CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA Number:	210875
Drug Name:	Kynmobi (Apomorphine Hydrochloride Sublingual Film)
Indication:	Acute, intermittent treatment of "OFF" episodes associated with Parkinson's disease
Applicant:	Sunovion Pharmaceuticals, Inc.
Dates:	Receipt date: March 29, 2018 PDUFA Goal Date: January 29, 2019
Review Priority:	Standard
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Keywords: clinical studies, mixed models, NDA review

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1 EXECUTIVE SUMMARY

This review described the statistical findings of Kynmobi (apomorphine hydrochloride sublingual film) as an acute, intermittent treatment of "OFF" episodes associated with Parkinson's disease. The review confirmed that Study CTH-300 - a randomized, double-blind, placebo-controlled, parallel-group study - in the 505(b)(2) new drug application provided statistical evidence that Kynmobi is efficacious: Kynmobi is statistically better than placebo in terms of the change from pre-dose to 30 minute post-dose in the Movement Disorders Society - Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part III (Motor Examination) score at Week 12.

2 INTRODUCTION

2.1 Overview

On March 29, 2018, Sunovion Pharmaceuticals, Inc. (the Applicant) submitted a 505(b)(2) new drug application (NDA) for apomorphine hydrochloride sublingual film (APL-130277 under the Applicant's clinical development program) as an acute, intermittent treatment of "OFF" episodes associated with Parkinson's disease (PD). The NDA submission lists Food and Drug Administration approved drug Apokyn® (NDA 021264) as the 505(b)(2) reference. The Applicant submitted one clinical study in the NDA to support the efficacy claim of APL-130277. This clinical study is summarized below and reviewed in Section 3.

Table 1. The clinical study in this review

Study Number	**Phase and Design**	**Maintenance Period (in week)**	**Study Arm (Number of randomized subjects per arm)**	**Study Population**
CTH-300	Phase3, randomized, double-blind, placebo-controlled, parallel-group	12	Placebo (54) Kynmobi (55)	Male and female subjects ≥ 18 years of age with Parkinson's disease

Source: statistical reviewer's summary

2.2 Data Sources

The electronic submission of this NDA is located at
\\cdsesub1\evsprod\NDA210875\0001\

The study reports are located at
\\cdsesub1\evsprod\NDA210875\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\parkinsons\5351-stud-rep-contr\cth-300\

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The datasets are located at
\\cdsesub1\evsprod\NDA210875\0001\m5\datasets\cth-300\

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

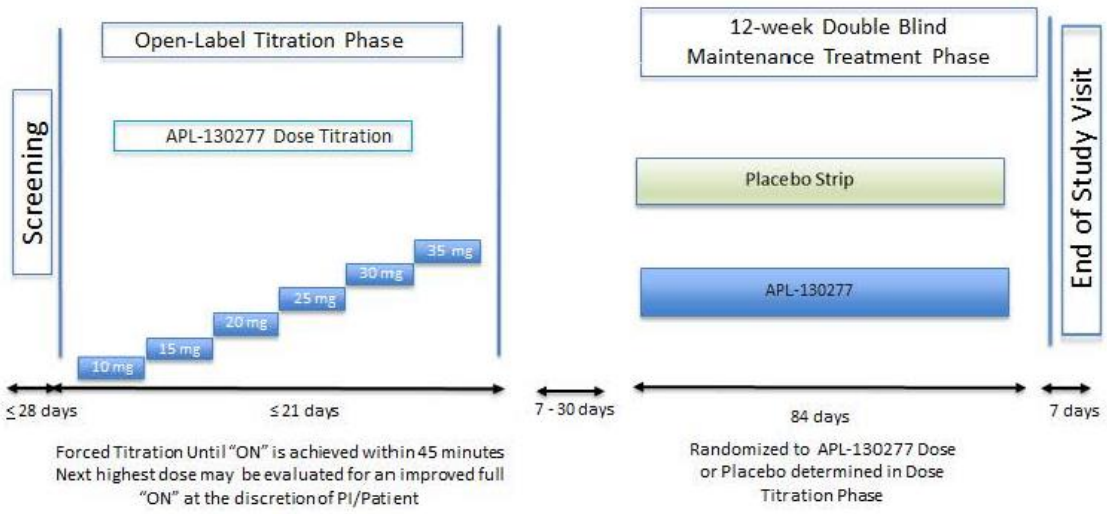
The data quality and analysis quality are adequate. The statistical reviewer was able to perform independent review using the Applicant's submitted datasets and confirm the Applicant's analysis results.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

