CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210875Orig1s000

CLINICAL REVIEW(S)

CLINICAL REVIEW

Application Type	**Resubmission – Class 2 (Complete Response)** 505(b)(2) Type 3 New Dosage Form
Application Number(s)	NDA 210875
Priority or Standard	Standard
Submit Date(s)	2019 November 21
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PDUFA Goal Date	2020 May 21
Division/Office	DN I, ON, OND
Reviewer Name(s)	Kenneth Bergmann, MD
Review Completion Date	2020 May 20
Established/Proper Name	APL-130277 (apomorphine hydrochloride sublingual thin film)
(Proposed) Trade Name	KYNMOBI
Applicant	Sunovion
Dosage Form(s)	Sublingual thin film
Applicant Proposed Dosing Regimen(s)	10, 15, 20, 25, 30 (b) (4) mg sublingually up to five times daily separated by at least 2 hours
Applicant Proposed Indication(s)/Population(s)	For the acute, intermittent treatment of "off" episodes associated with Parkinson's disease
Recommendation on Regulatory Action	Approvable, up to 30 mg per dose.
Recommended Indication(s)/Population(s)	Adults with Parkinson's disease and "off" episodes

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Glossary

AC	advisory committee
ADaM	Analysis Data Model
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDISC	Clinical Data Interchange Standards Consortium
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COMT	catechol-O-methyl transferase
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
CT	computerized tomography
DBS	deep brain stimulation
DMEPA	Division of Medication Error Prevention and Analysis
DSMB	Data Safety Monitoring Board
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
HF	human factors
ICH	International Council for Harmonization
IND	Investigational New Drug Application

ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MAED	MedDRA Adverse Event Diagnosis Tool
MAOI	monoamine oxidase inhibitor
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
MRI	magnetic resonance imaging
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	Parkinson's disease
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
PT	Preferred Term
RLD	reference listed drug
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SDTM	Study Data Tabulation Model
SGE	special government employee
SOC	standard of care
SPA	Special Protocol Assessment
TEAE	treatment emergent adverse event
UPDRS	Unified Parkinson's Disease Rating Scale

1. Executive Summary

1.1. Recommendation on Regulatory Action

Following review of the Complete Response, it is the opinion of this reviewer that the lack of sufficient information supporting the safe use of Kynmobi has been resolved. (b) (4) The use of Kynmobi dosed at 10 mg, 15 mg, 20 mg, 25 mg, and 30 mg up to five times a day *for the treatment of acute, intermittent treatment of* (b) (4) *"off" episodes associated with advanced Parkinson's disease* is approvable.

1.2. Introduction to the Complete Response

APL-130277 is a new dosage form of apomorphine, a dopamine agonist. Kynmobi, the provisionally approved commercial name for APL-130277, is apomorphine hydrochloride contained in a thin film for sublingual use. Apomorphine is currently approved as a subcutaneous injection (APOKYN®, NDA 21264) indicated for the treatment of acute, intermittent treatment of hypomobility, "off" episodes ("end-of-dose wearing off" and unpredictable "on/off" episodes) associated with advanced Parkinson's disease. Kynmobi is seeking approval (b) (4) via the 505(b)(2) regulatory pathway.

The applicant proposes a dose range of 10 (b) (4) mg by sublingual administration. Kynmobi is provided as 10, 15, 20, 25 and 30 mg thin films. (b) (4) Doses should be separated by at least 2 hours and may be taken up to 5 times daily.

Kynmobi requires dose titration and treatment is initiated with 10 mg. The dose level is increased until an adequate clinical response, "on" or mobile motor state, is attained. Because Kynmobi often causes nausea and vomiting when treatment is initiated, oral trimethobenzamide has been used as a concomitant antiemetic treatment and is recommended during titration. This treatment should only be continued as long as necessary to control nausea and vomiting. Most patients in the clinical trials supporting the APL-130277 application used trimethobenzamide 300 mg t.i.d. The Prescribing Information for Apokyn, the reference listed drug, also recommends the use of oral trimethobenzamide to prevent nausea.

The initial marketing application for Kynmobi was accepted for review on March 29, 2018. While approvable based on clinical efficacy, the full risk of APL-130277 could not be assessed and the application was determined to be unapprovable for this and other reasons (PDUFA goal date, January 29, 2019). The clinical safety of Kynmobi was not adequately supported in the original NDA application and newly submitted data in this re-submission is the major focus of this review.

Oropharyngeal adverse events observed in patients treated with Kynmobi were reported under multiple terms. Taken together, in our clinical analyses, oropharyngeal adverse events were reported in over 25% of patients treated with Kynmobi in the maintenance phase of the single randomized, blinded pivotal trial compared to 4% of patients on placebo. Oropharyngeal adverse events were also commonly observed in the on-going open-label long term study. These adverse events were a common reason for discontinuation in both studies. The relationship of these oropharyngeal adverse events to systematic hypersensitivity was also unclear.

Content of the Complete Response
The applicant was advised to provide a comprehensive discussion and summary of oropharyngeal adverse events with Kynmobi, to include an expert review from a qualified dermatologist and a reexamination of the safety database. Of particular interest was analysis of the possible association between oropharyngeal adverse events and systemic hypersensitivity, if any.

The CR letter also cited the other concerns that had been identified and communicated to the applicant during the review period:

- The human factors (HF) validation study conducted for the product did not evaluate the final intend-to-market packaging and did not provide enough evidence to demonstrate that the proposed product could be used safely. The study identified several use errors and close calls that occurred on critical tasks. A follow-up study was needed.

- Study CTH-203, a clinical pharmacology study necessary to support the scientific bridge between Kynmobi and the listed drug relied upon (Apokyn) in the 505(b)(2) application, required completion. This study includes data and information supporting a bridge between Kynmobi and Apo-go and between Apokyn and Apo-go.

1.3. Summary of the Previous Conclusion on Effectiveness

Reviewer's note: The following is the conclusion on the substantial evidence of effectiveness provided in the NDA first cycle clinical review. The study was judged by the reviewer to be of sufficient robustness and quality to support a claim of effectiveness for the treatment of "off" episodes in patients with Parkinson's disease. No additional evidence in support of effectiveness was submitted in the CR and clinical effectiveness is not considered further in this review.

Study CTH-300 (mITT n=109) evaluated APL-130277 compared to placebo in a 12-week blinded, randomized trial in which treatment was titrated to best clinical effect in producing the "on" motor state 30 minutes after administration as quantified by a reduction in the Part III motor score of the Unified Parkinson's Disease Rating Scale (UPDRS). This primary outcome

assessment was performed following drug administration at the week 12 clinic visit. The patient's own assessment of the "on" state was the basis of the key secondary outcome measure, the percentage of subjects with a subject-rated full "on" response within 30 minutes post-dose at the week 12 visit at the end of the maintenance treatment period.

Despite considerable dropout by the week 12 evaluation visit, APL-130277 was significantly superior to placebo in producing a reduction in the UPDRS motor score commensurate with an "on" state 30 minutes after administration. In the modified ITT population, the least squares mean Part III score was reduced by 11.1 points versus a mean 3.5-point reduction in the placebo arm (LS mean difference -7.6 [95% CI -11.5, -3.7]; p=0.0002). This was corroborated by prespecified sensitivity analyses of the primary endpoint. A statistically significant difference was seen in favor of APL-130277 versus placebo in the percentage of patients achieving a self-rated full "on" response within 30 minutes at the week 12 evaluation visit (41.2% vs 19.6%; adjusted odds ratio: 2.81 [95% CI: 1.04, 7.64]; p = 0.0426).

1.4. Summary of the Evaluation of Clinical Safety

As analyzed in the clinical review of the original NDA submission, the safety profile of treatment emergent adverse events resulting from apomorphine's mechanism of action during the clinical use of APL-130277 in advanced PD is consistent with that of the Reference Listed Drug. However, oropharyngeal adverse events and hypersensitivity reactions were commonly observed in addition and these were the focus of this CR submission.

The oropharyngeal and hypersensitivity adverse drug reactions were analyzed for the Phase 3 safety population (Pool C); 556 patients entered the titration phase of Kynmobi treatment and 408 entered a maintenance phase of study. A portion of the Phase 3 safety population consisted of patients who participated in the pivotal trial, Study 300, in which 139 patients were titrated to an effective and tolerable dose of open-label Kynmobi. Of those who went on to blinded maintenance treatment, 54 were subsequently assigned by random to the active arm of the double-blind portion of the study and 55 were assigned to placebo.

In the Pool C safety population, 82 patients had at least 6 months of treatment. Most received 15, 20, or 25 mgs as their highest single-dose level. Only 7 patients received 30 mg and 6 received 35 mg. (By design, the 35 mg patients had successfully tolerated the 30 mg dose level.) In Pool C, 64 patients had had 12 months or more of exposure but, again, only 8 had had exposure of 30 and 35 mg dose levels, respectively. The number of times these dose-levels were taken daily was determined by diary and this revealed that the 30 and 35 mg doses were not taken more than twice daily at 12 months. This lack of exposure experience at the 35 mg dose level suggests that limiting the dose range to 30 mg is prudent.

Oropharyngeal and hypersensitivity AEs were studied in the titration and maintenance phases of treatment in both randomized placebo-controlled and cumulative safety population. In the

blinded Study 300, 20% of patients had an oropharyngeal TEAE during titration and 35% had such an event during maintenance therapy up to 12 weeks in duration. This was corroborated in the cumulative safety population where, over a longer period of observation, 37 percent had any oropharyngeal TEAE during maintenance treatment.

Hypersensitivity reactions when defined by the Preferred Term "Hypersensitivity" were much less common: none occurred during titration periods in either Study 300 or Study 301. During maintenance treatment, this PT occurred in 7 % of patients receiving active drug in Study 300 but only 1% of patients in the cumulative safety population. Using the hypersensitivity cluster of PTs supplied by the applicant revealed more occurrences: 13% in Study 300 and 8.6% in the cumulative safety population. While angioedema was not uncommon (some oedema or swelling of body regions occurred in 15% of patients in Pool C), cases of anaphylactic drug reactions did not occur.

The ability of the patient to effectively open the drug packaging intended for market and to successfully self-administer APL-130277 is supported by the Human Factors studies submitted for review.

1.5. Risk – Benefit Assessment

The clinical efficacy of apomorphine sublingual thin film has been demonstrated and a reasonable safety profile has been established. While the events attributed to hypersensitivity were generally mild and resolved quickly on drug cessation, there were several instances of a more severe reaction requiring a more targeted medical intervention. When oropharyngeal or hypersensitivity reactions occurred, there was a strong likelihood that the patient would discontinue treatment.

The injectable form of apomorphine is available to PD patients (b) (4) but it is clearly a less convenient dosage form. The sublingual route is advantageous but unpleasant for a considerable number of users; use comes with the liability of drug-related oropharyngeal irritation and inflammation and hypersensitivity reactions. However, now that the frequency and severity of these TEAEs specific to apomorphine sublingual thin film are better defined, it may be adequately labeled in the Prescribing Information and the patient and their healthcare provider are able to make an informed decision about the risk and benefits of this treatment in relation to other available anti-PD treatments.

2. Therapeutic Context

The information on the therapeutic context, analysis of the condition, and analysis of available treatment options usually provided by this section can be found first cycle clinical review of the NDA submission.

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

This product is currently not marketed. Regulatory interactions leading up to the initial NDA submission are noted in the first cycle primary clinical review.

3.2. Summary of Presubmission/Submission Regulatory Activity

Following issuance of the Complete Response letter (CRL) on January 29, 2019, the applicant requested a Type A post-action meeting to discuss the CRL and reach agreement about the content of the re-submission. This meeting was held on April 2, 2019.

Discussion centered on three areas: Human Factors deficiencies, the scientific bridge to justify reliance on FDA's finding of safety for the RLD in this 505(b)(2) application, and the presentation of data to support a finding of clinical safety for Kynmobi.

The first two issues are discussed briefly in Section 4 below. Further information may be found in the reviews provided by the related disciplines.

With regard to clinical safety, the applicant proposed a list of clusters derived from the PTs in which to provide a framework for AE analysis. The proposed clusters were:

Oropharyngeal edema
Oropharyngeal inflammation / erythema
Oropharyngeal discoloration
Oropharyngeal infections
Oropharyngeal mass / neoplasm
Oropharyngeal numbness / changes in sensation
Oropharyngeal pain
Oropharyngeal ulcerations
Alterations in taste
Salivary complaints and oral dryness
Dental complaints
Trauma
Systemic hypersensitivity
Other

The Division responded that the list approximated the information that the Division was interested in and that the general aim should be the elimination of excessive granularity in the categorization of adverse event. The applicant was advised to add "anaphylaxis" and "angioedema" to the Systemic Hypersensitivity cluster.

The applicant was asked to present the data for all placebo-controlled, multiple-dose studies in patients with PD and all open-label studies in patients with PD in separate tables. The results are to be presented in a table for patients included in the original NDA plus the 120-Day Safety Update (column 1), a column with new adverse events since the 120-Day Update (column 2) and the new grand total of adverse events (column 3). The safety database and its analysis were to be complete at the time of the resubmission. The resubmission was to include all patients exposed to APL-130277 up to a cut-off date appropriate to the time of resubmission.

The Division noted that patients may additionally have adverse events consistent with hypersensitivity, including angioedema and symptoms of anaphylaxis. It was considered important to present the time course of oral adverse events and hypersensitivity and the relationship to duration of exposure and dose. It was emphasized that the applicant should use data from studies involving patients treated with repeated doses of APL-130277 to calculate the frequency of occurrence of adverse events.

The applicant was encouraged to provide expert opinion (dental, allergy/immunology) to assess the relationship of the oropharyngeal adverse events to events suggesting systemic hypersensitivity.

The extent of the intermittent use of Kynmobi was unclear in the initial submission and the applicant was asked to provide clarity in understanding the use of Kynmobi in the safety population, specifically what doses were taken, how frequently, and for how long. An assessment of the quality of the data supporting the exposure calculation was also requested.

It was communicated that the Division's aim is to understand the extent of safety information to support the use of the higher daily doses of APL-130277. To this end, the applicant was asked to submit the most accurate assessment of the actual daily use of APL-130277 at each dose level. It was noted that "PRN" does not offer useable information in this regard. The applicant was directed to discuss how exposure data was treated in the situation where patients returned diaries completed erroneously, where diaries are missing, or where the count of returned medication does not substantiate the assigned dose or the use reported by the patient.

The Division also emphasized that all datasets should conform to SDTM and ADaM standards, so that analytic review tools can function correctly.

3.3. Foreign Regulatory Actions and Marketing History

Not applicable.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Human Factors

Division of Medication Error Prevention and Analysis (DMEPA), in the Office of Medication Error Prevention and Risk Management (OMEPRM) evaluated the human factors validation study and labels and labeling for vulnerabilities that may lead to medication error.

Reviewer's note: I did not review this study and I rely upon the expertise of and review by my colleagues in the Office of Surveillance and Epidemiology (OSE), Division of Medication Error Prevention and Analysis (DMEPA) for the opinion in this section.

The applicant proposes the product be supplied in 30-count cartons and as a titration kit for patient and caregiver use which will contain a total of (b) (4) individually packaged films of: (b) (4) 10 mg films, (b) (4) 15 mg films, (b) (4) 20 mg films, (b) (4) 25 mg films, and (b) (4) 30 mg films. Both packaging configurations will include child-resistant cartons (b) (4) packaging).

Two HF validation studies were submitted as part of this CR. In the first study, the applicant provided the regular Instructions for Use (IFU) in the carton and an IFU specific to opening the child-resistant (CR) packaging was available on the study table. Following the completion of this first HF validation study, the applicant reorganized, changed, and combined the content of the 2 IFUs, based upon participant performance and root cause analysis. The goal of the second was to validate the user interface changes implemented following the first study.

From the DMEPA review:

> "The human factors (HF) validation study results identified use errors, close calls, and use difficulties with critical and non-critical tasks. We acknowledge the residual risk of user difficulty opening the child-resistant (CR) packaging. We note the intended users of the proposed product may experience dexterity impairments. We also note that subjective feedback in the HF validation studies indicated user difficulty opening the CR packaging due to dexterity impairments. However, we find that the Applicant has addressed the residual risk to the extent feasible with user interface improvements and by noting that users may seek alternative means to open the packaging, including utilizing caregiver assistance. We also acknowledge that the majority of the HF validation studies' participants correctly indicated how to store the product (i.e. away from children). As such, we find the residual risk of user difficulty opening the CR packaging acceptable."

Additional recommendations are made to the applicant to improve prominence, clarity, and understanding of important information in the IFU.

4.2. Clinical Pharmacology

The Office of Clinical Pharmacology (OCP) has reviewed the information submitted in the NDA and recommends approval. The OCP review notes that the sublingual route of administration for APL130277 has lower bioavailability compared to subcutaneous injection of the Reference Listed Drug. The bioavailability for APL-130277 relative to APOKYN is about 17% for AUC_{∞} and 12% for C_{max}. The dose range recommended for approval for APL-130277 is 10 to 30 mg, while APOKYN's approved dose range is 2-6 mg. Based on Study CTH-203, the exposures of apomorphine from the recommended highest dose of APL-130277 (30 mg) are lower for APL-130277 compared to the maximum dose of APOKYN.

Study CTH-203 was a relative bioavailability study conducted to assess the comparative PK of apomorphine from APL-130277, APOKYN (relied-upon listed drug), and APO-go (European product) in a 3-way crossover design. Based on this study, the predicted exposures of apomorphine (AUC) from the highest dose of APL-130277 are comparable to the exposures of apomorphine from the highest dose of subcutaneous APOKYN. Therefore, the clinical pharmacology 505(b)(2) assessment found it acceptable for the applicant to rely on FDA's finding of non-clinical safety and clinical pharmacology for APOKYN.

OCP also recommends a postmarketing requirement for the applicant to submit *in vitro* studies that evaluate the DDI potential for the major metabolite norapomorphine glucuronide, as listed in the original clinical pharmacology review for NDA 210875.

5. Sources of Clinical Data and Review Strategy

5.1. Relevant Clinical Studies

A total of 13 clinical studies have been completed in the APL-130277 clinical development program. This updated review of safety is limited to both the new and cumulative safety data with the cut-off date of May 10, 2019. In the main, the Phase 3 safety data comes from two studies:

- Study CTH-300 - Phase 3 randomized controlled efficacy and safety study
- Study CTH-301 - Long-term safety study

While the previously submitted safety data has been re-analyzed by the applicant, this CR also submits new data on 105 patients added in the ongoing Study 301 since the cutoff date for the first cycle (May 10, 2018) as well as additional adverse event data from those previously enrolled patients continuing through the interval between applications.

Table 1 Relevant studies (source: Module 2.7.6 Synopses of Individual Studies)

Study No.; Phase; Country	Objective(s) of Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Dosed Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
CTH-300 Phase 3 North America and Europe	Evaluate the efficacy and safety of APL versus placebo in PD patients over a 12-week period	Randomized, double-blind, placebo-controlled, parallel-group	**Products:** Titration with APL (10, 15, 20, 25, 30, and 35 mg, as tolerated) **Regimen:** 12-week maintenance phase, randomized to the effective dose of APL or matching placebo **Route:** Sublingual	141 enrolled / 109 randomized	Subjects with PD and "OFF" episodes	Approximately 135 days	Completed and reported Full Study Report
CTH-301 Phase 3 North America and Europe	Evaluate the long-term safety, tolerability, and efficacy of APL in PD patients	Open-label	**Products:** APL 10, 15, 20, 25, 30, and 35 mg **Regimen:** APL – starting dose of 10 mg and titrated upwards **Route:** Sublingual	As of the cutoff date (10 May 2019), 499 screened (86 rollover and 413 *de novo*) 427 enrolled in titration phase (78 rollover and 349 *de novo*) 345 enrolled in long-term safety phase (70 rollover and 275 *de novo*)	Subjects with PD and "OFF" episodes	Subjects may participate in the study until the Sponsor terminates the study, or until commercial availability of APL in the subject's country	Ongoing; Interim Study Report

5.2. Review Strategy

In accordance with FDA advice, the applicant analyzed the data from Studies 300 and 301 to compare the originally submitted data (Pool A or Pool 1), the data from the period between the original cutoff date and the cut-off date for this submission (Pool B or Pool 2), and the full set of cumulative data in Pool A + Pool B (Pool C or Pool 3).

Reviewer's note: While the applicant's documents used Pool letters and numbers interchangeably in their submission documents, in my review I use the lettered version exclusively which is consistent with its use in the ISS datasets.

Table 2 Data sources and analysis pools (source: SCS, Table 1, p 13)

	Data Source	Analysis conducted	Pool
A	Original 120-day Safety Update (data cutoff 10 May 2018)	Oropharyngeal Adverse Event Cluster Analysis	Analysis Pool 1 (CTH-300) CTH-300/CTH-301 Analysis Pool
B	New data newly reported between original 120-day Safety Update (10 May 2018) and new data cutoff (10 May 2019)	Selected outputs from original 120-day Safety Update and selected oral clusters analysis outputs	Analysis Pool 3 for re-run of original 120-day Safety Update. All other analyses (eg, oral clusters) on CTH-300/CTH-301 Analysis Pool
C	Cumulative data to next data cutoff date for response to the complete response letter Safety Update (10 May 2019)	Re-run original 120-day Safety Update outputs and new analysis including Oropharyngeal Adverse Event Cluster Analysis	Analysis Pool 3 for re-run of original 120-day Safety Update. All other analyses (eg, oral clusters) on CTH-300/CTH-301 Analysis Pool

Pool C, the cumulative data pool, is the major focus of this review:

- The blinded and controlled safety data in Pool A derived from completed Study 300 was reviewed in the first cycle and contains no new data, but it was reanalyzed in this review, and results are segregated by the titration and maintenance phases.

- The open-label data from Study 301 was inspected to see if the new open-label AE occurrences (Pool B) differ from the original open-label data in any way

- If review of the newly submitted data in Pool B reveals no new insight for any topic or category, that will be briefly outlined. In that case, the reader is referred to the pertinent discussion in the review of the original NDA submission. The aim of the review of Pool B data is to ascertain that it is consistent with the first cycle review of safety and that no new, novel, or unexpected events occurred.

- The major findings of safety from the first cycle review are summarized in places but not repeated unless directly relevant to the applicant's response to the CRL.

The primary focus of this review is to consider the method and results of analysis of adverse events using the clusters of oropharyngeal events Preferred Terms in the ISS ADAE dataset. In this regard, the clinical review team has relied upon the assistance provided in consultation by the Division of Dermatology and Dentistry, ODE III, CDER, and their contribution is referenced below.

6. Review of Relevant Individual Trials Used to Support Efficacy

Not applicable to this review

7. Integrated Review of Effectiveness

Not applicable to this review.

8. Review of Safety

8.1. Safety Review Approach

Newly occurring individual events that were significant, serious, or led to drug discontinuation are considered individually as in the original review.

The major focus of the review is the re-analysis of clusters of related events occurring in the oropharyngeal region and understanding their relationship to potential hypersensitivity. The discussion of this analysis may be found below in **Section 8.5 Analysis of Submission-Specific Safety Issues.**

8.2. Review of the Safety Database

8.2.1. Overall Exposure

The applicant's analysis of exposure is not exact. The exposure for this intermittently used treatment is derived from a count of returned medication and patient-reported diaries of use. The adequacy of this method is discussed below.

Safety Population
The complete cumulative safety data for Pool C consists of the following patients:

Table 3 Cumulative safety population in Pool C (source: SCS, Table 2, p 14)

	Titration	Maintenance/Treatment
Study	APL-130277 n	APL-130277 n
CTH-105	17	NA
CTH-105 + CTH-300	2	NA
CTH-201	31	25
CTH-201 + CTH-301	16	15
CTH-300	81	38
CTH-300 + CTH-301	57	16
CTH-300 + CTH-301 + CTH-201	1	0
CTH-301	351	314
Overall	556	408

Abbreviation: NA = not applicable.

Reviewer's note: *The **Study** column represents the study (or studies) source for each Safety Population patient by phase (Titration, Maintenance/Treatment) of participation. Subjects may be counted in more than one row based on the phase of their participation in a study. Study 105 is a Phase II study with 19 patients treated for up to 28 days and Study 201 is the Thorough QT study with 48 subjects treated up to 46 days. Of these 67 patients, only 15 patients (all from Study 201) entered a maintenance treatment phase.*

Exposure: Dose and Duration

The applicant's analysis of exposure is not exact. The exposure for this intermittently used treatment is derived from a count of returned medication and patient-reported diaries of use. The adequacy of this method is discussed in Section 8.2.3, below.

As noted above, 556 patients received at least one dose of APL-130277 with 408 of these patients reaching a period of maintenance treatment. As the titration phases of the studies were brief, with most (83%) titrating for 5 days or less (a median of 22 days, range 1 – 154 days), the bulk of chronic treatment safety data comes from the 408 patients who entered maintenance treatment. The table below shows the Safety Population exposure by duration. The category of *"< 3 months"* includes both titration and maintenance categories while longer durations represent maintenance treatment patients alone. These patients are represented exclusively by Studies 300 and 301, given their duration.

Table 4 Safety Population Pool C Cumulative Exposure (source: ISS Table 7.1.3 RC, Appendix 19.2, page 734)

ISS Pool C Duration of Exposure to APL-130277		
Number of Subjects Receiving at Least 1 Dose of Study Drug	n	556
Number of Subjects Receiving Drug in Titration Period Only	n	148
Number of Subjects Entering Maintenance Treatment	n	408
Exposure, Category (Months)		
< 3	n (%)	284 (51.1)
≥ 3 to < 6	n (%)	97 (17.4)
≥ 6 to < 9	n (%)	82 (14.7)
≥ 9 to < 12	n (%)	29 (5.2)
≥ 12	n (%)	64 (11.5)

However, this is an incomplete representation of APL-130277 use. APL-130277 could be taken as needed up to 5 times daily after being titrated to a dose that was both effective and tolerable for each individual patient. The titration period roughly established for each patient their useful dose, although there was alteration of this dose on occasion in the maintenance period. The amount of use for a given dose by patient was determined for the period between visits by counting the returned unused medicine and calculating a mean daily use in mg over that visit interval.

As noted in the first cycle review, the estimation of daily dosing was problematic. (The reader is directed to pages 80 -82 in that document for a discussion of missing data.) In brief:

Diaries:

For the two diary days prior to each maintenance period visit, patients were instructed to document the dosing time and ON/OFF status 30 minutes after dosing for up to 5 doses per day. If no dosing took place during one or two diary days, the participant was to document the lack of dosing in the diary. Sites were to review the dosing diary returned by the subjects and note in the CRF if the diary was not completed correctly.

In Study CTH-300, there were 133 Home Dosing Diaries dispensed and 114 diaries returned. Of these 114 diaries, 102 were entered as per protocol with 90 reported any dosing information. The percentage of diaries reporting any dosing information compared to diaries returned without dosing information decreased over visits. It is not clear whether the lack of dosage information is an omission or that the patient took no APL-130277 in the two days before the visit. (An FDA site inspection revealed that at one of the two sites audited, diaries were filled out incorrectly and did not reflect study medication use.)

In Study 301, the applicant evaluated the Long-Term Visit diaries for Visits 3 and 4 at 12 and 24 weeks, respectively. Over these two visits, which virtually all participants should have completed, there were 296 diaries dispensed and 205 returned (69%). 189 of these 205 diaries were entered as per protocol and 165 reported any dosing information. This represents that roughly 2/3 were filed out correctly and that 56% had information relevant to dosing.

Return of Study Medicine

The applicant reported that in the completed Study CTH-300, there were 136 records (CRF accountability forms) of dispensing and 133 records of return reported. Of the 133 records returned, 54 records had a discrepancy (missing or discrepancy 57/136 = 42%).

Similarly, in ongoing Study CTH-301, there were 527 records of dispensing from the first two maintenance treatment visits. Of these, 53 counts of returned medication were not reported and 193 of the 474 returned medication records had a discrepancy between the dispensed medication, what was reportedly taken, and what was returned (47%).

Additional factors to consider are how much drug might have been wasted due to difficulty opening the pouches, breaking or dropping the film, or the need to use of a new pouch for any reason. These issues were to be addressed in a new Human Factors study performed for this CR.

For this review, a request was made of the applicant to provide more detailed documentation of this calculation. They report that for the combined study population of Study 300 and 301, 357 had drug accountability data and 281 had diary data, and from this the dose and duration of use was imputed. (These 2 studies were the only longer-term multiple dose studies for which drug accountability and diary data were available.) They then used this as the basis for their calculations of dose, number of doses taken per day and AE rates. However, these numbers are opaque as the rate of diary completion was low and got lower as Study 301 (where data from patients with durations longer than 3 months were obtained) went on. In addition, though returned, some diaries omitted dosing information:

Table 5 Study 301 diary compliance by visit (source: compiled from ISS Appendix 19.2 Table 7.32_RC)

Long-term Study 301 visit	Study Week for Diary Return	Study Month for Diary Return	N diaries dispensed	N diaries returned	% returned	Dosing reported in diary
LTSV1 - LTSV3*	12	3	320	242	76%	229
LTSV1 - LTSV2*	4	1	198	154	78%	141
LTSV2 - LTSV3*	12	3	287	200	70%	182
LTSV3 - LTSV4	24	6	218	141	65%	125

LTSV4 - LTSV5	36	9	70	43	61%	35
LTSV5 - LTSV6	48	12	45	29	64%	25
LTSV6 - LTSV7	72	16	31	14	45%	13
LTSV7 - LTSV8	80	20	42	27	64%	25
LTSV8 - LTSV9	96	24	33	21	64%	21
LTSV9 - LTSV10	112	28	22	17	77%	16
LTSV10 - LTSV11	128	32	18	6	33%	5
LTSV11 - LTSV12	144	36	7	1	14%	2
Overall			325	263	81%	238
* Diary dispensing by visit was altered by protocol amendment after the start of the study						

From this, it is evident that there was no improvement in the conduct of the study with regard to insuring diary compliance in the interval between the original submission and this CR response. While roughly two-thirds of diaries were returned, only 57% at 6 months and 56% at one year of the dispensed diaries had dosing information included on their return. The applicant's calculation of the dose level (10 to 35 mg) and the number of times daily that a given dose was taken is also adversely affected by the lack of diary information.

An updated assessment of drug accountability was not addressed in the CR response, though the applicant performed calculations of dose-relatedness of adverse events. In the initial submission, dosing was presented as total mg/d based upon an estimation of dose in mg and average numbers of times daily that a dose might have been taken as imputed from diaries and visit dispensing. As recounted above, missing or discrepant data made this calculation unreliable in the original submission.

Using available accountability data by the highest dose a patient received in the study's maintenance phase, the applicant derived individual tables of extent of exposure by dose level.

Table 6 Studies 300 and 301 duration of exposure by highest dose level recorded during maintenance (source: derived from ISS Appendix 19.2, Table 7.24_RC)

APL-130277 Dose	< 3 months	3 to < 6 months	6 to < 9 months	9 to < 12 months	≥ 12 months	Total N
10 mg	33	16	5	6	9	69
15 mg	29	24	23	6	14	96
20 mg	22	17	21	5	17	82
25 mg	16	15	20	7	8	66
30 mg	9	12	7	2	8	38
35 mg	4	11	6	3	8	32

Total	113	95	82	29	64	383

Based upon the actual dose prescribed and dispensed in clinic and removing gaps between the end of Study 300 and 301, the applicant estimates the following duration of exposure by dose based upon the dose that was dispensed at a clinic visit, and not based on an estimate of what was taken from a counting of returned medication. (This is reported for only 302 of 408 Pool C patients (74%) who entered the maintenance phase.)

Reviewer's Note: The duration of the treatment gap between the last dose received in Study 300 and the first dose received in Study 301 was 16 days on average (range 25 to 117 days). In addition, initial enrollment in Study 301 was often followed by a gap before entering maintenance treatment, 29 days on average.

Table 7 Studies 300 and 301 duration of continuous exposure by dose level based upon dispensing at the prior visit (source: applicant Table S007-2A via Information Request)

	Actual maintenance dose of APL-130277 Dispensed in Clinic						
Dose Administered	10 mg	15 mg	20 mg	25 mg	30 mg	35 mg	Total (N= 302)
N continuing ≥ 90 days	29	51	51	38	19	16	204
N continuing ≥ 180 days	17	15	20	12	11	6	81
N continuing ≥ 365 days	3	3	4	3	2	2	17

A similar calculation was performed for the overall number of doses per day by dose level. This could not be calculated for all subjects because of missing data. It is imputed using the highest dose given to the patient during the maintenance period and averaged over the duration of days between visits and the count of returned medication.

Table 8 Studies 300 and 301 patients by average number of doses per day by highest dose level recorded during maintenance (source: derived from ISS Appendix 19.2, Table 7.25_RC)

Imputed average number of daily doses taken over the study period for highest dose administered							
APL-130277 Dose level	0 to <1	1 to <2	2 to <3	3 to <4	4 to <5	≥5	Total N
10 mg	36	20	5	2	1	0	64
15 mg	44	23	10	4	2	0	83
20 mg	37	27	8	3	2	0	77
25 mg	26	24	6	6	2	1	65
30 mg	16	14	4	3	0	0	37
35 mg	18	7	4	1	1	0	31
Total	177	115	37	19	8	1	357

Reviewer's Comment:
Across these tables, the differences in numbers of patients found in each cell by dose and duration of exposure reflect the presence of missing data, considering the gap between Study 300 and Study 301 for some patients, and whether the calculation used information on what was dispensed or what was returned, especially for the higher prescribed doses. What these calculations do not provide is the duration of use for a given dose level by the average number of uses per day over the treatment period. For example, for the 6 patients recorded as having taken 35 mg dose for six months in Table 7, how many doses did they take a day on average? Using Table 8, it is conceivable (and unknowable) that all averaged less than once a day, or that 4 of them took it 2 to 3 times daily. It is worth emphasizing that the available information points to very little use of the higher doses. This uncertainty in dose and exposure adversely affects our understanding of the relationship of dose to the development of adverse drug reactions, especially at the highest doses.

8.2.2. Relevant characteristics of the safety population:

This CR submission added 105 patients in open-label Study 301 to the Safety Population. As clinical sites continued enrollment, the newly added patients were virtually identical to those previously enrolled. As a result, the demographic characteristics of the Pool C safety population are unchanged from the initial review (i.e., no demographic or baseline measure moved more than 1% overall).

Table 9 Pool C cumulative safety population demographic characteristics (source: ISS, Table 11, partial, p 53)

	Statistics	APL-130277 N = 556
Age (years)[a]	n	556
	Mean (SD)	64.18 (8.895)
	Median	64.00
	Min, Max	38.0, 88.1
Age[a]		
< 65 years	n (%)	280 (50.4)
≥ 65 years	n (%)	276 (49.6)
Gender		
Male	n (%)	360 (64.7)
Female	n (%)	196 (35.3)
Ethnicity		
Hispanic or Latino	n (%)	55 (9.9)
Not Hispanic or Latino	n (%)	501 (90.1)
Race		
American Indian or Alaska Native	n (%)	1 (0.2)
Asian	n (%)	11 (2.0)
Black or African American	n (%)	14 (2.5)
Native Hawaiian or Other Pacific Islander	n (%)	1 (0.2)
White	n (%)	528 (95.0)
Other	n (%)	1 (0.2)

8.2.3. Adequacy of the safety database:

The requirement for the safety analysis was discussed with the applicant prior to CR submission. The submitted information fulfilled the request in a format that allowed review to proceed. The PD population studied is representative of the population in whom use is intended. The distribution of administered doses reflects the likely range of doses to be used in the intended PD population but, as noted in Section 8.2.1 above, the adequacy of support for the 35 mg dose is lacking.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

This submission was limited in scope with data from a previously implemented and on-going study. No new regulatory inspections were performed. The review of data in this submission has not raised any concern about its integrity.

8.3.2. Categorization of Adverse Events

The re-categorization and re-analysis of adverse event data was the focus of this CR response.

As the individual studies used different MedDRA versions, all AEs in the integrated database were re-coded by the applicant to a single MedDRA version 19.1 PT.

8.3.3. Routine Clinical Tests

No clinical laboratory tests were specifically performed to investigate a specific potential adverse event. Routine clinical laboratory tests and electrocardiography were performed at each Study 301 visit. These included tests of hematology, chemistry, urinalysis, and vital signs in lying and standing position.

8.4. Safety Results

8.4.1. Deaths

There were three deaths noted in the initial review of the development program. In the period between the May 10, 2018 and May 10, 2019 data cutoffs, four additional deaths occurred: None of the deaths appear plausibly related to drug.

(b) (6), a 79-year-old patient who was titrated to 15 mg APL-130277 and entered the maintenance/treatment phase of Study 301, experienced SAEs of pneumonia on Day 204 and cardio-pulmonary arrest on Day 231 resulting in death.

(b) (6), a 75-year-old patient who was titrated to 30 mg APL-130277 and entered the maintenance/treatment phase of Study 301, experienced an SAE of cardiac arrest on Day 123 that resulted in death.

The following were reported as events after the May 2019 data cut-off:

(b) (6), a 61-year-old patient, experienced an SAE of fall (“fall next to a pool”) resulting in death, 1 month and 6 days after the start of study medication.

(b) (6), a 75-year-old patient, developed aspiration pneumonia approximately 4 months after start of APL-130277 and died as a result.

8.4.2. Serious Adverse Events

In Pool B, 40 new SAEs were reported in 21 patients:

Subject Identifier	Sex	Age	Preferred Term	Study Day AE Began	AE Duration	Severity	Assigned Dose	Daily Frequency	Treatment	Outcome
(b) (6)	M	72	Acute myocardial infarction	653	4	Moderate	35	3	Unchanged	Recovered
	M	72	Subarachnoid haematoma	637	19	Moderate	35	3	Unchanged	Recovered
	M	72	Craniocerebral injury	637	32	Severe	35	3	Unchanged	Recovered
	M	72	**Fall**	637	17	Severe	35	3	Unchanged	Recovered
	M	72	Streptococcal sepsis	639	15	Severe	35	3	Unchanged	Recovered
	F	54	COPD	208	7	Moderate	25		Unchanged	Recovered
	F	67	Angina unstable	449	2	Mild	10	0	Unchanged	Recovered
	F	67	Chest pain	449	2	Mild	10	0	Unchanged	Recovered
	F	67	Chest pain	449	2	Mild	10	0	Unchanged	Recovered
	M	57	Myelopathy	572	45	Severe			Unchanged	Recovered
	M	70	**Mental status changes**	103	2	Moderate	25	0.5	Unchanged	Recovered
	M	58	**Psychotic disorder**	410	74	Severe	30	3.5	Withdrawn	Recovered
	M	62	Non-Hodgkin's lymphoma	877		Moderate	20	4	Unchanged	Not resolved
	M	62	Prostate cancer stage II	347	61	Severe	15	2.5	Unchanged	Recovered
	M	78	Cerebrovascular accident	198	2	Severe	15	2	Unchanged	Recovered
	M	79	Pneumonia	324	28	Severe	15	2	Interrupted	Death
	M	79	Cardio-respiratory arrest	351	1	Severe	15	2	Withdrawn	Death
	M	76	Hypoaesthesia	48	25	Mild	20	3	Unchanged	Recovered
	M	76	Atrial fibrillation	71	3	Moderate	20	3	Unchanged	Recovered
	M	76	Facial paresis	58	15	Moderate	20	3	Unchanged	Recovered
	M	52	Myocardial infarction	253	2	Severe	25	2.5	Unchanged	Recovered
	M	49	Acute myocardial infarction	744	1	Severe	35	1	Unchanged	Recovered

(b) (6)										
	M	75	Carbon dioxide increased	123		Moderate	30	0.5	Withdrawn	Not resolved
	M	75	Cardiac arrest	123	10	Severe	30	0.5	Withdrawn	Death
	M	75	Pneumonia aspiration	118		Severe	30	0.5	Withdrawn	Not resolved
	M	66	Basal cell carcinoma	92	36	Severe	20	2	Unchanged	Recovered
	M	66	Squamous cell carcinoma	92	5	Severe	20	2	Unchanged	Recovered
	M	66	Squamous cell carcinoma	92	5	Severe	20	2	Unchanged	Recovered
	M	73	Arthropathy	231	3	Moderate	20	4	Unchanged	Recovered
	M	73	Lumbar spinal stenosis	231	3	Moderate	20	4	Unchanged	Recovered
	M	70	Depression	125		Severe	15	2	Withdrawn	Not resolved
	M	70	Hepatitis toxic	117	9	Severe	15	2	Withdrawn	Recovered
	F	77	Fractured sacrum	506	3	Moderate	25	0	Unchanged	Recovered
	F	71	Intestinal obstruction	121	5	Moderate	30	4	Unchanged	Recovered
	F	71	**Dopamine dysregulation syndrome**	325	5	Moderate			Unchanged	Recovered
	F	72	Sternal fracture	30	61	Moderate			Unchanged	Recovered
	M	69	Duodenitis	41	3	Moderate	10		Unchanged	Recovered
	M	69	Obstructive uropathy	37	5	Moderate	10		Unchanged	Recovered
	M	55	Back pain	115		Severe	20	1	Unchanged	Not resolved
	M	55	Neuropathy peripheral	83	6	Severe	20	1	Unchanged	Recovered

The SAEs potentially attributable to treatment in some way are those in bold above. Given the polypharmacy for PD that patients are being treated with, it is difficult to hold Kynmobi fully responsible though it may have contributed in some way to behavioral adverse events, like any increase in dopaminergic treatment in this uniquely vulnerable population. In patient (b) (6) (PT hepatitis toxic), the abnormal liver functions began on Day 117 of Kynmobi treatment and was temporally related to the initiation of olanzapine and fluoxetine in combination for exacerbation of depression. The laboratory tests returned to normal with cessation of the antidepressant medications.

No novel or unexpected events occurred in this interval period.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

The source of the following is from analysis of ISS ADaM datasets ADSL and ADEX.

At the time of submission of the CR, 37 Pool B patients had successfully completed Study 301, 103 were ongoing and 77 had discontinued. Five of these discontinuations were attributed to significant and/or serious adverse events (see sections 8.4.2 and 8.4.4). A tabulation of all Pool B discontinuations is below:

Table 10 Pool B (May 2018 -May 2019) Reasons for discontinuation of APL-130277 (source: ADSL and ADAE datasets)

Reason for Discontinuation	N	%
ADVERSE EVENT	39	51%
LACK OF EFFICACY	9	12%
OTHER	5	6%
PROTOCOL VIOLATION	1	1%
WITHDRAWAL BY SUBJECT	23	30%
Total	77	100%

These categories were further inspected and generally were accurately applied to the participants. However, 7 of the 23 participants listed as “Withdrawal by Subject” had given as a reason that they did not like the medication effects, though no specific AE was reported.

For the 39 patients leaving the study for an adverse event, 57 events are listed by the study period in which they occurred.

Titration period AEs leading to discontinuation. Given the very brief exposure for most patients no dose was noted in the AE dataset.

Table 11 Pool B Adverse Events in Titration Phase leading to discontinuation of treatment (source: ADSL and ADAE datasets)

Subject Identifier	Sex	Age	Preferred Term	Severity	SAE	Study Day AE Began	AE Duration (Days)
(b) (6)	F	56	Nausea	Moderate	N	1	1
	M	64	Nausea	Moderate	N	1	2
	F	61	Electrocardiogram ST segment depression	Mild	N	3	4
	F	61	Electrocardiogram T wave abnormal	Mild	N	3	4
	F	61	Myocardial infarction	Mild	N	3	5
	F	58	Feeling abnormal	Severe	N	40	1
	M	60	Depressed level of consciousness	Mild	N	1	1
	M	60	Presyncope	Moderate	N	1	1
	M	73	Hypotension	Moderate	N	8	1
	M	73	Syncope	Moderate	N	8	1
	M	73	Arrhythmia	Mild	N	2	
	M	73	Tachycardia	Mild	N	2	

Maintenance period AEs leading to discontinuation: It is evident that oropharyngeal adverse events led to the bulk of the discontinuations and supports the notion that it likely takes chronic use for this group of AEs to manifest themselves.

Table 12 Pool B Adverse Events in Maintenance Phase leading to discontinuation of treatment (source: ADSL and ADAE datasets)

Subject Identifier	Sex	Age	Preferred Term	Assigned Dose	Mean Doses per Day	Severity	SAE	Study Day AE Began	AE Duration
(b) (6)	M	67	Oral candidiasis	25	2.5	Mild	N	552	
	M	46	Lip swelling	30		Moderate	N	22	7
	M	46	Swollen tongue	30		Moderate	N	21	3

(b) (6)									
	F	73	Oral candidiasis	25	1	Moderate	N	195	8
	F	68	Tongue oedema	15	0.75	Moderate	N	228	23
	F	54	Pharyngitis	20	3	Moderate	N	79	
	F	54	Swollen tongue	20	3	Moderate	N	79	
	F	67	Mouth ulceration	15	2	Moderate	N	164	
	M	61	Rash	10		Moderate	N	18	19
	F	66	Lip swelling	15	1	Moderate	N	120	78
	F	66	Paraesthesia oral	15	1	Moderate	N	120	78
	F	66	Paraesthesia oral	15	1	Moderate	N	120	
	M	74	Oral mucosal erythema	20	1	Moderate	N	303	200
	M	74	Tongue ulceration	20	1	Moderate	N	303	200
	M	73	Oral candidiasis	10	4.5	Moderate	N	375	21
	M	67	Lip swelling	30	1	Mild	N	122	1
	M	63	Stomatitis	20		Mild	N	20	3
	M	66	Oral mucosal erythema	20	2	Mild	N	142	9
	M	79	Glossodynia	20	1.5	Moderate	N	108	24
	F	66	Headache	10		Moderate	N	23	
	F	62	Herpes zoster disseminated	10	2	Moderate	N	89	76
	M	75	Carbon dioxide increased	30	0.5	Moderate	Y	123	
	M	75	Cardiac arrest	30	0.5	Severe	Y	123	10
	M	75	Pneumonia aspiration	30	0.5	Severe	Y	118	
	M	75	Tongue oedema	30	0.5	Mild	N	107	
	M	63	Oral discomfort	35	1.5	Mild	N	110	
	M	63	Tongue ulceration			Mild	N	160	2
	F	57	Dyskinesia	20	0	Mild	N	104	132
	M	70	Paraesthesia oral	15	0	Mild	N	114	12
	F	72	Lip swelling	25	0.5	Mild	N	58	3

(b) (6)	F	72	Tongue ulceration	25	0.5	Mild	N	58	15
	M	76	Aphthous ulcer	20	3	Moderate	N	88	14
	F	62	Nausea	30	1.5	Mild	N	132	1
	F	62	Vomiting	30	1.5	Mild	N	132	1
	M	66	Glossodynia	25	2.5	Moderate	N	74	11
	M	66	Swollen tongue	25	2.5	Moderate	N	74	11
	M	58	Psychotic disorder	30	3.5	Severe	Y	410	74
	M	83	Hallucination	20	1.5	Mild	N	199	183
	M	74	Lip swelling	20	2	Mild	N	65	23
	M	73	Ageusia	20		Mild	N	56	8
	M	73	Oedema mouth	20		Moderate	N	56	8
	F	45	Drug hypersensitivity	10		Moderate	N	43	14
	M	62	Fatigue	25	0	Moderate	N	211	1
	M	62	Headache	25	0	Moderate	N	211	1
	M	62	Nausea	25	0	Moderate	N	211	1

8.4.4. Significant Adverse Events

There were 25 severe adverse events reported in 15 patients (excluding the SAEs rated as severe in the previous Section 8.4.2). None of these were new or not previously known.

Table 13 Pool B (May 2018 -May 2019) Significant Adverse Events (source: ADSL and ADAE datasets)

Subject Identifier	Sex	Age	Preferred Term	Study Day Began	AE Duration	Treatment	Assigned Dose	Mean Doses per Day	Outcome
(b) (6)	M	72	Subdural haemorrhage	655	14	Unchanged	35	3	Recovered
	M	72	Syncope	637	1	Unchanged	35	3	Recovered

(b) (6)									
	F	57	Dizziness	4	1	Unchanged			Recovered
	F	66	Nausea	23		Unchanged	10		Not resolved
	M	58	Musculoskeletal pain	737		Unchanged	20	2	Not resolved
	M	58	Musculoskeletal pain	382		Unchanged	20	2	Not resolved
	M	58	Neck pain	382		Unchanged	20	2	Not resolved
	F	58	Feeling abnormal	40	1	Withdrawn			Recovered
	M	66	Squamous cell carcinoma	96	1	Interrupted	20	2	Recovered
	M	66	Squamous cell carcinoma	96	1	Interrupted	20	2	Recovered
	F	67	Radicular pain	875	2	Unchanged	10	1.5	Recovered
	F	67	Syncope	161	1	Interrupted	15		Recovered
	F	77	Back pain	592	33	Unchanged	25	0	Recovered
	F	77	Dyskinesia	199	2	Unchanged	25	2	Recovered
	F	77	On and off phenomenon	159	40	Unchanged	25	2	Recovered
	F	71	Mania	71	6	Unchanged	30	4	Recovered
	F	71	Orthostatic hypotension	292	4	Unchanged	30	1.5	Recovered
	M	67	Dyskinesia	179		Unchanged	25	4	Not resolved
	M	67	Dyskinesia	137	13	Unchanged	25	4	Recovered
	M	63	Pain	466		Unchanged	15	2.5	Not resolved
	F	49	Gastroenteritis viral	6	4	Unchanged			Recovered
	M	64	Orthostatic hypotension	34	1	Unchanged	30	2	Recovered
	M	64	Orthostatic hypotension	34	1	Unchanged			Recovered
	F	67	Mouth ulceration	149	12	Interrupted	15	2	Recovered
	M	55	Pain in extremity	113	1	Unchanged	20	1	Partially recovered

Four patients had severe events due to orthostatic hypotension or syncope, troublesome manifestations of PD and its dopaminergic treatment. It is likely that the addition of apomorphine to the treatment regimen adversely contributed to these events. This is a frequent and known adverse event.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

Proposed Prescribing Information – Section 6.1 Clinical Trials Experience
The draft label Patient Information table describing the incidence of placebo-controlled treatment emergent adverse events from Study 301 is included here and used as a basis for comparison to the additional adverse event information for Pool B, the events occurring between May 2018 and May 2019.

