evaluation.

A mixed linear model was used to calculate a point estimate, 95% confidence interval and p-value for the difference between active treatment groups and Placebo in the change from Baseline at Endpoint. The unstructured covariance model was used as output.

Source: Newron Table

Table 11: Secondary Efficacy Parameter: CGI - Change from Baseline Score at Endpoint (LOCF) for the ITT Population

Visit Category	High Dose Safinamide (N=89)		Low Dose Safinamide (N=90)		Placebo (N=90)	
	n	%	n	%	n	%
Endpoint (LOCF)						
Improvement	51	59.3	56	62.22	43	48.86
No Change or Worsening	35	40.7	34	37.78	45	51.14
Point estimate	10.2		13.1			
95% Confidence interval	[-4.8; 25.2]		[-1.9; 28.1]			
p-value	0.1822		0.0829			
Breslow-Day	0.5786		0.9937			

Source: Newron

Patients completing 24 weeks of observation, or patients who discontinued prematurely from Study 15 were eligible to enroll in the long-term, double blind extension study 017.

CDTL Comment

The results of Study NW-015 do not show safinamide provides clinically meaningful benefit to patients with PD on DA monotherapy.

Study 27918 (MOTION)

A Phase 3, double-blind, placebo-controlled, randomized trial 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 subjects with early PD treated with a stable dose of a single dopamine agonist. The study was conducted at 112 study centers in 20 countries in Europe, Eastern Europe, Canada < Mexico and in 23 sites in the US. The first patient enrolled on March 27, 2009, the last patient visit occurred on January 23, 2012. The original final study report was written on October 24, 2013 however, the sponsor amended the final report (Errata) on April 28, 2014.

The primary efficacy analysis was the changes from Baseline to Week 24 in motor symptoms UPDRS Part 3 scores in the ITT population. Secondary endpoints included the change in UPDRS Part 2 (activities of daily living) scores, cognition, change in global clinical status, responder rates with regard to motor symptoms, and health related quality of life.

A hierarchical procedure was used for the comparison of the primary endpoint between each safinamide dose to placebo. The safinamide 100-mg/day dose was compared with placebo first, if this comparison was statistically significant, then the safinamide 50-mg/day dose was compared to placebo. Testing of the 50 mg dose compared to placebo was not permitted if the 100 mg dose was not superior ($p > 0.05$). A sensitivity primary analysis of the primary endpoint (change in UPDRS Section III score) was performed in the ITT population using the On-Treatment Approach (i.e., approach in which only the On-Treatment efficacy data were used for analysis).

This primary endpoint was analyzed using an analysis of covariance (ANCOVA) model on the change from Baseline to Week 24, with fixed effects of treatment and region and the Baseline value of the UPDRS Section III score as the covariate.

An amended study report was submitted after a blinded review that reportedly occurred prior to database lock. After the blinded review of the data, the sponsor excluded patients from the primary analysis because of “major protocol violations.”

The results for the protocol specified primary efficacy measure in the ITT population (without exclusions) showed that, at Week 24, the LS mean difference between the safinamide and placebo groups was -1.96 (p=0.073) for the 100-mg/day dose and -1.95 (p=0.259) for the 50-mg/day dose.

However, an analysis of the amended ITT population that excluded efficacy data from 13 patients who were not receiving a “DA as monotherapy” at baseline (Table 12), showed a statistically significant (p=0.0396) LS mean (SE) treatment difference of -1.20 for the safinamide 100 mg/day group, compared to placebo. The same analysis for 50 mg/day (low dose) safinamide group compared to placebo was not statistically significant (p= 0.228) The sponsor argues this post hoc analysis (performed after completing the original final study report) indicates that inclusion of data from these 13 subjects may have adversely affected the primary efficacy analysis for the ITT population.

Table 12: Study 27918 (MOTION) Reason for Post Randomization Exclusion of 13 Patients

Table 20. Subjects Excluded From the MOTION Study Efficacy Analyses: Did Not Meet DA-Agonist Monotherapy Requirement or Did Not Take a Dose of Study Medication		
Subject ID Number	Region	Reason for Violating Dopamine Agonist Monotherapy Requirement at Baseline
Safinamide 50 mg/day		
003-0001	North America	Receiving carbidopa and levodopa
023-0006	Asia	Receiving trihexyphenidyl
092-0008	Eastern Europe	Receiving amantadine
Safinamide 100 mg/day		
023-0009	Asia	Receiving trihexyphenidyl
044-0001	Latin America	Receiving amantadine
045-0005	Latin America	Receiving biperiden
080-0001	Eastern Europe	Receiving biperiden
092-0010	Eastern Europe	Receiving biperiden
179-0008	Eastern Europe	Receiving amantadine
Placebo		
023-0007	Asia	Receiving trihexyphenidyl
023-0008	Asia	Receiving trihexyphenidyl
058-0003	Eastern Europe	Not receiving single dopamine agonist/not at stable dose
Note: An additional subject (Subject No. 159-0003 [North America]) was randomized to treatment (safinamide 100 mg/day) but did not receive any study medication and was discontinued after four days; therefore, this subject was also excluded from the analysis.		
Source: Appendix 16.2.12.4 .		

Source: Newron

All six patients assigned to the safinamide 100 mg group were taking a concomitant DA (Table 13). In addition to a DA, these patients were treated with an anticholinergic medication or amantadine. Both medications are not commonly prescribed for patients with PD because neither is considered to be first line agents because of their relative low potency for treating PD symptoms, and a high frequency of adverse events associated with these medications.

Table 13: Study 27918 (MOTION) Concomitant Medications for The 13 Patients Excluded from the Sponsor’s Analysis of the ITT Population

Usubjid (Study ID/Sub ID)	Trt01a	Amantadine	Biperiden	*Pramipexole	Ropinirole	Rotigotine	Sinemet	*Trihexyphenidyl
000002791 80230007	Placebo	0	0	0	1	0	0	1
000002791 80230008	Placebo	0	0	0	1	0	0	1
000002791 80580003	Placebo	0	0	0	0	0	0	0
000002791 80230009	Safinamide 100 mg/day	0	0	0	1	0	0	1
000002791 80440001	Safinamide 100 mg/day	1	0	1	0	0	0	0
000002791 80450005	Safinamide 100 mg/day	0	1	1	0	0	0	0
000002791 80800001	Safinamide 100 mg/day	0	1	1	0	0	0	0
000002791 80920010	Safinamide 100 mg/day	0	1	1	0	0	0	0
000002791 81790008	Safinamide 100 mg/day	1	0	0	0	1	0	0
000002791 80030001	Safinamide 50 mg/day	0	0	0	0	0	1	0
000002791 80230006	Safinamide 50 mg/day	0	0	0	1	0	0	1
000002791 80920008	Safinamide 50 mg/day	1	0	1	0	0	0	0

*Combined with Pramipexole HCL or Trihexyphenidyl HCL. Highlighted medications are FDA approved dopamine agonists
Source: CDTL

Table 14: Study 27918 (MOTION) Change in UPDRS Part 3 Scores for Patients Assigned to the Safinamide 100 mg/day Excluded from The Primary Endpoint

USUBJID	ITT FL	MITT FL	COMPL FL	TRT Per 01 Act	AVISIT	PARAM	Act Value	DTYPE	BASE	CHG
0000027918 0230009	Y	Y	Y	SAFIN AMID E 100 mg/day	Week 24	UPDRS SECTIO N 3	23		14	9
0000027918 0440001	Y	Y	N	SAFIN AMID	Week 24	UPDRS SECTIO	19	LOCF	19	0

				E 100 mg/day		N 3				
0000027918 0450005	Y	Y	Y	SAFIN AMID E 100 mg/day	Week 24	UPDRS SECTIO N 3	19		19	0
0000027918 0920010	Y	Y	Y	SAFIN AMID E 100 mg/day	Week 24	UPDRS SECTIO N 3	16		16	0
0000027918 1790008	Y	Y	Y	SAFIN AMID E 100 mg/day	Week 24	UPDRS SECTIO N 3	25		14	11

Source: CDTL

Subject 080-0001 improved -9 points from a baseline score of 18 to a Week 24 score of 9. All of the remaining 5 patients in the safinamide 100 mg group excluded from the primary analysis either did not improve or their score at Week 24 had substantially worsened compared to baseline (positive change (CHG) number) (See Table 14 above).

CDTL Comment:

Patients treated with an anticholinergic medication or amantadine in addition to a DA is not sufficient to exclude patients from the efficacy analysis after they were randomized and treated under the protocol. The Exclusion Criteria for Study 27918 specify patients must only be on a DA for treatment of PD, these patients were enrolled in the study, and met all other criteria for inclusion in the ITT population. The delay in excluding these patients raises concerns that multiple exploratory analyses were performed before making the decision to exclude these patients.

The results of Study 27918 and Study NW-015 failed to show superiority of safinamide compared to placebo according to the protocol specified primary analysis. The primary endpoint, the proportion of responders (30% improvement) on Part 3 of the UPDRS does not provide evidence of clinically meaningful benefit to patients with early stage PD. The sponsor has not met the statutory requirement to show evidence of effectiveness for safinamide as adjunct treatment with a DA in patients with PD.

Parkinson’s Patients on Concomitant Levodopa (Late Stage PD)

Study NW-1015/016 (NW-016)

A Phase 3, double-blind, placebo-controlled study to evaluate the efficacy and safety of a low (50 mg/day), and high (100 mg/day) dose of safinamide, as add-on therapy to a stable dose of levodopa, in patients with PD and motor fluctuations. Patients had to be treated with a stable dose of levodopa, but patients could also take stable dose of a dopamine agonist, and/or other PD medications (e.g., COMT inhibitor, anticholinergic, or amantadine).

The study was conducted in 52 study centers: 35 in India, 10 in Romania, and 7 in Italy. The first patient enrolled on January 13, 2007, and the last patients completed the last visit on October 28, 2008.

The total duration of the study was approximately 30 weeks, divided into the following periods:

- Screening period (10 days)
- Levodopa stabilization phase (4 weeks)
- Treatment period (24 weeks), with an optional 1-week taper phase.

All randomized patients completing the double-blind treatment period in this study could enter a 78-week, double-blind extension study (Study NW-1015/018).

Six hundred sixty nine patients were randomized to treatment (222 to placebo, 223 to safinamide 50 mg/day, and 224 to safinamide 100 mg/day), and 594 completed the study. The intent-to-treat (ITT) and safety populations included all 669 patients.

Ophthalmologic examinations were performed by a qualified ophthalmologist at Screening, Week 12, and Week 24 to monitor patients for signs of retinal degeneration that were observed in nonclinical studies.

Baseline Characteristics

The mean age in the Safinamide 50 mg, 100 mg and in the placebo group was 60-61 years. Approximately 70% of the population in each group was male. Asians accounted for approximately 80% of the patients in each group with whites accounting for approximately 19-20% in each arm of the study. Patients in the safinamide 50 mg group had a slightly shorter mean duration of PD at baseline 6.6 years, compared to approximately 7 years in the safinamide 100 mg/day and placebo groups.

Study Populations

Intent-to-Treat (ITT) Population: The ITT population was composed of all randomized patients, whether or not they received a dose of their assigned study drug or the correct treatment as designated in the protocol. The ITT population was used for the analysis of all efficacy parameters.

Retrieved Dropout (RDO) Population: The RDO population was composed of all randomized patients who discontinued prematurely, but returned for their efficacy assessment in the designated window period from Baseline. For a patient to be included in the RDO population, the patient must have returned for his or her scheduled efficacy assessments at Week 12 (Visit 6) and Week 24 (Visit 8) within the designated window. For these patients, the endpoint score was to be defined as the Week 24 score.

Patients with progressing disability related to PD during the study were permitted to receive Rescue Medication that was defined as an increase in the total daily dose of the PD therapy (i.e., 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. In most cases, patients who received rescue received an increase in levodopa. However, efficacy data (e.g., diary scores)

subsequent to the intervention were not included (censored) in the primary analysis. The last observation carried forward (LOCF) was used to impute efficacy data for patients having received rescue medication or discontinued for any reason. Investigators could decrease a patient's dose of levodopa if warranted, based upon the occurrence of AEs.

Planned Efficacy Analyses

On-treatment analysis: In this approach, patients' data were censored at the time of rescue medication intake or occurrence of RDO. The on-treatment mixed linear model analysis was the primary analysis.

On-and-off treatment analysis: In this approach, all available data were analyzed regardless of the intake of rescue medication and included RDO data. The On-and-Off-treatment mixed linear model analysis was performed for sensitivity purposes.

The multiplicity issue, given the three treatment groups, was managed by using a sequence of comparisons approach. The sequence to be used here is as follows:

- Step 1: Show that the 100 mg/day is superior to Placebo.
- Step 2: Show that the 50 mg/day is superior to Placebo.

Here the first step is based on a two-sided 5% test, and a significant result in the relevant direction is required to continue with the second step. The second step was also based on a two-sided test with alpha equal to 5%.

Primary Endpoint

The primary efficacy variable was the mean total daily ON time (ON time without dyskinesia plus ON time with non-troublesome dyskinesia) over 18 hours. Daily motor function was assessed using the Parkinson's disease Patient Diary. The On-treatment analysis (data was censored at the time of rescue medication intake), used a repeated measures analysis on the change from Baseline.

Secondary Endpoints

The sponsor's hierarchy for the secondary endpoints changed three times over five protocol revisions. The last protocol revision (version 5) containing the final change for the hierarchy of secondary endpoints is dated December 19, 2008, two months after the last patient completed the trial October 28, 2008. The database was originally locked on December 31, 2008.

Excerpt from Protocol Version 1 (January 9, 2006)

11.6.2 Secondary Efficacy Analysis

The secondary efficacy analysis will include the following:

- increase in mean “on” time following first morning dose of levodopa
- change in cognition (cognitive test battery)
- decrease in daily “off” time, as measured by diary cards
- improvement in the Dyskinesias Rating Scale during “on” phase
- UPDRS Section II during “on” phase (based on diary) - mean change from baseline to endpoint
- UPDRS Section III during “on” phase (based on diary) - mean change from baseline to endpoint
- CGI - Change from baseline - mean score in the course of the study
- CGI - Severity of illness – mean change from baseline to endpoint
- mean percentage reduction in levodopa dose.

The secondary efficacy measures will be evaluated in a hierarchical fashion. Each of the above variables will be analyzed sequentially as long as a significant difference between treatment groups is detected. If a significant difference is detected between the placebo group and the high dose group (150-200 mg/day), the analysis will proceed to compare the placebo group to the low dose group (50-100 mg/day). This approach should avoid the need for correcting the p-value due to multiplicity of testing.

Protocol Version 2 (May 15, 2007)

11.6.2 Secondary Efficacy Analysis

The secondary efficacy analysis will include the following:

- Decrease in total daily “off” time, as measured by diary cards
- decrease in mean “off” time following first morning dose of levodopa
- change in cognition (cognitive test battery)
- improvement in the Dyskinesias Rating Scale during “on” phase
- UPDRS Section II during “on” phase (based on diary) - mean change from baseline to endpoint
- UPDRS Section III during “on” phase (based on diary) - mean change from baseline to endpoint
- CGI - Change from baseline - mean score in the course of the study
- CGI - Severity of illness – mean change from baseline to endpoint
- mean percentage reduction in levodopa dose.

The secondary efficacy measures will be evaluated in a hierarchical fashion. Each of the above variables will be analyzed sequentially as long as a significant difference between treatment groups is detected. If a significant difference is detected between the placebo group and the high dose group (100 mg/day), the analysis will proceed to compare the placebo group to the low dose group (50-mg/day). This approach should avoid the need for correcting the p-value due to multiplicity of testing.

Excerpt from Protocol Version 5 December19, 2008)

PROTOCOL No. NW-1015/016/III/2006
Amendment No. 5, 19th December, 2008

6 of 19
FINAL

2. CHANGES TO THE PROTOCOL

Specific changes to the protocol are listed below. Each amended word, sentence or paragraph is referred to by the section and page numbers in the most recent version of the protocol dated 29th July 2008 (clean copy). New characters/words/sections are indicated in **bold and underlined text**. Text from the original document that has been deleted or replaced is indicated with a ~~strike through~~.

SYNOPSIS, p2

Methodology, p5

Study Objectives – Efficacy Evaluations:

Efficacy will be evaluated by the following:

- Primary efficacy variable:
 - Increase in mean daily “on” time (“on” time without dyskinesia plus “on” time with minor dyskinesia) during 18-hr diary recording period
- Secondary efficacy variables:
 - Decrease in total daily “off” time, as measured by diary cards
 - **UPDRS Section III during “on” phase (based on diary) – mean change from baseline to endpoint**
 - **CGI - Change from baseline - mean score in the course of the study**
 - **change in cognition (cognitive test battery)**
 - decrease in mean “off” time following first morning dose of levodopa
 - ~~change in cognition (cognitive test battery)~~
 - improvement in the Dyskinesias Rating Scale during “on” phase
 - UPDRS Section II during “on” phase (based on diary) – mean change from baseline to endpoint
 - ~~UPDRS Section III during “on” phase (based on diary) – mean change from baseline to endpoint~~
 - ~~CGI - Change from baseline – mean score in the course of the study~~
 - CGI- Severity of illness – mean change from baseline to endpoint
 - mean ~~percentage reduction~~ **percent change** in levodopa dose

The secondary efficacy analyses were analyzed according to the final hierarchy in Version 5 of the protocol and in the final Statistical analysis plan:

1. Decrease in total daily “off” time, as measured by diary cards – change from baseline to endpoint
2. **UPDRS Section III during “on” phase (based on diary) - mean change from baseline to endpoint**
3. **CGI - Change from baseline - mean score in the course of the study**
4. **Change in cognition (cognitive test battery) (analysis is beyond the scope of this document) mean change from baseline to endpoint (and to each evaluation done)**

5. Decrease in mean “off” time following first morning dose of levodopa – change from baseline to endpoint
6. Improvement in the Dyskinesias Rating Scale during “on” phase – change from baseline to endpoint
7. UPDRS Section II during “on” phase (based on diary) - mean change from baseline to endpoint
8. CGI - Severity of illness – mean change from baseline to endpoint Mean percentage reduction in levodopa dose – change from baseline to endpoint

For the decrease in total daily “off” time, decrease in mean “off” time following the first morning dose of levodopa, UPDRS - Sections II and III, and CGI-Severity, change from Baseline to Endpoint will be analyzed using analysis of covariance (ANCOVA) with baseline values as a covariate and treatment regimen and center as main effects.

The Dyskinesias Rating Scale (DRS) and the percentage reduction in levodopa dose, will be analyzed using the Wilcoxon Rank Sum Test. PROC NPAR1WAY with options WILCOXON and CLASS TREATMENT will be used. For DRS the changes from baseline will be considered irrespective of the most disabling dyskinesia.

The normal approximation z two-sided p-value will be used to determine statistical significance of the reduction in levodopa dose in 100 mg/day and 50 mg/day treatment groups, as compared to placebo.

For analyzing CGI - Change score, the Cochran-Mantel-Haenszel test (CMH3 for General Association Statistic) blocking on center, was used to compare the proportion of patients showing improvements (score of 1, 2, or 3) versus no change or worsening (scores of 4, 5, 6 or 7). PROC FREQ using center as stratification factor was employed.

Secondary efficacy analyses were performed on the mITT population using analysis of covariance (ANCOVA) models with treatment and center effects and endpoint specific baseline as the covariate. The “ON treatment” approach and the last observation carried forward (LOCF) method for imputing missing data were used for the analyses.

Blinded Analysis of Variance

The original protocol did not include an interim analysis however; a blinded assessment of the magnitude of the variance of the primary efficacy variable was performed. The blinded assessment of variance was performed when 220 patients completed visit 7 (18weeks).