Study CTH-300 was a Phase 3, randomized, double-blind, placebo-controlled, parallel-group, 2-arm, multi-center study to evaluate the efficacy, safety, and tolerability of APL-130277 in patients with PD. Approximately 126 patients were planned to be enrolled; approximately 114 patients were planned to be randomized in a 1:1 ratio to placebo and APL-130277 groups.

Figure 1. Design schematic



Source: Figure 1 on page 26 of the clinical study report body

Figure 1 depicted the study design schematic of Study CTH-300. The study consisted of a dose titration phase and a 12-week double-blind maintenance treatment phase. In the dose titration phase, patients had up to six titration visits. The minimum titration dose was 10 mg APL-130277; the maximum titration dose was 35 mg APL-130277.

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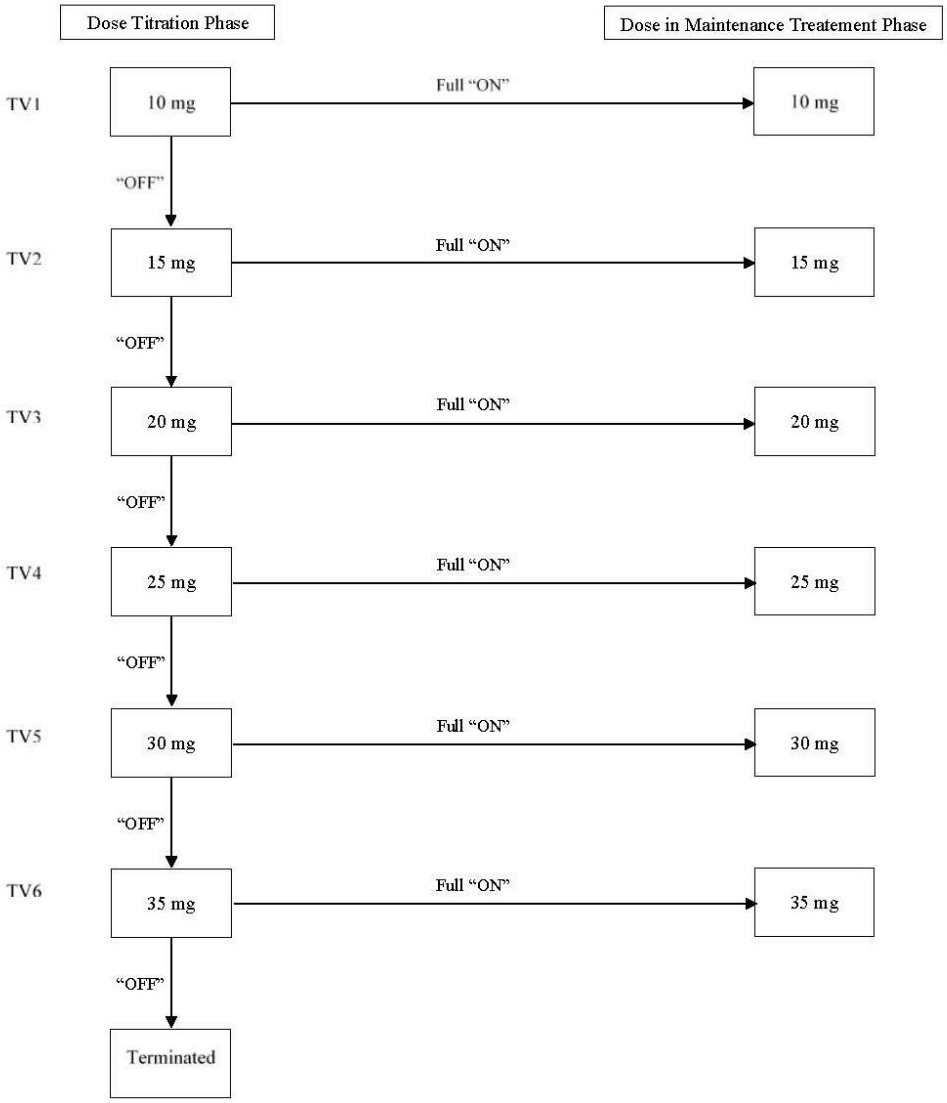
Figure 2. Dosing paradigm