Table 14 Proposed table of ADRs in at least 5% of patients treated with Kynmobi and greater than in placebo in the Titration or Maintenance Phases of Study 300

	Titration	Maintenance	
	TRADENAME (N=141) %	TRADENAME (N=54) %	(Placebo) N=55 %
Gastrointestinal disorders			
Nausea	21	28	4
Oral/pharyngeal soft tissue swelling[1]	1	15	0
Oral/pharyngeal soft tissue pain and paraesthesia[2]	2	11	2
Oral ulceration and stomatitis[3]	3	7	2
Oral mucosal erythema	4	7	4
Vomiting	4	7	0
Dry mouth	1	6	0
Nervous system disorders			
Somnolence	11	13	2
Dizziness	11	9	0
Headache	8	6	0
Respiratory, thoracic and mediastinal disorders			
Rhinorrhea	6	7	0
General disorders and administration site conditions			
Fatigue	3	7	0
Chills	6	4	0
Injury, poisoning and procedural complications			
Fall	4	6	2
Skin and subcutaneous tissue disorders			
Hyperhidrosis	4	6	4
Injury, poisoning and procedural complications			
Laceration	1	6	0
Immune system disorders			
Hypersensitivity[4]	0	6	0

[1] Includes lip swelling, lip edema, oropharyngeal swelling, gingival edema, edema mouth, swollen tongue, and pharyngeal edema
[2] Includes throat irritation, glossodynia, oral paresthesia, oral pain, oropharyngeal pain, gingival pain, and oral hypoesthesia
[3] Includes lip ulceration, oral mucosal blistering, cheilitis, stomatitis, and tongue ulceration
[4] Includes hypersensitivity, swelling face, oral allergy syndrome and urticaria

Less common but potentially serious adverse reactions include including hallucinations, delusions, impulse control disorder, compulsive behaviors, and decreases in blood pressure.

Adverse Events in the inter-application period from May 2018 to May 2019 (Pool B)
The source of this information is the revised cumulative ISS datasets ADSL and ADAE for those individuals (USUBJID) flagged "yes" for the variable NEWSUBFL. This segregated individuals and their data for the period starting from the date of the first cycle 120-day Safety Update through the cutoff date for this CR submission. This encompassed 105 new patients enrolled in ongoing Study 301 but also added new adverse event occurrences for another 112 individuals continuing in Study 301. These two datasets were analyzed using the MedDRA Adverse Event Diagnosis tool (MAED) to provide a head count for the number of discrete AEs reported in Pool B.

Reviewer's Note: No attempt was made to edit the file to remove the excessive granularity of oral AEs. This is addressed in the applicant's analysis of oropharyngeal events in Section 8.5 below.

There were 1163 AE events reported in these 217 patients. Of these, 350 were unique Preferred Terms but 252 of them occurred twice or less and were either obviously unrelated or a feature of PD itself. The table below is representative of the most common AEs reported and considered by the reviewer to be likely related to drug. As is evident when compared to the proposed table of ADRs in Section 6.1 of the prescribing information, this interval AE data is quite consistent with the results of placebo-controlled Study 300. For this reason, Pool B data by itself was not analyzed further.

Table 15 Pool B Adverse Events occurring May 2018 to May 2019 (source: ISS ADSL and ADAE)

Preferred Terms	Count of Events	Head Count (N)	AE Events Rated Severe
Total AEs in Pool B	1163	217	
Nausea	111	75	1
Yawning	51	29	
Somnolence	45	28	
Dizziness	39	26	1
Orthostatic hypotension	32	16	3
Oral mucosal erythema	30	16	
Dyskinesia	25	16	
Fall	21	16	1
Fatigue	21	15	
Headache	19	15	
Hyperhidrosis	18	13	
Vomiting	16	12	
Glossodynia	12	8	
Lip swelling	11	7	
Ageusia	9	7	
Contusion	9	6	
Paraesthesia oral	9	6	
Rhinorrhoea	9	6	
Stomatitis	8	5	
Dry mouth	7	5	
Dysgeusia	7	4	
Mouth ulceration	7	4	1
Oral candidiasis	7	3	
Syncope	3	3	2

8.4.6. Laboratory Findings

There is no new information or data concerning clinical laboratory.

8.4.7. Vital Signs

There is no new information or data concerning vital signs.

8.4.8. Electrocardiograms (ECGs)

There is no new information or data concerning electrocardiography.

8.5. Analysis of Submission-Specific Safety Issues

The following serious adverse reactions were reviewed in the first application cycle and are included in the Warnings and Precautions section of labeling. Except for **Oral Mucosal Irritation** and **Hypersensitivity,** no new information was submitted in the CR that requires reanalysis of these adverse drug reactions.

- Nausea and Vomiting
- Falling Asleep During Activities of Daily Living and Somnolence
- Syncope/Hypotension/Orthostatic Hypotension
- Oral Mucosal Irritation
- Hypersensitivity
- Falls
- Hallucinations/Psychotic Behavior
- Impulse Control/Compulsive Behaviors
- QTc Prolongation and Potential for Proarrhythmic Effects

8.5.1. Oral Mucosal Irritation

Reviewer's Note: This section is assessed in consultation with reviewers in the Division of Dermatology and Dentistry who were asked to comment on the applicant's analyses and conclusions and the applicant's expert opinions. The conclusions drawn in this section are in alignment with their assessment.

The applicant submitted a Clinical Summary Oropharyngeal Adverse Events (Module 5.5.2) and performed an analysis of clusters of oropharyngeal and systemic hypersensitivity adverse events and their co-occurrence. The applicant's analysis of oropharyngeal adverse events parsed the Pool C cumulative safety dataset into clinically relevant categories and looked at the occurrence of Preferred Terms in the titration and maintenance treatment epochs of Studies 300 and 301.

The clusters were treated as adverse events of special interest (AESI), each with their own specific analysis plan. The applicant used MedDRA standardized queries (SMQ) using narrow SMQ terms where available and all Preferred Terms under the specified Higher Level Terms or Higher Level Group Terms as defined in the MedDRA dictionary. If an SMQ did not exist in MedDRA for a cluster of interest, a custom search list of Preferred Terms was created for this purpose.

Each named cluster below is hyperlinked to the appendix in which the Preferred Terms that comprise that cluster are listed.

Oropharyngeal edema
Oropharyngeal inflammation / erythema
Oropharyngeal discoloration
Oropharyngeal infections
Oropharyngeal mass / neoplasm
Oropharyngeal numbness / changes in sensation
Oropharyngeal pain
Oropharyngeal ulcerations
Alterations in taste
Salivary complaints and oral dryness
Dental complaints
Trauma
Other
Systemic hypersensitivity

In addition, the applicant submitted the opinions of two outside expert opinions and photographs of oral lesions occurring in patients from ongoing Study 301 for review.

Reviewer's note: *The applicant's cluster data below is reorganized from multiple ISS tables in order to provide a more interpretable flow of information. The sources used to confirm the information are the ADSL, ADAE, and ADTTE (time to event) datasets.*

Oropharyngeal Adverse Event Clusters

In the double-blind population of Study 300, the following clusters occurred. Overall, oropharyngeal events occurred roughly equally at all dose levels but appears increased with duration of exposure moving from titration to the maintenance period. (Oropharyngeal discoloration was not reported).

Table 16 Oropharyngeal AEs by cluster in the randomized study population (source: ISS Table 8.49.3_RA)

Oropharyngeal Cluster	Blinded Population Study 300 N = 141					
	Titration (N=141)		Maintenance APL-130277 (N=54)		Maintenance Placebo (N=55)	
	Head Count (%)	Events	Head count (%)	Events	Head count (%)	Events
Any Oropharyngeal TEAEs	20 (14.2)	38	19 (35.2)	44	6 (10.9)	8
Alterations in taste	3 (2.1)	7	3 (5.6)	3	0	0
Dental complaints	0	0	0	0	2 (3.6)	2
Oropharyngeal edema	1 (0.7)	1	9 (16.7)	11	0	0
Oropharyngeal infections	1 (0.7)	1	1 (1.9)	1	0	0
Oropharyngeal inflammation/	6 (4.3)	13	6 (11.1)	6	3 (5.5)	3
Oropharyngeal mass/neoplasm	0	0	1 (1.9)	1	0	0
Oropharyngeal numbness/	1 (0.7)	1	1 (1.9)	2	0	0
Oropharyngeal pain	3 (2.1)	3	6 (11.1)	7	1 (1.8)	1
Oropharyngeal ulcerations	4 (2.8)	4	4 (7.4)	8	1 (1.8)	1
Other	1 (0.7)	1	1 (1.9)	1	0	0
Salivary complaints and oral dryness	3 (2.1)	6	3 (5.6)	4	0	0
Trauma	1 (0.7)	1	0	0	1 (1.8)	1

It becomes clear that the incidence of events in every category increases with duration of exposure as demonstrated by Pool C, the cumulative data pool with a large open-label population.

Table 17 Oropharyngeal AEs by study period in the Pool C cumulative safety population (source: ISS Table 8.49.2_RC and ISS Table 8.49.4_RC)

Oropharyngeal Cluster	Pool C (Cumulative Safety Population Study 300 + Study 301)			
	Titration N=508		Maintenance N=383	
	Head Count (%)	Events	Head count (%)	Events
Any Oropharyngeal TEAEs	65 (12.8)	110	141 (36.8)	390
Alterations in taste	9 (1.8)	17	25 (6.5)	29
Dental complaints	2 (0.4)	2	12 (3.1)	15
Oropharyngeal discoloration	0	0	5 (1.3)	5
Oropharyngeal edema	2 (0.4)	2	46 (12.0)	71
Oropharyngeal infections	2 (0.4)	2	21 (5.5)	25
Oropharyngeal inflammation/ erythema	23 (4.5)	33	33 (8.6)	40
Oropharyngeal mass/neoplasm	0	0	1 (0.3)	1
Oropharyngeal numbness/ sensation	4 (0.8)	4	14 (3.7)	22
Oropharyngeal pain	7 (1.4)	8	45 (11.7)	62
Oropharyngeal ulcerations	14 (2.8)	15	59 (15.4)	88
Other	5 (1.0)	6	5 (1.3)	5
Salivary complaints and oral dryness	6 (1.2)	10	17 (4.4)	20
Trauma	8 (1.6)	11	6 (1.6)	7

The most commonly occurring events when compared to placebo with Kynmobi were oropharyngeal edema, inflammation/ edema, pain, and ulcerations. Only oropharyngeal edema appeared to take time to develop, occurring most in maintenance treatment, the others occurring in both epochs.

In chronic treatment, the incidences of AEs in all clusters increase to a clinically significant degree, with over a third of patents developing AEs in at least one cluster. Events, in particular those related to the oropharyngeal edema, oropharyngeal pain, and oropharyngeal ulceration clusters, are more likely to occur with longer exposure.

Most events were mild to moderate in severity, whether occurring in the titration or maintenance phases of treatment, and only rarely of a serious nature. As noted above, the applicant underreported discontinuations due to oropharyngeal adverse events as some patients reported their desire to discontinue the study in only general terms. In Pool C, the applicant reports that 66 of 383 patients (17%) discontinued drug due to oropharyngeal adverse events in the maintenance phase of treatment. However, of the patients that did develop an AE represented by a PT in one of these clusters, 47% (66 of 141) discontinued treatment. These discontinuations reflected AEs in the most common clusters noted above and were more often of a moderate severity. Five patients discontinued for 7 events considered to be severe (edema, inflammation and ulcerations) and 3 patients had SAEs:

Table 18 Oropharyngeal SAEs in Pool C (source: ISS Table 68, page 176)

[Unique Subject ID]/ Subsequent IDs/ Study	Oropharyngeal Cluster/ Preferred Term/ Verbatim Term	AE Start Date and Time/ Study Phase/ Study Day[a]	AE Stop Date and Time/ Study Day[b]/ Treatment Discontinuation Date	Dose Level at the Event	D: Duration (days) F: Frequency R: Relationship to Study Treatment S: Severity	A: Action Taken O: Outcome C: Concomitant Therapy
(b) (6)	Oropharyngeal inflammation / erythema/ Pharyngeal erythema/ ERYTHEMA IN POSTERIOR PHARYNX	17FEB2018 13:00/ Maintenance/ Treatment Phase/ 115 (107) [220]	18FEB2018 / 116 (108) [221]/ 17FEB2018	10 mg	D: 2 F: ONCE R: PROBABLE S: SEVERE	A: DRUG WITHDRAWN O: RECOVERED/ RESOLVED C: No
	Oropharyngeal infections/ Oral candidiasis/ ORAL CANDIDA TO MOUTH	26JAN2018/ Maintenance/ Treatment Phase/ 102 (67)	11FEB2018 / 118 (83)/ 10FEB2018	25 mg	D: 17 F: INTERMITTENT R: UNLIKELY S: MODERATE	A: DRUG WITHDRAWN O: RECOVERED/ RESOLVED C: Yes
	Oropharyngeal ulcerations/ Lip blister/ PAINFUL BLISTERS TO LOWER LIPS	26JAN2018/ Maintenance/ Treatment Phase/ 102 (67)	13FEB2018 / 120 (85)/ 10FEB2018	25 mg	D: 19 F: CONTINUOUS R: UNLIKELY S: MODERATE	A: DRUG WITHDRAWN O: RECOVERED/ RESOLVED C: Yes

Abbreviations: AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities.
[a] Study day was calculated as the AE start date - date of first dose within study + 1. The study day in parentheses was calculated as the AE start date - date of first dose in the relevant study phase + 1. The study day in brackets was calculated as the AE start date - date of first dose in CTH-300 + 1.
[b] Study day was calculated as the AE stop date - date of first dose within study + 1. The study day in parentheses was calculated as the AE stop date - date of first dose in the relevant study phase + 1. The second study day in brackets was calculated as the AE stop date - date of first dose in CTH-300 + 1.

There appears to be a dose relation to events in these clusters, with fewer events at lower dose ranges, but this relationship should be viewed with caution due to the uncertainty related to

data pertaining to the dose level and frequency of its daily administration. There are relatively too few patients receiving the higher doses of 30 and 35 mg/d to draw such a conclusion.

Most events were reported to have spontaneously resolved (86% in Pool C maintenance treatment). However, it is not clear as to whether this was determined by active determination of an end date for the event or reflects the date when the AE was no longer reported.

8.5.2. Systemic Hypersensitivity

The applicant's analysis of hypersensitivity was informed by cases identified by Standardized MedDRA Query (SMQ) for hypersensitivity and angioedema. (Angioedema is a PT within the hypersensitivity SMQ and should be considered a subset of that group.) In addition, for clarity within the analysis, PTs that were captured using the oropharyngeal clusters above were removed from the systemic hypersensitivity cluster. It should also be noted that some PTs in this hypersensitivity cluster are, by themselves, quite nonspecific and possibly of no relation to hypersensitivity, e.g., peripheral edema, conjunctivitis, allergic rhinitis, lacrimation, etc.).

In the titration period of Study 300, terms denoting hypersensitivity were encountered in 6 patients. In four, the PT was "flushing" and often encountered as an autonomic side effect. One patient was identified as having peripheral edema on 30 mg/d. In the maintenance treatment phase of Study 300, seven patients were identified with targeted PTs versus 2 in the placebo arm.

Table 19 Hypersensitivity PTs in Study 300 (source: ISS Table 8.49.7_RA and Table 8.49.9_RA)

Hypersensitivity Cluster	Randomized Study 300					
	Titration (N=141)		Maintenance APL-130277 (N=54)		Maintenance Placebo (N=55)	
	Head Count (%)	Events	Head count (%)	Events	Head count (%)	Events
Systemic hypersensitivity	6 (4.3)	10	7 (13.0)	17	2 (3.6)	5
Flushing	4 (2.8)	7	2 (3.7)	2	1 (1.8)	3
Conjunctivitis	1 (0.7)	1	0	0	0	0
Oedema peripheral	1 (0.7)	1	1 (1.9)	1	1	0
Rhinitis allergic	1 (0.7)	1	0	0	0	0
Hypersensitivity	0	0	4 (7.4)	11	1 (1.8)	3
Lacrimation increased	0	0	1 (1.9)	1	0	0
Swelling face	0	0	1 (1.9)	1	0	0
Urticaria	0	0	1 (1.9)	1	0	0
Erythema	0	0	0	0	1 (1.8)	1

Peripheral swelling	0	0	0	0	1 (1.8)	1

By contrast, in the Pool C cumulative safety population with increased duration of treatment, there were many more patients so identified.

Table 20 Hypersensitivity PTs by treatment period in Pool C (source: ISS Table 8.49.8_RC and Table 8.49.10_RC)

Systemic Hypersensitivity	Pool C (Cumulative Safety Population Study 300 + Study 301)			
	Titration N=508		Maintenance N=383	
	Head Count (%)	Events	Head count (%)	Events
Any Hypersensitivity TEAEs	21 (4.1)	28	33 (8.6)	65
Hypersensitivity	0	0	5 (1.3)	18
Peripheral swelling	0	0	5 (1.3)	5
Flushing	9 (1.8)	12	4 (1.0)	4
Oedema peripheral	1 (0.2)	1	4 (1.0)	4
Lacrimation increased	5 (1.0)	7	3 (0.8)	3
Rash	0	0	3 (0.8)	3
Swelling face	0	0	3 (0.8)	5
Conjunctivitis	1 (0.2)	1	2 (0.5)	2
Erythema	0	0	2 (0.5)	2
Throat tightness	0	0	2 (0.5)	2
Urticaria	0	0	2 (0.5)	2
Wheezing	1 (0.2)	1	2 (0.5)	2
Allergic cough	0	0	1 (0.3)	2
Asthma	1 (0.2)	1	1 (0.3)	4
Drug hypersensitivity	1 (0.2)	1	1 (0.3)	1
Face oedema	0	0	1 (0.3)	1
Rash maculo-papular	1 (0.2)	1	1 (0.3)	1
Rhinitis allergic	1 (0.2)	1	1 (0.3)	2
Skin exfoliation	0	0	1 (0.3)	1
Sneezing	0	0	1 (0.3)	1
Blister	0	0	0	0
Mucosal erosion	1 (0.2)	1	0	0

One Pool C patient had SAEs related to hypersensitivity and asthma. This person had a prior history of asthma and had Kynmobi treatment continued despite an asthma attack that was poorly responsive to medication. This finally resulted in drug cessation and hospitalization. This case was discussed in the first cycle review:

Table 21 Pool C patient with SAE of hypersensitivity and asthma (source: ISS Table 87, page 219)

[Unique Subject ID]/ Subsequent IDs/ Study	Preferred Term/ Verbatim Term	AE Start Date and Time/ Study Phase/ Study Day[a]	AE Stop Date and Time/ Study Day[b]/ Treatment Discontinuation Date	Dose Level at the Event	D: Duration (days) F: Frequency R: Relationship to Study Treatment S: Severity	A: Action Taken O: Outcome C: Concomitant Therapy
(b) (6)	Asthma/ EXACERBATION OF ASTHMA	15APR2017/ Maintenance/ Treatment Phase/ 124 (95)	20APR2017 / 129 (100)/ 05MAY2017	25 mg	D: 6 F: INTERMITTENT R: NOT RELATED S: SEVERE	A: DOSE NOT CHANGED O: RECOVERED/ RESOLVED C: Yes
	Asthma/ EXACERBATION OF ASTHMA	06AUG2017/ Maintenance/ Treatment Phase/ 237 (208)	13AUG2017 / 244 (215)/ 05MAY2017	25 mg	D: 8 F: ONCE R: NOT RELATED S: MODERATE	A: DOSE NOT CHANGED O: RECOVERED/ RESOLVED C: Yes

Abbreviations: AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities

In the titration phase of Pool C patients, one patient discontinued due to excessive lacrimation on the fourth day of using 25 mg dose level. In the maintenance phase of the cumulative safety population, 5 subjects discontinued due to hypersensitivity reactions:

(b) (6) (10 mg APL-130277) 'oral contact allergic reaction to investigational product' with onset on Day 43 that resolved after approximately 14 days following discontinuation of study drug.

(b) (6): throat tightness with onset on Day 146 (20 mg which resolved following discontinuation of study drug after approximately 2 days. Concurrently, the subject had events in the PT clusters of oropharyngeal edema (pharyngeal oedema, verbatim term 'throat swelling') and oropharyngeal pain (oral discomfort, verbatim term 'burning sensation in mouth') which resolved without intervention.

(b) (6): swelling of lower half of face with onset on Days 15 and 46 (10 mg); these events were considered probably related to study drug and resolved the same day, following drug interruption and administration of medical treatment for the Day 15 event and discontinuation of study drug for the Day 46 event. Approximately 6 days prior to the first, event, the subject experienced a mild event of peripheral swelling (verbatim term 'swelling of left lower leg [calf]') which was ongoing at the time of onset of the first swelling face episode.

(b) (6) (10 mg APL-130277) had 'rash on the right forearm' with onset on Day 18 that resolved after approximately 19 days following discontinuation of study drug.

(b) (6): throat tightness with onset on Day 40 (10 mg). The event resolved after

approximately 3 days following discontinuation of study drug and administration of medical treatment. The subject experienced no other oropharyngeal or systemic hypersensitivity events.

When Pool C titration and maintenance epochs are combined, 93 systemic hypersensitivity cluster events were reported for 51 subjects (10.0%). The most frequently reported TEAEs by PT were flushing (12 subjects, 2.4%) and lacrimation increased (8 subjects, 1.6%); incidence of all other events was ≤ 1.0%. Aside from those noted above, most events were mild to moderate in severity. Those events that were considered on the moderate end of the spectrum included episodes of flushing, lacrimation increased, hypersensitivity, peripheral swelling, rash, swelling face, drug hypersensitivity, rash maculo-papular, throat tightness, urticaria, allergic cough, asthma, and face edema.

Intersection of Oropharyngeal Events and Hypersensitivity
The applicant states that, of the 508 patients exposed to APL-130277 in the combined titration phase and maintenance/treatment phase, 111 (21.9%) experienced multiple oropharyngeal cluster and/or systemic hypersensitivity TEAEs.

The applicant performed a cross-tabulation of the oropharyngeal clusters and the systemic hypersensitivity cluster for the pool C cumulative safety population. There were no co-occurrences of severe oropharyngeal cluster events with severe systemic hypersensitivity events.

Table 22 Co-occurrence of Oropharyngeal AEs with the Hypersensitivity Cluster in Pool C (source: ISS Table 8.54.6_RC)

Pool C patients co-occurrence in systemic hypersensitivity cluster (N=508)	N (%)
Oropharyngeal ulcerations	12 (2.4)
Oropharyngeal inflammation / erythema	10 (2.0)
Oropharyngeal pain	14 (2.8)
Oropharyngeal edema	13 (2.6)
Alterations in taste	6 (1.2)
Oropharyngeal infections	6 (1.2)
Salivary complaints and change in numbness	6 (1.2)
Oropharyngeal numbness / change in sensation	5 (1.0)
Dental complaints	0

Trauma	2 (0.4)
Other	3 (0.6)
Oropharyngeal discoloration	2 (0.4)

Time to Events

An additional way to look at the relationship between oropharyngeal events and systemic hypersensitivity is to follow the evolution of these events. The following graphs illustrate the prevalence of PTs related to clusters of interest (with severity) over the time of participation of the Pool C cumulative safety population (top: all oropharyngeal PTs; bottom: all Hypersensitivity PTs). Under each column is the N for the week of the study. The column height indicates the percent of patients that week having an oropharyngeal event of any PT (top) or any hypersensitivity PT (bottom). The number of subjects at risk at the beginning of each weekly interval is the denominator for the percentage calculation.

It is worthwhile to note that the bulk of hypersensitivity emerges earlier in exposure during the first year, while oropharyngeal events continue to appear over the course of the exposure. However, as duration of treatment gets longer, the number of participants reaching that time point becomes quite small. Therefore, it is unclear that there is any meaning to have oropharyngeal events in 20 percent of patients at week 144 when that represents only 2 of 10 patients at that milestone.

In contrast, as the participating number of patients falls each week of the study until there are few left, no PTs related to hypersensitivity are occurring.

Nevertheless, for any given patient, it is apparent that both classes of phenomenon can occur at almost any time and that oropharyngeal events are likely to be more persistent.

Figure 1 Time-to-Event distribution of prevalence for Oropharyngeal AE Clusters (source: ISS Appendix 19.2 Figure 5.3.2_RC p 2064)

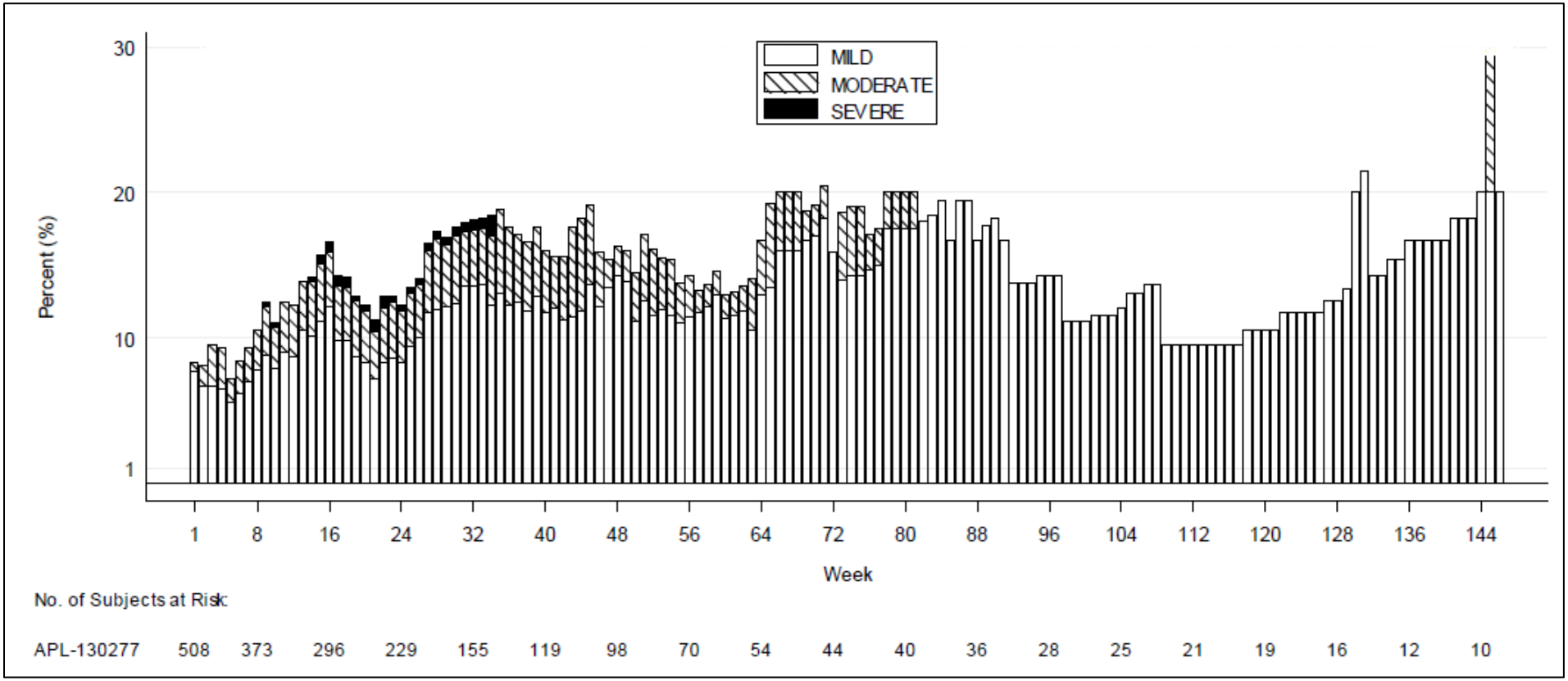
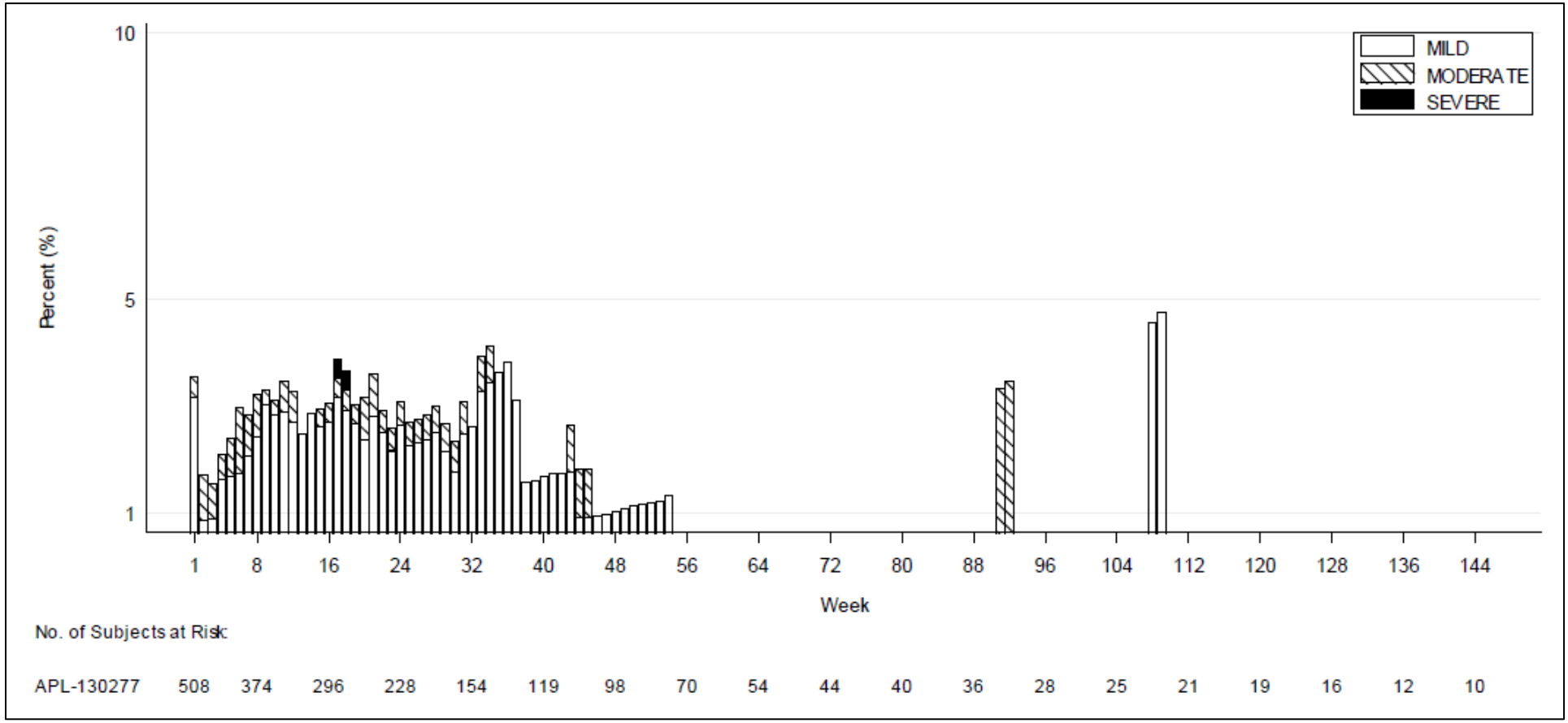


Figure 2 Time-to-Event distribution of prevalence for the Hypersensitivity AE Cluster (source: ISS Appendix 19.2 Figure 5.3.4_RC p 2064)



This differential in time course of development of oropharyngeal and hypersensitivity adverse events is also reflected in the

following figures representing cumulative occurrence of any event in these categories, illustrating the risk over time for any PT to occur (Kaplan-Meier plot of time to first onset in days).

Figure 3 Kaplan-Meier plot of the time course to development of first oropharyngeal adverse event by patient (source: ISS Appendix 19.2 Figure 5.1.2_RC p 2007).

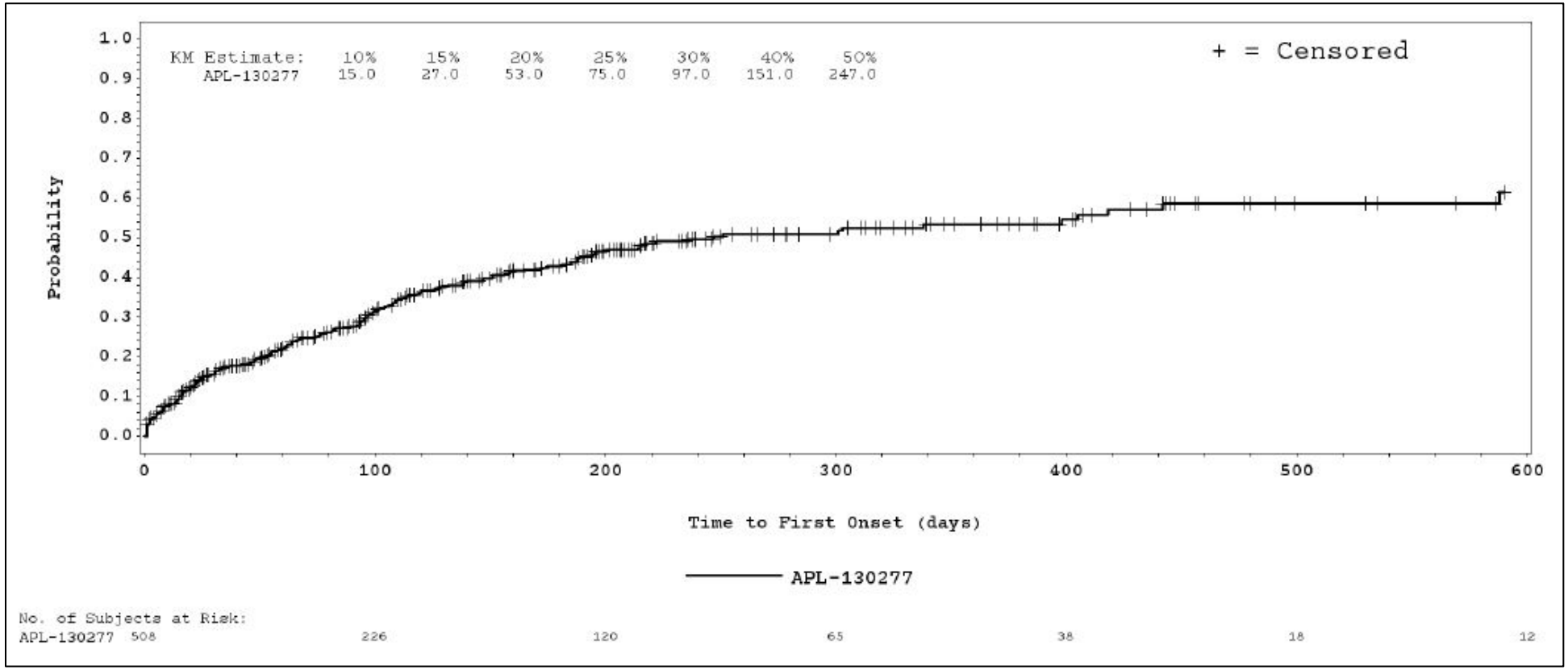
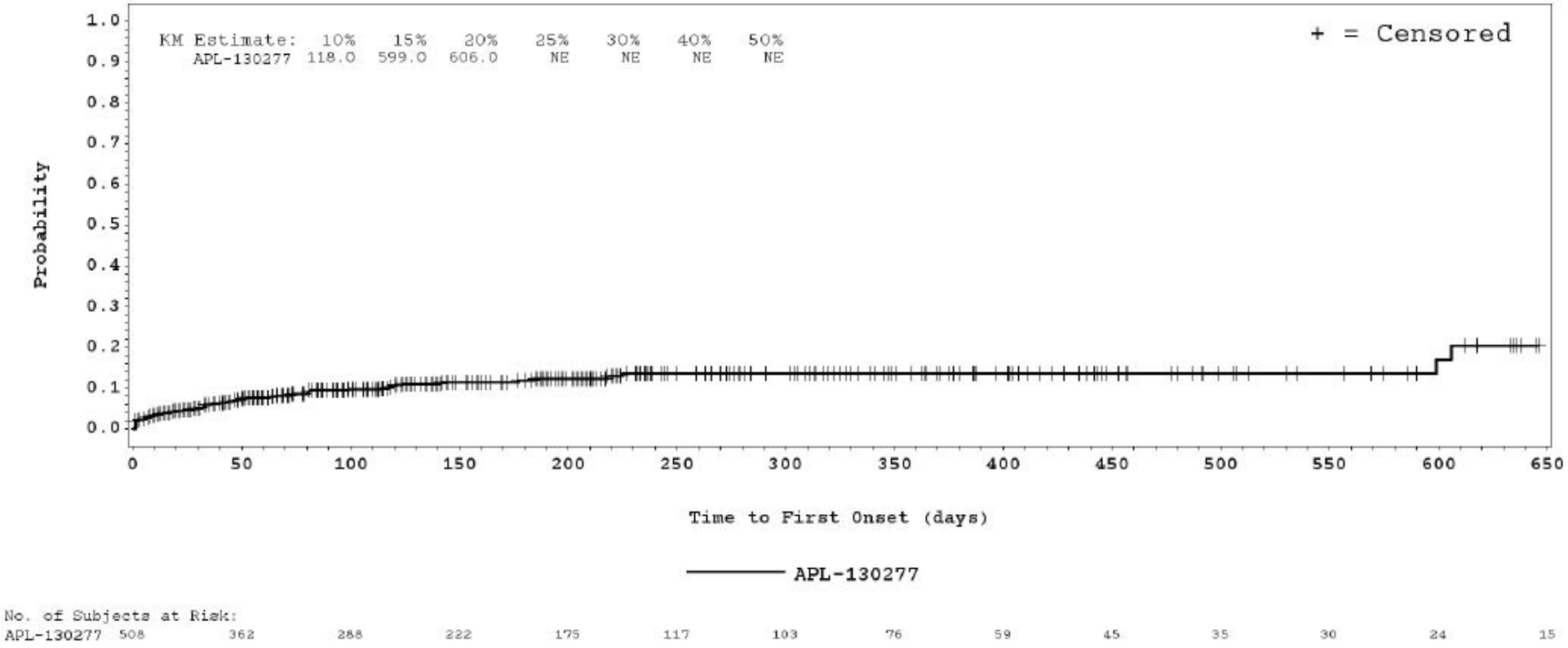


Figure 4 Kaplan-Meier plot of the time course to development of first hypersensitivity adverse event by patient (source: ISS Appendix 19.2 Figure 5.1.4_RC p 2021).



Angioedema

Angioedema manifests as sudden localized, non-pitting swelling of certain body parts including skin and mucous membranes. It is triggered by immune allergic mechanisms via mast cells and/or bradykinins. The applicant conducted an analysis of angioedema in Pool C cumulative safety population patients (most receiving open-label APL-130277) in maintenance treatment using a broad MedDRA SMQ. This search included events that were discovered under the hypersensitivity cluster. However, when tallied separately in the Pool C maintenance population, there were 58 of 383 patients (15%) who had events suggestive of angioedema. These events occurred across all dose levels.

It is worthwhile to note that these patients were identified in the hypersensitivity cluster associated with other events and angioedema does not appear to occur by itself or carry a specific degree of severity of allergic reaction.

Table 23 Angioedema SMQ in Pool C maintenance patients (source: adapted from ISS Appendix ISS 19.2, Table 8.19.8_RC p 1275)

Pool C Studies 300 +301 Maintenance Population (N=383)			
	Head Count	%	Events
Angioedema SMQ	58	15.1	111
Lip swelling	21	5.5	30
Swollen tongue	14	3.7	16
Hypersensitivity	5	1.3	18
Lip oedema	5	1.3	5
Peripheral swelling	5	1.3	5
Mouth swelling	4	1	4
Oedema peripheral	4	1	4
Oedema mouth	3	0.8	4
Pharyngeal oedema	3	0.8	3
Swelling face	3	0.8	5
Oropharyngeal swelling	2	0.5	2
Palatal swelling	2	0.5	2
Throat tightness	2	0.5	2
Tongue oedema	2	0.5	2
Urticaria	2	0.5	2

Anaphylaxis

Anaphylaxis is an acute, life-threatening systemic reaction with varied clinical presentations and severity that results from the sudden systemic release of immune mediators from inflammatory cells. When considering adverse hypersensitivity reactions, it is necessary to consider whether

anaphylactic drug reactions also occurred. The applicant did not report any cases.

The MedDRA SMQ for anaphylaxis has several levels of case inclusion determined by groups of Preferred Term. SMQ Narrow A includes PTs that contain the term "anaphylactic" but also terms related to shock. Narrow SMQ search of the Pool C safety population using the ADAE dataset revealed no individuals fitting this category.

The Broad SMQ for anaphylaxis has 3 levels of collected PTs (Broad B, C, and D), each one successively broadening the scope of the SMQ search and thereby reducing its specificity. Narrow A and Broad B, C, and D Preferred Terms are listed in Appendix 13.3.15. Anaphylaxis SMQ Preferred Terms. After analyzing the ADAE dataset, ten patients were counted more than once across levels. These duplications were eliminated, retaining the highest SMQ level assigned to the case. Level D was also eliminated from further consideration; the PTs added to this level describe decreased blood pressure. This is a common AE for this drug and thus adding these PTs to those in Levels B and C does not meaningfully contribute to the analysis.

Table 24 Anaphylaxis SMQ in Pool C safety population (source: ADSL and ADEX datasets)

SMQ cases	Pool C Safety Population	
	Head Count (n)	SMQ Counts (n)
Total	116	
Narrow A	0	0
Broad B	47	65
Broad C	42	71
Broad D	27	35

The PTs found in Levels B and C are also problematic. The terms in these levels that describe swelling or edema are highlighted in yellow in the appendix. Level B adds this descriptor to mostly the lower face while Level C adds it to features of the upper face. However, swelling of the face is common with APL-130277 by itself. Its lack of association with other characteristics suggestive of anaphylaxis suggests it is a more of a local phenomenon, either a hypersensitivity or a local inflammatory response. Angioedema is a Level C Preferred Term.

Finally, performing a text search on all narratives in the original NDA and CR submissions revealed that terms related to "anaphylaxis" or "anaphylactic" were not used.

Applicant's Conclusions

The applicant provided thumbnail descriptions for each patient who had clinical presentation of an event in one cluster that evolved to an event in another cluster, who had multiple events in 1 or more clusters and evolved to include other events in additional clusters or had events in

one or more clusters that were more severe in extent.

Reviewing these cases individually did not clarify the connections among clusters any further, but the applicant suggested these conclusions:

- Multiple oral events occurred during titration from 10 to 35 mg APL 130277.
- Oral events that were more common in maintenance treatment were concurrent or temporally close in the setting of continued treatment.
- Patients who experienced concurrent events that resolved on continued treatment would subsequently develop a recurrence of the same events or other events in different clusters that eventually led to treatment discontinuation.
- Together, these observations suggest that continued treatment in the setting of one or more oral events can lead to the development of oral events in other clusters that may result in treatment discontinuation.
- Dose interruption or reduction resulting in resolution of the initial event followed by resumption of treatment led to the recurrence or the onset of multiple oral events that resulted in treatment discontinuation.
- The development of concurrent or recurrent events following dose interruption or reduction led to treatment discontinuation in most cases.
- The mini-narratives suggest that, although most patients' oral events are tolerated or resolve spontaneously soon after treatment discontinuation, rechallenge can lead to recurrence or onset of new events, often with a more aggressive course.

Reviewer's comment: *I find these conclusions to be reasonable and they are supported by the large numbers of dropout with varied reasons encountered over the course of treatment with APL-130277.*

Consultation by the Division of Dermatology and Dentistry (DDD) ODE III
Clinical reviewers in the Division of Dermatology and Dentistry (DDD) were asked to provide an expert evaluation of the contents of the CR. The materials they reviewed include:

- Clinical Overview 2.5. APL-130277
- Clinical Summary 5.5.2. Oropharyngeal Adverse Events
- Integrated Summary of Safety Section 1.1.2. - The oropharyngeal adverse events cluster analyses
- Integrated Summary of Safety Section 4.4 -4.9 – Response to Complete Response Letter
  - 4.4 Oropharyngeal Adverse Event Cluster Analysis
  - 4.5 Systemic Hypersensitivity Adverse Event Cluster Analysis
  - 4.6 Co-occurrences of Oropharyngeal Clusters and of Oropharyngeal Clusters with Systemic Hypersensitivity Events
  - 4.7 Evolution of Events

  - 4.8 Angioedema and Hypersensitivity Reaction Events
  - 4.9 Expert Review
- Integrated analysis of safety data -resubmission, Statistical Analysis Plan and Integrated Summary of Safety Reviewers Guide
- ISS Appendix 19.2 - Tables, figures and graphs referred to but not included in the text.
- Published literature

The reader is referred to their valuable contribution for full details of their analysis. The following comments are cited from the executive summary of the evaluation of the CR submission by DDD:

- The applicant has addressed the request for a detailed, comprehensive evaluation of the oropharyngeal adverse events, including cluster and time-to-event analysis.
- The labeling should reflect the multi-fold increase in oropharyngeal AE between titration and treatment/maintenance phase. Patients treated with APL-130277, regardless of the dose, may not experience a TEAE during the titration phase, but they can appear during the treatment phase.
- The labeling should reflect the dose-dependent increase for any oropharyngeal AE, although the clinical trials were not designed and adequately powered to evaluating the dose-effect.
- The labeling should reflect the potential for an increase of oral leucoplakia for patients treated with APL-130277 at the 30-mg dose and counsel patients about regular dental visits.
- The photographs of oral and skin abnormalities of new events in the ongoing open-label study CTH-301 are not diagnostic or clinically informative.
- The oropharyngeal adverse events do not appear to be related to systemic hypersensitivity.
- The expert reviews have limitations, but appear reasonable in their evaluations and conclusions.

Reviewer's Comment: I agree with these observations, except for a dose level relationship to allergy and local irritation-based AEs. I found that the data is confounded by the fact that a given dose level may be given from 1 to 5 times a day, changing the total daily dose while at a given dose-level, while the applicant reported AEs by the assigned dose at the previous visit. In addition, AEs may have a stronger relationship to the time duration of exposure than to dose; the AE may take time to develop. Further, the titration dose-level was regularly increased by schedule and clinical need.

Even for the maintenance phase, there is insufficient data on the relationship between the

assigned dose level, the total daily dose, and number of individual doses taken per day to distinguish whether these adverse drug reactions of special interest are related to dose, frequency of use, or duration of use. Finally, there is not enough data at the higher dose levels to support a conclusion of dose relatedness.

I also agree that the low-resolution photographs of oral lesions were uninformative. The opinions of the applicant's experts are reflected in the applicant's conclusions.

8.6. Integrated Assessment of Safety

The applicant fulfilled their obligation to respond to the questions concerning the clinical safety of APL-130277 and to submit a safety update in accordance with 21 CFR 314.50(d)(5)(vi)(b).

As analyzed in the clinical review of the original NDA submission, the safety profile of treatment-emergent adverse drug reactions resulting from apomorphine's mechanism of action during the clinical use of APL-130277 in advanced PD is consistent with that of the reference listed drug. However, oropharyngeal adverse events and hypersensitivity reactions were commonly observed in addition. The characterization of this latter safety risk is the focus of this CR submission.

The oropharyngeal and hypersensitivity adverse drug reactions were analyzed for the Phase 3 safety population (Pool C); 556 patients entered the titration phase of Kynmobi treatment and 408 entered a maintenance phase of study. In the Pool C safety population, 82 patients had at least 6 months of treatment. Most received 15, 20, or 25 mgs. Only 7 patients received 30 mg and 6 received 35 mg. (By design, the 35 mg patients had successfully tolerated the 30 mg dose level.) In Pool C, 64 patients had had 12 months or more of exposure but, again, only 8 had had exposure of 30 and 35 mg dose levels, respectively. The number of times these dose-levels were taken daily was determined by diary and this revealed that the 30 and 35 mg doses were not taken more than twice daily at 12 months. This lack of exposure experience at the 35 mg dose level suggests that limiting the dose range to 30 mg is prudent.

Oropharyngeal and hypersensitivity AEs were studied in the titration and maintenance phases of treatment in both randomized placebo-controlled and cumulative safety population. In the blinded Study 300, 20% of patients had an oropharyngeal TEAE during titration and 35% had such an event during maintenance therapy up to 12 weeks in duration. This was corroborated in the cumulative safety population where, over a longer period of observation, 36.8 percent had any oropharyngeal TEAE during maintenance treatment.

Hypersensitivity reactions when defined by the Preferred Term "Hypersensitivity" were much less common: none occurred during titration periods in both Studies 300 and 301. During maintenance treatment, this PT occurred in 7 % of patients receiving active drug in Study 300 but only 1.3% of patients in the cumulative safety population. Using the hypersensitivity cluster

of PTs supplied by the applicant revealed more occurrences: 13% in Study 300 and 8.6% in the cumulative safety population. However, as discussed above, many of the PTs in the cluster were non-specific for hypersensitivity and could (and did) occur independently. While angioedema was not uncommon (some oedema or swelling of body regions occurred in 15% of patients in Pool C), cases of anaphylactic drug reactions did not occur.

While the events attributed to hypersensitivity were generally mild and resolved quickly on drug cessation, there were several instances of a more severe reaction requiring a more targeted medical intervention. When oropharyngeal or hypersensitivity reactions occurred, there was a strong likelihood that the patient would discontinue treatment.

The ability of the patient to effectively open the drug packaging intended for market and to successfully self-administer APL-130277 is supported by the Human Factors studies submitted for review.