Unblinded Analysis of the Safety Data

An unplanned interim analysis for safety (ophthalmology data only) was performed per protocol Amendment 4. This unblinded interim safety analysis was performed after the first 350

randomized patients were enrolled and the dataset included 301 patients who completed 24 weeks of treatment.

Database Unlocking

The original study database was locked on December 31, 2008 with 6 queries outstanding. These queries comprised a variety of domains and included clarification of 2 CGI ratings, 1 levodopa dose, 1 AE, 1 SAE, and 1 concomitant medication. After unblinding, during the statistical analysis, minor issues with the drug kit numbers, AE stop and start dates, and discontinuation reasons needed clarification.

- The database was unlocked on January 13, 2009, updated, and then relocked on January 15, 2009. Statistical analyses, as per the study SAP were performed on the relocked database.
- The study database was unlocked again on July 31, 2010, updated, and then relocked on August 20, 2010. The update to the database contained all the issues outlined in the errata list and documented in the relock documentation.
- The core study database was unlocked for a third time on September 13, 2010, and then relocked on September 16, 2010 to correct AE and laboratory AE discrepancies. The final statistical tables, including the ad-hoc tables, were produced based on the September 16, 2010 version of the study database.

The changes that followed each database unlocking and relocking cannot be traced to a specific date. In all, the sponsor provided over 2000 pages showing tracked changes to demographic data, concomitant medications, clinical laboratory values and efficacy outcomes including the primary efficacy outcomes. The changes in efficacy outcome tables were caused by minor corrections in the number of patients in the ITT population that did not significantly change the efficacy results.

FDA Statistical Review of Efficacy

Dr. Xiangmin Zhang, PhD was the FDA statistical reviewer for this NDA. After filing, it was discovered, the sponsor made several errors in the NDA submission for derived variables that were not adequately described in the Define files. In several instances, clarification was needed because references to study endpoints used inconsistent terminology in the protocol that differed from the terms used in the final study report. The correct protocol specified analyses were not presented in the completed study report. Dr. Zhang noted errors in the sponsor's results for the MMRM analysis of the efficacy Study 016. These analyses were corrected (Table 15) and resubmitted (July 24, 2015) following an information request from Dr. Zhang.

Excerpt from the July 1, 2015 email request to the Sponsor

“You ignored the treatment-by-visit interaction when you calculated the LS estimates. The LS estimates should use the last visit (i.e. Week 24 for Study 016 and Week 102 for combined studies 016/018). In the SAS programs, you need to include an ESTIMATE statement (or a LSMEANS statement) for the treatment-by-visit interaction to obtain the correct LS differences and p-values”

Efficacy Results

The result for the primary efficacy variable was the mean total daily ON time (ON time without dyskinesia plus ON time with non-troublesome dyskinesia) over 18 hours (Table 16-highlighted) was significant for the 100 mg and 50 mg safinamide groups compared to placebo, regardless of whether the ANCOVA or MMRM analysis was used, and the result was not meaningfully changed when the correct analysis was applied.

When the sponsor resubmitted the correct analyses they include the MMRM and ANCOVA analyses for all of the primary and secondary endpoints (Table 16), they included several additional analyses were not specified in the SAP. The testing procedure for the secondary endpoints should have stopped at the change in cognition (cognitive test battery) mean change from baseline to endpoint (and to each evaluation done) for the 100 mg dose. The sponsor’s conclusion for the results of the Cognitive Assessment in study 016 appears below.

Protocol No: NW-1015/016/III/2006 Statistical Analysis Report on Cognitive Assessment

“Throughout all Cogtest assessments performed, neither of the two treatment doses showed any consistent significant differences within any of the subgroups assessed.” There were only two statistically significant differences, one each within the ‘Responders’ and ‘Freezing’ subgroups, with the high dose group.

The key secondary endpoints, OFF time, the UPDRS Part 3 (Table 15 highlighted) and the mean change in CGI-C were statistically significant under the sponsor’s gatekeeping procedure. The Statistical Analysis Plan included the change in mean CGI-C scores over the course of the study as the prespecified hierarchy of secondary endpoints. The results of the CGI-C does not appear in Table 15 but the CGI-C at Visit 8 (Endpoint) was significant for the safinamide 50 mg (66% improved, p=0.001) and the 100 mg group (64% Improved, p=0.009) compared to placebo (55% improved).

Table 15: Study 016: Corrected Analysis for the Efficacy Endpoints LSPD Patients (mITT Population).

Study 016: Change from Baseline at Endpoint ("ON treatment" approach)					
Efficacy Parameter	Statistic (a)	mITT Population			
		MMRM Analysis (b)		ANCOVA (LOCF) Analysis (c)	
		50 mg/day (n=217)	100 mg/day (n=216)	50 mg/day (n=217)	100 mg/day (n=216)
ON without T Dysk (h)	LS Diff vs Pbo p-value	0.50 0.0356	0.53 0.0238	0.46 0.0387	0.55 0.0134
ON without Dysk (h)	LS Diff vs Pbo p-value	0.41 0.1463	0.56 0.0470	0.46 0.0710	0.64 0.0122
ON with NT Dysk (h)	LS Diff vs Pbo p-value	0.08 0.6834	-0.04 0.8360	-0.03 0.8641	-0.14 0.4349
ON with T Dysk (h)	LS Diff vs Pbo p-value	0.11 0.4080	0.06 0.6669	0.11 0.3488	0.06 0.6438

OFF Time (h)	LS Diff vs Pbo	-0.54	-0.53	-0.55	-0.57
	p-value	0.0088	0.0110	0.0049	0.0037
Asleep Time (h)	LS Diff vs Pbo	-0.07	-0.05	-0.03	-0.03
	p-value	0.4565	0.5909	0.7622	0.7174
UPDRS I	LS Diff vs Pbo	0.02	-0.02	0.02	0.00
	p-value	0.8460	0.8968	0.8484	0.9920
UPDRS II	LS Diff vs Pbo	-0.38	-0.75	-0.49	-0.91
	p-value	0.3253	0.0523	0.1718	0.0121
UPDRS III	LS Diff vs Pbo	-1.71	-2.24	-1.75	-2.48
	p-value	0.0373	0.0065	0.0212	0.0011
UPDRS II + III	LS Diff vs Pbo	-2.06	-3.00	-2.19	-3.37
	p-value	0.0654	0.0075	0.0334	0.0010
UPDRS I +II +III	LS Diff vs Pbo	-2.47	-3.23	-2.57	-3.25
	p-value	0.0269	0.0040	0.0203	0.0036

ANCOVA=Analysis of Covariance; Dysk=Dyskinesia; h = hours; LOCF=Last Observation Carried Forward; LS Diff vs Pbo=Least Squares Mean Difference vs. Placebo; LSPD=Late-Stage Parkinson’s Disease; MMRM=Mixed Model Repeated Measures; mITT=modified Intent-to-Treat; NT=Non-troublesome; ON=ON Time; T=Troublesome; UPDRS=Unified Parkinson’s Disease Rating Scale (Section I – Mentation, Behavior and Mood ; Section II - Activities of Daily Living; Section III – Motor Examination).

a. p-value for comparison between safinamide and placebo; significant effects (p<0.05) are in **bold text**.

b. MMRM model for change from Baseline to Endpoint includes treatment, center, and visit and treatment-by-visit as fixed effects, and baseline value as a covariate, using an unstructured variance-covariance matrix.

c. ANCOVA model is based on change from Baseline to Endpoint with treatment and center as main effects and baseline value as a covariate.

NOTE: gray shading indicates values that have changed to non-significant upon re-analysis.

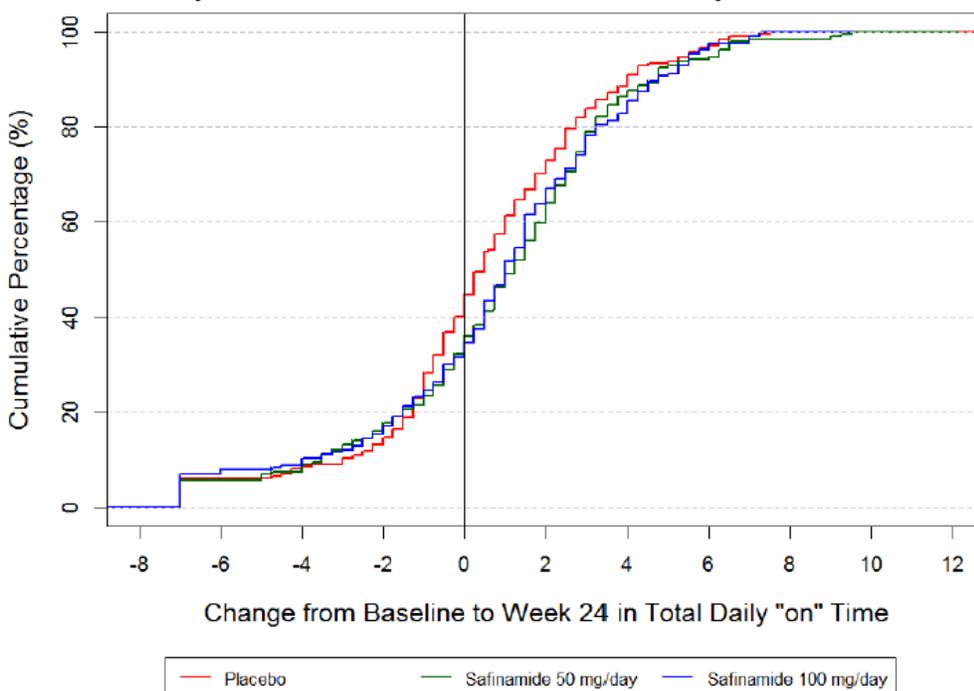
Source: ISE Tables 12.3.1.1, 12.3.1.2, 12.3.1.3, 12.3.1.4, 12.3.1.5, 12.3.1.6, 12.3.1.7, 12.3.1.8, 12.3.1.9, 12.3.1.10, 12.3.1.11.

Source: Newron

Dr. Zhang notes that the difference compared to placebo for the change in ON time without Troublesome Dyskinesia is relatively small compared to placebo. She illustrates this point in Figure 1.

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Fig. 1: Study 016 Cumulative Distribution Function for the Change from Baseline to Week 24 in Total daily “ON” Time Without Troublesome Dyskinesia



Source: FDA Statistical Review

CDTL Comment

The analysis of the primary endpoint changed slightly in the corrected MMRM analysis but the results still showed that safinamide 100 mg and 50 mg daily was superior to placebo. The results for OFF time, the UPDRS, Part 3 and the CGI-C (secondary endpoints) were significant ($p > 0.05$).

I agree with the conclusions of Dr. Zhang and Dr. Kapcala (FDA clinical reviewer) that the results of study 016, shows safinamide 50 mg and 100 mg provides clinically meaningful benefit in treating the motor symptoms in PD in patients taking concomitant levodopa.

Study 27919 (SETTLE)

Study 27919 was a double-blind, placebo-controlled, parallel-group, randomized, Phase 3 trial, comparing a dose range of 50 mg – 100 mg of safinamide, versus placebo as add-on therapy to a stable dose of levodopa in PD patients with motor fluctuations. Patients who met the entry criteria at baseline were randomized (1:1) to receive safinamide (50-100 mg/day) or placebo. Patients were started on 50 mg of safinamide (dose level 0) once daily in the morning.

The trial included up to 24 weeks of treatment in the double-blind phase, followed by a 1-week taper phase before treatment was discontinued, or patients were offered continued treatment in a 3-year, open-label extension study (28850). The total duration of the trial was approximately 34.5 weeks. The Screening period (10 days) was followed by a levodopa stabilization phase (four weeks), the treatment period (24 weeks), a one-week taper phase, and a safety follow-up phase (four weeks). The investigator then optimized (changed doses or timing of dose administration) the PD medications during the screening period, if necessary, to minimize motor symptoms.

Investigators increased the dose in all patients to 100 mg daily (targeted dose) based on tolerance. Patients were started on safinamide 50 mg (dose level 0) or matching placebo for 14 days. If patients did not tolerate the increase to 100 mg of safinamide (dose level 1) their dose could be reduced to 50 mg. If patients did not tolerate 50 mg daily, the investigator could hold study medication for 3 consecutive doses, and attempt to restart at the 50 mg dose or discontinue study medication.

Eight hundred fifty one patients were screened; 302 (35.5%) of these patients were considered screening failures. Overall, 549 patients were randomized to treatment (274 to safinamide and 275 to placebo), and 478 completed the study. A total of 549 patients comprised the Intent-to-Treat (ITT) Population, and 549 comprised the Safety Population.

Patients were enrolled at 119 centers in 21 countries including: 9 in India, 2 in Malaysia, 4 in South Korea, 3 in Taiwan, 5 in Thailand, 3 in Estonia, 7 in Slovakia, 5 in Canada, 28 in the United States, 2 in Australia, 2 in Austria, 6 in Belgium, 6 in France, 14 in Germany, 8 in Hungary, 6 in Israel, 1 in the Netherlands, 3 in New Zealand, 6 in Spain, 2 in Switzerland, and 4 in the United Kingdom. The first patient enrolled on March 5, 2009 and the last patient completed the study on February 23, 2012.

Key Inclusion Criteria

- Diagnosis of idiopathic PD of more than 3 years duration, with a Hoehn and Yahr stage of I-IV during an off phase. The diagnosis was based on medical history and neurological examination.
- Was levodopa-responsive and receiving treatment with a stable dose of levodopa three to ten doses per day of any levodopa preparation (including CR, IR, or a combination of CR/IR), plus benserazide/carbidopa on a stable dose of other concomitant medications for the treatment of PD.
- Have motor fluctuations, with >1.5 hours off time during the day (excluding morning akinesia)

Key Exclusion Criteria

- Be in a late stage of PD, and experiencing severe, disabling peak-dose or biphasic dyskinesia and/or unpredictable or widely swinging fluctuations in their symptoms.
- Evidence of dementia or cognitive dysfunction, as indicated by a MMSE score < 22, or a score ≥ 3 on item 1 (mentation) of the UPDRS Section I at screening.
- Stereotactic surgery as a treatment for his/her PD.
- Ophthalmologic history including any of the following conditions: albino subjects, family history of hereditary retinal disease, progressive and/or severe diminution of visual acuity (i.e., 20/70), retinitis pigmentosa, retinal pigmentation due to any cause, any active retinopathy or ocular inflammation (uveitis), or diabetic retinopathy.

Analysis Populations

The **Intent-to-Treat (ITT)** Population was defined as all the patients who were randomized to either safinamide or to placebo. The primary analysis was based on the ITT Population. The ITT Population was used for analysis of all efficacy endpoints, as well as for the summaries of all demographic parameters and disease characteristics.

The **Modified Intent-to-Treat (MITT)** Population included all randomized patients who received treatment, had a baseline assessment and at least one set of post-baseline primary efficacy endpoint data. The MITT Population was used for the primary endpoint daily ON time analysis and the key secondary endpoint analyses. The MITT Population provided a key supportive analysis to the ITT analysis. Sensitivity analyses in the Completer and Per-Protocol populations were also performed.

Baseline Characteristics

The mean age of patients in the safinamide and placebo groups was approximately 62 years. Approximately 60% of the enrolled patients were male. Approximately two thirds of the patients were white, 32% were Asian and the remaining patients were Black. There were no significant differences in baseline UPDRS subscale scores between the safinamide and placebo groups.

Blinded Variability Assessment

A blinded variability assessment was performed to confirm that the variability for the primary efficacy parameter in this trial did not exceed the estimated variance ($SD=2.35$ for change from baseline to Week 24 in daily on time). This evaluation was performed after 25-30% of subjects completed the 24-week treatment period. This re-estimate of the variability was intended to be used to re-calculate the sample size. The results indicated that the variability was slightly larger than the original assumption. Under the planned sample size, the power of the study was slightly reduced from 90% to 87%. The Sponsor considered that 87% power was acceptable for this study.

Primary Efficacy Analysis

The primary efficacy endpoint was change from Baseline to Week 24 in total daily “ON” time without troublesome dyskinesia over 18 hours as measured by diary cards. The primary efficacy analysis was performed on the MITT population using an ANCOVA model, with treatment and region effects and baseline value of the total daily “ON” time as the covariate. The “ON treatment” approach and LOCF method were used for the analysis.

The secondary efficacy analyses for the endpoints of total daily “OFF” time, UPDRS Part III score, UPDRS Part 2 score, and PDQ-39 summary index were performed on the MITT population using ANCOVA models with treatment and region effects and endpoint specific baseline as the covariate. The sponsor listed the key secondary endpoints in a hierarchy for testing. Because patients were treated with 50 mg or 100 mg the two dose groups were combined in one group, it is not known if the 100 mg dose is responsible for the effect on the primary endpoint, and if results for the secondary endpoints for either individual dose improved.

The study also allowed the use of rescue medication such as an increase in the dose of levodopa (if not already at the highest permissible dose or at the subject’s maximum tolerated dose) or the use of other anti-Parkinsonian agents. All of the Week 24 assessments were to be completed prior to initiating rescue treatment. Following the intervention, the subject should have continued in the

trial as per protocol, according to the schedule of assessments. Dr. Kapcala notes the number of patients with efficacy data censored was very large (placebo - 54, 100 mg - 39).

The On-Treatment Approach used in Study 016 was used in SETTLE. In this approach, only the On-Treatment efficacy data were used for analysis. These data included all post-baseline efficacy data collected up to patients had an increase of anti-Parkinsonian treatment, premature treatment discontinuation, or end of treatment, whichever occurred first. Missing values for the endpoints at Week 24 were imputed by a Last Observation Carried Forward (LOCF) approach using the last post-baseline On-Treatment value.

Table 16: Study 27919 (SETTLE) Summary of Total Daily 'ON' Time(a) and Change from Baseline by Timepoint and Treatment Group - On-Treatment (ANCOVA [LOCF]), Modified ITT Population

Timepoint	Statistics	Safinamide (n=270)		Placebo (n=273)	
		Value	Change	Value	Change
Baseline	n (missing)	270 (0)		273 (0)	
	Mean ±SD	9.30 ±2.43		9.09 ±2.47	
	Median	9.50		9.25	
	Min; Max	0.8; 16.5		0.0; 15.5	
Week 24	n (missing)	268 (2)	268 (2)	273 (0)	273 (0)
	Mean ±SD	10.72 ±2.77	1.44 ±2.81	9.63 ±2.78	0.53 ±2.44
	Median	10.75	1.25	9.75	0.50
	Min; Max	1.3; 17.3	-7.0; 13.8	0.0; 17.0	-8.5; 9.5
	LS Mean (SE)		1.53 (0.16)		0.54 (0.16)
	LS Diff vs Placebo (SE)		0.99 (0.21)		
	95% CI of LS Diff		(0.58, 1.39)		
	p-value vs Placebo		<0.001		

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(a) 'On time' is defined as 'on' time without dyskinesia plus 'on' time with minor dyskinesia.

Parametric ANCOVA model is based on the change from baseline to endpoint with fixed effects for treatment, region and baseline value as a covariate.

All p-values, LS means, and confidence intervals are calculated from the ANCOVA model.

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Source: CDTL Modified from Sponsor's Table

Table 17: Study 27919 (SETTLE): Summary of Secondary and Tertiary Efficacy Endpoints (ITT Population [LOCF]) In Hierarchical Sequence

Efficacy Measure	Safinamide 50-100 mg/day (n=274)	
	LS Mean Treatment Difference vs Placebo	p-value vs. Placebo
OFF Time (a)	-1.03 (-1.40, -0.67)	<0.001
UPDRS Section III (a)	-1.82 (-3.01, -0.62)	0.003
UPDRS Section II (a)	-0.43 (-1.02, 0.16)	0.149
CGI-C (mean score at endpoint) (b)	-0.44 (-0.62, -0.27)	<0.001
CGI-C (% patients with improvement) (c)	57.5% vs. 41.8%	<0.001
CGI-S (a)	-0.13 (-0.24, -0.03)	0.012
PDQ-39 Summary Index (a)	-2.33 (-3.98, -0.68)	0.006
EQ-5D Index Score (a)	0.06 (0.03, 0.09)	<0.001
OFF Time post morning dose of L-dopa (a)	-0.18 (-0.28, -0.09)	<0.001
Percent change in L-dopa dose	-1.89 (-3.44; -0.33)	0.018
DRS (a)	0.23 (-0.14, 0.60)	0.223
Patient's Global Impression of Change (PGIC) (b)	-0.40 (-0.57, -0.22)	<0.001

GRID-HAMD (17-item) (a)	-0.31 (-0.93, 0.30)	0.317
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ITT=Intent to Treat; LOCF=Last observation carried forward; LS=Least squares.

