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STATISTICAL REVIEW(S)
Statistical Review and Evaluation

CARCINOGENICITY STUDIES

IND/NDA Number: NDA 207-145
Drug Name: Safinamide
Indication(s): 105 Week Rat and Mouse Carcinogenicity Studies
Applicant: Sponsor: Newron Pharmaceuticals SpA
Via Ludovico Ariosto 21, 20091 Bresso, Milan, Italy

Performing laboratory:

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Biometrics Division: Division of Biometrics -6
Statistical Reviewer: Mohammad Atiar Rahman, Ph.D.
Concurring Reviewer: Karl Lin, Ph.D.
Medical Division: Division of Neurology Products
Reviewing Pharmacologist: LuAnn McKinney, Ph.D.
Project Manager: Stacy Metz
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1. Background

In this submission the sponsor included reports of two animal carcinogenicity studies, one in mice and one in rats. These studies were intended to assess the carcinogenic potential of safinamide when administered orally daily by gavage at appropriate drug levels for 104 weeks. Results of this review have been discussed with the reviewing pharmacologist Dr. McKinney.

In this review the phrase "dose response relationship" refers to the linear component of the effect of treatment, and not necessarily to a strictly increasing or decreasing mortality or tumor incidence rate as dose increases.

2. Mouse Study

Two separate experiments were conducted, one in male and one in female mice. In each of these two experiments there were three treated groups and one vehicle control group. Two hundred and forty CrI: CD-1™ (ICR) BR mice of each sex were assigned randomly to the treated and control groups in equal size of 60 mice per group. The dose levels for treated groups were 50, 100 or 200 mg/kg/day. In this review these dose groups were referred to as the low, medium, and high dose groups, respectively. The mice in the control group received the vehicle (water for formulation at 5 mL/kg).

During the administration period all mice were inspected visually at least twice daily for evidences of ill-health, mortality, or reaction to treatment. In addition, a more detailed weekly physical examination, which included palpation, was performed on each mouse to monitor general health.

The bodyweight of each mouse was recorded one week before commencement of treatment (Week -1), on the day that treatment commenced (Week 0), at weekly intervals for the first 16 weeks of treatment, thereafter once every four weeks and before necropsy.

2.1. Sponsor's analyses

2.1.1. Survival analysis

The sponsor presented the number of deaths in life-tables and proportions of survival by Kaplan-Meier survival curves. The presented tables divided the study into time strata, where the strata were defined as those weeks during which there were deaths. The mortality data were analyzed using the logrank tests (Mantel 1966, Peto 1974).

The following statistical tests were carried out:

1) Two-tailed test for dose response relationship with dose level.
2) Two-tailed pairwise comparison test of each treatment group against the control group.
Where the test for dose response relationship was statistically significant the highest dose group was excluded and the trend response relationship was repeated (using a one-tailed test) until the test was no longer statistically significant.

**Sponsor’s findings:** Sponsor’s analysis showed 36 (60%), 31 (52%), 32 (53%), and 44 (73%); and 32 (53%), 42 (70%), 36 (60%), and 37 (62%) number (percentage) of deaths in control, low, medium and high dose groups in male and female mice, respectively. Sponsor’s analysis showed statistically significant (p=0.045) increased mortality in the male mouse high dose group compared to their control. The sponsor concluded that there were no associated treatment-related pathological factors contributories to death.

### 2.1.2. Tumor data analysis

The sponsor analyzed the tumor incidence data using the methods outlined in the paper of Peto et al. (1980) for positive dose response relationships and the Fisher exact test for pairwise comparisons of the treated groups with the control. For Peto analysis the sponsor first classified the tumor types as fatal and incidental, and analyzed them using the death rate and prevalence methods, respectively. For the evaluation of incidental tumors, intervals used were Weeks 1-52, 53-74, 75-88, 89-96, 97-101 and 102-107, and for the analysis of fatal tumors, the week of death was used for such analysis.

**Reviewer’s comment:** Since the study was 104 week long, it is not clear why the sponsor chose Week 102-107 as their last interval. Appropriately, either they could choose intervals like Week 97-104 and ‘Terminal Sacrifice’ or Week 97-101, Week 102-104, and ‘Terminal Sacrifice’ for male mice; and Week 97-100 and ‘Terminal Sacrifice’ for female mice.

**Adjustment for multiple testing:** The sponsor compared their calculated p-values against test levels 0.001, 0.01, 0.05, p<0.1, and 0.1 for both dose response and pairwise tests. The sponsor commented that because of the number of statistical tests carried out there is an inevitable danger that some of the findings marked as statistically significant do not represent true treatment effects. The sponsor further commented that in interpreting the findings, account is taken particularly of the level of significance and of the existence of a dose-related trend; the consistency of findings over the two sexes is also taken into account.

**Sponsor’s findings:** The sponsor’s analysis showed statistically significant increased incidence of skin fibrosarcoma in low dose group of male mice and both sexes combined (p<0.05) compared to their relevant controls. The dose response relationship of this tumor type, however, was not significant. The analysis did not show statistically significant dose response relationship or increased incidence of any other tumor type in either sex. The sponsor commented that the ranges and incidence of observed tumor types were typical to those reported in aged CD-1 mice.

### 2.2. Reviewer’s analyses

To verify the sponsor’s analyses and to perform additional analyses suggested by the reviewing pharmacologist, this reviewer independently performed survival and tumor data analyses. Data used
in this reviewer's analyses were provided by the sponsor electronically.

2.2.1. Survival analysis

The survival distributions of mice in four treatment groups were estimated using the Kaplan-Meier product limit method. The dose response relationship was tested using the likelihood ratio test and the homogeneity of survival distributions was tested using the log-rank test. The Kaplan-Meier curves for survival rates are given in Figures 1A and 1B in the appendix for male and female mice, respectively. The intercurrent mortality data are given in Tables 1A and 1B in the appendix for male and female mice, respectively. Results of the tests for dose response relationship and homogeneity of survivals, are given in Tables 2A and 2B in the appendix for male and female mice, respectively.

**Reviewer’s findings:** This reviewer’s analysis showed 36 (60%), 31 (52%), 32 (53%), and 44 (73%) number (percent) of deaths in male mice and 32 (53%), 42 (70%), 36 (60%), and 37 (62%) number (percent) of deaths in female mice in control, low, medium, and high dose groups, respectively. The tests showed statistically significant dose response relationship in mortality across control and treated groups in male mice. The pairwise comparisons showed statistically significant increased mortality in the male mouse high dose group compared to their control. The female mice mortality did not show statistically significant difference among treatment groups.

2.2.2. Tumor data analysis

The tumor data were analyzed for dose response relationships and pairwise comparisons of treated groups with control. Both the dose response relationship tests and pairwise comparisons were performed using the Poly-K method described in the paper of Bailer and Portier (1988) and Bieler and Williams (1993). In this method an animal that lives the full study period \( w_{max} \) or dies before the terminal sacrifice but develops the tumor type being tested gets a score of \( s_h = 1 \). An animal that dies at week \( w_h \) without a tumor before the end of the study gets a score of \( s_h = \left( \frac{w_h}{w_{max}} \right)^k < 1 \). The adjusted group size is defined as \( \Sigma s_h \). As an interpretation, an animal with score \( s_h = 1 \) can be considered as a whole animal while an animal with score \( s_h < 1 \) can be considered as a partial animal. The adjusted group size \( \Sigma s_h \) is equal to N (the original group size) if all animals live up to the end of the study or if each animal that dies before the terminal sacrifice develops at least one tumor, otherwise the adjusted group size is less than N. These adjusted group sizes are then used for the dose response relationship (or the pairwise) tests using the Cochran-Armitage test. One critical point for Poly-K test is the choice of the appropriate value of \( k \), which depends on the tumor incidence pattern with the increased dose. For long term 104 week standard rat and mouse studies, a value of \( k=3 \) is suggested in the literature. Hence, this reviewer used \( k=3 \) for the analysis of this data. For the calculation of p-values the exact permutation method was used. The tumor rates and the p-values of the tested tumor types are listed in Tables 3A and 3B in the appendix for male and female rats, respectively.

**Multiple testing adjustment:** For the adjustment of multiple testing this reviewer used the methodologies suggested in the FDA guidance for statistical design and analysis of
carcinogenicity studies. For dose response relationship tests, the guidance suggests the use of test levels of $\alpha=0.005$ for common tumors and $\alpha=0.025$ for rare tumors for a submission with two species, and a significance level $\alpha=0.01$ for common tumors and $\alpha=0.05$ for rare tumors for a submission with one species in order to keep the false-positive rate at the nominal level of approximately 10%. A rare tumor is defined as one in which the published spontaneous tumor rate is less than 1%. For multiple pairwise comparisons of treated group with control the guidance suggests the use of test levels of $\alpha=0.01$ for common tumors and $\alpha=0.05$ for rare tumors, in order to keep the false-positive rate at the nominal level of approximately 10% for both submissions with two or one species.

It should be noted that the FDA guidance recommendation for multiple testing for dose response relationship is based on a publication by Lin and Rahman (1998). In this work the authors investigated the use of this rule for Peto analysis. However, in a later work Lin and Rahman (2008) showed that this rule for multiple testing for dose response relationship is also suitable for Poly-K tests.

**Reviewer’s findings:** Following tumor types showed p-values less than or equal to 0.05 either for dose response relationship and/or pairwise comparisons of treated groups with control.

**Tumor Types with P-Values ≤ 0.05 for Dose Response Relationship and/or Pairwise Comparisons of Treated Groups and Control in Mice**

<table>
<thead>
<tr>
<th>Sex</th>
<th>Organ Name</th>
<th>Tumor Name</th>
<th>Cont</th>
<th>Low</th>
<th>Med</th>
<th>High</th>
<th>Dose Resp</th>
<th>C vs L</th>
<th>C vs M</th>
<th>C vs H</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>Skin</td>
<td>Malignant Fibrosarcoma</td>
<td>1</td>
<td>8</td>
<td>6</td>
<td>2</td>
<td>0.4648</td>
<td>0.0231</td>
<td>0.0797</td>
<td>0.3920</td>
</tr>
</tbody>
</table>

Based on the criteria of adjustment for multiple testing discussed above, the incidence of the above or any other observed tumor types was not considered to have statistically significant dose response relationship or increased incidence in any of the treated groups compared to their respective control in either sex of mice.

### 3. Rat Study

Two separate experiments were conducted, one in male and one in female rats. In each of these two experiments there were three treated groups and one vehicle control group. Two hundred and sixty Crl:CD®(SD)IGS BR rats of each sex were assigned randomly to the treated and control groups in equal size of 65 rats per group. The dose levels for treated groups were 25, 50 or 100 mg/kg/day. In this review these dose groups would be referred to as the low, medium, and high dose groups, respectively. The rats in the control group received the vehicle (water for formulation at 5 mL/kg). As mentioned above, the study was intended to be continued for 104 weeks. However, due to excessive mortality all remaining female rats were terminally sacrifices at Week 102 when there were 15 surviving animals in the low dose group. Dosing of the male rats continued up to Week 104.
During the administration period all rats were inspected visually at least twice daily for evidence of ill-health, mortality, or reaction to treatment. In addition, a more detailed weekly physical examination, which included palpation, was performed on each rat to monitor general health. The bodyweight of each rat was recorded one week before commencement of treatment (Week -1), on the day that treatment commenced (Week 0), at weekly intervals for the first 16 weeks of treatment, thereafter once every four weeks up to Week 104 for males and up to Week 100 for females and before necropsy. Week 100 was the last scheduled recording for females as they were terminated in Week 102 due to strain-specific mortality.

3.1. Sponsor's analyses

3.1.1. Survival analysis

The sponsor analyzed the rat survival data using similar statistical methodologies as they used to analyze the mouse survival data.

Sponsor’s findings: Sponsor’s analysis showed 37 (57%), 42 (65%), 35 (54%), and 27 (42%), and 46 (71%), 50 (77%), 44 (68%), and 43 (66%) number (percentage) of deaths in the control, low, medium and high dose groups, in in male and for female rats, respectively. Sponsor’s analysis did not show statistically significance differences in mortalities among treatment groups in either sex of rats. The sponsor concluded that the mortality incidence in rats was not adversely affected by treatment.

3.1.2. Tumor data analysis

The sponsor did not present much elaboration of the statistical methodologies they used to analyze the tumor data. However, the presented results in Table 10 of the sponsor’s report indicates that the sponsor also analyzed the rat tumor data using similar statistical methodologies as they used to analyze the mouse tumor data.

Adjustment for multiple testing: For the adjustment of multiple testing the sponsor used similar methodology as they used to analyze the mouse tumor data.

Sponsor’s findings: The sponsor’s analyses did not show statistically significant dose response relationship among the treatment groups in any of the observed tumor types in either sex. Pairwise comparisons also did not show statistically significant increased incidence in treated groups compared to the control in any of the observed tumor types in either sex. The sponsor commented that the range of tumors encountered was similar in type and incidence to that commonly observed in CD rats.