The injectable form of apomorphine is available to PD patients (b) (4) but it is clearly a less convenient dosage form. The sublingual route is advantageous but unpleasant for a considerable number of users; use comes with the liability of drug-related oropharyngeal irritation and inflammation and hypersensitivity reactions. However, now that the incidence of these TEAEs specific to apomorphine sublingual thin film is better defined with regard to frequency and severity, it may be appropriately labeled in the Prescribing Information and the patient and their healthcare provider are able to make an informed decision about the risk and benefits of this treatment in relation to other available anti-PD treatments.

9. Advisory Committee Meeting and Other External Consultations

Not applicable to this review

10. Labeling Recommendations

10.1. Prescription Drug Labeling

Information relevant to labeling is described in Section 8.5 above and the content of Prescribing Information has been in discussion with the applicant during the review period.

11. Risk Evaluation and Mitigation Strategies (REMS)

An acceptable safety profile for this drug has been submitted and there are no additional risk management strategies required beyond the recommended labeling. The safe and effective use of Kynmobi in the treatment of "off" episodes in PD can be adequately described in the drug labeling.

12. Postmarketing Requirements and Commitments

No clinical PMR or PMC is proposed. There are no further efficacy or safety issues that must be explored at this time.

13. Appendices

13.1. References

None.

13.2. Financial Disclosure

Not applicable to this review.

13.3. Preferred Terms by Adverse Event Cluster.

13.3.1. Oropharyngeal edema

Epiglottic oedema
Gingival oedema
Gingival swelling
Lip oedema
Lip swelling
Mouth swelling
Oedema mouth
Oedema mucosal
Oropharyngeal swelling
Palatal oedema
Palatal swelling
Pharyngeal oedema
Swollen tongue
Tongue oedema

13.3.2. Oropharyngeal inflammation / erythema

Epiglottic erythema
Epiglottitis
Epiglottitis obstructive
Gingival erythema
Gingivitis
Gingivitis ulcerative
Glossitis
Lichen planus
Lineal gingival erythema
Noninfective gingivitis
Oral mucosal erythema
Parotitis
Periodontitis
Pharyngeal erythema
Pharyngeal inflammation
Tonsillar erythema
Tonsillar inflammation
Behcet's syndrome
Buccal mucosal roughening
Oral lichen planus
Oral pruritus
Oral submucosal fibrosis
Parotid gland enlargement
PFAPA syndrome
Pharyngeal exudate
Sjogren's syndrome
Tongue pruritus

13.3.3. Oropharyngeal discoloration

Gingival discolouration
Gingival hyperpigmentation
Leukoplakia oral
Oral mucosal discolouration
Oral pigmentation
Oropharyngeal plaque
Tongue discolouration
Oral leukoedema
Tongue pigmentation

13.3.4. Oropharyngeal infections

Abscess of salivary gland
Abscess oral
Acute postoperative sialadenitis
Adenoiditis
Angina gangrenous
Aspergillosis oral

Bacterial parotitis
Cellulitis pharyngeal
Chronic tonsillitis
Foot and mouth disease
Gingival abscess
Hand-foot-and-mouth disease
Herpangina
Herpes pharyngitis
Herpes simplex pharyngitis
Herpes zoster pharyngitis
Infective glossitis
Laryngitis
Lip infection
Ludwig angina
Mumps
Necrotising ulcerative gingivostomatitis
Necrotising ulcerative periodontitis
Oral bacterial infection
Oral candidiasis
Oral fungal infection
Oral helminthic infection
Oral herpes
Oral infection
Oral pustule
Oral tuberculosis
Oral viral infection
Oro-pharyngeal aspergillosis
Oropharyngeal candidiasis
Oropharyngeal gonococcal infection
Oropharyngitis fungal
Parotid abscess
Peritonsillar abscess
Peritonsillitis
Pharyngeal abscess
Pharyngeal chlamydia infection
Pharyngitis
Pharyngitis bacterial
Pharyngitis mycoplasmal
Pharyngitis streptococcal
Pharyngoconjunctival fever of children
Pharyngotonsillitis
Salivary gland induration
Staphylococcal parotitis
Staphylococcal pharyngitis
Strawberry tongue
Subglottic laryngitis
Tongue abscess
Tongue fungal infection
Tonsillar exudate
Tonsillitis
Tonsillitis bacterial
Tonsillitis fungal
Tonsillitis streptococcal
Tonsillolith
Uvulitis
Viral parotitis
Viral pharyngitis
Viral tonsillitis

13.3.5. Oropharyngeal mass / neoplasm

Acinic cell carcinoma of salivary gland
Adenocarcinoma of salivary gland
Adenoid cystic carcinoma of salivary gland
Benign salivary gland neoplasm
Buccal polyp
Carcinoma ex-pleomorphic adenoma
Epiglottic carcinoma
Epiglottic cyst
Epiglottic mass
Epulis
Giant cell epulis
Gingival cancer
Gingival cyst
Gingival polyp
Leukoplakia
Lip and/or oral cavity cancer
Lip and/or oral cavity cancer recurrent
Lip and/or oral cavity cancer stage 0

Lip and/or oral cavity cancer stage I
Lip and/or oral cavity cancer stage II
Lip and/or oral cavity cancer stage III
Lip and/or oral cavity cancer stage IV
Malignant palate neoplasm
Melanoplakia oral
Metastases to mouth
Metastases to pharynx
Metastases to salivary gland
Metastases to tonsils
Metastatic salivary gland cancer
Mouth cyst
Mucoepidermoid carcinoma of salivary gland
Oral cavity cancer metastatic
Oral fibroma
Oral haemangioma
Oral hairy leukoplakia
Oral neoplasm
Oral neoplasm benign
Oral papilloma
Oropharyngeal cancer
Oropharyngeal cancer recurrent
Oropharyngeal cancer stage 0
Oropharyngeal cancer stage I
Oropharyngeal cancer stage II
Oropharyngeal cancer stage III
Oropharyngeal cancer stage IV
Oropharyngeal lymphoepithelioma
Oropharyngeal neoplasm
Oropharyngeal neoplasm benign
Oropharyngeal squamous cell carcinoma
Papillary cystadenoma lymphomatosum
Pharyngeal cancer
Pharyngeal cancer metastatic
Pharyngeal cancer recurrent
Pharyngeal cancer stage 0
Pharyngeal cancer stage I
Pharyngeal cancer stage II
Pharyngeal cancer stage III
Pharyngeal cancer stage IV
Pharyngeal cyst
Pharyngeal leukoplakia
Pharyngeal mass
Pharyngeal neoplasm
Pharyngeal neoplasm benign
Pharyngeal polyp
Pleomorphic adenoma
Salivary gland adenoma
Salivary gland cancer
Salivary gland cancer recurrent
Salivary gland cancer stage 0
Salivary gland cancer stage I
Salivary gland cancer stage II
Salivary gland cancer stage III
Salivary gland cancer stage IV
Salivary gland neoplasm
Squamous cell carcinoma of pharynx
Squamous cell carcinoma of the oral cavity
Squamous cell carcinoma of the tongue
Throat cancer
Tongue cancer metastatic
Tongue cancer recurrent
Tongue carcinoma stage 0
Tongue carcinoma stage I
Tongue carcinoma stage II
Tongue carcinoma stage III
Tongue carcinoma stage IV
Tongue cyst
Tongue dysplasia
Tongue neoplasm
Tongue neoplasm benign
Tongue neoplasm malignant stage unspecified
Tongue polyp
Tonsil cancer
Tonsil cancer metastatic
Tonsillar cyst
Tonsillar neoplasm
Tonsillar neoplasm benign

13.3.6. Oropharyngeal numbness / changes in sensation

Dysaesthesia pharynx
Hypoaesthesia oral
Oral dysaesthesia
Oral hyperaesthesia
Paraesthesia oral
Pharyngeal hypoaesthesia
Pharyngeal paraesthesia

13.3.7. Oropharyngeal pain

Burn oral cavity
Burning mouth syndrome
Burning sensation
Gingival discomfort
Gingival pain
Glossodynia
Lip pain
Odynophagia
Oropharyngeal discomfort
Oral discomfort
Oral pain
Oropharyngeal pain
Tongue discomfort
Throat irritation

13.3.8. Oropharyngeal ulcerations

Angina bullosa haemorrhagica
Angular cheilitis
Aphthous ulcer
Chapped lips
Cheilitis
Contact stomatitis
Epiglottis ulcer
Gingival erosion
Gingival blister
Gingival ulceration
Lip blister
Lip exfoliation
Lip ulceration
MAGIC syndrome
Mouth ulceration
Nicotinic stomatitis
Oral mucosal blistering
Oral mucosal eruption
Palatal ulcer
Pharyngeal enanthema
Pharyngeal erosion
Pharyngeal lesion
Pharyngeal ulceration
Oropharyngeal blistering
Tongue blistering
Tongue ulceration
Tonsillar ulcer
Stomatitis
Stomatitis haemorrhagic
Stomatitis necrotising
Stomatitis radiation
Oral mucosa erosion
Oral mucosal exfoliation
Sialometaplasia

13.3.9. Alterations in taste

Ageusia

Dysgeusia
Hypogeusia

13.3.10. Salivary complaints and oral dryness

Aptyalism
Dry mouth
Dry throat
Lip dry
Noninfective sialoadenitis
Ranula
Saliva altered
Saliva discolouration
Salivary duct inflammation
Salivary duct obstruction
Salivary duct stenosis
Salivary gland atrophy
Salivary gland calculus
Salivary gland cyst
Salivary gland disorder
Salivary gland enlargement
Salivary gland fistula
Salivary gland mass
Salivary gland mucocoele
Salivary gland pain
Salivary hypersecretion
Sialoadenitis
Tongue dry
Foaming at mouth
Sordes
Tongue coated

13.3.11. Dental complaints

Dental caries
Periodontal destruction
Periodontal disease
Periodontal inflammation
Pulpitis dental
Sensitivity of teeth
Tooth abscess
Tooth discolouration
Tooth fracture
Tooth infection
Tooth loss

13.3.12. Trauma

Chronic cheek biting
Corrosive oropharyngeal injury
Gingival bleeding
Gingival injury
Lip injury
Mouth injury
Mouth haemorrhage
Oral contusion
Oral mucosa haematoma
Pharyngeal injury
Pharynx radiation injury
Radiation salivary gland injury
Tongue biting
Tongue injury
Traumatic ulcerative granuloma with stromal eosinophilia

13.3.13. Other

Acquired macroglossia
Adenoidal disorder
Adenoidal hypertrophy
Ankyloglossia acquired
Atrophic glossitis
Auriculotemporal syndrome
Buccoglossal syndrome
Chronic throat clearing
Coating in mouth
Cobble stone tongue
Exposed bone in jaw
Gingival atrophy
Gingival disorder
Gingival hypertrophy
Gingival hypoplasia
Gingival pruritus
Gingival recession
Glossoptosis
Hypertrophy of tongue papillae
Mikulicz's disease
Mikulicz's syndrome
Oral allergy syndrome
Oral cavity fistula
Oral disorder
Oral mucosa atrophy
Oral mucosal hypertrophy
Oral papule
Oral toxicity
Oropharyngeal cobble stone mucosa
Oropharyngeal scar
Palatal disorder
Palatal dysplasia
Palatal palsy
Parotid duct obstruction
Parotid gland haemorrhage
Parotid lipomatosis
Pharyngeal disorder
Pharyngeal dyskinesia
Pharyngeal fistula
Pharyngeal haematoma
Pharyngeal haemorrhage
Pharyngeal hypertrophy
Pharyngeal mucosa atrophy
Pharyngeal necrosis
Pharyngeal pouch
Pharyngeal stenosis
Plicated tongue
Protrusion tongue
Pyostomatitis vegetans
Scalloped tongue
Sialectasia
Sialocele
Sialogram abnormal
Submaxillary gland enlargement
Swallow study abnormal
Throat lesion
Tongue atrophy
Tongue disorder
Tongue eruption
Tongue geographic
Tongue haematoma
Tongue haemorrhage
Tongue infarction
Tongue movement disturbance
Tongue necrosis
Tongue paralysis
Tongue spasm
Tonsillar atrophy
Tonsillar disorder
Tonsillar haemorrhage
Tonsillar hypertrophy
Velopharyngeal incompetence

13.3.14. Systemic hypersensitivity

Acute generalised exanthematous pustulosis
Acute respiratory failure
Administration site dermatitis
Administration site eczema
Administration site hypersensitivity
Administration site photosensitivity reaction
Administration site rash
Administration site recall reaction
Administration site urticaria
Administration site vasculitis
Airway remodelling
Allergic bronchitis
Allergic colitis
Allergic cough
Allergic cystitis
Allergic eosinophilia
Allergic gastroenteritis
Allergic hepatitis
Allergic keratitis
Allergic myocarditis
Allergic oedema
Allergic otitis externa
Allergic otitis media
Allergic pharyngitis
Allergic respiratory disease
Allergic respiratory symptom
Allergic sinusitis
Allergic transfusion reaction
Allergy alert test positive
Allergy test positive
Allergy to chemicals
Allergy to fermented products
Allergy to immunoglobulin therapy
Allergy to surgical sutures
Allergy to vaccine
Alpha tumour necrosis factor increased
Alveolitis
Alveolitis allergic
Anaphylactic reaction
Anaphylactic shock
Anaphylactic transfusion reaction
Anaphylactoid reaction
Anaphylactoid shock
Anaphylaxis treatment
Angioedema
Antiallergic therapy
Antibody test abnormal
Antibody test positive
Antiendomysial antibody positive
Anti-insulin antibody increased
Anti-insulin antibody positive
Anti-insulin receptor antibody increased
Anti-insulin receptor antibody positive
Anti-neutrophil cytoplasmic antibody positive vasculitis
Application site dermatitis
Application site eczema
Application site hypersensitivity
Application site photosensitivity reaction
Application site rash
Application site recall reaction
Application site urticaria
Application site vasculitis
Arthritis allergic
Aspirin-exacerbated respiratory disease
Asthma
Asthma late onset
Asthma-chronic obstructive pulmonary disease overlap syndrome
Asthmatic crisis
Atopy
Auricular swelling
Blepharitis allergic
Blister
Blister rupture
Blood immunoglobulin A abnormal
Blood immunoglobulin A increased
Blood immunoglobulin D increased
Blood immunoglobulin E abnormal
Blood immunoglobulin E increased
Blood immunoglobulin G abnormal
Blood immunoglobulin G increased

Blood immunoglobulin M abnormal
Blood immunoglobulin M increased
Breast oedema
Breast swelling
Bromoderma
Bronchial hyperreactivity
Bronchial oedema
Bronchospasm
Bullous impetigo
Caffeine allergy
Capillaritis
Catheter site dermatitis
Catheter site eczema
Catheter site hypersensitivity
Catheter site rash
Catheter site urticaria
Catheter site vasculitis
Charcot-Leyden crystals
Choking
Choking sensation
Chronic eosinophilic rhinosinusitis
Chronic hyperplastic eosinophilic sinusitis
Circulatory collapse
Circumoral oedema
Conjunctival oedema
Conjunctivitis
Conjunctivitis allergic
Contrast media allergy
Contrast media reaction
Corneal exfoliation
Corneal oedema
Cutaneous vasculitis
Cytokine release syndrome
Cytokine storm
Dennie-Morgan fold
Dermatitis
Dermatitis acneiform
Dermatitis allergic
Dermatitis atopic
Dermatitis bullous
Dermatitis contact
Dermatitis exfoliative
Dermatitis exfoliative generalised
Dermatitis herpetiformis
Dermatitis infected
Dermatitis psoriasiform
Device allergy
Dialysis membrane reaction
Distributive shock
Documented hypersensitivity to administered product
Drug cross-reactivity
Drug eruption
Drug hypersensitivity
Drug provocation test
Drug reaction with eosinophilia and systemic symptoms
Ear swelling
Eczema
Eczema infantile
Eczema nummular
Eczema vaccinatum
Eczema vesicular
Eczema weeping
Encephalitis allergic
Encephalopathy allergic
Endotracheal intubation
Eosinophil count abnormal
Eosinophil count increased
Eosinophil percentage abnormal
Eosinophil percentage increased
Eosinophilia
Eosinophilia myalgia syndrome
Eosinophilic bronchitis
Eosinophilic granulomatosis with polyangiitis
Eosinophilic oesophagitis
Eosinophilic pneumonia
Eosinophilic pneumonia acute
Eosinophilic pneumonia chronic
Epidermal necrosis
Epidermolysis
Epidermolysis bullosa
Erythema

Erythema multiforme
Erythema nodosum
Exfoliative rash
Eye allergy
Eye oedema
Eye swelling
Eyelid oedema
Face oedema
Fixed drug eruption
Flushing
Gastrointestinal oedema
Generalised erythema
Generalised oedema
Genital rash
Genital swelling
Giant papillary conjunctivitis
Gleich's syndrome
Haemolytic transfusion reaction
Haemorrhagic urticaria
Hand dermatitis
Henoch-Schonlein purpura
Henoch-Schonlein purpura nephritis
Heparin-induced thrombocytopenia
Hereditary angioedema
HLA marker study positive
Hypersensitivity
Hypersensitivity vasculitis
Idiopathic angioedema
Idiopathic urticaria
Immediate post-injection reaction
Immune complex level increased
Immune thrombocytopenic purpura
Immune tolerance induction
Immune-mediated adverse reaction
Immunoglobulins abnormal
Immunoglobulins increased
Immunology test abnormal
Implant site dermatitis
Implant site hypersensitivity
Implant site photosensitivity
Implant site rash
Implant site urticaria
Incision site dermatitis
Incision site rash
Infantile asthma
Infusion site dermatitis
Infusion site eczema
Infusion site hypersensitivity
Infusion site photosensitivity reaction
Infusion site rash
Infusion site recall reaction
Infusion site urticaria
Infusion site vasculitis
Injection site dermatitis
Injection site eczema
Injection site hypersensitivity
Injection site photosensitivity reaction
Injection site rash
Injection site recall reaction
Injection site urticaria
Injection site vasculitis
Instillation site hypersensitivity
Instillation site rash
Instillation site urticaria
Interstitial granulomatous dermatitis
Interstitial lung disease
Intestinal angioedema
Iodine allergy
Kaposi's varicelliform eruption
Kounis syndrome
Lacrimation increased
Laryngeal dyspnoea
Laryngeal obstruction
Laryngeal oedema
Laryngitis allergic
Laryngospasm
Laryngotracheal oedema
Leukotriene increased
Limbal swelling
Local swelling
Localised oedema
Mast cell degranulation present
Mechanical urticaria
Medical device site dermatitis

Medical device site eczema
Medical device site hypersensitivity
Medical device site photosensitivity reaction
Medical device site rash
Medical device site recall reaction
Medical device site urticaria
Mesenteric panniculitis
Mucocutaneous rash
Mucocutaneous ulceration
Mucosa vesicle
Mucosal erosion
Mucosal exfoliation
Mucosal necrosis
Mucosal ulceration
Multiple allergies
Nasal crease
Nasal obstruction
Nasal oedema
Necrotising panniculitis
Nephritis allergic
Neurodermatitis
Neutralising antibodies positive
Nikolsky's sign
Nipple oedema
Nipple swelling
Nodular rash
Noninfective conjunctivitis
Non-neutralising antibodies positive
Obstructive airways disorder
Occupational asthma
Occupational dermatitis
Oculomucocutaneous syndrome
Oculorespiratory syndrome
Oedema
Oedema genital
Oedema neonatal
Oedema peripheral
Orbital oedema
Oropharyngeal spasm
Palisaded neutrophilic granulomatous dermatitis
Palpable purpura
Panniculitis
Pathergy reaction
Penile exfoliation
Penile oedema
Penile swelling
Perineal rash
Periorbital oedema
Peripheral oedema neonatal
Peripheral swelling
Perivascular dermatitis
Photosensitivity reaction
Pneumonitis
Prurigo
Pruritus
Pruritus allergic
Pruritus generalised
Pulmonary eosinophilia
Radioallergosorbent test positive
Rash
Rash erythematous
Rash follicular
Rash generalised
Rash macular
Rash maculo-papular
Rash maculovesicular
Rash morbilliform
Rash neonatal
Rash papulosquamous
Rash pruritic
Rash pustular
Rash rubelliform
Rash scarlatiniform
Rash vesicular
Reaction to azo-dyes
Reaction to colouring
Reaction to drug excipients
Reaction to preservatives
Reactive airways dysfunction syndrome
Red man syndrome
Respiratory arrest
Respiratory distress

Respiratory failure
Respiratory tract oedema
Reversible airways obstruction
Rhinitis allergic
Rhinitis perennial
Scleral oedema
Scleritis allergic
Scrotal oedema
Scrotal swelling
Seasonal allergy
Septal panniculitis
Serum sickness
Serum sickness-like reaction
Shock
Shock symptom
Skin erosion
Skin exfoliation
Skin necrosis
Skin oedema
Skin reaction
Skin swelling
Skin test positive
Sneezing
Soft tissue swelling
Solar urticaria
Solvent sensitivity
Status asthmaticus
Stevens-Johnson syndrome
Stoma site hypersensitivity
Stoma site rash
Streptokinase antibody increased
Stridor
Suffocation feeling
Swelling
Swelling face
Symmetrical drug-related intertriginous and flexural exanthema
Throat tightness
Tongue exfoliation
Toxic epidermal necrolysis
Toxic skin eruption
Tracheal obstruction
Tracheal oedema
Tracheostomy
Transplantation associated food allergy
Type I hypersensitivity
Type II hypersensitivity
Type III immune complex mediated reaction
Type IV hypersensitivity reaction
Upper airway obstruction
Urticaria
Urticaria cholinergic
Urticaria chronic
Urticaria contact
Urticaria papular
Urticaria physical
Urticaria pigmentosa
Urticaria vesiculosa
Urticarial vasculitis
Vaccination site dermatitis
Vaccination site eczema
Vaccination site exfoliation
Vaccination site hypersensitivity
Vaccination site photosensitivity reaction
Vaccination site rash
Vaccination site recall reaction
Vaccination site urticaria
Vaccination site vasculitis
Vaccination site vesicles
Vaginal exfoliation
Vaginal oedema
Vaginal ulceration
Vasculitic rash
Vessel puncture site rash
Vessel puncture site vesicles
Visceral oedema
Vulval oedema
Vulval ulceration
Vulvovaginal rash
Vulvovaginal swelling
Vulvovaginal ulceration
Wheezing

13.3.15. Anaphylaxis SMQ Preferred Terms

Note: PTs containing the term oedema or swelling are highlighted in yellow; see Section 8.5, above for explanation.

SMQ Narrow A

Anaphylactic reaction
Anaphylactic shock
Anaphylactic transfusion reaction
Anaphylactoid reaction
Anaphylactoid shock
Circulatory collapse
Dialysis membrane reaction
Kounis syndrome
Procedural shock
Shock
Shock symptom
Type I hypersensitivity

SMQ Broad B

Acute respiratory failure
Asthma
Bronchial oedema
Bronchospasm
Cardio-respiratory distress
Chest discomfort
Choking
Choking sensation
Circumoral oedema
Cough
Cyanosis
Dyspnoea
Hyperventilation
Irregular breathing
Laryngeal dyspnoea
Laryngeal oedema
Laryngospasm
Laryngotracheal oedema
Mouth swelling
Nasal obstruction
Oedema mouth
Oropharyngeal oedema
Oropharyngeal spasm
Oropharyngeal swelling
Pharyngeal oedema
Pharyngeal swelling
Respiratory arrest
Respiratory distress
Respiratory dyskinesia
Respiratory failure
Reversible airways obstruction
Sensation of foreign body
Sneezing
Stridor
Swollen tongue
Tachypnoea
Throat tightness
Tongue oedema
Tracheal obstruction
Tracheal oedema
Upper airway obstruction
Wheezing

SMQ Broad C

Acquired C1 inhibitor deficiency
Allergic oedema
Angioedema
Circumoral swelling
Erythema
Eye oedema

Eye pruritus
Eye swelling
Eyelid oedema
Face oedema
Fixed eruption
Flushing
Hereditary angioedema with C1 esterase inhibitor deficiency
Injection site urticaria
Lip oedema
Lip swelling
Nodular rash
Ocular hyperaemia
Oedema
Oedema blister
Periorbital oedema
Periorbital swelling
Pruritus
Pruritus allergic
Rash
Rash erythematous
Rash pruritic
Skin swelling
Swelling
Swelling face
Swelling of eyelid
Urticaria
Urticaria papular

SMQ Broad D
Blood pressure decreased
Blood pressure diastolic decreased
Blood pressure systolic decreased
Cardiac arrest
Cardio-respiratory arrest
Cardiovascular insufficiency
Diastolic hypotension
Hypotension

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05/21/2020 12:42:30 AM

GERALD D PODSKALNY
05/21/2020 08:32:31 AM

Date	01/29/2019
From	Gerald D. Podskalny, DO, MPHS Eric Bastings, MD
Subject	Summary Review
NDA/BLA # **Supp #**	NDA 210875
Proprietary / Established (USAN) names	Kynmobi/Apomorphine hydrochloride
Dosage forms / strength	Sublingual film/ 10 mg, 15 mg, 29 mg, 25 mg and 30 mg
Proposed Indication(s)	The acute, intermittent treatment of "OFF" episodes associated with Parkinson's disease (b) (4)
Recommended:	Complete Response

1. Introduction

Sunovion Pharmaceuticals Inc. (Applicant), submitted a 505(b)(2) new drug application (NDA) for Kynmobi (apomorphine sublingual film) that relies, in part, on the FDA's previous findings of safety for the listed drug Apokyn (apomorphine hydrochloride injection). The listed drug, Apokyn subcutaneous injection (NDA 21-264), is approved for the treatment of "acute, intermittent treatment of hypomobility, off episodes ("end-of-dose wearing off" and unpredictable "on/off" episodes) in patients with advanced Parkinson's disease. The applicant is seeking approval for a similar indication. The applicant is proposing the tradename "Kynmobi" for the product, and that name will be used for the rest of this summary review.

2. Background/Regulatory History

A pre-IND meeting was held with the applicant in April 2011. During this meeting the Agency provided guidance on CMC, clinical, and nonclinical plans to support a 505(b)(2) application. An End-of-Phase 2 meeting was held in February 2015. At that meeting, FDA reached a general agreement on the Phase 3 clinical development program.

The applicant conducted a relative bioavailability study (CTH-200) designed to bridge Kynmobi and Apo-go, an apomorphine subcutaneous injection marketed outside of the United States. The applicant also submitted interim results of an ongoing relative bioavailability study (CTH-203) between Apokyn, Apo-go and Kynmobi. In addition, the applicant attempted to establish sameness between Apo-go and Apokyn based on composition and in vitro data.

The applicant also submitted the results from a controlled clinical trial, Study CTH-300, to support the effectiveness of Kynmobi. Local tolerability of the new

sublingual (SL) route of administration was assessed in Study CTH-300, and in open-label study CTH-301. The applicant also proposed relying on nonclinical and clinical pharmacology information from Apokyn (through a bridging approach).

3. Chemistry, Manufacturing, and Controls

The CMC review team is presented in Table 1.

Table 1. Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER	OPQ OFFICE
Drug Substance	Ben Zhang	Suong Tran	ONDP
Drug Product	Rao Kambhampati	Wendy Wilson-Lee	
Environmental			
Labeling			
Process	Yuesheng Ye	Nallaperumal Chidambaram	OPF
Facility		Ruth Moore	
Biopharmaceutics	Gerlie Geiser	Ta-Chen Wu	ONDP
Regulatory Business Process Manager	Dahlia Walters		OPRO
Application Technical Lead	Wendy Wilson-Lee		ONDP

Source: OPQ Review

Dr. Zhang noted that the applicant referenced DMF (b) (4) for all of the information to support the drug substance. The DMF has been reviewed and found acceptable on August 15, 2018. The revised specifications for the drug product are adequate. A concern about the proposed limit for an impurity (b) (4) was resolved during the review. The justification of the specification proposed to limit (b) (4) is acceptable based on the expected lifetime of exposure in patients with Parkinson's disease of 10 years or less (see Dr. Freed's Supervisory Memo).

The drug product reviewer concluded the proposed shelf-life of 36 months is acceptable when drug packages are stored at 25ºC, based on the real-time stability data. All stability studies met the specification criteria for microbial limits.

All facilities listed in the application were found to be acceptable.

The biopharmaceutics reviewer does not recommend approval of the application, "mainly due to an outstanding deficiency related to the lack of a final report for a clinical PK study essential to establish the bridge between the US Listed Drug product and the active comparator/European (EU) drug product used in another critical relative BA study". The biopharmaceutics reviewer also notes that "The

Applicant was not able to provide comparative in vitro data with respect to the functional performance characteristics (e.g., activation force, volume dispensed, dispensing time, extended needle length, leakage rate) of the device components of these two drug-device combination products. Thus, it was deemed necessary to rely mainly on in vivo comparative PK data from Study CTH-203 to establish "sameness" of these two drug-device combination products, i.e., Listed Drug, APOKYN® Auto-pen (multi-dose cartridge, formulation with benzyl alcohol) versus Apo-go PEN (multi-dose cartridge, formulation without benzyl alcohol)." I refer the reader to the Biopharmaceutics review for further details.

OPQ Recommendation

OPQ's recommends a Complete Response action, based on the Biopharmaceutics deficiencies described above.

4 Nonclinical Pharmacology/Toxicology

Luann McKinney, PhD, was the primary nonclinical reviewer for this application with Dr. Lois Freed, PhD, providing the supervisory nonclinical review.

The nonclinical studies submitted with the application included a 13-week oral toxicity of apomorphine where apomorphine was administered by oral gavage. The applicant also conducted a 28-day local toxicity study of apomorphine in hamsters where KYNMOBI was applied to the buccal mucosa. No drug-related effects were observed in the study in rats, and no local irritation was detected in the study conducted in hamsters.

Drs. Freed and McKinney concluded that the studies did not include adequate margins (metabolite exposure or apomorphine concentration) compared to humans; "however, neither study was considered essential for clinical development or an NDA."

Dr. McKinney had concerns regarding an impurity (b) (4) which was positive for bacterial mutagenicity in an adequately conducted (Q)SAR evaluation. Dr. Freed, in her supervisory memo, concluded that "the specification limit would result in a total daily dose of (b) (4) at the MRHD. This is acceptable from a nonclinical standpoint because the anticipated human use, for the proposed indication, is ≤10 years, for which the daily limit for a mutagenic impurity is (b) (4) March 2018)."

Nonclinical Recommendation
From a nonclinical standpoint, there is no objection to approval of the NDA (assuming an adequate bridge can be provided to Apokyn).

5 Clinical Pharmacology

Mariam Ahmed, PhD, was the primary Office of Clinical Pharmacology (OCP) reviewer for this application. Secondary review and concurrence was provided by Kevin Krudys, PhD., and Sreedharan Sabarinath, PhD. Final sign-off from OCP was provided by Mehul Mehta, PhD.

The applicant conducted a bridging study (Study CTH-200) between the to-be-marketed formulation of Kynmobi and APO-go (an apomorphine product for SC injection marketed outside of the United States). Study CTH-200 was a single-dose, single-center, randomized, two-way crossover study in healthy subjects (N=19) designed to assess the PK, safety, and tolerability of single doses of 15 mg Kynmobi and 2 mg of SC APO-go. The apomorphine exposure following administration of Kynmobi was approximately 19% of that of APO-go. The dose normalized apomorphine Cmax following administration of Kynmobi was approximately 11% of that after administration of APO-go. That study, however, does not establish a bridge to Apokyn, the listed drug.

The applicant also conducted was a 3-period crossover relative bioavailability study (Study CTH-203), in which patients received Kynmobi or the corresponding dose of APO-go or Apokyn. The applicant only submitted an interim report of the first 5 subjects who completed the study, and not the final report for Study CTH-203. As OCP considers the final report essential to adequately bridge Apokyn and Kynmobi, OCP is recommending a Complete Response action.

5.1 Drug-Drug Interactions

Dr. Ahmed noted that the current in vitro drug-drug interaction (DDI) guidance recommends that the DDI potential of a more polar metabolite than the parent needs to be evaluated if the metabolite has systemic exposure that is similar to or higher than the parent. In this case, in vitro studies are needed to evaluate the DDI potential of two major metabolites from KYNMOBI, apomorphine glucuronide and norapomorphine glucuronide.

5.2 Demographic Interactions/Special Populations

No dose adjustment is recommended based on gender or age. OCP does not recommend dose adjustment for subjects with mild or moderate renal impairment, but Kynmobi is not recommended in subjects with severe renal impairment. Kynmobi can be administered to patients with mild/moderate hepatic impairment with careful monitoring; however, treatment with Kynmobi is not recommended in patients with severe hepatic impairment.

5.3 Thorough QT Study

Gopichand Gottipati was the primary reviewer for the Thorough QT (TQT) study provided in this application (Study 201). The other members of the Interdisciplinary Review Team for QT Studies (IR-TQT) were Dhananjay D Marathe, Janell E Chen, Dalong Huang, Mohammad A Rahman, Michael Y Li, and Christine E Garnett. The applicant was required to submit results from a TQT study because an outstanding postmarketing commitment for the listed drug for a TQT study. In addition, Kynmobi has higher plasma levels of some metabolites that are not found with the listed drug and may have a QT effect.

The doses evaluated in the TQT study do not cover the exposures associated with the clinical dosing regimen. In addition, the sample size of the study was too small to detect dose-response for QTc prolongation. The IR-TQT team recommended removing language from labeling that describes the TQT study results because the results are inconclusive.

Office of Clinical Pharmacology Recommendation:
OCP conclusion is as follow: "The adequacy of the bridging cannot be fully evaluated without the final PK report of the ongoing study CTH-203 and therefore, we recommend not approving the application at this time".

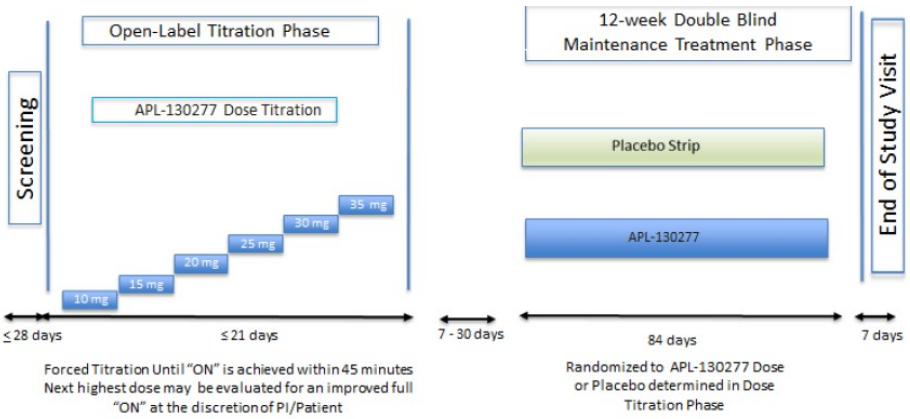
In addition, the applicant will need to evaluate the potential DDI for apomorphine glucuronide and norapomorphine glucuronide, which could be addressed as a postmarketing requirement.

6 Clinical/Statistical

Xiangmin Zhang, Ph.D. is the primary statistical reviewer for this application. Supervisory concurrence for the review findings was provided by Kun Jin, Ph.D., Team Leader and Hsien Ming Hung, Ph.D., Director, Division of Biometrics I. Kenneth Bergmann, M.D., is the primary clinical reviewer for this NDA.

As another dosage form of apomorphine (Apokyn) is already approved for the indication proposed by the applicant, a single efficacy study was required to establish the effectiveness of Kynmobi. That evidence was provided by the results of Study CTH-300. The study design included three phases, with a screening period followed by an open-label titration phase lasting up to 21 days, and a 12-week maintenance phase. In the titration phase, all patients started with a 10-mg film (Figure 2). The dose was increased at each visit until patients achieved a "Full-ON" state, as assessed by patients and the investigator, or reached the maximum dose of 35 mg. The dose resulting in a "Full-ON" state was the dose of Kynmobi or matching placebo patients were randomized to in the maintenance phase of the study.

Figure 2. Study CTH-300 Design Schematic



APL-130277 = Kynmobi

6.1 Baseline Demographic and Disease Characteristics

At baseline, the mean age was similar in both the placebo and Kynmobi groups. Overall, the study population was two-thirds male and one-third female. Patients in the study were 93% white. Baseline disease characteristics were similar between the groups with respect to time since diagnosis, duration of motor fluctuations and OFF time.

Table 2. Study CTH-300 Patient Disposition

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)[c]	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
APL-130277 = Kynmobi

Of the 109 patients randomized, 108 were from 27 sites in the United States. One patient in the ITT population was from a site in Canada.

6.2 Study Endpoint

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 (MV4). The key secondary efficacy endpoint was the percentage of subjects with a patient-rated full "ON"

response within 30 minutes of dosing at the Week 12 visit (MV4). These endpoints, taken together, are appropriate to assess the treatment of OFF episodes.

The primary endpoint was analyzed in the modified intent-to-treat (mITT) population using a mixed model with repeated measure (MMRM). The key secondary endpoint was analyzed using a generalized linear mixed model on binary data with logit link. Details of the analysis models are included in Dr. Zhang's review. The primary and key secondary endpoints were planned to be tested sequentially, each test at the two-sided significance level of 0.05.

6.3 Efficacy Results

The results for the change from pre-dose to 30 minutes post-dose for the MDS-UPDRS Part III score at Week 12 showed that Kynmobi was associated with a significantly greater reduction of UPDRS Part III scores, compared with placebo (p-value = 0.0002). The least square Kynmobi-placebo difference was -7.6 points (95% Confidence Interval [CI] (-11.5, -3.7)) (Table 3).

Dr. Zhang states that the applicant's sensitivity analyses support the results from the primary analysis.

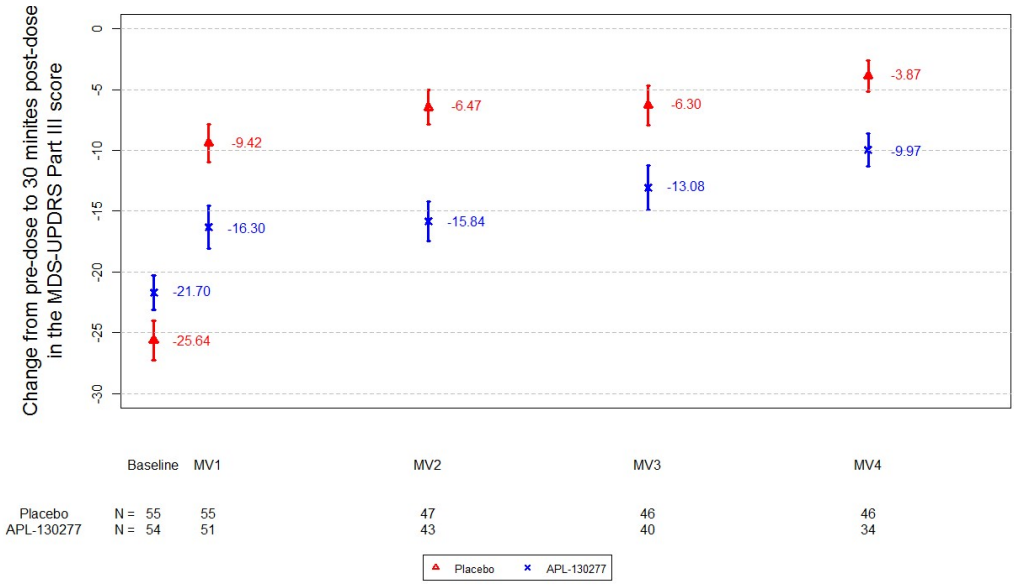
Table 3. Primary Endpoint: Study CTH-300 The Analysis of The Change from Pre-dose to 30 minutes Post-dose in the MDS-UPDRS Part III Score at Week 12 (mITT population)

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: statistical review
APL-130277 = Kynmobi

Dr. Zhang commented that the change from pre-dose to post-dose UPDRS Part III scores decreased between the beginning and the end of the study for both treatment groups (Figure 3), but the trends could have been affected by high percentages of missing observations in both treatment groups.

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: FDA statistical reviewer
APL-130277 = Kynmobi

Kynmobi was significantly better than placebo (p-value = 0.0426) for 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)) (see Table 4).

Table 4. Key Secondary Endpoint: Analysis of the Percentage of Subjects with a Subject-Rated Full "ON" Response Within 30 Minutes at Week 12 (MV4) (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: Source: FDA statistical review
APL-130277 = Kynmobi

An assessment of dose-response (Table 5) showed that all doses, except the 30-mg dose, were associated with a reduction in MDS-UPDRS Part III score at 30-minutes post-dose at the Week 12 (MV4) visit.

Table 5. 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)

	Placebo				Kynmobi			
	Baseline		Week 12		Baseline		Week 12	
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
10 mg	13	-22.3	12	-3.5	7	-25.6	4	-9.5
15 mg	11	-27.9	8	-3.6	18	-18.8	12	-13.4
20 mg	16	-24.9	15	-4.3	7	-20.6	4	-9.5
25 mg	9	-29.1	7	-6.9	12	-23.8	8	-10.0
30 mg	5	-25.4	4	1.50	4	-23.3	2	1.5
35 mg	1	-25.0	0	- (-)	6	-22.0	4	-6.3
Total	55	-25.6	46	-3.9	54	-21.7	34	-10.0

Source: FDA statistical reviewer
APL-130277 = Kynmobi

Dr. Zhang found no evidence from the subgroup analyses to suggest Kynmobi was more effective in a specific gender, or age group. The study population was 93% white, leaving too few patients in other racial groups to perform meaningful comparisons.

7 Safety

Kenneth Bergmann, MD was the primary safety reviewer for the application. Dr. Gerald David Podskalny, DO, MPHS provided secondary review and concurrence.

Dr. Bergmann's safety review focused on studies CTH-300 and CTH-301. Study 300 provided the controlled safety experience for Kynmobi, and Study 301 was an open-label safety study, which was still ongoing at the time of the review, but for which interim results were submitted. Study 301 enrolled new patients, and rollover patients who participated in studies CTH-300 or Study CTH 201 (a 3-period cross-over study to assess the effects of Kynmobi on QTc in 48 patients with Parkinson's disease).

7.1 Exposure

Dr. Bergmann notes that 451 patients and 99 healthy subjects received at least one dose of Kynmobi. The applicant proposed relying upon the FDA's previous finding of safety of Apokyn to support the systemic safety of Kynmobi. However, as discussed above, the bridging data were not found acceptable by OPQ and OCP.

The primary goal of long-term safety study CTH-301 was to evaluate the local safety and tolerability of chronic administration of Kynmobi.

Few patients used 60 mg or more per day. No patient took the maximum recommended dose of 35 mg 5 times per day (170 mg total) for 6 months or longer (Table 6).

Table 6. Number of Subjects Exposed to Kynmobi in Studies CTH-300 and CTH-301 by Categorical Extent of Exposure and Overall Average Total Daily Dose Category During the Maintenance/Treatment Phase

Extent of Exposure Category (months)	Overall Average Total Daily Dose Category (mg)								
	<20	**20 to <40**	**40 to <60**	**60 to <80**	**80 to <100**	**100 to <120**	**120 to <140**	**140 to <160**	**≥160**
<3	57	15	5	1	0	0	1	0	0
3 to <6	40	20	9	0	2	2	0	0	1
6 to <9	33	20	20	5	4	1	0	0	0
9 to <12	5	4	5	3	2	0	1	0	0
≥12	1	3	3	0	0	0	0	0	0
Total	**136**	**62**	**42**	**9**	**8**	**3**	**2**	**0**	**1**

Source 120-Day Safety Update P-28

Dr. Bergman commented that the calculation of patient exposure was difficult because of the study design that allowed for incomplete recording of daily medication use and the formatting of study datasets did not allow rollover patients to be tracked from Study 300 to Study 301. The applicant met the minimum exposure requirements agreed upon at Pre-NDA meeting (for 100 patients treated for at least 6 months) to adequately assess the long-term local (oropharyngeal) safety of Kynmobi.

7.2 Deaths

Three patients died during participation in any study included in the NDA. One patient in study CTH-300 with a long history of diabetes mellitus and hypercholesterolemia suffered a cardiac arrest. Another patient accidentally drowned while on vacation and a third patient died because of a psoas abscess with sepsis. The applicant could not exclude that treatment with Kynmobi was a contributing factor in the death of the patient who died from cardiac arrest. However, no definitive conclusion can be made about that single case. Dr. Bergmann's concluded that other two deaths are not likely related to treatment with Kynmobi. Overall, these cases do not raise a safety concern about Kynmobi.

7.3 Serious Adverse Events

In Study CTH-300, two patients treated with Kynmobi experienced a treatment-emergent serious adverse event (SAE). In Study CTH-301, 13 patients experienced an SAE. The two cases with fatal outcomes were discussed above. For the other 11 SAEs, Dr. Bergmann's assessment is that hypotension/syncope, altered mental state and fall were related or possibly related to use of Kynmobi. These events are known safety issues with the listed drug.

A woman with a history of asthma experienced severe worsening asthma and hypersensitivity pneumonitis during treatment with Kynmobi in Study 301. Kynmobi contains metabisulfites, and this patient with a history of asthma should have been excluded from the study.

7.4 Discontinuations

In controlled Study CTH-300 (n=109), 9% of patients treated with Kynmobi discontinued because of an adverse event in the titration phase, and 28% in the maintenance phase (Table 7).

Table 7. Discontinuation in the Titration Phase by Reason in Study CTH-300 (copied from Dr. Bergman's review)

Study 300 Titration	Sponsor CSR (N=141)	
AE	12 (8.5%)	
Lack of efficacy	11 (7.8%)	
Withdrew consent	8 (5.7%)	
Lost to follow-up	1 (0.7%)	
Study 300 Maintenance	Active (N=54)	Placebo (N=55)
AE	15 (27.8%)	5 (9.1%)
Lack of efficacy	0	1 (1.8%)
Withdrew consent	4 (7.4%)	3 (5.5%)
Death	1 (1.9%)	0

Adverse dropouts in the titration phase were mostly related to known safety issues with apomorphine (e.g., hypotension, dizziness and nausea). In the maintenance phase, many events were related to oropharyngeal adverse reactions (see Table 8).

Table 8. Adverse reactions leading to discontinuation in the maintenance phase of Study CTH-300 (copied from Dr. Bergman's review)

Maintenance Phase					
APL-130277					
10 mg (N=2)	15 mg (N=3)	20 mg (N=2)	25 mg (N=5)	30 mg (N=2)	35 mg (N=1)
Fall	Somnolence	Gingival oedema	Nausea	Swollen tongue	Disorientation
Oropharyngeal pain	Lip swelling	Lip oedema	Vomiting	Oral mucosal erythema	Fatigue
Oropharyngeal swelling	Swelling face	Oedema mouth	Lip swelling		Rhinorrhoea
Pharyngeal erythema	Urticaria	Delusion	Lip ulceration		
	Irritable bowel syndrome		Oral mucosal erythema		
			Oral allergy syndrome		
			Tongue polyp		
			Oropharyngeal swelling		
Placebo:					
10 mg (N=1)	15 mg (N=1)	20 mg (N=1)	25 mg (N=0)	30 mg (N=1)	35 mg (N=0)
Noninfective gingivitis	Erythema	Decreased appetite		Abnormal dreams	
Oral pain		Disturbance in attention		Confusional state	
Peripheral swelling		Dyskinesia		Hyperhidrosis	
		Muscle spasms		Nightmare	
				Somnolence	

In Study 301 (n=312), 251 patients (80%) were de novo participants, while the rest rolled over from Study 300. In that study, 56 patients (de novo or roll-over) discontinued treatment with Kynmobi early because of an adverse event in the maintenance phase. When the titration and maintenance periods are combined, 125 de novo patients (i.e., about half of the de novo population) withdrew early, with 70 patients citing an adverse event as causing the withdrawal (see Table 9).

Table 9. Discontinuation in Study CTH-301 (Titration + Maintenance Phase): De novo versus Roll-Over Patients

STATUS	REASON	APL-130277 De Novo	APL-130277, Rollover	APL-130277 All
Discontinued	Adverse Event	70	14	84
Discontinued	Death	2	0	2
Discontinued	Lack of Efficacy	11	1	12
Discontinued	Lost to Follow-Up	4	1	5
Discontinued	Other	3	1	4
Discontinued	Protocol Violation	5	0	5
Discontinued	Withdrawal by Subject	30	2	32
Discontinued	All	125	19	144

Source: CDTL

The two patients who died were discussed above. Five patients withdrew because of an adverse event that was serious. Nausea (n=16), lip swelling (8), mouth ulceration (7), and stomatitis (7) were the most frequently reported adverse events associated with early withdrawal in the titration and maintenance periods.

As in Study 300, oropharyngeal adverse reactions were a common reason for withdrawal in the maintenance phase of Study 301 (see Table 10).