Analysis of changes from Baseline (Visit 3) to Endpoint (Visit 8 – Week 24 or last available observation [LOCF])

- a. Parametric ANCOVA Model, based on change from baseline to endpoint, with fixed effects for treatment and region, and baseline value as covariate. All p-values (2-sided), LS means, and CIs are calculated from the ANCOVA model.
- b. Parametric ANOVA Model, based on change from baseline to endpoint, with fixed effects for treatment and region. All p-values, LS means, and confidence intervals are calculated from the ANCOVA model.
- c. Odds ratio and 95% CI are estimated using a Logistic regression model with treatment and region as fixed effects. All p-values are based on Wald Chi-square test from the Logistic regression model.

Source: Newron

CDTL Comment

The results for the primary endpoint analysis for Study 27919 (SETTLE) shows that safinamide 50 mg to 100 mg is superior to placebo for improving ON time without troublesome dyskinesia. The sponsor did not conduct a dose response analysis or supply information in the efficacy datasets to determine if the effect was only found in patients treated with 100 mg. The efficacy and ADSL datasets do not show the actual dose patients were treated with during this trial.

The analysis of the secondary showed that safinamide was statistically superior to placebo for the change from baseline for total OFF time and the change in UPDRS Part 3 scores. Safinamide was not shown to be superior to placebo of the UPDRS Part 2 scores (p=0.149), prohibiting further testing of secondary endpoints under the gatekeeping procedure.

Long-Term Extension Studies

Safety data for all of the blinded extension studies were analyzed separately from the original placebo controlled studies. In the extension trials, the dose of PD medications could be changed based on individual patient needs. Although allowing changed in PD medication is understandable from a patient care perspective, it confounds comparisons between safinamide and placebo. Increasing the dose of PD medications (including levodopa) biases against safinamide for efficacy and would increase the frequency of adverse reactions caused by PD medications other than safinamide in both groups.

Early Stage PD

Study 27938

A Phase 3, double-blind, placebo-controlled extension trial to investigate the long-term efficacy and safety of low (50 mg/day) and high (100 mg/day) dose safinamide, as add-on therapy in subjects with early idiopathic Parkinson’s disease treated with a stable dose of a single dopamine agonist.

October 2011, Merck-Serono returned all rights for safinamide to Newron Pharmaceuticals which led to a decision to terminate the Extension Trial 27938 early PD. All subjects enrolled in the Extension Trial 27938 were asked to complete the following visits immediately: Week 78 / Early Termination, Week 79 (Taper Visit), and Week 83 Safety Follow-up Visit. All subjects enrolled in

the trial were to be followed for safety until 4 weeks after their last administration of safinamide, as detailed in the scheduled visits described in the protocol (Week 83 Safety Follow-up Visit).

The sponsor did not conduct an efficacy analysis using the available data.

Study NW-1015/017/III/2003

Study 017, a Phase III, double-blind, placebo-controlled, 12-month extension to Study 015, was a multi-national study, evaluating the long-term safety and efficacy of a dose range of 50 to 200 mg/day safinamide taken orally, compared to Placebo, as add-on therapy to a stable dose of a single dopamine agonist in outpatients with early Parkinson's disease.

Primary efficacy analysis for the pooled Safinamide group had a longer mean and median time to 'Intervention' or last follow-up, compared with Placebo (559 days – pooled safinamide vs. 466 days – placebo); however, this difference did not reach statistical significance (p-value = 0.3342).

Late Stage PD

Study NW-1015/018/III/2006 (NW-018)

Study 018 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).

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 timepoint.

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).

The results of the controlled extension trials did not support the efficacy of safinamide in early or late PD. In study 018 (Late stage PD), the dose of safinamide (or placebo) remained stable during the 78-week treatment period, the dose of levodopa was increased (open label), if necessary to treat a worsening of the patient's PD symptoms. This changed the levodopa dose confounded both the efficacy and safety analyses since an effect on dyskinesia could have been caused by a change in levodopa dose. Likewise, newly reported adverse events could have been due to levodopa or safinamide.

Efficacy Conclusion

I agree with the conclusions of Drs. Kapcala and Zhang, the information contained in this NDA does not support the effectiveness of safinamide in patients with early PD treated with a stable dose of a DA. Even if the results of study 009 were judged to be positive, the results of two larger studies in early PD failed to show benefit.

Safinamide 50 mg and 100 mg was shown to be effective in patients with PD treated with a stable dose of a DOPA decarboxylase inhibitor and levodopa, with or without other medications approved for the treatment of PD in study 016 and 27919.

Dr. Zhang noted there was a significant effect of gender in studies 016 and Study 27919 (SETTLE). The treatment benefit appeared to be greater in men compared to women. This observation was caused by the higher proportion of males enrolled in both studies (approximately 2.5 times the number of women enrolled). PD disproportionately affects males; the gender distribution in both studies is consistent with the gender distribution of PD described in the literature.

8. Safety

Exposure

I agree with Dr. Kapcala's conclusion that exposure to safinamide is adequate for continuous exposure for more than 6 months and more than 12 months. The patient exposure exceeds the ICH guideline for an NME of 1500 patients exposed, 1949 patients were exposed to safinamide.. In general, patient exposure during the safinamide clinical development program is higher than the exposure seen in most applications for new medications to treat PD. In open label studies alone, 744 patients were treated with the highest recommended dose (100 mg daily) for 12 months or longer (Table 18).

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Table 18: Exposure Parameters for Safinamide Pooled Group 15 (Open-label) Trials

	Safinamide (100 mg/day) (N=1025)
Mean (SD) treatment duration, years	2.07 (1.384)
Median treatment duration (yrs)	1.88
Mean (SD) treatment duration, weeks	108.05 (72.240)
Median treatment duration, weeks	98.14
Patients with exposure, n (%)	
At least one day	1025 (100.0)
≥4 weeks	1013 (98.8)
≥12 weeks	979 (95.5)
≥6 months	881 (86.0)
≥12 months	744 (72.6)
≥18 months	606 (59.1)
≥24 months	479 (46.7)
≥3 years	222 (21.7)
≥4 years	169 (16.5)

Source: Newron

Disposition in Controlled Trials of Safinamide

Early Stage Parkinson’s Disease Patients Treated with a Dopamine Agonist

The proportion of patients who discontinued early because of an adverse event was higher in the placebo group compared to the proportion of patients in the 50 mg and 100 mg (Table 19).

Table 19: Studies 015 and 27918 (MOTION) Discontinuations

REASON	Safinamide 50 mg/day N=227 N (%)	Safinamide 100 mg/day N=317 N (%)	Safinamide 200 mg/day N=89 N (%)	Any Safinamide N=633 N (%)	Placebo N=315 N (%)
Adverse Event	4(2)	8(3)	5(6)	17(3)	15 (5)
Lack Of Efficacy	12(5)	4(1)	2(2)	18(3)	1(0)
Lost To Follow-Up	4(2)	7(2)	1(1)	12(2)	6(2)
Non-Compliance	2(1)	2(1)	1(1)	5(1)	0(0)
Other	1(0)	0(0)	0(0)	1(0)	0(0)
Termination By Investigator	0(0)	2(1)	3(3)	5(1)	3(1)
Termination By Sponsor	3(1)	0(0)	0(0)	3(0)	0(0)
Withdrew Consent	3(1)	6(2)	7(8)	16(3)	11(3)

Source: CDTL

Table 20: Disposition Late PD Studies 016 and 27919 (SETTLE) (excluding 018 extension) Safety Population

REASON	Safinamide 50 mg/day N=223 N (%)	Safinamide 100 mg/day N=498 N (%)	Total Any Safinamide N=721 N (%)	Placebo N=497 N (%)
Adverse Event	11 (5)	26 (5)	37 (5)	23 (5)
Death	0 (0)	5 (1)	5 (1)	3 (1)
Lack Of Efficacy	0 (0)	1 (0)	1 (0)	3 (1)
Lost To Follow-Up	4 (2)	12 (2)	16 (2)	10 (2)
Non-Compliance	1 (0)	2 (0)	3 (0)	2 (0)
Other	0 (0)	0 (0)	0 (0)	2 (0)
Termination By Investigator	0 (0)	4 (1)	4 (1)	0 (0)
Withdrew Consent	5 (2)	9 (2)	14 (2)	17 (3)
TOTAL	21 (10)	59 (12)	80 (11)	60 (12)

Source CDTL

Deaths in Early PD Studies

The Sponsor has performed analyses for all 61 deaths that occurred during the clinical development program, 59 of the reported deaths that occurred within 30 days of the last dose of study medication, as defined in the study protocols. The two patients excluded from the analysis dies outside of the 30-day post treatment window.

Deaths in Studies 015 and 27918 (MOTION)

There were no deaths reported in patients taking 50 mg, 100 mg or the 200 mg dose of safinamide.

Deaths in Study 017

Study 017 was an extension to Study NW-1015/015/III/2003, and is a Phase III, double-blind, placebo-controlled, 12-month study, evaluating the long-term safety and efficacy of a dose range of safinamide of 50 to 200 mg/day, orally, compared to Placebo, as add-on therapy to a stable dose of a single dopamine agonist in outpatients with early PD. The two reported deaths (Table 21) in this study are unrelated to safinamide.

Table 21: Study 017 (extension of Study 015) Deaths Early Stage PD (Safety Population)

USUBJID	Age	Sex	Race	Arm	AE Study Day	Preferred Terms	Outcome
000101501 50210012	76	M	White	Safinamide 50-100 mg/day	-4 254 255	Malnutrition Urinary tract infection Sepsis Renal failure Dehydration	Fatal
000101501 50190008	66	M	Asian	Placebo	178	Chikungunya virus infection	Fatal

Deaths in Study 27938

Study 27938 was a Phase 3, double-blind, placebo-controlled extension trial to investigate the long-term efficacy and safety of low (50 mg/day) and high (100 mg/day) dose safinamide, as add-on therapy in subjects with early idiopathic PD treated with a stable dose of a single dopamine agonist. Then sponsor Merck-Serono decided to terminate Study 27938 early and return the rights to safinamide to Newron. There were two reported deaths in the study population before the study was terminated (Table 22)

Table 22: Patients Deaths in Study 27938 (Early Stage PD) Motion DB, PC Extension Study

USUBJID	Age	Sex	Race	Arm	AEStudy Day	Preferred Terms	Outcome
000002791 80480009	60	M	White	Safinamide 100 mg/day	690	Acute myocardial infarction	Fatal
000002791 81790003	56	M	White	Safinamide 50 mg/day	315	Myocardial infarction	Fatal

Death in Late Stage PD Studies

Deaths in Pooled Controlled Studies NW1015-016 and 27919 (SETTLE) Late Stage Parkinson’s Disease

The patient deaths reported in the sponsor’s datasets for the placebo-controlled portions of studies 016 and 27919 (Table 23), are the same as the sponsor’s analysis. There is no specific adverse event that appears to be causally related to safinamide.

Table 23: Deaths in Pooled Studies NW-1015 016 and 27919 (SETTLE) Safety Population, Initial Placebo Controlled Period (excluding the Extension Period of Study 018)

USUBJID	AEOU T	AETE01FL	AETE02FL	AEDECOD	TRTP	AGE (years)	SEX
*10150160770001	Fatal	Y	N	Road Traffic Accident	Placebo	55	M
279193120003	Fatal	Y	N	Myocardial Ischaemia	Placebo	71	M
279195010002	Fatal	Y	N	Acute Lymphocytic Leukaemia Pancytopenia	Placebo	71	F
10150160100007	Fatal	Y	N	Pneumonia	Safinamide 100 mg/day	80	M
10150160190001	Fatal	Y	N	Death	Safinamide 100 mg/day	67	F
10150160200009	Fatal	Y	N	Death	Safinamide 100 mg/day	60	F
10150160440015	Fatal	Y	N	Anaemia GGT Increased Pleural Effusion	Safinamide 100 mg/day	60	F
279192300002	Fatal	Y	N	Parkinson's Disease	Safinamide 100 mg/day	69	M

Source CDTL Table *Patient died after study participation ended.

Study 018 was a long-term (18 months) double blind, placebo controlled extension study that enrolled patient who completed Study 016. Patients continued to take the same treatment and dose they received in Study 016 (safinamide 50 mg/day, safinamide 100 mg/day, or placebo), along with the same dose of levodopa and any other antiparkinsonian treatments. The ITT population included 544 patients (175 in the placebo group, 189 in the safinamide 50 mg/day group, and 180 in the safinamide 100 mg/day group).

There were 6 (3.4%) deaths reported in patients who received placebo, 5 (2.6%) deaths in the safinamide 50 mg group and 7 (3.9%) deaths in the safinamide 100 mg group (Table 24). Cardiovascular disease and pneumonia was the most common causes of death for patients in all of the treatment arms. There are the most frequent cause of death reported in patients with advanced PD (Pennington, Snell, Lee, & Walker, 2010)

Table 24: Deaths reported in Study 018 (DB, PC extension study) Late Stage PD Excluding Deaths reported in Study 016 Safety Population

USUBJID	AGE (years)	SEX	TRTP	AEOUT	AEDECOD
10150160130008	53	F	Safinamide 50 mg/day	Fatal	Cardio-Respiratory Arrest Diabetic Ketoacidosis Leptospirosis Malaria Sepsis
10150160290022	73	M	Safinamide 50 mg/day	Fatal	Sudden Death
10150160200004	68	M	Safinamide 50 mg/day	Fatal	Silent Myocardial Infarction
10150160440005	70	M	Safinamide 50 mg/day	Fatal	Colonic Pseudo-Obstruction
10150160400001	62	M	Safinamide 50 mg/day	Fatal	Hepatic Encephalopathy Hepatitis Viral
10150160280009	79	M	Safinamide 100 mg/day	Fatal	Cardio-Respiratory Arrest Pneumonia Aspiration Renal Failure Acute Sepsis
10150160270009	64	M	Safinamide 100 mg/day	Fatal	Sudden Death
10150160280019	70	M	Safinamide 100 mg/day	Fatal	Sudden Death
10150160290019	61	M	Safinamide 100 mg/day	Fatal	Myocardial Infarction
10150160710016	56	M	Safinamide 100 mg/day	Fatal	Anaemia Bronchopneumonia Metastases To Lung Respiratory Failure
10150160330001	72	M	Safinamide 100 mg/day	Fatal	Cardiac Arrest Cerebellar Infarction Vertebrobasilar Insufficiency

10150160330007	67	M	Safinamide 100 mg/day	Fatal	Myocardial Infarction
10150160410002	56	M	Placebo	Fatal	Sudden Cardiac Death
10150160500012	72	M	Placebo	Fatal	Confusional State Decubitus Ulcer Pyrexia Sepsis
10150160290035	69	F	Placebo	Fatal	Sudden Death
10150160280022	71	M	Placebo	Fatal	Aspiration Cardiopulmonary Failure Pyramidal Tract Syndrome
10150160280005	73	M	Placebo	Fatal	Collapse Of Lung Dehydration Pneumonia Aspiration Pyrexia
10150160160006	44	F	Placebo	Fatal	Cardiac Arrest

Source CDTL

There were 29 deaths reported in Open Label Study 28850 (Table 25). Cardiovascular disease was the most commonly reported adverse event associated with a fatal outcome in this study.

Table 25: Deaths in Open Label Study 28850

USUBJID	STUDYID	SEX	AGE	TRTP	AEDECOD	AEOUT
279194140001	28850	M	70	Safinamide 100 mg/day	COMPLETED SUICIDE	FATAL
279193250003	28850	M	74	Safinamide 100 mg/day	ARRHYTHMIA	FATAL
279193550001	28850	M	69	Safinamide 100 mg/day	CARDIAC ARREST	FATAL
279193760001	28850	M	59	Safinamide 100 mg/day	COLON CANCER	FATAL
279193840003	28850	M	60	Safinamide 100 mg/day	CARDIAC FAILURE	FATAL
279193860001	28850	M	61	Safinamide 100 mg/day	PULMONARY EMBOLISM	FATAL
279194060004	28850	M	78	Safinamide 100 mg/day	NEOPLASM MALIGNANT	FATAL
10150160010021	28850	M	59	Safinamide 100 mg/day	SUDDEN DEATH	FATAL
10150160050003	28850	M	57	Safinamide 100 mg/day	PANCREATIC CARCINOMA METASTATIC	FATAL
10150160050010	28850	M	75	Safinamide 100 mg/day	SEPSIS	FATAL
10150160080004	28850	M	68	Safinamide 100 mg/day	SEPTIC SHOCK	FATAL
10150160160007	28850	M	66	Safinamide 100 mg/day	DEATH	FATAL
10150160220002	28850	M	77	Safinamide 100 mg/day	DEATH	FATAL
10150160220011	28850	M	41	Safinamide 100 mg/day	SUDDEN DEATH	FATAL
10150160280010	28850	M	74	Safinamide 100 mg/day	ACUTE MYOCARDIAL INFARCTION	FATAL
10150160290012	28850	M	63	Safinamide 100 mg/day	PNEUMONIA	FATAL

					ASPIRATION	
10150160330013	28850	M	67	Safinamide 100 mg/day	MYOCARDIAL INFARCTION	FATAL
10150160330018	28850	M	54	Safinamide 100 mg/day	PNEUMONIA ASPIRATION	FATAL
10150160370004	28850	M	51	Safinamide 100 mg/day	ABDOMINAL PAIN UPPER	FATAL
*10150160370004	28850	M	51	Safinamide 100 mg/day	RESTLESSNESS	FATAL
10150160380014	28850	M	70	Safinamide 100 mg/day	SUDDEN DEATH	FATAL
10150160390008	28850	F	75	Safinamide 100 mg/day	SUDDEN DEATH	FATAL
10150160390014	28850	F	58	Safinamide 100 mg/day	SUDDEN DEATH	FATAL
10150160400001	28850	M	62	Safinamide 100 mg/day	HEPATIC ENCEPHALOPATHY	FATAL
10150160440004	28850	M	67	Safinamide 100 mg/day	PANCYTOPENIA	FATAL
10150160610002	28850	M	61	Safinamide 100 mg/day	ACUTE MYOCARDIAL INFARCTION	FATAL
10150160710028	28850	M	57	Safinamide 100 mg/day	PULMONARY EMBOLISM	FATAL
10150160920004	28850	M	73	Safinamide 100 mg/day	ACUTE RESPIRATORY FAILURE	FATAL
0001015016020007	28850	F	61	Safinamide 100 mg/day	DEATH	FATAL

*Duplicate Listing in the sponsor's database

Serious Adverse Events

Pooled Placebo Controlled Efficacy Studies

Table 26 Early Stage PD Studies 1015015 and Study 27918

Arm	N Patients (%)
Placebo (N=315)	7 (2)
Safinamide 200 mg/day (N=89)	2 (2)
Safinamide 100 mg/day (N=317)	12 (4)
Safinamide 50 mg/day (N=226)	9 (4)

Thirty patients reported 43 SAEs in the pooled efficacy trials in patients on a stable dose of a dopamine agonist (Early stage PD) (Table 26). The proportion of patients experiencing an SAE in the safinamide 50 mg and 100 mg groups was twice the proportion of patients with reporting an SAE in the placebo group. No SAE Preferred Term was observed in more than one patient in the combined safinamide treatment groups. After combining related Preferred Terms Atrial fibrillation/flutter and Maculopathy/Macular edema were observed in 2 patients.