Source: figure on page 21 of the protocol

Figure 2 depicted the dosing paradigm of the dose titration phase. Before each titration visit or maintenance visit, patients were instructed to take their last dose of Levodopa (L-Dopa) and any other adjunctive PD medication no later than midnight on the evening prior and skip their regular morning does of L-Dopa or any other adjunctive PD medications on the day of the visit. During each titration visit, the patients was presented to the clinic in an "OFF" state then treated with APL-130277; the patient and investigator assessed whether the patient responded to the APL-130277 with a full "ON" response within 45 minutes of taking APL-130277. Per the clinical study protocol, a patient-assessed full "ON" is defined as "a period of time where medication is providing benefit with regard to mobility, stiffness and slowness and where a patient feels he/she can perform normal daily activities; AND the response is comparable to or better than their normal response to PD medications prior to enrolling in the study"; an investigator-assessed full

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"ON is defined as "per clinical judgment, the period of time where the Investigator feels the medication is providing benefit with regard to mobility, stiffness and slowness and the patient has adequate motor function to allow them to perform their normal daily activities". Patients who achieved a full "ON" response, as assessed by the patient and investigator, within 45 minutes of taking APL-130277 proceeded to randomization and the maintenance treatment phase at this dose, otherwise, patients were titrated to the next dose level in the next titration visit.

Following the dose titration phase, patients were randomized in a 1:1 ratio to placebo and APL-130277 groups and returned to the clinics at monthly interval during the 12-week double-blind maintenance treatment phase. Per the Schedule of Event Table in the protocol, the randomization and Maintenance Visit 1 (MV1) were planned to occur on Day 23, Maintenance Visit 2 (MV2) on Day 51, Maintenance Visit 3 (MV3) on Day 79, and Maintenance Visit 4 (MV4) on Day 100, with a window of ± 2 days. This indicates that the actual time length from randomization to MV4 was around 11 weeks and less than 12 weeks.

The primary efficacy endpoint was the change from pre-dose to 30 minutes post-dose in the MDS-UPDRS Part III score at Week 12 (i.e. MV4).

The key secondary efficacy endpoint was the percentage of subjects with a patient-rated full "ON" response within 30 minutes at Week 12.

3.2.2 Statistical Methodologies

The efficacy analysis population was the modified intent-to-treat (mITT) population, defined as all subjects who were randomized, received at least one dose of study medication, and had at one post-randomization evaluation.

The primary endpoint was analyzed using a mixed model with repeated measure (MMRM), with treatment, visit (MV1, MV2, MV3, and MV4), treatment by visit interaction as fixed effects and the change from pre-dose to 30 minutes post-dose in the MDR-UPDRS Part III score at the last titration visit as the covariate. The unstructured variance-covariance matrix was used for the analysis.

The key secondary endpoint was analyzed using a generalized linear mixed model on binary data with logit link. The model included treatment, visit (MV1, MV2, MV3, and MV4), and treatment by visit interaction as fixed effects and the "ON/OFF" assessment at the last titration visit as the covariate. The unstructured variance-covariance matrix was used for the analysis.

The primary and key secondary endpoints were planned to be tested sequentially, each test at the two-sided significance level of 0.05.