Table 10. Adverse reactions leading to discontinuation in the maintenance phase of Study CTH-300 (copied from Dr. Bergman's review)

Study 301					
Roll-over population and de novo population after titration.					
10 mg (N=12)	15 mg (N=12)	20 mg (N=11)	25 mg (N=6)	30 mg (N=9)	35 mg (N=6)
Palpitations	Dyskinesia	Throat tightness	Lip blister	Dyskinesia (2)	Nausea
Feeling abnormal (2)	Oral herpes	Mouth lip or tongue swelling (4)	Mouth swelling	Freezing phenomenon	Confusional state
Somnolence	Throat irritation	Oral mucosal erythema	Dental caries	Lip swelling (3)	Dysarthria
Dizziness (2)	Mouth swelling	GERD	Dysgeusia	Fatigue	Hypoaesthesia oral
Nasal congestion	Glossodynia (2)	Vomiting or nausea (6)	Asthenia	Mouth ulceration	Oropharyngeal pain
Rhinorrhoea	Feeling abnormal	Tongue discomfort	Depression	Stomatitis	Lip exfoliation
Spontaneous penile erection	Head discomfort	Gingivitis	Back pain	Oropharyngeal pain	Oral discomfort
Vomiting or nausea (4)	Mouth ulceration (2)	Head injury	Angular cheilitis	Dysphagia	Oral mucosal blistering
Yawning	Vomiting or nausea (3)	Hypersomnia	Oral discomfort	Leukoplakia oral	Lip swelling (2)
Lip, face swelling (2)	Parkinson's disease	Syncope		Oropharyngeal pain	Mouth ulceration
Oral discomfort		Disorientation			
Salivary hypersecretion		Lip, tongue or mouth ulceration (3)			
Anxiety		Oral pain			
Dyskinesia					
Fatigue (2)					
Mouth ulceration (2)					
Asthenia					
Hot flush					
Syncope					
Hypoaesthesia oral (2)					
Stomatitis (2)					
Dry mouth					

7.5 Common Adverse Events

In study CTH-300 (controlled), randomization occurred at the time of entering the maintenance phase, when patients were assigned to placebo or the titrated dose of Kynmobi (all patients received Kynmobi during titration). If the analysis of adverse events is limited to the maintenance phase (as presented in Table 11), adverse events in patients who discontinued in the titration phase are not counted. The most common adverse reactions in the maintenance phase of Study 300 were nausea and dizziness. Oropharyngeal adverse reactions were reported in 26% of patients in the maintenance phase of Study 300 (see Table 11).

Table 11. Adverse Reactions ≥ 4% in the Kynmobi Group and Greater than Placebo in the Maintenance Phase of Study 300

Adverse Reactions	KYNMOBI (n=54) %	Placebo (n=55) %
Nausea	28	4
Vomiting	7	0
Somnolence	13	2
Fatigue	7	0
Yawning	4	2
Oral mucosal erythema	7	4
Dry mouth	6	0
Glossodynia	4	0
Lip oedema	4	0
Lip swelling	4	0
Lip ulceration	4	0
Oropharyngeal swelling	4	0
Throat irritation	4	0
Ageusia	4	0
Total Unique Cases (Oropharyngeal AEs)	14 (26%)	2 (4%)
Dizziness	9	0
Laceration	6	0
Falls	6	2
Hyperhidrosis	6	4
Flushing	4	0
Chills	4	0
Headache	6	0
Diarrhoea	4	2
Bronchitis	4	2
Anxiety	4	2

Source: CDTL

Among the 32 patients who discontinued for any reason (including adverse events) in the titration phase of Study CTH-300, 25 reported 155 adverse events before they left the study.

Table 12 shows the adverse reactions reported in patients who discontinued in the titration phase of Study 300, compared with adverse reactions in all patients who completed the titration phase.

Table 12. Adverse Reactions in ≥ 2% Patients Withdrew Early vs. Patients who Completed the Titration Phase in Study CTH-300

	Early Withdrawal (N = 32)			Titration Completed (N = 109)		
Preferred Term	**Events**	**Number of subjects**	**Proportion (%)**	**Events**	**Number of subjects**	**Proportion (%)**
Nausea	19	12	38	21	17	16
Dizziness	10	8	25	11	8	7
Somnolence	15	8	25	15	10	9
Headache	11	7	22	5	4	4
Yawning	9	6	19	19	11	10
Chills	5	4	13	6	4	4
Rhinorrhoea	7	4	13	9	5	5
Vomiting	4	4	13	2	2	2
Dyspepsia	3	3	9	0	0	0
Fatigue	3	3	9	1	1	1
Hot flush	4	3	9	2	1	1
Hyperhidrosis	6	3	9	3	3	3
Constipation	2	2	6	0	0	0
Dysgeusia	6	2	6	1	1	1
Feeling cold	4	2	6	0	0	0
Musculoskeletal stiffness	2	2	6	0	0	0
Oral mucosal erythema	2	2	6	12	4	4
Orthostatic hypotension	2	2	6	0	0	0
Pallor	2	2	6	0	0	0
Presyncope	2	2	6	0	0	0
Pyrexia	3	2	6	1	1	1

Source: CDTL

Table 13 shows the adverse reactions reported in open-label study CTH-301. The adverse reactions are similar in ranking and frequency as the adverse reactions reported in controlled Study CTH-300.

Table 13. AEs by Preferred Terms for Unique Patients ≥ 2% in Study CTH-301 (Safety population)

Preferred Term	Titration (N=308) %	Maintenance (N=259) %	Titration + Maintenance (N=308) %
All	78	254	292
Nausea	8	16	21
Yawning	7	5	11
Somnolence	4	5	8
Oral mucosal erythema	4	5	8
Dizziness	3	5	7
Fatigue	3	5	7
Headache	5	2	6
Dyskinesia	2	4	5
Fall	1	5	5
Lip swelling	0	6	5
Orthostatic hypotension	3	2	5
Mouth ulceration	0	5	4
Dysgeusia	2	2	4
Hyperhidrosis	1	3	4
Stomatitis	0	4	4
Vomiting	1	3	4
Rhinorrhoea	1	3	3
Back pain	1	2	3
Dry mouth	0	3	3
Glossodynia	0	3	3
Oral candidiasis	0	3	3
Oropharyngeal pain	0	3	3
Swollen tongue	0	3	3
Hypoaesthesia oral	1	2	2
On and off phenomenon	0	3	2
Ageusia	0	2	2
Anxiety	0	2	2
Blood pressure increased	1	1	2
Cough	1	1	2
Dyspnoea	0	2	2
Hypotension	1	2	2
Insomnia	0	2	2
Lacrimation increased	1	1	2
Lip ulceration	1	1	2

Preferred Term	Titration (N=308) %	Maintenance (N=259) %	Titration + Maintenance (N=308) %
Syncope	0	2	2
Urinary tract infection	0	2	2
Arthralgia	0	2	2
Contusion	0	2	2
Dental caries	0	2	2
Feeling abnormal	0	2	2
Feeling cold	1	1	2
Hypertension	1	0	2
Oral discomfort	0	2	2
Oral pain	0	2	2
Parkinson's disease	0	2	2

Source: CDTL

7.6 Special Safety Concerns

Oropharyngeal edema and pain, and events suggestive of angioedema

Early in the review, the review team noticed patients with adverse events suggestive of angioedema. The team asked the applicant to conduct Standardized MedDRA queries for angioedema and anaphylaxis, to include all subjects exposed to Kynmobi.

In Study CTH-300, 9 patients treated with Kynmobi who experienced oral adverse events withdrew from the study, versus a single patient in the placebo group who withdrew because of oral pain and noninfective gingivitis. None of these events were serious.

In addition, a variety of oropharyngeal adverse events were observed in patients treated with Kynmobi, mostly in the maintenance phase (Table 14). As many as 16% of patients in the maintenance phase experienced adverse reactions compatible with oropharyngeal edema, versus none on placebo.

Table 14. Oropharyngeal Edema reported as an Adverse Reaction in Study 300

Event	Titration Kynmobi (n=141)	Maintenance		Titration or maintenance Kynmobi (n=141)
		Kynmobi (n=54)	Placebo (n=55)	
Gingival edema	0	1	0	1
Lip edema	0	2	0	2
Lip swelling	1	2	0	3
Oedema mouth	0	1	0	1
Oral allergy syndrome	0	1	0	1

Event	Titration	Maintenance		Titration or
Oropharyngeal swelling	0	2	0	2
Pharyngeal edema	0	1	0	1
Swelling face/soft palate	0	1	0	1
Swollen tongue	0	1	0	1
Stomatitis	0	1	0	1
Oropharyngeal Edema - Total Events	1	13	0	14
Unique patients with Oropharyngeal Edema	1 (<1%)	9 (16%)	0	10 (7%)

Source: CDTL

In the maintenance phase, oropharyngeal adverse reactions causing pain were reported in 9% of patients treated with Kynmobi, vs. 2% on placebo (Table 15).

Table 15. Oropharyngeal Pain reported as an Adverse Reaction in Study 300

Event	**Titration Kynmobi (n=141)**	**Maintenance**		**Titration or maintenance Kynmobi (n=141)**
		Kynmobi (n=54)	**Placebo (n=55)**	
Gingival pain	0	1	0	1
Glossodynia	0	2	0	2
Oral pain	0	1	1	2
Oropharyngeal pain	1	1	0	2
Oropharyngeal Pain - Total Events	1	5	1	7
Unique patients with Oropharyngeal Pain	1 (<1%)	5 (9%)	1 (2%)	6 (4%)

Source: CDTL

In Study CTH-301, the most frequently reported adverse events associated with early withdrawal include lip swelling (8), mouth ulceration (7), and stomatitis (7). A patient withdrew with serious adverse events of dysphagia, dyspnea, and pharyngeal erythema. He experienced mouth burning for 3 weeks while on Kynmobi 10 mg. The applicant submitted a MedWatch Report (2018SUN000675) to the IND, which included information stating the patient was admitted to the hospital after presenting to the emergency department. The patient was noted to have an edematous posterior pharynx and required treatment with intravenous steroids and oral diphenhydramine.

The incidence of oropharyngeal hypoesthesia was similar in patients treated with Kynmobi and those on placebo in the maintenance phase of Study 300 (Table 16).

Table 16. Oropharyngeal Hypoesthesia reported as an Adverse Reaction in Study 300

Event	Titration Kynmobi (n=141)	Maintenance		Titration or maintenance Kynmobi (n=141)
		Kynmobi (n=54)	Placebo (n=55)	
Hypoaesthesia	2	0	1	3
Hypoaesthesia oral	0	1	0	1
Paraesthesia oral	1	1	0	2
Oropharyngeal Hypoaesthesia - Total Events	3	1	0	6
Unique patients with Oropharyngeal Hypoaesthesia	3 (2%)	1 (2%)	1 (2%)	5 (4%)

Source: CDTL

In open-label Study 301, oropharyngeal adverse events causing edema (Table 17) were reported in 13% of patients in the maintenance phase, versus none in the titration phase.

Table 17. Oropharyngeal Edema reported as an Adverse Reaction in Study 301

Event	Titration Kynmobi (n=308)	Maintenance Kynmobi (n=252)
Gingival edema	0	1
Lip edema	0	1
Lip swelling	0	21
Oedema mouth	0	4
Oral allergy syndrome	0	0
Oropharyngeal swelling	0	0
Pharyngeal edema	0	2
Swelling face/soft palate	0	5
Swollen tongue	0	10
Stomatitis	0	18
Oropharyngeal Edema - Total Events	0	62
Unique patients with Oropharyngeal Edema	0	34 (13%)

In open-label Study 301, similarly to Study 300, oropharyngeal adverse events causing pain were reported more frequently in the maintenance phase (8%) than in the titration phase (1%) (Table 18). The time course of these events suggest that duration of exposure is a key factor in their development.

Table 18. Oropharyngeal Pain reported as an Adverse Reaction in Study 301

Event	Titration Kynmobi (n=308)	Maintenance Kynmobi (n=252)	Titration or maintenance Kynmobi (n=308)
Gingival pain	0	0	0
Glossodynia	0	8	8
Oral pain	0	5	5
Oropharyngeal pain	2	7	9
Oropharyngeal Pain - Total Events	2	20	22
Unique patients with Oropharyngeal Pain	1 (<1)	19 (8%)	20 (7%)

Source: CDTL

Oropharyngeal hypoesthesia adverse events were reported in 3% of patients in the maintenance phase and 1% of patients in the titration phase of Study 301 (Table 19).

Table 19. Oropharyngeal Hypoesthesia reported as an Adverse Reaction in Study 301

Event	Titration Kynmobi (n=308)	Maintenance Kynmobi (n=252)	Titration or maintenance Kynmobi (n=308)
Hypoaesthesia	0	0	0
Hypoaesthesia oral	2	5	7
Paraesthesia oral	0	2	2
Oropharyngeal Hypoaesthesia - Total Events	2	9	10
Unique patients with Oropharyngeal Hypoaesthesia	2 (1%)	7 (3%)	9 (3%)

Source: CDTL

As oropharyngeal adverse reactions are not reported in the labeling of the listed drug, Apokyn, we asked for a review of postmarketing experience with Apokyn for events suggestive of angioedema. Charlene M. Flowers, RPh, Safety Evaluator Division of Pharmacovigilance I searched the FDA Adverse Event Reporting System (FAERS) database for multiple types of hypersensitivity reports with apomorphine. Her search identified only a single serious FAERS case of anaphylaxis with Apokyn (apomorphine) SC administration. There were 9 total case reports of "lip swelling, swelling face and mouth swelling"; the highest EB05 score was 0.238 for "swollen tongue" (3 reports). Dr. Flowers concluded the number of reports were low, and the EB05 scores were below the threshold of concern. This information shows a sharp contrast between Apokyn and Kynmobi for the number of oropharyngeal adverse reactions.

7.7 Laboratory Findings

Dr. Bergmann's found that there were no meaningful differences in clinical laboratory assessments. No Hy's Law cases occurred. Shift tables revealed no consistent or unusual patterns of abnormality outside of what could be considered usual laboratory variation.

7.8 Vital Signs

Dr. Bergmann noted that in the maintenance phase of Study 300, a higher percentage of subjects in the Kynmobi group had a reduction of ≥ 20 mmHg for the change in orthostatic systolic blood pressure (SBP) or ≥ 10 mmHg drop in diastolic blood pressure (DBP) (42.6% Kynmobi; 36.4% placebo). Similar results were observed in patients treated with Kynmobi in the maintenance phase of Study CTH-301. Hypotension is a known safety issue for Apokyn.

7.9 Electrocardiograms

Patients with Parkinson's disease enrolled in clinical trials of Kynmobi had premorbid cardiovascular disease, including electrocardiographic abnormality. Few patients had prolonged QT or minor arrhythmias. None of these events were serious.

7.10 Safety Analyses in Subgroups

Dr. Bergmann found that adverse events were similar in male and female patients. Elderly patients were more likely to experience nausea and vomiting following treatment with Kynmobi.

7.11 Discussion of Safety Findings

As discussed above, there is a clear signal for oropharyngeal adverse reactions with Kynmobi. These include various symptoms related to oropharyngeal edema, with pain and hypoesthesia also reported. These reactions led to treatment withdrawal in a substantial number of patients treated with Kynmobi. The oropharyngeal adverse reaction was reported as serious in one patient. All cases for which information was available appeared to have resolved with discontinuation of the drug. Overall, the applicant's characterization of the oropharyngeal adverse reactions is inadequate. The description of the time to onset, duration of the symptoms, time to recovery, associated abnormalities (e.g., clinical laboratory abnormalities), need for medical intervention and time to recovery was not adequately described by the applicant. The safety sections of the submission did not show the unique patients who experience a cluster of oral adverse events. The action letter will request the applicant submit a clear and comprehensive assessment of oropharyngeal adverse reaction and hypersensitivity-related adverse reactions.

At a minimum, information about oropharyngeal adverse reactions would need to be positioned prominently in the Warnings and Precautions section, and prescribers would be instructed to inform patients about the risk.

Adverse reactions not related to local swelling were similar in type to those observed in clinical studies of the listed drug. Nausea, somnolence and dizziness were the most commonly reported adverse reactions in the controlled and uncontrolled trial populations.

7 Financial Disclosure

Dr. Bergmann found the applicant complied with the requirement to disclose financial interests, arrangements, and payments under (see 21 CFR § 54.4(a)(3).

8.1 Proprietary Name

DMEPA completed its' review of the proprietary name and concluded the proposed proprietary name, Kynmobi is conditionally acceptable.

8.2 Pediatric Study Requirements

The applicant submitted an agreed initial Pediatric Plan. The NDA include a request for a full waiver for studies. The Pediatric Review Committee (PeRC) granted the Applicant's request for a full waiver on October 31, 2018, based on the Applicant's justification that the necessary studies are impossible or highly impracticable.

8 Labeling

Labeling discussions were deferred because of deficiencies resulting in a complete response action.

9.1 Human Factors Validation Study

The Division consulted the Division of Medication Error Prevention and Analysis (DMEPA) to review the Applicant's Human Factors Validation (HF) study. The review team from DMEPA included Ebony Whaley, PharmD, BCPPS DMEPA Safety Evaluator; Lolita White, PharmD, DMEPA Team Leader; Quynh Nhu Nguyen, MS, DMEPA Associate Director for Human Factors; and Danielle Harris, PharmD, BCPS, DMEPA Deputy Director.

The HF validation study included trained and untrained patients, caregivers and healthcare providers (total 91 participants-15 per group with one extra untrained patient) identified numerous use errors and close calls while subjects attempted to performed critical tasks. The most frequent errors increased the risk that patients would receive an underdose. Thirty-three participants swallowed before the film fully dissolved, 7 failed to visually check if the film completely dissolved before swallowing and 16 patients were unable to determine if the film had fully dissolved. The applicant did not provide data to demonstrate that proposed mitigations and changes to the IFU are effective and do not introduce new use-related risks.
The sponsor proposed a titration kit for Kynmobi; however, the titration kit was not assessed in the initial use-related risk analysis (URRA) submitted under the IND or in the HF validation study.

The Division sent the Applicant a Discipline Review (DR) letter on November 21, 2018, outlining the deficiencies in the HF Validation study, and an informal teleconference with the applicant on November 27, 2018, to discuss these issues. The Applicant was aware that the HF validation study deficiencies were potential approvability issues.

The deficiency in HF assessment are the basis for the complete response action. A new HF study will be needed.

10 DSI Audits

Clinical site inspections were requested for two domestic sites. The Office of Scientific Investigations (OSI) complete inspections of Site #1007 and Site #1029. OSI concluded: "The studies appear to have been conducted adequately, and the data generated by these sites appear acceptable in support of the respective indication."

11 Conclusions and Recommendations

Although the applicant submitted adequate information to support the efficacy of Kynmobi for the treatment of intermittent OFF episodes in patients with Parkinson's disease, serious deficiencies in human factors preclude the approval of this product: the Instructions for Use and the titration kit packaging do not ensure safe and effective use of Kynmobi in patients with advanced Parkinson's disease. The applicant will need to assess the ability of patients to use of the child-resistant packaging, and repeat the human factors validation study to address the risk for medication errors.

In addition, the applicant has not provided an adequate bridge to Apokyn, the listed drug referenced in the application. An adequate bridge will be needed to support the systemic safety of Apokyn. As only an interim report of Study 203 was submitted, the applicant must complete Study 203 and provide the final report for Study 203 in the response to the CR letter. This is necessary to justify the relevance of

comparative data between Kynmobi and Apo-go to support the scientific appropriateness of reliance on FDA's finding of safety for Apokyn. In addition, the applicant will need to clearly describe the data and information that support the scientific bridge between Kynmobi and the listed drug relied upon (Apokyn), which may include data and information supporting a bridge between Kynmobi and Apo-go and between Apokyn and Apo-go.

Moreover, oropharyngeal adverse reactions were commonly observed in patients treated with Kynmobi. The submission did not include a systematic evaluation of these events. The applicant needs to present a comprehensive discussion and summary of oropharyngeal adverse reactions, clearly showing the onset, evolution, time course, and time to resolution of these events, and their association to systemic hypersensitivity (if any). Updated analyses from ongoing Study 301 also need to be provided by the applicant.

If the application is approved following resubmission and review, information about oropharyngeal adverse reactions would be positioned prominently in the Warnings and Precautions section of labeling, and prescribers would be instructed to inform patients about the risk.

12 Comments to Applicant

Comments to the applicant will be conveyed in the Action Letter.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

GERALD D PODSKALNY
01/29/2019 09:26:40 PM

ERIC P BASTINGS
01/29/2019 09:32:41 PM

CLINICAL REVIEW

Application Type	505(b)(2) Type 3 New Dosage Form, non-NME
Application Number(s)	NDA 210875
Priority or Standard	Standard
Submit Date(s)	3/29/2018
Received Date(s)	3/29/2018
PDUFA Goal Date	1/29/2019
Division/Office	DNP, ODE I, OND
Reviewer Name(s)	Kenneth Bergmann, MD
Review Completion Date	1/29/2019
Established/Proper Name	APL-130277 (apomorphine hydrochloride sublingual thin film)
(Proposed) Trade Name	KYNMOBI
Applicant	Sunovion
Dosage Form(s)	Sublingual thin film
Applicant Proposed Dosing Regimen(s)	10, 15, 20, 25, 30 (b) (4) sublingually up to five times daily separated by at least 2 hours
Applicant Proposed Indication(s)/Population(s)	For the acute, intermittent treatment of "off" episodes associated with Parkinson's disease
Recommendation on Regulatory Action	Not Approvable (Complete Response)
Recommended Indication(s)/Population(s) (if applicable)	Adults with Parkinson's disease and "off" episodes

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Glossary

AC	advisory committee
ADaM	Analysis Data Model
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDISC	Clinical Data Interchange Standards Consortium
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COMT	catechol-O-methyl transferase
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
CT	computerized tomography
DBS	deep brain stimulation
DMEPA	Division of Medication Error Prevention and Analysis
DSMB	Data Safety Monitoring Board
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
HF	human factors
ICH	International Council for Harmonization
IND	Investigational New Drug Application

ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MAED	MedDRA Adverse Event Diagnosis Tool
MAOI	monoamine oxidase inhibitor
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
MRI	magnetic resonance imaging
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	Parkinson's disease
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
PT	Preferred Term
RLD	reference listed drug
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SDTM	Study Data Tabulation Model
SGE	special government employee
SOC	standard of care
SPA	Special Protocol Assessment
TEAE	treatment emergent adverse event
UPDRS	Unified Parkinson's Disease Rating Scale

1. Executive Summary

1.1. Product Introduction

APL-130277 is a new dosage form of apomorphine, a dopamine agonist. KYNMOBI, the provisionally approved commercial name for APL-130277, is apomorphine hydrochloride contained in a thin film for sublingual use. Apomorphine is currently approved as a subcutaneous injection (APOKYN®, NDA 21264) indicated for the treatment of *acute, intermittent treatment of hypomobility, "off" episodes ("end-of-dose wearing off" and unpredictable "on/off" episodes) associated with advanced Parkinson's disease.* KYNMOBI is seeking approval (b) (4) via the 505(b)(2) regulatory pathway.

The applicant proposes a dose range of 10 (b) (4) by sublingual administration. KYNMOBI is provided as 10, 15, 20, 25 and 30 mg thin films. (b) (4) Doses should be separated by at least 2 hours and may be taken up to 5 times daily.

KYNMOBI requires dose titration and is initiated with 10 mg. The dose level is increased until an adequate clinical response, "on" or mobile motor state, is attained. Because KYNMOBI often causes nausea and vomiting when treatment is initiated (and often continuing during chronic use), oral trimethobenzamide has been used as a concomitant antiemetic treatment. Most patients in the clinical trials supporting the APL-130277 application used trimethobenzamide 300 mg t.i.d.

1.2. Conclusions on the Substantial Evidence of Effectiveness

Study CTH-300 (mITT n=109) evaluated APL-130277 compared to placebo in a 12-week blinded, randomized trial in which treatment was titrated to best clinical effect in producing the "on" motor state 30 minutes after administration as quantified by a reduction in the Part III motor score of the Unified Parkinson's Disease Rating Scale (UPDRS). This primary outcome assessment was performed following drug administration at the week 12 clinic visit. The patient's own assessment of the "on" state was the basis of the key secondary outcome measure, the percentage of subjects with a subject-rated full "on" response within 30 minutes post-dose at the week 12 visit in the maintenance treatment phase.

Despite considerable dropout by the week 12 evaluation visit, APL-130277 was significantly superior to placebo in producing a reduction in the UPDRS motor score commensurate with an "on" state 30 minutes after administration. In the modified ITT population, the least squares mean Part III score was reduced by 11.1 points versus a mean 3.5-point reduction in the placebo arm (LS mean difference -7.6 [95% CI -11.5, -3.7]; p=0.0002). This was corroborated by prespecified sensitivity analyses of the primary endpoint.

A statistically significant difference was seen in favor of APL-130277 versus placebo in the percentage of patients achieving a self-rated full "on" response within 30 minutes at the week 12 evaluation visit (41.2% vs 19.6%; adjusted odds ratio: 2.81 [95% CI: 1.04, 7.64]; p = 0.0426)

The study was judged by the reviewer to be of sufficient robustness and quality to support a claim of effectiveness for the treatment of "off" episodes in patients with Parkinson's disease.

While approvable based on clinical efficacy, the full risk of APL-130277 cannot be assessed. There is one outstanding issue that renders the application non-approvable:

- The KYNMOBI package dispensed to patients for drug administration in both Study CTH-300 and in the long-term safety study, CTH-301, was not the intended-to-be marketed packaging. Thus, the human factors study validating whether patients could correctly use the medication was insufficient. For this reason, the Division of Medication Error Prevention and Analysis recommends a Complete Response. The packaging for this thin film drug product is of special importance in this motorically vulnerable and disadvantaged population.

This clinical reviewer agrees with the assessment the DMEPA reviewer and finds the APL-130277 application to be non-approvable at this time.

1.3. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

APL-130277 (apomorphine sublingual thin film) is being developed to treat the episodic "off" periods that can occur in moderately advanced PD patients who suffer from lapses in the motor benefit provided by regularly scheduled medications.

Because the risk profile of this investigational product cannot be fully determined, it is not approvable. A Complete Response is recommended.

Parkinson's disease (PD) is a debilitating, incurable disease that degenerates the nerve cells that produce the chemical messenger dopamine. It is the second most common neurodegenerative disorder after Alzheimer's disease. The average age of onset is 55 years of age and it is estimated to affect one million Americans. Core motor symptoms include bradykinesia (a decrease in spontaneity and movement), rigidity, tremor, and postural instability. These are often the recognizable first sign of illness and provide a basis for clinical diagnosis. Non-motor symptoms are also common. There is no cure for Parkinson's disease; however, there are FDA approved treatments to manage the symptoms of Parkinson's disease, especially the motor deficit.

Effective pharmacologic treatment options for Parkinson's disease include the following: carbidopa-levodopa formulations, dopamine agonists, catechol-O-methyltransferase (COMT) inhibitors, monoamine oxidase inhibitors-B inhibitors (MAOI), anticholinergics, and amantadine. Deep brain stimulation (DBS) is also an effective, though invasive, therapeutic option for the motor symptoms of Parkinson's disease in selected patients. Motor fluctuations, especially periods of "off" time and "on" time with troublesome dyskinesia (involuntary movements) often result from the therapeutic drug effect on motor symptoms wearing off intermittently. This can occur rarely or as often as every dosing interval of the patient's regular medication. These "off" periods put the patient at an increased risk for a diminished functional status and disease-related emotional deterioration. Apomorphine, the reference listed product for this application is currently available (b) (4) administered in sterile solution form by subcutaneous injection.

The efficacy of APL-130277, apomorphine thin film sublingually administered, was demonstrated by Study CTH-300. Using PD patients on standard drug treatment with at least 2 hours of "off" time daily, Study CTH-300 evaluated the efficacy and safety of APL-130277 with an initial open label titration period followed by randomization into a double-blind 12-week maintenance period. Treatment was initially titrated to the dose that produced an "on" state 30 minutes after administration (10 to 35 mg sublingually). For those patients that tolerated the medication and demonstrated a beneficial response during titration, the patient's individual dose was then used to randomize treatment to active drug or placebo.

Of the 141 patients entering the titration phase, 109 (77%; APL-130277 n=54; placebo n=55) were successfully randomized to the blinded maintenance treatment phase of the study where the patient self-administered the drug at home when needed. The subject was evaluated monthly by being dosed and observed at a clinic visit. In the maintenance period, the effective dose was 15, 20, or 25 mg for 2/3 of the PD patients.

For those remaining in the study at the 12 week visit, APL-130277 (n=34) or placebo (n=46) was administered in clinic to the patient with an "off" period induced by withholding the day's PD medication. Using the UPDRS Part III motor score in the "off" period as a baseline, the UPDRS motor score was rated at 30 minutes following sublingual administration of active drug or placebo. The reduction in the motor score (i.e. improvement) constituted the primary efficacy outcome measure. The key secondary efficacy outcome measure was the percentage of patients attaining a self-rated fully "on" motor state at 30 minutes. As measured by both outcomes, the APL-130277 treated patients improved more than the placebo treated patients to a statistically significant degree. The amount of benefit achieved by the patients treated with APL-130277 is similar to that of the reference listed drug as described in its prescribing information (apomorphine for subcutaneous injection, NDA 21264).

The safety profile of apomorphine is well characterized. It is a powerful stimulant of dopamine, noradrenergic, and serotonergic receptors, creating many adverse drug reactions from "off target" action. Because of this, apomorphine can be difficult to tolerate. The safety of APL-130277 was observed in Study CTH-300 and Study CTH-301, a long term open label safety study. Of 392 PD patients being introduced to medication in the titration phase of Studies 300 and 301, 311 (79 %) went on to maintenance treatment. The most commonly observed treatment related side effects are nausea and vomiting, sleepiness, and symptoms related to the lowering of blood pressure. Because of the common occurrence of nausea, patients are given antiemetic medication (trimethobenzamide) during titration of APL-130277 and if they continue to experience nausea during maintenance treatment.

Patients treated with APL-130277 experienced a variety of allergic reactions both locally in the mouth and systemically. These occurred frequently enough so that a description of these reactions should be added to the prescribing information to alert healthcare providers, patients and caregivers.

This drug would add a considerable measure of convenience to the use of a drug substance known to be effective for the treatment of "off" episodes in PD while omitting the need for subcutaneous injection. However, inability to fully quantify the risk of APL-130277 makes it non-

approvable, that is, the packaging used in the clinical trials is not the same as the packaging that will be used in commercial distribution. The uncertainty regarding the ability of the PD patient to manipulate and open the drug packaging potentially increases the risk of the patient not being able to be dosed correctly. Alternatively, it may lead the patient and/or caregiver to create solutions that may undermine the integrity of the thin film drug product.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Parkinson's disease is a debilitating, incurable disease that degenerates the nerve cells that produce the chemical messenger dopamine. • Parkinson's disease is the second most common neurodegenerative disorder after Alzheimer's disease. It begins in middle age; the average age of onset is 55 years of age. The prevalence of Parkinson's disease rises with age: 0.5 - 1% among persons age 65 to 69; 1-3% among persons 80+ years of age. • Core motor symptoms include bradykinesia (a decrease in spontaneity and movement), rigidity, tremor, and postural instability. These are often the recognizable first sign of illness and provide a basis for clinical diagnosis. • Other symptoms may include depression, anxiety, and other emotional changes; difficulty in swallowing, chewing, and speaking; urinary problems or constipation; skin problems; and sleep disruptions. • Motor fluctuations, especially periods of "Off" time and "On" time with troublesome dyskinesia (involuntary movements) often accompany drug treatment of the motor symptoms. These put the	Parkinson's disease is a common, progressive, degenerative neurological disorder. It is a serious brain disease that exacts a considerable physical and emotional toll from patients. Over time it can significantly impact a patient's quality of life and place a heavy burden on patients' ability to live independently and functionally perform daily tasks without assistance.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	patient at an increased risk for disease-related emotional deterioration.	
Current Treatment Options	• There is no cure for Parkinson's disease; however, there are FDA approved treatments to manage the symptoms of Parkinson's disease, especially the motor deficit. • Pharmacologic treatment options for Parkinson's disease include the following: carbidopa-levodopa formulations, dopamine agonists, catechol-O-methyltransferase (COMT) inhibitors, monoamine oxidase inhibitors-B inhibitors (MAOI), anticholinergics, and amantadine. • Apomorphine administered by subcutaneous injection is approved for the episodic treatment of motor "off" periods. • Other treatments sometimes used to treat the emotional and behavioral aspects of Parkinson's disease include antidepressants and anxiolytics. • Deep brain stimulation (DBS) is also an effective, though invasive, therapeutic option for the motor symptoms of Parkinson's disease. DBS may result in significant benefit. Downsides include, the surgery itself, neuropsychiatric adverse effects, and limited effectiveness if the implanted device is off target. Thus, many patients are unable or reluctant to undergo DBS. • Patients also pursue a holistic approach to treatment that often includes exercise and changes in diet.	Drug treatments for the motor disability of PD are available; however, efficacy varies from patient to patient and may also be accompanied by side effects which may limit benefits or preclude use of these medications. Most moderately advanced PD patients have daily periods of time when their medication fails to work well to improve their motor function. Additionally, the frequency of dosing and route of administration can often be burdensome on patients. Side effects of medication frequently limits the ability for the patient to take fully effective doses of drugs. Thus, there is a continued need for additional well-tolerated, safe and effective treatment options.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• Using PD patients on standard drug treatment with at least 2 hours of "off" time daily, Study CTH-300 evaluated the efficacy and safety of APL-130277 with an initial open label titration period followed by randomization into a double-blind 12-week maintenance period. • Treatment was initially titrated to the dose that produced an "on" state 30 minutes after administration (10 to 35 mg sublingually). For those patients that tolerated the medication and demonstrated a beneficial response during titration, the patient's individual dose was then used to randomize treatment to active drug or placebo. • Of the 141 patients entering the titration phase, 109 (77%; APL-130277 n=54; placebo n=55) were successfully randomized to the blinded maintenance treatment phase of the study where the patient self-administered the drug at home when needed. The subject was evaluated monthly by being dosed and observed at a clinic visit. In the maintenance period, the effective dose was 15, 20, or 25 mg for 2/3 of the PD patients. • For those remaining in the study at the 12 week visit, APL-130277 (n=34) or placebo (n=46) was administered in clinic to the patient with an "off" period induced by withholding the day's PD medication. Using the UPDRS Part III motor score in the "off" period as a baseline, the UPDRS motor score was rated at 30 minutes following sublingual administration of active drug or placebo. The reduction in the motor score (i.e. improvement) constituted the primary efficacy outcome measure. The key secondary efficacy outcome measure was the percentage of patients attaining a self-rated fully "on" motor state at 30 minutes. • On average, the UPDRS motor score for the APL-130277 treated arm	APL-130277 in doses from 10 to 35 mg was effective in significantly improving (reducing) the UPDRS Part III motor score 30 minutes after administration. This was associated with the patient attaining a self-rated satisfactory and clinically meaningful "on" state. The effect size was similar in magnitude to the subcutaneous injection of apomorphine, the route of administration for the currently approved reference listed drug. APL-130277 may be a more convenient option for PD patients suffering from "off" episodes due to its sublingual route of administration.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	was significantly reduced by 7.6 points more than the placebo treated arm (least squares mean: -11.1 vs. -3.5; p=0.0002). • Patients treated with APL-130277 reported reaching an "on" motor state twice as often as those receiving placebo. This was also a statistically significant difference (41.2% vs. 19.6%; p=0.0426). • This is similar to the benefit achieved with the reference listed drug as described in its prescribing information (apomorphine for subcutaneous injection, NDA 21264).	
Risk and Risk Management	**Risk** • Apomorphine is a potent but nonselective stimulant of dopamine, noradrenergic, and serotonergic receptors, creating many adverse drug reactions from "off target" action. • Because of this, apomorphine can be difficult to tolerate. The safety of APL-130277 was observed in Study 300 and Study 301, a long term open label safety study with both new and "roll-over" patients. • Of 392 PD patients being introduced to medication in the titration phase of Studies 300 and 301, 311 (79 %) went on to maintenance treatment. In Study 300, while 54 entered maintenance treatment on double-blinded APL-130277, by the evaluation visit at week 12 only 34 (63 %) remained; 46 of 55 (84%) of placebo treated patients reached this visit. • The most commonly observed treatment related side effects are nausea and vomiting, sleepiness, symptoms related to the lowering of blood pressure, and a variety of hypersensitivity reactions. • Nausea and vomiting is common and expected with apomorphine; patients are administered antiemetic medication during titration of	While effective in the treatment of "off" periods, APL-130277 is difficult to tolerate. This is likely a direct effect of its mechanism of action. Apomorphine is a potent but nonselective stimulant of dopamine, noradrenergic and serotonergic receptors in the central and peripheral nervous systems, creating many adverse drug reactions from "off target" action. This is reflected in the most common adverse events seen in the titration and maintenance phases of the clinical studies performed in support of safety. Because of this, APL-130277 is difficult to tolerate, even when taken with anti-emetic drugs designed to alleviate the most common adverse event, nausea and

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	APL-130277 and if they continue to experience nausea during maintenance treatment. • Hypersensitivity reactions (swollen lips, mouth, and tongue, mouth ulceration, inflammation of the gums, and flushing) occurred more often in chronic treatment. Anaphylaxis was rare but did occur. • This drug is used episodically as a rescue treatment for "off" periods. In both Studies 300 and 301, documenting the number of times a day APL-130277 was used was to be reported by patient diaries for the two days prior to clinic visits and usage was to be confirmed by count of returned unused medication and packaging. Both measures had a high rate of protocol non-compliance, bringing their accuracy into question. • The package in which drug was dispensed to patients for outpatient use was not the intended-to-be marketed packaging. As a result, the human factors study validating whether patients could correctly use the medication was insufficient, especially when conflated with the poor accounting of returned medication and patient use data. **Risk Management** • The safety profile of treatment emergent side effects during the clinical use of APL-130277 is like that of the Reference Listed Drug except for the quantity and quality of hypersensitivity reactions observed. Most of these are mild and recognizable and may be treated with discontinuation and symptomatic treatment. They should however be described in the prescribing information for this product as they distinguish this product from the RLD. • The Division of Medication Error Prevention and Analysis (DMEPA) finds that there was no assessment of the APL-130277 titration kit	vomiting. Allergic reactions to APL-130277 occurred frequently in the safety population. While these were generally mild and usually resolved with discontinuation, the patient experience differs enough from the side effect profile of the innovator (which is also labeled for a general hypersensitivity warning) that it should be identified in the prescribing information label. The inadequacy of the drug packaging cannot be corrected by a risk management solution and leads to the recommendation of a **Complete Response**: The uncertainty regarding the ability of the PD patient to manipulate and open the drug packaging potentially increases the risk of the patient not being able to be dosed. It may lead the patient and/or caregiver to create solutions that may undermine the integrity of the thin film drug product and its safe use.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	(b) (4) intended for marketing. The results of the Human Factors validation study did not demonstrate that the user interface is safe and effective for use. A new HF study with the intend-to-market package is needed and DMEPA recommends a **Complete Response.**	

1.4. Patient Experience Data

The primary efficacy outcome measure for APL-130277 was the reduction in the motor symptoms as measured by the Unified Parkinson's Disease Rating Scale (UPDRS), Part III motor examination 30 minutes following sublingual administration. To corroborate that the observed reduction in the UPDRS score was of clinical significance, the patient was asked to rate that they had obtained a full "on" response within 30 minutes. This was the key secondary outcome efficacy measure for the pivotal trial supporting the efficacy of APL-130277.

Table 1 Patient experience data relevant to this application.

X	The patient experience data that was submitted as part of the application include:			Section where discussed:
	X	Clinical outcome assessment (COA) data, such as		Section 6.1, Study 300 endpoints
		X	Patient reported outcome (PRO)	
		□	Observer reported outcome (ObsRO)	
		□	Clinician reported outcome (ClinRO)	
		□	Performance outcome (PerfO)	
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	X	Patient-focused drug development or other stakeholder meeting summary reports		Section 2.1, Analysis of Condition
	□	Observational survey studies designed to capture patient experience data		
	□	Natural history studies		
	□	Patient preference studies (e.g., submitted studies or scientific publications)		
	□	Other: (Please specify)		
□	Patient experience data that were not submitted in the application, but were considered in this review:			
		□	Input informed from participation in meetings with patient stakeholders	
		X	Patient-focused drug development or other stakeholder meeting summary reports	Therapeutic Context, Current Treatment Options
		□	Observational survey studies designed to capture patient experience data	
		X	Other: (Please specify)	Reviewer's clinical experience
□	Patient experience data was not submitted as part of this application.			

2. Therapeutic Context

2.1. Analysis of Condition

Parkinson's disease (PD) is a chronic progressive degenerative disorder of the central nervous system, with slowly progressive degeneration of the nigrostriatal dopamine system. The predominant motor symptoms are tremor, increased muscle tone and bradykinesia, but non-motor symptoms also cause considerable disability. The underlying pathophysiology of the motor symptoms is a deficiency of dopamine in neuronal terminals in the striatum.

The estimated incidence of PD is 4.5 to 16 per 100.000 persons/year. The prevalence of PD is between 175 to 350 / 100,000 population in the US. Parkinson's disease is associated with eventual disability or death. Untreated PD had a mortality rate of 80 % within 10 years of diagnosis, but even successfully treated PD patients without dementia still experience a shortened life span.

Parkinson's disease as a clinical syndrome is likely the final clinical result of a variety of brain pathologies, some acquired and some with a genetic contribution. PD has been described in every population, race and ethnic group and in both sexes.

The diagnosis is made clinically, using established criteria derived from the presence of the major motor symptoms of the disease: bradykinesia, rigidity and tremor. More recently, imaging studies with ligands that demonstrate dopaminergic function in the striatum have been a technology used to help support the clinical diagnosis.

Non-motor symptoms generally occur during the illness and can antedate the development of the motor signs. These are often more troublesome than the motor symptoms for which a range of pharmacological and surgical treatments exist.

A public FDA patient-focused drug development meeting (in which this reviewer participated) was held on September 22, 2015.[1] The meeting assembled the perspectives of patients, caretakers and other patient representatives on the most significant effects of their disease, its impact on daily life, and their experiences with currently available therapies. The key themes the report of the meeting emphasized included symptoms and their management.

- Parkinson's disease is a progressive, devastating disease. Participants emphasized the difficulty of living with the unexpected onset and progression of symptoms. Many described living with daily motor symptoms which included bradykinesia, dyskinesia, tremor and dystonia. In addition to motor symptoms, participants also highlighted sleep disturbances, cognitive impairment, fatigue, and constipation.

[1] https://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM498266.pdf

- The meeting reiterated the complexity of Parkinson's disease management. Participants described the burden of selecting the best available treatments to address their symptoms, the complexity of managing proper timing of medications in addition to pill burden (number and frequency of pills taken throughout the day), and the need for adjustment of their medication regimen because of unpredictable symptoms, changes in daily demands leading to increases in symptoms, as well as disease progression.

Among the motor symptoms, the bradykinesia of PD and the dyskinesia resulting from its treatment were rated most problematic. Freezing of gait was also disturbing. Motoric fluctuations are often eclipsed by more troublesome symptoms for which there are few or no treatment options: freezing, imbalance, cognitive impairment, sleep disturbance, orthostatic hypotension, and depression. However, the periodic loss of medication effect on mobility remains problematic for many patients.

- Participants expressed frustration with periods of "off-time," which was described as unpredictable exacerbation of symptoms during which medications were less effective. A few described the unpredictability that off-time brought into their lives on a daily basis. One participant shared, "[symptoms] can vary not only from day to day, but from hour to hour." This comment resonated with many participants. One participant stated, "the various off-and-on states, is what makes this disease so hard to live with." Another participant described experiencing "several months of good on-time, and then off-time where I can't even stabilize myself with a walker."

At least one participant shared an experience of using [subcutaneously injected] apomorphine to control unexpected symptoms in the work place. Several perspectives were provided on ideal treatments for Parkinson's disease. The top three aspects of ideal treatment desired by commenters included medications with less "off" time, better symptom control, and *fewer side effects* [emphasis added].

2.2. Analysis of Current Treatment Options

Levodopa (L-dihydroxyphenylalanine or L-dopa) is a dopamine precursor which is decarboxylated in the brain to become dopamine. It is combined with carbidopa, a dopa-decarboxylase (DDC) inhibitor, so that this conversion takes place mostly within the central nervous system. This remains an effective symptomatic therapy of PD motor symptoms four decades following its introduction. However, with each passing year of levodopa treatment, more fluctuations in motor control occur. These often become disabling. Motor complications involve fluctuations, erratic or unstable responses to medications (e.g. wearing-off phenomena) and dyskinesia or involuntary movements.

Current scientific concepts suggest that the wearing off of the therapeutic effect of levodopa at

intervals ("off" states) during the day is closely related to waning levels of levodopa in the blood and dopamine in the brain (related to the fairly short plasma half-life levodopa). Treatments have been developed to extend the action of levodopa. These include extended release formulations and drugs that reduce the catabolism of levodopa peripherally before it gets to the brain (catechol-o-methyl transferase inhibitors) as well as after it has been converted to dopamine in the central nervous system (monoamine oxidase B inhibitors). Artificial dopamine receptor agonists have also been developed to directly act upon the central dopamine receptors. These have served to generally extend dopaminergic tone in the CNS from dose to dose and often allow for some reduction of levodopa dose which may result in lessened dyskinesia. Some agents that affect other neurotransmitter systems are also used, particularly for tremor reduction (anticholinergics) or reduction of dyskinesia (amantadine). Finally, apomorphine, an injectable non-selective dopamine agonist is approved in the US for episodic use in treating "off" states that occur as drug effects wear off. This application is intended to support the administration of apomorphine by the sublingual route for the alleviation of "off" periods.

Beginning with the approval of levodopa (NDA 16912) in 1970, there are now over two dozen drug products approved for PD based upon their effectiveness on alleviating the motor symptoms of the disorder. Only subcutaneous injection of apomorphine is currently approved for the episodic treatment of "off" states.

Table 2 Types of currently available anti-Parkinson medication

Dopamine precursor	levodopa		Catabolic inhibitors:	
			DOPA decarboxylase	carbidopa
Dopamine agonist	apomorphine			
	bromocriptine		COMT	entacapone
	pramipexole			tolcapone
	ropinirole			
			MAO-B	selegiline
Anticholinergic	amantadine			rasagiline
	trihexyphenidyl			
	benztropine		Antiglutamatergic	amantadine

Direct electrical stimulation or ablative lesions of the basal ganglia outflow (thalamus, pallidum, or subthalamic nucleus) have also been effective in alleviating the motor symptoms of PD in a selected group of patients.

There are other classes of drugs that assist in the treatment of non-motor symptoms but those are not touched upon here.

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

APL-130277 is not currently in commercial distribution. The product upon which it relies for aspects of development, APOKYN® (apomorphine for subcutaneous injection, NDA 21264) has been approved in the US since 2004 (b) (4).

3.2. Summary of Presubmission/Submission Regulatory Activity

IND 110955 for APL-130277 sublingual thin film was opened in the US in July, 2014, for the treatment of episodic "off" periods in patients with Parkinson's disease.

The regulatory interactions with the sponsor that were most relevant to the clinical development of APL-130277 are summarized below. (These do not include additional interactions between the sponsor and the QT-IRT during the development of the TQT study protocol.)

Pre-IND Type B Meeting (April 20, 2011)
The sponsor was told that the intended population (i.e., Parkinson's disease patients experiencing "off" symptoms) should be able to interact with the packaging to administer medication correctly at the correct dose. As a result, FDA recommended the following actions be taken:

- Study the intended population to ensure that they can easily interact with the packaging to administer the product correctly.
- Data should be submitted to show that patients with the same severity of motor symptoms of the intended population can open your product package with a reasonable amount of effort.

"If bioequivalence to the RLD were not demonstrated then clinical trials demonstrating safety and efficacy would be required to support the safe and effective use in the intended PD population."

"Trials should be designed keeping in mind what claims are intended to be made with regard to supporting chronic use, number of times a day it may be administered, and the safety of repeat doses within a 24-hour period. Clinical data for both efficacy and safety will be required to provide support for the frequency of repeated dosing within a 24-hour period for the treatment of "off" periods."

"Because "off" periods are more frequent and prolonged in patients with advanced PD, you should consider recruiting patients who report at least 2 hours of "off" time in a 24-hour

period. This may help insure that clinically appropriate "off" periods are induced by withholding the morning anti-PD medication."

"Long-term data is also more likely to be required if, there is a novel or acute toxicity associated with your product, the presence of a new metabolite or one that is present in greater concentration compared to the levels associated with APOKYN® (i.e., because of the different route of administration). The need for long-term data will also depend on how the profile of adverse drug reactions compare to the marketed product."

"If controlled trials are required, a blinded, randomized, placebo controlled trial that demonstrates continued effectiveness for at least 12 weeks that supports the proposed claim is required to provide evidentiary support of efficacy and safety in patients treated for a chronic, non-life-threatening, chronic illness such as PD. Appropriate comparison to placebo will help define the drug effect and safety profile. This is especially important where a high rate of nausea, vomiting, dizziness and/or syncope could be observed."

"Pharmacokinetic and pharmacodynamic interactions between thin-film delivered sublingual apomorphine and any anti-emetic co-treatment must be appropriately clarified in a trial setting."

End of Phase 2 Type B Meeting (February 4, 2015)
Synopses of the protocols for Study 300 and 301 were submitted but due to insufficient detail only general responses were provided to the sponsor.

"We are concerned about the ability to maintain blinding of treatment assignment in study CTH-300. The patient's experience with APOKYN® prior to enrolling with APL-130277 in the Dose Titration Phase will likely make it possible for patients to discern which treatment arm they have been assigned to, based on the difference in taste, tongue sensation and effect on their Parkinson's disease. A demonstration of dose-response by adding a low dose arm of APL-130277 may help to address that concern."

Reviewer's comment: The sponsor addressed this by creating an open label titration period for all patients prior to randomizing to active vs placebo arms. This determined the best effective dose for each PD patient but, as will be seen, this titration period also suffered from much drop out and ultimately created a selectively enriched PD population for the blinded portion of the trial.

"Study populations should be clearly defined and correspond to the specified data analyses. The intent-to-treat population, which includes all patients who are randomized and receive at least one dose of investigational product, should be the primary population for the primary analysis. The mean change from baseline is assessed only in patients with a baseline and a post-baseline measurement. Therefore, imputation of missing values at baseline by the site-specific average is not acceptable."

"To strongly control overall type- I error in testing the primary, co-primary (if any), and key secondary endpoints, adjustment for multiplicity should be implemented in the analyses."

There was concern that unblinding by adverse reaction (especially nausea and vomiting) could compromise the blinding of the study. "A very robust clinical effect of the drug may lessen concerns about the potential effect of any lapse in blinding upon the trial."