Table 27SAEs in Late PD Studies 016 and SETTLE

Arm	N Patients (%)
Placebo (N=497)	42 (9)
Safinamide 100 mg/day (N=498)	43 (9)
Safinamide 50 mg/day (N=223)	9 (4)

Ninety four patients reported 150 SAEs in the double blind, placebo controlled efficacy trials in patients taking safinamide in conjunction with levodopa (Late Stage PD). The proportion of patients reporting SAEs were similar in the high dose safinamide and placebo groups (Table 27). The Preferred Terms observed in more than 2 patients in the 50 mg and 100 mg safinamide groups combined are Falls (5), Cataract operation (4), Fracture (3), and 2 patients with Breast Cancer, Hallucinations, Urinary Tract Infection (UTI), Parkinson's disease and Dyspnea.

**Table 28: Study 1015/017 (Early Stage PD extension study)
Serious Adverse Events**

Arm	N Patients (%)
Placebo (N=78)	5 (6)
Safinamide 150-200 mg/day (N=69)	5 (9)
Safinamide 50-100 mg/day (N=80)	8 (10)

In Study 017, 18 patients reported 29 serious adverse events (Table 28). The only Preferred Terms reported in more than one patient in Study 017 treated with safinamide are Coronary Artery Disease (2) and UTI (2).

**Table 29 Patients with Serious Adverse Events in Study 27938 Motion Extension
(Early Stage PD extension study)**

Arm	N Patients (%)
Placebo (N=154)	11 (7)
Safinamide 100 mg/day (N=179)	10 (6)
Safinamide 50 mg/day (N=174)	9 (5)

Thirty patients reported experiencing 44 SAEs in Study 27938 (Table 29). At least two patient treated with safinamide reported the Preferred Terms Angina (2), Bile duct stone (2), Cholelithiasis (3), and Osteoarthritis (2).

**Table 30: Study 018 (Extension study Late Stage PD)
Serious Adverse Events**

Arm	N Patients (%)
Placebo (N=175)	22 (13)
Safinamide 100 mg/day (N=180)	26 (14)
Safinamide 50 mg/day (N=189)	29 (15)

Seventy-seven patients reported 170 Serious Adverse Events (SAE) in Study 018 (Table 30), which are too many to list in the body of this review. The only Preferred terms reported in more than one patient treated with safinamide are: Cardiac Arrest/Sudden Death (4), Fall (9), Sepsis (5), Parkinson's Disease (4), MI (4) Renal Failure/Acute Renal Failure (4) Respiratory Failure (3), and

UTI, Confusional State, Hyponatremia, Injury, Insomnia, Gastroenteritis, Anemia all reported in 2 patients.

Table 31: Serious Adverse Reactions s in at least 2 Patients Study 28850 Open Label Early and Late Stage PD

AEBODSYS	AEDECOD	Safinamide 50-100 mg/day (N=964)	%
Gastrointestinal Disorders	Inguinal Hernia	9	0.93
Respiratory, Thoracic And Mediastinal Disorders	Pneumonia Aspiration	6	0.62
Injury, Poisoning And Procedural Complications	Femoral Neck Fracture	5	0.52
Psychiatric Disorders	Hallucination	5	0.52
Musculoskeletal And Connective Tissue Disorders	Osteoarthritis	5	0.52
General Disorders And Administration Site Conditions	Sudden Death	5	0.52
Injury, Poisoning And Procedural Complications	Femur Fracture	4	0.41
Nervous System Disorders	Dyskinesia	4	0.41
Nervous System Disorders	Parkinson's Disease	4	0.41
Infections And Infestations	Cellulitis	4	0.41
Metabolism And Nutrition Disorders	Hyponatraemia	4	0.41
Eye Disorders	Cataract	4	0.41
Reproductive System And Breast Disorders	Benign Prostatic Hyperplasia	4	0.41
Injury, Poisoning And Procedural Complications	Fall	3	0.31
Nervous System Disorders	Cerebrovascular Accident	3	0.31
Nervous System Disorders	Convulsion	3	0.31
Gastrointestinal Disorders	Diarrhoea	3	0.31
General Disorders And Administration Site Conditions	Death	3	0.31
Respiratory, Thoracic And Mediastinal Disorders	Pulmonary Embolism	3	0.31
Cardiac Disorders	Acute Myocardial Infarction	3	0.31
Cardiac Disorders	Cardiac Failure	3	0.31
Renal And Urinary Disorders	Urinary Retention	3	0.31
Metabolism And Nutrition Disorders	Hypoglycaemia	3	0.31
Injury, Poisoning And	Road Traffic Accident	2	0.21

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Procedural Complications			
Injury, Poisoning And Procedural Complications	Wrist Fracture	2	0.21
Psychiatric Disorders	Aggression	2	0.21
Psychiatric Disorders	Confusional State	2	0.21
Psychiatric Disorders	Hallucination, Auditory	2	0.21
Psychiatric Disorders	Hallucination, Visual	2	0.21
Psychiatric Disorders	Suicide Attempt	2	0.21
Nervous System Disorders	Carpal Tunnel Syndrome	2	0.21
Gastrointestinal Disorders	Abdominal Pain	2	0.21
Infections And Infestations	Erysipelas	2	0.21
Infections And Infestations	Sepsis	2	0.21
Infections And Infestations	Urinary Tract Infection	2	0.21
Musculoskeletal And Connective Tissue Disorders	Arthralgia	2	0.21
Musculoskeletal And Connective Tissue Disorders	Intervertebral Disc Protrusion	2	0.21
Musculoskeletal And Connective Tissue Disorders	Lumbar Spinal Stenosis	2	0.21
Musculoskeletal And Connective Tissue Disorders	Spinal Column Stenosis	2	0.21
General Disorders And Administration Site Conditions	Asthenia	2	0.21
General Disorders And Administration Site Conditions	Pain	2	0.21
General Disorders And Administration Site Conditions	Pyrexia	2	0.21
Respiratory, Thoracic And Mediastinal Disorders	Dyspnoea	2	0.21
Respiratory, Thoracic And Mediastinal Disorders	Pneumonitis	2	0.21
Cardiac Disorders	Coronary Artery Disease	2	0.21
Cardiac Disorders	Myocardial Infarction	2	0.21
Metabolism And Nutrition Disorders	Dehydration	2	0.21
Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps)	Prostate Cancer	2	0.21

Source: CDTL

The SAEs reported in open label study 28850 (Table 31) are similar to those observed in the placebo controlled studies and the long-term extension studies.

Nonserious Adverse Reactions

Table 32: Nonserious Adverse Reactions Studies 015 and Motion Early Stage PD $\geq 2\%$ in Any Safinamide Group and Greater than Placebo.

PT	Safinamide 50 mg/day (N = 226)		Safinamide 100 mg/day (N = 317)		Safinamide 200 mg/day (N = 89)		Placebo (N = 315)	
	Number of subjects	(%)	Number of subjects	(%)	Number of subjects	(%)	Number of subjects	(%)
Nausea	13	6	30	9	8	9	23	7
Dizziness	18	8	20	6	4	4	18	6
Headache	13	6	17	5	4	4	22	7
Back pain	13	6	16	5	3	3	21	7
Somnolence	17	8	14	4	4	4	23	7
Arthralgia	12	5	12	4	3	3	9	3
Insomnia	11	5	12	4	1	1	13	4
Abdominal pain upper	3	1	11	3	1	1	10	3
Cough	8	4	11	3	5	6	9	3
Oedema peripheral	8	4	11	3	3	3	14	4
Hypertension	3	1	10	3	7	8	8	3
Vomiting	1	0	10	3	2	2	10	3
Urinary tract infection	12	5	9	3	2	2	10	3
Nasopharyngitis	13	6	8	3	5	6	8	3
Diarrhoea	9	4	7	2	1	1	10	3
Fatigue	7	3	7	2	1	1	6	2
Gastritis	0	0	7	2	5	6	5	2
Pain in extremity	6	3	7	2	3	3	5	2
Anxiety	7	3	6	2	5	6	8	3
Cataract	2	1	6	2	0	0	4	1
Conjunctivitis	1	0	6	2	0	0	0	0
Paraesthesia	6	3	6	2	0	0	4	1
Alanine aminotransferase increased	1	0	5	2	1	1	2	1
Onychomycosis	2	1	5	2	0	0	4	1
Pyrexia	2	1	5	2	5	6	10	3
Vision blurred	0	0	5	2	2	2	3	1
Abdominal pain	4	2	4	1	0	0	3	1

Asthenia	3	1	4	1	2	2	8	3
Fall	5	2	4	1	1	1	13	4
Hypercholesterolaemia	0	0	4	1	0	0	3	1
Upper respiratory tract infection	6	3	4	1	2	2	4	1
Vertigo	5	2	4	1	1	1	2	1
Abdominal distension	1	0	3	1	1	1	0	0
Depressed mood	0	0	3	1	0	0	0	0
Depression	9	4	3	1	1	1	9	3

Table 33: Nonserious Adverse Reactions Late PD Studies Placebo Controlled 016 and 27919 (SETTLE) Preferred Terms Incidence $\geq 2\%$ in Any Safinamide Group and Greater than Placebo.

PT	Safinamide 50 mg/day (N=223)		Safinamide 100 mg/day (N=498)		Placebo (N = 497)	
	N Patients	%	N	%	N Patients	%
Dyskinesia	47	21	87	18	44	9
Fall	8	4	31	6	19	4
Nausea	7	3	28	6	21	4
Headache	13	6	26	5	27	5
Urinary tract infection	6	3	24	5	18	4
Parkinson's disease	14	6	21	4	23	5
Cataract	15	7	19	4	19	4
Hypertension	13	6	15	3	14	3
Pain in extremity	6	3	10	2	12	2
Orthostatic hypotension	5	2	10	2	7	1
Weight decreased	8	4	9	2	13	3
Anxiety	4	2	9	2	6	1
Cough	4	2	8	2	5	1

Source: CDTL Table

The highest proportion AEs was for patients with dyskinesia in the late stage PD. Dyskinesia has the largest disproportion of nonserious adverse reactions observed between early and late stage patients. This is expected because dyskinesia typically seen within 5 to 10 years after starting levodopa, and more of these patients with a longer disease duration would meet criteria for late PD.

The sponsor removed patients with pre-existing hypertension from the percentage of patients with hypertension but did not correct the coding of hypertension in the AEDECOD variable listed in the AE analysis dataset. The frequency of hypertension shown in Table 33 reflects was created using the AEDECOD in the sponsor’s dataset.

Nonserious Adverse Reactions Double Blind Placebo Controlled Extension Studies

Table 34: Study NW-1015-017 Early PD Extension Study DB, PC Nonserious Adverse Reactions ≥ 5% and Greater for Any Safinamide Dose Compared to Placebo

AEBODSYS	AEDECOD	Safinamide 150-200 mg (N= 69) %	Safinamide 50-100 mg (N= 80) %	Placebo (N=78) %
Eye disorders	Scotoma	3	9	8
Eye disorders	Cataract	10	5	6
Eye disorders	Vision blurred	1	6	1
Nervous system disorders	Dizziness	3	8	5
Nervous system disorders	Headache	4	5	1
Gastrointestinal disorders	Abdominal pain upper	6	6	4
Gastrointestinal disorders	Nausea	3	6	5
Gastrointestinal disorders	Gastritis	6	4	1
Musculoskeletal and connective tissue disorders	Back pain	1	13	6
Psychiatric disorders	Anxiety	4	5	3
Vascular disorders	Hypertension	1	6	1

Source: CDTL Table

In Table 34, the sponsor recoded adverse events AEDECOD using information from the verbatim term for the in-text tables but they did not change the coding of the events in their AEDECOD variable in the AE datasets. Examples of this were found for the AEDECOD coding of scotoma and cataracts, where scotoma was recoded to cataract based on information in the verbatim term. The verbatim code of scotoma caused by cataract, and the AEDECOD was changed from scotoma to cataract. The recoding is responsible for a minor difference (1 or 2 patients in some groups) between the sponsor’s analyses of the percent of adverse reactions in the table above.

Table 35: Study 27938 Early Stage PD Motion Extension Study DB, PC Nonserious Adverse Reactions PD ≥ 5% and Greater for Any Safinamide Dose Compared to Placebo

AEBODSYS	AEDECOD	Safinamide 100 mg (N=179) %	Safinamide 50 mg (N=174) %	Placebo (N=154) %
Musculoskeletal and connective tissue disorders	Back pain	5	10	5
Nervous system disorders	Dizziness	1	5	3
Injury, poisoning and procedural complications	Fall	4	6	2

Source: CDTL Table

Table 36: Study018 Late Stage PD DB, PC Extension Study Nonserious Adverse Reactions PD ≥ 5% and Greater for Any Safinamide Dose Compared to Placebo

AEBODSYS	AEDECOD	Safinamide 50 mg N=189 %	Safinamide 100 mg N=180 %	Placebo N=180 %
Nervous system disorders	Parkinson's disease	17	19	16
Nervous system disorders	Tremor	5	1	4
Investigations	Weight decreased	7	5	5
Eye disorders	Cataract	10	10	9
General disorders and administration site conditions	Pyrexia	8	5	7
Gastrointestinal disorders	Constipation	7	3	5
Musculoskeletal and connective tissue disorders	Pain in extremity	6	3	3
Musculoskeletal and connective tissue disorders	Arthralgia	5	2	3
Psychiatric disorders	Insomnia	9	3	3
Injury, poisoning and procedural complications	Fall	7	5	6

Table 37: Nonserious Adverse Reactions Open Label Studies 28850 Incidence \geq 2% Early and Advanced PD

SOC	Preferred Term	Safinamide 50-100 mg/day N=964	%
Nervous System Disorders	Dyskinesia	106	11
Injury, Poisoning And Procedural Complications	Fall	61	6
Musculoskeletal And Connective Tissue Disorders	Back Pain	58	6
Infections And Infestations	Urinary Tract Infection	53	5
Gastrointestinal Disorders	Constipation	49	5
Nervous System Disorders	Parkinson's Disease	44	5
Gastrointestinal Disorders	Nausea	42	4
Musculoskeletal And Connective Tissue Disorders	Arthralgia	41	4
Nervous System Disorders	Dizziness	39	4
Eye Disorders	Cataract	39	4
Nervous System Disorders	Headache	36	4
Musculoskeletal And Connective Tissue Disorders	Pain In Extremity	36	4
Psychiatric Disorders	Hallucination	35	4
Gastrointestinal Disorders	Diarrhoea	32	3
Psychiatric Disorders	Insomnia	32	3
General Disorders And Administration Site Conditions	Pyrexia	32	3
Infections And Infestations	Nasopharyngitis	29	3
General Disorders And Administration Site Conditions	Oedema Peripheral	29	3
Nervous System Disorders	On And Off Phenomenon	27	3

Investigations	Weight Decreased	27	3
Psychiatric Disorders	Depression	24	2
General Disorders And Administration Site Conditions	Asthenia	24	2
Infections And Infestations	Upper Respiratory Tract Infection	21	2
Psychiatric Disorders	Anxiety	21	2
Blood And Lymphatic System Disorders	Anaemia	21	2
Musculoskeletal And Connective Tissue Disorders	Musculoskeletal Pain	19	2
Respiratory, Thoracic And Mediastinal Disorders	Cough	19	2
Vascular Disorders	Hypertension	19	2
Psychiatric Disorders	Hallucination, Visual	18	2
Nervous System Disorders	Somnolence	16	2
Nervous System Disorders	Tremor	16	2
Gastrointestinal Disorders	Abdominal Pain Upper	16	2
Respiratory, Thoracic And Mediastinal Disorders	Dyspnoea	16	2
Investigations	Platelet Count Decreased	15	2

Source: CDTL Table

The frequency of nonserious adverse reactions in open label study 28850 (Table 37) is similar to those reported in patients enrolled in long-term controlled extension studies. The most frequently reported Preferred Terms suggest this population was predominantly composed of patients with advanced PD.

Adverse Reactions of Special Interest

Impulse Control Disorders (ICD)

Fourteen patients treated with safinamide developed at least one ICD (Table 38). One patient was treated with 50 mg and the remaining 13 received treatment with 100 mg. The majority of the patients were classified as having Late Stage PD. Pathological/compulsive gambling was the most

commonly reported ICD Followed by Hypersexuality. The sponsor used the Questionnaire for Impulsive-Compulsive Disorders in Parkinson’s Disease (QUIP) in Study 27919 (SETTLE) a change from baseline score could not be computed for 72% of enrolled patients because of missing baseline or end of study data (Table 39). The QUIP data are inadequate to base conclusion to assess the potential of safinamide to cause ICD. The adverse event data in the NDA indicate patients treated with Safinamide developed ICD. Because ICDs have the potential to cause serious legal and financial consequences, and personal embarrassment the safinamide label should include the class language warning about the potential to develop ICD that is included in all dopaminergic products used to treat PD.

Table 38: Impulse Control Disorders Reported in ISS Studies 016 and 27919 (SETTLE) Late Stage PD Adverse Event Tables Safinamide 50 mg and 100 mg

USUBJID	Preferred Term
00000279180320004	Gambling
00000279181550002	Compulsions
00000279192200006	Hypersexuality
00000279193500006	Compulsions
00000279193550002	Hypersexuality
00000279193600004	Compulsive Sexual Behaviour Gambling
00000279194150002	Hypersexuality
00000279194340001	Obsessive Thoughts
00000279194720001	Gambling
00000279194720007	Gambling
00000279195500006	Obsessive Thoughts
00010150160510005	Obsessive-Compulsive Personality Disorder Pathological Gambling
00010150160710017	Pathological Gambling
00010150160710018	Pathological Gambling

Source: CDTL

Table 39: Study 27919 (SETTLE) Late Stage PD QUIP Scores

Table 63. QUIP Scale (Total Score) Value and Change from Baseline by Timepoint and Treatment Group – Safety Population					
Timepoint	Statistics	Safinamide (n=274)		Placebo (n=275)	
		Value	Change	Value	Change
Baseline	n (missing)	168 (106)		163 (112)	
	Mean ±SD	1.05 ±2.14		0.97 ±1.90	
	Median	0.00		0.00	
	Min; Max	0.0; 15.0		0.0; 9.0	
Endpoint (LOCF) ^a	n (missing)	171 (103)	159 (115)	174 (101)	154 (121)
	Mean ±SD	1.02 ±2.09	-0.03 ±1.96	1.05 ±2.17	0.13 ±1.83
	Median	0.00	0.00	0.00	0.00
	Min; Max	0.0; 9.0	-8.0; 8.0	0.0; 13.0	-9.0; 10.0

Abbreviations: LOCF, last observation carried forward; QUIP, Questionnaire for Impulsive-Compulsive Disorders in Parkinson’s Disease; SD, standard deviation.
^a Endpoint (LOCF) = Week 24 or last available observation.
 Source: EOT Table 15.3.98

Source: Newron

Ocular Safety Information

The sponsor instituted ophthalmological monitoring of patients enrolled in clinical trials of safinamide. This was in response to the nonclinical study findings of retinal degeneration. The review division consulted Wiley A. Chambers, MD, in the Division of Transplant and Ophthalmology Products (DTOP), to review the sponsor's ophthalmological report.

In summary, Dr. Chambers found several critical limitations in the ophthalmological data. In Studies 015 and 017 (early stage PD), ophthalmological examination were added to the ongoing study protocols. Patients did not have pretreatment ophthalmological assessments and assessments were only performed at the final study visit, leaving no basis for comparison.

In Studies 016 and in the long-term controlled extension study 018, patients received clinical assessments including an assessment of visual acuity, color vision, an automated visual field exam, and a fundus exam. A central reader without knowledge of the patient's treatment assignment interpreted the core data. However, Dr. Chambers commented; "These studies proved difficult to interpret due to the number of abnormalities at baseline, the use of a color vision test which does not detect blue/yellow confusion, and the number of missing values."