Reference ID: 4851403

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

Table 2. Patient disposition (randomized population)

Disposition	Placebo (N = 55) n (%)	APL-130277 (N = 54) n (%)	Total (N = 109) n (%)
Received at least one dose in Maintenance Treatment Phase (Maintenance Phase Safety Population)[e]	55 (100)	54 (100)	109 (100)
Completed study	46 (83.6)	34 (63.0)	80 (73.4)
Discontinued after randomization	9 (16.4)	20 (37.0)	29 (26.6)
AE	5 (9.1)	15 (27.8)	20 (18.3)
Subject withdrew consent	3 (5.5)	4 (7.4)	7 (6.4)
Lack of efficacy	1 (1.8)	0	1 (0.9)
Death	0	1 (1.9)	1 (0.9)

Abbreviations: AE = adverse event

Source: Table 7 on page 63 of the clinical study report body

Table 2 presented the patient disposition of the randomized population. For Study CTH-300, the randomized population is also the mITT population. A total of 219 subjects were screened in 32 study centers in the United States (US) and 1 center in Canada; a total of 109 subjects were randomized in 27 centers in the US and 1 center in Canada. Among the 109 randomized patients, 55 patients (50.5%) were randomized to the placebo group and 54 (49.5%) to the APL-130277 group.

A total of 80 patients completed the study: 46 in the placebo group and 34 in the APL-130277 group. Compared to patients in the placebo group, more patients in the APL-130277 group discontinued due to adverse events: 15 patients in the APL-130277 group discontinued due to adverse events versus 4 patients in the placebo discontinued for the same reason.

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Table 3. Patient demographics (mITT population)

Characteristic	Double-blind Maintenance Treatment Phase mITT Population[a]		
	Placebo (N = 55)	APL-130277 (N = 54)	Overall (N = 109)
Age (years)[b] n	55	54	109
Mean (SD)	62.5 (8.12)	62.9 (9.79)	62.7 (8.95)
Median	62.0	63.5	63.0
Min, max	46, 79	43, 78	43, 79
< 65 years, n (%)	34 (61.8)	30 (55.6)	64 (58.7)
≥ 65 years, n (%)	21 (38.2)	24 (44.4)	45 (41.3)
Gender, n (%)			
Male	31 (56.4)	37 (68.5)	68 (62.4)
Female	24 (43.6)	17 (31.5)	41 (37.6)
Ethnicity, n (%)			
Hispanic or Latino	3 (5.5)	3 (5.6)	6 (5.5)
Not Hispanic or Latino	52 (94.5)	51 (94.4)	103 (94.5)
Race, n (%)			
Asian	1 (1.8)	4 (7.4)	5 (4.6)
Black or African American	2 (3.6)	0	2 (1.8)
Native Hawaiian or Other Pacific Islander	1 (1.8)	0	1 (0.9)
White	51 (92.7)	50 (92.6)	101 (92.7)

Abbreviations: BMI = body mass index; SD = standard deviation; max = maximum; min = minimum
[a] The mITT Population and Maintenance Phase Safety Population were identical, with the same number of subjects included in both populations (placebo: 55; APL-130277: 54)
[b] As measured on the date of informed consent.

Source: selected from Table 10 on pages 66-67 of the clinical study report body

Table 3 summarized the patient demographic characteristics of the mITT population. The treatment groups appeared similar in terms of age, gender, and race. The average age of the mITT population was approximately 62.7 years (standard deviation (SD) = 8.95). Overall, there were more male patients than female patients in the study. The majority of the mITT population was White.

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Table 4. Patient baseline characteristics (mITT population)

Characteristic	Placebo N = 55	APL-130277 N = 54	All N = 109
Time since diagnosis of PD (year)			
Mean (SD)	9.3 (3.84)	8.7 (4.25)	9.0 (4.04)
Median	8.0	7.0	8.0
Min, Max	2, 22	2, 20	2, 22
Time since motor fluctuations started (year)			
Mean (SD)	4.5 (3.78)	4.7 (3.92)	4.6 (3.83)
Median	3.0	4.0	4.0
Min, Max	0.5, 22.0	0.5, 21.0	0.5, 22.0
Number of "OFF" episodes typically experienced per day			
Mean (SD)	3.8 (1.40)	3.9 (1.17)	3.9 (1.29)
Median	4	4	4
Min, Max	1, 8	2, 8	1, 8
Typical lengths of "OFF" episodes (minute)			
Mean (SD)	66.1 (30.09)	63.7 (31.91)	64.9 (30.89)
Median	60	60	60
Min, Max	30, 150	20, 210	20, 210
Total daily levodopa dose (mg)			
Mean (SD)	1007.7 (562.33)	1058.7 (563.30)	1033.0 (560.78)
Median	900	1000	950
Min, Max	400, 2940	400, 2900	400, 2940

mITT: modified intent-to-treat; N: number of patients; PD: Parkinson's disease; SD: standard deviation.