Agreement was reached concerning efficacy endpoints: change from baseline on the UPDRS Part III motor scale, "provided that a positive result on the change in the UPDRS, Part 3 is supported by the key secondary endpoint (percentage of patients with a patient-determined full ON response within 30 minutes at [week 12]). APL-130277 is being studied for its ability to provide "on- demand therapy for the treatment of OFF episodes in levodopa responsive patients with PD"; however, numerical improvement from baseline on the UPDRS, Part 3 score assesses the motor symptoms of PD but does not assess clinically meaningful reversal of OFF episodes…. FDA agreed that a very robust change at 13 weeks from baseline in UPDRS Part III scores will support clinical effectiveness, but in the case of a less robust motor effect, the patient perception of the ON period becomes more important. The sponsor suggested that the ON and OFF state will be easily differentiated by the patient, but FDA expressed concern that some milder patients may not find it so clear-cut. In the presence of a lower but statistically significant response in UPDRS Part III, the key secondary measures become important in determining the clinical meaningfulness of the result."

Agreement was also reached concerning the parameters of the safety monitoring plan.

The sponsor asked if "following 206 patients for 6 months and up to 63 patients for 9 months sufficient to ascertain any concerns regarding the safety for APL-130277? " FDA agreed, "unless unexpected safety findings are identified that may require further testing."

The sponsor proposed subdivision and characterizations of multiple conditions that result in the "off" state. FDA responded that "In study CTH-300, you plan to conduct in office evaluations of patients in a "functional off state" by withholding their morning Parkinson's medications. We anticipate that the indication would not specify which type of "OFF" the drug is indicated for."

FDA noted that "the proposed dosing regimen needs to be supported by clinical data derived the safety and efficacy information from the controlled clinical trial experience included in your NDA submission."

Use-related risk analysis in package design was addressed and discussion took place regarding the need for a human factors validation study. This is discussed further in the Division of Medication Error Prevention and Analysis (DMEPA) review of the validation study and package evaluation.

The letter conveying meeting minutes to the sponsor also highlighted the need to implement and use data standards for the design, conduct, and analysis of the proposed clinical studies.

Advice / Information Request (April 14, 2016)
The FDA notified the sponsor that there were concerns about establishing the "sameness" of APOKYN® and APO-go® products manufactured in 2016. One concern is that the determination that the two products are bioequivalent was made in 2004, and the APO-go® product may have changed, and the products may no longer be bioequivalent."

Advice / Information Request (March 21, 2017)
An amendment to Study 300 was submitted to the IND and advice was given concerning proposed changes to the SAP and other concerns related to this pivotal trial:

"…Domperidone is not an approved drug in the U.S. The information from patients treated with domperidone and APL-130277 does not appear capable to support an application for APL-130277."

"You are planning an unblinded dose escalation titration, which is an enrichment procedure. Therefore, you should carefully describe all enrichment failures (e.g., those who cannot tolerate APL-130277 or who never achieve an "on" state) in the study report and datasets."

"Dyskinesia must be carefully evaluated and recorded in the protocol, including whether "troublesome" or "non-troublesome"."

"If the protocol allows dosing of up to 5 "off" periods daily, you will need to show that the exposure from the maximum recommended daily dose of APL-130277 is not greater than the exposure resulting from the maximum recommended dose of APOKYN® described in labeling, in order to rely on safety information from APOKYN®."

"The protocol states that the DSMB will evaluate the trial after 50% of patients have completed the titration phase. The interim analysis should be fully described in the SAP before the study is initiated, especially if the results are used to change the design of the study. You need to prospectively describe all unblinded or blinded reviews of the efficacy data in the protocol and SAP. The protocol and SAP should describe in detail the firewall between the board and sponsor/CRO personnel. No one involved in the conduct of the trial may participate or be present in any DSMB activities."

Statistical guidance was given regarding the UPDRS rating to be used as the baseline for efficacy evaluation and methods for imputation of missing data. "To test the impact of how missing data are handled, you should perform sensitivity analysis at least for the primary efficacy analysis population, mITT. In the case of monotone missingness, the analysis will not include the situation that all post- randomization values are missing."

Guidance Type C Meeting - Written Responses (May 26, 2017)
The size of the safety population was agreed upon. For specified AEs, "analysis should include time to occurrence, the actual dose at which the AE occurred, concomitant medications, and the outcome of the event."

"Indicate whether there was a process in place for the identification and prospective evaluation of the AESI listed. Include in your analysis, the list of terms (e.g., MedDRA Preferred Terms) with details of how these events were elicited, evaluated, and reported."

"In addition to narratives for deaths, SAEs, AEs leading to withdrawal from a study, and other significant adverse events, you should provide narratives for patients with AEs leading to dose reductions, and for patients who withdrew consent to participate in a study as a result of an AE. These should be provided regardless of whether the event was considered to be study drug related."

The sponsor was explicitly reminded to follow CDISC standards, especially for the ISS datasets. "Use the same Unique Subject Identifier for controlled and uncontrolled studies so that patients who rolled over from the double-blind trial to the open follow-up study are not counted as separate individuals and that exposures are correctly calculated."

Reviewer's comment: It should be noted that the sponsor largely ignored the advice given in this communication and the advice given at the preNDA meeting regarding dataset standards. This omission did not result in a Refuse to File recommendation as it was felt that clinical review was still possible and would clarify these situations. (The full extent to which the submitted datasets did not adhere to data standards was not fully recognized by the clinical reviewer at the time of the filing meeting.)

PreNDA Type B Meeting (February 6, 2018)
The details of the structure and format of the NDA submission was agreed upon, considering advice previously given to the sponsor.

Specific advice was given regarding the support for individual dose levels:

> "FDA recognized that in the pivotal clinical trials, APL-130277 was administered using a flexible and intermittent dosing schedule, so that the requirement for having information from at least 100 patients treated with dosages of APL-130277 intended for clinical use for 6 months or longer, with at least half treated with the highest recommended dose, does not directly apply."
>
> "FDA stated that dosages described in labeling would need to be supported by the clinical trials (controlled and long-term) experience. The Sponsor should provide a clear and unambiguous presentation of the doses (mg) used, the number of doses taken each

day, and for how many days each dose was used in the submission. The Sponsor clarified that the number of doses taken each day by each patient can only be inferred and calculated from the number of doses dispensed at each visit and the number of doses returned at the following visit. The dose and frequency of administration is only available from patient diaries kept for the two-day period prior to scheduled study visits."

"FDA suggested that diary information from the two days prior to each visit be provided to support the maximum daily dose and frequency of administration described in labeling (i.e., mg dose x number of times taken in each day). The Sponsor is encouraged to present the experience supporting the use of APL-130277 in ways that show the varied patterns of use among individuals but clearly indicate how adverse events are related to dose and method of use. This information should also be identifiable in the datasets for review."

Other Regulatory Interaction

Agreement was reached concerning the initial Pediatric Study Plan in August, 2015. (A request for a full waiver was made at the time of NDA submission; DNP agrees with granting the waiver as PD does not occur in the pediatric population.)

Fast track status was granted in August, 2016.

The requested proprietary name *KYNMOBI* was deemed conditionally acceptable by DMEPA in June, 2018.

3.3. Foreign Regulatory Actions and Marketing History

This product is not currently commercially available.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

The clinical team requested OSI inspection of two clinical sites in the single pivotal trial supporting efficacy of APL-130277. The sites were selected because of the number of protocol violations; there were no obvious reasons to suspect data integrity at these sites. The sponsor also performed audits of clinical sites and supporting clinical research organizations and had obtained satisfactory results. Discussion of the findings of the OSI inspections may be found in the discussion of Data Quality and Integrity in the review of Study 300.

4.2. Product Quality

The drug product, APL-130277 (apomorphine hydrochloride) sublingual film, is a soluble, blue to green (b) (4) film strip designed to deliver apomorphine systemically by sublingual administration. (b) (4)

Five strengths of APL-130277 (10, 15, 20, 25, and 30 mg) are manufactured by (b) (4)

Dosage units are individually packaged into peelable composite foil laminate pouches.

4.3. Clinical Microbiology

This section is not relevant to this review.

4.4. Nonclinical Pharmacology/Toxicology

The pharmacology / toxicology review team finds that there are no outstanding concerns impacting approvability.

In nonclinical studies in rabbit and golden hamster, the sublingual drug product produced no irritation to oral or cheek pouch mucosa.

Pyridoxine HCl is a major component (b) (4) of the drug product (b) (4) film and, at the sponsor's maximum proposed dose, the daily dose of pyridoxine would be (b) (4). Although (b) (4) daily dose administered for pyridoxine-dependent seizures, it is the clinical team's opinion that (b) (4) of this substance that is generally regarded as safe (GRAS) is acceptable.

In stability studies, three degradant impurities were identified. Two are structurally like apomorphine and are not considered to be of concern; the third, (b) (4) is specified at an acceptable intake based on the advanced age of the patient population.

Reviewer's comment: In discussion with the review team, it is apparent that there is no useful animal model to predict human hypersensitive to drug substance or product.

4.5. Clinical Pharmacology

Apomorphine is a non-ergoline, non-selective dopamine agonist that binds dopamine receptor subtypes with approximately equal affinity.

Table 3 Apomorphine binding affinity to dopamine receptors (source: sponsor pharmacology written summary, page 7)

	D1	D2(S)	D2(L)	D3	D4	D5
Affinity (pKi)	6.43 ± 0.05	7.46 ± 0.05	7.08 ± 0.01	7.59 ± 0.07	8.36 ± 0.07	7.83 ± 0.11

Apomorphine was identified in the 19th century and had experimental use as a treatment for Parkinson's disease by Schwab in 1951. However, its side effect profile, notably hypotension and nausea and vomiting, and its poor oral bioavailability impeded its usefulness as a medicinal product.

In addition to dopamine receptors, apomorphine has remarkably equally potent affinity for all alpha adrenergic and serotonin receptors (α 1A, 1B, 1D, 2A, 2B, and 2C; ^5HT 1A, 1B, 1D, 2A, 2B, and 2C). This provided a mechanistic basis for its most troublesome side effects and likely accounts for much of its poor tolerability in the clinical setting. There is both experimental and clinical evidence that the profound nausea and hypotension are related to the direct action of apomorphine on the pars postrema (chemotactic trigger zone in the medulla) which is supplied by a portal circulation with direct exposure to the peripheral blood stream.

The safety pharmacology has been previously reviewed by FDA for the RLD for this 505(b)(2) product and is found in the label for APOKYN®, NDA 21264. Reference is made by the sponsor to studies conducted in support of the development of APOKYN®. The sponsor has conducted no new nonclinical safety pharmacology studies with APL-130277 but did perform a Thorough QT study reviewed below in Section 8.4.9.

Similarly, the sponsor conducted no new nonclinical studies or studies to investigate the distribution, metabolism, excretion or drug interaction of apomorphine.

The sponsor did study absorption properties of the thin film in rabbits and performed human a clinical pharmacology study (CTH-200) relevant to understanding the properties of the sublingual thin film dosage form used in this submission. The clinical pharmacology reviewer summarized the following points:

> In clinical studies, following sublingual (SL) administration of the 15 mg dose in healthy volunteers, the time to maximum concentration (T_{max}) ranged from 0.5 to 1 hour. Compared with the subcutaneous formulation, the relative bioavailability of APL-130277 is approximately 19%. Apomorphine exposure increased with increasing APL-130277 dose; however, the increase in C_{max} and AUC was less than dose proportional over the dose range of 10 to 50 mg.
>
> After SL administration of 15 mg of APL-130277 15 mg, the geometric mean of the

apparent volume of distribution, the geometric mean of apparent clearance, and the median terminal half-life ($t_{½}$) were 3630 L, 1440 L/h, and 1.75 h, respectively.

Apomorphine is eliminated mainly through metabolism with small amount excreted unchanged in urine after SL administration (i.e. 0.03 % of the apomorphine dose). The major metabolic pathway for apomorphine from APL-130277 is sulfation and glucuronidation by multiple sulfotransferase and glycosyltransferase enzymes, with limited N-demethylation catalyzed by multiple enzymes, including CYP2B6, CYP2C8 and CYP3A4/5, followed by conjugation.

Change in the route of administration from SC to SL resulted in significant changes in the metabolic profile. Observed AUC values of apomorphine sulfate, apomorphine glucuronide, and norapomorphine glucuronide exposures were 4.4, 15.8, and 9.1-fold greater following SL administration compared to SC administration.

As with the RLD, no dose adjustment is required in patients with mild/moderate renal impairment or mild/moderate hepatic impairment. Also like the RLD, APL-130277 is not recommended in patients with severe renal impairment or severe hepatic impairment

Bridge to Apokyn (RLD)
The sameness of the APO-go® and APOKYN® drug components was assessed by the OPQ Biopharmaceutics Branch and it was concluded as adequate. For further details, the reader is referred to the review by Dr. Gerlie Gieser, biopharmaceutics reviewer. Based on the interim analysis from study CTH-203, the relative bioavailability of KYNMOBI relative to APOKYN® and APO-go® is similar (i.e. 19% and 19.6%, respectively). Similarly, the ratio of the dose normalized C_{max} for KYNMOBI is also similar relative to APOKYN® and APO-go® (i.e. 15% and 14.8%, respectively).

Taken together, these studies support the PK bridging of KYNMOBI to the RLD APOKYN®.

4.6. Devices and Companion Diagnostic Issues

This section is not relevant to this application.

4.7. Consumer Study Review

The Division of Medication Error Prevention and Analysis has evaluated the use of the packaging for the drug product and has recommended a Complete Response. The fact that the packaging intended for market was not the packaging used in the clinical efficacy and safety studies and was not the packaging subject to human factors validation study by the sponsor is problematic. This has created a safety issue that interferes with the approvability of the APL-130277. This topic is explored in greater detail in Section 8.7.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

A total of 10 clinical studies have been completed and 3 clinical studies are ongoing in the APL-130277 clinical development program.

As of the data cut-off date of this submission, January 19, 2018, 497 subjects received at least 1 dose of APL-130277, including 408 subjects with PD and 89 healthy volunteers. By the time of the 120-day safety update (May 10, 2018), 451 PD patients had received at least 1 dose of APL-130277. A detailed list of the studies in the development plan may be found in Appendix 13.1.

Study CTH-300 is the well-controlled, blinded and randomized trial providing the evidence for efficacy, comparing the ability of APL-130277 to turn a PD patient from "off" to "on" within 30 minutes as measured by the Unified Parkinson's Disease Rating Scale (UPDRS) in 54 patients on active drug versus 55 patients given placebo (intent-to-treat population). Of these 109 participants, 56 rolled over into the open label extension trial, CTH-301, and 202 additional *de novo* patients entered this study.

STUDIES IN HEALTHY VOLUNTEERS

- Prototype formulations of APL-130277 (Studies CTH-101, CTH-102, and CTH-103)
- Comparative studies of APL-130277 formulations (Studies CTH-104, CTH-106, and CTH-107)
- Comparative bioavailability study with subcutaneous apomorphine (Study CTH-200)

STUDIES IN SUBJECTS WITH PD

- Study CTH-105 - Open-label dose-ranging in patients with PD
- Study CTH-201 - Thorough QT study
- Study CTH-300 - Phase 3 randomized controlled efficacy and safety study
- Study CTH-301 - Long-term safety study
- Study CTH-203 - Ongoing comparative bioavailability study to APO-go® or APOKYN®
- Study CTH-302 – Open label preference study of APL-130277 vs subcutaneous apomorphine.

Reviewer's note:

- *Only Studies 301, 203, and 302 are ongoing. No data from 203 and 302 is submitted (One is a pK study that has 5 patients entered and the other had not begun. The sponsor reports that there were SAEs or unusual side effects to date.)*
- *Only Study CTH-300 provides well-controlled efficacy data in support of the proposed use.*

- *All studies in the development program are relevant to the review of safety but only the maintenance treatment period of Study CTH-300 provides controlled safety data for the drug when used in the way intended for labeling. Study CTH-301 provides open label long-term data to support its chronic use. Study CTH-301 contains both patients that rolled over from Study CTH-300 and patients enrolled de novo.*
- *Both Studies 300 and 301 had initial open label titration periods for determining the best tolerated and effective dose in PD patients newly exposed to APL-130227 therapy for "off" episodes.*
- *Studies 300 and 301 account for 87 % of the PD patients in the development program and the safety profile from these studies is described in detail in Section 8.*

Table 4 Controlled study in support of efficacy and safety: NCT 02469090

Study No.; Phase; Country	Objective(s) of Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Dosed Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
CTH-300 Phase 3 North America and Europe	Evaluate the efficacy and safety of APL versus placebo in PD patients over a 12-week period	Randomized, double-blind, placebo-controlled, parallel-group	**Products:** Titration with APL (10, 15, 20, 25, 30, and 35 mg, as tolerated) **Regimen:** 12-week maintenance phase, randomized to the effective dose of APL or matching placebo **Route**: Sublingual	141 enrolled / 109 randomized	Subjects with PD and "OFF" episodes	Approximately 135 days

Table 5 Study to support safety: NCT 02542696

Study No.; Phase; Country	Objective(s) of Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Dosed Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
CTH-301 Phase 3 North America and Europe	Evaluate the long-term safety, tolerability, and efficacy of APL in PD patients	Open-label	**Products:** APL 10, 15, 20, 25, 30, and 35 mg **Regimen:** APL – starting dose of 10 mg and titrated upwards **Route**: Sublingual	As of the cutoff date (19 Jan 2018), 272 subjects have enrolled (57 rollover subjects and 215 *de novo* subjects) A total of 257 subjects have received at least 1 dose of APL (55 rollover subjects and 202 *de novo* subjects)	Subjects with PD and "OFF" episodes	Subjects may participate in the study until the Sponsor terminates the study, or until commercial availability of APL in the subject's country

Table 6 Other study pertinent to the review of safety: NCT 03187301

Study No.; Phase; Country	Objective(s) of Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Dosed Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
CTH-201 Phase 2 North America and Europe	Evaluate the effect of APL compared with placebo on QTc intervals in PD patients	Randomized, double-blind, placebo controlled, 3-period crossover, positive control, QT evaluation	**Products:** APL (10, 15, 20, 25, 30, 35, 40, 50, and 60 mg [starting dose of 10 mg and titrated upwards]); moxifloxacin (400 mg); placebo **Regimen:** Single doses; APL and placebo administered in a double-blind fashion and moxifloxacin administered open-label in a 3-way balanced crossover. **Route**: Sublingual (APL and placebo) or oral (moxifloxacin)	48 enrolled / 41 randomized to crossover assessment phase 40 subjects were dosed in the crossover assessment phase and completed the study	Subjects with PD	Maximum duration: 46 days (from Screening to End of Study visit)

5.2. Review Strategy

The maintenance treatment period of Study 300 provides the evidentiary basis of efficacy for APL-130277 for the treatment of "off" states in PD. This 12-week long period of blinded and

randomized treatment of "off" periods in PD was comprehensively analyzed in the Division of Biometrics I, Office of Biostatistics. Their review of the Statistical Analysis Plan and efficacy analysis is heavily relied upon in this review.

Together with Study 300, Study 301 provides most the safety population in the APL-130277 development program. The safety population is divided into three groups for analysis:

1. The titration periods of Studies 300 and 301 are analyzed for an understanding of the safety and tolerability of APL-130277 when first introduced into previously apomorphine-naïve PD patients. (Naïve is defined as no recent exposure.)
2. The double-blinded and randomized maintenance period of Study 300 provides a snapshot of the blindly-assessed safety in a small placebo-controlled population in whom maintenance treatment has been successfully introduced, i.e. an enriched population of PD patients who tolerate apomorphine and have a positive clinical response.
3. The entire safety population (PD patients who received at least one dose of medication) provides an overall assessment of the (mostly open-label) safety of APL-130227 in the chronically treated PD population.

The main period of Study 300 provides the evidentiary support for the efficacy of APL-130277, and is reviewed in Section 6.1.2 below; Section 7 is omitted.

The safety of APL-130277 for all exposed participants in the development program is discussed in an integrated fashion in Section 8 of this review.

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. CTH-300: A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Examine the Efficacy, Safety and Tolerability of APL-130277 in Levodopa Responsive Patients with Parkinson's Disease Complicated by Motor Fluctuations ("OFF" Episodes)

6.1.1. Study Design

Overview and Objective

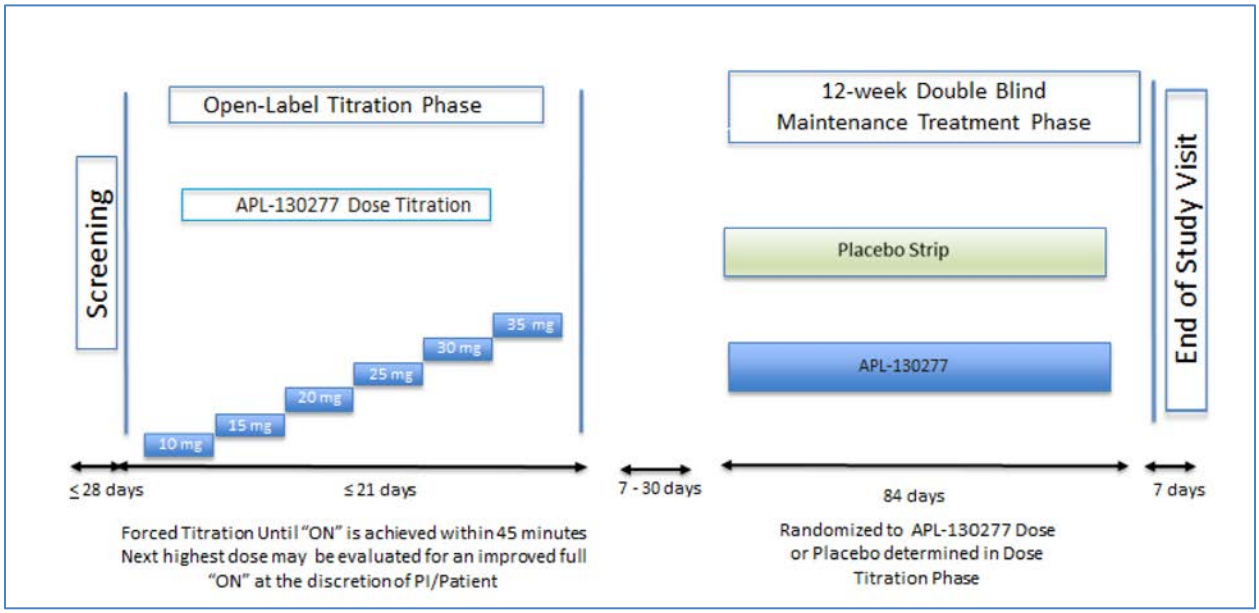
This multi-center, Phase III, blinded, randomized and placebo-controlled study is designed to evaluate the efficacy, safety and tolerability of multiple treatments of APL-130277 in patients with PD who experience motor fluctuations ("off" episodes).

Trial Design

A traditional trial design was used to evaluate APL-130277. Informed consent was obtained at the initial screening visit. Once enrolled, all patients entered a Titration Period (TP) in which individual responses to single ascending doses of APL- 130277 were evaluated in a clinic setting to determine the initial starting dose for treating "off" episodes in an outpatient setting. Once completed and an effective dose established for each patient, patients were randomized to either the APL-130277 or placebo treatments in a 1:1 ratio and enter the Maintenance Treatment Phase of the study. If a patient could not tolerate the drug or an effective dose was not found within the study's dose range, that patient left the study.

During the Maintenance Phase (MP), patients returned to the clinic at 4 week intervals for three safety and efficacy assessments (including the primary endpoint assessments) following the initial randomization/treatment visit. Patients also self-administer study medication to treat up to 5 "off" episodes per day for 12 weeks in the at-home portion of the study, and provide diary recordings of use and effect for the two days prior to each clinic visit.

Figure 1 Study 300 overall schema (source: CSR, p.26)



Trial Location

This study was performed at 29 US clinical sites and one site in Canada.

Choice of Control Group

The control group for treatment comparison in the maintenance period was randomly drawn from the study population which is identical to the PD population for whom this treatment is

intended.

Diagnostic Criteria

United Kingdom Parkinson's Disease Brain Bank Clinical Diagnostic Criteria (a standard method of clinical diagnosis) were used to identify PD patients.

Key Inclusion/Exclusion Criteria

In addition to fulfilling diagnostic criteria, the patient had to have a clinically meaningful response to levodopa treatment with well-defined early morning "off" episodes, as determined by the site investigator. They must have been receiving a stable levodopa-based treatment at least 3 times a day (q.i.d. in the case of Rytary) for at least 4 weeks prior to screening. Adjunctive MAO-B inhibitors must have been stable for 8 weeks prior to screening while other adjunctive medications must have been unchanged for 4 weeks prior. The PD medication regimen was to remain unchanged during the study.

Patients had to have at least one well defined "off" episode per day with a total daily "off" time duration of ≥ 2 hours during the waking day based on patient self-assessment. Patient and/or caregiver required training in performing home dosing diary assessments of the motor state and must be able to recognize "on" and "off" states.

Patients had to have PD Stage III or less on the modified Hoehn and Yahr scale in the "ON" state and be cognitively intact (Mini Mental State Examination score > 25).

Patients were excluded if they had evidence of

- Hallucinations in the 6 months prior to enrollment
- History of clinically significant Impulse Control Disorder
- Atypical or secondary parkinsonism.
- Previous neurosurgical treatment of PD.
- Continuous subcutaneous (s.c.) apomorphine infusion or Duodopa/Duopa use.
- Treatment with any form of s.c. apomorphine within 7 days prior to the initial screening visit.
- Patients that stopped prior s.c. apomorphine due to systemic safety concerns or lack of efficacy.
- Hypersensitivity to apomorphine hydrochloride or any of the ingredients of APOKYN® (notably sodium metabisulfite); Tigan (trimethobenzamide hydrochloride; patients from US sites only); or domperidone (patients from non-US sites only).
- Poor oral health (e.g. canker sores).
- Current use of selective 5HT3 antagonists (e.g., ondansetron), dopamine antagonists (excluding quetiapine or clozapine) or dopamine depleting agents.
- Suicidality

Usual protections against pregnancy were applied.

Dose Selection

The selected dose range for APL-130277 was based upon clinical pharmacology study and previous clinical experience with apomorphine as a drug substance in the treatment of Parkinson's disease.

The effective dose for each participant in Study 300 was determined in the open titration phase of the study prior to blinded randomization to either the effective dose or its placebo equivalent. The aim of titration was to get to an effective dose, but also the highest dose still well tolerated by the patient. (In most cases this was the same does used in the blinded treatment period.)

Study Treatments

APL-130277 is a near square (b) (4) film containing apomorphine hydrochloride. Each package of investigational drug product (unit dose pouch) specified the dose and each film was identified by alphanumeric printing. Films were provided in 5 strengths: 10 mg, 15 mg, 20 mg, 25 mg and 30 mg. Two sublingual thin films were administered sequentially to form the 35 mg dose (a 20 mg dose first followed immediately by the 15 mg dose).

Clinic treatments were administered in the morning with the last anti-PD medication administered the night before. For the evaluation visits in the blinded portion of the trial, the administration of the study drug was done in the clinic by the staff. Patients were expressly prohibited from self-administration at clinic visits. For the at-home diary-recorded days, the patient or caregiver placed the films in the mouth. The procedure was as follows (study protocol, page 73):

> "Using gloved hands, or a single-use plastic disposable tweezers, staff will place the product beneath the tongue, with the drug side facing up towards the tongue (i.e., the side of the film that does not have an alphanumeric printing), and ask patients to close their mouth naturally. Patients should not swallow the medication and should also try not to swallow their saliva for at least 3 minutes. If, upon inspection at the three minute mark, the film is not completely dissolved, patients should be instructed to close their mouth and hold the study medication under their tongue for another minute (i.e., maximum of 4 minutes in total). If the patient feels the film has fully dissolved prior to the three minute mark, they should indicate this to site staff by raising their hand, who will then verify. If upon inspection, the film is not completely dissolved, patients should be instructed to close their mouth again and hold the study medication under their tongue. Staff may verify at regular intervals, as appropriate, for a duration maximum of 4 minutes in total."

Reviewer's comment: It is important to note that no study personnel had the opportunity to observe the patient's self-administration in any evaluable manner. As a result, there was no

knowledge acquired as to how a patient with moderately advanced PD might handle the medication packaging when in an "off" period. Based upon this reviewer's clinical experience with advanced PD, it is likely that the somewhat complex administration procedure described above was not followed exactly for the home administrations. The reader is encouraged to simulate the experience by placing a mint under the tongue and hold it there for at least three minutes without swallowing.

In the 12-week MP, the patients were instructed to continue with their regular PD medication regimen, but should dose themselves with their randomized treatment (APL-130277 or placebo) if they experience an "off" episode (e.g., morning akinesia, wearing "off" at the end of a levodopa dosing interval, dose failure, sudden "off", etc.) during the day while on their current treatment regimen. Patients were instructed to dose up to 5 "off" episodes per day, with dosing no closer than 2 hours.

Assignment to Treatment and Blinding

The patients were centrally randomized to blinded treatments for the MP of the study in a 1:1 ratio by an automated phone system administered by the biostatistics section of the Clinical Research Organization (CRO). No stratification was employed. The strength administered was that determined in the titration phase. Procedures were in place to maintain the blinding of the study medication and the assignment from the patient and staff.

Anti-nausea medication use was mandated by the protocol to help prevent unintentional unblinding by treatment-related nausea and vomiting, a common occurrence with apomorphine. In the TP, eligible patients were supplied with anti-nausea medication (US sites - Tigan® [trimethobenzamide hydrochloride; 300 mg t.i.d.]; non-US site – domperidone [10 mg b.i.d.]), to be taken daily beginning 3 days before first treatment. During the MP, the anti-nauseant could be discontinued at the discretion of the investigator.

Dose Modification and Discontinuation

In the Titration Phase (maximum 21 days) doses were increased every 3 days until the patient achieved a good "on" response within 45 minutes. Patients with intolerable "off" periods and/or a failure to turn "on" at the highest tolerated dose and/ or inability to tolerate the treatment were discontinued from the study.

If an "on" period was achieved, the next higher dose could be evaluated at the investigator's discretion. The lowest effective dose was to be used in the Maintenance Phase of the study.

Administrative Structure

This is a sponsor-created protocol executed by Sunovion and the contracted clinical research organization. Site principal investigators were required to sign statements of adherence to applicable regulations and good clinical practice. Sunovion was responsible for quality control and assurance checks at all sites. Clinical monitors conducted site visits. Individual

investigators were responsible for enrollment, consenting, collection of data, and maintenance of all source documents.

A Data Safety Monitoring Board (DSMB) composed of members not participating in the trial was responsible for monitoring patient safety, and with the support of an independent statistician, review safety data as required by the DSMB charter. The composition, responsibility and general overview of procedures was specified in the DSMB Charter before any review. The DSMB, under specific circumstances, could suggest revisions to the current protocol to improve patient safety. The DSMB was run and staffed by (b) (4), an outside agency. The officers of (b) (4) are established experts in PD and the conduct of clinical trials. In addition, the DSMB chairperson, PD expert, and dental expert are all well qualified for their respective roles in the DSMB. The first version of the DSMB charter is dated January 8, 2016 with minor changes amended January 8, 2017.

The independent statistician had access to the randomization code, and was to receive regular database transfers. For each safety meeting, the statistician was to prepare summary tables, listings and figures, as appropriate, to aid the DSMB in deciding on patient safety. The DSMB met to adjudicate questions regarding eligibility for enrollment into Study 300 and Study 301. Safety data for review was to include SAEs, AEs that are related to the oropharyngeal examinations, and any other safety data required by the DSMB to make an assessment. Safety monitoring reviews include an unblinded evaluation of all premature discontinuations, adverse events, serious adverse events, adverse events of special interest (AESIs), vital signs, laboratory, and electrocardiogram (ECG) data. The charter specifically indicated the AESIs noted in Section 8, submission specific safety issues including oropharyngeal Findings (focal reddening, edema, ulcerations) and oral pain/discomfort.

The performance of the DSMB is discussed in Section 8.3.1 of this review regarding issues related to submission quality.

Table 7 Study 300 schedule of events (source: protocol, pages 16-20)

				Dose Titration Phase[1]						Maintenance Treatment Phase								
Procedures	**Screening Visits[2]**		**Telephone Call[3]**	**Titration Visit 1**	**Titration Visit 2**	**Titration Visit 3**	**Titration Visit 4**	**Titration Visit 5**	**Titration Visit 6**	**Maintenance Visit 1[1]**	**Telephone Call**	**Maintenance Visit 2**	**Telephone Call**	**Maintenance Visit 3**	**Telephone Call**	**Maintenance Visit 4**	**End of Study Visit[20]**	**Dose Adjustment Visit**
Study Visit	**SV1**	**SV2**	**T1**	**TV1**	**TV2**	**TV3**	**TV4**	**TV5**	**TV6**	**MV1**	**T2**	**MV2**	**T3**	**MV3**	**T4**	**MV4**	**EOS**	**N/A**
Day (+/- 2 days)	**-28 to -3**		**-4**	**1**	**4**	**7**	**10**	**13**	**16**	**23**	**37**	**51**	**55**	**79**	**93**	**100**	**107**	**N/A**
Outpatient Visit[4]	X	X[4]		X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X		X		X		X	X	X
Written Informed Consent	X																	
Reconfirmation of Consent		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Review Entry Criteria	X	X																
Review Restriction Criteria				X	X	X	X	X	X	X	X	X	X	X	X	X		X
Medical History/Demographics		X[2]																
Complete Physical Exam, including Oropharyngeal Exam[5]		X[2]								X		X		X		X	X	
Abbreviated Physical Exam, including Oropharyngeal Exam[6]				X	X	X	X	X	X									
Anti-nausea Medication (starts on Day-3)[7]		X	X[3]	X	X	X	X	X	X	X		X		X				
BMI, weight and height[8]		X[2]								X		X		X		X	X	
Vital Signs (BP, HR, RR and Temp) [9, 10]		X[2]		X	X	X	X	X	X	X		X		X		X	X	X
12-Lead ECG[10, 11]		X[2]		X	X	X	X	X	X	X		X		X		X	X	
Clinical Laboratory Tests		X															X	
MMSE		X																
Modified Hoehn and Yahr		X																
MDS-UPDRS Parts I, II and IV		X														X		
MDS-UPDRS Part III[10, 12]		X		X	X	X	X	X	X	X		X		X		X		

				Dose Titration Phase[1]						Maintenance Treatment Phase								
Procedures	Screening Visits[2]		Telephone Call[3]	Titration Visit 1	Titration Visit 2	Titration Visit 3	Titration Visit 4	Titration Visit 5	Titration Visit 6	Maintenance Visit 1[1]	Telephone Call	Maintenance Visit 2	Telephone Call	Maintenance Visit 3	Telephone Call	Maintenance Visit 4	End of Study Visit[20]	Dose Adjustment Visit
Study Visit	SV1	SV2	T1	TV1	TV2	TV3	TV4	TV5	TV6	MV1	T2	MV2	T3	MV3	T4	MV4	EOS	N/A
Day (+/- 2 days)	-28 to -3		-4	1	4	7	10	13	16	23	37	51	55	79	93	100	107	N/A
Confirmation of L-Dopa Responsiveness		X																
Clinical Confirmation of "OFF" or full "ON"[13]		X		X	X	X	X	X	X	X		X		X		X		
Patient Confirmation of "OFF" or full "ON"[13]		X		X	X	X	X	X	X	X		X		X		X		
Randomization										X								
In-Clinic Dosing[14]				X	X	X	X	X	X	X		X		X		X		
Dispense Study Medication for Outpatient Dosing										X		X		X				X
Collect Study Medication												X		X		X	X[21]	X
Provide Patient Dosing Diary[15]				X[16]						X		X		X				X
Collect Patient Dosing Diary[15]										X		X		X		X		X
Patient "OFF" versus "ON" Training		X[17]																
Treatment Compliance												X		X		X	X[21]	X
C-SSRS[18]		X		X	X	X	X	X	X	X		X		X		X	X	
PDQ-39		X								X		X		X		X	X[21]	
PGI[19]										X		X		X		X	X[21]	
CGI[19]										X		X		X		X	X[21]	
Epworth Sleepiness Scale		X								X		X		X		X	X[21]	
Caregiver Burden (Zarit Burden Interview [ZBI])[22]		X								X		X		X		X	X[21]	

				Dose Titration Phase[1]						Maintenance Treatment Phase								
Procedures	Screening Visits[2]		Telephone Call[3]	Titration Visit 1	Titration Visit 2	Titration Visit 3	Titration Visit 4	Titration Visit 5	Titration Visit 6	Maintenance Visit 1[1]	Telephone Call	Maintenance Visit 2	Telephone Call	Maintenance Visit 3	Telephone Call	Maintenance Visit 4	End of Study Visit[20]	Dose Adjustment Visit
Study Visit	SV1	SV2	T1	TV1	TV2	TV3	TV4	TV5	TV6	MV1	T2	MV2	T3	MV3	T4	MV4	EOS	N/A
Day (+/- 2 days)	-28 to -3		-4	1	4	7	10	13	16	23	37	51	55	79	93	100	107	N/A
Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease Rating Scale (QUIP-RS)		X								X		X		X		X	X[21]	
European Quality of Life – 5 Dimensions (EQ-5D)		X								X		X		X		X	X[21]	
Outpatient Self-Administration Training										X								
AEs/Serious AEs (SAEs)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Previous/Current Concomitant Medications		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Record Reason(s) for Dose Adjustment																		X

Notes:

- Physical examination to include the oropharyngeal cavity: a visual inspection of the inside of each cheek, the inside of the upper and lower lip, the surface of the tongue, and under the tongue, performed just prior to dosing and 2 hours after.
- Electrocardiography performed just prior to dosing and 50 minutes after.

- MDS-UPDRS Part III (Motor Function) was assessed at time = 0 (just prior to dosing), 15, 30, 45, 60 and 90 minutes post dosing at the Screening Visit (SV2), TV1 to TV6, and MV1 to MV4.
- Sites were to call each patient 3 days before an in-clinic visit during the Maintenance Treatment Phase to remind patients to complete the Patient Dosing Diary. Diary recorded the time when patient self-administers a dose and the patient self-evaluated "on/off" status at 30 minutes following dosing.
- Patient "off" versus "on" training occurred with investigator/patient confirmation of "off" or "on" at SV2.

Dietary Restrictions / Special Instructions

None. The study drug was administered without regard to meals.

Concurrent Medications

During the study, PD medications were to remain stable during the Maintenance Treatment Phase of the study, except for modifications needed for safety reasons (with discussion with the Medical Monitor). The anti-nausea regimen is discussed above.

Treatment Compliance

Treatment compliance was assessed at the 2nd, 3rd and 4th visits in the MP. Patients were also queried by telephone contact about compliance and safety between the MP visits. This was to include asking about adverse events. Treatment compliance was to be measured by counting the number of unused study medication pouches returned by patients at each in-clinic visit during the MP of this study relative to the amount given at the preceding visit. Discrepancies in the amount taken and returned were to be followed-up by the investigator and documented in the CRF.

Study monitors were to verify the data being reported in the CRF versus the study medication returned by each patient.

Reviewer comment: It is worth noting that there was no pre-planned protocol driven assessment for documenting the number of daily doses of study medication taken between outpatient visits in the MP. The patient did not have to take medication every day or could take it up to five times daily during the four week inter-visit period.

Rescue Medication

At any point in the clinic visits, patients in the "off" state who, in the opinion of the investigator, could no longer tolerate their "off" state could receive rescue L-dopa (and/or other adjunctive PD medication) at their usual dosage, or at a dosage considered appropriate by the site investigator to achieve an "on" state.

Participant Completion, Discontinuation, or Withdrawal

Treatment was assessed at the 2nd, 3rd and 4th visits in the MP at roughly 4 week intervals. Patients were also queried by telephone contact about compliance and safety between the MP visits. This was to include asking about adverse events. If discontinuation occurred, an attempt to restart treatment was made if medically appropriate. Reasons for discontinuation, the date and outcome were to be recorded in the eCRF. Patients lost to follow-up were to have three documented attempts to re-establish contact.

Patients leaving the study were not replaced, though it should be noted that enrollment continued until enough patients made it through the Titration Phase to ensure sufficient numbers of patients in the Maintenance Period.

Study Endpoints

The endpoints for this study (and the measured outcomes underlying these endpoints) have been commonly used to assess the motor efficacy of anti-parkinson medication. Only those included in the Statistical Analysis Plan hierarchy of testing are discussed as results.

Primary Endpoint

Mean change from pre-dose in MDS-UPDRS (Movement Disorder Society -Unified Parkinson's Disease Rating Scale) Part III Motor Examination score at 30 minutes after dosing at the 12 week visit (MV4) of the Maintenance Treatment Phase.

Key Secondary Endpoint

Percentage of patients with a patient-rated (i.e.: self-rated) full "on" response within 30 minutes at the 12 week visit (MV4) of the Maintenance Phase.

Protocol definition of motor "on" state:

- When assessed by the patient, the protocol defines a full "on" state as a period where medication was providing benefit for mobility, stiffness and slowness and where the patient felt he/she could perform normal daily activities. The response is comparable to or better than their normal response to PD medications prior to enrolling in the study.

- When assessed by the investigator using clinical judgement, the full "on" state is defined as the period of time where the site investigator felt the medication was providing benefit with regard to mobility, stiffness and slowness and the subject had adequate motor function to allow them to perform their normal daily activities.

Secondary Outcomes

- The percentage of instances where a full "on" response was achieved at 30 minutes after self-administration of study medication based on the home dosing diary entries.
- Change from pre-dose in MDS-UPDRS Motor score at 15 minutes at the 12 week visit (MV4) of the Maintenance Treatment Phase.

- Time (in minutes) to when study medication is starting to have an effect.
- Percent of patients with a patient-rated full "on" response within 30 minutes, whose duration from time when study medication begins to have an effect until their "off" (if applicable) lasts for at least 30 minutes at the 12 week visit (MV4) of the Maintenance Phase.
- CGI-I post dosing.
- PGI-I post dosing.
- PDQ-39.
- MDS-UPDRS – Part II: Motor Aspects of Experiences of Daily Living.
- Evaluation of safety and tolerability data collected.

Safety Assessment

- Clinical laboratory assessments performed in Study 300 are described in Section 8.3.3. below.
- Specific assessments included electrocardiography, vital signs and oropharyngeal examination. These are described in Section 8.4.

As illustrated in the Schedule of Event table from the protocol, 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, each with a window of ± 2 days. The length of time from randomization to MV4 was approximately 11 weeks.

Statistical Analysis Plan

The SAP was finalized on November 2, 2017. A single minor amendment was made on December 20, 2017 before the locking of the database on December 21, 2017.

While the protocol was not subject to any prior agreement with the sponsor, discussion concerning the SAP took place with the sponsor during presubmission regulatory meeting interaction. At the EOP2 meeting of February 4, 2015, a general synopsis of Study 300 was submitted and advice was given regarding the baseline evaluation and method of imputation of a missing outcome. Concern was raised about the need to control Type I error resulting from multiplicity of testing for the primary and secondary outcomes.

The sponsor submitted a draft SAP (version 1.5, dated May 6, 2015) and requested advice on February 28, 2017. Written responses delivered March 21, 2017 included advice concerning which visit to use as a baseline covariate in the analysis model, imputation models for analysis of the key secondary endpoint, required subgroup analyses, and sensitivity analysis regarding missing data in the mITT population.

The focus of the SAP is the analysis of the efficacy endpoints in the 12-week main treatment

period of Study 300 where APL-130277 was compared to placebo.

Methods

The efficacy analysis population was the modified intent-to-treat (mITT) population of Study 300, defined as all subjects who were randomized into the maintenance treatment period, received at least one dose of study medication, and had at least one post-randomization evaluation.

From the Division of Biometrics review:

> "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."

In the original protocol, the remainder of the secondary endpoints were not listed in a planned hierarchy of statistical analysis. However, in this SAP the sponsor did list a specific hierarchy for secondary testing to address multiplicity in analysis:

1. Percent of patients with a patient-rated full "ON" response within 30 minutes, whose duration from time when study medication begins to have an effect until their "OFF" (if applicable) lasts for at least 30 minutes at MV4
2. Patient Global Impression of Improvement (PGI): The percentage of patients improved (i.e., very much improved, much improved or minimally improved) at MV4
3. Clinician Global Impression of Improvement (CGI): The percentage of patients improved (i.e., very much improved, much improved or minimally improved) at MV4
4. Mean change from SV to MV4 in MDS-UPDRS – Part II: Motor Aspects of Experiences of Daily Living
5. The percentage of instances where a full "ON" response was achieved at 30 minutes after self- administration of study treatment in the outpatient setting based on the home dosing diary entries during the 2 days prior to MV4
6. Mean change from SV to MV4 in PDQ-39 summary index score

7. Mean change from pre-dose in MDS-UPDRS MOTOR score at 15 minutes at MV4
8. Time (in minutes) to when study medication is starting to have an effect at MV4

Testing was to continue if the previously ranked endpoint remained statistically significant at the $p < 0.05$ level.

Several different methods to handle the missing data in efficacy assessments were proposed. For the primary efficacy analysis, likelihood-based modeling approach will be used to handle incomplete data. Sensitivity analysis for primary efficacy data will be conducted using the Multiple Imputation approach, i.e. by replacing each missing value with a set of plausible values that represent the uncertainty about the right value to impute. LOCF will also be used for sensitivity analysis

Subgroup testing was to be performed as required by the CFR, as well as a variety of other exploratory analyses regarding treatment response. No interim analyses were planned.

Reviewer's comment: No statistical issues were identified in the SAP.

Protocol Amendments

The first patient was enrolled into Study 300 on June 18, 2015 and the last patient completed December 11, 2017. The final versions of the protocol (2.0 in US and 2.1 in Canada) were created prior to the initiation of the trial (May 6, 2015, and June 19, 2015, respectively). Amendments to prior versions of the protocol were procedural in nature.

6.1.2. Study Results

Compliance with Good Clinical Practices

The sponsor attests that Study 300 was conducted in accordance with the International Council for Harmonization (ICH) Guidance for Industry E6 Good Clinical Practice (GCP): Consolidated Guidance and pursuant to the Code of Federal Regulations 21 CFR § 50 and § 56. The study protocol, including the final version of the patient informed consent document, was approved by the Institutional Review Board (IRB)/ independent ethics committee (IEC) before enrollment of any subjects into the study. The opinion of the IRB/IEC was dated and given in writing. A copy of the letter of approval from the IRB/IEC and a copy of the approved informed consent form were received the Sponsor prior to shipment of drug supplies to the clinical investigator.

Financial Disclosure

Financial disclosure information was reviewed and the sponsor has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry *Financial Disclosure by Clinical Investigators* (see also financial disclosure form,

Appendix 13.2). In Study 300, no investigators or subinvestigators received compensation beyond acceptable limits apart from (b) (4). His income was from unrelated outside activities.

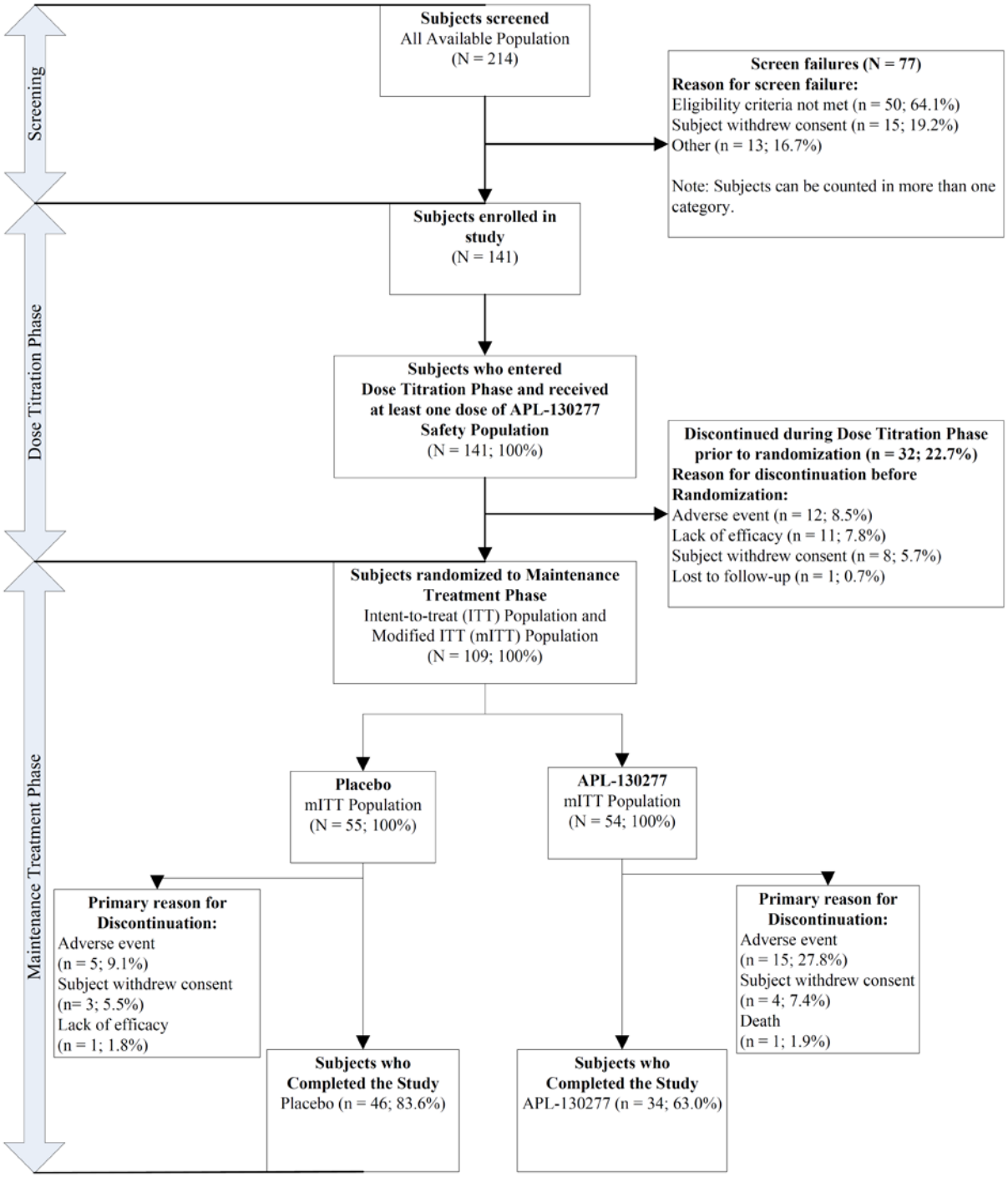
Dr. (b) (4) site screened (b) (4) patients and randomized (b) (4) None discontinued in the titration phase but one subject discontinued in the maintenance period. It was not possible for the data from this one site to have undue influence on the outcome of the study. In addition, procedures were in place to minimize any potential for compromise of the study: randomization, blinding, and external audit.