3.2. Reviewer's analyses

Similar to mouse study, to verify the sponsor’s analyses and to perform additional analyses suggested by the reviewing pharmacologist, this reviewer independently performed survival and tumor data analyses of this study. Data used in this reviewer's analyses were provided by the
3.2.1. Survival analysis

For survival data analysis, this reviewer used the same statistical methodologies as for mouse survival data analysis. The Kaplan-Meier curves for survival rates are given in Figures 2A and 2B in the appendix for male and female rats, respectively. The intercurrent mortality data are given in Tables 4A and 4B in the appendix for male and female rats, respectively. Results of the tests for dose response relationship and homogeneity of survivals, are given in Tables 5A and 5B in the appendix for male and female rats, respectively.

**Reviewer’s findings:** This reviewer’s analysis showed 37 (57%), 42 (65%), 35 (54%), and 27 (42%), and 46 (71%), 50 (77%), 44 (68%), and 43 (66%) number (percentage) of deaths in the control, low, medium and high dose groups, in male and for female rats, respectively. The tests did not show statistically significant dose response relationship in mortality across control and treated groups in either sex of rats. The pairwise comparisons also did not show statistically significant increased mortality in any of the treated groups in either sex of rats compared to their respective control.

**Reviewer’s comment:** The sponsor’s count showed 50 and 44 deaths in female rat low and medium dose groups, while this reviewer’s count showed 48 and 42 number of deaths in these two dose groups, respectively. These differences are due to the facts that there were two female rats (#356 and #370) in low dose group, and two female rats (#401 and #444) in medium dose group that died naturally during the terminal sacrifice weeks. This reviewer counted these animals with survivors, while the sponsor counted them with dead.

3.2.2. Tumor data analysis

For tumor data analysis, this reviewer used the same statistical methodologies as he used for the mouse tumor data analysis.

**Multiple testing adjustment:** For the adjustment of multiple testing this reviewer used the used the same adjustment method as he used for the mouse tumor data analysis.

**Reviewer’s findings:** Following tumor types showed p-values less than or equal to 0.05 either for dose response relationship and/or pairwise comparisons of treated groups and control.

<table>
<thead>
<tr>
<th>Tumor Types with P-Values ≤ 0.05 for Dose Response Relationship or Pairwise Comparisons of Treated Groups and Control in Rats</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
</tr>
<tr>
<td>-----</td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td>Uterus</td>
</tr>
</tbody>
</table>

Reference ID: 3859195
Based on the criteria of adjustment for multiple testing discussed in mouse data analysis section, none of the above or any other observed tumor types was considered to have statistically significant dose response relationship in either sex of rats. The pairwise comparison showed statistically significant increased incidence of thyroid glands C-Cell carcinoma in male rat low dose group compared to their control.

4. Evaluation of the validity of design of mouse and rat studies

As has been noted, except for a significant pairwise comparison between male rat low dose group and their control for the increased incidence of thyroid glands c-cell carcinoma, there were no other significant dose response relationships and/or pairwise comparisons in the incidence of any other tumor types. However, before drawing any conclusion regarding the carcinogenic or non-carcinogenic potential of the study drug in mice and rats, it is important to look into the following two issues, as have been pointed out in a paper by Haseman (1984).

(i) Were enough animals exposed, for a sustained amount of time, to the risk of late developing tumors?
(ii) Were dose levels high enough to pose a reasonable tumor challenge to the animals?

There is no consensus among experts regarding the number of animals and length of time at risk, although most carcinogenicity studies are designed to run for two years with about fifty to sixty animals per treatment group. The following are some rules of thumb regarding these two issues, as suggested by experts in this field.

Haseman (1985) has done an investigation on the first issue. He gathered data from 21 studies using Fischer 344 rats and B6C3Fl mice conducted at the National Toxicology Program (NTP). It was found that, on the average, approximately 50% of the animals in the high dose group survived the two-year study period. Also, in a personal communication with Dr. Karl Lin of Division of Biometrics-6, Haseman suggested that, as a rule of thumb, a 50% survival of 50 initial animals or 20 to 30 animals still alive in the high dose group, between weeks 80-90, would be considered as a sufficient number and adequate exposure. In addition Chu, Cueto and Ward (1981), suggested that "to be considered adequate, an experiment that has not shown a chemical to be carcinogenic should have groups of animals with greater than 50% survival at one-year."

It appears, from these three sources that the proportions of survival at 52 weeks, 80-90 weeks, and two years are of interest in determining the adequacy of exposure and number of animals at risk.

Regarding the question of adequate dose levels, it is generally accepted that the high dose should be close to the maximum tolerated dose (MTD). In the paper of Chu, Cueto and Ward (1981), the following criteria are mentioned for dose adequacy. A high dose is considered as close to MTD if any of the criteria is met.
(i) “A dose is considered adequate if there is a detectable loss in weight gain of up to 10% in a dosed group relative to the controls.”

(ii) “The administered dose is also considered an MTD if dosed animals exhibit clinical signs or severe histopathologic toxic effects attributed to the chemical.”

(iii) “In addition, doses are considered adequate if the dosed animals show a slight increased mortality compared to the controls.”

We will now investigate the validity of the safinamide mouse and rat carcinogenicity studies, in the light of the above guidelines.

4.1. Mouse Study

The following is the summary of survival data of mice in the high dose groups:

**Percentage of Survival in the High Dose Groups at the End of Weeks 52, 78, and 91 in Mice**

<table>
<thead>
<tr>
<th></th>
<th>End of 52</th>
<th>End of 78</th>
<th>End of 91</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>72%</td>
<td>48%</td>
<td>40%</td>
</tr>
<tr>
<td>Female</td>
<td>98%</td>
<td>88%</td>
<td>70%</td>
</tr>
</tbody>
</table>

Based on the survival criterion Haseman proposed, it may be concluded that not enough male mice were exposed to the high dose for a sufficient amount of time.

The following table shows the percent differences in mean body weight gains in mice from the concurrent control, defined as

\[
\text{Percent difference} = \frac{(\text{Final BW} - \text{Baseline BW})_{\text{treated}} - (\text{Final BW} - \text{Baseline BW})_{\text{control}}}{(\text{Final BW} - \text{Baseline BW})_{\text{control}}} \times 100
\]

**Percent Difference in Mean body Weight Gain from Controls in Mice**

<table>
<thead>
<tr>
<th></th>
<th>Male</th>
<th>Female</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low</td>
<td>Mediu m</td>
<td>High</td>
<td>Low</td>
<td>Medium</td>
<td>High</td>
</tr>
<tr>
<td>Male</td>
<td>9.09</td>
<td>5.59</td>
<td>-9.79</td>
<td>-4.03</td>
<td>-10.07</td>
<td>-26.17</td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Source: Table 3 “Bodyweight - group mean values (g)” of Sponsor’s report

Therefore, relative to control the high dose male mice had about 10% and the female mice had more than 26% decrement in their body weight gain.
The mortality rates at the end of the experiment were as follows:

<table>
<thead>
<tr>
<th>Mortality Rates End of the Experiment in Mice</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Control</td>
</tr>
<tr>
<td>60%</td>
</tr>
<tr>
<td>Low</td>
</tr>
<tr>
<td>52%</td>
</tr>
<tr>
<td>Medium</td>
</tr>
<tr>
<td>53%</td>
</tr>
<tr>
<td>High</td>
</tr>
<tr>
<td>73%</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td>53%</td>
</tr>
<tr>
<td>Low</td>
</tr>
<tr>
<td>70%</td>
</tr>
<tr>
<td>Medium</td>
</tr>
<tr>
<td>60%</td>
</tr>
<tr>
<td>High</td>
</tr>
<tr>
<td>62%</td>
</tr>
</tbody>
</table>

This shows that the mortality rate in the high dose group was 13% and 9% higher than the control in the male and female mice, respectively.

Thus, from the body weight gain and mortality data it can be concluded that the used high dose level might have reached the MTD for male mice. From the body weight gain data it can be concluded that the used high dose level might have exceeded the MTD for female mice. For a final determination of the adequacy of the doses used, other clinical signs and histopathological toxic effects must be considered.

### 4.1. Rat Study

The following is the summary of survival data of rats in the high dose groups:

**Percentage of Survival in the High Dose Group at the End of Weeks 52, 78, and 91 in Rats**

<table>
<thead>
<tr>
<th>Percentage of survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>End of 52 weeks</td>
</tr>
<tr>
<td>End of 78 weeks</td>
</tr>
<tr>
<td>End of 91 weeks</td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>97%</td>
</tr>
<tr>
<td>85%</td>
</tr>
<tr>
<td>69%</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td>95%</td>
</tr>
<tr>
<td>72%</td>
</tr>
<tr>
<td>49%</td>
</tr>
</tbody>
</table>

Based on the survival criterion Haseman proposed, it may be concluded that enough rats were exposed to the high dose for a sufficient amount of time.

The following table shows the percent differences in mean body weight gains in rats from the concurrent control,

**Percent Difference in Mean body Weight Gain from Controls in Rats**

<table>
<thead>
<tr>
<th>Percent Difference in Mean body Weight Gain from Controls in Rats</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
</tr>
<tr>
<td>------</td>
</tr>
<tr>
<td>Low</td>
</tr>
<tr>
<td>-5.41</td>
</tr>
</tbody>
</table>

Source: Table 4 “Bodyweight - group mean values (g)” of Sponsor’s report

Therefore, relative to the control the male rats in high dose group had more than 34% and the female rats had more than 27% decrements in their body weight gains.
The mortality rates at the end of the experiment were as follows:

**Mortality Rates at the End of the Experiment in Rats**

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Low</th>
<th>Medium</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>57%</td>
<td>65%</td>
<td>54%</td>
<td>42%</td>
</tr>
<tr>
<td>Female</td>
<td>29%</td>
<td>26%</td>
<td>35%</td>
<td>34%</td>
</tr>
</tbody>
</table>

This shows that the mortality rates in the male rats high dose group is 15% lower than their control, while that in female rats is 5% higher than their control.

Thus, from the mortality and the body weight gain data it can be concluded that the used high dose level might have exceeded the MTD in female rats. From the body weight gain data it can also be concluded that the used high dose level might have exceeded the MTD in male rats. However, the mortality data do not support it. For a final determination of the adequacy of the doses used, other clinical signs and histopathological toxic effects must be considered.

5. **Summary**

In this submission the sponsor included reports of two animal carcinogenicity studies, one in mice and one in rats. These studies were intended to assess the carcinogenic potential of safinamide when administered orally daily by gavage at appropriate drug levels for 104 weeks.

In this review the phrase "dose response relationship" refers to the linear component of the effect of treatment, and not necessarily to a strictly increasing or decreasing mortality or tumor incidence rate as dose increases.

**Mouse Study:** Two separate experiments were conducted, one in male and one in female mice. In each of these two experiments there were three treated groups and one vehicle control group. Two hundred and forty Crl: CD-1™ (ICR) BR mice of each sex were assigned randomly to the treated and control groups in equal size of 60 mice per group. The dose levels for treated groups were 50, 100 or 200 mg/kg/day. The mice in the control group received the vehicle (water for formulation at 5 mL/kg).

During the administration period all mice were inspected visually at least twice daily for the evidences of ill-health, mortality, or reaction to treatment. In addition, a more detailed weekly physical examination, which included palpation, was performed on each mouse to monitor general health. The bodyweight of each mouse was recorded one week before commencement of treatment (Week -1), on the day that treatment commenced (Week 0), at weekly intervals for the first 16 weeks of treatment, thereafter once every four weeks and before necropsy.

The tests showed statistically significant dose response relationship in mortality across control and treated groups in male mice. The pairwise comparisons showed statistically significant increased mortality in the male mouse high dose group compared to their control. The tests did not show statistically significant dose response relationship or increased incidence in any treated group.
compared to their respective control in any of the observed tumor types in either sex of mice.

The mortality and body weight gain data indicate that the used high dose level might have reached the MTD for male mice and might have exceeded for female mice. For a final determination of the adequacy of the doses used, other clinical signs and histopathological toxic effects must be considered.

**Rat Study:** Two separate experiments were conducted, one in male and one in female rats. In each of these two experiments there were three treated groups and one vehicle control group. Two hundred and sixty Cr::CD®(SD)IGS BR rats of each sex were assigned randomly to the treated and control groups in equal size of 65 rats per group. The dose levels for treated groups were 25, 50 or 100 mg/kg/day. The rats in the control group received the vehicle (water for formulation at 5 mL/kg). The study was intended to be continued for 104 weeks. However, due to excessive mortality all remaining female rats were terminally sacrifices at Week 102 when there were 15 surviving animals in the low dose group. Dosing of the male rats continued up to Week 104.

During the administration period all rats were inspected visually at least twice daily for evidence of ill-health, mortality, or reaction to treatment. In addition, a more detailed weekly physical examination, which included palpation, was performed on each rat to monitor general health.

The bodyweight of each rat was recorded one week before commencement of treatment (Week -1), on the day that treatment commenced (Week 0), at weekly intervals for the first 16 weeks of treatment, thereafter once every four weeks up to Week 104 for males and up to Week 100 for females and before necropsy. Week 100 was the last scheduled recording for females as they were terminated in Week 102 due to strain-specific mortality.