Source: selected from Table 11 on pages 68-69 of the clinical study report body

Table 4 summarized the patient baseline characteristics of the mITT population. The placebo group and APL-130277 group appeared similar. Patients in the mITT population were diagnosed with PD with an average diagnose length of 9.0 years (SD = 4.04) at study baseline. On average, patients had experienced motor fluctuations for approximately 4.6 years (SD = 3.83) at study baseline.

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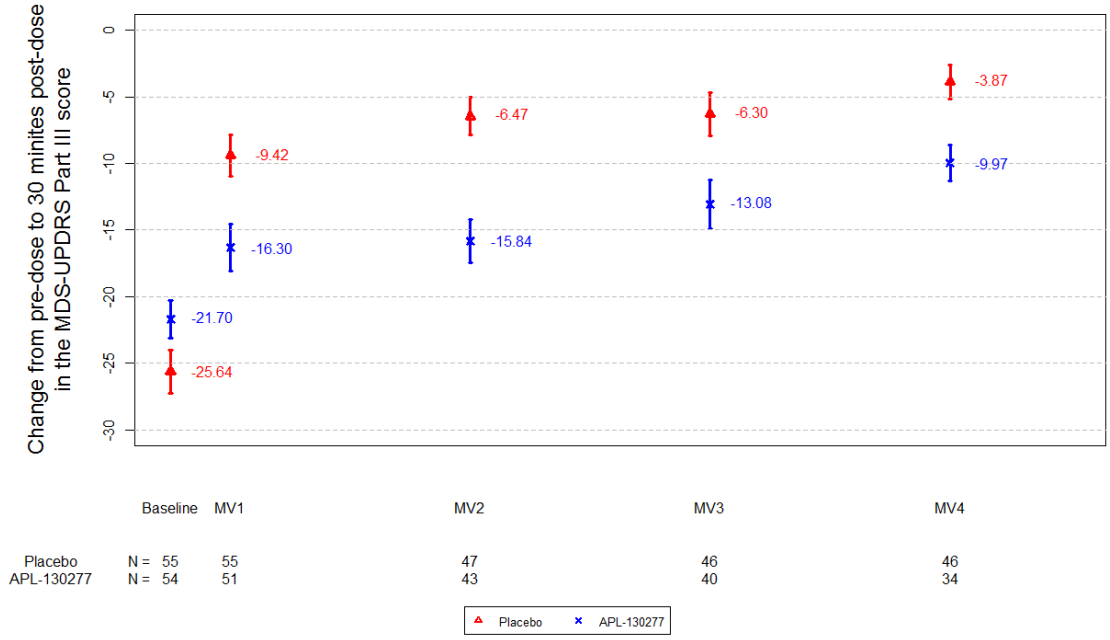
3.2.4 Results and Conclusions

Figure 3. Observed mean (± standard error) change from pre-dose to 30 minutes post-dose in the MDS-UPDRS Part III score by visit and treatment (mITT population)



Source: statistical reviewer

Figure 3 illustrated observed means of the change from pre-dose to 30 minutes post-dose in the MDS-UPDRS Part III score by visit and treatment for the mITT population. The APL-130277 group appeared to have consistent mean improvements of the MDS-UPDRS Part III score based on the observed mean changes from pre-dose to post-dose assessments. Such improvements were on average greater than those from the placebo group at each maintenance visit. However, the placebo effect also appeared to exist. The observed mean changes of pre-dose to post-dose appeared to decrease over time for both treatment groups, but the trends could be affected by high percentages of missing observations in both treatment groups. The percentages of missing observations at MV4 were 16.4% and 37.0% for the placebo group and APL-130277 group, respectively.