Patient Disposition

This trial employed an open-label titration period to ascertain the best effective dose followed by randomization into a blinded, parallel maintenance treatment period using that same dose. This enrichment process allowed only successfully titrated patients to enter the controlled portion of the trial. The efficacy analysis tested only this controlled portion of the trial. It did so at each of the four visits in the maintenance period set 4 weeks apart (the first maintenance treatment visit included randomization into the blinded portion of the trial).

This process for enrichment and randomization is illustrated in the sponsor's flow diagram below:

Figure 2 Study 300 disposition of all enrolled patients (source: CSR, p. 60)



The patients who successfully titrated to an effective dose in the enrichment process were randomized into the main period of the trial with most using the same dose achieved in titration. Following titration into randomization, in the APL-130277 arm, 6 of 54 were given the next lower dose level, while 7 of 55 in the placebo arm were so treated.

Table 8 Study 300 maintenance phase dose in ITT by highest dose achieved in titration (source: CSR, p. 80)

Randomized Treatment Assigned dose	Highest Dose Level Received During Dose Titration						
	10 mg (N = 15) n (%)	15 mg (N = 30) n (%)	20 mg (N = 25) n (%)	25 mg (N = 20) n (%)	30 mg (N = 11) n (%)	35 mg (N = 8) n (%)	Total (N = 109) n
Placebo	**8 (14.5)**	**15 (27.3)**	**16 (29.1)**	**9 (16.4)**	**5 (9.1)**	**2 (3.6)**	**55**
10 mg	8 (61.5)	4 (30.8)	1 (7.7)	0	0	0	13
15 mg	0	11 (100)	0	0	0	0	11
20 mg	0	0	15 (93.8)	1 (6.3)	0	0	16
25 mg	0	0	0	8 (88.9)	0	1 (11.1)	9
30 mg	0	0	0	0	5 (100)	0	5
35 mg	0	0	0	0	0	1 (100)	1
APL-130277	**7 (13.0)**	**15 (27.8)**	**9 (16.7)**	**11 (20.4)**	**6 (11.1)**	**6 (11.1)**	**54**
10 mg	7 (100)	0	0	0	0	0	7
15 mg	0	15 (83.3)	3 (16.7)	0	0	0	18
20 mg	0	0	6 (85.7)	1 (14.3)	0	0	7
25 mg	0	0	0	10 (83.3)	2 (16.7)	0	12
30 mg	0	0	0	0	4 (100)	0	4
35 mg	0	0	0	0	0	6 (100)	6

Abbreviations: ITT: Intention-to-treat
Note: Percentages are based on the row totals.

Protocol Violations/Deviations

The sponsor provided line listings but no discussions of protocol deviations. The sponsor counted 3 major protocol violations, all in the active treatment arm of the maintenance period: 2 visits out of window and a procedure not otherwise specified not performed per the protocol.

Review of all protocol deviations line listing for the maintenance treatment period revealed most violations to be out of window variations for a variety of measures or "procedure not per protocol". These were generally small deviations and did not affect measures that might

change the outcome of the trial. The exception to this occurred with missing diary data and faulty medication accountability. The following information was provided by the sponsor in response to an information request made after omissions were noted in the submitted datasets.

Reviewer's note: Because this information is important to supporting dose and duration of exposure for APL-130277 in the safety population, it is discussed further in the integrated safety analysis.

For the two diary days prior to each maintenance period visit, patients were instructed to document the dosing time and ON/OFF status 30 minutes after dosing for up to 5 doses per day. If no dosing took place during one or two diary days, the participant was to document the lack of dosing in the diary. Sites were to review the dosing diary returned by the subjects and note in the CRF if the diary was not completed correctly.

The Home Dosing Dairy was dispensed to all participants at the last three evaluation visits in the maintenance period. There were 133 diaries dispensed and 114 diaries returned. Of these 114 diaries, 102 were entered as per protocol with 90 reported any dosing information. A similar pattern was observed for each dose level but the percentage of diaries reporting any dosing information compared to the number of diaries returned decreased over visits.

With regard to accounting for dispensed investigation drug product, the sponsor reports that there were 136 records (CRF accountability forms) of drug dispensing and 133 records of return reported. Of the 133 records returned, 54 records had a discrepancy (missing or discrepancy 57/136 = 42%).

Table of Demographic Characteristics

This section will focus only upon the 109 patients of the modified intent to treat population used for efficacy analysis. The entire safety population of the study, i.e. those entering the titration period and those dropping out in titration or main period of the trial are described in the integrated analysis of safety in Section 8 below.

Table 9 Study 300 Demographic characteristics of patients reaching the maintenance phase (source: datasets)

Demographic Parameters	Treatment Group		
	Placebo arm (N=55) n (%)	APL-130277 arm (N=54) n (%)	**Total** (N=109)
Sex			
Male	31 (56%)	37 (69%)	68 (59%)
Female	24 (44%)	17 (32%)	41 (38%)
Age			
Mean years (SD)	62.5	62.9	62.7
Median (years)	62	63.5	63
Min, max (years)	46, 79	43, 78	43, 79
Age Group			
min - < 65 years	34 (62%)	30 (56%)	64 (59%)
≥ 65 years	21 (38%)	24 (44%)	45 (41%)
> 65 - < 75 years	13 (24%)	15 (28%)	28 (26%)
≥ 75 years	5 (9%)	7 (13%)	12 (11%)
Race			
White	51 (93%)	50 (93%)	101 (93%)
Black or African American	2 (4%)	0	2 (2%)
Asian	1 (2%)	4 (7%)	5 (5%)
American Indian or Alaska Native	0	0	0
Native Hawaiian or Other Pacific Islander	1 (2%)	0	0 (1%)
Ethnicity			
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%)
Region			
United States	55	53	108
Canada	0	1	1
PD at Study Entry			
Mean (years)	9.3	8.7	9.0
Median	8	7	8
Range	2, 22	2, 20	2,22
"Off" UPDRS Part III Motor at SV2	43.9 (SD 13.9)	43.1 (SD 14.2)	43.5 (SD 13.4)
UPDRS Total at SV2	71.5 (SD 21.5)	68.8 (SD 19.7)	70.2 (SD 20.6)

There were no differences of importance between the baseline demographic and Parkinson's disease related features of the two arms of the maintenance period population.

The medical history of the two arms were also similar with equal incidence of general medical

disorders by system organ class, with special attention to hypertension and orthostatic hypotension, cardiovascular risk factors, gastrointestinal illness and psychiatric disorders. Of special note 13 of 55 (24%) placebo patients and 7 of 54 (13%) APL-130277 treated patients had a past medical history of "drug hypersensitivity", though that history was not otherwise characterized.

Table 10 Study 300 PD pharmacotherapy (prior and concomitant) by safety and mITT populations (source: CSR, page 76)

Table 14: Concomitant PD Medications (Safety Population and mITT Population)

	Safety Population	Double-blind Maintenance Treatment Phase mITT Population		
ATC Level 4 Preferred Term	Overall (N = 141) n (%)	Placebo (N = 55) n (%)	APL-130277 (N = 54) n (%)	Overall (N = 109) n (%)
Subjects with at least one concomitant PD medication	**141 (100)**	**55 (100)**	**54 (100)**	**109 (100)**
Dopa and dopa derivatives	**141 (100)**	**55 (100)**	**54 (100)**	**109 (100)**
Sinemet	126 (89.4)	46 (83.6)	49 (90.7)	95 (87.2)
Stalevo	19 (13.5)	10 (18.2)	8 (14.8)	18 (16.5)
Madopar	1 (0.7)	1 (1.8)	0	1 (0.9)
Dopamine agonists	72 (51.1)	31 (56.4)	30 (55.6)	61 (56.0)
Pramipexole	30 (21.3)	10 (18.2)	13 (24.1)	23 (21.1)
Ropinirole	25 (17.7)	11 (20.0)	10 (18.5)	21 (19.3)
Rotigotine	15 (10.6)	9 (16.4)	6 (11.1)	15 (13.8)
Ropinirole hydrochloride	2 (1.4)	1 (1.8)	1 (1.9)	2 (1.8)
Monoamine oxidase B inhibitors	58 (41.1)	24 (43.6)	22 (40.7)	46 (42.2)
Rasagiline	47 (33.3)	18 (32.7)	18 (33.3)	36 (33.0)
Selegiline	10 (7.1)	6 (10.9)	3 (5.6)	9 (8.3)
Rasagiline mesylate	2 (1.4)	0	2 (3.7)	2 (1.8)
Adamantane derivatives	29 (20.6)	16 (29.1)	8 (14.8)	24 (22.0)
Amantadine	28 (19.9)	16 (29.1)	7 (13.0)	23 (21.1)
Amantadine hydrochloride	1 (0.7)	0	1 (1.9)	1 (0.9)
Other dopaminergic agents	11 (7.8)	5 (9.1)	5 (9.3)	10 (9.2)
Entacapone	11 (7.8)	5 (9.1)	5 (9.3)	10 (9.2)
Other antiepileptics	1 (0.7)	0	1 (1.9)	1 (0.9)
Gabapentin	1 (0.7)	0	1 (1.9)	1 (0.9)
Tertiary amines	1 (0.7)	0	0	0
Trihexyphenidyl	1 (0.7)	0	0	0

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

The sponsor gave no tally of rescue medication needed, an analysis of compliance, or of anti-nausea medication needed in the maintenance period beyond including line listings in the submission. Across the study, 90 % of patients continued anti-nausea medication after it became optional.

Efficacy Results – Primary Endpoint

It is evident that the active arm suffered more drop-outs than the placebo arm. Drop-outs occurred at all dose levels and the rate of dropping out does not appear to be dose related. Dropouts are considered further in Section 8, Review of Safety.

Table 11 Study 300 Disposition of the randomized ITT population (CSR, page 63)

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)

The table below is derived from the sponsor's EX dataset and illustrates the number of participants by dose across the four visits of the maintenance treatment period. Maintenance Visit 4 (MV4) is the evaluation visit for the primary outcome. The 30 and 35 mg dose levels are not particularly well represented by the study's end at the time of the endpoint evaluation visit (MV4).

That it took 141 patients to enter open label titration to reach the completer population of 80 at MV4 makes a clear statement as to the generally difficult obstacle for many patients to be able to tolerate this treatment.

Table 12 Study 300 Maintenance phase ITT population by dose and visit (source: datasets)

ITT Population	Maintenance Visit (Study Day ± 2 days)			
Dose (n, %)	MV1 (Day 23)	MV2 (Day 51)	MV3 (Day 79)	MV4 (Day 100)
Placebo	55 (100%)	47 (85%)	46 (84%)	46 (84%)
APL-130277 (all dose levels)	54 (100%)	43 (80%)	40 (74%)	34 (63%)
Active treatment: n (%) by dose level				**n (%) remaining at MV4 evaluation:**
10 mg	7 (13%)	6	5	4 (57%)
15 mg	18 (33%)	13	13	12 (66%)
20 mg	7 (13%)	5	5	4 (57%)
25 mg	12 (19%)	11	10	8 (66%)
30 mg	4 (7%)	4	3	2 (50%)
35 mg	6 (11%)	4	4	4 (66%)

Used episodically on demand, apomorphine by subcutaneous injection has been demonstrated to therapeutically effective in moving a PD patient from an "off" state to an "on" state, and it is approved for that purpose. From the clinical pharmacology perspective as noted above, the sublingual delivery system for apomorphine in this application ought to have similar abilities. The test of this was evaluating the ability of the test product in comparison to placebo to achieve an "on" state in a patient by staff administered drug and observed in a clinic setting.

Primary Outcome Analysis

The sponsor's analysis of efficacy has been replicated by the Office of Biostatistics. From their review, using the mITT population:

> "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.

As confirmed by the biostatical review, APL-130277 was superior to placebo when assessed by the UPDRS Part III Motor score 30 minutes after administration at the week 12 visit (MV 4).

Table 13 Study 300 UPDRS Part III primary outcome analysis (source: CSR, page 85)

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.

Reviewer' comment: For comparison, the RLD performed a crossover study in 17 patients across a range of doses (2 to 10 mg) who had previously been stabilized on APOKYN® treatment. The patients were demographically the same as the Study 300 population and the clinical effect, as assessed by change from baseline UPDRS motor score, was similar.

Table 14 UPDRS Part III after treatment with the RLD (source: APOKYN®, NDA 21264, prescribing information)

Treatment	Baseline UPDRS Motor Score	Mean Change from Baseline	Difference from Placebo
Placebo	40.1	- 3.0	NA
APOKYN	41.3	- 20.0	- 17.0

The Biostatistics reviewer provided the following chart of change from baseline to week 12 in UPDRS III motor score by dose and suggests that there does not appear to be a dose-response relationship. However, it is difficult to demonstrate dose response because of the trial design. It is possible that only the poorest responders will continue to be titrated to the highest doses and the numbers of patients also become quite small for the purposes of meaningful analysis.

Table 15 Study 300 UPDRS Part III reduction by dose at week 12 (source: Biostatistics review)

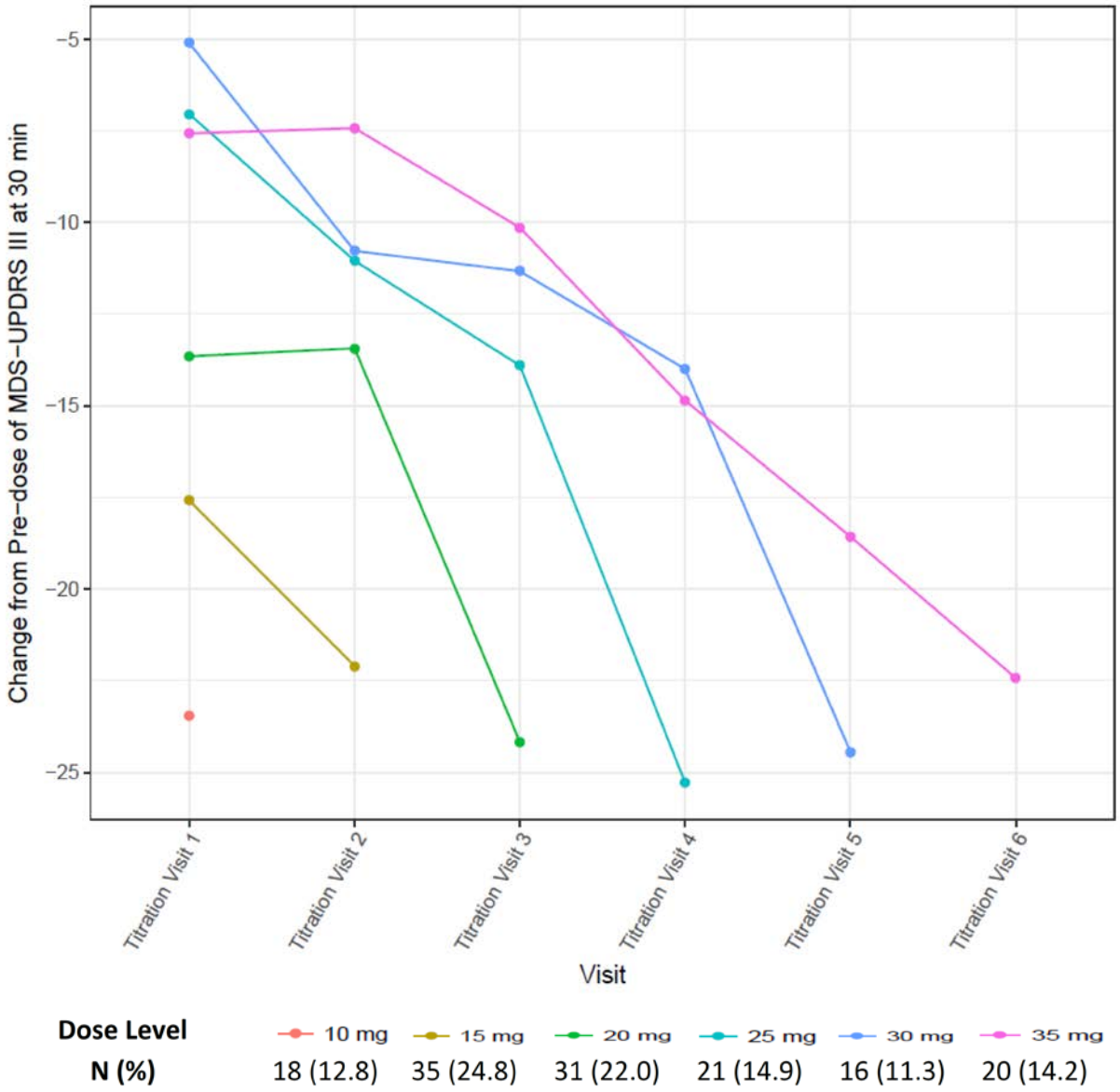
Randomized Doses	Placebo				APL-130277			
	Baseline		Week 12		Baseline		Week 12	
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
10 mg	13	-22.3 (12.25)	12	-3.5 (7.42)	7	-25.6 (11.53)	4	-9.5 (10.38)
15 mg	11	-27.9 (10.34)	8	-3.6 (7.65)	18	-18.8 (9.39)	12	-13.4 (8.95)
20 mg	16	-24.94 (13.84)	15	-4.3 (11.04)	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

The clinical pharmacology reviewer demonstrates an intra-individual dose response relationship. While each patient at their final effective dose has an approximately equivalent effect on the UPDRS motor outcome measure, the individual patient improves more with each increase in dose. The following graph from the clinical pharmacology review illustrates the improvement in the UPDRS at 30 minutes following dose administration stratified by the final effective therapeutic dose the patient reached.

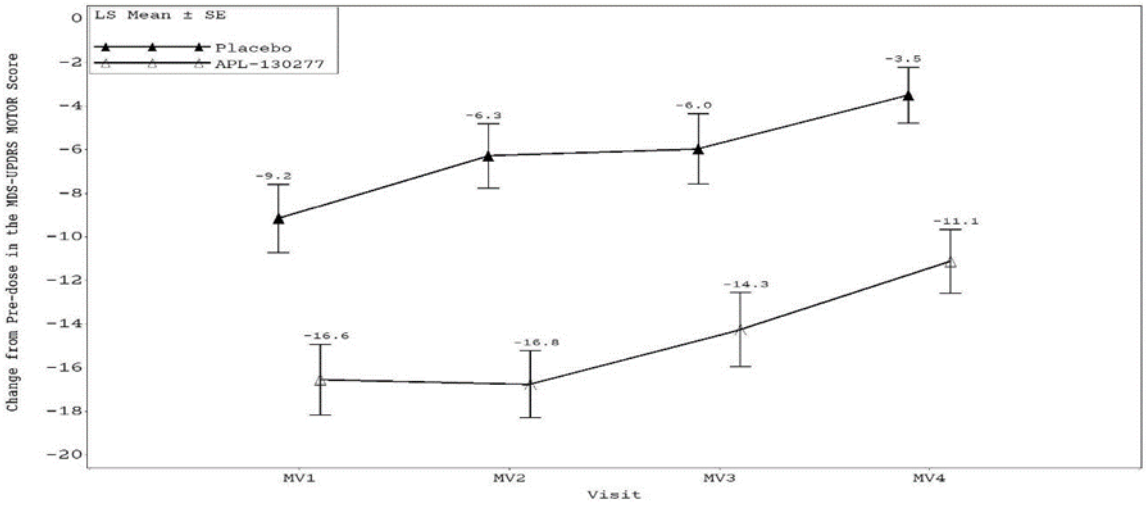
Figure 3 Study 300 Intra-individual dose response: UPDRS Part III by titration visit (source: Clinical Pharmacology review, page 14)



The sponsor also performed sensitivity analyses with missing data using various imputation methods and these supported the primary outcome as well.

The results were reproducible at all of the assessment visits over the 12 week MP.

Figure 4 Study 300 mITT LS mean change in UPDRS Part III 30 minutes post dose by maintenance phase visit (source: CSR appendix, Figure 14.2.1.1.2)



Key Secondary Outcome

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 sponsor's responder analysis, disregarding the missing observations at MV4, found 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)).

In the sponsor's prespecified categorical sensitivity analysis, this significance was lost (Cochran-Mantel-Haenszel test, nominal p=0.174) if it were assumed that patients whose data were missing at each visit were assumed to have not reached a full "on" response at 30 minutes.

Subgroup Analysis

Subgroup analysis by sex, race, or age were unrevealing of a difference in response to APL-130277. With all but one clinical site being in the US, geographical region was irrelevant.

Data Quality and Integrity

JMP Clinical routines were used to analyzed the ISE and ISS datasets for unusual lack of variability and other indices of possible fraudulent data. None were found. Individual sites were also inspected for rates of adverse event reporting by the number of patients enrolled and this also appeared to be within usual parameters for all clinical sites. No one site enrolled enough patients to drive the efficacy results.

Two sites were picked for routine inspection by the Division of Clinical Compliance Evaluation, Office of Scientific Investigations, based upon numbers of patients enrolled for both Study 300 and 301 but also what appeared to be a larger than usual number of protocol violations.

An audit of the study records of all subjects enrolled was conducted. Records reviewed included, but were not limited to, informed consent documents, source documents, monitoring documents, IRB/sponsor communications, financial disclosure, test article accountability, inclusion/exclusion criteria, adverse event reports, laboratory results, concomitant medications, protocol deviations, key secondary efficacy endpoint (subject-rated ON response), and primary efficacy endpoint (MDS-UPDRS Part III scores). At the request of the clinical review team, particular attention was paid to adverse events as reflected in source documents and the accuracy of diary and medication accounting.

Site 1007 enrolled 5 patients into each study and was inspected August 27-31, 2018. Diaries were present for four out of five randomized patients. They were correctly filled out. Adverse events were also recorded accurately. Of interest, one patient, (b) (6), had pharyngeal edema, swelling of the tongue, and difficulty swallowing and left the trial. I confirmed that this person was identified in the hypersensitivity SMQ. This site was issued an NAI letter.

Site 1029 randomized 4 patients into Study 300 and 5 in Study 301 and was inspected as described above. In this case, two of the patients in Study 300 did not fill out their diaries correctly. These subjects entered dose times for the concomitant medication, carbidopa/levodopa, rather than for the study drug. There was no documentation at the site that these subjects had been retrained on how to complete the diaries correctly or any clarification of the dosing of study medication. As a result, study drug dosing for these two patients was considered unreliable. A patient withdrew for the adverse event of mouth swelling and this was accurately recorded. Based on the inspection findings, the site was issued a VAI letter.

The sponsor also performed quality audits for this pivotal trial while it was in progress. These audits included 8 clinical sites (including Site 1007 but not Site 1029), as well as the CRO, the organization providing DSMB services, and the central laboratory. The sponsor documented findings in an audit report and issued certificates of satisfactory performance for all. Actual

audit reports were not supplied in the application and there appeared to be no reason for the clinical team to request them.

Efficacy Results – Secondary and other relevant endpoints

The primary and key secondary endpoints were planned to be tested sequentially, each test at the two-sided significance level of 0.05. They are presented in the hierarchical order listed in the sponsor's SAP (numbered according to the table that follows).

3. Percent of patients with a patient-rated full "ON" response within 30 minutes, whose duration from time when study medication begins to have an effect until their "OFF" (if applicable) lasts for at least 30 minutes at MV4
4. Patient Global Impression of Improvement (PGI): The percentage of patients improved (i.e., very much improved, much improved or minimally improved) at MV4
5. Clinician Global Impression of Improvement (CGI): The percentage of patients improved (i.e., very much improved, much improved or minimally improved) at MV4
6. Mean change from SV to MV4 in MDS-UPDRS – Part II: Motor Aspects of Experiences of Daily Living
7. The percentage of instances where a full "ON" response was achieved at 30 minutes after self- administration of study treatment in the outpatient setting based on the home dosing diary entries during the 2 days prior to MV4
8. Mean change from SV to MV4 in PDQ-39 summary index score
9. Mean change from pre-dose in MDS-UPDRS MOTOR score at 15 minutes at MV4
10. Time (in minutes) to when study medication is starting to have an effect at MV4

Table 16 Study 300 Summary of secondary endpoint results tested by hierarchy (source: CSR, page 102)

Endpoint	Hierarchy	Placebo (N = 55)	APL-130277 (N = 54)	Statistic and p-value
Percentage of subjects at MV4 with a subject-rated full "ON" response within 30 minutes post-dose that has a duration of at least 30 minutes	3	Yes: 14.5% No: 69.1% Missing: 16.4% Predicted Response Rate: 0.14	Yes: 22.2% No: 40.7% Missing: 37.0% Predicted Response Rate: 0.31	Adjusted Odds Ratio 2.80 (95% CI: 1.00, 7.84) p = 0.0501
Patient Global Impression of Improvement (PGI-I) at MV4: The percentage of subjects improved (ie, very much improved, much improved or minimally improved)	4	20.0% Improved 80.0% Not improved	37.0% Improved 63.0% Not improved	p = 0.0615
Clinician Global Impression of Improvement (CGI-I) at MV4: The percentage of subjects improved (ie very much improved, much improved or minimally improved)	5	20.0% Improved 80.0% Not improved	40.7% Improved 59.3% Not improved	p = 0.0270
Mean change from SV to MV4 in MDS-UPDRS Part II: Motor Aspects of Experience of Daily Living	6	LS mean (95% CI) 2.095 points (0.749, 3.440)	LS mean (95% CI) 0.995 points (-0.559, 2.549)	LS mean difference (95% CI) -1.100 points (-3.159, 0.959) p = 0.2906

The patient's self-rated assessment of turning on at 30 minute corroborates the key secondary responder's analysis extending the definition to include an "on" period that lasts 30 minutes. The patients' and investigators' Global Impression of Improvement also agree with the superiority of APL-130277 over placebo.

The UPDRS Part II (Activities of Daily Living Scale) does not demonstrate improvement and ends the testing hierarchy. However, it should be noted that Part II may not have been suitable for the task assigned to it. The instructions for this self-rated scale state *"We are interested in your average or usual function over the past week including today."* It is easy to see that the benefit of a medication with a brief episodic use, no matter how effective, may not be captured by asking the question in this way.

6.2. CTH-301: An Open-Label, Phase 3 Study Examining the Long-Term Safety, Tolerability and Efficacy of APL-130277 in Levodopa Responsive Patients with Parkinson's Disease Complicated by Motor Fluctuations ("OFF" Episodes)

6.2.1. Study Design

Overview and Objective

The primary objective of this multicenter open label study is to evaluate the long-term safety and tolerability of APL-130277 in patients with levodopa-responsive PD with motor fluctuations and "off" periods. The patient population, drug treatment, titration for new patients, and measures of safety are the same as for CTH-300.

PD patients who had completed any of the APL-130277 studies in the drug development program were eligible to enroll in this study. In addition, approximately 100 *de novo* patients (i.e.: not previously in any APL-130277 study) were expected to be enrolled and be subject to a titration process identical to that used in CTH-300 to determine the appropriate dose. The overall number of subjects was not pre-determined as this is an extension study of long term safety.

During Year 1 of Study 301, patients will return to the clinic at 4 weeks for long-term study (LTS) Visit 2 (LTS V2), 12 weeks for LTS Visit 3 (LTS V3), 24 weeks for LTS Visit 4 (LTS V4), 36 weeks for LTS Visit 5 (LTS V5), and 48 weeks for LTS Visit 6 (LTS V6). At LTS V3, LTS V4, LTS V5, and LTS V6, patients will be dosed with APL-130277 and the procedures performed at these visits will be like those performed at LTS V1. LTS V2 will be a safety visit only.

At the in-clinic visits the study staff administers the investigational medication to the patient as in Study 300.

Following LTS V6, for subsequent years of this long-term study, patients will be asked to return to the clinic every 4 months (16 weeks ± 1 week). These visits are for safety assessment only.

The patient diary documenting use and efficacy of APL-130277 for the two days prior to every clinic visit will be performed for all visits in all years of the study.

Trial Design

Trial Location

This study is being performed at 45 US sites, 7 in Canada and 10 in Great Britain.

Choice of Control Group

There is no control group for this open-label treatment study in the PD population for whom

this treatment is intended to be marketed.

Diagnostic Criteria

United Kingdom Parkinson's Disease Brain Bank Clinical Diagnostic Criteria (a standard method of clinical diagnosis) were used to identify PD patients.

Key Inclusion/Exclusion Criteria

The inclusion and exclusion criteria are identical to those of Study 300. For both rollover and new patients, the following additional criteria apply.

Roll-over patients:

- Completion of any of the following studies: CTH-201, CTH-203, CTH-300, or CTH-302 and, in the opinion of the Investigator, would benefit from continued treatment with APL-130277.
- No major increases in concomitant PD medications since completion of any of the following studies: CTH-201, CTH-203, CTH-300, or CTH-302.
- Development of canker or mouth sores since completing a previous clinical study using APL-130277.
- Current suicidal ideation as evidenced by answering "yes" to Question 4 or 5 on the suicidal ideation portion of the C-SSRS at the Screening Visit (SV1).

Reviewer's comment: The exclusion criteria for oral cavity pathology may have had the effect of eliminating from Study 301 a few roll-over patients who were susceptible to hypersensitivity reactions. It is not clear if the sponsor considered these to be related to hypersensitivity or just "local irritation" from use of the drug product.

De novo Patients:

The criteria for entry in CTH-300 apply to the *de novo* population with the addition of the above exclusions for oral pathology and suicidal ideation.

Dose Selection

Rollover patients will resume treatment with APL-130277 at the dose he/she was administered prior to completing CTH-301. If this dose is no longer considered tolerable or effective, the patient will return to the clinic for dose adjustment visits until a new tolerable or effective dose is established. Newly treated patients proceed through the titration process to be completed within 21 days.

Study Treatments

Study treatment and administration of open-label APL-130277 are identical to Study 300. There is no blinding or randomization in this study.

Administrative Structure

This is a sponsor-created protocol executed by Sunovion and the contracted clinical research organization. Site principal investigators were required to sign statements of adherence to applicable regulations and good clinical practice. Sunovion was responsible for quality control and assurance checks at all sites. Clinical monitors conducted site visits. Individual investigators were responsible for enrollment, consenting, collection of data, and maintenance of all source documents. Many of the US investigators in this study also participated in Study 300. The Data Safety Monitoring Board (DSMB) as constituted for Study 300 also monitored this study.

Dietary Restrictions / Special Instructions

None.

Concurrent Medications

During the study, PD medications were to remain stable during the Maintenance Treatment Phase of the study, except for modifications needed for safety reasons (with discussion with the sponsor's Medical Monitor).

Any selective $^5HT_3$ antagonist (e.g., ondansetron, granisetron, dolasetron, palonosetron, alosetron) are prohibited from 30 days prior to the initial screening through termination from the study, as are all antipsychotics.

Anti-emetic medication allowed are either domperidone (10 mg b.i.d.; non-US sites) or Tigan® (trimethobenzamide hydrochloride; 300 mg t.i.d.; US sites) to overcome the potential nausea associated with apomorphine administration. In this study, anti-emetics are not administered prophylactically during titration but are used only if needed and investigators are instructed that they "should be stopped" when titration is finished unless "clinically indicated".

Treatment Compliance

Treatment compliance is assessed by counting the number of unused study medication pouches returned by patients at each in-clinic visit during the MP of this study relative to the amount given at the preceding visit. Discrepancies in the amount taken and returned were to be followed-up by the investigator and documented in the CRF.

Study monitors were to verify the data being reported in the CRF versus the study medication returned by each patient.

Rescue Medication

At any point in the clinic visits, patients in the "off" state who, in the opinion of the investigator, could no longer tolerate their "off" state could receive rescue L-dopa (and/or other adjunctive PD medication) at their standard dosage, or at a dosage considered appropriate by the Investigator to achieve an "on" state.

Study Endpoints

Primary Endpoint

- Evaluation of safety and tolerability data collected, including 12-lead ECGs, orthostatic hypotension (OH), oropharyngeal and dopaminergic AEs, C-SSRS, Questionnaire for Impulsive- Compulsive Disorders in Parkinson's Disease Rating Scale (QUIP- RS), and the Epworth Sleepiness Scale (ESS) assessments.

Secondary Endpoints

- Mean change from pre-dose in MDS-UPDRS Part III Motor Examination (MDS-UPDRS MOTOR) score at 15, 30 and 60 minutes after dosing at Week 24, Week 36, and Week 48 visits (LTS V4, V5, and V6) of the LTS Phase.
- Percentage of patients with a patient-rated full "ON" response within 30 minutes at Week 24, Week 36, and Week 48 visits (LTS V4, V5, and V6) of the LTS Phase.

- The percentage of instances where a full "ON" response was achieved within 30 minutes after self-administration of study medication at Week 24, Week 36, and Week 48 visits (LTS V4, V5, and V6) of the LTS Phase based on the home dosing diary entries.

- Clinical Global Impression of Improvement (CGI-I) post dosing.

- Patient Global Impression of Improvement (PGI-I) post dosing.

- Parkinson's Disease Questionnaire-39 (PDQ-39).

- MDS-UPDRS – Part II: Motor Aspects of Experiences of Daily Living

Safety Assessment

- Clinical laboratory assessments performed in Study 300 are described in Section 8.3.3. below.
- Specific assessments included electrocardiography, vital signs and oropharyngeal examination. These are described in Section 8.4.

Statistical Analysis Plan

This is primarily a safety study. All patients who are enrolled to this study and receive one dose of study medication will be included in the safety population, but they will also be in a mITT population for efficacy analysis if there is one post enrollment efficacy evaluation.

A tabulation and descriptive analysis of the safety results, adverse events and clinical laboratory information was planned.

Protocol Amendments

There were no amendments to this study protocol.

Data Quality and Integrity: Sponsor's Assurance

The sponsor offers a statement to perform quality control checks and assures the integrity of all data generated by this study.

6.2.2. Study Results

Reviewer's comment: This study together with Study 300 constitutes 87% of all PD patients treated with APL-130277 and this study contains all the chronically treated (i.e.: longer than three months) patients in the development program. For this reason, the findings from this ongoing study are discussed in Section 8, Review of Safety and are mostly derived from the datasets submitted for the ISS 120 day Safety Update.

The sponsor did not submit a clinical study report for Study 301, providing tables, figures and listings in its stead. The sponsor described the findings in part in the ISS for the original submission and as the follow-up report for the 120-day Safety Update to the ISS. Using this format, the sponsor did not analyze the safety results particularly deeply. These tables, figures, and line listings represent the population of Study 301 at the time of the original NDA submission with a safety population of n=257 at that time.

Compliance with Good Clinical Practices

The sponsor asserts that they agree to conduct this study in accordance with all laws, regulations and guidelines of the pertinent regulatory authorities, including and in accordance with the April 1996 ICH Guidance for Industry E6 GCP and in agreement with the Declaration of Helsinki (including all applicable amendments).

Financial Disclosure

Financial disclosure information was reviewed and the sponsor has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry Financial Disclosure by Clinical Investigators. In Study 301, no investigators or subinvestigators received compensation beyond acceptable limits except for Dr. (b) (4) as described above for Study 300. His site entered (b) (4) patients into Study 301: (b) (4) .

Patient Disposition

The origins of patients in Study 301 as of the 120 day Safety Update (May 10, 2018) is as follows:

Table 17 Study 301 sources of patients (source: ISS 120 day SU datasets)

Source of Study 301 PD Safety Population		
Study	N	Percent
CTH-201 (TQT Study) +CTH-301	5	1.6%
CTH-300+CTH-301	56	18.2%
CTH-300+CTH-301+CTH-201	1	0.3%
CTH-301 *(de novo)*	246	79.9%
Total	308	100.0%

At the time of the original NDA submission, January 19, 2018, 272 PD patients had enrolled into Study 301, either rolling over or entering de novo. Their progress through titration and into the maintenance phase of treatment as tabulated in the ADSL dataset confirms the sponsor's tally:

Table 18 Study 301 Disposition of patients discontinued in the titration phase (source: original submission study datasets)

Titration Phase: Patients enrolled (original NDA submission)	**Rollover n=57 (21%)**	**De Novo n=215 (79%)**	**Overall n=272 (100%)**
Patients who received at least one dose of study medication (Safety Population)	55 (96.5)	202 (94.0)	257 (94.5)
Patients discontinued before Maintenance Phase	3 (5.3)	33 (15.3)	36 (13.2)
Reason for discontinuation			
Adverse event	2 (3.5)	11 (5.1)	13 (4.8)
Patient withdrew consent	0	11 (5.1)	11 (4.0)
Protocol violation	0	4 (1.9)	4 (1.5)
Lost to follow-up	0	0	0
Lack of efficacy	1 (1.8)	5 (2.3)	6 (2.2)
Sponsor terminated the study	0	0	0
Death	0	0	0
Other	0	2 (0.9)	2 (0.7)
Ongoing in Titration Phase at time of NDA submission	7 (12.3)	23 (10.7)	30 (11.0)

At that time, 205 PD patients had gone on to the maintenance phase. These numbers reflect the patients who had reached Long Term Visit 4 (6 month visit):

Table 19 Study 301 Disposition of patients discontinued in the maintenance phase (source: original submission study datasets)

Maintenance Treatment	Rollover n (%)	De Novo n (%)	Overall n (%)
Patients in Maintenance Population	47 (100)	158 (100)	205 (100)
Patients who reached the 6 month visit	30 (63.8)	61 (38.6)	91 (44.4)
Patients discontinued during the Maintenance Phase	7 (14.9)	76 (48.1)	83 (40.5)
Primary reason for early discontinuation			
Adverse event	5 (10.6)	50 (31.6)	55 (26.8)
Patient withdrew consent	1 (2.1)	15 (9.5)	16 (7.8)
Protocol violation	0	1 (0.6)	1 (0.5)
Lost to follow-up	1 (2.1)	4 (2.5)	5 (2.4)
Lack of efficacy	0	4 (2.5)	4 (2.0)
Sponsor terminated the study	0	0	0
Death	0	1 (0.6)	1 (0.5)
Other	0	1 (0.6)	1 (0.5)
Ongoing in Mantenance Phase	16 (34.0)	28 (17.7)	44 (21.5)

Having previously successfully completed an APL130277 study, as might be expected a greater percentage of rollover patients were reaching the 6 month visit than newly entered de novo patients. At the time of the NDA submission, the rollover patients had a mean of 128 days exposure in Study 301 while the *de novo* patients had 100 days on average.

Reviewer's comment: Since the entire long term safety population for APL-130277 (treatment greater than 3 months) comes exclusively from Study 301, these tables are updated and discussed in Section 8, Review of Safety.

Protocol Violations/Deviations

A listing of protocol deviations was not submitted for this study.

Demographic and Other Baseline Characteristics

Because this study constitutes the long terms safety population of the development program, demographic and related characteristics are described in the Review of Safety, Section 8.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Patient diaries and medication dispensing and return counts are discussed in the Review of Safety.

Efficacy Results - Primary Endpoint

There was no formal efficacy analysis planned for this open label study. The sponsor tallies the observed responses to treatment at clinic visits over the first 6 months of Study 301. It appears on face that the reduction in motor scores as measured by UPDRS Part III is roughly maintained over that period in the study population.

Table 20 Study 301 Reduction in UPDRS 30 minutes after APL-130277 administration by visit (source: sponsor Summary of Clinical Efficacy, page 71)

Visit	Statistic	Rollover (N = 47)	*De Novo* N = 158)	Overall (N = 205)
Baseline	n	47	158	205
	Mean (SD)	-23.6 (13.72)	-23.5 (13.24)	-23.5 (13.32)
	Median	-23.0	-22.0	-22.0
	Min, Max	-62, -2	-85, 4	-85, 4
LTS V1 (Day 1)	n	46	155	201
	Mean (SD)	-24.1 (13.28)	-23.0 (13.62)	-23.3 (13.52)
	Median	-24.5	-21.0	-22.0
	Min, Max	-57, 8	-75, 12	-75, 12
LTS V3 (Month 3)	n	33	90	123
	Mean (SD)	-20.1 (11.48)	-22.7 (15.73)	-22.0 (14.71)
	Median	-17.0	-20.0	-19.0
	Min, Max	-49, -5	-73, 12	-73, 12
LTS V4 (Month 6)	n	29	63	92
	Mean (SD)	-21.3 (14.80)	-21.4 (13.70)	-21.4 (13.98)
	Median	-18.0	-19.0	-18.5
	Min, Max	-49, 3	-67, 4	-67, 4

This motor improvement is corroborated by the patient's own assessment of having reached an "on" state by 30 minutes after treatment with APL-130277 in clinic. The "missing" category in the table belongs to patients who reached the treatment visit but did not have sufficient data collected to confirm whether they had turned "on" at 30 minutes. The sponsor does not explain how this occurrence happened.

Table 21 Study 301 Percent of patients self-reporting satisfactory "on" state by visit (source: sponsor Summary of Clinical Efficacy, page 73)

Visit	Category	Rollover (N = 47)	*De Novo* (N = 158)	Overall (N = 205)
LTS V1 (Day 1)	**Observed "ON" Response Within 30 Minutes[a], n (%)**	47	158	205
	Yes	33 (70.2)	116 (73.4)	149 (72.7)
	No	14 (29.8)	41 (25.9)	55 (26.8)
	Missing	0	1 (0.6)	1 (0.5)
LTS V3 (Month 3)	**Observed "ON" Response Within 30 Minutes[a], n (%)**	47	158	205
	Yes	26 (55.3)	67 (42.4)	93 (45.4)
	No	8 (17.0)	25 (15.8)	33 (16.1)
	Missing	13 (27.7)	66 (41.8)	79 (38.5)
LTS V4 (Month 6)	**Observed "ON" Response Within 30 Minutes[a], n (%)**	47	158	205
	Yes	20 (42.6)	47 (29.7)	67 (32.7)
	No	10 (21.3)	16 (10.1)	26 (12.7)
	Missing	17 (36.2)	95 (60.1)	112 (54.6)

Data Quality and Integrity - Reviewers' Assessment

Two clinical sites that participated in both Study 300 and Study 301 were audited by OSI and these results are discussed above. The sponsor's datasets confirm the results of observations reported in the SCE however omissions or poorly executed protocol procedures such as missing observances of the patient's assessment of "on" state in the table above or poor compliance with diaries and drug accounting remain unexplained.

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

The efficacy of APL-130277 is supported by Study 300, a single pivotal trial. It is discussed in Section 6.1.2 above.

8. Review of Safety

8.1. Safety Review Approach

The review of safety for APL-130277 includes all persons who received one or more doses of the medicinal product. The aim of this section was to determine the safety of the intend-to-market product, evaluating the drug by size of individual dose, numbers of doses taken in a day, and duration of exposure.

This was not a straightforward analysis; the drug is intended for intermittent use in advanced PD patients and the number of doses taken by patients over time in the pivotal and long-term safety studies were not recorded daily. In addition, this drug can be difficult to tolerate. Studies required a titration period which sustained a substantial number of drop-outs. On a practical level, the open label titration periods for Study 300 and for *de novo* enrolled (non-rollover) patients in Study 301 were identical and these are combined. The blinded comparison of the APL-130227 treatment arm to placebo in Study 300 is analyzed separately from the remainder of the safety population.

Difficulty in the assessment of safety was additionally confounded by the submission of ISS datasets that did not adhere to prescribed data standards. Review using an integrated approach to safety was dependent upon two amendments to the NDA submission that only partially satisfied our requests for information.

After initial review of the submission it became plainly evident that treatment emergent adverse events signaling drug hypersensitivity were occurring. This had not been adequately addressed in the original submission and the sponsor was asked to update their safety population experience, review their data, and submit a new analysis with updated datasets. The update was received by the Division on October 8, 2018.

For this review, while all early phase studies are examined for severe or serious events, the bulk of safety information comes from the Phase 3 Studies 300 and 301, constituting 87% of all PD patients in the development program. Study 300 provides placebo-controlled and blinded collection of safety events. Study 301 covers long-term open label administration of drug. Study 301 includes both roll-over patients from Study 300 and *de novo* treated patients. Both Study 300 and 301 had initial periods of open-label titration of APL-130277 and in these periods both studies were subject to considerable drop out of participants due to intolerability.

The small numbers of patients in the development program and the broad dose range of intended drug treatment make relationship of adverse event by dose or demographic factors inconclusive.

In addition to hypersensitivity, the reference listed drug has labeled warnings and precautions and these are addressed as submission specific safety issues below.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

Since the initial submission (cut-off date January 19, 2018), there have been additions to the safety population, i.e.: patients participating in the open label extension Study 301. The safety population data used for this integrated review is derived from datasets submitted by the sponsor on October 8, 2018 that included new ISS ADSL and ADAE datasets containing a unique USUBJID (universal subject identifier) for everyone in the development program, missing in the original submission. This is the safety population encompassed by the 120-day Safety Update to the ISS (cut-off date May 10, 2018).

There were 540 participants in the development program for APL-130277 of which 99 were healthy volunteers. There were 451 patients with PD and, because of the need for dose titration, all PD patients received at least one dose of APL-130277. Some patients participated in more than one study. Identifying all unique participants in Studies 300 + 301 (regardless of participation in other studies) totals 392 PD patients or 87% of those receiving any active drug product in the development program. Of these 392 PD patients, 291 entered a maintenance treatment period in at least one of these studies, though most (246) participated in Study 301 alone. The remainder of patients who participated only in Studies 105 or 201 had brief exposures. Study 105 was a single ascending dose study from 10 to 30 mg and Study 201 was the Thorough QT Study with patients titrated from 10 to 60 mg as single doses for comparison to moxifloxacin. Unless these patients went on to either Study 300 and or 301, they did not contribute to exposures of any significant duration. No new, novel, or unexpected adverse events occurred in these two brief studies or among any of the human volunteers.

Because the patients in Studies 300 and 301 constitute all chronically treated patients in the program, the safety review of TEAE focuses upon this population.

Table 22 Development program PD safety population by study (source: corrected ISS datasets)

PD Safety Population by Study		
Study	N	Percent
CTH-105	17	3.8%
CTH-105+CTH-300	2	0.4%
CTH-201 *(TQT study)*	42	9.3%
CTH-201+CTH-301	5	1.1%

CTH-300 *(DB)*	82	18.2%
CTH-300+CTH-301	56	12.4%
CTH-300+CTH-301+CTH-201	1	0.2%
CTH-301 *(OLEX)*	246	54.5%
Total	451	100.0%
Studies 300 +301	392	86.9%

Because the use of apomorphine sublingual thin film is intended for intermittent dosing, i.e.: rescuing the patient from an "off" period which may occur a variable number of times a day, a traditional measure of exposure (mg/d x number of days) is not particularly useful here. Ideally, we should know how many thin strips of each dose were taken each day by each patient in Studies 300 and 301. As detailed in the discussion below on patient diaries and returned study drug, this is not able to be precisely quantified.

How exposure was to be determined was not discussed with the sponsor during the IND period design and these studies were not subject to the SPA process. During the Type B pre-NDA meeting (February 6, 2018) discussion as reflected above in Section 3, Regulatory History made the following points as cited from the meeting minutes:

> "FDA recognized that in the pivotal clinical trials, APL-130277 was administered using a flexible and intermittent dosing schedule, so that the requirement for having information from at least 100 patients treated with dosages of APL-130277 intended for clinical use for 6 months or longer, with at least half treated with the highest recommended dose, does not directly apply.
> FDA stated that dosages described in labeling would need to be supported by the clinical trials (controlled and long-term) experience. The Sponsor should provide a clear and unambiguous presentation of the doses (mg) used, the number of doses taken each day, and for how many days each dose was used in the submission.
> The Sponsor clarified that the number of doses taken each day by each patient can only be inferred and calculated from the number of doses dispensed at each visit and the number of doses returned at the following visit. The dose and frequency of administration is only available from patient diaries kept for the two-day period prior to scheduled study visits.
>
> FDA suggested that diary information from the two days prior to each visit be provided to support the maximum daily dose and frequency of administration described in labeling (i.e., mg dose x number of times taken in each day).
>
> The Sponsor is encouraged to present the experience supporting the use of APL-130277 in ways that show the varied patterns of use among individuals but clearly indicate how adverse events are related to dose and method of use. This information should also be identifiable in the datasets for review."

The sponsor's method of quantification for drug usage gives an average estimate of APL-130277 mg/d over the interval between visits. It does not capture the minimum and maximum number of strips in a day or how many times APL-130277 was dosed in a day, which by protocol was only recorded for the few days prior to a study visit. Strips were dispensed at a visit with the remainder (returned drug) to be counted at the next visit. In this quantification, a considerable amount of diary data is missing. The sponsor provided an assessment of exposure in the initial submission, but because of deficiencies in the ISS datasets, it was not possible to fully corroborate the dose and duration of use for each participant. Corrected ISS datasets that identified individual subjects across all studies in which they participated were submitted on October 8, 2018 for the ADSL, ADAE, and ADEX datasets.