The tests did not showed statistically significant dose response relationship in mortality across control and treated groups in either sex of rats. The pairwise comparisons also did not show statistically significant increased mortality in any of the treated groups in either sex of rats compared to their respective control. The tests did not showed statistically significant dose response relationship in any of the observed tumor types in either sex of rats. The pairwise comparison showed statistically significant increased incidence of thyroid glands C-Cell carcinoma in male rat low dose group compared to their control.

The mortality and body weight gain data indicate that the used high dose level might have exceeded the MTD in female rats. From the body weight gain data it can also be concluded that the used high dose level might have exceeded the MTD in male rats. However, the mortality data do not support it. For a final determination of the adequacy of the doses used, other clinical signs and histopathological toxic effects must be considered.

Mohammad Atiar Rahman, Ph.D.
Mathematical Statistician

Concur: Karl Lin, Ph.D.
Team Leader, Biometrics-6
cc: Archival NDA 207-145
Dr. McKinney
Ms. Metz

Dr. Tsong
Dr. Lin
Dr. Rahman
Ms. Patrician
### 6. Appendix

#### Table 1A: Intercurrent Mortality Rate
##### Male Mice

<table>
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<tr>
<th>Week Range</th>
<th>0 mg/kg/day</th>
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<td>53 - 78</td>
<td>14 / 35 00</td>
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<tr>
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<td>5 / 43 33</td>
<td>7 / 40 00</td>
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<td>7 / 51 67</td>
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Total: N=60

* Cum. %: Cumulative percentage except for Ter. Sac.

#### Table 1B: Intercurrent Mortality Rate
##### Female Mice

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<th>Week Range</th>
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</thead>
<tbody>
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<td>0 - 52</td>
<td>3 / 5 00</td>
<td>4 / 6 67</td>
<td>6 / 11 67</td>
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<tr>
<td>53 - 78</td>
<td>10 / 21 67</td>
<td>8 / 36 67</td>
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<td>79 - 91</td>
<td>9 / 36 67</td>
<td>10 / 53 33</td>
<td>11 / 60 00</td>
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<td>92 - 104</td>
<td>10 / 53 33</td>
<td>11 / 60 00</td>
<td>19 / 61 67</td>
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Total: N=60

* Cum. %: Cumulative percentage except for Ter. Sac.

#### Table 2A: Intercurrent Mortality Comparison
##### Male Mice

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<td>Homogeneity</td>
<td>Log-Rank</td>
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C vs. H

#### Table 2B: Intercurrent Mortality Comparison
##### Female Mice

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### Table 3A: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons
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<th>100 mg Med N=60</th>
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<th>P_Value Dos Resp</th>
<th>P_Value C vs. L</th>
<th>P_Value C vs. M</th>
<th>P_Value C vs. H</th>
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Table 3B: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons
Female Mice

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Table 4A: Intercurrent Mortality Rate in Male Rats

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Total N=65

Cum. %: Cumulative percentage except for Ter. Sac.

Table 4B: Intercurrent Mortality Rate Female Rats

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Total N=65

Cum. %: Cumulative percentage except for Ter. Sac.

Table 5A: Intercurrent Mortality Comparison Male Rats

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Table 5B: Intercurrent Mortality Comparison Female Rats

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Table 6B: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons
Female Rats

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<td>SCHWANNOMA</td>
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<td>50 mg</td>
<td>100 mg</td>
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<td>P_Value C vs. M</td>
<td>P_Value C vs. H</td>
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</table>

Reference ID: 3859195
Figure 1A: Kaplan-Meier Survival Functions for Male Mice

Tests for Dose-Response and Homogeneity
Intercurrent Mortality RateAll Dose Groups with Combined Control
Male Mice

Figure 1B: Kaplan-Meier Survival Functions for Female Mice

Tests for Dose-Response and Homogeneity
Intercurrent Mortality RateAll Dose Groups with Combined Control
Female Mice
Figure 2A: Kaplan-Meier Survival Functions for Male Rats

Figure 2B: Kaplan-Meier Survival Functions for Female Rats
7. References


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/s/

MOHAMMAD A RAHMAN
12/11/2015

KARL K LIN
12/12/2015
Concur with review
NDA Number: 207,145
Drug Name: Xadago (safinamide) Tablet 50 mg, 100 mg
Indication: Parkinson's Disease
Applicant: Newron Pharmaceuticals S.p.A.
Dates: Receipt Date: December 29, 2014
        PDUFA Goal Date: March 29, 2016
Review Priority: Standard
Biometrics Division: Division of Biometrics I
Statistical Reviewer: Xiangmin Zhang, Ph.D.
Concurring Reviewers: Kun Jin, Ph.D., Team Leader
                       Hsien Ming Hung, Ph.D., Director
Medical Division: Division of Neurology Products
Clinical Team: Leonard Kapcala, M.D., Clinical Reviewer
               Gerald Podskalny, D.O., Team Leader
               Eric Bastings, M.D., Deputy Director
               William Dunn, M.D., Director
Project Manager: Stacy Metz, Pharm.D.
Keywords: analysis of covariance, clinical studies, mixed models, NDA review
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1 EXECUTIVE SUMMARY

This review describes the efficacy findings of Xadago as an add-on therapy to patients with idiopathic Parkinson’s disease. The review confirms that Study 016 and Study 27919 in the 505(b)(1) new drug application provided sufficient efficacy evidences that Xadago is efficacious as an add-on therapy to a stable dose of levodopa in Parkinson’s disease patients with motor fluctuations: Xadago tablet (50 mg, 100 mg) is statistically significantly better than placebo in increasing total daily “on” time (“on” time without dyskinesia plus “on” time with non-troublesome dyskinesia) by week 24.

2 INTRODUCTION

2.1 Overview

Newron Pharmaceuticals S.p.A. (the sponsor) developed Xadago (safinamide) as an add-on therapy for the treatment of idiopathic Parkinson’s disease. The sponsor submitted the original 505(b)(1) new drug application (NDA) for Xadago on May 29, 2014. The original NDA submission was refused to file due to a lack of sufficient organization to permit timely, efficient, and complete review, as explained in the FDA letter sent to the sponsor on July 28, 2014. The sponsor re-submitted the NDA on December 26, 2014.

Figure 1. Safinamide clinical development program

The clinical development program for safinamide is summarized in Figure 1. In order to support the efficacy claims of safinamide, the sponsor included one Phase 2 study, four Phase 3 studies and three extension studies in the NDA re-submission. Among these studies, Study 27938, the
extension study to Study 27918, was terminated early due to transfer of sponsorship therefore did not provide any efficacy results. The studies in the NDA re-submission are for two sub-populations of Parkinson’s disease patients:

(1) Patients with early idiopathic Parkinson’s disease, who are receiving a stable dose of a single Dopamine agonist

(2) Patients with idiopathic Parkinson’s disease with motor fluctuations, who are receiving a stable dose of levodopa

Table 1. List of studies in this review

<table>
<thead>
<tr>
<th>Study Number</th>
<th>Phase and Design</th>
<th>Treatment Period (in week)</th>
<th>Study Arm (Number of randomized patients per arm)</th>
<th>Study Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>009</td>
<td>Phase 2, parallel-group, fixed dose</td>
<td>12</td>
<td>Placebo 0.5 mg/kg/day (57) 1.0 mg/kg/day (57)</td>
<td>Patients with early idiopathic Parkinson’s disease who are receiving a stable dose of a single Dopamine agonist&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>015</td>
<td>Phase 3, parallel-group, fixed dose</td>
<td>24</td>
<td>Placebo 100 mg/day (90) 200 mg/day (89)</td>
<td></td>
</tr>
<tr>
<td>27918 (MOTION)</td>
<td>Phase 3, parallel-group, fixed dose</td>
<td>24</td>
<td>Placebo 50 mg/day (225) 100 mg/day (227)</td>
<td></td>
</tr>
<tr>
<td>016</td>
<td>Phase 3, parallel-group, fixed dose</td>
<td>24</td>
<td>Placebo 50 mg/day (222) 100 mg/day (223)</td>
<td>Patients with idiopathic Parkinson’s disease with motor fluctuations, who are receiving a stable dose of levodopa</td>
</tr>
<tr>
<td>27919 (SETTLE)</td>
<td>Phase 3, parallel-group, flexible dose</td>
<td>24</td>
<td>Placebo 50-100 mg/day (275) (274)</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> Study 009 study population also included patients with early idiopathic Parkinson’s disease who are de novo (i.e. currently untreated).

Source: Reviewer’s summary

Study 016 and Study 27919 are reviewed in more details in this statistical review. Study 009, Study 015, and Study 27918 are summarized in the Appendix.

2.2 Data Sources

The electronic submission of this NDA is located at

\cdsesub\evsprod\NDA207145\n
The study reports are located at

\cdsesub\evsprod\NDA207145\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\early-pd-tx-da-agonist\5351-stud-rep-contr\
The datasets are located at

\cdsesub1\evsprod\NDA207145\0000\m5\datasets
\cdsesub1\evsprod\NDA207145\0016\m5\datasets

The SAS programs are located at

\cdsesub1\evsprod\NDA207145\0007\m5\datasets
\cdsesub1\evsprod\NDA207145\0016\m5\datasets
\cdsesub1\evsprod\NDA207145\0021\m5\datasets
\cdsesub1\evsprod\NDA207145\0035\m5\datasets

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The data quality is acceptable. The majority of the data comply with CDISC standards. Some datasets for Study 015, Study 016, and the extension study to Study 016 were also submitted in legacy data format, along with the responses to FDA’s information requests for additional analyses. The reviewer was able to perform independent review and confirm sponsors’ analysis results using the submitted datasets.

The reviewer had found multiple discrepancies between sponsor’s analysis results in the clinical study reports and the reviewer’s preliminary independent analysis results. It turned out that for some studies the sponsor did not follow the statistical methods pre-specified in the protocols/Statistical Analysis Plans (SAPs). Several information requests were sent asking the sponsor to apply the correct analytical methods and to produce appropriate results. The sponsor complied with FDA’s requests for additional analyses and submitted corrected results.

3.2 Evaluation of Efficacy

3.2.1 Study 016

3.2.1.1 Design and Endpoints

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 safinamide 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, safinamide 50 mg/day, and safinamide 100 mg/day. Patients were screened in 52 study centers in India, Italy, and Romania.

The primary endpoint was the change from Baseline to Week 24 in total daily “on” time during 18-hour diary recording period. The “on” time here and for the rest of this statistical review refers to “on” time without dyskinesia plus “on” time with non-troublesome dyskinesia.
The secondary efficacy endpoints included:
- Change from Baseline to Week 24 in total daily “off” time, as measured by diary cards
- Change from Baseline to Week 24 in Unified Parkinson's Disease Rating Scale (UPDRS) Section III score during “on” phase
- Change from Baseline to Week 24 in UPDRS Section II score during “on” phase

3.2.1.2 Statistical Methodologies

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 was 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.

The 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.

3.2.1.3 Patient Disposition, Demographic and Baseline Characteristics

A total of 900 patients were screened, of which 669 (74.3%) randomized. Among the 669 randomized patients, 222 (33.2%) were randomized to the placebo group, 223 (33.3%) to the safinamide 50 mg/day group, and 224 (33.5%) to the safinamide 100 mg/day group. 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 patient disposition is presented in Figure 2. The safinamide 100 mg/day group had more withdrawals, compared to the safinamide 50 mg/day group and placebo group. Adverse event
was the main reason for patient withdrawal, followed by withdrawal of consent and lost to follow up.

Table 2. Study 016 patient demographic characteristics, ITT population

<table>
<thead>
<tr>
<th>Statistics</th>
<th>Placebo N = 222</th>
<th>Safinamide 50 mg/day N = 223</th>
<th>Safinamide 100 mg/day N = 224</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>59.4 (9.41)</td>
<td>60.1 (9.65)</td>
<td>60.1 (9.19)</td>
</tr>
<tr>
<td>Median</td>
<td>60.0</td>
<td>61.0</td>
<td>60.0</td>
</tr>
<tr>
<td>Min, Max</td>
<td>34, 77</td>
<td>35, 78</td>
<td>35, 80</td>
</tr>
<tr>
<td>Gender [N (%)]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>160 (72.1)</td>
<td>157 (70.4)</td>
<td>163 (72.8)</td>
</tr>
<tr>
<td>Female</td>
<td>62 (27.9)</td>
<td>66 (29.6)</td>
<td>61 (27.2)</td>
</tr>
<tr>
<td>Race [N (%)]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>180 (81.8)</td>
<td>180 (80.7)</td>
<td>179 (79.9)</td>
</tr>
<tr>
<td>White</td>
<td>42 (18.9)</td>
<td>43 (19.3)</td>
<td>45 (20.1)</td>
</tr>
</tbody>
</table>

%: percentage based on the number of patients in each treatment group ITT population; ITT: intent-to-treat; N: number of patients; SD: standard deviation.