After discussions with the review division, the sponsor modified their ophthalmological monitoring program used in Studies 27918 (MOTION), and 27919 (SETTLE), the MOTION Extension study (27938), the Cognition study (024), the LID study (023) studies, and the Open-Label Extension (OLE) study (28850). In addition to the core ophthalmological data collected in previous studies, Optical Coherence Tomography (OCT) and/or Electroretinography (ERG) was added to the battery of tests in a subset of patients. Once again, a central reader interpreted the results for the core assessments. The OCTs were read by an independent neuro-ophthalmologist.

The ability to interpret the core ophthalmological data from these studies was limited by a high percentage of missing data. The central reader reported 10% to 67% missing core data. Information from a limited number of OTC examinations was variable, for example, a patient may have worsen in one eye but improved in the other eye by the end of the study compared to Baseline, with respect retinal nerve fiber layer (RNFL) thickness and total macular volume.

Dr. Chambers commented, that despite the limitation of the data," approximately a third of all patients (including placebo) experienced decreased ocular function during the clinical trials however, "It has not been possible to distinguish between impaired vision due to the underlying condition, the inability to perform ocular assessment testing, and adverse events related to the use of the drug product."

CDTL Comment

The ophthalmological data are not sufficient to exclude or confirm that the retinal degeneration observed in nonclinical studies is relevant to patients taking safinamide. Retinal degeneration was also observed in nonclinical studies for dopamine agonist (DA) medications. Patients must have been on a stable dose of a dopamine agonist to enter clinical studies of safinamide in early PD, and many patients enrolled in late PD studies were also treated with a DA. Recently, retinal thinning detected on OCT was also reported in patients with early, untreated PD (Kirbas, Turkyilmaz,

Tufekci, & Durmus, 2013). The retinal degeneration observed in early untreated PD patients also appears worsens with time.

The potential for retinal degeneration caused by other medications prescribed for the treatment for PD (e.g., DA), unrelated retinal disease, and retinal disease associated with PD, all confound the ability to interpret the clinical ophthalmological study data. Additional clinical studies to evaluate the potential of safinamide to cause retinal degeneration seem unlikely to yield interpretable results.

In the submitted label, the sponsor proposed contraindicating safinamide in patients with pre-existing retinal or macular degeneration. This approach seems too restrictive in the absence of a causal relationship of safinamide to retinal degeneration, and the presence of comorbidities that cause retinal degeneration in patients with PD. The clinical team recommends providing the information describing retinal degeneration in animal studies in the Warnings and Precautions section of the Safinamide label, with the recommendation to monitor patients for visual loss if they have a history of retinal disease.

Vital Signs

I concur with Dr. Kapcala’s analysis of vital sign information from studies on Patients taking DA with safinamide (Early) and in patients treated with a stable dose of levodopa (Late). Safinamide did have a small effect on lowering mean standing systolic (SBP). There were no clinically meaningful changes in mean heart rate or significant disproportion in the number of outlying values.

Orthostatic Blood Pressure

Patients were assessed for orthostatic changes in BP during Studies 016 and SETTLE. The late stage PD population was analyzed because it is population covered in the approved indication. In addition, patients with PD treated with levodopa, with or without other PD medications are more likely to suffer hypotension caused by autonomic insufficiency due to PD, and the BP lower effects of PD medications. The results shown below represents the worst case, where the change in BP was measured after patients moved from the supine and remained standing for 1 minute, 3 minutes, or up to 5 minutes (SETTLE study only). The “worst case” is the visit and timepoint with the largest mean drop in standing systolic BP is highlighted in table 40 below, the orthostatic decline in systolic BP was less pronounced at other visits and timepoints (duration patients remained standing, 1, 3 or 5 minutes depending on the study).

Table 40: Study 016 (Late PD) Change in Systolic BP Worst Case, Week 12 After 3 Minutes Standing

	TRT01A											
	PLACEBO				SAFINAMIDE 100 mg/day				SAFINAMIDE 50 mg/day			
	CHG				CHG				CHG			
AVISIT	N	Mean	Min	Max	N	Mean	Min	Max	N	Mean	Min	Max
Baseline	0	.	.	.	0	.	.	.	0	.	.	.
End of Study	7	-3.7	-36	18	7	-3.4	-30	16	5	-1.6	-50	16

	TRT01A											
	PLACEBO				SAFINAMIDE 100 mg/day				SAFINAMIDE 50 mg/day			
	CHG				CHG				CHG			
	AVISIT	N	Mean	Min	Max	N	Mean	Min	Max	N	Mean	Min
Endpoint	213	-1.7	-60	42	216	-2.2	-45	60	218	-0.28	-82	46
Screening	0	.	.	.	0	.	.	.	0	.	.	.
Unscheduled	4	8.5	-2	20	2	-1	-8	6	3	-0.67	-14	8
Visit 3	1	0	0	0	0	.	.	.	0	.	.	.
Visit 4	212	-1.3	-60	40	216	-1.9	-45	40	218	-2.1	-70	31
Visit 5	206	-2.6	-80	50	210	-1.1	-52	64	213	-1.1	-70	36
Visit 6	204	-1.0	-44	40	208	-2.2	-44	40	211	-0.4	-60	50
Visit 7	197	-0.6	-50	42	202	-3.0	-44	46	204	-1.1	-60	50
Visit 8	197	-1.8	-60	42	195	-2.0	-45	60	201	-0.1	-82	46

In Study 016, 8 patients in the placebo and safinamide 100 mg groups had at least a Systolic Blood Pressure ≤ 90 and ≥ 20 mmHg Decrease from Baseline compared to 11 in the safinamide 10 mg group.

Table 41: SETTLE Study (Late PD) Change in Systolic BP Worst Case, Week 12 After 3 Minutes Standing

	TRTA								
	PLACEBO				SAFINAMIDE 50-100 mg/day				
	CHG				CHG				
	AVISIT	N	Mean	Min	Max	N	Mean	Min	Max
Screening	0	.	.	.	0
Baseline	0	.	.	.	0
Baseline (post-dose)	270	0.02	-46.0	49.0	273	-1.79	-40.0	36.0	
Week 2	271	-2.48	-79.0	38.0	269	-2.80	-52.0	42.0	
Week 4	265	-1.40	-43.0	42.0	265	-2.15	-40.0	34.0	
Week 8	258	-1.38	-49.0	60.0	259	-1.77	-44.0	43.0	
Week 12	253	-0.96	-70.0	46.0	253	-2.90	-55.0	34.0	
Week 18	246	-1.67	-70.0	59.0	248	-2.49	-45.0	35.0	
Week 24	241	-1.47	-62.0	47.0	244	-1.15	-50.0	40.0	
Week 25	71	-3.77	-66.0	37.0	60	-2.78	-40.0	52.0	
Week 29	71	-3.94	-91.0	36.0	54	-0.06	-36.0	45.0	
Week 24 (ED)	22	-4.91	-58.0	28.0	20	-2.60	-33.0	40.0	
Unscheduled	5	-1.80	-14.0	27.0	20	-0.05	-26.0	21.0	
Changes in PD Treatment	11	-6.18	-35.0	25.0	2	0.50	-4.0	5.0	

In addition, there was an equal number of patients in SETTLE with at least one systolic BP value ≤ 90 with ≥ 20 mmHg decrease from Baseline in the safinamide group (N=5), and the placebo group (N=5).

Weight Change

Patients prescribed medications for the treatment of PD may experience weight gain related to edema. Edema was not a frequently observed adverse reaction in this application. Changes in weight were small, increased, or decreased, and patients with weight change meeting the sponsor (somewhat arbitrary) 7% weight change were similar in each direction (Tables 42 and 44).

Table 42: Study 016 Analysis $\geq 7\%$ Weight Change from Baseline to Endpoint in the Safety Population

ARM	Patients with Available baseline and Endpoint Data N	Wt Loss 7% N (%)	Wt Gain 7% N (%)
Placebo	222	9 (4)	12 (5)
Safinamide 100 mg/day	223	13 (6)	14 (6)
Safinamide 50 mg/day	223	10 (2)	7 (3)

Endpoint: Visit 8 (Week 24) or last available observation Vital sign variables with missing data will not be imputed. If a Baseline value is missing, no change from Baseline will be calculated.

Table 43: SETTLE $\geq 7\%$ Weight Change in The Safety Population

ARM	Patients with Available Data N	Wt Loss 7% N (5)	Wt Gain 7% N
Placebo	230	29 (13)	29 (13)
Safinamide 50-100 mg/day	231	36 (16)	36 (16)

Non-missing values no imputation

Clinical Laboratory Data

I concur with Dr. Kapcala’s recommendation to advise prescribers about the potential for hyponatremia in patients treated with safinamide. Hyponatremia is reported with other medication approved for the treatment of PD (dopamine agonists). It is plausible that safinamide might exacerbate or cause hyponatremia.

The difference in the proportion of patients treated with safinamide who shifted HDL cholesterol levels from normal to low compared to placebo was pronounced in the late PD population however, there was no apparent relationship to increasing dose.

Shifts from normal to high for hepatic transaminases are less clear for patients with late PD. The proportion of patients who shifted from normal to high is similar to the proportion of patients who shifted from high to normal. In the early PD subgroup, the proportion of patients with an AST and ALT value that shifted from normal to high during the study is substantially greater than the proportion of patients who shifted to low. The proportion of patients with a shift in AST or ALT was from normal to high was also greater in patients treated with safinamide compared to placebo in early and late PD patients (Table 44).

Table 44: Incidence of Abnormal Shifts (from High/Normal Baseline to Low and from Low/Normal Baseline to High at Any Time in Pooled Trials for Early Parkinson's Disease- and Late Parkinson's Disease-LSPD)

Clinical Laboratory Analyte and Treatment Group	Early Parkinson's Disease Pool of Studies 15 & MOTION	Late Parkinson's Disease Pool of Studies 16 & SETTLE
---	---	--

	Shift to Low	Shift to High	Shift to Low	Shift to High
ALT				
Placebo	1	8	13	3
Saf 50	0	8	12	5
Saf 100	0	13	12	7
Pool 50/100	0	11	12	6
Saf 200	0	13		
Pool 50/100/200	0	11		
AST				
Placebo	1	4	5	3
Saf 50	1	7	6	7
Saf 100	1	9	4	6
Pool 50/100	1	8	5	6
Saf 200	0	3		
Pool 50/100/200	1	8		
Bilirubin				
Placebo	0	4	10	3
Saf 50	1	4	23	3
Saf 100	1	4	12	2
Pool 50/100	1	4	15	3
Saf 200	0	1		
Pool 50/100/200	1	4		

Source: Newron **Highlight** Indicates > 2 % Higher Than Placebo

Two patients met laboratory criteria for classification as a Hy’s Law case. AST and ALS ≥ 3X ULN and a bilirubin ≥ 2X the ULN. The two patient Hy’s Law cases (Table 45) had alternate explanations for their laboratory abnormalities. The first patient was diagnosed with pancreatic carcinoma with liver metastasis and the second patient developed biopsy confirmed hepatocellular carcinoma.

Table 45: Hy’s Law Cases in ISS Clinical Laboratory Datasets

USUBJID	Cause
00010150160050003	Pancreatic CA
00010150160500007	Hepatocellular carcinoma

The effect of safinamide on AST, ALT, HDL and serum sodium should be described in labeling to make prescribers aware of the potential effects on these laboratory tests.

Electrocardiogram (ECG)

I agree with Dr. Kapcala’s conclusion that the analysis of ECG data found there was no meaningful change in mean or median ECG parameters. One patient discontinued from the trial for an adverse event of QTc prolongation. The analysis of outliers did not reveal a disproportion of outliers with events that suggested there is an increased risk for arrhythmia or cardiac conduction abnormality associated with safinamide.

CDTL Safety Conclusions

I agree with Dr. Kapcala’s conclusion that the safety profile of safinamide is similar to that of other FDA approved MAO-B inhibitor. The current Class Language in the label warning prescribers about the potential for Impulse Control Disorder, Hallucinations and Psychosis, Hypertension, Tyramine Interaction, Serotonin Syndrome, Hyperpyrexia and Confusion, Retinal Pathology, and Melanoma should be included in the safinamide label.

I agree with the Office of Clinical Pharmacology's recommendation to impose a PMR to require the sponsor complete a study to evaluate the effect of NW-1689 causing inhibition of BCRP, on drugs that are BCRP substrates. The sponsor's previous study used a weak BCRP substrate to assess the potential DDI instead of one of the BCRP substrates recommended by FDA.

9. Advisory Committee Meeting

Although safinamide is an NME, if approved, it would be the second molecular entity and the fourth product in the class of selective MAO-B inhibitor approved in the US. The intended user population for safinamide is identical to the population described in the labels of the approved MAO-B inhibitors [rasagiline (Azilect) and selegiline (Eldepryl)].

9. Pediatrics

PeRC granted a full PREA Waiver was granted (April 22, 2015) for this application. The full waiver is justified because Parkinson's disease is uncommon in the pediatric population completing pediatric studies is impracticable.

10. Other Relevant Regulatory Issues

Financial disclosures

The sponsor had difficulty obtaining financial disclosure forms for principal investigators following the unanticipated change in ownership. Merck Serono and Newron conducted clinical trials. Merck-Serono conducted several pivotal clinical trials prior to returning the IND to Newron. The studies supporting the application for adjunctive treatment in patients taking levodopa ((Late Stage PD (LSPD)), Studies 016 and SETTLE are the most important. Study 016 had 52 enrolling sites and SETTLE had 119 enrolling sites.

Financial information from studies supporting the indication for treatment of patients with early PD does not impact the studies for late stage PD. The use in early PD should not be included in the approved indication because the clinical trials results did not show substantial evidence of effectiveness.

Dr. Kapcala examined the financial disclosure information in detail. Section 3 in the table 46 shows the sites where financial disclosures were not obtained despite the sponsor's repeated efforts. The number of missing financial disclosures in study 016 are concerning because more than half of the sites in the study were missing financial disclosures for the site PIs. In SETTLE, relatively few sites were missing financial disclosures for the site PIs. There were 13 investigators with "possible" disclosable financial relationships with the respective study sponsor. The size of each study (total N~675) suggests it unlikely that any one investigator could change the efficacy results for either study. The investigators were blind to treatment assignment of the sequence of how patients were assigned at their site also decreases the likelihood a site investigator could have changed the study results.

Table 46: Status of Financial Disclosures by Study

Principal Investigators					
Indication	Trial	Sponsor	Section 1	Section 2	Section 3
ESPD	009	Newron	25	-	4
	015	Newron	14	-	12
	017	Newron	15	-	11
	MOTION	(b) (4)	112	6	11
LSPD	016	Newron	24	-	29
	018	Newron	24	-	31
	SETTLE	(b) (4)	124	4	7

Clinical Investigators, excluding Principal Investigators					
Indication	Trial	Sponsor	Section 1	Section 2	Section 3
ESPD	009	Newron	42	-	24
	015	Newron	24	-	71
	017	Newron	26	-	63
	MOTION	(b) (4)	178	1	365
LSPD	016	Newron	65	-	155
	018	Newron	67	-	151
	SETTLE	(b) (4)	215	1	318

GCP and Ethical Issues

The sponsor attested that the trials in the application were conducted according to the Declaration of Helsinki, ethical principles and Good Clinical Practices (GCP) outlined in the ICH Guidance or Tripartite Guideline for GCP. The sponsor states there was IRB oversight for all study sites in the US, and independent ethics committees were consulted for sites outside of the US. The sponsor provided debarment certification covering the studies in the NDA.

The review division requested site inspections at two clinical study sites (Table 47).

Table 47: OSI Audits Results

Name of CI, Site #, and Location	Protocol and # of Subjects	Inspection Dates	Final Classification
Rupam Borgohain, MD Punjab, Hyderabad India Site#016	Protocols 1015/016 & 1015/018 39 and 33 subjects	6/1-5/2015	NAI
Jozsef Szasz, MD.Ph.D Mures, Romania 540136 Site# 071	Protocols 1015/016 & 1015/018 39&34 subjects	5/11-15/2015	VAI

Dr. Borgohain’s site was selected because he enrolled patients for studies 015 and 018 (extension study). Fifty-one patients were screened and 34 patients completed study 015 and 24 completed the open label extension study 018. The inspection reports found study related documents were

occasionally misfiled and study binders were in poor condition but there were no findings that effected the reliability of the data.

Dr. Jozsef Szasz's site was selected because he enrolled patients for study 016 and 018. Forty-five patients were screened, 8 patients were screen failures and 37 were enrolled. The ORA investigation found minor protocol deviations and inadequate record keeping. Two patients did not sign the latest version of the informed consent. The investigators accounting of study medication was incomplete. The PI also made corrections to source documents incorrectly, obliterating the original response. The data collected at Dr. Szasz's site was considered to be reliable and acceptable in support of the pending application.

11. Other Relevant Regulatory Issues

The sponsor was referred to the FDA draft guidance on Assessment of Abuse Potential of Drugs in the Pre-NDA meeting minutes sent to the sponsor on September 16, 2013. However, the sponsor did not submit adequate nonclinical or clinical assessments of abuse potential in the NDA. Although the omissions of abuse liability studies did not prevent NDA filing, abuse liability information is needed to complete labeling.

The nonclinical studies assessing abuse potential submitted in the NDA were conducted early in development. The sponsor's abuse liability information was based on receptor binding studies and nonclinical studies (from 2005-07) that do not adequately assess the abuse potential of safinamide.

The sponsor was informed they needed to submit additional clinical and nonclinical abuse potential assessments in the 74-Day Letter sent on March 12, 2015. The sponsor responded to the Agency's request for additional abuse potential studies on March 29, 2015, taking the position that additional nonclinical abuse potential assessments were not necessary. However, the response revealed additional shortcomings of the previously completed studies reinforcing the need to conduct additional nonclinical assessments. The sponsor submitted nonclinical abuse potential study protocols for FDA comment on July 2, 2015.

On July 24, 2015, the CSS review team sent the sponsor comments to revise the draft protocols nonclinical abuse liability studies. The final list for the nonclinical preclinical abuse liability studies are:

- RS1414: Evaluation of the discriminative properties of Newron's compound, safinamide, and a reference comparator compound in rats trained to discriminate d-amphetamine from saline.
- RS1426: Evaluation of the discriminative properties of Newron's compound, safinamide, and a reference comparator compound in rats trained to discriminate midazolam from saline.
- RS1415: Determination of the potential of Newron's compound, safinamide, to induce tolerance and dependence in male rats.
- RS1425: Determination of the potential of Newron's compound, safinamide, to induce tolerance and dependence in female rats

- RS1417: Rhesus monkey intravenous self-administration protocol: cocaine reference and test substance substitution.

The sponsor submitted the analysis of adverse events associated with signs of withdrawal from their completed clinical trials. To date, three of the four requested nonclinical abuse potential studies have been submitted to the NDA. On March 10, 2016, the sponsor sent the Agency an email stating the study results of the midazolam in study in rats “will be delayed to around April 15, 2016”. The PDUFA deadline for the action on the safinamide NDA is March 29, 2016.

Dr. Randall-Thompson (CSS) reviewed the nonclinical abuse liability studies, except for study RS1426. The key findings from her review are:

- The pre-clinical drug discrimination study (Study RS1414) using amphetamine as the training drug indicates that the interceptive cues produced by safinamide are weakly similar to the interceptive cues induced by the stimulant, amphetamine. This assessment is designed to assess if safinamide produces effects that are similar to the effects produced by a stimulant. Since safinamide produces sedative effects, a discrimination test using a sedative/depressant is needed to further characterize safinamide’s effects.
- The pre-clinical self-administration study (Study RS1417) has significant methodological deficiencies: inappropriate positive control; too high of a fixed ratio response schedule (FR-30); no treatment exposure randomization; low number of subjects (4 primates); tested low doses that do not produce C_{max} levels comparable to the C_{max} levels of human therapeutic doses; designed only to test safinamide for stimulant effects.
 - Although the self-administration study has significant deficiencies, two out of the 4 primates (50%) were shown to self-administer safinamide indicating an abuse signal.