The sponsor's estimation of exposure, corroborated by the ISS datasets, is as follows:

Table 23 Safety population (n=451) duration of exposure (source: ISS corrected datasets)

Dosage Range	Number of patients exposed to the study drug:				
	<3 months	≥3 to <6 months	≥6 to <9 months	≥9 to <12 months	12 months or longer
10 to 35 mg	N= 260 (58%)	N=80 (17.7%)	N=83 (18.4%)	N=20 (4.4%)	N=8 (1.8%)

The average exposure was 92 days with a range of 1 to 427 days. This calculation excluded gaps between studies for patients who participated in more than one study. The most important gap in chronic treatment occurred for those patients rolling over from Study 300 into Study 301. The average gap between studies for rollover patients (n=54) was 43 days (range 13-104; 90th percentile 67 days). Given that the intended indication is intermittent use for rescue from PD symptoms, this is not unreasonable and resembles its intended use. More than 100 patients were administered drug for greater than 6 months.

Calculation of the exposure in chronically treated patients for any given dose in the dose range (10 to 35 mg) is subject to certain conditions. Each patient got a range of doses in titration and the received a given dose for most or all the maintenance treatment period. The patient could take up to 5 doses daily. Because the out-patient portion of the maintenance treatment period was only reported at intermittent clinic visits and documented by two days of patient diaries and returned film counts at each visit, the actual exposure is a well-intentioned estimate at best.

Despite this being a rescue medication given episodically up to a maximum of 5 times daily, the sponsor in their submission did not break down exposure by the modal dose level for a chronically treated patient in the safety population. This makes it difficult to understand how many patients regularly used the higher dose ranges, e.g.: the 35-mg dose. Instead, they submitted exposure levels representing the product of the possible number of doses per day x

the dose in milligrams. By this reckoning, 10 mg taken five times in a day would have the same daily exposure as 25 mg taken twice. The possible combinations of doses for each total daily dose range are illustrated in the sponsor's table below.

Table 24 Combinations of APL-130277 thin film to reach a given total daily dose (source: sponsor ISS 120d SU, page 27)

	Exposure by estimated daily total dose (mg)								
	<20	20 to <40	40 to <60	60 to <80	80 to <100	100 to <120	120 to <140	140 to <160	≥160
Dose regimens (number of doses × dose level in mg)	1×10 or 1×15	1×(20,25,30,35) 2×(10,15) 3×10	2× (20,25) 3×15 4×10, 5×10	2× (30,35) 3× (20,25) 4×15 5×15	3× (25,30) 4× (20,25)	3×35 4× (25) 5× (20)	4× (30,35) 5×25	5× (30)	5×35

The sponsor then created this next table to illustrate the extent of exposure by total daily dose. Number of patients in Studies 300 + 301 (the chronically treated patients who reached the maintenance phase: n = 263 of 392 [67%]) by categories of total daily dose and length of exposure:

Table 25 Safety Population exposure by estimated average total daily dose (source: sponsor ISS 120d SU, page 28)

Extent of Exposure Category (months)	Overall Average Total Daily Dose Category (mg)								
	<20	**20 to <40**	**40 to <60**	**60 to <80**	**80 to <100**	**100 to <120**	**120 to <140**	**140 to <160**	**≥160**
<3	57	15	5	1	0	0	1	0	0
3 to <6	40	20	9	0	2	2	0	0	1
6 to <9	33	20	20	5	4	1	0	0	0
9 to <12	5	4	5	3	2	0	1	0	0
≥12	1	3	3	0	0	0	0	0	0
Total	**136**	**62**	**42**	**9**	**8**	**3**	**2**	**0**	**1**

Most (>90%) received less than 60 mg/d of APL-130277, but again it is difficult to understand what the size of individual doses were for this average daily dose. The calculations are based on the patient's self-reported use (diaries) and accounting of returned drug at clinic visits in the maintenance period. Patients for whom data is missing and those who did not reach the maintenance treatment are omitted from this table.

This is a legitimate approach if there is no dose relation to adverse drug reactions. This notion is discussed when looking at adverse events but at bottom it is difficult to assess. Considerable dropping out occurred at every dose in titration, not every dose was reached in the titration process, and common adverse drug reactions occurred at all doses.

The corrected ISS datasets allowed for a more precise estimation of the exposure by actual dose level reached in the titration period across the 392 patients who participated in Study 300 and/or Study 301:

Table 26 Safety population duration of use (months) by dose level (source: corrected ISS datasets)

		Duration of use (months) by dose level					
Dose Level	**N (100%)**	**<1**	**≥1 to <3**	**≥3 to <6**	**≥6 to <9**	**≥9 to <12**	**≥12**
10 mg	51 (13%)	23	11	9	6	2	0
15 mg	103 (26%)	26	24	22	28	3	0
20 mg	77 (20%)	18	13	15	23	5	3
25 mg	66 (17%)	14	22	11	14	5	0
30 mg	38 (10%)	10	9	10	4	3	2
35 mg	57 (15%)	19	12	13	8	2	3
Total	**392 (100%)**	**110**	**91**	**80**	**83**	**20**	**8**

Missing data

To recap the instructions to patients that were similar in both studies, for the maintenance phase of treatment, patients were dispensed medication pouches containing the dose selected during the titration phase. Subjects were instructed to take a single dose of the medication on an as-needed basis to treat "off" episodes and not to exceed 5 doses per day. Subjects were also instructed to keep all empty pouches and study drug cartons, and return these along with all unused study medication. At the next maintenance visit, the site was to count all pouches (used and unused), and verify that the number of pouches dispensed were equal to the number of pouches returned.

An information request was made to the sponsor to provide a more accurate assessment of exposure including an analysis of the return of study medicine and home diary completion by dose level and visit for Studies 300 and 301. The response to the information request was received May 18, 2018 and the 120-day Safety Update (cut-off date May 10, 2018; submitted July 27, 2018) included an expanded analysis of exposure and the sponsor's report on compliance with these study elements (1.11.4 Information Amendment received May 18, 2018). The figures below are as reported by the sponsor with my review of line listings.

Diaries

For the two diary days prior to each maintenance period visit, patients were instructed to

document the dosing time and ON/OFF status 30 minutes after dosing for up to 5 doses per day. If no dosing took place during one or two diary days, the participant was to document the lack of dosing in the diary. Sites were to review the dosing diary returned by the subjects and note in the CRF if the diary was not completed correctly.

In Study CTH-300, the Home Dosing Dairy was dispensed to all participants at the last three evaluation visits in the maintenance period. There were 133 diaries dispensed and 114 diaries returned. Of these 114 diaries, 102 were entered as per protocol with 90 reported any dosing information. A similar pattern was observed for each dose level but the percentage of diaries reporting any dosing information compared to diaries returned decreased over visits. It is not clear whether the lack of dosage information is an omission or that the patient took no APL-130277 in the two days before the visit. (An FDA site inspection revealed that at one of the two sites audited, diaries were filled out incorrectly and did not reflect study medication use.)

In Study 301, the sponsor evaluated the performance of diaries per protocol Version 3 and evaluated the Long Term Visit diaries for Visits 3 and 4 at 12 and 24 weeks, respectively. (Protocol Version 4, implemented May 30, 2017, dictates that diaries are dispensed to participants for every visit over the ongoing study.) Over these two visits, which virtually all participants should have completed, there were 296 diaries dispensed and 205 returned (69%). 189 of these 205 diaries were entered as per protocol and 165 reported any dosing information. This represents that roughly 2/3 were filed out correctly and that 56% had information relevant to dosing.

Return of Study Medicine

The sponsor reports that in the completed Study CTH-300, there were 136 records (CRF accountability forms) of dispensing and 133 records of return reported. Of the 133 records returned, 54 records had a discrepancy (missing or discrepancy 57/136 = 42%).

Similarly, in ongoing Study CTH-301, there were 527 records of dispensing from the first two maintenance treatment visits. Of these, 53 counts of returned medication were not reported and 193 of the 474 returned medication records had a discrepancy between the dispensed medication, what was reportedly taken, and what was returned (47%).

The sponsor argues that the effect of the discrepancies is small and that may be true for Study 300. However, following review of the 12 pages of line listings for errors in drug accountability for Study 301, these protocol deviations should not be considered small.

One factor impossible to determine is how much drug might have been wasted due to difficulty opening the pouches and necessitating use of a new pouch or dropping medication and the need to open a new pouch. Even though the to-be-marketed packaging was not used in either study, difficulty in opening the product could result in less efficacious use and diminished compliance with the elements needed for safe use. (see also the DMEPA review of human

factors study and the need for additional study Section 8.7 Specific Safety Studies, below).

Reviewer comment on diaries and return of study medicine. What these two study components were intended to document were the number of times a day the patient may have taken the medication and whether it was effective in turning the patient "on". The accounting for unused medication was to support the patient's purported use of study drug over the time between maintenance visits. With so much information missing (and not knowing whether this lack was due to disease- or treatment-related factors), the data and its subsequent uncritical interpretation by the sponsor does not seem to accomplish this.

8.2.2. Relevant characteristics of the safety population:

Of the 392 subjects of the safety population for Studies 300 + 301, 311 entered a maintenance treatment period after the initial titration period while 81 patients did not. There are no significant differences in the demographic characteristics of those who progressed from titration to maintenance treatment and those who did not. Years of PD duration also had no effect.

Table 27 Safety population demographic characteristics (source: corrected ISS datasets)

Demographic Parameters	Study 300+301 Safety Population N=392	Titration only vs. Titration + Maintenance	
		Titration but not maintenance (all reasons) N=81 (21 %)	Titration and maintenance treatment N=311 (79 %)
Sex			
Male	253 (65%)	51 (63%)	201 (65%)
Female	139 (35%)	30 (37%)	109 (35%)
Age			
Mean years (SD)	64.4	65.4	64.1
Median (years)	65	66	64
Min, max (years)	38, 86	45,86	38,83
Age Group			
Min - < 65 years	193 (49%)	35 (43%)	158 (51%)
≥ 65 years	199 (51%)	46 (57%)	153 (49%
> 65 - < 75 years	151 (39%)	36 (44%)	115 (37%)
≥ 75 years	48 (12%)	10 (12%)	38 (12%)
Race			
White	375 (96%)	77 (95%)	298 (96%)
Black or African American	5 (1.2%)	2 (2.5%)	3 (1%)
Asian	11 (2.8%)	2 (2.5%)	9 (3%)
American Indian or Alaska Native	0	0	0

Native Hawaiian or Other Pacific Islander	1 (0.3%)	0	1 (0.3%)
Ethnicity			
Hispanic or Latino	24 (6.1%)	2 (2.5%)	22 (7%)
Not Hispanic or Latino	368 (94%)	79 (97.5%)	289 (93%)
Region			
United States	347 (89%)	74 (91%)	273 (88%)
Rest of the World			
Canada	8 (2%)	1 (1.2%)	7 (2%)
Great Britain	37 (9%)	6 (7.4%)	31 (10%)
PD at Study Entry			
Mean (years)	8.4	8.1	8.5
95% CI	8.0-8.8	7.1-9.1	8.1-8.9
Range	0.5 -24	0.5-25	1-22
"On" Hoehn-Yahr Stage < 2.5	287 (74%)	62 (77%)	225 (73%)
"On" Hoehn-Yahr Stage ≥ 2.5	101 (26%)	19 (23%)	82 (27%)

The distribution of persons in the safety population who did or did not go on to maintenance treatment was analyzed by dose and the effect of age, sex, race and ethnicity. The results of categorical analyses show that neither age group (<65, 65–74, ≥75) nor sex are significant factors in this outcome. The race and ethnicity calculations suffered from cells that were too small for a statistically valid result. The duration of PD at study entry and the Hoehn-Yahr stage during the "on" period also had no relation to this outcome.

Table 28 Safety population highest dose achieved during titration (source: corrected ISS datasets)

Highest dose achieved during titration					
Titration but not maintenance treatment (n=81)	**Count**	**% of Total**	**Titration and maintenance treatment (n=311)**	**Count**	**% of Total**
10	14	17.3%	10	37	11.9%
15	16	19.8%	15	86	27.7%
20	11	13.6%	20	66	21.2%
25	10	12.3%	25	56	18.0%
30	7	8.6%	30	31	10.0%
35	23	28.4%	35	34	10.9%
50	0	0.0%	50	1	0.3%
All	81	100.0%	All	311	100.0%

Reviewer's note: The single patient who received 50 mg was in the TQT Study 201.

Baseline Anti-Parkinson Medication Use
The baseline concomitant therapies for the individual's PD treatment were investigated for a relationship to not progressing on to maintenance treatment. There was no effect of baseline use for amount of levodopa (<500 mg, 500 -<900 mg, or ≥900 mg) or MAO-B inhibitor. However, there was an effect related to the use of dopamine agonists (DA): if the patient was taking a dopamine agonist at baseline there was a *greater* likelihood of moving on to maintenance treatment following titration. Of patients taking a DA at baseline, 194 of 230 (84%) went on to maintenance therapy. Of patients not taking a baseline DA, 117 of 162 (72%) went on to maintenance treatment. This was positive by contingency analysis using both Pearson and Likelihood Ratios (χ^2=0.0037). One possible explanation is that a patient whose physiology is not robust enough to tolerate DAs is also not sufficiently robust to tolerate apomorphine. Anti-hypertensive drug treatment at baseline also had no effect.

Antiemetic Use
Participants were required to use antiemetic medication (trimethobenzamide) during dose titration in Study 300 but could be discontinued at the discretion of the investigator in the maintenance phase. Antiemetic pre-treatment was permitted throughout Study 301 if needed. Study 301 added sites in Great Britain and participants could also use domperidone (not available in the US) as did the single Canada site in Study 300.

In Study 300 safety population (n=138), most participants (132, 96%) took an antiemetic, trimethobenzamide for all but one Canadian patient receiving domperidone. Of the patients who did not proceed to the maintenance randomization for any reason, 97% were also receiving an anti-emetic.

In the safety population for Study 301 (n=312) many participants came from other studies; 251 patients were *de novo* participants who had not been in any previous study or had been in a placebo treatment arm of a previous study (80%). Of the *de novo* patients in this study, 49 were given domperidone during titration, 35 of whom continued to use it after the titration period. Trimethobenzamide was used by 176 *de novo* patients. Antiemetic medications were not used by 26 (10%) of the *de novo* participants.

8.2.3. Adequacy of the safety database:

The requirement for the safety database was discussed prior to NDA submission with the sponsor. The submitted information fulfilled the need for six months' exposure across the proposed dose range of APL-130277. The PD population studied is representative of the population in whom use is intended. The distribution of administered doses reflects the likely range of doses to be used in the intended PD population.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

The review of data in this submission has not raised any concern about its integrity.
The procedures employed for data collection on out-patient drug usage (daily use) through patient-reported diaries and accountability procedures for returned drug were specified by the protocols for Study 300 and 301. These procedures were limited in design and poorly executed as discussed above in Section 8.2.1 Overall Exposure.

The sponsor's assessment and interpretation of the safety data was lacking in depth. This is most apparent in the failure of recognition and lack of discussion of hypersensitivity reactions to APL-130277, despite urticaria resulting in drug discontinuation, and the more common occurrence of lip swelling as a TEAE. This lack was accompanied by an incredible dispersion of hypersensitivity-related Preferred Terms in the AE database. Most unbelievably, even at the time of the 120-day safety update, the sponsor listed just 4 cases of the AESI "hypersensitivity" for patients in the titration period and 1 case in the maintenance treatment period of Study 300 and 301.

The composition and function of the DSMB was discussed above in the description of Study 300 in Section 6. The DSMB met on June 6, 2016, August 5, 2016, October 14, 2016 and October 6, 2017 to discuss both Study 300 and 301. The minutes of the open session meetings are reviewed. Safety summaries were prepared by the sponsor for the DSMB who discussed them in both closed and open sessions:

Meeting minutes of June 6, 2016: "4 [subjects] discontinued due to what appears to be an allergic reaction: swelling around the face and oral cavity…. These subjects did not have problems in titration but only during maintenance. The allergy resolved in all subjects within a few days of stopping the IP. Some individuals do have allergies to vitamin B6 and/or sulfites (present in the excipients) which [Sunovion] is recommending be evaluated in follow-up of the AE. Suggested approach, as discussed, was skin testing and potentially additional antibody testing, if needed. Before procedures are implemented, [Sunovion] will determine if consent is needed for these additional tests since the allergy is now resolved in all of these patients."

Meeting minutes of August 5, 2016: "No additional allergic reactions reported since last DSMB meeting"

Meeting minutes of October 14, 2016: noted 4 cases of oral symptoms and lip swelling. "Nothing striking."

Meeting minutes of October 6, 2017: "[One member] requested that the DSMB look closely at the apparent emerging trend in oral events (e.g., lip & tongue swelling, pain, oral ulcers, etc.).

[Another member] indicated that he had noticed the same and the DSMB would review closely during the closed session and provide their guidance subsequent to the call to the Sunovion DSMB chair."

This was the last meeting of the DSMB as submitted in this application. No changes were suggested to the studies as a result of any of these meetings.

Reviewer's comment: In reading the minutes, it seems likely that the information presented to the DSMB concerning oropharyngeal symptoms and possible hypersensitivity did not capture the true nature and extent of the AESI. With the number of treatment emergent adverse events potentially covered within the hypersensitivity SMQ as presented below, to this reviewer it appears that the sponsor either volitionally or through utter carelessness failed to recognize and appropriately interpret and present the findings to the DSMB.

By individual study, the structure of the data provided conformed to currently required data standards. However, the datasets for the ISS were seriously flawed and required several requests to the sponsor to correct these inadequacies and address hypersensitivity. These requests and responses are noted in the relevant places in this review. The most serious flaw, lack of a unique subject identifier (USUBJID) for everyone in the development program, resulted in the inability to track the same patient who participated in more than one study. Lack of conformance to the 'one line-one patient' standard in the ADSL and DM datasets confounded this and made it impossible to link patients across studies until the sponsor supplied a partial fix toward the end of the review cycle. Most importantly, these deficiencies resulted in the inability to use the FDA review tools employed to carry out higher level analyses of data. Not all of these deficiencies were recognized in the filing review period and the full impact only became evident later in the review cycle. Following receipt of updated datasets in closer compliance with the CDISC standards from the sponsor, it was possible to analyze the information provided to make a reasonably secure assessment of the risks and benefit of the drug product in the study population.

8.3.2. Categorization of Adverse Events

Some issues commonly reviewed here have been covered in the previous section on submission quality. The superficiality of coding verbatim descriptions to PTs and their subsequent analysis prompted the reviewer to verify the analysis and discussion of AESIs. For this reason, I concluded that the sponsor's approach concerning specific AEs was not adequate and the safety evaluations in Sections 8.4 – 8.7 are based upon my own review.

All AEs in the ISS were coded (or re-coded, where necessary) using MedDRA version 19.1.

The protocol addressed the recording and categorization of adverse events in a generally standard fashion giving definitions of severity, seriousness, duration, relatedness to the

investigational drug, and actions to be taken. Querying the patient about the occurrence of AEs was addressed in a single sentence. No statement was made about how long after drug cessation should an adverse event still be considered related. Unless a patient came in unexpectedly or called, TEAEs were recorded at the next scheduled outpatient visit.

8.3.3. Routine Clinical Tests

No clinical laboratory tests were specifically performed to investigate a specific potential adverse event. No previous specific laboratory abnormality had been described in the RLD. In Study 300, laboratory assessments were only performed at baseline (screening) and the end of the study. In Study 301, laboratory assessments were performed at baseline, week 12 of the maintenance treatment phase and, beginning at week 64, every 16 weeks through treatment and at end of treatment. The laboratory studies were of a routine nature:

> Hematology: hemoglobin, hematocrit, red blood cell (RBC) count, RBC indices, mean corpuscular hemoglobin (MCH), MCH concentration (MCHC), platelet count (or estimate), white blood cell (WBC) count including differential.
>
> Serum Chemistry: albumin, total bilirubin, total protein, alkaline phosphatase, chloride, alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea, creatinine, glucose, sodium, potassium, uric acid, globulin.
>
> Urinalysis: pH, specific gravity, blood, glucose, protein, ketones.
>
> Blood pressure and heart rate were assessed at rest in lying and standing positions (3 minutes apart) prior to dosing and 60 minutes following the administered dose.
>
> ECGs were taken just prior to dosing and at 50 minutes after dosing. They were performed in the recumbent position after 5 minutes of rest with measurement of heart rate and PR, QRS, and RR intervals. QT intervals were recorded with both Fridericia's and Bazett's corrections)

8.4. Safety Results

8.4.1. Deaths

Three deaths occurred in the development program for APL-130277. All occurred on active treatment.

Reviewer's comment: None are convincingly related to drug treatment, though the contribution to cardiac arrest cannot be absolutely ruled out.

Table 29 Safety population - deaths (source: datasets)

Study	Subject Number	Study Phase	APL-130277 Dose	Preferred Term	Start Day of Event Relative to Start of Dosing	Duration of Event (Days)
CTH-300	(b) (6)	Maintenance	15 mg	Cardiac arrest (cardiac arrest)	18	1
CTH-301		Maintenance	20 mg	Sepsis (psoas abscess - day 50)	95	11
CTH-301		Titration	35 mg	Drowning	55	1

(b) (6): A 74-year-old man in the APL-130277 group with an 8-year history of PD, 26-year history of diabetes mellitus, and 3-year history of hypercholesterolemia, who was titrated to 15 mg APL-130277 and then randomized to APL-130277 in the maintenance phase, experienced a TEAE of cardiac arrest that resulted in death on Day 7 of the maintenance treatment. It is unclear how many doses the patient may have self-administered in this week. His screening ECG contained premature ventricular contractions that were considered by the investigator to be benign. Note that this patient had been through the titration phase and had also been receiving trimethobenzamide 300 mg prn for the week prior to death. The sponsor's opinion was that drug treatment cannot be ruled out as a contributing factor.

(b) (6): A 58-year-old woman with PD (9 years) and psoriatic arthritis in the APL-130277 group, who was titrated to 20 mg APL-130277 and entered the maintenance phase, experienced an SAE of sepsis on Day 95 of the maintenance phase that resulted in death. She also suffered from candidiasis, avascular necrosis of the hip, and blood cultures positive for staphylococcus epidermis. She had not been in a previous study and entered this one directly.

(b) (6): A 56-year-old man had discontinued study drug on Day 16 due to mouth ulceration. The patient was on continuing care in the study for this ulceration when he accidently drowned on vacation about 5 weeks after his last dose.

8.4.2. Serious Adverse Events

In Study 300, 8 AEs occurring in 6 patients of 622 reported adverse events were designated as serious (SAE). Two patients never received drug (staphylococcal infection, myocardial infarction) and two patients were in the placebo arm (cholecystitis, acute diabetic renal injury with encephalopathy). These are omitted from the table below.

In Study 301, 24 AEs occurring in 13 patients of 970 reported adverse events were designated as serious (SAE).

Table 30 Safety population - serious adverse events (source: datasets)

USUBJID	Sex	Age	Drug Dose (mg)	Study Day	Description of Event	Severity	Sponsor's causality assessment
(b) (6)	M	74	15	18	Cardiac arrest, death	Severe	POSSIBLE
	M	64	15	81	hypokalemia and exacerbation of congestive heart failure	Mod	Not related
	M	68	25	22	Deep vein thrombosis, leg	Severe	Not related
	F	80	25	75	UTI, acute kidney failure, rhabdomyolosis, encephalopathy and fall	Mod	Unlikely
	M	71	15	5	Glioblastoma	Severe	Not related
	M	70	25	103	Altered mental state	Mod	Unlikely
	M	67	15	14	Hypotension and syncope	Severe	PROBABLE
	M	62	15	193	Prostate cancer, Stage II	Severe	Not related
	M	78	15	64	Subcortical stroke	Severe	Unlikely
	F	63	25	127, 178	Fall, compression fracture of L1, ongoing	Mod	Not related
	M	71	25	180, 220	Severe back pain, discovery of bone cancer	Severe	Not related
	M	55	20	81, 115	Femoral nerve irritation, low back pain	Severe	Not related
	F	62	25	124, 237	Exacerbation of asthma	Severe	Not related
	M	63	30	108	Hip fracture	Mod	Not related
	F	58	20	74	Hip pain (avascular necrosis), psoas abcess, and sepsis	Mod	Not related

The narratives have been reviewed and the following comments are added.

- The dose of APL-130277 was not changed for any event except in the case of (b) (6) (glioblastoma) and (b) (6) (bone cancer) where it was withdrawn.
- Of the reported SAEs, the sponsor considered only (b) (6) (hypotension and syncope) to be clearly related to study drug.
- The sponsor considered the cardiac death in (b) (6) to be potentially related to study drug. This 74-year-old man is described under 8.4.1 Deaths, above.
- (b) (6) had a day of poor responsiveness and confusion. He had a history of macroangiopathic changes on MRI of the brain and orthostatic hypotension. In addition to study drug, he was taking levodopa, rotigotine, and clonazepam. The event resolved despite continuation of the study drug.
- (b) (6) had a fall resulting in vertebral fracture but reported no symptoms of dizziness, syncope or orthostasis. Systolic blood pressure was recorded at 104 mmHg but orthostatic measurements were not performed.
- (b) (6) hip fracture occurred when the patient slipped while running.
- (b) (6) is a 62-year-old woman with an established history of asthma. She used salbutamol and budesonide/formoterol inhalers chronically. Prednisolone had previously been used in exacerbations of her condition. She had not participated in other APL-130277 studies. Medication profile suggests that she lost control of her asthma by day 68 and required prednisolone until day 200 when she withdrew from the study. Her CT scan of the lung showed "a prominent mosaic pattern" of infiltrate, suggesting "hypersensitivity pneumonitis." It appears to have not been recognized that

APL-130277 may have contributed to the decompensation of her asthma (see the discussion on hyposensitivity below). Despite the development of the need for chronic steroids and two intervening exacerbations requiring treatment that were characterized as "severe" and "moderate," the overall asthma condition was considered by the investigator to be "mild."

Reviewer's comment: None are convincingly related to drug treatment except for (b) (6) *who developed a prolonged exacerbation of asthma that was unlike her previous medical history and with radiographic evidence of a hypersensitivity reaction. The label for the RLD currently describes a warning for patients with allergy to sulfites and that use can provoke "life-threatening asthmatic attacks."*

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

Long clinical experience with the drug substance, apomorphine, has demonstrated that tolerability can be difficult and is commonly associated with emesis and hypotension related to the drug's mechanism of action. The study designs for both Studies 300 and 301 considered the expectation that not all patients would adequately respond to or tolerate APL-130277. The dropouts following drug treatment are reviewed keeping this in mind. The blinded, placebo-controlled maintenance treatment period following randomization in Study 300 and the open-label titration periods of Study 300 and Study 301 (the latter for *de novo* participants) are each considered separately.

Reviewer's note: For this section, I compared the sponsor's reported tally for discontinuations resulting from adverse events in two ways. The AE datasets were inspected for outcome of the reported event and the ADSL dataset listed reasons for non-completion. Review of these indicate that the sponsor's tally is correct.

Attention was paid to the 15 patients in Study 300 who withdrew consent and left the study. It does not appear that the occurrence of an AE (13 of 15 had a reported AE) was directly related to their withdrawal from the study. Nevertheless, two suffered from yawning and one had vomiting which are related to the mechanism of action of apomorphine. While not necessarily related to withdrawal, the unpleasantness of apomorphine treatment cannot be completely divorced from the reasons why patients may have left the study by withdrawing consent.

Study 300:
The sponsor reports that 141 PD patients entered the dose titration phase and received at least one dose of active drug. Of these, 12 discontinuations occurred for reasons of an AE. After patients entered the maintenance phase there were three times the discontinuation due to AE in the treatment arm as compared to placebo:

Table 31 Study 300 dropouts and discontinuations (source: datasets)

Study 300 Titration	Sponsor CSR (N=141)	
AE	12 (8.5%)	
Lack of efficacy	11 (7.8%)	
Withdrew consent	8 (5.7%)	
Lost to follow-up	1 (0.7%)	
Study 300 Maintenance	Active (N=54)	Placebo (N=55)
AE	15 (27.8%)	5 (9.1%)
Lack of efficacy	0	1 (1.8%)
Withdrew consent	4 (7.4%)	3 (5.5%)
Death	1 (1.9%)	0

Reviewer's note: The categorization of the adverse events was poor and, as the reader will see, not critically interpreted by the sponsor and often split among different terms that could result in different SOCs. Occasionally the decoded verbatim term was imprecise (e.g. "diaphoretic" coded as "hyperhydrosis"). There were many events related to oral cavity discomfort or potential signs of hypersensitivity. I discuss these categories below when I touch on submission specific safety issues. The tables demonstrate the sponsor's lack of a uniform approach to interpretation of these events.

As recorded in the AE datasets for each study, in the titration period interruption of treatment occurred with 28 recorded adverse events in 14 patients (not 12, as reported; average age 68 years, range 54-86).

Table 32 Study 300 AEs by titration dose level resulting in interruption of treatment (source: datasets)

Titration Phase				
10 mg (N=3)	15 mg (N=4)	20 mg (N=5)	25 mg (N=1)	30 mg (N=1)
Somnolence	Abdominal pain upper	Nausea or vomiting (3)	Nausea	Head discomfort
Presyncope	Dizziness	Somnolence (2)		Joint stiffness
Dizziness	Headache	Dizziness (3)		Musculoskeletal discomfort
Orthostatic hypotension	Orthostatic hypotension	Vision blurred		
	Suicidal ideation	Headache		
		Asthenia		
		Diaphoresis		
		Hypotension		
		Pallor		
		Syncope		

As recorded in the datasets, in the maintenance period, interruption of treatment occurred with 39 recorded adverse events in 19 (not 20) patients (average age 63 years, range 50-76).

Table 33 Study 300 AEs by maintenance dose level resulting in interruption of treatment (source: datasets)

Maintenance Phase					
APL-130277					
10 mg (N=2)	15 mg (N=3)	20 mg (N=2)	25 mg (N=5)	30 mg (N=2)	35 mg (N=1)
Fall	Somnolence	Gingival oedema	Nausea	Swollen tongue	Disorientation
Oropharyngeal pain	Lip swelling	Lip oedema	Vomiting	Oral mucosal erythema	Fatigue
Oropharyngeal swelling	Swelling face	Oedema mouth	Lip swelling		Rhinorrhoea
Pharyngeal erythema	Urticaria	Delusion	Lip ulceration		
	Irritable bowel syndrome		Oral mucosal erythema		
			Oral allergy syndrome		
			Tongue polyp		
			Oropharyngeal swelling		
Placebo:					
10 mg (N=1)	15 mg (N=1)	20 mg (N=1)	25 mg (N=0)	30 mg (N=1)	35 mg (N=0)
Noninfective gingivitis	Erythema	Decreased appetite		Abnormal dreams	
Oral pain		Disturbance in attention		Confusional state	
Peripheral swelling		Dyskinesia		Hyperhidrosis	
		Muscle spasms		Nightmare	
				Somnolence	

In Study 300, of the 67 recorded adverse events resulting in drug withdrawal, 11 were considered severe (orthostatic hypotension, nausea and vomiting, sleepiness and fatigue). All adverse events resolved during the observation period except for 3 patients with symptoms related to hypersensitivity reactions (hives, lip swelling, sore mouth, mucosal erythema). Other non-resolved AEs were related to the patient's underlying disease state. These were considered mild or moderate by the observer.

In Study 301, for which no study report is provided, two distinct populations were studied. The patients who completed Study 300 and rolled over into Study 301 are in some sense enriched by the fact that those persons sensitive to adverse events sufficient to discontinue drug have already left the program. The other population are new enrollees not previously exposed to APL-130277 and expected to have an experience like the initial titration population in Study 300.

I derived the numbers of patients withdrawn from Study 301 due to adverse event from the ADAE and ADSL datasets update submitted at the time of the 120-day Safety Update.

In Study 301, discontinuation of treatment occurred with 132 recorded adverse events in 71

patients. The titration phase of new patients accounted for 31 adverse events leading to discontinuation in 19 patients, while 101 adverse events leading to discontinuation occurred in 56 patients of the population not requiring titration.

Table 34 Study 301 AEs by titration dose level resulting in discontinuation in *de novo* patients (source: datasets)

Study 301					
***De novo* population during titration**					
10 mg (N=6)	15 mg (N=8)	20 mg (N=1)	25 mg (N=3)	30 mg (N=1)	35 mg (N=0)
Dizziness (2)	Glioblastoma	Heart rate decreased	Heart rate decreased	Dizziness	
Nausea (3)	Hypertension (3)	Mental status changes	Nausea	Sedation	
Somnolence (2)	Nausea		Arthralgia	Yawning	
Dysgeusia	Ocular icterus		Asthenia		
Yawning	Diaphoresis		Dizziness		
	Somnolence		Lacrimation increased		
			Myalgia		
			Nasal congestion		

Reviewer's comment: In Study 300, patients who are listed as discontinued due to AEs in the Titration Period in the DM dataset matched the those found in the AE dataset. However, this is not the case in Study 301.

De novo patients (n=244) required titration of APL-130277. In the ADAE dataset, 19 of these patients discontinued due to the specified AE listed in Table 34 above. However, this does not agree with the ADSL dataset. The DCS1REAS domain lists the disposition of the participants of Study 301 and by this reckoning, 70 patients discontinued due to AE and 30 others are listed as withdrawn by subject. In all, 125 of the 244 de novo patients (51%) subject to titration did not continue in the study, a higher rate of discontinuation than Study 300.

Of the 30 "withdrawal by subject" occurrences, the specific reason listed in the DC1REASP domain was related to an adverse event in 6. Of the 70 participants discontinued due to an AE listed as occurring in the Titration Period, their duration of participation in Study 301 suggests that in most cases the AE occurred after the initial titration and that the categorization of when the AE occurred was incorrect. However, the sum of the individuals discontinuing in the Maintenance Phase of Study 301 in the AE dataset is too low to contain all the discontinuations listed in the ADSL dataset.

Taken all together, this suggests that TEAEs were underreported in Study 301.

Table 35 Study 301 AEs by dose level resulting in discontinuation during maintenance treatment (source: datasets)

Study 301					
Roll-over population and de novo population after titration.					
10 mg (N=12)	15 mg (N=12)	20 mg (N=11)	25 mg (N=6)	30 mg (N=9)	35 mg (N=6)
Palpitations	Dyskinesia	Throat tightness	Lip blister	Dyskinesia (2)	Nausea
Feeling abnormal (2)	Oral herpes	Mouth lip or tongue swelling (4)	Mouth swelling	Freezing phenomenon	Confusional state
Somnolence	Throat irritation	Oral mucosal erythema	Dental caries	Lip swelling (3)	Dysarthria
Dizziness (2)	Mouth swelling	GERD	Dysgeusia	Fatigue	Hypoaesthesia oral
Nasal congestion	Glossodynia (2)	Vomiting or nausea (6)	Asthenia	Mouth ulceration	Oropharyngeal pain
Rhinorrhoea	Feeling abnormal	Tongue discomfort	Depression	Stomatitis	Lip exfoliation
Spontaneous penile erection	Head discomfort	Gingivitis	Back pain	Oropharyngeal pain	Oral discomfort
Vomiting or nausea (4)	Mouth ulceration (2)	Head injury	Angular cheilitis	Dysphagia	Oral mucosal blistering
Yawning	Vomiting or nausea (3)	Hypersomnia	Oral discomfort	Leukoplakia oral	Lip swelling (2)
Lip, face swelling (2)	Parkinson's disease	Syncope		Oropharyngeal pain	Mouth ulceration
Oral discomfort		Disorientation			
Salivary hypersecretion		Lip, tongue or mouth ulceration (3)			
Anxiety		Oral pain			
Dyskinesia					
Fatigue (2)					
Mouth ulceration (2)					
Asthenia					
Hot flush					
Syncope					
Hypoaesthesia oral (2)					
Stomatitis (2)					
Dry mouth					

In Study 301, all but 10 of these events resolved, the remainder including 2 patients with oropharyngeal irritation and the rest with AEs due to underlying disease state. The only AE considered severe was “glioblastoma” discovered in one patient.

Reviewer’s comment: The adverse events potentially due to the drug product are either related to local effects on the oropharyngeal cavity, including indications of possible hypersensitivity, or those related to the mechanism of action of apomorphine and its physiological effects on the dopaminergic and nor adrenergic receptors. For those AEs mechanistically related to the physiological effects of apomorphine, no clear dose-relationship to the occurrence of adverse events is apparent.

The adverse events potentially signaling hypersensitivity are more apparent in the more chronically treated patients than in the titration groups that represent a much shorter exposure to active drug product.

A comparison of all treatment emergent adverse events in the group of patients who dropped out during open-label titration to those who remained in Phase 3 studies is made below in Section 8.4.5.

8.4.4. Significant Adverse Events

At the time of the 120-day Safety Update for the APL-130277 development program, 2104 adverse events had been reported by the sponsor in 392 patients in Studies 300 and 301. These AEs were characterized as to severity and whether they were considered by the sponsor to be related or unrelated to study drug. (Being related to study drug included characterizations of possible, possible, and definite.) This table is derived from the 120-day Safety Update ADAE dataset.

Table 36 Safety population AEs by severity (source: datasets)

	Mild		Moderate		Severe		All	
	N	%	N	%	N	%	N	%
Related	932	44.3%	363	17.3%	68	3.2%	1363	64.8%
Unrelated	511	24.3%	191	9.1%	39	1.9%	741	35.2%
All	1443	68.6%	554	26.3%	107	5.1%	2104	100.0%

In the "severe" category, 107 events occurred in 62 patients. Of these, 27 events in 20 patients were also considered as SAEs and were discussed above. These events were roughly equally distributed between titration and maintenance phases. Each increasing dose level had fewer severe TEAEs. This makes sense; these AEs would occasion withdrawal from the study or reduction to a lower and better tolerated dose and each successive dose level had fewer individuals susceptible to the adverse treatment effects of apomorphine.

The table below lists the events by dose at which they occurred and in descending order of frequency. It is apparent that these commonly occurring adverse drug reactions are related to the pharmacologic mechanism of apomorphine action.

Table 37 Safety population: severe AEs occurring in at least two patients - Preferred Term by dose level (source: datasets)

Not SAE, graded "severe"	Dose (mg)						
Preferred Term	**10**	**15**	**20**	**25**	**30**	**35**	**All**
Nausea	4	1	3	2	2	2	14
Somnolence	3		2	4			9
Dizziness	2	1		4	1		8
Fatigue				1	1	1	3
Muscle spasms		1			2		3
Syncope	1	1	1				3
Vomiting		1	1	1			3
Dyskinesia	1			1			2
Hyperhidrosis (Diaphoresis)				1	1		2

Orthostatic hypotension	1					1	2

Reviewer's comment: There were no new, novel, or unexpected events or events of unusual severity reported.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

This section provides an overview of all reported treatment emergent adverse reactions using Study 300 for placebo controlled blinded comparison of AEs and Study 301 for AEs from longer term open-label exposure. The corrected ISS demographic dataset ADSL made it possible to link persons in Study 300 to those who rolled into Study 301, though the datasets were still insufficient to perform a fully integrated analysis. In some cases, I made line by line data corrections to be able to format the data for use.

The initial sponsor-supplied table for adverse events occurring in 5% or more patients treated with APL- 130277 in the blinded maintenance period of Study 300 intended for Section 6.1 of the label was the following:

Table 38 Study 300 Sponsor's proposed adverse event table in Prescribing Information

Adverse Reaction	**KYNMOBI (N = 54) n (%)**	**PLACEBO (N = 55) n (%)**
Nausea	15 (28)	2 (4)
Somnolence	7 (13)	1 (4)
Dizziness	5 (9)	0 (0)
Oral mucosal erythema	4 (7)	2 (4)
Vomiting	4 (7)	0 (0)
Fatigue	4 (7)	0 (0)
Rhinorrhoea	4 (7)	0 (0)
Hyperhidrosis	3 (6)	2 (4)
Falls	3 (6)	1 (2)
Headache	3 (6)	0 (0)
Dry Mouth	3 (6)	0 (0)
Laceration	3 (6)	0 (0)

The sponsor also proposed the following and based their discussion of benefit and risk upon these findings:

> "No clear relationship was observed between adverse events and total daily dose (i.e. considering dose and number of doses administered per day at time of the adverse event).
>
> In pooled clinical studies, 10% KYNMOBI-treated patients during titration reported an

> oral adverse event including oral mucosal erythema (4%), and at frequency ≤ 1%, lip ulceration, oral disorder, dry mouth, hypoaesthesia oral, and mouth ulceration. During maintenance treatment 29% KYNMOBI-treated patients experienced an oral adverse event including oral mucosal erythema (5%), lip swelling (5%), mouth ulceration (4%), dry mouth (4%), stomatitis (4%), glossodynia (3%), oral candidiasis (3%), oropharyngeal pain (3%), swollen tongue (3%), ageusia (2%) and oral pain (2%)."

Of note, specific hypersensitivity reactions to APL-130277 were not described and the proposed label contained only the same sulfite sensitivity notice as the RLD in Warnings and Precautions 5.1.

Using the MedDRA Adverse Event Diagnosis tool (MAED), the adverse event datasets from the blinded and open-label studies were reviewed and analyzed. Certain events that were unlikely to be related to drug (squamous cell carcinoma, chills) or were similarly present in active and placebo arms (diarrhea, anxiety, yawning) were removed.

My analysis of the double blinded portion of Study 300 generally confirmed the sponsors' table: However, notable omissions occurred using the 5% cutoff for the table. The MAED table for the maintenance period of Study 300 below illustrates the AEs at 3% or greater, adding the Preferred Terms: *glossodynia, lip oedema, lip swelling, mouth ulceration, oedema peripheral, oropharyngeal swelling,* and *throat irritation*.

This nicely illustrates the obvious splitting of related phenomenon that was overlooked by the sponsor. Of note is that nausea and vomiting also appear separately, a dubious distinction for this drug substance. Emesis and falls and hypersensitivity are submission-specific adverse events of special interest and these are discussed further below.

Table 39 Study 300 Maintenance phase AEs by unedited Preferred Terms (source: datasets)

Study 300 Maintenance Period	*APL-130277 (N = 54)*			*PLACEBO (N = 55)*		
PT	*Events*	*Number of subjects*	*Proportion (%)*	*Events*	*Number of subjects*	*Proportion (%)*
Nausea	18	15	27.78	2	2	3.64
Somnolence	12	8	14.81	2	2	3.64
Dizziness	6	5	9.26	0	0	0
Oral mucosal erythema	5	5	9.26	2	2	3.64
Fatigue	5	4	7.41	0	0	0
Rhinorrhoea	5	4	7.41	0	0	0
Vomiting	5	4	7.41	0	0	0
Dry mouth	3	3	5.56	0	0	0
Fall	3	3	5.56	1	1	1.82
Headache	3	3	5.56	0	0	0
Hyperhidrosis	3	3	5.56	2	2	3.64
Laceration	3	3	5.56	1	1	1.82
Lip ulceration	4	3	5.56	0	0	0
Ageusia	2	2	3.7	0	0	0
Anxiety	2	2	3.7	1	1	1.82
Bronchitis	2	2	3.7	2	1	1.82
Chills	3	2	3.7	0	0	0
Diarrhoea	2	2	3.7	1	1	1.82
Flushing	2	2	3.7	0	0	0
Glossodynia	2	2	3.7	0	0	0
Lip oedema	2	2	3.7	0	0	0
Lip swelling	2	2	3.7	0	0	0
Mouth ulceration	2	2	3.7	1	1	1.82
Oedema peripheral	2	2	3.7	0	0	0
Oropharyngeal swelling	2	2	3.7	0	0	0
Squamous cell carcinoma	4	2	3.7	0	0	0
Throat irritation	2	2	3.7	0	0	0
Yawning	3	2	3.7	2	2	3.64

The titration period in Study 300 suffered from a considerable number of adverse event-related dropouts. The AEs from those patients who left the study are compared to the titration period AEs of patients who were successfully titrated to a tolerable and effective dose and then went into the double-blind maintenance portion of Study 300. These appear to be representative of

those side effects that would dissuade a PD patient from using APL-130277. Events occurring in more than one person who dropped out are shown in the table below. These are not necessarily the reason for which the patient left the study. Those were discussed above. It appears that the AEs encountered are not qualitatively different in these two groups. However, an individual's tolerability of AE-related discomfort may account for the leaving the study.

Table 40 Study 300 comparison of AEs in patients not progressing past titration and those who entered maintenance treatment (source: datasets)

Study 300 Dropouts	*APL-Not assigned (N = 32)*			*Titrated (N = 109)*		
PT	*Events*	*Number of subjects*	*Proportion (%)*	*Events*	*Number of subjects*	*Proportion (%)*
Nausea	19	12	37.5	21	17	15.6
Dizziness	10	8	25	11	8	7.34
Somnolence	15	8	25	15	10	9.17
Headache	11	7	21.88	5	4	3.67
Yawning	9	6	18.75	19	11	10.09
Chills	5	4	12.5	6	4	3.67
Rhinorrhoea	7	4	12.5	9	5	4.59
Vomiting	4	4	12.5	2	2	1.83
Dyspepsia	3	3	9.38	0	0	0
Fatigue	3	3	9.38	1	1	0.92
Hot flush	4	3	9.38	2	1	0.92
Hyperhidrosis	6	3	9.38	3	3	2.75
Constipation	2	2	6.25	0	0	0
Dysgeusia	6	2	6.25	1	1	0.92
Feeling cold	4	2	6.25	0	0	0
Musculoskeletal stiffness	2	2	6.25	0	0	0
Oral mucosal erythema	2	2	6.25	12	4	3.67
Orthostatic hypotension	2	2	6.25	0	0	0
Pallor	2	2	6.25	0	0	0
Presyncope	2	2	6.25	0	0	0
Pyrexia	3	2	6.25	1	1	0.92

Finally, below is a listing for the most AE by Preferred Term that occurred in 3% or more of the entire safety population in studies 300 +301 (N=392). Again, closely related PTs that reflect the same pathological process are in evidence here and addressed as AESI below.

Table 41 Safety population (n=392) AEs by unedited PTs (source: datasets)

Study 300 + 301 APL-130277 Safety Population (N = 392)							
PT	*Events*	*Number of subjects*	*Proportion (%)*	*PT*	*Events*	*Number of subjects*	*Proportion (%)*
Nausea	157	107	27.3	Chills	22	17	4.3
Yawning	108	57	14.5	Nasopharyngitis	15	15	3.8
Somnolence	89	52	13.3	Anxiety	15	14	3.6
Dizziness	72	49	12.5	Dysgeusia	23	14	3.6
Oral mucosal erythema	53	36	9.2	Hypertension	15	14	3.6
Headache	50	34	8.7	Urinary tract infection	16	14	3.6
Fatigue	43	31	7.9	Dry mouth	16	13	3.3
Fall	30	26	6.6	Back pain	12	12	3.1
Hyperhidrosis	32	24	6.1	Lip ulceration	13	12	3.1
Vomiting	25	22	5.6	Stomatitis	19	12	3.1
Rhinorrhoea	36	21	5.4	Flushing	15	11	2.8
Dyskinesia	24	19	4.9	Glossodynia	11	11	2.8
Mouth ulceration	23	19	4.9	Contusion	11	10	2.6
Lip swelling	24	18	4.6	Oral candidiasis	10	10	2.6
Orthostatic hypotension	30	18	4.6	Oropharyngeal pain	13	10	2.6

8.4.6. Laboratory Findings

In Study 300, clinical laboratory studies were only performed on entry to the study and at its conclusion. In Study 301, laboratory assessments were performed at baseline, week 12 of the maintenance treatment phase followed by lab collections at month 16, 20 and 24 and at the end of treatment.

Specific testing performed in both Study 300 and 301 are described in Section 8.3.3. above.

No meaningful differences in clinical laboratory assessment were found. No Hy's Law cases occurred. Shift tables revealed no consistent or unusual patterns of abnormality outside of what could be considered usual laboratory variation.

Of note, in the placebo-controlled population of Study 300, eosinophil % in the peripheral smear were elevated in equal numbers (8%). A modest increase in azotemia occurred more often in the APL-130277 group than in controls (24% vs 15%). In the development program safety population, 11% had occurrences of modestly increased eosinophils and 20% of the population had a modest increase in BUN. There was no clear clinical significance to these findings.

8.4.7. Vital Signs

In Study 300 vital signs (including supine and standing blood pressure) were performed at every titration visit, and at each in clinic visit at the maintenance phase. In Study 301 vital signs were

performed at baseline and all titration visits and all subsequent in clinic visits (months 1, 3, 6, 9, 12, 16, 20 and 24.

At post-baseline measurements in the safety population, hypertension (SBP > 140 mmHg) was common both in supine and standing positions (61% and 54% respectively). During the titration period, in the full safety pool, 40.6% of subjects had a reduction of ≥ 20 mmHg SBP (Δ standing - supine/sitting) or ≥ 10 mmHg DBP (Δ standing - supine/sitting) after treatment with active drug. This is consistent with the central catecholaminergic physiological effects of APL-130277 and other dopamine agonists.

In the Study 300 maintenance phase of treatment, a higher percentage of subject in the APL-130277 group had a reduction of ≥ 20 mmHg for Δ SBP or ≥ 10 mmHg Δ DBP (42.6% APL-130277; 36.4% placebo).

In the open label safety population receiving maintenance treatment, the results were similar: 36.7% of subjects had a reduction of ≥ 20 mmHg SBP or ≥ 10 mmHg for DBP.

A relatively small number of these developed symptomatic orthostatic hypotension. This is discussed in Section 8.5.5.

8.4.8. Electrocardiograms (ECGs)

In Study 300, triplicate ECGs were collected 50 minutes post dose at each titration visit and during the double-blind placebo-controlled maintenance phase visits. There were 54 subjects on APL-130277 in this period of CTH-300 and none of the participants had a post-dose QTcF >500 ms or a change in QTcF greater than 60 ms. In Study 301, ECG was also performed at each titration visit and then at month 1, 3, 6, 9, 12, 16, 20 and 24 during maintenance treatment.

Resting ECG parameters: HR, PR interval, QRS interval, RR interval, QT interval, QT interval corrected for heart rate using Fridericia's correction (QTcF), and QT interval corrected for heart rate using Bazett's correction (QTcB) were collected pre-dose and post-dose at all visits enumerated above.