Source: Selected from Tables 5.1 and 5.2 on pages 230-231 of sponsor’s clinical study report

The patient demographic characteristics of the intent-to-treat (ITT) population, defined as all patients randomized, are summarized in Table 2. The treatment groups appeared similar in terms of age, gender and race. The ITT population was mainly Asian patients and had an average age of approximately 60 years. More than 70% of the ITT population were males.
Table 3. Study 016 patient baseline characteristics, ITT population

<table>
<thead>
<tr>
<th>Statistics</th>
<th>Placebo N = 222</th>
<th>Safinamide 50 mg/day N = 223</th>
<th>Safinamide 100 mg/day N = 224</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hoehn and Yahr Stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage 1 [N (%)]</td>
<td>3 (1.4)</td>
<td>3 (1.3)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Stage 1.5 [N (%)]</td>
<td>4 (1.8)</td>
<td>2 (0.9)</td>
<td>6 (2.7)</td>
</tr>
<tr>
<td>Stage 2 [N (%)]</td>
<td>38 (17.1)</td>
<td>35 (15.7)</td>
<td>43 (19.2)</td>
</tr>
<tr>
<td>Stage 2.5 [N (%)]</td>
<td>63 (28.4)</td>
<td>67 (30.0)</td>
<td>57 (25.4)</td>
</tr>
<tr>
<td>Stage 3 [N (%)]</td>
<td>80 (36.0)</td>
<td>88 (39.5)</td>
<td>87 (38.8)</td>
</tr>
<tr>
<td>Stage 4 [N (%)]</td>
<td>34 (15.3)</td>
<td>28 (12.6)</td>
<td>31 (13.8)</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>2.8 (0.67)</td>
<td>2.8 (0.62)</td>
<td>2.8 (0.64)</td>
</tr>
<tr>
<td>Median</td>
<td>3.0</td>
<td>3.0</td>
<td>3.0</td>
</tr>
<tr>
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<td>1.0, 4.0</td>
<td>1.0, 4.0</td>
<td>1.5, 4.0</td>
</tr>
</tbody>
</table>

MMSE

| Mean (SD)                   | 27.9 (2.10)     | 28.1 (1.95)                 | 27.9 (2.18)                 |
| Median                      | 28.0            | 29.0                        | 28.5                        |
| Min, Max                    | 19, 30          | 22, 30                      | 21, 30                      |

GRID-HAMD-17

| Mean (SD)                   | 5.9 (3.70)      | 6.0 (3.70)                  | 6.0 (3.54)                  |
| Median                      | 5.0             | 6.0                         | 5.5                         |
| Min, Max                    | 0, 17           | 0, 16                       | 0, 17                       |

%: percentage based on the number of patients in each treatment group ITT population; GRID-HAMD-17: grid version of Hamilton rating scale for depression (17-item scale); ITT: intent-to-treat; MMSE: Mini-Mental State Examination; N: number of patients; SD: standard deviation.

Source: Selected from Tables 7, 8, and 9 on pages 235-240 of sponsor’s clinical study report

The patient baseline characteristics of the ITT population are summarized in Table 3. The three treatment groups appeared similar in terms of Hoehn and Yahr Stage, Mini-Mental State Examination, and grid version of Hamilton Rating Scale for Depression (17-item scale).
3.2.1.4 Results and Conclusions

Figure 3. Study 016 mean (± standard error) of change from Baseline in total daily "on" time by week and treatment

Source: Reviewer

Figure 3 illustrates the mean of change from Baseline in total daily “on” time by week and treatment for Study 016 mITT population. It shows that the safinamide 50 mg/day group and safinamide 100 mg/day group had consistent average improvements of total daily “on” time over the 24-week treatment duration and such improvements were on average greater than those from the placebo group. However, according to Figure 3, the safinamide 50 mg/day group and safinamide 100 mg/day group did not appear to differ significantly. The numbers of observations in each treatment group at each visit are also presented in Figure 3. The mITT population sizes were 212, 216, and 217 for the placebo group, safinamide 50 mg/day group, and safinamide 100 mg/day group, respectively. The rates of missing observations at Week 24 were 18.4%, 16.6%, and 15.7% for the placebo group, safinamide 50 mg/day group, and safinamide 100 mg/day group, respectively. Compared to the other two treatment groups, the placebo group missed more observations at Week 24.
Figure 4 illustrates the empirical cumulative distribution function (CDF) curves for the endpoint of change from Baseline to Week 24 in total daily “on” time under the three treatment groups. In Figure 4, patients that dropped out due to adverse event, lack of efficacy, non-compliance, or withdrawal of consent were treated as treatment failures. For those patients, their changes from Baseline to Week 24 in total daily “on” time were assigned a change from Baseline value of -7.0 hours (the minimum of the change from Baseline before this imputation was -6.0 hours). The assigned value of -7.0 hours was simply used to demonstrate the effect of treating certain dropped-out patients as treatment failures on the shapes of the CDF curves and on graphical assessment of treatment effects. For patients that dropped out due to other reasons, their last available values were used. The CDF curves in the figure illustrate the cumulative percentages of patients who achieved the levels of change from Baseline to Week 24 in total daily “on” time shown on the horizontal axis. For example, the horizontal solid line in the figure shows that approximately 40%-45% of the patients in the placebo group had zero or negative changes from Baseline to Week 24 in total daily “on” time, compared to approximately 30%-35% of safinamide-treated patients. The overall leftward shifts of the safinamide 50 mg/day and safinamide 100 mg/day CDF curves, compared to the placebo CDF curve, indicate that safinamide-treated patients had more improvements in total daily “on” time. Statistical analyses of more rigor are presented next.

Source: Reviewer
Table 4. Study 016 analyses of the primary and secondary endpoints, mITT population

<table>
<thead>
<tr>
<th>Efficacy Parameter</th>
<th>Statistic (a)</th>
<th>MMRM Analysis (b)</th>
<th>ANCOVA (LOCF) Analysis (c)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>50 mg/day (n=217)</td>
<td>100 mg/day (n=216)</td>
<td>50 mg/day (n=217)</td>
</tr>
<tr>
<td>ON without T Dysk (h)</td>
<td>LS Diff vs Pbo</td>
<td>p-value</td>
<td>LS Diff vs Pbo</td>
</tr>
<tr>
<td></td>
<td>0.50</td>
<td>0.53</td>
<td>0.46</td>
</tr>
<tr>
<td>ON without Dysk (h)</td>
<td>LS Diff vs Pbo</td>
<td>p-value</td>
<td>LS Diff vs Pbo</td>
</tr>
<tr>
<td></td>
<td>0.41</td>
<td>0.56</td>
<td>0.46</td>
</tr>
<tr>
<td>ON with NT Dysk (h)</td>
<td>LS Diff vs Pbo</td>
<td>p-value</td>
<td>LS Diff vs Pbo</td>
</tr>
<tr>
<td></td>
<td>0.08</td>
<td>-0.04</td>
<td>-0.03</td>
</tr>
<tr>
<td>ON with T Dysk (h)</td>
<td>LS Diff vs Pbo</td>
<td>p-value</td>
<td>LS Diff vs Pbo</td>
</tr>
<tr>
<td></td>
<td>0.11</td>
<td>0.06</td>
<td>0.11</td>
</tr>
<tr>
<td>OFF Time (h)</td>
<td>LS Diff vs Pbo</td>
<td>p-value</td>
<td>LS Diff vs Pbo</td>
</tr>
<tr>
<td></td>
<td>-0.54</td>
<td>-0.53</td>
<td>-0.55</td>
</tr>
<tr>
<td>Asleep Time (h)</td>
<td>LS Diff vs Pbo</td>
<td>p-value</td>
<td>LS Diff vs Pbo</td>
</tr>
<tr>
<td></td>
<td>-0.07</td>
<td>-0.05</td>
<td>-0.03</td>
</tr>
<tr>
<td>UPDRS I</td>
<td>LS Diff vs Pbo</td>
<td>p-value</td>
<td>LS Diff vs Pbo</td>
</tr>
<tr>
<td></td>
<td>0.02</td>
<td>-0.02</td>
<td>0.02</td>
</tr>
<tr>
<td>UPDRS II</td>
<td>LS Diff vs Pbo</td>
<td>p-value</td>
<td>LS Diff vs Pbo</td>
</tr>
<tr>
<td></td>
<td>-0.38</td>
<td>-0.75</td>
<td>-0.49</td>
</tr>
<tr>
<td>UPDRS III</td>
<td>LS Diff vs Pbo</td>
<td>p-value</td>
<td>LS Diff vs Pbo</td>
</tr>
<tr>
<td></td>
<td>-1.71</td>
<td>-2.24</td>
<td>-1.75</td>
</tr>
<tr>
<td>UPDRS II + III</td>
<td>LS Diff vs Pbo</td>
<td>p-value</td>
<td>LS Diff vs Pbo</td>
</tr>
<tr>
<td></td>
<td>-2.06</td>
<td>-3.00</td>
<td>-2.19</td>
</tr>
<tr>
<td>UPDRS I +II +III</td>
<td>LS Diff vs Pbo</td>
<td>p-value</td>
<td>LS Diff vs Pbo</td>
</tr>
<tr>
<td></td>
<td>-2.47</td>
<td>-3.23</td>
<td>-2.57</td>
</tr>
</tbody>
</table>

ANCOVA = Analysis of Covariance; Dysk = Dyskinesia; h = hours; LOCF = Last Observation Carried Forward; LS Diff vs Pbo = Last 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: Table 1 on page 4 of sponsor’s information amendment submitted on July 24, 2015
Table 4 includes the primary and secondary analysis results as well as analysis results on endpoints that were not pre-specified in the study protocol/SAP. Table 4 was submitted to FDA in the responses to FDA’s information requests for additional analyses. It provided correct primary and secondary analysis results, as opposed to the incorrect results in the clinical study report that relied on deviations from pre-specified statistical methods.

In terms of the primary endpoint of the change from Baseline to Week 24 in total daily “on” time, safinamide 50 mg/day and safinamide 100 mg/day were statistically significantly better than placebo (p-values under MMRM = 0.0356 and 0.0238, respectively), with least square safinamide-placebo differences of 0.50 hour (95% CI = (0.03, 0.96)) and 0.53 hour (95% CI = (0.07, 1.00)), respectively. The rates of missing observations at Week 24 (15%-20% each treatment group) were not alarmingly unusual in clinical trials in neurology. Sensitivity analyses using ANCOVA models with LOCF (Table 4) or without LOCF (not shown) confirmed that safinamide 50 mg/day and 100 mg/day were statistically significantly better than placebo. Therefore, the primary analysis results are reasonably robust in spite of missing data.

In terms of the change from Baseline to Week 24 in total daily “off” time, safinamide 50 mg/day and safinamide 100 mg/day appeared statistically significantly better than placebo (nominal p-values under ANCOVA-LOCF = 0.0049 and 0.0037, respectively), with least square safinamide-placebo differences of -0.55 hour (95% CI = (-0.93, -0.17)) and -0.57 hour (95% CI = (-0.95, -0.19)), respectively. Safinamide 50 mg/day and safinamide 100 mg/day also appeared statistically significantly better than placebo (nominal p-values under ANCOVA-LOCF = 0.0212 and 0.0011, respectively), in terms of the change from Baseline to Week 24 in UPDRS Section III score, with least square safinamide-placebo differences of -1.75 points (95% CI = (-3.24, -0.36)) and -2.48 points (95% CI = (-3.97, -1.00)), respectively. Only safinamide 100 mg/day was statistically significantly better than placebo (nominal p-value under ANCOVA-LOCF = 0.0121), in terms of the change from Baseline to Week 24 in UPDRS Section II score, with a least square safinamide-placebo difference of -0.91 point (95% CI = (-1.61, -0.20)).

3.2.2 Study 27919

3.2.2.1 Study Design and Endpoints

Study 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 a dose range (50-100 mg/day) of safinamide 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 safinamide 50-100 mg/day. Patients were screened in 126 study centers in Asia, Eastern Europe, Latin America, North America, and Western Europe and enrolled in 119 study centers.
The design of Study 27919 is presented in Figure 5.

The primary endpoint was the change from Baseline to Week 24 in total daily “on” time, as measured by diary cards.

The secondary endpoints were:
- Change from Baseline to Week 24 in total daily “off” time as measured by diary cards
- Change from Baseline to Week 24 in UPDRS Section III score during “on” phase
- Change from Baseline to Week 24 in UPDRS Section II score during “on” phase
- 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

### 3.2.2.2 Statistical Methodologies

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 the LOCF method were used for the analysis.

The secondary efficacy analyses for the endpoints of total daily “off” time, UPDRS Section III score, UPDRS Section II 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 secondary efficacy analysis for the proportion of improvement in CGI change was performed using a logistic regression with treatment and region effects. The “on treatment” approach and the LOCF method were used for the secondary analyses.

The multiple testing of the secondary efficacy endpoints was handled in a pre-specified hierarchical fashion to control the family-wise type I error at the two-sided significance level $\alpha = 0.05$. The secondary endpoints were tested in the order as presented in Section 3.2.2.1.
### 3.2.2.3 Patient Disposition, Demographic and Baseline Characteristics

A total of 851 patients were screened, of which 549 (64.5%) randomized. Among the 549 randomized patients, 275 (50.1%) were randomized to the placebo group and 274 (49.9%) to the safinamide 50-100 mg/day group. A total of 478 patients completed the study: 237 in the placebo group and 241 in the safinamide 50-100 mg/day group.