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Table 5. Analysis of the change from pre-dose to 30 minutes post-dose in the MDS-UPDRS Part III score at Week 12 (mITT population)

Visit	Statistic	Placebo (N=55)	APL-130277 (N=54)
Maintenance Visit 4 (MV4)	n	46	34
	LS Mean (SE)	-3.5 (1.29)	-11.1 (1.46)
	95% Confidence Interval	-6.1, -0.9	-14.0, -8.2
	P-value	0.0081	<0.0001
	LS Mean Difference (APL-130277 - Placebo) (SE)	-	-7.6 (1.96)
	95% Confidence Interval	-	-11.5, -3.7
	P-value	-	0.0002

Abbreviations: LS = least square; SE = standard error; MDS-UPDRS = Movement Disorders Society Unified Parkinson's Disease Rating Scale; mITT = modified Intention-to-treat.
Note: Reduction in score = improvement.

Source: Table 21 on page 85 of the clinical study report body

Table 5 presented the analysis results of the change from pre-dose to 30 minutes post-dose in the MDS-UPDRS Part III score at Week 12. APL-130277 was statistically significantly better than placebo (p-value = 0.0002), with a least square APL-130277-placebo difference of -7.6 points (95% Confidence Interval (CI) = (-11.5, -3.7)). The Applicant performed several sensitivity analyses with missing data imputed under the missing at random assumption and the missing not at random assumption, respectively. The results from these sensitivity analyses supported the primary analysis results. For example, the Applicant used multiple imputation assuming that the trajectories of the patients after discontinuation follow those of the placebo group and obtained a nominal p-value = 0.0068. Applicant's tipping point analysis assumed that trajectories of the patients in the APL-130277 group after discontinuation are worse by delta and showed that the statistical significance was lost when delta was greater than 8 points in MDS-UPDRS Part III score.

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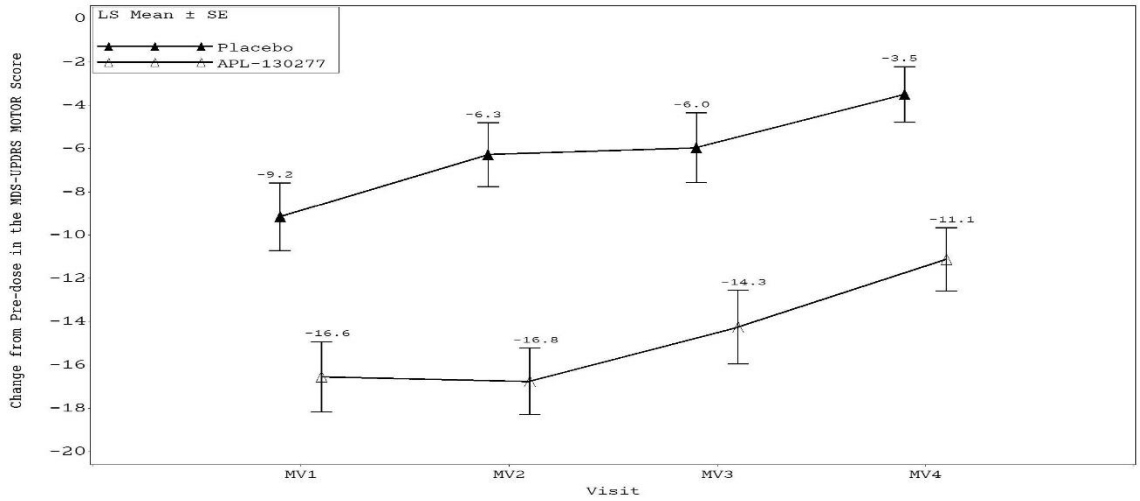
Figure 4. Least square mean (± standard error) change from pre-dose to 30 minutes post-dose in the MDS-UPDRS Part III score by visit and treatment (mITT population)



Source: Figure 14.2.1.1.2 of the clinical study report

Figure 4 illustrated estimated means of the change from pre-dose to 30 minutes post-dose in the MDS-UPDRS Part III score by visit and treatment for the mITT population. The least square means were estimated from the primary analysis model. This figure confirmed the findings from **Figure 3**. Both the placebo effect and drug effect appeared to diminish over time while the APL-130277-placebo difference appeared to be consistent over time. The difference between the observed mean and least square mean for the APL-130277 group is the largest at MV4, compared to the differences of observed mean and least square mean for the APL-130277 group at other maintenance visits. This is likely caused by the high percentage of missing observations at MV4.