Due to lack of data characterizing the effects of safinamide as a sedative/ depressant, and due to the methodology deficiencies with the self-administration study, the abuse potential studies submitted by” the Sponsor cannot be fully relied upon to determine safinamide’s relative abuse potential”. In addition based on the results of Study RS1417 showing that two of four monkeys self-administered safinamide, Dr. Randall-Thompson concluded a HAPS was needed to evaluate he abuse potential of safinamide in humans.

The sponsor is not able to complete HAPS and submit the results by the PDUFA deadline. In addition, the sponsor did not conduct an adequate clinical evaluation of withdrawal and dependence. This new information regarding the potential for abuse and the need for a HAPS serves as the primary reason for the Complete Response Action. The sponsor could submit the clinical assessment of dependence and withdrawal as a PMR.

12. Labeling

Proprietary name: The FDA sent a letter to the sponsor notifying them proprietary name Xadago was approved on 2/24/2015.

DMEPA Recommendations for Labeling Sent to Newron

1. Full Prescribing Information

- a. Add the intended route of administration to Section 11 *Description* to comply with 21 CFR 201.57 (c)(12)(B).
- b. Remove trailing zeros from the dosing regimens in Section 14.1 to prevent misinterpretation of information related to studied doses.
- c. Remove the 14-count physician sample blister packs from Section 16.1 as these presentations are not intended for sale.

2. Carton and immediate container labels (if problems are noted)

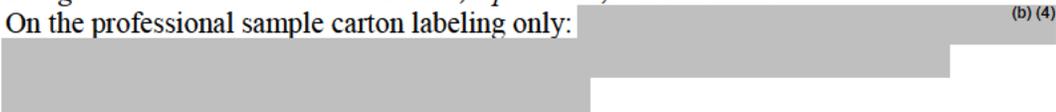
Carton and Container labeling recommendations from DMEPA were sent to the sponsor on two occasions the last set of comments by DMEPA were sent to the sponsor on March 7, 2016.

We have reviewed the revised container labels and carton labeling submitted January 11, 2016 and have the following recommendations for Newron Pharmaceuticals:

A. Trade Container Labels

- 1. Relocate the net quantity statement (i.e., ‘30 tablets’ and ‘90 tablets’) to the Principle Display Panel (PDP), for example, to the bottom right of the PDP. While we acknowledge this revision was made in response to our previous recommendation, the net quantity should remain on the PDP in a location separate from and less prominent than the statement of strength. See *Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors; April 2013, Lines 456-463.*

B. Professional Sample Carton Labeling

- 1. Relocate the net quantity statement (i.e., ‘1 blister card contains 14 tablets’) to the Principle Display Panel (PDP), for example, to the top right of the PDP. While we acknowledge this revision was made in response to our previous recommendation, the net quantity should remain on the PDP in a location separate from and less prominent than the statement of strength. See *Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors; April 2013, Lines 456-463.*
- 2. On the professional sample carton labeling only: (b) (4)


Patient labeling/Medication guide

Labeling for the approved MAO-B inhibitors do not include a Medication Guide or have a PPI. The sponsor included a Medication Guide in draft labeling however, the review team does not believe a medication Guide or PPI will help ensure safe use of safinamide.

13. Recommendations/Risk Benefit Assessment

Recommended Regulatory Action

Complete Response

Risk Benefit Assessment

Based on the results of the cocaine self-administration study (RS1417) showing that safinamide is associated with reinforcing behavior in two of four animals, the CSS concluded a HAPS is needed to evaluate the abuse potential of safinamide in humans. The sponsor is also unable to characterize the effects of safinamide as a sedative/ depressant, and methodology deficiencies in the self-administration study indicate the results of the study do not adequately assess safinamide's abuse potential. I agree the potential reinforcement caused by safinamide in nonclinical studies needs additional investigation. Other MAO-B inhibitors are available to patients with PD and none of the marketed products is associated with the potential for abuse.

The sponsor has shown safinamide provides benefit to patients with PD, treated with a stable dose of levodopa with, or without other medications to treat PD. The results of the sponsor's clinical trials 016 and SETTLE meet the statutory requirement for substantial evidence of effectiveness in patients with PD taking levodopa. The sponsor has not shown benefit in patients treated with safinamide as adjunctive treatment to a stable dose of a dopamine agonist, without concomitant levodopa. The safety profile of safinamide is similar to other MAO-B inhibitors approved for the treatment of PD.

Dividing PD into an Early, Middle and Late stages is arbitrary, and it does not define an easily recognizable user population. The Indication should be to increase ON time as adjunctive treatment for patients with PD taking a levodopa-containing product, with or without additional medication for the treatment of PD, or a similar statement.

Recommendation for Postmarketing Risk Evaluation and Management Strategies

A REMS is not recommended by the review. Following DRISK's Evaluation to determine if a REMS is necessary (3/9/2016), the DRISK review team concurred with the review division's opinion that a REMS was not necessary for safinamide.

Recommendation for other Postmarketing Requirements and Commitments

If safinamide is approved after resubmission, the approval action should include a postmarketing requirement (PMR) to study the potential of safinamide and its metabolite NW-1689 to act as an inhibitor of BCRP. The sponsor is aware of the PMR study and agreed to the milestone listed below.

NW-1689 is a major metabolite of safinamide found in plasma at levels that are approximately 160% of parent compound, safinamide. NW-1689 inhibited BCRP in vitro with an IC₅₀ of 3.7 ± 0.5 μM. The average maximal plasma concentration of Safinamide was approximately 4 μM in Parkinson's disease patients treated with the highest recommended dose of 100 mg/day. Based on the information from in vitro studies, there is a need for further in vivo drug interaction study at post-approval stage. Substrates of BCRP include methotrexate, mitoxantrone, imatinib, irrinotecan, lapatinib, rosuvastatin, sulfasalazine, topotecan. Inhibition of BCRP could increase plasma concentrations of these substrates, resulting in toxicity.

The sponsor completed a drug-drug interaction study to evaluate the effects of inhibition of BCRP by the NW-1689 metabolite but they used a weak substrate of BCRP, diclofenac, which

OCP considered inadequate. The PMR is required under FDAAA based on the new safety information of a potential drug-drug interaction.

Postmarketing Requirement

A clinical trial in healthy volunteers to compare the single-dose pharmacokinetics of a BCRP substrate, either rosuvastatin or sulfasalazine, alone and after administration of multiple doses of safinamide (100 mg/day).

The sponsor proposed the following milestone dates for submission of the PMR

Final Protocol Submission: 06/16

Trial Completion: 11/16

Final Report Submission: 03/17

Recommended Comments to Applicant

Recommendations to the sponsor are included in the Complete Response Letter.

References

- Anderson, N., & Borlak, J. (2006). Drug-induced phospholipidosis. *FEBS Lett*, 580(23), 5533-5540. doi: 10.1016/j.febslet.2006.08.061
- Kirbas, S., Turkyilmaz, K., Tufekci, A., & Durmus, M. (2013). Retinal nerve fiber layer thickness in Parkinson disease. *J Neuroophthalmol*, 33(1), 62-65. doi: 10.1097/WNO.0b013e3182701745
- Kumar, N., Van Gerpen, J. A., Bower, J. H., & Ahlskog, J. E. (2005). Levodopa-dyskinesia incidence by age of Parkinson's disease onset. *Mov Disord*, 20(3), 342-344. doi: 10.1002/mds.20360
- Pennington, S., Snell, K., Lee, M., & Walker, R. (2010). The cause of death in idiopathic Parkinson's disease. *Parkinsonism & Related Disorders*, 16(7), 434-437. doi: 10.1016/j.parkreldis.2010.04.010
- Siderowf, A., McDermott, M., Kieburtz, K., Blindauer, K., Plumb, S., Shoulson, I., & Parkinson Study, G. (2002). Test-retest reliability of the unified Parkinson's disease rating scale in patients with early Parkinson's disease: results from a multicenter clinical trial. *Mov Disord*, 17(4), 758-763. doi: 10.1002/mds.10011

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/s/

GERALD D PODSKALNY
03/23/2016

Division Director Summary Review for Regulatory Action

Date	(electronic stamp)
From	Eric Bastings, MD. Deputy Director.
Subject	Division Director Summary Review
NDA/BLA #	207145
Supplement #	
Applicant	Newron
Date of Submission	12/29/14
PDUFA Goal Date	03/29/2016
Proprietary Name / Non-Proprietary Name	Safinamide (Xadago)
Dosage Form(s) / Strength(s)	50 mg and 100 mg oral tablets
Applicant Proposed Indication(s)/Population(s)	<ol style="list-style-type: none"> 1. Add-on therapy to a single dopamine agonist at a stable dose in early stage, (b)(4) Parkinson's disease (PD) patients 2. Add-on therapy to (b)(4) L-dopa alone or in combination with other PD drugs in mid- to late-stage (b)(4) PD patients.
Recommended Action for NME:	Complete response
Recommended Indication/Population(s)	Adjunctive treatment to levodopa/carbidopa in patients with Parkinson's disease experiencing "off" episodes

Material Reviewed/Consulted	Names of discipline reviewers
OND Action Package, including:	
Medical Officer Review	Leonard Kapcala
Statistical Review	Xiangmin Zhang
Pharmacology Toxicology Review	LuAnn McKinney
Clinical Pharmacology Review	Histrina Dimova
OPDP	Aline Moukhtara
OSI	Antoine El-Hage
CDTL Review	Gerald D. Podskalny
OSE/DMEPA	Justine Harris
OSE/DRISK	Erin Hachey
OPQ/Drug Substance	Sharon Kelly
OPQ/Drug Product	Sherita McLamore
OPQ/Process/Microbiology	Mark Johnson
OPQ/Facility	Tracie Sharp and Franck Wackes
OPQ/Biopharmaceutics	Okpo Eradiri
OPQ/Project/Business Process Manager	Dahlia A. Woody
OPQ/Application Technical Lead	Martha R. Heimann
OPQ/ Environmental Assessment	James Laurenson
Ophthalmology	Wiley Chambers
Controlled Substance Staff	Alicja Lerner
QT Study Review	Huifang Chen

OND=Office of New Drugs
 OPQ=Office of Pharmaceutical Quality
 OPDP=Office of Prescription Drug Promotion
 OSI=Office of Scientific Investigations
 CDTL=Cross-Discipline Team Leader
 OSE= Office of Surveillance and Epidemiology
 DEPI= Division of Epidemiology
 DMEPA=Division of Medication Error Prevention and Analysis
 DRISK=Division of Risk Management

1. Background

The 505(b)(1) new drug application under review is for safinamide (Xadago), proposed as add-on therapy to a single dopamine agonist at a stable dose in early stage, (b) (4) Parkinson's disease (PD) patients, and as add-on therapy to (b) (4) L-dopa alone or in combination with other PD drugs in mid- to late-stage (u) (4) Parkinson's disease patients. The applicant proposes safinamide doses of 50 mg to 100 mg, once daily.

Safinamide is a selective monoamine oxidase type B (MAO-B) inhibitor. Several medications of that class are already approved and marketed. Inhibition of MAO-B activity, by blocking the catabolism of dopamine, may result in an increase in dopamine levels and a subsequent increase in dopaminergic activity in the brain.

The application is a resubmission. The original application for safinamide received a "Refused to File" letter on July 28, 2014, because the application was poorly organized, making it difficult or impossible to navigate.

As discussed by Dr. Podskalny, the review of this application was difficult, because of numerous issues with the submission, including missing or unusable datasets, and missing SAS programs. These issues resulted in numerous requests for information from the review team, and to an extension of the review clock in response to a major amendment submitted on August 31, 2015.

2. Product Quality

I concur with the conclusions reached by the chemistry review team regarding the acceptability of the manufacturing of the drug product and drug substance. Manufacturing site inspections were acceptable. Stability testing supports an expiry of (b) (4) months, at room temperature. There are no outstanding product quality issues.

3. Nonclinical Pharmacology/Toxicology

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharmacology/toxicology issues that preclude approval.

Retinal degeneration (atrophy of the outer nuclear layer) was found in 13-week toxicology studies in rats and mice, but not in monkeys, increasing in severity with increasing dose and duration of exposure. In combination drug studies that included safinamide and pramipexole, at doses of pramipexole that did not cause retinal changes, the combination exacerbated the retinal lesions caused by safinamide. Degeneration of the outer nuclear layer was not exacerbated by combination treatment with levodopa/carbidopa.

Based on a lack identified retinal changes in clinical studies, and the absence of change in monkey studies, the applicant concluded that the retinal atrophy is a rodent phenomenon and that there is no increased risk for patients. The applicant noted that published reports of other drugs have described similar retinal changes, but that none of these have been associated with retinal changes. Dr. Freed, supervisory pharmacologist, notes that while the applicant is correct in stating that retinal findings were not identified in humans, an expert review of the relevant human data concluded that the methodology used by the applicant was inadequate to detect drug-induced changes. Therefore, Dr. Freed recommends that the retinal findings be considered potentially relevant to humans and described in labeling. I agree.

The review team also notes that safinamide was teratogenic in rat when administered alone and exacerbated the teratogenicity of levodopa/carbidopa in both rat and rabbit. Carcinogenicity studies were negative in two species.

4. Clinical Pharmacology

I concur with the conclusions reached by the clinical pharmacology reviewer and the biopharmaceutics reviewer that there are no outstanding clinical pharmacology or biopharmaceutics issues that preclude approval.

The applicant developed different formulations and dosage forms of safinamide before selecting the final to-be-marketed formulation, a tablet manufactured by (b) (4). A capsule formulation was used in Study 009 and Study 015, while a tablet formulation different from the to-be-marketed tablet was used in Study 27918 (see below for description of studies). Adequate bridging studies between these formulations were conducted by the applicant.

There was no meaningful food effect on safinamide pharmacokinetics (PKs). Safinamide is about 90% bound to plasma proteins, and primarily metabolized by hepatic nonmicrosomal enzymes cytosolic amidases (e.g., MAO-A), with a minor role for CYP3A4. Several aldehyde dehydrogenase (ALDH) and UGT isoenzymes are involved in the final stages of metabolism. Safinamide predominant human circulating metabolite, NW-1689, has levels that exceed those of the parent, and was adequately qualified in nonclinical studies.

The clinical pharmacology reviewer notes that the potential for drug-drug interaction at the ALDH or UGT steps is limited because several isoenzymes in each system are involved in metabolism. The reviewer observes that the PKs of safinamide and its metabolites do not change appreciably after multiple doses.

Safinamide is renally eliminated, after approximately 95% of safinamide goes through metabolic transformation. Safinamide PKs are not substantially changed in patients with moderate or severe renal impairment, and the clinical pharmacology reviewer agrees with the applicant that patients with renal impairment do not require dose adjustment.

In patients with mild hepatic impairment, there was a 30% increase in safinamide AUC, which does not warrant a dose adjustment. In patients with moderate hepatic impairment, safinamide AUC increased by approximately 80%. The clinical pharmacology reviewer recommends that the daily dose of safinamide be limited to 50 mg in patients with moderate hepatic impairment, and that safinamide should be contraindicated in patients with severe hepatic impairment. I agree. Population PKs analyses support no need for dose adjustment based on age, gender or race.

Safinamide is a weak inhibitor of CYP1A2 and a weak inducer of CYP3A4; the clinical pharmacology reviewer does not consider these effects as clinically significant.

The clinical pharmacology reviewer, however, notes that the NW-1689 metabolite has a potential to inhibit intestinal Breast Cancer Resistance Protein (BCRP) at a dose of 100 mg (the recommended high dose in labeling), and that intestinal BCRP limits systemic exposure to various drugs, such as chemotherapy agents and statins. The reviewer believes the applicant did not adequately evaluate that issue in the development program, and should be asked to conduct an in vivo study to evaluate the potential for NW1689 to inhibit BCRP, as a post-marketing requirement (PMR). The clinical pharmacology reviewer recommends the following PMR:

1. A clinical study to characterize drug-drug interaction of safinamide and BCRP substrates in healthy volunteers NW-1689 is a major metabolite of safinamide found in plasma at the concentration of approximately 160% of parent compound, safinamide. NW-1689 inhibited BCRP with an IC50 of $3.7 \pm 0.5 \mu\text{M}$. The average maximal plasma concentration of Safinamide was approximately $4 \mu\text{M}$ in Parkinson's disease patients treated with the highest dose of 100 mg/day. Based on this information from in vitro evaluation, there is a need for further in vivo drug interaction study at post-approval stage. Substrates of BCRP include methotrexate, mitoxantrone, imatinib, irrinotecan, lapatinib, rosuvastatin, sulfasalazine, topotecan.

The clinical pharmacology reviewer notes that there are several pharmacodynamic interactions between MAO-B inhibitors and analgesics, other MAO inhibitors, decongestants, and several classes of antidepressants. These drug interactions are described in marketed MAO inhibitors labels (i.e., rasagiline and selegiline), and the review team recommends the safinamide label to include similar contraindications and warning statements. I agree.

Nonselective and selective MAO inhibitors also have the potential for interaction with dietary tyramine. The applicant conducted a dedicated tyramine study in healthy subjects. The study showed that safinamide, 100 mg and 350 mg, respectively, potentiated the pressor effect of tyramine by 1.6-fold and 1.8-fold versus placebo, compared to 2.2-fold for selegiline 10 mg (another MAO-B inhibitor), and 6-fold for phenelzine 30 mg (active control). In addition, rasagiline and selegiline, both selective MAO-B inhibitors approved for the treatment of PD, have class language advising prescribers to inform patients that ingestion of foods or beverages with high levels (>150 mg) of tyramine could cause hypertension. The review team recommends similar language for safinamide. I agree.

A thorough QT study showed that safinamide 100 mg and 350 mg dose causes dose-dependent QT shortening. QT prolongation was not observed.

5. Clinical Microbiology

Not applicable.

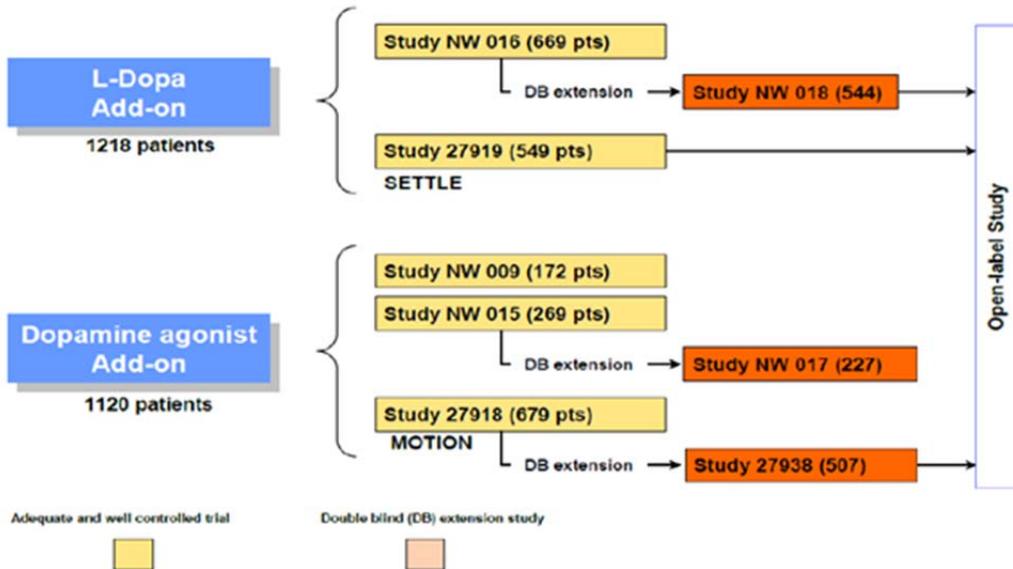
6. Clinical/Statistical-Efficacy

The applicant is seeking indications in two distinct populations, as an add-on therapy:

- Mid- to late-stage (b) (4) PD patients receiving L-dopa alone, or in combination with other PD medications
- Early stage, (b) (4) PD patients receiving dopamine agonist monotherapy.