**Figure 6. Study 27919 patient disposition**

<table>
<thead>
<tr>
<th></th>
<th>Placebo 275 Randomized</th>
<th>Placebo 275 Treated</th>
</tr>
</thead>
<tbody>
<tr>
<td>241 Completed</td>
<td></td>
<td>33 Discontinued</td>
</tr>
<tr>
<td>34 Discontinued</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20 Other Reasons</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 Death</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 LTFU</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 AE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 AE</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>safinamide 274 Randomized</th>
<th>safinamide 274 Treated</th>
</tr>
</thead>
<tbody>
<tr>
<td>245 Completed</td>
<td></td>
<td>30 Discontinued</td>
</tr>
<tr>
<td>29 Discontinued</td>
<td></td>
<td>30 Discontinued</td>
</tr>
<tr>
<td>Reasons for Discontinuation from Study</td>
<td>Reasons for Discontinuation of Treatment</td>
<td></td>
</tr>
<tr>
<td>12 AE</td>
<td>14 AE</td>
<td></td>
</tr>
<tr>
<td>3 LTFU</td>
<td>3 LTFU</td>
<td></td>
</tr>
<tr>
<td>1 Death</td>
<td>1 Death</td>
<td></td>
</tr>
<tr>
<td>13 Other</td>
<td>11 Other</td>
<td></td>
</tr>
<tr>
<td>2 Death</td>
<td>2 Death</td>
<td></td>
</tr>
<tr>
<td>20 Other</td>
<td>17 Other</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: AE, adverse event; LTFU, lost to follow-up; LoE, lack of efficacy

Source: EOT Tables 15.1.2 and 15.1.3

Source: Figure 1 on page 92 of sponsor’s clinical study report

The patient disposition is presented in **Figure 6**. There were 63 discontinuations from study: 22 (34.9%) patients discontinued due to adverse event, 5 (7.9%) patients were lost to follow up, 3 (4.8%) patients died before completing the study, and 33 (52.4%) patients discontinued for other reasons.
Table 5. Study 27919 patient demographic characteristics, ITT population

<table>
<thead>
<tr>
<th>Demographic Characteristic</th>
<th>Statistics</th>
<th>Safinamide (n=274)</th>
<th>Placebo (n=275)</th>
<th>Total (n=549)</th>
<th>p-value(a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>n (missing)</td>
<td>274 (0)</td>
<td>275 (0)</td>
<td>549 (0)</td>
<td>0.554</td>
</tr>
<tr>
<td>Mean ±SD</td>
<td>61.7 ±0.0</td>
<td>62.1 ±8.9</td>
<td>61.9 ±6.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>62.5</td>
<td>62.0</td>
<td>62.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Min; Max</td>
<td>40; 80</td>
<td>30; 79</td>
<td>30; 80</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td>n (missing)</td>
<td>274 (0)</td>
<td>275 (0)</td>
<td>549 (0)</td>
<td>0.452</td>
</tr>
<tr>
<td>Male</td>
<td>n (%)</td>
<td>171 (62.4)</td>
<td>163 (59.3)</td>
<td>334 (60.8)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>n (%)</td>
<td>103 (37.6)</td>
<td>112 (40.7)</td>
<td>215 (39.2)</td>
<td></td>
</tr>
<tr>
<td>Ethnicity</td>
<td>n (missing)</td>
<td>274 (0)</td>
<td>275 (0)</td>
<td>549 (0)</td>
<td>0.993</td>
</tr>
<tr>
<td>Hispanic/Latin American</td>
<td>n (%)</td>
<td>8 (2.9)</td>
<td>8 (2.9)</td>
<td>16 (2.9)</td>
<td></td>
</tr>
<tr>
<td>Not Hispanic/Latin American</td>
<td>n (%)</td>
<td>266 (97.1)</td>
<td>267 (97.1)</td>
<td>533 (97.1)</td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td>n (missing)</td>
<td>274 (0)</td>
<td>275 (0)</td>
<td>549 (0)</td>
<td>0.353</td>
</tr>
<tr>
<td>American Indian or Alaskan Native</td>
<td>n (%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Black or African American</td>
<td>3 (1.1)</td>
<td>2 (0.7)</td>
<td>5 (0.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>183 (66.8)</td>
<td>186 (66.4)</td>
<td>371 (67.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>88 (32.1)</td>
<td>85 (30.6)</td>
<td>173 (31.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Native Hawaiian or Other Pacific Islander</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Source: Table 15.1.5 on pages 216-220 of sponsor’s clinical study report

The patient demographic characteristics of the ITT population are summarized in Table 5. The treatment groups appeared similar in terms of age, gender and race. The ITT population was mainly White patients and had an average age of approximately 62 years. The ITT population had more males than females.
Table 6. Study 27919 patient baseline characteristics, ITT population

<table>
<thead>
<tr>
<th>Demographic Characteristic</th>
<th>Statistics</th>
<th>Safinamide (n=274)</th>
<th>Placebo (n=275)</th>
<th>Total (n=549)</th>
<th>p-value(a)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>UPDRS Section I</strong></td>
<td>n (missing)</td>
<td>274 (0)</td>
<td>275 (0)</td>
<td>549 (0)</td>
<td>0.880</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>1.26 ±1.34</td>
<td>1.28 ±1.49</td>
<td>1.27 ±1.42</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Min, Max</td>
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<td>0.0, 7.0</td>
<td>0.0, 7.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>UPDRS Section II</strong></td>
<td>n (missing)</td>
<td>271 (3)</td>
<td>272 (3)</td>
<td>543 (6)</td>
<td>0.355</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>9.97 ±5.67</td>
<td>10.43 ±6.32</td>
<td>10.20 ±5.96</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>10.00</td>
<td>10.00</td>
<td>10.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Min, Max</td>
<td>0.0, 28.0</td>
<td>0.0, 35.0</td>
<td>0.0, 35.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>UPDRS Section III</strong></td>
<td>n (missing)</td>
<td>274 (0)</td>
<td>275 (0)</td>
<td>549 (0)</td>
<td>0.378</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>22.35 ±11.75</td>
<td>23.25 ±12.87</td>
<td>22.80 ±12.32</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>22.00</td>
<td>23.00</td>
<td>22.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Min, Max</td>
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<td>0.0, 74.0</td>
<td>0.0, 74.0</td>
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<td></td>
</tr>
<tr>
<td><strong>UPDRS Section IV</strong></td>
<td>n (missing)</td>
<td>272 (2)</td>
<td>275 (0)</td>
<td>547 (2)</td>
<td>0.964</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>5.94 ±2.04</td>
<td>5.96 ±2.88</td>
<td>5.95 ±2.90</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
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<td>6.00</td>
<td>6.00</td>
<td></td>
<td></td>
</tr>
<tr>
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<td>0.0, 18.0</td>
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<td></td>
</tr>
<tr>
<td>Hoehn and Yahr Staging</td>
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<td>274 (1)</td>
<td>548 (1)</td>
<td>0.301</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>2.48 ±0.59</td>
<td>2.49 ±0.61</td>
<td>2.49 ±0.60</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>2.50</td>
<td>2.50</td>
<td>2.50</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Min, Max</td>
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<td>1.5, 4.0</td>
<td>1.0, 4.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>MMSE</strong></td>
<td>n (missing)</td>
<td>274 (0)</td>
<td>275 (0)</td>
<td>549 (0)</td>
<td>0.910</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>28.65 ±1.48</td>
<td>28.64 ±1.58</td>
<td>28.65 ±1.52</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>28.00</td>
<td>28.00</td>
<td>28.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Min, Max</td>
<td>23.0, 30.0</td>
<td>23.0, 30.0</td>
<td>23.0, 30.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>GRID-HAMD-17</strong></td>
<td>n (missing)</td>
<td>274 (0)</td>
<td>275 (0)</td>
<td>549 (0)</td>
<td>0.477</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>4.74 ±4.04</td>
<td>4.96 ±4.13</td>
<td>4.87 ±4.09</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>4.00</td>
<td>4.00</td>
<td>4.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Min, Max</td>
<td>0.0, 17.0</td>
<td>0.0, 17.0</td>
<td>0.0, 17.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>CGI-S</strong></td>
<td>n (missing)</td>
<td>274 (0)</td>
<td>272 (3)</td>
<td>546 (3)</td>
<td>0.095</td>
</tr>
<tr>
<td>Normal/not at all ill</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Borderline ill</td>
<td>7 (2.6)</td>
<td>7 (2.6)</td>
<td>7 (2.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mildly ill</td>
<td>54 (19.7)</td>
<td>45 (16.5)</td>
<td>59 (18.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderately ill</td>
<td>162 (59.1)</td>
<td>180 (69.8)</td>
<td>192 (58.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Markedly ill</td>
<td>48 (17.5)</td>
<td>60 (22.1)</td>
<td>108 (19.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severely ill</td>
<td>-3 (1.1)</td>
<td>3 (1.1)</td>
<td>6 (1.1)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(a) For continuous variables, p-value is calculated using a two-way ANOVA with treatment and region as fixed effects. For categorical variables, p-value is calculated using a CMH test stratified by region.

Source: Table 15.1.5 on pages 216-220 of sponsor’s clinical study report

The patient baseline characteristics of the ITT population are summarized in Table 6. The treatment groups appeared similar in terms of UPDRS section specific scores, Hoehn and Yahr Stage, Mini-Mental State Examination, grid version of Hamilton Rating Scale for Depression (17-item scale), and Clinical Global Impression-Severity scores.
3.2.2.4 Results and Conclusions

Figure 7. Study 27919 mean (± standard error) of change from Baseline in total daily "on" time by week and treatment

Source: Reviewer

Figure 7 illustrates the mean of change from Baseline in total daily “on” time by week and treatment for Study 27919 mITT population. Similar to Figure 3, it shows that the safinamide treatment group had consistent average improvements of total daily “on” time over the 24-week treatment duration and such improvements were on average greater than those from the placebo group. The numbers of observations in each treatment group at each visit are also presented in Figure 7. The mITT population sizes were 268 and 273 for the placebo group and safinamide 50-100 mg/day group, respectively. The rates of missing observations at Week 24 were 19.8% and 14.4% for the placebo group and safinamide 50-100 mg/day group, respectively. The placebo group missed more observations at Week 24 than the safinamide 50-100 mg/day group.
Figure 8. Study 27919 empirical cumulative distribution functions for the change from Baseline to Week 24 in total daily "on" time

![Graph showing cumulative distribution functions for change from Baseline to Week 24 in total daily "on" time under two treatment groups: Placebo and Safinamide 50-100 mg/day.]

Source: Reviewer

Figure 8 illustrates the empirical cumulative distribution function (CDF) curves for the endpoint of change from Baseline to Week 24 in total daily “on” time under the two treatment groups. In Figure 8, the dropped-out patients were treated similarly as were treated in Figure 4: patients that dropped out due to adverse event, lack of efficacy, non-compliance, or withdrawal of consent were treated as treatment failures and assigned a change from Baseline value of -8.0 hours (the minimum of the change from Baseline before this imputation was -7.0 hours); for patients that dropped out due to other reasons, their last available values were used. The overall leftward shift of the safinamide 50-100 mg/day CDF curve, compared to the placebo CDF curve, indicates that safinamide-treated patients had more improvements in total daily “on” time. The leftward shift of the safinamide 50-100 mg/day CDF curve on the left end, compared to the placebo CDF curve on the left end, demonstrates how a lower percentage of treatment failures in the safinamide 50-100 mg/day group would favor the assessment of the treatment effect of safinamide. Statistical analyses of more rigor are presented next.
Table 7. Study 27919 analysis of the primary endpoint, ANCOVA, LOCF, mITT population

<table>
<thead>
<tr>
<th>Timepoint</th>
<th>Statistics</th>
<th>Safinamide (n=270)</th>
<th>Placebo (n=273)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Value</td>
<td>Change</td>
</tr>
<tr>
<td>Week 24</td>
<td>n (missing)</td>
<td>268 (2)</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Mean ±SD</td>
<td>10.72 ±2.77</td>
<td>1.44 ±2.81</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>10.75</td>
<td>1.25</td>
</tr>
<tr>
<td></td>
<td>Min, Max</td>
<td>1.3; 17.3</td>
<td>-7.0; 13.8</td>
</tr>
<tr>
<td></td>
<td>LS Mean (SE)</td>
<td>1.53 (0.16)</td>
<td>0.99 (0.21)</td>
</tr>
<tr>
<td></td>
<td>LS Diff vs Placebo</td>
<td>0.99 (0.21)</td>
<td>0.54 (0.16)</td>
</tr>
<tr>
<td></td>
<td>95% CI of LS Diff</td>
<td>(0.58, 1.39)</td>
<td>(0.58, 1.39)</td>
</tr>
<tr>
<td></td>
<td>p-value vs Placebo</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

| Table 15.2.2 on pages 316-317 of sponsor’s clinical study report |

The analysis results of the primary endpoint are presented in Table 7. Safinamide 50-100 mg/day was statistically significantly better than placebo (p-value < 0.001) in terms of change from Baseline to Week 24 in total daily “on” time, with a least square safinamide-placebo difference of 0.99 hour (95% CI = (0.58, 1.39)). Similar results were obtained using the observed case population or per protocol population. Other sensitivity analyses using MMRM models also confirmed the primary analysis results. Therefore, although there was an apparent difference of the numbers of missing observations at Week 24 between the placebo group and safinamide 50-100 mg/day group, the analyses results appeared not affected significantly.
Table 8. Study 27919 analyses of the secondary endpoints, ANCOVA, LOCF, mITT population