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Table 6. Analysis of the percentage of subjects with a subject-rated full "ON" response within 30 minutes at Week 12 (mITT population)

Visit	Category	Statistic	Placebo (N=55)	APL-130277 (N=54)	P-value
Maintenance Visit 4 (MV4)	Observed "ON" Response within 30 Minutes				
	Yes	n (%)	9 (16.4)	14 (25.9)	
	No	n (%)	37 (67.3)	20 (37.0)	
	Missing	n (%)	9 (16.4)	20 (37.0)	
	Predicted Response Rate		0.16	0.35	
	95% Confidence Interval		0.081, 0.296	0.210, 0.525	
	Adjusted Odds Ratio			2.81	0.0426
	95% Confidence Interval			1.036, 7.644	

Abbreviations: mITT = modified Intention-to-treat; MV4 = maintenance visit 4.

Source: Table 27 on page 95 of the clinical study report body

Table 6 presented the analysis results of the percentage of subjects with a subject-rated full "ON" response within 30 minutes at Week 12. Disregarding the missing observations at MV4, the observed responder rates were 9/46 (19.57%) and 14/34 (41.18%) for the placebo group and APL-130277 group, respectively. APL-130277 was statistically significantly better than placebo (p-value = 0.0426) in terms of the percentage of subjects with a subject-rated full "ON" response within 30 minutes at Week 12, with an adjusted Odds Ratio of 2.81 (95% CI = (1.036, 7.644)). However, the Applicant's pre-specified sensitivity analysis - Cochran-Mantel-Haenszel test - did not have a nominally significant p-value (nominal p-value = 0.174). Additional sensitivity analysis by the statistical reviewer imputing all missing data as non-responses did not have a nominally significant p-value either.

3.3 Evaluation of Safety

Please refer to Dr. Kenneth Bergmann's clinical review for a detailed evaluation of safety.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

Overall, there is no compelling evidence from the subgroup analyses that a specific gender, race, or age subgroup benefits differently from APL-130277.

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Gender

Table 7. Subgroup analysis by gender of the change from pre-dose to 30 minutes post-dose in the MDS-UPDRS Part III score at Week 12 (mITT population)

Gender	Change from pre-dose to 30 minutes post-dose in the MDS-UPDRS Part III score	Placebo	APL-130277
Baseline			
Female	N	24	17
	Means (SD)[a]	-26.6 (11.49)	-27.2 (9.23)
Male	N	31	37
	Means (SD)[a]	-24.9 (12.80)	-19.2 (10.08)
Week 12			
Female	N	17	10
	Means (SD)[a]	-6.9 (10.93)	-7.5 (8.21)
Male	N	29	24
	Means (SD)[a]	-2.1 (6.54)	-11.0 (7.82)

MDS-UPDRS: Movement Disorders Society -Unified Parkinson's Disease Rating Scale; mITT: modified intent-to-treat; N: number of mITT patients; SD: standard deviation.

[a] Obtained from all observations in the gender specific mITT population, without imputation.

Source: selected from Table 14.2.1.9.2 of the clinical study report

As shown in **Table 7**, for both the female group and male group, the observed mean change from pre-dose to 30 minutes post-dose in MDS-UPDRS III score of the APL-130277 group was higher than that of the placebo group.

Race

As shown in **Table 3**, 92.7% of the mITT population was White. The numbers of patients in other races are so small that the analysis of other races would not be informative. Therefore, subgroup analyses by race were not performed.