Figure 1, copied from Dr. Podskalny's memo, summarizes the safinamide development program.

Figure 1: Safinamide development program



Mid- to late-stage Parkinson's disease (add-on to L-Dopa)

Study 016

Study 016 was a 24-week, double-blind, placebo-controlled study to evaluate the efficacy of safinamide 50 mg/day and 100 mg/day as add-on therapy in PD patients with motor

fluctuations on a stable dose of levodopa. Patients could also be on stable doses of a dopamine agonist, and/or other PD medications (e.g., COMT inhibitor, anticholinergic, or amantadine).

A total of 660 patients were planned to be randomized in a 1:1:1 ratio.

Study 016 started with a screening period (10 days), during which the investigator was to optimize (doses or timing) background PD medications to minimize motor symptoms. This was followed by a levodopa stabilization phase (4 weeks), and the double-blind treatment period (24 weeks).

Patients with progression of PD-related disability were permitted to receive rescue medication, defined as an increase of at least 20% in the total daily dose of the concomitant PD therapy (i.e., levodopa, dopamine agonist, or any other antiparkinsonian treatment) or a new PD drug. Efficacy data subsequent to the intervention were not included in the primary analysis.

The primary efficacy variable was the change in mean total daily “on time” (“on time” without dyskinesia plus “on time” with non-troublesome dyskinesia) over an 18-hour recording period (i.e., 6:00 AM to 12:AM) between baseline and Week 24. The safinamide 100 mg/day group was tested first, and only if there was a significant difference compared with the placebo group was the safinamide 50 mg/day group to be tested.

Secondary endpoints were as follows:

- Change from baseline in total daily “off time”
- Change from baseline to Week 24 in UPDRS Part III score
- Clinical Global Impression of change (CGI) at Week 24
- Change in cognition (cognitive test battery)
- Change from baseline to Week 24 in “off time” following first morning dose of levodopa
- Change in from baseline to Week 24 in Dyskinesias Rating Scale score
- Change from baseline to Week 24 in UPDRS Part II score
- Change from baseline to Week 24 in CGI - severity of illness
- Change from baseline to Week 24 in levodopa dose

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. If the difference between the safinamide 100 mg/day and placebo groups was not statistically significant for a particular variable, statistical tests on subsequent variables were performed only to obtain nominal p-values, but not for hypothesis testing.

The UPDRS Part III is a rated examination of the motor system and of patient mobility. It has intrinsic limitations, as it mixes assessments of impairment (e.g., tremor, finger tap, hand movement, rigidity) and function (e.g., arising from chair, gait), but the division has extensive

experience with the UPDRS scale, which has been used to support approval of multiple PD drugs. The UPDRSP Part II assesses activities of daily living.

A total of 222 patients were randomized to the placebo group, 223 to safinamide 50 mg/day, and 224 to safinamide 100 mg/day. A total of 594 patients completed the study: 197 in the placebo group, 202 in the safinamide 50 mg/day group, and 195 in the safinamide 100 mg/day group.

The review team confirms statistically significant results for the primary endpoint for both doses, along with significant results for both doses of safinamide vs. placebo for change from baseline in “off time” and in UPDRS Part III scores (Table 1

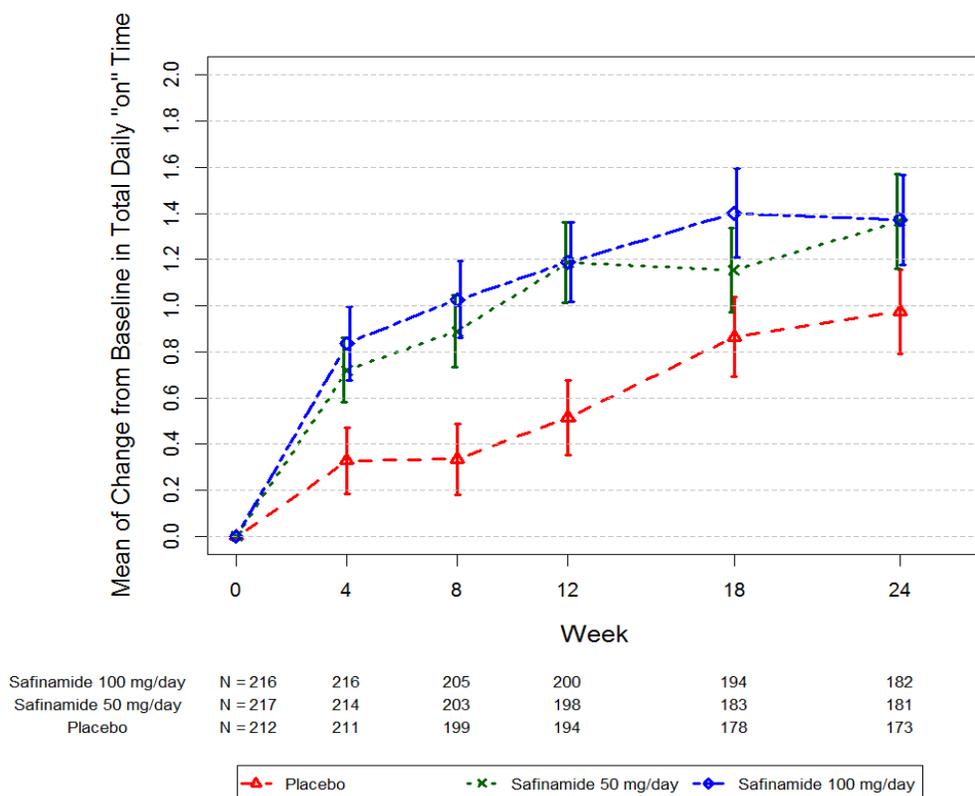
Table 1: Efficacy results of Study 016 (adapted from Table 15 of Dr. Podskalny’s review and from Table 12 of applicant’s study report)

LS = least square

Hierarchical testing of secondary endpoints stopped at the change in cognition. The statistical reviewer also notes that the safinamide 50 mg and safinamide 100 mg groups did not appear to differ significantly in efficacy results. This is illustrated by the figure below, which shows a graphical representation of the primary endpoint results.

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Figure 2: Mean of change from baseline in total daily "on" time by week and treatment in Study 016 (copied from Figure 3 of the statistical review)



Overall, I agree that Study 016 clearly supports to efficacy of both safinamide 50 mg and safinamide 100 mg for the treatment of PD patients with motor fluctuations on a stable dose of levodopa.

Patients from Study 016 could be rolled into Study 018, a double-blind extension trial (up to 1.5 years of additional year of treatment) of Study 16. The primary endpoint in Study 018 was the dyskinesia rating scale, developed to evaluate involuntary movements often associated with drugs for treatment of Parkinson's disease. There was no significant difference between either safinamide group and placebo for that outcome in Study 018.

Study 27919 (SETTLE)

Study 27919 was a 24-week, double-blind, placebo-controlled, parallel-group, randomized, Phase 3 trial, comparing a dose range of safinamide (50 to 100 mg) versus placebo, as add-on

therapy to a stable dose of levodopa in PD patients with motor fluctuations and at least 1.5 hour of “off time” during the day.

A total of 484 patients were planned to be randomized in a 1:1 ratio to placebo or safinamide.

As Study 016, Study 27919 started with a 10-day screening period, followed by a 4-week levodopa stabilization phase, and a 24-week double-blind treatment period.

Patients were started on 50 mg of safinamide once daily in the morning for 14 days. The dose was to be increased to 100 mg daily (targeted dose). If patients did not tolerate the increase to 100 mg, their dose could be reduced to 50 mg. If patients did not tolerate 50 mg daily, study medication could be held for 3 consecutive doses, and then restarted at the 50 mg dose, or discontinued.

The primary efficacy endpoint was the change from baseline to Week 24 in total daily “on time” without troublesome dyskinesia (over 18 hours).

Secondary endpoints were:

- Change from baseline to Week 24 in total daily “off time”
- Change from baseline to Week 24 in UPDRS Part III score
- change from baseline to Week 24 in UPDRS Part II score
- Proportion of patients with scores 1, 2, or 3 (showing improvement) on the Clinical Global Impression (CGI) change scale at Week 24
- Change from baseline to Week 24 in Parkinson's Disease Questionnaire (PDQ-39) score.

The multiple testing of secondary efficacy endpoints was handled in a pre-specified hierarchical fashion.

Overall, 549 subjects were randomized to treatment (274 to safinamide and 275 to placebo), and 478 completed the study. As in Study 016, the protocol allowed the use of rescue medication, such as an increase in the dose of levodopa or use of other PD drug, in which case the patient was to be censored; 54 patients on placebo and 39 patients on safinamide were rescued.

The study met its primary endpoint ($p < 0.001$), with a safinamide-placebo difference of 1 hour (Figure 3, Table 2).

Figure 3: Mean change from baseline in total daily "on" time by week and treatment in Study 27919 (copied from Figure 7 of statistical review)

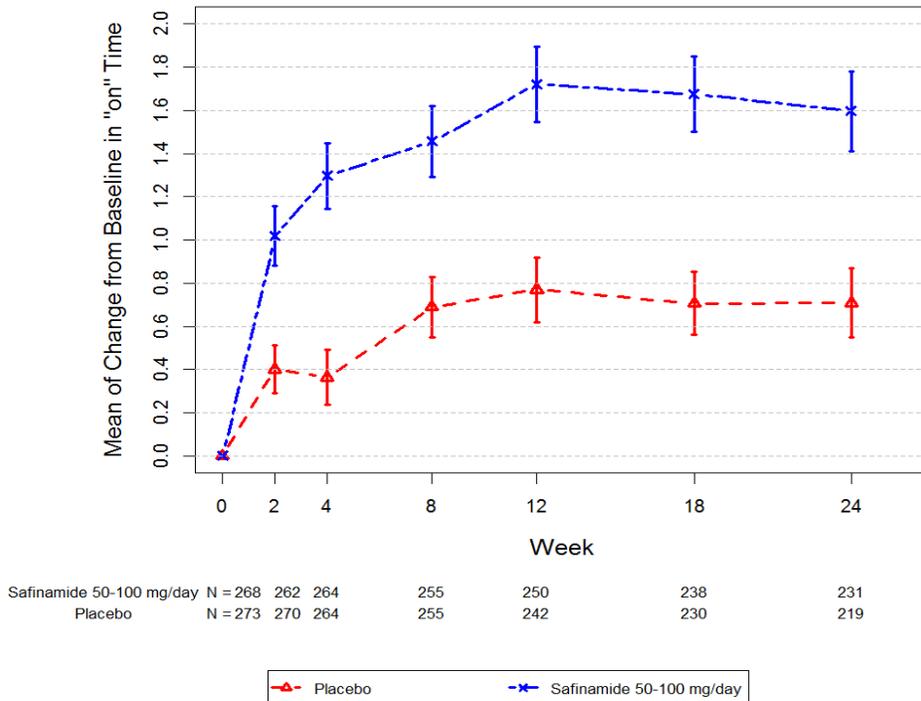


Table 2: Primary efficacy results in Study 27919: Total daily “on” time without troublesome dyskinesia

	Safinamide	Placebo (mean)
Week 24 (mean)	10.7 h	9.6 h
Change from baseline (LS mean)	1.5 h*	0.5 h

h= hour *p<0.001vs. placebo

In addition, safinamide was significantly better than placebo for the change from baseline in “off time” and the change in UPDRS Part III scores. According the multiple testing procedure, the testing stopped at the first nonsignificant contrast, i.e., the change from baseline in UPDRS Part II scores (p=0.214).

Table 3: Secondary endpoint results in Study 27919

	Safinamide	Placebo (mean)
Change from baseline in total daily “off time” (LS mean)	-1.67*	-0.61
Change from baseline in UPDRS Part III	-3.55 ⁺	-1.85
Change from baseline in UPDRS Part II	-1.15 ^{NS}	-0.79

*p<0.001 +p=0.005 NS = non-significant

Overall, I agree that Study 27919 clearly supports the efficacy of a dose range of 50 to 100 mg of safinamide for the treatment of PD patients with motor fluctuations on levodopa, and provides independent substantiation to Study 016.

Study 016 and Study 27919 also provide a strong prior to be considered in the interpretation of early PD studies, which are discussed below.

Early stage Parkinson’s disease (Dopamine agonist add-on)

The applicant conducted three clinical studies in early PD: Study 009, Study 15, and Study 27918.

Study 009

Study 009 was a 12-week, double-blind, placebo-controlled phase 2 study in early PD patients, either untreated (i.e., “de novo”) or treated with a stable dose of a dopamine agonist.

A total of 150 patients were planned to be randomized in a 1:1:1 ratio to safinamide 0.5 mg/kg/day, safinamide 1.0 mg/kg/day or placebo.

The primary outcome of Study 009 was a comparison of UPDRS Part III responder rates, defined as at least a 30% improvement in UPDRS Part III scores from baseline to Week 12. A secondary analysis (without multiplicity adjustment) looked at the subgroups of patients on a stable dose of a dopamine agonist, and the subgroup of untreated patients.

A total of 172 patients were randomized. The median dose of safinamide administered was 39 mg/day for the 0.5 mg/kg/day group, and 78 mg/day for the 1mg/kg/day group.

The safinamide 1 mg/kg group had a significantly greater responder rate than placebo, while the responder rate for the safinamide 0.5 mg/kg group trended in the right direction, but did not reach statistical significance (Table 4).

Table 4: Efficacy results of Study NW009 (copied from Dr. Podskalny’s memo)

Responder Rates(a) (n/% of Patients)	Safinamide 0.5 mg/kg/day		Safinamide 1.0 mg/kg/day		Placebo		P-value vs. Placebo Group (Logistic regression analysis)	
	n/N	%	n/N	%	n/N	%	Saf 0.5 mg/kg	Saf 1.0 mg/kg
Population								
Total population	17/55	30.9	21/56	37.5	12/56	21.4	0.143	0.018
Single DA-agonist (n=101)	12/33	36.4	16/34	47.1	7/34	20.6	0.195	0.006
De novo (n=66)	5/22	22.7	5/22	22.7	5/22	22.7	0.874	0.925

Dr. Podskalny and Dr. Kapcala discuss that using a 30% responder rate for the UPDRS Part III in an early PD population allows meeting the responder definition with small absolute score changes, as was observed in a number of patients. A prespecified sensitivity analysis looking at absolute UPDRS score changes did not reach nominal significance (p=0.1935), but favored

safinamide numerically (-3.3 for safinamide 1mg/kg, -2.6 for safinamide 0.5mg/kg, -0.6 for placebo), with a clear dose response. The lack of statistical significance in the contrast for absolute score change must be placed in the context of a relatively small and underpowered study. In addition, a post hoc analysis using an alternative statistical method (ANCOVA) yielded a nominally significant contrast for the UPDRS Part III score change from baseline.

Dr. Kapcala and Podskalny conclude that Study 009 did not show that safinamide provides a clinical meaningful benefit to patients with early PD.

While I agree that the primary endpoint of Study 009 does not have very clear clinical meaningfulness, because of the specific responder definition used, I note that the study met its primary objective for the 1 mg/kg safinamide dose group. To put the drug effect in context, I looked at the treatment effect, assessed by change in UPDRS (Part 1, 2, and/or 3) of drugs approved for the treatment of PD, and note the magnitude of change observed in Study 009 is in the range of those observed for other PD drugs (Table 5). Therefore, I find Study 009 overall supportive of efficacy of safinamide 1mg/kg for the treatment of early PD.

Table 5: UPDRS Part III results in approved PD drugs (copied from drug labels)

	UPDRS Part	Score change from baseline (Drug)	Score change from baseline (Placebo)	Treatment effect (Drug minus placebo)
Azilect 1mg (monotherapy in early PD)	1+2+3	3.9	0.1	- 3.8*
Azilect 1mg (adjunct to levodopa)	1+2+3	-3.6	-1.2	-2.8*
Neupro 2 mg (early PD)	2+3	-3.5	-1.4	-2.1*
Neupro up to 6 mg (early PD)	2+3	-4.0	+1.3	-5.3*
Neupro up to 8 mg (early PD)	2+3	-6.8	-2.3	-4.5*
Mirapex (early PD)	2 3	1.9 5	-0.4 -0.8	-1.5* -4.2*
Mirapex (early PD)	2 3	1.8 4.2	0.3 0.6	-1.5* -3.6*
Mirapex (late PD)	2 3	2.7 5.6	0.5 2.8	-2.2* -2.8*
Mirapex CR (early PD)	2+3	-8.1	-5.1	-3*

I=mentation II=ADLs III=motor function *statistically significant

Study 015

Study 015 was a 24-week randomized, double-blind, placebo-controlled, parallel-group, phase 3 study comparing two doses of safinamide (100 mg/day and 200 mg/day) versus placebo, as add-on therapy to a stable dose of a single dopamine agonist in early PD patients.

A total of 240 patients were planned to be randomized in a 1:1:1 ratio.

The primary endpoint was the change from baseline to Week 24 in the UPDRS part III total score.

For the primary endpoint, safinamide 200 mg/day was no better than placebo ($p=0.65$). Testing of the low dose was not permitted under the gatekeeping procedure; however, safinamide 100 mg was nominally better than placebo ($p=0.04$). Sensitivity analyses using several different methods of imputation did not change the results for the primary analysis. The CGI-C was not significantly better than placebo for either dose of safinamide ($p=0.57$ for safinamide 200 mg and $p=0.99$ for safinamide). Overall, Study NW-015 is not supportive of the efficacy of safinamide in the early PD population.

Patients from Study 015 could roll into Study 017, a double-blind extension of Study 15 (up to nearly one additional year). Considering the negative results of Study 015, Study 017 is not contributing any useful efficacy information, and I will not discuss it further.

Study 27918 (MOTION)

Study 27918 was a 24-week, double-blind, placebo-controlled, randomized, 3-arm, phase 3 study to evaluate the efficacy of safinamide as add-on therapy to a single dopamine agonist at a stable dose in early PD patients.

A total of 666 patients were planned to be randomized in a 1:1:1 ratio to safinamide 50 mg/day, safinamide 100 mg/day or placebo.

The primary efficacy endpoint was the change from baseline to Week 24 in UPDRS Part III scores.

Secondary endpoints included the following, to be tested in hierarchical order:

- UPDRS Part II (ADL) score change from baseline to Week 24
- Proportion of subjects with scores 1,2,3 (showing improvement) on the CGI change scale at Week 24
- PDQ-39 score change from baseline to WK-24.

The protocol-specified primary efficacy results show a trend favoring safinamide 100 mg vs. placebo (LS difference vs. placebo of -1.04, $p=0.073$), but no significant difference between safinamide 50 mg and placebo (LS difference vs. placebo of -0.69, $p=0.259$). The applicant sent an amended study report based on a blinded review that reportedly occurred prior to database lock. That analysis excluded data from 13 patients (6 on safinamide 100 mg, 3 on

safinamide 50 mg, and 3 on placebo) who were receiving prohibited concomitant medications at baseline, primarily anticholinergic medications or amantadine. The contrast between safinamide high dose and placebo was nominally significant for that analysis ($p=0.040$, score difference of -1.20). The contrast for the low dose vs. placebo remained not significant ($p=228$). It is not clear that the amended analysis is more valid than the original analysis, or changes the study conclusions.

Among secondary endpoints, there is a trend favoring safinamide 100 mg/kg for the UPDRS Part II ($p=0.085$), but with a very small treatment effect size (about -0.5 point). The proportion of responders on the CGI was 46% for safinamide 100 mg/day vs. 40% for placebo ($p=0.094$). There was a nominal benefit for safinamide 100 mg/kg for the PDQ-39 ($p=0.036$), a patient-reported outcome designed to address aspects of functioning and well-being for PD patients.