<table>
<thead>
<tr>
<th></th>
<th>Safinamide 50 -100 mg/day</th>
<th>Placebo</th>
<th>Change from Baseline</th>
<th>Change from Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Week 24</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Value</td>
<td>268 (2)</td>
<td>268 (2)</td>
<td>273 (0)</td>
<td>273 (0)</td>
</tr>
<tr>
<td>Change from Baseline</td>
<td>-1.58 ±2.94</td>
<td>-1.50</td>
<td>5.00</td>
<td>5.00</td>
</tr>
<tr>
<td>Total daily “off” time</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n (missing)</td>
<td>263 (7)</td>
<td>263 (7)</td>
<td>266 (7)</td>
<td>266 (7)</td>
</tr>
<tr>
<td>Mean ±SD</td>
<td>18.80 ±11.04</td>
<td>-3.50 ±7.72</td>
<td>21.08 ±11.80</td>
<td>-2.05 ±7.82</td>
</tr>
<tr>
<td>Median</td>
<td>17.00</td>
<td>-3.00</td>
<td>18.50</td>
<td>-1.00</td>
</tr>
<tr>
<td>Min; Max</td>
<td>1.0; 53.0</td>
<td>-43.0; 27.0</td>
<td>1.0; 64.0</td>
<td>-28.0; 35.0</td>
</tr>
<tr>
<td>LS Mean (SE)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LS Diff vs Placebo (SE)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>95% CI of LS Diff</td>
<td>(-1.67 (0.14)</td>
<td>-1.06 (0.19)</td>
<td>(-1.43, -0.69)</td>
<td>(-0.61 (0.14)</td>
</tr>
<tr>
<td>p-value vs Placebo</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UPDRS Section III total score</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n (missing)</td>
<td>264 (6)</td>
<td>264 (6)</td>
<td>266 (7)</td>
<td>266 (7)</td>
</tr>
<tr>
<td>Mean ±SD</td>
<td>8.94 ±5.49</td>
<td>-1.02 ±3.48</td>
<td>9.61 ±5.95</td>
<td>-0.74 ±3.74</td>
</tr>
<tr>
<td>Median</td>
<td>9.00</td>
<td>-1.00</td>
<td>9.00</td>
<td>0.00</td>
</tr>
<tr>
<td>Min; Max</td>
<td>0.0; 28.0</td>
<td>-11.0; 9.0</td>
<td>0.0; 28.0</td>
<td>-13.0; 13.0</td>
</tr>
<tr>
<td>LS Mean (SE)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LS Diff vs Placebo (SE)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>95% CI of LS Diff</td>
<td>(-0.37 (0.30)</td>
<td>-0.37 (0.30)</td>
<td>(-0.56, 0.21)</td>
<td>-0.79 (0.22)</td>
</tr>
<tr>
<td>p-value vs Placebo</td>
<td>0.214</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UPDRS Section II total score</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n (missing)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| ANCOVA: analysis of covariance; CI: confidence interval; LOCF: last observation carried forward; LS: least squares; mITT: modified intent-to-treat; UPDRS: Unified Parkinson's Disease Rating Scale.

Results were obtained from ANCOVA models with treatment and region effects and endpoint specific baseline as the covariate.

Source: Tables 15.2.9, 15.2.16, 15.2.23 on pages 330-331, 344-345, 358-359, respectively, of sponsor’s clinical study report

The analysis results of the secondary endpoints are summarized in Table 8. Safinamide 50-100 mg/day was statistically significantly better than placebo (p-value < 0.001) in terms of change from Baseline to Week 24 in total daily “off” time, with a least square safinamide-placebo difference of -1.06 hours (95% CI = (-1.43, -0.69)). Safinamide was also statistically significantly better than placebo (p-value = 0.005) in terms of change from Baseline to Week 24 in UPDRS Section III score, with a least square safinamide-placebo difference of -1.70 points (95% CI = (-2.89, -0.50)).

According the multiple testing procedure specified in the protocol and SAP, the testing should stop when safinamide was not statistically significantly better than placebo (p-value = 0.214) in terms of change from Baseline to Week 24 in UPDRS Section II score.
Sensitivity analyses on the secondary endpoints were performed using ANCOVA models with the LOCF method on different analysis populations and using MMRM on different analysis populations. The sensitivity analysis results were similar to the analysis results in Table 8.

3.3 Evaluation of Safety

Please refer to Dr. Kapcala’s clinical review for a detailed evaluation of safety.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

In this section, all model-based analyses on subgroups are post-hoc and for exploratory purpose. Some subgroups may not have large enough sample sizes to detect statistically significant differences between treatment groups. Overall, there is no compelling evidence from the subgroup analyses in Section 4.1 that a specific gender, race, age, or geographic region subgroup may benefit differently from the safinamide treatment.

4.1 Gender, Race, Age, and Geographic Region

4.1.1 Study 016

Table 9. Study 016 analysis of the primary endpoint by gender, MMRM, mITT population

<table>
<thead>
<tr>
<th>Gender</th>
<th>Change from Baseline to Week 24 in total daily “on” time</th>
<th>Placebo</th>
<th>Safinamide 50 mg/day</th>
<th>Safinamide 100 mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>60</td>
<td>65</td>
<td>59</td>
</tr>
<tr>
<td></td>
<td>Means (SD) a</td>
<td>1.16 (2.191)</td>
<td>1.15 (2.419)</td>
<td>1.35 (2.545)</td>
</tr>
<tr>
<td></td>
<td>LS mean b</td>
<td>0.68</td>
<td>1.00</td>
<td>1.13</td>
</tr>
<tr>
<td></td>
<td>LS diff. vs. placebo (SE) b</td>
<td>0.32 (0.455)</td>
<td>0.45 (0.459)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>p-value c</td>
<td>0.4863</td>
<td>0.3293</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>152</td>
<td>152</td>
<td>157</td>
</tr>
<tr>
<td></td>
<td>Means (SD) a</td>
<td>0.90 (2.455)</td>
<td>1.46 (2.876)</td>
<td>1.38 (2.669)</td>
</tr>
<tr>
<td></td>
<td>LS mean c</td>
<td>0.77</td>
<td>1.47</td>
<td>1.36</td>
</tr>
<tr>
<td></td>
<td>LS diff. vs. placebo (SE) c</td>
<td>0.70 (0.283)</td>
<td>0.59 (0.278)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>p-value c</td>
<td>0.0132</td>
<td>0.0399</td>
<td></td>
</tr>
</tbody>
</table>

LS: least squares; mITT: modified intent-to-treat; MMRM: mixed effect model repeated measures; N: number of patients in the mITT population; SD: standard deviation; SE: standard error.
a Obtained from all observations in the gender specific mITT population that were on treatment at Week 24, without imputation for missing data.
b Obtained from MMRM on all female patients in the mITT population, with treatment, center, visit, and treatment-by-center interaction as fixed effects and baseline value of the total daily “on” time as the covariate. The “on treatment” approach was used.
c Obtained from MMRM on all male patients in the mITT population, with treatment, center, visit, and treatment-by-center interaction as fixed effects and baseline value of the total daily “on” time as the covariate. The “on treatment” approach was used.

Source: Reviewer

Reference ID: 3837155
According to the results in Table 9, male patients appeared to have greater improvements in total daily “on” time under safinamide treatments than female patients. Safinamide 50 mg/day and safinamide 100 mg/day appeared statistically significantly better than placebo for male patients (nominal p-values = 0.0132 and 0.0339, respectively) but not for female patients. The sample sizes of the female patients may be too small to detect statistically significant differences between treatment groups.

Table 10. Study 016 analysis of the primary endpoint by race, MMRM, mITT population

<table>
<thead>
<tr>
<th>Race</th>
<th>Change from Baseline to Week 24 in total daily “on” time</th>
<th>Placebo</th>
<th>Safinamide 50 mg/day</th>
<th>Safinamide 100 mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asian</td>
<td>N 171</td>
<td>176</td>
<td>173</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Means (SD)(^a) 1.07 (2.371)</td>
<td>1.54 (2.702)</td>
<td>1.49 (2.606)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>LS mean(^b) 0.85</td>
<td>1.49</td>
<td>1.39</td>
<td></td>
</tr>
<tr>
<td></td>
<td>LS diff. vs. placebo (SE)(^b) 0.64 (0.252)</td>
<td>0.54 (0.250)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>p-value(^b) 0.0117</td>
<td>0.0326</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>N 41</td>
<td>41</td>
<td>43</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Means (SD)(^a) 0.61 (2.421)</td>
<td>0.71 (2.860)</td>
<td>0.90 (2.713)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>LS mean(^c) 0.41</td>
<td>0.56</td>
<td>0.93</td>
<td></td>
</tr>
<tr>
<td></td>
<td>LS diff. vs. placebo (SE)(^c) 0.15 (0.603)</td>
<td>0.53 (0.609)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>p-value(^c) 0.8015</td>
<td>0.3902</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

LS: least squares; mITT: modified intent-to-treat; MMRM: mixed effect model repeated measures; N: number of patients in the mITT population; SD: standard deviation; SE: standard error.

\(^a\) Obtained from all observations in the race specific mITT population that were on treatment at Week 24, without imputation for missing data.

\(^b\) Obtained from MMRM on all Asian patients in the mITT population, with treatment, center, visit, and treatment-by-center interaction as fixed effects and baseline value of the total daily “on” time as the covariate. The “on treatment” approach was used.

\(^c\) Obtained from MMRM on all White patients in the mITT population, with treatment, center, visit, and treatment-by-center interaction as fixed effects and baseline value of the total daily “on” time as the covariate. The “on treatment” approach was used.

Source: Reviewer

According to the results in Table 10, Asian patients appeared to have greater improvements in total daily “on” time under safinamide treatments than White patients. Safinamide 50 mg/day and safinamide 100 mg/day appeared statistically significantly better than placebo for Asian patients (nominal p-values = 0.0117 and 0.0326, respectively) but not for White patients. The sample sizes of White patients may be too small to detect statistically significant differences between treatment groups.
Table 11. Study 016 analysis of the primary endpoint by age, MMRM, mITT population

<table>
<thead>
<tr>
<th>Age</th>
<th>Change from Baseline to Week 24 in total daily “on” time</th>
<th>Placebo</th>
<th>Safinamide 50 mg/day</th>
<th>Safinamide 100 mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 65 years</td>
<td>N</td>
<td>143</td>
<td>142</td>
<td>144</td>
</tr>
<tr>
<td></td>
<td>Means (SD) (^a)</td>
<td>1.01 (2.488)</td>
<td>1.50 (2.799)</td>
<td>1.35 (2.538)</td>
</tr>
<tr>
<td></td>
<td>LS mean (^b)</td>
<td>0.77</td>
<td>1.38</td>
<td>1.31</td>
</tr>
<tr>
<td></td>
<td>LS diff. vs. placebo (SE) (^b)</td>
<td>0.60 (0.290)</td>
<td>0.53 (0.290)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>p-value (^b)</td>
<td>0.0376</td>
<td>0.0674</td>
<td></td>
</tr>
<tr>
<td>≥ 65 years</td>
<td>N</td>
<td>69</td>
<td>75</td>
<td>72</td>
</tr>
<tr>
<td></td>
<td>Means (SD) (^a)</td>
<td>0.90 (2.183)</td>
<td>1.09 (2.642)</td>
<td>1.42 (2.837)</td>
</tr>
<tr>
<td></td>
<td>LS mean (^c)</td>
<td>0.79</td>
<td>1.28</td>
<td>1.30</td>
</tr>
<tr>
<td></td>
<td>LS diff. vs. placebo (SE) (^c)</td>
<td>0.49 (0.438)</td>
<td>0.50 (0.440)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>p-value (^c)</td>
<td>0.2684</td>
<td>0.2535</td>
<td></td>
</tr>
</tbody>
</table>

LS: least squares; mITT: modified intent-to-treat; MMRM: mixed effect model repeated measures; N: number of patients in the mITT population; SD: standard deviation; SE: standard error.

\(^a\) Obtained from all observations in the age group specific mITT population that were on treatment at Week 24, without imputation for missing data.

\(^b\) Obtained from MMRM on all patients < 65 years in the mITT population, with treatment, center, visit and treatment-by-center interaction as fixed effects and baseline value of the total daily “on” time as the covariate. The “on treatment” approach was used.

\(^c\) Obtained from MMRM on all patients ≥ 65 years in the mITT population, with treatment, center, visit and treatment-by-center interaction as fixed effects and baseline value of the total daily “on” time as the covariate. The “on treatment” approach was used.

Source: Reviewer

According to the results in Table 11, patients < 65 years appeared to have greater improvements in total daily “on” time under safinamide treatments than patients ≥ 65. Only safinamide 50 mg/day appeared statistically significantly better than placebo for patients < 65 years (nominal p-value = 0.0376). The sample sizes of patients ≥ 65 years may be too small to detect statistically significant differences between treatment groups.