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Age

Table 8. Subgroup analysis by age group of the change from pre-dose to 30 minutes post-dose in the MDS-UPDRS Part III score at Week 12 (mITT population)

Age Group	Change from pre-dose to 30 minutes post-dose in the MDS-UPDRS Part III score	Placebo	APL-130277
Baseline			
< 65 years	N	34	30
	Means (SD)[a]	-26.4 (12.18)	-23.7 (9.15)
≥ 65 years	N	21	24
	Means (SD)[a]	-24.4 (12.33)	-19.3 (11.60)
Week 12			
< 65 years	N	28	18
	Means (SD)[a]	-4.4 (9.21)	-9.9 (9.23)
≥ 65 years	N	18	16
	Means (SD)[a]	-3.1 (7.83)	-10.0 (6.59)

MDS-UPDRS: Movement Disorders Society -Unified Parkinson's Disease Rating Scale; mITT: modified intent-to-treat; N: number of mITT patients; SD: standard deviation.

[a] Obtained from all observations in the age group specific mITT population, without imputation.

Source: selected from Table 14.2.1.8.2 of the clinical study report

As shown in **Table 8**, for both the "< 65 years" group and "≥ 65 years" group, the observed mean change from pre-dose to 30 minutes post-dose in MDS-UPDRS III score of the APL-130277 group was higher than that of the placebo group.

Geographic Region

Study CTH-300 was conducted mainly in the US. Only one patient the mITT population was from a Canadian study center. Therefore, subgroup analysis by geographic region (US vs. non-US) was not performed.

Reference ID: 4865103

4.2 Other Special/Subgroup Populations

Table 9. Subgroup analysis by randomized dose of the change from pre-dose to 30 minutes post-dose in the MDS-UPDRS Part III score at Week 12 (mITT population)

Randomized Doses	Placebo				APL-130277			
	Baseline		Week 12		Baseline		Week 12	
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
10 mg	13	-22.3 (12.25)	12	-3.5 (7.42)	7	-25.6 (11.53)	4	-9.5 (10.38)
15 mg	11	-27.9 (10.34)	8	-3.6 (7.65)	18	-18.8 (9.39)	12	-13.4 (8.95)
20 mg	16	-24.94 (13.84)	15	-4.3 (11.04)	7	-20.6 (7.91)	4	-9.5 (3.00)
25 mg	9	-29.1 (12.19)	7	-6.9 (8.19)	12	-23.8 (10.84)	8	-10.0 (5.40)
30 mg	5	-25.4 (13.61)	4	1.50 (3.87)	4	-23.3 (11.59)	2	1.5 (3.54)
35 mg	1	-25.00 (-)	0	- (-)	6	-22.0 (14.75)	4	-6.3 (7.93)
Total	55	-25.6 (12.16)	46	-3.9 (8.63)	54	-21.7 (10.44)	34	-10.0 (7.98)

mITT: modified intent-to-treat; n: number of patients; SD: standard deviation.

Source: selected from Table 14.2.1.10.2 and Table 14.2.1.1.2 in the clinical study report

Except for the groups with higher randomized doses, such as the group of patients that had 30 mg as the randomized dose and the group of patients that had 35 mg as the randomized dose, other randomized dose groups had higher observed mean change from pre-dose to 30 minutes post-dose in MDS-UPDRS III score in the APL-130277 group than in the placebo group at Week 12.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

No statistical issues were identified.

5.2 Collective Evidence

One clinical study, Study CTH-300, in this NDA submission provided efficacy evidence that Kynmobi is efficacious as a treatment of "OFF" episodes associated with Parkinson's disease: Kynmobi is statistically better than placebo in terms of the change from pre-dose to 30 minutes post-dose in the MDS-UPDRS Part III score at Week 12.

5.3 Conclusions and Recommendations

Based on the statistical evidence from Study CTH-300, the statistical reviewer concluded that Kynmobi is superior to placebo in treating "OFF" episodes associated with Parkinson's disease.

Reference ID: 4861403

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/s/

XIANGMIN ZHANG
12/19/2018

KUN JIN
12/19/2018
I concur with the review.

HSIEN MING J HUNG
12/19/2018