Overall, Study 27918 indicates a marginal trend in favor of safinamide 100 mg/kg, but considering the entirety of the evidence, the study is overall negative.

Patients from Study 27918 could be rolled into Study 27938, which was a double-blind extension of Study 27918. Study 27938 does not contribute efficacy data in support of an approval in the early PD population, as the applicant terminated the trial before completion and did not conduct an efficacy analysis.

Efficacy conclusions

Mid-to-late stage Parkinson's disease

The applicant provided data from two positive studies in Parkinson's disease patients with motor fluctuations in which safinamide was added to a stable dose of levodopa. Both studies showed a significant effect of safinamide 50 mg to 100 mg on total daily "on time" without troublesome dyskinesia. Both studies also show a superiority of safinamide over placebo for "off time" and for UPDRS Part III score change, a scale assessing motor symptoms of PD that has been used to support approval of a number of PD drugs. I agree with the team that the efficacy of safinamide 50 mg to 100 mg has been established as adjunct treatment for PD patients on stable doses of levodopa who experience "off time".

Early stage Parkinson's disease

Considering the results of the studies in early PD, Dr. Kapcala and Dr. Podskalny conclude that the applicant has not met the statutory requirement to show evidence of effectiveness for safinamide as adjunct treatment with a DA in patients with PD. Indeed, the results from the three studies conducted in patients with early Parkinson's disease are inconsistent. The initial phase 2 study (Study 009) provides data supportive of the efficacy of safinamide 1 mg/kg in early PD, but the meaningfulness of the benefit is in question, as the endpoint used a responder definition that does not necessarily represent a meaningful benefit, and the comparison of absolute UPDRS Part III scores between safinamide and placebo was not nominally significant using the prespecified method of analysis. There was, however, a dose response in UPDRS

scores (effect size of 2.6 points for safinamide 0.5mg/kg and 3.3 points for safinamide 1mg/kg). The encouraging results of Study 009 were however not substantiated by the much larger phase 3 studies, with Study 015 clearly failed its primary objective, and Study 27918 showed a trend in favor of the 100 mg dose of safinamide, but with a very small effect size, and inconsistent secondary endpoints.

Despite the strong prior provided by the evidence of efficacy in the mid-to-late PD population, I cannot find sufficient evidence in early PD studies to support a description in labeling of the use of safinamide in the early PD population, either as monotherapy or as an add-on drug.

7. Safety

Exposure

I agree with the review team that the extent of exposure to safinamide is sufficient to allow an adequate safety analysis. A total of 1949 patients were exposed to safinamide, with 1438 patients treated with the highest recommended dose (100 mg) for at least 12 months. There is also additional safety experience from an open-label extension study (Study 28850), into which patients from various controlled studies could be rolled over from. The exposure of safinamide well exceeds ICH E1 recommendations.

Deaths

Across all safinamide studies, there were 61 deaths, including 59 deaths that occurred within 30 days of the last dose of study medication. Across controlled studies, the incidence of deaths was similar between the safinamide and placebo treatment groups (about 2.2/100 patient-years). Deaths were mostly observed in the late stage population, with cardiovascular disease and pneumonia as most common causes of death. These are not unexpected in that population. There were very few deaths in the early PD population.

Serious adverse events (other than death)

Although serious adverse events (SAEs) were generally more common for patients on safinamide than on placebo, no specific pattern or safety signal emerged. For example, in a pooled analysis of the two large phase 3 studies in early PD (Study 15 and Study 27918 [MOTION]), the overall incidence of patients with at least one SAE was 4% for safinamide 50 mg, 4% for safinamide 100 mg, versus 2% for placebo. In a pooled analysis of the two large phase 3 studies in late PD (Study 16 and Study 27919 [SETTLE]), the incidence of SAEs was 8% for safinamide 100 mg, 4% for safinamide 50 mg, and 9% for placebo.

There was no significant excess of study dropouts for safinamide-treated patients versus placebo. In early PD phase 3 controlled studies, the overall incidence of patients with early dropout was 2% for safinamide 50 mg, 4% for safinamide 100 mg, and 6% for placebo. In late PD phase 3 controlled studies, the overall incidence of patients with early dropout was 5% for safinamide 50 mg, 6% for safinamide 100 mg, and 4% for placebo. In late PD patients, there

was a slightly greater incidence of dropouts related to dyskinesia for safinamide (1%) than for placebo. This finding is not expected for an effective PD treatment in the more advanced PD population.

Adverse events of special interest

Dr. Kapcala also looked at a number of safety events of special interest (based on class effects or nonclinical findings in safinamide toxicity studies):

- Hepatotoxicity
- Skin Melanoma
- Phototoxicity
- Serotonin Syndrome
- Hypertensive Crisis
- Fractures and Falls
- Ocular Adverse
- Neuropsychiatric
- Cardiovascular
- Dyskinesia
- Drug Abuse, Dependence, and Withdrawal
- Suicidality Adverse

I will only comment below on events for which a possible signal was identified.

Serotonin syndrome

Dr. Kapcala describes a case of serotonin syndrome, possibly resulting from an interaction between safinamide and fluoxetine, an SSRI. Dr. Kapcala believes that the label should reflect that serotonin syndrome has been observed in the safinamide development program. I agree.

Hypertensive crisis

There were three reports of “hypertensive crisis” (two for safinamide and one for placebo). All patients had a history of hypertension and had been taking anti-hypertensive medication. Dr. Kapcala notes there were no details regarding the cases. Considering that none of these cases was coded as a serious adverse event and that no patient discontinued from the trial nor experienced a change in study medication, the clinical significance of these events appears low.

Neuropsychiatric events

There was a slight excess of neuropsychiatric events for patients on safinamide. In late PD patients treated with safinamide 100 mg in clinical studies, there was an increased incidence of insomnia (4 % on drug vs. 2 % for placebo) and anxiety (2 % on drug vs. 1 % for placebo). The incidence of anxiety was also increased for the safinamide 50 mg dose (2 %). That signal was not seen in the early PD population.

Dyskinesia

In the late PD population, dyskinesia was reported with a higher incidence for safinamide (18% for safinamide 100 mg, and 21% for safinamide 50 mg) than for placebo (9%). Discontinuation due to dyskinesia occurred in 1.4% of safinamide-treated patients, vs. 0.4% for placebo. There was no signal for dyskinesia in the early PD population. As noted above, dyskinesia is an expected adverse reaction for an effective PD drug in the late PD population.

Fractures and falls

There was a slightly higher incidence of fracture and/or falls in safinamide-treated patients in the late PD population. In the pooled phase 3 studies in late PD patients, the incidence of events suggestive of a fall was 3.1% for safinamide 50 mg, 5.2% for safinamide 100 mg, vs. 3.6% for placebo. The incidence of fractures was 1.8% for safinamide 50 mg, 1.4% for safinamide 100 mg, vs. 0.6% for placebo. These events are possibly related to the increased mobility of safinamide-treated patients, which raises the risk of fall.

Hypotensive events

Dr. Kapcala discusses a possible increase in hypotensive events. However, I am not convinced that there is a true signal, as the incidence of hypotensive events on safinamide 100 mg was similar to that observed in the placebo group.

Ocular adverse events

Due to the nonclinical safety signal described above, there was an extensive ocular safety monitoring in safinamide clinical trials. The monitoring included an assessment of visual function in controlled trials, including visual acuity, color vision, visual field, and fundus examination in about 2000 patients, with over 1000 patients contributing up to 2 years of observation. In addition, evaluations using slit lamp, measurements of intraocular pressure, and external eye examinations were performed in some studies; OCT was obtained in about 400 patients and ERG in 20 patients. As discussed by the review team, there was considerable heterogeneity in the ocular monitoring across studies, which constrains the pooling of data for most ocular monitoring measures.

No excess of ocular adverse reactions could be identified in safinamide-treated patients in any of the studies. However, Dr. Chambers, FDA ophthalmology consultant who reviewed the data, notes that it is not possible to distinguish between impaired vision due to the underlying condition, inability to perform ocular assessment testing, and adverse events related to safinamide.

Sleep attacks/sudden onset of sleep

Dr. Kapcala notes that there was one event of sleep attack and two events of sudden onset of sleep for safinamide 100 mg in controlled studies, versus none for placebo. Dr. Kapcala also notes a signal for somnolence. However, the incidence of somnolence reported as an adverse

event at the proposed maximum recommended dose of safinamide (100 mg) was similar to that observed in the placebo group (e.g., 4% vs. 4% in pooled phase 3 studies in early PD; 2% vs. 3% in Study 16 (late PD), and 4% vs. 3% in Study 27919 (late PD). Also, an assessment of sedation with the Epworth Sleepiness Scale showed similar results between treatment groups. Therefore, I do not believe there is clear treatment-associated somnolence, but labeling should warn about the risk of sleep attacks, a well-known class effect.

Impulsive/compulsive behavior

As described by Dr. Kapcala, a small number of events (n=10) compatible with impulsive or compulsive behavior were seen in late PD patients treated with safinamide 100 mg, versus none for placebo. The events included libido increased, psychotic disorder, emotional disorder, hypersexuality, hypomania, obsessive thoughts, restlessness, and “thinking abnormal”. Impulsive/compulsive behavior is part of class labeling for PD drugs, and should be described in the safinamide label.

There was no signal in early PD patients.

Common adverse reactions

Table 6 and Table 7, adapted from Dr. Kapcala’s review, show common adverse reactions with an incidence at least 2% greater than placebo at any dose of safinamide in pooled controlled phase 3 trials, respectively in early and mid- to late-stage PD patients. In those tables, adverse reactions with an incidence at least 2% greater for safinamide 100 mg or 200 mg than for placebo are bolded.

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Table 6: Common adverse reactions (incidence at least 2% and greater than placebo at any dose of safinamide) in early PD studies (adapted from Dr. Kapcala’s review)

	Safinamide 50 mg N=226	Safinamide 100 mg N=317	Safinamide 200 mg N=89	Placebo N=315
Nausea	6	9	9	7
Abdominal Pain/Discomfort	5	9	9	3
Gastritis	0	2	6	2
Anxiety	3	2	6	3
Pyrexia	1	2	6	3
Nasopharyngitis	6	3	6	3
Hypertension/ Increased Blood Pressure	1	3	8	3
Hypotension (including orthostatic)	2	1	5	2
Cough	4	4	6	3
Dizziness	8	6	5	6
Somnolence	8	4	5	7
Arthralgia	5	4	3	3
Urinary tract infection	5	3	2	3
Insomnia	5	4	1	4
Depression	4	1	1	3
Diarrhea	4	2	1	3
Paresthesia	3	2	0	1
Vertigo	3	1	1	1
Conjunctivitis	0	2	0	0

In the early PD population, common adverse reactions with incidence at least 2% greater for safinamide 100 mg or 200 mg than for placebo, in decreasing order of frequency, were nausea, abdominal pain/discomfort, hypertension, anxiety, gastritis, nasopharyngitis, pyrexia, cough, and hypotension. The only adverse reaction with an incidence at least 2% or greater than placebo at the 100 mg dose of safinamide (maximum recommended daily dose) was abdominal pain/discomfort.

Table 7: Common adverse events (incidence at least 2% and greater than placebo) in late PD studies (adapted from Dr. Kapcala’s review)

	Safinamide 50 mg N = 223	Safinamide 100 mg N =498	Placebo N =487
Dyskinesia	21	18	9
Nausea	3	6	4
Fall	4	6	4
Insomnia	1	4	2
Contusion	0	2	0
Hypertension/ Increased Blood Pressure	7	3	3
Blood Glucose Increase/ Hyperglycemia	4	2	1
Eosinophil count Increase	2	0	0
Chest Pain / Discomfort	3	1	1
Vertigo	2	1	1
Pyuria	3	1	1

In the late PD population, common adverse reactions with an incidence at least 2% and greater for safinamide 100 mg than for placebo, in decreasing order of frequency, were dyskinesia, nausea, fall, insomnia, and contusion.

Laboratory findings

In outlier analyses, Dr. Kapcala identified apparent signals for shifts to increased serum ALT and AST, decreased serum sodium, and decreased HDL cholesterol during safinamide treatment. Dr. Kapcala did not identify any Hy’s law case. There was no signal for increased ALT or AST to above three-fold the upper limit of normal. The minor shifts identified by Dr. Kapcala are of unclear clinical significance.

Vital signs

There were no noteworthy changes in central tendency analyses of vital signs. In outlier analyses, however, Dr. Kapcala describes several possible signals, including both systolic and diastolic blood pressure increases and decreases.

Dr. Kapcala also observes that labels of PD drugs that increase the dopaminergic tone have class labeling that describes an increased risk for hypotension or orthostatic hypotension. Of note, I do not believe that there was a noteworthy signal for increased blood pressure or hypertension reported as adverse reaction in late PD studies, at the doses proposed for marketing, as the incidence of hypertension was the same for safinamide 100 mg and for placebo. Also, I note that ambulatory blood pressure monitoring was obtained in about 117 patients in early and late PD, and the results did not raise any safety concern.

I summarize the vital signs shift tables from Dr. Kapcala’s review in Table 8.

Table 8: Vital signs outlier analyses (adapted from Dr. Kapcala’s table 76-79).

	Study 15 (early PD) Safinamide 100 mg/ placebo (%)	Motion Study (early PD) Safinamide 100 mg/ placebo (%)	Study 16 (late PD) Safinamide 100 mg/ placebo (%)	SETTLE Study (late PD) Safinamide 100 mg/ placebo (%)
SBP Increase > 20 mm Hg (supine)	13/6	-	-	-
DBP increase > 10 mm Hg	29/13	-	-	28/24
DBP increase > 20 mm Hg	6/2	-	-	-
DBP decrease > 10 mm Hg	-	34/30	33/28	40/37
DBP decrease > 20 mm Hg	-	-	-	-
Pulse increase > 15 BPM	-	16/11	-	-

– no meaningful difference between safinamide or placebo

Overall, these shifts analyses do not identify a clear systematic signal, or raise significant safety concerns.

ECGs and TQT study

No safety concern was identified on ECGs or in the TQT study.

Tyramine challenge trials

Non selective monoamine oxidase inhibition can lead to tyramine accumulation and serious resulting hypertension. In a dedicated tyramine sensitivity study, a slight effect on tyramine accumulation was observed for safinamide 100 mg. The magnitude of the effect, however, was less than that selegiline, a currently approved MAO-B inhibitor that does not have any dietary restriction for tyramine, and was used as active control in the safinamide tyramine study.

8. Advisory Committee Meeting

This drug was not referred to an advisory committee meeting, as it is the third of its therapeutic class, and does not present any unique safety or efficacy issues.

9. Pediatrics

A full pediatric waiver will be issued, as Parkinson’s disease is very rare in the pediatric population, and clinical studies are not practicable in that population.

10. Other Relevant Regulatory Issues

OSI inspections

Two study sites were inspected, one in India, and one in Romania. There were no inspection findings that affect the reliability of the data.

Drug abuse potential

The CSS reviewer recommends a complete response action because of inadequate characterization of the abuse potential of safinamide. According to the CSS reviewer, the nonclinical drug discrimination study conducted by the applicant (Study RS1414) indicates that the interceptive cues produced by safinamide are weakly similar to those induced by amphetamine. However, that study was designed to assess whether safinamide produces effects similar to those produced by a stimulant. Since safinamide has sedative effects, the CSS reviewer considers that a discrimination study using a sedative/depressant is necessary to further characterize safinamide abuse potential. The applicant is conducting a study assessing the interceptive cues of safinamide in comparison to midazolam, a sedative drug (Study RS1426), but that study has not yet been submitted to the NDA.

The CSS reviewer also notes that the nonclinical self-administration study (Study RS1417) has significant design issues, which limit its interpretability:

- a. Inappropriate positive control (positive control was not a CNS depressant)
- b. Fixed ratio response schedule (FR-30) too high, as depressants produce lower levels of responding
- c. No randomization to treatment
- d. Low number of subjects (4 primates)
- e. The tested doses did not produce peak exposure levels comparable to those seen with human therapeutic doses
- f. The study was designed to test safinamide only for stimulant effects.

Notwithstanding these design issues, the highest dose of safinamide (1.5 mg/kg) evoked a response in two of the four monkeys (i.e., 50% of subjects tested), which to the CSS reviewer indicates that safinamide may have positive reinforcing properties. Therefore, the CSS reviewer finds a clinical study necessary to assess the abuse potential of safinamide.

Finally, the CSS reviewer finds that the clinical dependence and withdrawal assessment conducted by the applicant is insufficient because a systematic evaluation of dependence, withdrawal and rebound was not performed. The CSS reviewer asks that the applicant submit the results of an evaluation of dependence and withdrawal.

I agree with the CSS reviewer conclusions and recommendations.

DRISK

The DRISK reviewer recommends that no REMS is necessary for this product. I agree.

11. Labeling

The proposed tradename, Xadago, was found acceptable by DMEPA.

There are no outstanding labeling issues.

12. Postmarketing

Although the drug is approved in Europe, there is insufficient experience to contribute any useful information.

13. Decision/Action/Risk Benefit Assessment

The data from the two studies in Parkinson's disease (PD) patients on stable doses of levodopa and who experience "off" episodes provide independent substantiation of efficacy, and support approval of safinamide for use in that population. Both studies showed a significant effect of safinamide 50 mg to 100 mg on total daily "on time" without troublesome dyskinesia, a clearly relevant clinical endpoint which has been used to support approval of a number of PD drugs. Both studies also show a superiority of safinamide over placebo for the UPDRS Part III, a scale assessing motor symptoms of PD that has also been used to support approval of a number of PD drugs.

The three studies conducted in patients with early Parkinson's disease had inconsistent results, which do not support the use of safinamide as monotherapy or as adjunctive treatment to dopamine agonists. While the initial phase 2 study (Study 009) provided encouraging results supportive of the efficacy of safinamide 1mg/kg in early Parkinson's disease, these results were not substantiated by the much larger phase 3 studies, which both failed to reach statistical significance for their primary endpoints, and had inconsistent results for secondary endpoints.

The safety experience for safinamide was largely as expected for a drug of this therapeutic class, with dyskinesia as most common adverse reaction in the more advanced PD population. Labeling should include the typical MAO-B inhibitors class labeling, with warnings and precautions about the risk for hypertension, serotonin syndrome, falling asleep during activities of daily living and somnolence, hypotension, dyskinesia, hallucinations, impulse control issues and compulsive behaviors, and withdrawal-emergent hyperpyrexia and confusion. Some events related to these class effects were observed in safinamide-treated patients.

Because of the deficiencies described above in the assessment of the abuse potential of safinamide, I recommend a complete response action. Once the necessary information on abuse potential is submitted, I believe the safety and efficacy data submitted by the applicant should support approval of safinamide as adjunctive treatment to levodopa/carbidopa in patients with Parkinson's disease experiencing "off" episodes.

I recommend the following Post-Marketing Requirement:

1. A clinical study to characterize drug-drug interaction of safinamide and BCRP substrates in healthy volunteers NW-1689 is a major metabolite of safinamide found in plasma at the concentration of approximately 160% of parent compound, safinamide. NW-1689 inhibited BCRP with an IC₅₀ of $3.7 \pm 0.5 \mu\text{M}$. The average maximal plasma concentration of Safinamide was approximately $4 \mu\text{M}$ in Parkinson's disease patients treated with the highest dose of 100 mg/day. Based on this information from in vitro evaluation, there is a need for further in vivo drug interaction study at post-approval stage. Substrates of BCRP include methotrexate, mitoxantrone, imatinib, irinotecan, lapatinib, rosuvastatin, sulfasalazine, topotecan.

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/s/

ERIC P BASTINGS
03/23/2016