Study 016 was conducted outside the United States. Therefore, the reviewer did not perform any subgroup analysis by region.
### 4.1.2 Study 27919

Table 12. Study 27919 analysis of the primary endpoint by gender, ANCOVA, LOCF, mITT population

<table>
<thead>
<tr>
<th>Gender</th>
<th>Change from Baseline to Week 24 in total daily “on” time</th>
<th>Placebo</th>
<th>Safinamide 50-100 mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td></td>
<td>111</td>
<td>100</td>
</tr>
<tr>
<td>Means (SD)(^a)</td>
<td></td>
<td>0.59 (2.415)</td>
<td>1.71 (2.615)</td>
</tr>
<tr>
<td>LS mean(^b)</td>
<td></td>
<td>0.45</td>
<td>1.84</td>
</tr>
<tr>
<td>LS diff. vs. placebo (SE)(^b)</td>
<td></td>
<td>1.39 (0.330)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>p-value(^b)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td></td>
<td>162</td>
<td>168</td>
</tr>
<tr>
<td>Means (SD)(^a)</td>
<td></td>
<td>0.50 (2.457)</td>
<td>1.28 (2.915)</td>
</tr>
<tr>
<td>LS mean(^c)</td>
<td></td>
<td>0.64</td>
<td>1.35</td>
</tr>
<tr>
<td>LS diff. vs. placebo (SE)(^c)</td>
<td></td>
<td>0.71 (0.269)</td>
<td>0.0087</td>
</tr>
<tr>
<td>p-value(^c)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ANCOVA: analysis of covariance; LOCF: last observation carried forward; LS: least squares; mITT: modified intent-to-treat; N: number of patients in the mITT population; SD: standard deviation; SE: standard error.

\(^a\) Obtained from all observations in the gender specific mITT population that were on treatment at Week 24, with LOCF imputation for missing data.

\(^b\) Obtained from ANCOVA model on all female patients in the mITT population, with treatment and region effects and baseline value of the total daily “on” time as the covariate. The “on treatment” approach and the LOCF method were used.

\(^c\) Obtained from ANCOVA model on all male patients in the mITT population, with treatment and region effects and baseline value of the total daily “on” time as the covariate. The “on treatment” approach and the LOCF method were used.

Source: Reviewer

According to the results in Table 12, female patients appeared to have greater improvement in total daily “on” time under safinamide 50-100 mg/day than male patients. Safinamide 50-100 mg/day appeared statistically significantly better than placebo for female patients (nominal p-value < 0.0001) and male patients (nominal p-value = 0.0087).
Table 13. Study 27919 analysis of the primary endpoint by race, ANCOVA, LOCF, mITT population

<table>
<thead>
<tr>
<th>Race</th>
<th>Change from Baseline to Week 24 in total daily “on” time</th>
<th>Placebo</th>
<th>Safinamide 50-100 mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Means (SD) (^a)</td>
<td>0.71 (2.267)</td>
<td>1.20 (2.749)</td>
</tr>
<tr>
<td></td>
<td>LS mean (^b)</td>
<td>1.20</td>
<td>2.03</td>
</tr>
<tr>
<td></td>
<td>LS diff. vs. placebo (SE) (^b)</td>
<td>0.83 (0.323)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>p-value (^b)</td>
<td>0.0112</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>N</td>
<td>85</td>
<td>87</td>
</tr>
<tr>
<td>White</td>
<td>N</td>
<td>186</td>
<td>178</td>
</tr>
<tr>
<td></td>
<td>Means (SD) (^a)</td>
<td>0.45 (2.523)</td>
<td>1.55 (2.862)</td>
</tr>
<tr>
<td></td>
<td>LS mean (^c)</td>
<td>0.50</td>
<td>1.60</td>
</tr>
<tr>
<td></td>
<td>LS diff. vs. placebo (SE) (^c)</td>
<td>1.10 (0.266)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td></td>
<td>p-value (^c)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ANCOVA: analysis of covariance; LOCF: last observation carried forward; LS: least squares; mITT: modified intent-to-treat; N: number of patients in the mITT population; SD: standard deviation; SE: standard error.

\(^a\) Obtained from all observations in the race specific mITT population that were on treatment at Week 24, with LOCF imputation for missing data.

\(^b\) Obtained from ANCOVA model on all Asian patients in the mITT population, with treatment and region effects and baseline value of the total daily “on” time as the covariate. The “on treatment” approach and the LOCF method were used.

\(^c\) Obtained from ANCOVA model on all White patients in the mITT population, with treatment and region effects and baseline value of the total daily “on” time as the covariate. The “on treatment” approach and the LOCF method were used.

Source: Reviewer

According to the results in Table 13, safinamide 50-100 mg/day appeared statistically significantly better than placebo for Asian patients (nominal p-value = 0.0112) and White patients (nominal p-value < 0.0001). As summarized in Table 5, the numbers of Black patients were 2 and 3 for the placebo group and safinamide 50-100 mg/day group, respectively. The numbers are so small that analysis of Black patients will not provide conclusive results on the Black population. Therefore, the reviewer did not perform any subgroup analysis on the Black population.
<table>
<thead>
<tr>
<th>Age</th>
<th>Change from Baseline to Week 24 in total daily “on” time</th>
<th>Placebo</th>
<th>Safinamide 50-100 mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 65 years</td>
<td>N</td>
<td>156</td>
<td>157</td>
</tr>
<tr>
<td></td>
<td>Means (SD)</td>
<td>0.60 (2.461)</td>
<td>1.41 (2.883)</td>
</tr>
<tr>
<td></td>
<td>LS mean</td>
<td>0.50</td>
<td>1.45</td>
</tr>
<tr>
<td></td>
<td>LS diff. vs. placebo (SE)</td>
<td></td>
<td>0.96 (0.271)</td>
</tr>
<tr>
<td></td>
<td>p-value</td>
<td></td>
<td>0.0005</td>
</tr>
<tr>
<td>≥ 65 years</td>
<td>N</td>
<td>117</td>
<td>111</td>
</tr>
<tr>
<td></td>
<td>Means (SD)</td>
<td>0.44 (2.409)</td>
<td>1.48 (2.714)</td>
</tr>
<tr>
<td></td>
<td>LS mean</td>
<td>0.50</td>
<td>1.57</td>
</tr>
<tr>
<td></td>
<td>LS diff. vs. placebo (SE)</td>
<td></td>
<td>1.08 (0.323)</td>
</tr>
<tr>
<td></td>
<td>p-value</td>
<td></td>
<td>0.0010</td>
</tr>
</tbody>
</table>

ANCOVA: analysis of covariance; LOCF: last observation carried forward; LS: least squares; mITT: modified intent-to-treat; N: number of patients in the mITT population; SD: standard deviation; SE: standard error.

a Obtained from all observations in the age group specific mITT population that were on treatment at Week 24, with LOCF imputation for missing data.

b Obtained from ANCOVA model on all patients < 65 years in the mITT population, with treatment and region effects and baseline value of the total daily “on” time as the covariate. The “on treatment” approach and the LOCF method were used.

c Obtained from ANCOVA model on all patients ≥ 65 years in the mITT population, with treatment and region effects and baseline value of the total daily “on” time as the covariate. The “on treatment” approach and the LOCF method were used.

Source: Reviewer

According to the results in Table 14, safinamide 50-100 mg/day appeared statistically significantly better than placebo for patients < 65 years (nominal p-value = 0.0005) and patients ≥ 65 years (nominal p-value = 0.0010).
Table 15. Study 27919 analysis of the primary endpoint by region, LOCF, mITT population

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Treatment</th>
<th>Region</th>
<th>N</th>
<th>Mean</th>
<th>SD</th>
<th>Median</th>
<th>Min</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change from Baseline to Week 24 in total daily “on” time</td>
<td>Placebo</td>
<td>Asian-Pacific</td>
<td>84</td>
<td>0.71</td>
<td>2.28</td>
<td>0.50</td>
<td>-4.25</td>
<td>9.25</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Eastern Europe</td>
<td>30</td>
<td>0.76</td>
<td>2.49</td>
<td>0.38</td>
<td>-4.75</td>
<td>9.50</td>
</tr>
<tr>
<td></td>
<td></td>
<td>North America</td>
<td>51</td>
<td>0.14</td>
<td>2.60</td>
<td>0.25</td>
<td>-6.50</td>
<td>8.00</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Western Europe</td>
<td>108</td>
<td>0.52</td>
<td>2.47</td>
<td>0.50</td>
<td>-5.50</td>
<td>8.50</td>
</tr>
<tr>
<td></td>
<td>Safinamide 50-100 mg/day</td>
<td>Asian-Pacific</td>
<td>83</td>
<td>1.15</td>
<td>2.81</td>
<td>0.75</td>
<td>-6.25</td>
<td>13.75</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Eastern Europe</td>
<td>30</td>
<td>2.16</td>
<td>2.85</td>
<td>1.63</td>
<td>-4.25</td>
<td>7.75</td>
</tr>
<tr>
<td></td>
<td></td>
<td>North America</td>
<td>49</td>
<td>1.34</td>
<td>2.86</td>
<td>1.25</td>
<td>-7.00</td>
<td>9.25</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Western Europe</td>
<td>106</td>
<td>1.51</td>
<td>2.78</td>
<td>1.50</td>
<td>-6.00</td>
<td>12.50</td>
</tr>
</tbody>
</table>

LOCF: last observation carried forward; mITT: modified intent-to-treat; N: number of patients at Week 24, with LOCF imputation for missing data; SD: standard deviation.

Source: Reviewer

The region specific descriptive statistics on the change from Baseline to Week 24 in total daily “on” time are presented in Table 15. It appeared that the safinamide-placebo difference in the mean change of “on” time from Baseline to Week 24 was the smallest for Asian-Pacific (safinamide-placebo difference of mean changes = 0.44 hour) and largest for Eastern Europe (safinamide-placebo difference of mean changes = 1.40 hours). The primary analysis of Study 27919 used an ANCOVA model on the mITT population with treatment and region effects and baseline value of the total daily “on” time as the covariate, which yielded a p-value of 0.492 for the region effect. The insignificant p-value for the region effect indicated that the regions were not statistically significantly different from each other, when accounting for treatment and total daily “on” time at Baseline.

4.2 Other Special/Subgroup Populations

No other subgroups were analyzed.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

Except for issues with analysis quality (see Section 3.1 of this review), there are no other statistical issues.
5.2 Collective Evidence

Study 016 and Study 27919 provided sufficient efficacy evidences that Xadago is efficacious as an add-on therapy to a stable dose of levodopa in Parkinson’s disease patients with motor fluctuations: Xadago tablet (50 mg, 100 mg) is statistically significantly better than placebo in increasing total daily “on” time (“on” time without dyskinesia plus “on” time with non-troublesome dyskinesia) by week 24.

5.3 Conclusions and Recommendations

Based on the statistical evidences from Study 016 and Study 27919, the reviewer concludes that Xadago tablet (50 mg, 100 mg) is efficacious as an add-on therapy to a stable dose of levodopa in Parkinson’s disease patients with motor fluctuations.
APPENDIX A. Description of Studies with Insufficient Evidence for Drug Efficacy

A.1 Study 009

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 are 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. A total of 172 patients were actually randomized. The median doses were 39.0 mg/day and 78.1 mg/day for the 0.5 mg/kg/day group and 1.0 mg/kg/day group, respectively.
Table 16. Study 009 patient disposition

The patient disposition is presented in Table 16. The patient discontinuation did not appear similar across treatment groups. The safinamide 1.0 mg/kg/day group and placebo group had more discontinuations, compared to the safinamide 0.5 mg/kg/day group.

The safinamide 1.0 mg/kg/day group and placebo group also had more major protocol deviations/violations, compared to the safinamide 0.5 mg/kg/day group (details not shown, see table 6.2-a on page 53 of sponsor’s clinical study report).

Reference ID: 3837155
Table 17. Study 009 analysis of the primary endpoint

<table>
<thead>
<tr>
<th>Overall</th>
<th>Treatment Group</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Safinamide 0.5 mg/kg</td>
<td>Safinamide 1.0 mg/kg</td>
<td>Placebo</td>
<td>Total</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>N = 56</td>
<td>N = 56</td>
<td>N = 56</td>
<td>N = 167</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visit 5</td>
<td>n</td>
<td>53</td>
<td>52</td>
<td>52</td>
<td>157</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>2 (3.6%)</td>
<td>4 (7.1%)</td>
<td>4 (7.1%)</td>
<td>10 (6.0%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not Improved</td>
<td>41 (74.5%)</td>
<td>41 (73.2%)</td>
<td>47 (83.9%)</td>
<td>129 (77.2%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Improved</td>
<td>12 (21.8%)</td>
<td>11 (19.6%)</td>
<td>5 (8.9%)</td>
<td>28 (16.8%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visit 7</td>
<td>n</td>
<td>51</td>
<td>50</td>
<td>50</td>
<td>151</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>4 (7.3%)</td>
<td>6 (10.7%)</td>
<td>6 (10.7%)</td>
<td>16 (9.6%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not Improved</td>
<td>38 (69.1%)</td>
<td>32 (57.1%)</td>
<td>40 (71.4%)</td>
<td>110 (69.9%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Improved</td>
<td>13 (23.6%)</td>
<td>18 (32.1%)</td>
<td>10 (17.9%)</td>
<td>41 (24.8%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Final Visit</td>
<td>n</td>
<td>55</td>
<td>56</td>
<td>56</td>
<td>167</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not Improved</td>
<td>38 (69.1%)</td>
<td>35 (62.5%)</td>
<td>44 (78.6%)</td>
<td>117 (70.1%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Improved</td>
<td>17 (30.9%)</td>
<td>21 (37.5%)</td>
<td>12 (21.4%)</td>
<td>50 (29.9%)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

N = Number of patients
n = Number of patients with data available
Calculation of percentages based on N
* A responder is defined as an improvement of at least 30% in UPDRS III from baseline

Table 2: Proportion of Responders at Final Visit: Logistic Regression

<table>
<thead>
<tr>
<th>Term</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment: Safinamide 0.5</td>
<td>1.99</td>
<td>0.81, 4.89</td>
<td>0.1315</td>
</tr>
<tr>
<td>Treatment: Safinamide 1.0</td>
<td>2.99</td>
<td>1.23, 7.27</td>
<td>0.0157</td>
</tr>
<tr>
<td>Baseline UPDRS III</td>
<td>0.98</td>
<td>0.94, 1.03</td>
<td>0.4445</td>
</tr>
<tr>
<td>Single DA only</td>
<td>1.96</td>
<td>0.81, 4.73</td>
<td>0.1359</td>
</tr>
<tr>
<td>Single DA / prior PD treatment</td>
<td>1.86</td>
<td>0.74, 4.68</td>
<td>0.1846</td>
</tr>
<tr>
<td>Country: Belgium &amp; France</td>
<td>0.45</td>
<td>0.11, 1.93</td>
<td>0.2842</td>
</tr>
<tr>
<td>Country: Germany</td>
<td>0.18</td>
<td>0.06, 0.60</td>
<td>0.0049</td>
</tr>
<tr>
<td>Country: Poland</td>
<td>1.28</td>
<td>0.55, 3.00</td>
<td>0.5645</td>
</tr>
</tbody>
</table>

Reference groups for categorical variables: Placebo, de Novo, and country: Italy

Pairwise Comparisons

<table>
<thead>
<tr>
<th></th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Safinamide 0.5 mg/kg - Placebo</td>
<td>2.24</td>
<td>0.89, 5.67</td>
<td>0.0880</td>
</tr>
<tr>
<td>Safinamide 1.0 mg/kg - Placebo</td>
<td>3.19</td>
<td>1.28, 7.97</td>
<td>0.0131</td>
</tr>
<tr>
<td>Safinamide 1.0 - Safinamide 0.5</td>
<td>1.49</td>
<td>0.64, 3.47</td>
<td>0.3681</td>
</tr>
</tbody>
</table>

CI = Confidence Interval

Source: Tables 1 and 2 on pages 602-603 of sponsor’s clinical study report
The analysis results of the primary endpoint are presented in Table 17. The primary endpoint was the proportion of patients considered to have achieved a response, defined as an improvement of at least 30% in the UPDRS Section III total score between baseline and the end of the study. The primary efficacy analysis was performed on the ITT population using a logistic regression model that includes UPDRS Section III score at Baseline, treatment, patient’s treatment history (de novo, single dopamine agonist only, or single dopamine agonist with prior Parkinson’s disease treatment), and country. The LOCF method was used for imputing missing data. Although safinamide 1.0 mg/kg/day was statistically significantly better than placebo (p-value = 0.0131), the study did not provide efficacy evidences for the 50 mg/day and 100 mg/day dose recommendations. The efficacy evidence from Study 009 was not confirmed by Study 015 or Study 27918 because those studies failed to demonstrate the superiority of safinamide to placebo for early Parkinson’s disease patients who were receiving a single dopamine agonist at a stable dose.

A.2 Study 015

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. 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.
### Table 18. Study 015 patient population

<table>
<thead>
<tr>
<th></th>
<th>High Dose Safinamide</th>
<th>Low Dose Safinamide</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>Number of patients randomized and treated</td>
<td>89</td>
<td>100.0</td>
<td>90</td>
</tr>
<tr>
<td><strong>Completed study</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>70</td>
<td>78.7</td>
<td>81</td>
</tr>
<tr>
<td>No</td>
<td>19</td>
<td>21.3</td>
<td>9</td>
</tr>
<tr>
<td>Total</td>
<td>89</td>
<td>100.0</td>
<td>90</td>
</tr>
<tr>
<td><strong>Primary reason for withdrawal</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lack of efficacy</td>
<td>2</td>
<td>2.2</td>
<td>0</td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>1</td>
<td>1.1</td>
<td>0</td>
</tr>
<tr>
<td>Non-compliance</td>
<td>1</td>
<td>1.1</td>
<td>0</td>
</tr>
<tr>
<td>Non-serious adverse event</td>
<td>4</td>
<td>4.5</td>
<td>2</td>
</tr>
<tr>
<td>Serious adverse event</td>
<td>1</td>
<td>1.1</td>
<td>1</td>
</tr>
<tr>
<td>Termination by Investigator</td>
<td>2</td>
<td>2.2</td>
<td>2</td>
</tr>
<tr>
<td>Withdrawal of consent</td>
<td>7</td>
<td>7.9</td>
<td>3</td>
</tr>
<tr>
<td>Other</td>
<td>1</td>
<td>1.1</td>
<td>1</td>
</tr>
<tr>
<td><strong>Primary reason for withdrawal not AEs or SAEs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>1</td>
<td>1.1</td>
<td>0</td>
</tr>
<tr>
<td>Non-compliance</td>
<td>1</td>
<td>1.1</td>
<td>0</td>
</tr>
<tr>
<td>Termination by clinical Investigator</td>
<td>1</td>
<td>1.1</td>
<td>1</td>
</tr>
<tr>
<td>Withdrawal of consent</td>
<td>1</td>
<td>1.1</td>
<td>1</td>
</tr>
</tbody>
</table>

*Source: Table 10.1 on page 80 of sponsor’s clinical study report*

The patient disposition is presented in Table 18. The patient discontinuation did not appear similar across treatment groups. The safinamide 200 mg/day group had more discontinuations, compared to the safinamide 100 mg/day group and placebo group. The safinamide 200 mg/day group also had more adverse events (serious and non-serious), compared to the safinamide 100 mg/day group and placebo group.

Reference ID: 3837155
### Table 19. Study 015 analysis of the primary endpoint

<table>
<thead>
<tr>
<th>Study 015</th>
<th>Visit/Week</th>
<th>Statistic</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Placebo</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>N=87</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Safinamide 100 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>N=86</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Safinamide 200 mg</td>
</tr>
<tr>
<td></td>
<td>Visit 8/</td>
<td>Mean Change (SD)</td>
<td>-3.6 (7.08)</td>
</tr>
<tr>
<td></td>
<td>Week 24 (Endpoint)</td>
<td>[95% CI]</td>
<td>--</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Point Estimate</td>
<td>--</td>
</tr>
<tr>
<td></td>
<td></td>
<td>p-value vs Placebo</td>
<td>--</td>
</tr>
</tbody>
</table>

A mixed linear model was used to calculate a point estimate, 95% CI and p-value for the difference between active treatment groups and Placebo in the change from Baseline to Endpoint. The unstructured covariance structure was used as output.

Source: Table 1 on page 2 of sponsor’s information amendment submitted on April 17, 2015

The analysis results of the primary endpoint are presented in Table 19. The primary endpoint was the change from Baseline to Week 24 in the UPDRS Section III total score. 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 total 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 safinamide 200 mg/day group failed to show superiority to placebo (p-value = 0.6540). As a result, the testing of the safinamide 100 mg/day group should stop.

### A.3 Study 27918

Study 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.
The design of Study 27918 is presented in Figure 9.

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.

Table 20. Study 27918 patient disposition

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Safinamide 50 mg/day (n=227)</th>
<th>Safinamide 100 mg/day (n=227)</th>
<th>Placebo (n=225)</th>
<th>Total (n=679)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects who were randomized (ITT population)</td>
<td>227 (100.0)</td>
<td>227 (100.0)</td>
<td>225 (100.0)</td>
<td>679 (100.0)</td>
</tr>
<tr>
<td>Treated Subjects with a subsequent safety assessment (Safety population)</td>
<td>226 (99.8)</td>
<td>227 (99.8)</td>
<td>226 (99.8)</td>
<td>679 (99.8)</td>
</tr>
<tr>
<td>Modified ITT population (MITT)</td>
<td>225 (99.1)</td>
<td>227 (99.8)</td>
<td>221 (96.1)</td>
<td>673 (98.8)</td>
</tr>
<tr>
<td>Completer population</td>
<td>198 (87.7)</td>
<td>210 (92.5)</td>
<td>201 (89.3)</td>
<td>599 (88.4)</td>
</tr>
<tr>
<td>Per Protocol population (PP)</td>
<td>193 (86.0)</td>
<td>200 (87.7)</td>
<td>189 (84.0)</td>
<td>582 (86.6)</td>
</tr>
<tr>
<td>Subjects who discontinued from treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse event</td>
<td>20 (12.3)</td>
<td>17 (7.9)</td>
<td>27 (12.0)</td>
<td>64 (9.4)</td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>3 (1.3)</td>
<td>2 (0.9)</td>
<td>3 (1.3)</td>
<td>8 (1.2)</td>
</tr>
<tr>
<td>Lack of efficacy</td>
<td>30 (13.1)</td>
<td>3 (1.3)</td>
<td>2 (0.9)</td>
<td>35 (5.1)</td>
</tr>
<tr>
<td>Death</td>
<td>2 (0.9)</td>
<td>1 (0.5)</td>
<td>1 (0.4)</td>
<td>4 (0.6)</td>
</tr>
<tr>
<td>Other</td>
<td>14 (6.2)</td>
<td>9 (3.9)</td>
<td>12 (5.3)</td>
<td>35 (5.1)</td>
</tr>
<tr>
<td>Subjects who discontinued treatment and completed study</td>
<td>2 (0.9)</td>
<td>3 (1.3)</td>
<td>0 (0.0)</td>
<td>5 (0.7)</td>
</tr>
<tr>
<td>Subjects who completed treatment and discontinued study</td>
<td>1 (0.4)</td>
<td>1 (0.4)</td>
<td>0 (0.0)</td>
<td>2 (0.3)</td>
</tr>
<tr>
<td>Subjects who discontinued from study</td>
<td>28 (12.3)</td>
<td>17 (7.9)</td>
<td>24 (10.7)</td>
<td>69 (10.3)</td>
</tr>
<tr>
<td>Adverse event</td>
<td>3 (1.3)</td>
<td>4 (1.8)</td>
<td>11 (4.9)</td>
<td>18 (2.7)</td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>1 (0.4)</td>
<td>4 (1.8)</td>
<td>4 (1.8)</td>
<td>9 (1.3)</td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Other</td>
<td>24 (10.6)</td>
<td>9 (4.0)</td>
<td>9 (4.0)</td>
<td>42 (6.2)</td>
</tr>
<tr>
<td>Subjects who changed anti-Parkinson's treatment prior to Week 24</td>
<td>7 (3.1)</td>
<td>9 (3.9)</td>
<td>7 (3.1)</td>
<td>22 (3.3)</td>
</tr>
</tbody>
</table>

Source: Table 15.1.3 on page 203 of sponsor’s clinical study report
The patient disposition is presented in Table 20. The patient discontinuation did not appear similar across treatment groups. The safinamide 50 mg/day group and placebo group had more discontinuations, compared to the safinamide 100 mg/day group. The placebo group had more adverse events, compared to the safinamide 50 mg/day group and safinamide 100 mg/day group.

Table 21. Study 27918 analysis of the primary endpoint

<table>
<thead>
<tr>
<th>Timepoint</th>
<th>Statistics</th>
<th>Safinamide 50 mg/day</th>
<th>Safinamide 100 mg/day</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>(n=226)</td>
<td>(n=227)</td>
<td>(n=224)</td>
</tr>
<tr>
<td></td>
<td>Value</td>
<td>Change</td>
<td>Value</td>
<td>Change</td>
</tr>
<tr>
<td>LS Diff vs Placebo</td>
<td>-0.69 (0.58)</td>
<td>-1.04 (0.58)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(SE)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>95% CI of LS Diff</td>
<td>(1.93, 0.44)</td>
<td>(2.17, 0.10)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>p-value vs Placebo</td>
<td>0.232</td>
<td>0.073</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Source: Table 15.2.5 on pages 295-296 of sponsor’s clinical study report

The analysis results of the primary endpoint are presented in Table 21. The primary endpoint was change from Baseline to Week 24 in the UPDRS Section III total score. The primary efficacy analysis was performed on the mITT 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. Both the safinamide 100 mg/day and safinamide 50 mg/day groups failed to show superiority to placebo (p-values = 0.073 and 0.232, respectively). 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 better than placebo. Each test was to be conducted at the two-sided significance level $\alpha = 0.05$. 

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/s/

XIANGMIN ZHANG
10/22/2015

KUN JIN
10/22/2015
I concur with the review.

HSIEN MING J HUNG
10/23/2015