The incidence of increases in QTcF interval of > 30 ms to 60 ms was 5.3%, and the incidence of increases in QTcB interval of > 30 ms to 60 ms was 6.6%. Increases of > 60 ms in QTcF and QTcB intervals were rare (0.8% each). The clinical significance of this, if any, cannot be determined. There was a considerable rate of premorbid cardiovascular disease in the safety population including electrocardiographic abnormality. No other emergent conduction defects appear to be drug related.

8.4.9. TQT Study

The primary objective of the thorough QT study (Study CTH-201) was to evaluate the effect of APL-130277 compared with placebo on QTc intervals in subjects with PD complicated by motor fluctuations. The primary endpoint was the time-matched change from baseline in QTc, placebo-adjusted and corrected for HR based on the QTcF method (ΔΔQTcF). Assay sensitivity was to be demonstrated by inclusion of a positive control, moxifloxacin. This protocol was commented upon by the QT-IRT prior to beginning the study.

The study consisted of a titration phase and a 3-way crossover phase. During titration starting at 10 mg, the dose of APL-130277 was individually titrated based on effectiveness and tolerability to determine the appropriate dose of APL-130277 that turned a subject with PD from a practically defined "off" state to an "on" state. Subjects could increase their dose 2 more dose levels as tolerated above the initial dose that resulted in an "on" response. The highest tolerable dose was the dose at randomization.

Participants who successfully completed an initial dose titration phase were randomized in equal numbers to 1 of 6 possible treatment sequences to receive single doses of APL-130277, placebo, and moxifloxacin in a 3-way crossover design. APL-130277 and placebo were administered in a double-blind fashion and moxifloxacin was administered open-label. Baseline ECGs (mean of 3 sets of triplicate ECGs) were obtained over approximately 1 hour prior to dosing in Period 1 of the crossover phase using a Holter monitor device. Triplicate 12-lead ECGs were obtained at t = 0 (just prior to dosing; Periods 2 and 3 only), 15, 30, 45, and 60 minutes after dosing and at 2, 3, 4, 8, 12, and 24 hours after dosing.

The ECG Population (ITT equivalent) was defined as all patients who were randomized, received at least 1 dose of study drug, and had at least 1 evaluable pre-dose ECG and 1 evaluable on-treatment post-dose ECG within the same treatment period. Baseline and post-dose ECG data for each treatment period were analyzed using a mixed effects model, and the estimates of ΔΔQTc and its 2-sided 90% confidence interval (CI) at each time point were performed using a least-squares (LS) mean procedure.

QT-IRT Review

Reviewer's note: These findings are condensed verbatim from the QTIRT review. The interested reader is referred to their careful review for details.

Review of Study 201 found that the TQT study is inconclusive to exclude a 10-ms mean increase in the QTc interval at recommended clinical dosing regimen (10 mg starting dose with titration up to a highest dose of 35 mg, with a maximum of 5 doses per day and the consecutive doses separated by at least 2 hours). The basis for their opinion is cited verbatim:

Doses evaluated do not cover the exposures associated with clinical dosing regimen. Based on the design, the final dose levels were achieved through individual titrations based on tolerability rather than by randomized treatment assignment. The higher dose groups did not result in higher exposures compared to lower dose groups as would have been expected with linear PK. The mean Cmax across dose levels is ~4 ng/mL, which is inadequate to cover C_{max} of the maximum recommended therapeutic dose of 35 mg (~9 ng/ml). Furthermore, higher exposures are expected in patients with renal impairment (50% higher C_{max} with renal impairment).

Lack of dose-response for QTc prolongation. In central tendency analysis for pooled dose levels (10-50 mg), the largest upper bound of the 2-sided 90% CI for the mean ΔΔQTcF was 9.8 ms, with the corresponding mean of 6.3 ms. When the same analysis was used to assess dose-response, the QTc effects for 10- and 20-mg dose levels were different despite having similar exposures: the largest mean ΔΔQTc exceeded 10 ms at 4 timepoints for the 10 mg dose whereas it was below 10 ms for the 20 mg dose at all timepoints. These discrepant findings could be caused by the small number of subjects within each dose level and the study was not powered to detect dose-response. Furthermore, there were too few patients receiving 15 mg and doses above 20 mg (2 for 25 mg, 3 for 35 mg and 1 for 50 mg) to be able to adequately characterize the change in QTc interval at those dose levels.

Lack of ability to adequately characterize concentration-QTc relationship. A concentration-QTc analysis would have been the more appropriate analysis for this titration study design to project the QTc effects at dose/exposures of interest. However, the data did not support a direct effect linear C-QTc model. Potential reasons for the poor fit is narrow range of exposures (higher doses did not provide higher concentrations); and possible time delay between peak QTc effects and peak concentrations.

Reviewer's comment: We agree with the QT-IRT description of Study 201, their analysis, and findings. The reference listed drug for this 505(b)(2) application, APOKYN®, carries Warning and Precautions language for QTc prolongation in the label. (b) (6)

8.4.10. Immunogenicity

This section is not applicable to this submission.

8.5. Analysis of Submission-Specific Safety Issues

As labeled for the reference listed drug, adverse events of certain categories are of special

interest due (AESI) either to the physiological actions of the drug substance, apomorphine, or phenomena that could be ascribed to the drug substance and/or drug product. In the RLD label these are:

Hypersensitivity
Nausea and Vomiting
Falling Asleep During Activities of Daily Living and Somnolence
Syncope; Hypotension/Orthostatic Hypotension
Falls
Hallucinations/Psychotic-Like Behavior
Dyskinesias
Impulse Control/Compulsive Behaviors
Coronary Events
QTc Prolongation and Potential for Proarrhythmic Effects

QTc prolongation is discussed above in Section 8.4.9. Events related to others warnings found in the RLD label were not encountered here (withdrawal-emergent hyperpyrexia and confusion, fibrotic complications, priapism). There were three reports of spontaneous penile erections in the safety population.

One case of malignant melanoma occurred in the safety population, a 76-year-old man who had been titrated on APL-130277 but was randomized to the placebo arm of Study 300.

Reviewer's comment: It is apparent in the rate of occurrence of the AEs discussed below that events occur much more commonly in the larger safety population overall than in the smaller controlled trial population. While the safety population contains mostly open-label observations, it also includes observations made during the ascending dose titration of the study drug, a time when adverse events may be expected to occur more often.

The exception to this may be hypersensitivity AEs which appear to depend upon length of exposure, i.e., increasing with duration of treatment.

8.5.1. Hypersensitivity

The RLD is labeled for hypersensitivity reactions considered related to sulfite allergy. Exclusion criteria in the APL-130277 trials included hypersensitivity to APOKYN® with specific mention of sodium metabisulfite. It is an excipient of both APOKYN® and APL-130277 drug products in comparable amounts.

During clinical review, it became apparent that hypersensitivity reactions occurred at a rate greater than expected, especially given the experience with the RLD.

To facilitate review, a case definition was established by OSE for a pharmacovigilance review of

the RLD and it was used in this clinical review as well.

FAERS and Vigibase SMQ search criterion were used to obtain cases of potential within the wide spectrum of hypersensitivity reactions:

- Anaphylactic reaction (broad)
- Angioedema (broad)
- Hypersensitivity (broad)
- Severe cutaneous adverse reactions (broad)

Cases of angioedema following administration of apomorphine were included based on the following criteria:

- Clinical diagnosis of angioedema as stated by the reporter
- Rapid development of unexplained swelling from the neck up including the face, lips, mouth, throat, larynx, or eyes, with or without airway compromise.

Initial clinical review

Using the blinded, maintenance population in CTH-300, I looked at patients in the AE dataset with a past medical history of asthma (found in the MH dataset). With this very small sample, it cannot be determined if a history of asthma plays a role in being positive for an AE in either the broad hypersensitivity SMQ or the broad angioedema SMQ.

Table 42 Study 300 maintenance population with past medical history of asthma (source: datasets)

CTH-300	N = 99	Subjects w/AE by Hypersens SMQ	Subjects w/ AE by Angioedema SMQ	Positive Asthma PMH (N=10)	Asthma Subjects in Either SMQ (N=1)
MP Active	54	11 (20%)	10 (18.5%)	3 (5.5%)	1 of 12
MP Placebo	55	2 (4%)	1 (2%)	7 (12.7%)	0 of 19

Information Request

In September 2018, the following request was made to the sponsor. It was returned October 8. The requested fix of the datasets was to allow an integrated review of hypersensitivity symptoms in the safety population.

> 1. For the entire APL-130277 safety population, i.e. the 497 subjects (both volunteers and PD patients) who received at least one dose of APL-130277 through the cut-off date for the 120-day safety update, create revised ADSL, ADAE, and ADEX datasets for the ISS that are strictly compliant with the ADaM standard, (e.g., each unique patient in ADSL should occupy only one row). The USUBJID and study identifiers for each patient should be identical to the ones previously used in the prior ISS datasets and should be consistent across the requested datasets.

2. We note that there are a considerable number of adverse events reported in different SOCs suggesting hypersensitivity and angioedema. For the entire APL-130277 safety population through the cut-off date for the 120-day safety update, analyze for and discuss all adverse events suggestive of drug hypersensitivity. This should include all AEs regardless of the assessment of causal relationship to the investigational drug and regardless of severity, and should also include patients receiving placebo. Perform this analysis using the following MedDRA SMQs:

Hypersensitivity (broad)
Angioedema (broad)
Anaphylactic reaction, (broad)
Severe cutaneous reaction (broad)

Include events that may have occurred after drug was stopped or shortly after a patient may have left the study. Look for instances of rechallenge and events that resolved, worsened, or reoccurred with continued use of the drug.

Sponsor's Clinical Information Amendment

The sponsor created new ADSL, ADAE and ADEX datasets, but the new USUBJID still did not allow relational connection to the full range of previously submitted individual study and ISS datasets. As a result, while individual subjects were traceable to the original datasets, analysis of the role of secondary demographic and treatment factors to hypersensitivity was still hampered.

Hypersensitivity

The sponsor performed the SMQ analyses in two pools: the controlled data population in Study 300 (Pool 1: n=54 active, n=55 placebo) in the titration/maintenance phases and a safety population (Pool 3) of all those who received at least one dose of APL-130277.

Reviewer's comment: It should also be noted that the SMQs used in these analyses have many Preferred Terms in common and thus many subjects were counted in more than one SMQ. The cases in SMQs should not be considered additive of cases suggesting all forms of hypersensitivity.

Pool 1 patients who made it through titration to the point where they were randomized to blinded treatment provide the only blinded, placebo- controlled reports of AEs. While a selective and non-representative treatment sample, it suggests the clear majority of hypersensitivity reports do come from the actively treated patients. A likely hypothesis is that the reporting of hypersensitivity symptoms is less affected by knowing the treatment status of patients in comparison to efficacy ratings.

The difference in these two groups is immediately apparent in the number of different SMQ-related Preferred Terms reported in the two pools: 15 in Pool 1 and 29 in Pool 3. However, these tables are not useful as constructed because many of these preferred terms are single

occurrences. The many different preferred terms are variations of the same type of adverse event (splitting). As an example, the sponsors Pool 1 table for the hypersensitivity SMQ illustrates how the various Preferred Terms for swelling (yellow) were reported in the original AE dataset:

Table 43 Study 300 maintenance phase population -example of PT splitting (source, sponsor Clinical Information Amendment 1.11.3, page 7)

	APL-130277 N = 54 (SY = 10.237)			Placebo N = 55 (SY = 11.307)		
Preferred Term	**Subjects n (%)**	**Events**	**IR[a]**	**Subjects n (%)**	**Events**	**IR[a]**
Any TEAE	11 (20.4)	18	1.76	2 (3.6)	2	0.18
Flushing	2 (3.7)	2	0.20	0	0	0.00
Lip oedema	2 (3.7)	2	0.20	0	0	0.00
Lip swelling	2 (3.7)	2	0.20	0	0	0.00
Oropharyngeal swelling	2 (3.7)	2	0.20	0	0	0.00
Gingival oedema	1 (1.9)	1	0.10	0	0	0.00
Hypersensitivity	1 (1.9)	1	0.10	0	0	0.00
Mouth ulceration	1 (1.9)	1	0.10	1 (1.8)	1	0.10
Oedema mouth	1 (1.9)	1	0.10	0	0	0.00
Oral allergy syndrome	1 (1.9)	1	0.10	0	0	0.00
Pharyngeal oedema	1 (1.9)	1	0.10	0	0	0.00
Stomatitis	1 (1.9)	1	0.10	0	0	0.00
Swelling face	1 (1.9)	1	0.10	0	0	0.00
Swollen tongue	1 (1.9)	1	0.10	0	0	0.00
Urticaria	1 (1.9)	1	0.10	0	0	0.00
Erythema	0	0	0.00	1 (1.8)	1	0.10

[a] Incidence rate is calculated as event count divided by the exposure to study medication (expressed as patient years).
SY = subject years: Reference: Table S006-05

The effect of this excessive granularity becomes clearer when a selected group of Preferred Terms related to swelling, oral pain and allergy are used to illustrate the occurrence of hypersensitivity reactions in Study 300.

Table 44 Study 300 selected Preferred Terms related to oral allergy (source: datasets)

Study 300	Safety Pop (n=141)		Titration Pop (n=141)		Maintenance Period (n=109; active n=54, placebo n=55)			
PT	Events All	Head Count	Events in Titration	Head Count	Events in Maintenance	APL-130277 Head Count	Events in Maintenance	Placebo Head Count
Gingival oedema	1				1			
Lip oedema	2				2			
Lip swelling	3		1		2			
Oedema mouth	1				1			
Oral allergy syndrome	1				1			
Oropharyngeal swelling	2				2			
Pharyngeal oedema	1				1			
Swelling face / soft palate	1				1			
Swollen tongue	1				1			
Edema_Total	13	10	1	1	12	9	0	0
Gingival pain	1				1			
Glossodynia	2				2			
Oral pain	*2				1		1	
Oropharyngeal pain	2		1		1			
Pain_Total	7	7	1	1	5	6	1	1
Hypoaesthesia	4		2		2			
Hypoaesthesia oral	1				1			
Paraesthesia oral	2		1		1			
Aesthesia_Total	7	5	3	3	4	2	0	0
All Events Total	**27**	**19 (13.5 %)**	**5**	**5 (3.5 %)**	**21**	**14 (25.9 %)**	**1**	**1 (1.8 %)**

A similar analysis for Study 301 corroborates the experience of Study 300.

Reviewer's comment: It is my opinion that the lesser incidence of reported events noted in the long term open label study is related to study methodology and protocol processes related to the querying for adverse events. Visits occurred at infrequent intervals and the high rate of dropout (71 patients) may in part be related to unreported or unrecognized adverse events. There is no clinical evidence suggesting that hypersensitivity reactions decrease over time.

Table 45 Study 301 selected Preferred Terms related to oral allergy (source: datasets)

Events occuring in Study 301	Safety Pop (n=308)		Titration Pop (n=215)		MP Pop (n=272)	
PT	Events All	Head Count	Events in Titration	Head Count (TP)	Events in Maintenance	Head Count (MP)
Gingival oedema	1				1	
Lip oedema	1				1	
Lip swelling	21				21	
Oedema mouth (includes swelling)	4				4	
Oral allergy syndrome	0				0	
Oropharyngeal (includes palatal) swelling	1				1	
Pharyngeal oedema	2				2	
Swelling face	4				4	
Swollen tongue	10				10	
Edema_Total	44	27	0	0	44	27
Gingival pain	0				0	
Glossodynia	8				8	
Oral pain	7				7	
Oropharyngeal pain	11		2		9	
Pain_Total	26	19	2	1	24	18
Hypoaesthesia	1				1	
Hypoaesthesia oral	11		2		9	
Paraesthesia oral	2				2	
Aesthesia_Total	14	8	2	2	12	6
All Events Total	**84**	**45 (14.6 %)**	**4**	**3 (1.4 %)**	**80**	**42 (15.4 %)**

Several conclusions are apparent:

- The wide variety of hypersensitivity reactions to APL-130277 are common.
- They occur with greater frequency with duration of exposure.
- If individual events are looked at in isolation (excessive granularity), the spectrum of clinical phenomenology in hypersensitivity reactions results in omitting cases of such reactions. For this reason, the Standardized MedDRA Query (SMQ) is useful to look at such events by grouping relevant Preferred Terms.

This becomes clearer when one uses SMQs to group appropriate Preferred Terms as the sponsor did in analyses request by the clinical review team. These analyses greatly overlap the numbers of individual patients in each SMQ as related SMQs encompass related PTs. Nevertheless, it yields an accurate picture of the consistency of hypersensitivity-related TEAEs.

Analyzing the Pool 3 safety population, the sponsor found that 74 of 540 patients (13.7%) were identified by the Hypersensitivity SMQ. Most (57 of the 74) were identified in the maintenance phase of Studies 300 or 301 rather than the titration phase, again suggesting duration of exposure to APL-130277 affects the development of hypersensitivity reactions. An example of

this is stomatitis which occurred in only one patient in Study 300 but was an AE in 12 patients in Study 301. In this long-term study stomatitis was noted beginning between 12 and 307 days, with an average of 87 days.

The full set of oral allergy Preferred Terms and number of individual patients in which they occurred in the APL-130277 safety population is listed below.

Table 46 Safety Population PTs related to oral allergy (source: datasets)

Preferred Term	N	%	Preferred Term	N	%
Oral mucosal erythema	35	8	Aphthous ulcer	2	0
Lip swelling	18	4	Chapped lips	2	0
Mouth ulceration	17	4	Gingival erythema	2	0
Dry mouth	13	3	Lip blister	2	0
Stomatitis	12	3	Lip pain	2	0
Glossodynia	11	2	Mouth haemorrhage	2	0
Lip ulceration	10	2	Mouth injury	2	0
Oropharyngeal pain	10	2	Oropharyngeal swelling	2	0
Ageusia	9	2	Pharyngeal erythema	2	0
Swollen tongue	9	2	Drug hypersensitivity	1	0
Hypoaesthesia oral	8	2	Gingival oedema	1	0
Oral discomfort	6	1	Gingival pain	1	0
Oral pain	6	1	Gingival swelling	1	0
Salivary hypersecretion	6	1	Gingival ulceration	1	0
Throat irritation	6	1	Gingivitis	1	0
Dental caries	5	1	Hypersensitivity	1	0
Cheilitis	4	1	Lip dry	1	0
Mouth swelling	4	1	Oedema mouth	1	0
Oral disorder	4	1	Oral allergy syndrome	1	0
Oral mucosal blistering	4	1	Oral contusion	1	0
Paraesthesia oral	4	1	Oral mucosal eruption	1	0
Tongue ulceration	4	1	Oral papule	1	0
Leukoplakia oral	3	1	Palatal swelling	1	0
Lip oedema	3	1	Pharyngeal ulceration	1	0
Pharyngeal oedema	3	1	Sensitivity of teeth	1	0
Swelling face	3	1	Tongue blistering	1	0
Tongue injury	3	1	Tongue discomfort	1	0
Angular cheilitis	2	0	Tongue polyp	1	0

In four patients, three events were assessed as severe and 3 met serious criteria; these were discussed above in the sections on severe reactions and SAEs. One patient ((b) (6)) had an anaphylactic reaction and is discussed below.

Table 47 Safety population - hypersensitivity SMQ outcome (source: datasets)

Resolved:	57 (77%)
Recurrence with continued dosing:	9 (12.2%)
Recurrence following re-challenge:	9 (12.2%)
Worsened (either on drug or after discontinuation):	4 (5.4%)

In this table, patients may be counted twice (e.g.: as both recurring and worsened) and patients whose AE outcome was "not recovered" are in the total but not otherwise listed.

Angioedema

In Pool 1 SMQ PTs referring to angioedema were seen in 10 (18.5%) APL-130277 and 1 (1.8%) placebo treated subject during the maintenance/treatment phase. The most commonly reported events in the APL-130277 treatment arm included lip edema, lip swelling and oropharyngeal edema (2 patients each). The time to event onset varied, but most occurred after > 30 days of treatment. Of note, a single event of peripheral swelling (verbatim: allergic reaction – puffy hands) occurred in a placebo-treated subject.

In the Pool 3 analysis, the sponsor found that 45 of 540 (8.3%) patients in the safety population fulfilled the SMQ for angioedema. Only 4 of these occurred during titration, the rest during maintenance treatment. The most common adverse events were lip swelling, occurring in 5.2% and swollen tongue in 2.8% of APL-130277-treated subjects. The 45 subjects reporting an event in the angioedema SMQ had the following outcome.

Table 48 Safety population - angioedema SMQ outcome (source: datasets)

Resolved:	34 (75.6%)
Recurrence with continued dosing:	3 (6.7%)
Recurrence following re-challenge:	4 (8.9%)
Worsened (either on drug or after discontinuation):	3 (6.7%)

Reviewer's comment: Angioedema in the placebo patient is notable in that the placebo thin strip does not contain metabisulfite as an excipient. Angioedema was noted to occur at the 10, 15, 20, 25, and 30 mg doses.

Anaphylaxis

The sponsor used rigorously applied consensus criteria[2] for defining anaphylaxis in their retrospective analysis and found few cases. Unfortunately, it is not clear how rigorously the study population was evaluated and reported when the relevant adverse events occurred and whether all relevant emergent clinical phenomena were fully investigated. The investigation of suspect cases was never defined *a priori* in any protocol and so it is likely inappropriate to consider the *post hoc* application of these criteria captured all possible cases. For example, review of one Med Watch 15-day safety report revealed a patient who stopped drug for an initially mild hypersensitivity reaction but required hospitalization for symptoms of possible anaphylaxis (dyspnea and oropharyngeal swelling) after leaving the study.

Table 49 Sponsor's clinical criteria for anaphylaxis (source: sponsor Clinical Information amendment and citation)

Table 6: Clinical Criteria for Anaphylaxis as Defined by Sampson et al

(b) (4)

Using these criteria in a MedDRA SMQ analysis performed by MAED, 2 of 54 active maintenance treatment patients and no placebo patients were identified in Pool 1. In the Pool

[2] Sampson, H.A., et al. Second symposium on the definition and management of anaphylaxis: summary report--Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol. 2006 Feb;117(2):391-7. DOI: 10.1016/j.jaci.2005.12.1303

3 safety population, 7 additional patients were identified.

Table 50 Safety population: cases of possible anaphylaxis identified by MedDRA SMQ

Pool 1:	Pool 3
(b) (6)	

Following review of the narratives, only four of the patients have a constellation of symptoms that suggest the possibility of mild anaphylaxis. The other patients listed in the table above were likely cases of oral hypersensitivity with additional apomorphine-related side effects that were short lived and temporally related to medication ingestion. The combination of any hypersensitivity AE and a drug mechanism of action-related side effect of flushing, orthostatic hypotension or gastrointestinal distress would be identified as a potential case in a search by the MedDRA SMQ for all Preferred Terms suggesting anaphylaxis.

Table 51 Safety population: possible cases of anaphylaxis (source: narratives)

Pool 1	Sex / Age	Dose	Exposure at Start of AE	Duration	Clinical findings and course
(b) (6)	M / 63	20 mg	20 d	23 d	Gingival, lip, and mouth edema. Diphenhydramine begun. Drug was withdrawn on Day 23. Symptoms persisted until Day 40.
	F / 72	10 mg	64 d	6 d	Oropharyngeal pain, orpharyngeal swelling, pharyngeal edema. Drug withdrawn at next visit and symptoms resolved on Day 70
	M / 75	10 mg	107 d	9 d	Mouth burning began on Day 91. Hospitalized on Day 107 with pharyngeal edema, dyspnea, dysphagia. Treated with methylprednisolone and diphenhydramine. Resolved on Day 116.
	M / 66	35 mg	32 d	168+ d	Lip and tongue swelling, oropharyngeal pain. Symptoms and APL-130277 treatment continued and by study day 45 intermittent swelling was occuring in the lips, tongue, and face. By study day 51 chelitis had occurred. Symptoms were considered mild and drug was contined until day 200. Retrospectively the patient was reported to be dyspneic during this period.

Reviewer's comment: Because of the episodic nature of visits in Study 301, most patients experienced adverse events suggestive of hypersensitivity for some time before worsening. All

the patients suspected of having anaphylaxis had a prodromal period of symptoms generally of an oropharyngeal nature that were reported at the time of the next clinic visit. Some of the reporting, including 15-day MedWatch safety reports, were quite remote from the inciting event (in some cases months). Of interest, in some narrative reports, there is also discussion concerning the use of which preferred terms to report the events and it may be that the full extent of adverse drug reactions was not noted. For example, if erythema or edema was reported as an AE in one part of the mouth, it appears that it was not considered important to report other oropharyngeal areas involved. It is evident that there were no uniform criteria for assessing hypersensitivity events, even severe or serious ones. This promoted the splitting of Preferred Terms and contributed to the sponsor's minimizing this risk.

Analysis of oral skin reactions (mostly mouth ulcerations, stomatitis, mucosal blistering, and related symptoms) added no additional cases beyond those found in the above SMQs. Of interest, only five patients developed hives, which healthcare providers generally think of as one of the more common allergic reaction to drugs. However, each of these patients had other evidence of hypersensitivity related phenomena consistent with a generalized reaction.

Safety Population: Hypersensitivity related PTs occurring in patients with skin rash			
USUBJID	Preferred Term	USUBJID	Preferred Term
(b) (6)	Eosinophil count increased	(b) (6)	Oral pain
	Lip swelling		Oropharyngeal pain
	Oral mucosal blistering		Stomatitis
	Swelling face		Ageusia
	Urticaria		Stomatitis
			Rash maculo-papular
	Lip swelling		
	Swollen tongue		Urticaria papular
	Urticaria		Glossodynia
			Gingival erythema
	Rash erythematous		
	Mouth ulceration		

OSE Pharmacovigilance Review

The Division of Pharmacovigilance was asked to review hypersensitivity reactions reported for the RLD and the information in this section is taken directly from the OSE review. APOKYN® (NDA 21264, apomorphine subcutaneous injection for "off" periods in PD) is the only other apomorphine product currently approved in the US but other apomorphine products are marketed outside the US. DPV extended the review to include Uprima (sublingual apomorphine approved outside the US in 2001 for the treatment of erectile dysfunction) reports in the VigiBase database.

Using the U.S. Food and Drug Administration's (FDA) Adverse Event Reporting System (FAERS) database and the World Health Organization's (WHO) VigiBase database and published literature DPV sought possible cases of angioedema and anaphylaxis. The published medical literature was also reviewed. Cases so identified were then inspected further for relevance.

While the DPV reviewer found multiple types of hypersensitivity reports with apomorphine, DPV identified only a single serious FAERS case of anaphylaxis with APOKYN® (apomorphine) SC administration. This single case was culled from 321 possible cases of hypersensitivity using broad SMQ searches for angioedema, hypersensitivity, severe cutaneous reactions and anaphylactic reactions. This number was reduced due to the following exclusions:

- Duplicates (n= 30)
- Did not meet case definitions (n=248)
  - Swelling: injection site or extremities (labeled) (n=70)
  - Non-serious cases (N=178)
- Insufficient information for assessment (n=23)
- Alternative etiology: swelling from trauma (n=3)
- Did not meet case definitions (n=16)
  - Non-serious outcome (n=16)

The single identified case:

FAERS/MFR#s (b) (6)

A 67-year-old female with a history of Parkinson's disease started Apokyn injection 0.4 mls, 4-5 times daily. On day 27 of Apokyn therapy, she injected herself and "moments later" experienced tongue swelling and breathing difficulties. On hospital admission, Apokyn was discontinued and she received diphenhydramine and methylprednisolone to manage her "anaphylactic reaction." She was discharged from the hospital the following day. Concomitant medications included pramipexole, carbidopa/levodopa, and warfarin, which were of long-term use.

Data mining of adverse events of interest in FAERS found terms related to hypersensitivity but their occurrence did not rise to the strength needed to be considered a signal (EB05 > 2, i.e. occurs twice as frequently as the background rate with other drugs in the database).

Table 52 FAERS data mining for selected hypersensitivity events (source: OSE Pharmacovigilance review)

Table 6. Data Mining Results Using Empirica Signal for Selected Hypersensitivity Events Reported with Apomorphine, Sorted by EB05 Scores in Ascending Order. *					
	MedDRA preferred terms (PT)	**N**	**EB05**	**EBGM**	**EB95**

1	*Anaphylactic reaction*	1	0.044	0.21	0.694
2	*Lip swelling*	2	0.143	0.459	1.184
3	*Swelling face*	3	0.146	0.385	0.866
4	*Mouth swelling*	1	0.169	0.798	2.635
5	*Swollen tongue*	3	0.238	0.628	1.414
** A score (EB05) of ≥ 2 indicates 95% confidence that a drug-event combination appears at least twice the expected rate when considering all other drugs and events in the database*					

DPV concluded that they were not able to offer comment to suggest apomorphine's formulations (SC or SL) with or without sulfite derivatives have any clinical relevance to the occurrence of hypersensitivity reactions. Their review of the FAERS data does not support changes to the current APOKYN® (apomorphine) label.

Reviewer's comment: This reviewer is most appreciative of DPVs assistance and efforts in this regard and agrees with their assessment of the data. This reviewer also acknowledges the considerable assistance of the entire clinical review team and thanks them for their assistance with, and interpretation of the hypersensitivity analyses.

Review of RLD composition

The composition of the RLD (APOKYN®) appears in the product label. From that the exposure to metabisulfite in both APOKYN® and KYNMOBI by dose can be calculated.

(b) (4)

[redacted]

Reviewer's comment: Sodium metabisulfite is present in roughly the same amount in both drug products. However, on face, even though APOKYN® is labeled for hypersensitivity (potentially

reducing active reporting of that adverse event), it appears that the considerable treatment emergent hypersensitivity found in APL-130277 is not clearly related to this compositional factor.

Finally, from the current review of submitted data, it does not appear possible to predict who might have a predilection to hypersensitivity reactions. There is evidence to support that TEAEs related to hypersensitivity should be labeled for APL-130277 differently than the RLD which has only general warnings and contraindications related to metabisulfite.

8.5.2. Oropharyngeal Examination

In Study 300 oropharyngeal examination was performed at every titration visit and at each in clinic maintenance visit. In Study 301, oropharyngeal examination was performed at screening, at each titration visits (up to 6 such visits if needed) and in the maintenance treatment phase at Months 1, 3, 6, 9, 12, 16, 20 and 24. A specific concern about the repeated application of the APL-130277 thin film against oral mucosa was the potential to develop local pathology from irritation. This is not clearly able to be differentiated from hypersensitivity based on symptoms alone and indeed, the sponsor's SMQ looked at the combined AESI category of stomatitis, oral ulcers, and oral irritation or allergic/sensitivity. There is a cogent argument to be made that these mucosal disorders should be considered part and parcel of the hypersensitivity-based adverse drug reactions and not simply "local irritation."[3]

The most commonly reported oral events were lip swelling, oral mucosal erythema, mouth ulceration, stomatitis, dry mouth, and glossodynia. In the safety population of Study 300 + 301, 12 (4.1%) of PD patients had stomatitis, while 12 (4.5%) had mouth ulcerations. In only one case was the stomatitis considered severe. These AESI appeared at all levels of exposure. When one added in the occurrence of any oral irritation including possible hypersensitivity or allergy, fully 94 (32.3%) of the PD safety population had such a TEAE related to this AESI category. It is important to note that 54 different Preferred Terms related to oral AEs (covering the gingiva, tongue, lips, mouth, palate and pharynx) were reported in the maintenance treated safety population. The range of events illustrates the difficulty in assigning a specific etiology to the oral pathology.

8.5.3. Nausea and Vomiting

Nausea and vomiting were commonly occurring AEs and, as noted above, occasioned dropouts especially during the titration period. These were analyzed by the sponsor separately but did not change when combined as higher-level terms in the table below.

[3] Scully, C. and Bagan, J.V. Adverse drug reactions in the orofacial region. Crit Rev Oral Biol Med. 2004 Jul 1;15(4):221-39.

Table 54 Study 300 Nausea and vomiting symptoms in the maintenance phase (source: datasets)

Study 300 Maintenance Period	*APL-130277 (N = 54)*			*PLACEBO (N = 55)*		
PT	*Events*	*Number of subjects*	*Proportion (%)*	*Events*	*Number of subjects*	*Proportion (%)*
Nausea	18	15	27.78	2	2	3.64
Vomiting	5	4	7.41	0	0	0
HLT						
Nausea and vomiting symptoms	23	15	27.78	2	2	3.64

This percentage of persons suffering from nausea and vomiting is no different in the safety population for Studies 300 +301 where this AE was observed or reported in 111 of 392 (28%) PD patients. It was more commonly reported among patients who dropped out during the titration phase of treatment. Most patients in the Study 300+301 safety population received antiemetic treatment but where it was not received (as an option) during maintenance therapy in Study 301 the sponsor reports a greater instance of nausea and vomiting as an AE.

8.5.4. Falling Asleep During Activities of Daily Living and Somnolence

In the blinded maintenance period of Study 300, 8 of 54 patients (14.8%) on active treatment reported somnolence as opposed to 2 of 55 (3.6%) in the placebo arm. Somnolence overall was reported by 52 of 392 (13.3%) PD patients in the safety population. When grouping AEs by higher level terms, this increased slightly by adding two patients with the AE of hypersomnia. Somnolence maps to the Nervous System SOC while the latter maps to Psychiatric disorders.

One episode of sudden onset of sleep (sleep attack) was reported in the Study 300 + 301 safety population.

8.5.5. Syncope; Hypotension/Orthostatic Hypotension

No episodes of syncope occurred in the placebo-controlled period of Study 300. Syncope occurred in 7 PD patients (1.8%) of the Study 300 +301 safety population. Three of these episodes were rated as “severe” (though not as a SAEs) and were related to dropping out in the titration phase of study.

In the Study 300 + 301 safety population, all 28 AEs with verbatim descriptions using a variation of “dizziness” or “feeling faint” were coded to the PT “dizziness” in the nervous system disorders SOC. “Lightheaded” in some form was listed as the verbatim description for 37 events; in all but one the PT decode was also “dizziness”. Only one such AE was coded as “hypotension.” Unfortunately, “lightheadedness” as a LLT in MedDRA codes as the PT

"dizziness," inappropriately so. The verbatim description of dizziness includes in some cases "post dose" and was more likely hypotension as well.

The word "orthostatic" appears in five PTs related to orthostatic hypotension. It may map to either the nervous system disorders SOC or the vascular disorders SOC depending on the presumed etiology. In the placebo-controlled period of Study 300, "orthostatic" or "hypotension" appears as an AE for one patient in the active arm and none in the placebo arm. However, "dizziness" is coded as an AE for 5 patients (9.3%) in the active arm and is not reported in placebo patients.

The result is similar in the AE dataset for the Study 300 + 301 safety population:

Table 55 Studies 300 and 301 low blood pressure related events (source: datasets)

Study 300 + 301 APL-130277 Safety Population (N = 392)			
PT	*Events*	*Number of subjects*	*Proportion (%)*
Dizziness	72	49	12.5
Orthostatic hypotension	30	18	4.59
Hypotension	10	9	2.3
Presyncope	7	6	1.53
Blood pressure decreased	1	1	0.26
Blood pressure systolic decreased	1	1	0.26

When these lower level terms and preferred terms that suggest hypotension are recoded, the results are not much changed in the maintenance period of Study 300; 3 patients are reported to have an AE of dizziness and 1 with orthostatic hypotension (in all, 7%). All were in the active treatment arm.

However, when verbatim descriptions of "lightheadedness" or "feeling faint" or "dizziness post dose" are recoded as orthostatic hypotension and combined with other events suggesting lowering of blood pressure, there are a total of 91 AEs reported in 59 PD patients or 27.3 % of the safety population.

Reviewer's comment: This is expected and consistent with the drug's physiologic properties. It is also consistent with the observed dropping of systolic blood pressure in vital sign measurement after APL-130277 administration.

8.5.6. Falls

Falls, with or without associated injury, occur frequently over the course of PD. The differences observed in the placebo-controlled period of maintenance treatment are noted.

Table 56 Study 300 Falls and injuries in the maintenance phase (source: datasets)

Study 300 Maintenance Period	*APL-130277 (N = 54)*			*PLACEBO (N = 55)*		
PT	*Events*	*Number of subjects*	*Proportion (%)*	*Events*	*Number of subjects*	*Proportion (%)*
PT Fall	3	3	5.56	1	1	1.82
HLGT Bone and joint injuries	1	1	1.85	3	2	3.64
HLGT Injuries NEC	10	5	9.26	4	3	5.45

However, over the course of chronic use, the percentage of patients with AEs related to falls and injury increase. The standardized MedDRA query for *Accidents and Injuries* focuses on personal injury and accidents but excludes risk factors (e.g.: dizziness, somnolence, and self or iatrogenic injury). It also excludes events with multiple possible etiologies (e.g. hemorrhage, hematoma).

Using MAED, a narrow SMQ analysis was performed on both the MP population and the safety population. In the MP population, the number of patients fulfilling search criteria were equivalent (5/54 active and 4/55 placebo).

When the SMQ was performed in the safety population, this increased considerably with 67 of 392 patients (17%) fulfilling search criteria. The following table elaborates on the most common events occurring in this population.

Table 57 Studies 300 and 301 Falls and injuries in the safety population (source: datasets)

Study 300 + 301 APL-130277 Safety Population (N = 392)			
Level / Term	*Events*	*Number of subjects*	*Proportion (%)*
PT			
Fall	30	26	6.63
HLGT			
Bone and joint injuries	18	15	3.83
Injuries NEC	86	60	15.31
HLGT Bone and Joint includes:			
Bone and joint injuries NEC	3	3	0.77
Limb fractures and dislocations	12	10	2.55
Skull fractures, facial bone fractures and dislocations	1	1	0.26
HLGT Injuries NEC includes:			
Non-site specific injuries NEC	38	30	7.65
Contusion	11	10	2.55
Laceration	6	6	1.53

Because it would seem logical that the susceptibility to orthostasis might predispose to falls, the analysis was performed to see where these two phenomena might intersect in the chronically treated safety population. However, the majority experienced either one event or the other; only 5 patients reported (or had observed) both hypotension and falls as AEs. The sponsor reports that falls were more common in patients who had orthostatic hypotension in their medical history at study entry.

Reviewer's comment: It is difficult to know whether there is a general relationship of increased falls and injury to APL-130277 treatment versus the underlying moderately advanced PD in patients with consequential "off" periods. There is insufficient information available to link the time and date of falls to time and date of dosing with APL-130277.

8.5.7. Hallucinations, Psychotic-Like Behavior, Impulse Control Disorder and Suicidality

A variety of AEs relating to behavior were reported in the MP of Study 300 but held no distinguishing pattern regarding treatment:

Table 58 Study 300 Behavioral AEs in the maintenance phase (source: datasets)

Study 300 Maintenance Period	*APL-130277 (N = 54)*			*PLACEBO (N = 55)*		
PT	*Events*	*Number of subjects*	*Proportion (%)*	*Events*	*Number of subjects*	*Proportion (%)*
Abnormal dreams	0	0	0	1	1	1.82
Confusional state	0	0	0	1	1	1.82
Delusion	1	1	1.85	0	0	0
Disorientation	1	1	1.85	0	0	0
Disturbance in attention	0	0	0	1	1	1.82
Encephalopathy	0	0	0	1	1	1.82
Memory impairment	1	1	1.85	0	0	0
Obsessive-compulsive disorder	1	1	1.85	0	0	0

In the safety population, a variety of behavioral AEs were reported, none of which were unusual for the advanced PD population, nor did they occur very often. These PTs are distilled into individual PD patients captured by the narrow SMQs reported in the table below. Of the reported suicidality, there was only one instance of actual suicide attempt reported in the safety population while participating in the study.

It should be noted that depression is a prominent non-motor symptom of the PD. Screening for suicidality at baseline in the Study 300 + 301 population emphasizes this. There were 24 patients (6.1%) in this pool with a positive baseline C-SSRS response (assessing any lifetime history) for suicidal ideation of “wish to be dead”, and 13 patients (3.4%) with a positive baseline C-SSRS response for suicidal ideation of nonspecific active suicidal thoughts. Positive baseline C-SSRS responses for suicidal behavior were reported by 3 patients (0.8%) with an actual attempt, 1 patient (0.3%) with an interrupted attempt, and 1 patient (0.3%) with an aborted attempt.

Table 59 Studies 300 and 301 Behavioral AEs in the safety population (source: datasets)

Study 300 + 301 APL-130277 Safety Population (N = 392)			
PT	*Events*	*Number of subjects*	*Proportion (%)*
Abnormal dreams	2	2	0.51
Depressed mood	1	1	0.26
Depression	3	3	0.77
Disorientation	3	2	0.51
Disturbance in attention	3	3	0.77
Hallucination	3	2	0.51
Hallucination, visual	3	3	0.77
Hypersexuality	1	1	0.26
Impulse-control disorder	1	1	0.26
Obsessive-compulsive disorder	1	1	0.26
Panic attack	1	1	0.26
Paranoia	1	1	0.26
Psychomotor hyperactivity	3	3	0.77
SMQ			
Psychosis and psychotic disorders	9	7	1.79
Depression and suicide/self-injury	6	6	1.53

8.5.8. Dyskinesia

As expected for an episodically-used drug with a short half-life, no notable effect was found on the study population. In the open label study representing most of the safety population, PD drug treatment regimens were not fixed. SMQs representing a wider array of PTs related to extrapyramidal syndromes were not additionally revealing.

Table 60 Study 300 Dyskinesia reported as an AE in the maintenance phase (source: datasets)

Study 300 Maintenance Period	*APL-130277 (N = 54)*			*PLACEBO (N = 55)*		
PT	*Events*	*Number of subjects*	*Proportion (%)*	*Events*	*Number of subjects*	*Proportion (%)*
Dyskinesia	0	0	0	1	1	1.82
Dystonia	0	0	0	1	1	1.82

Table 61 Studies 300 and 301 Dyskinesia reported as an AE in the safety population (source: datasets)

Study 300 + 301 APL-130277 Safety Population (N = 392)			
PT	*Events*	*Number of subjects*	*Proportion (%)*
Dyskinesia	24	19	4.85
Dystonia	1	1	0.26

Reviewer's comment: Most PD patients with consequential off periods also have some dyskinesia during "on" periods.

8.5.9. Coronary Events, QTc Prolongation, and Potential for Proarrhythmic Effects

The reader is also directed to the section of this review discussing the Thorough QT Study 201.

The tables below are summaries of all PTs related to notable alterations in an ECG taken at patient visits. In the maintenance period of Study 300, the PTs in the active arm relate to two patients, compared to one patient in the placebo arm.

Using the MH dataset in the ISS and the 120-day safety update, it was determined that 81 patients in the Study 300 + 301 safety population had preexisting cardiac disorders. Of these 81, 48 had preexisting history of cardiac arrhythmias and 32 had preexisting coronary artery disease. Tabulating MHHLT and MHLLT MedDRA term levels, ventricular arrhythmias had occurred previously in 3 patients, supraventricular arrhythmias in 20 patients and atrial arrhythmias in 29.

Cardiac events did occur at a level that would be expected in this population. As tabulated below, one patient each on active treatment had an event related to cardiac conduction and ischemic heart disease, respectively, in the MP of Study 300 and in 11 patients in the entire safety population.

QTc abnormalities were reported as AESI if post dose they were greater than 450 msec uncorrected. The changes corrected for QTcF never exceeded 60 msec and most were less than 30 msec. Comparing the AE datasets to the ISS and 120-day safety update written reports indicates these events were accurately reported.

Table 62 Study 300 Cardiac events reported as AEs in two patients in the maintenance phase (source: datasets)

Study 300 Maintenance Period	*APL-130277 (N = 54)*			*PLACEBO (N = 55)*		
Level	*Events*	*Number of subjects*	*Proportion (%)*	*Events*	*Number of subjects*	*Proportion (%)*
PT						
Electrocardiogram QT prolonged	1	1	1.85	0	0	0
Bundle branch block right	1	1	1.85	0	0	0
Cardiac arrest	1	1	1.85	0	0	0
Cardiac failure congestive	1	1	1.85	0	0	0
HLT						
Cardiac conduction disorders	1	1	1.85	0	0	0
SMQ						
QT Prolongation	1	1	1.85	0	0	0
Cardiac arrythmias	2	1	1.85	1	1	1.82

Table 63 Studies 300 and 301 Cardiac events reported as AEs in 11 patients in the safety population (source: datasets)

Study 300 + 301 APL-130277 Safety Population (N = 392)			
Level	*Events*	*Number of subjects*	*Proportion (%)*
HLGT			
Cardiac arrhythmias	12	11	2.81
HLT			
Cardiac conduction disorders	5	5	1.28
ECG investigations	8	6	1.53
Heart rate and pulse investigations	3	3	0.77
PT			
Atrioventricular block first degree	1	1	0.26
Bundle branch block right	2	2	0.51
Defect conduction intraventricular	2	2	0.51
Electrocardiogram QT prolonged	5	4	1.02
Electrocardiogram T wave abnormal	2	2	0.51
QRS axis abnormal	1	1	0.26
SMQ			
QT prolongation	5	4	1.02
Cardiac arrythmias	15	11	2.81
Cardiac arrythmias - Conduction defects	10	8	2.04
Ischemic Heart Disease (broad SMQ)	4	4	1.02

The single episode of QT prolongation in Study 300 occurred in patient CTH-300-1029-006 (M/75) during a titration phase visit at the 20-mg dose. His QTc measurement (pre-dose 459 to 466 msec by Fredericia correction) varied throughout the study by a few msec. He had a previous medical history of coronary artery stenting, left ventricular hypertrophy, and premature atrial contractions. He was later randomized to placebo. He is also one of the 4 patients counted by SMQ in the safety population.

In Study 301, three patients had reported QT prolongation. (Two had also participated in Study 300.)

Table 64 Study 301 QT prolongation (source: datasets)

USUBJID	Sex	Age	Phase	Dose	Previous Medical History
(b) (6)	M	66	Maintenance	35 mg	Long QT, RBBB, Unstable Angina
	M	69	Titration	10 mg	1st degree AV block, PACs
	M	46	Maintenance	35 mg	No cardiac history

(b) (6) had a modest increase in QTcF to 469 msec at the same visit where a right bundle branch block was first noted on his ECG. He was continued his dose and his QTcF remained around 457 msec.

(b) (6) experienced a post dose increase in QTc during titration. No narrative was provided but a summary of electronic case report forms is reviewed. A modest increase in QTc was felt to be related to drug but the patient continued to be titrated and remained on 15 mg dose for 165 days without further abnormal QTc measurement.

(b) (6) has a QTc increase post dose of 20 msec but with Fredericia correction this decreased by 3 msec post dose (397 msec).

8.6. Safety Analyses by Demographic Subgroups

The demographics of the safety population for Study 300 + 301 (n=292) indicate that it was a homogeneous population that varied mostly with regards to sex and age. Race and ethnicity were not represented in numbers sufficient to make a cogent analysis of differential risk to adverse events and disease related features are evenly distributed across the groups and subgroups of interest and do not contribute to our understanding of the safety of APL-130277.

The occurrence of TEAEs were similar in both male and female patients in the Study 300+301 safety population. Remarkably enough advanced age did not more commonly lead to dropping out in the titration periods and, in general, age was not a determinant of the frequency or type of adverse events. The one notable exception was that advancing age appeared to be associated with a lesser occurrence of nausea and vomiting as an AE.

8.7. Specific Safety Studies/Clinical Trials

Additional clinical studies were performed to investigate QT prolongation (Thorough QT Study 201, discussed above) and evaluating the packaging of the apomorphine thin film for sublingual use.

This latter study of human factors validation was performed by the sponsor after protocol review by OSE Division of Medication Error Prevention and Analysis (DMEPA) to address areas of vulnerability that may lead to medication errors. This is especially important given fundamentally difficult-to-open packaging of a relatively fragile medication for patients with a moderately advanced illness affecting their motor function.

The sponsor proposes the product be supplied in 30-count cartons and as a titration kit for patient and caregiver use which will contain a total of (b) (4) individually packaged films of: (b) (4) 10 mg films, (b) (4) 15 mg films, (b) (4) 20 mg films, (b) (4) 25 mg films, and (b) (4) 30 mg films. Both packaging configurations will include child-resistant cartons.

Despite performance of the study, a major deficiency in understanding risk related to use persists in that the sponsor's use related risk analysis did not evaluate the final packaging intended for market, the titration kit, or the child resistant packaging.

The interested reader is referred to the full DMEPA review of the sponsor's submission, but in summary they conclude that the human factors validation study is inadequate:

> *"The results of the HF validation study did not demonstrate that the user interface is safe and effective for use, and the sponsor implemented revisions to the user interface without providing additional validation data to demonstrate effectiveness of revisions.*
>
> *Additionally, we identified a deficiency that the sponsor failed to include the intend-to-market packaging* (b) (4) *as part of the HF validation study. Given the intended user populations and the clinical manifestation of their disease state, we have insufficient data to demonstrate that intended users can use the proposed product packaging and product interface safely and effectively…*
>
> *…We recommend that the Sponsor consider additional user interface design modifications and implement our recommendations prior to validating these revisions in another HF validation study to demonstrate that the product can be used by the intended users safely and effectively."*

*Reviewer's comment: In response to a Discipline Review letter issued November 21, 2018, t*he *sponsor states (December 7, 2018, page 9):*

> "APL-130277 has been shown in several clinical studies to be safely and effectively self-administered by hundreds of subjects with PD and OFF episodes, including the Phase 3 acute efficacy and long-term safety studies (Studies CTH-300 and CTH-301, respectively)."

In my opinion, the sponsor's position is not supported by observation and data. In any case, that conclusion cannot be applied to the intend to market packaging which will be more complex than that used in the studies.

In both Study 300 and 301, at clinic visits in the titration and maintenance phase when dosing the patient, it was the clinical trial personnel who administered the medication. By protocol, patients were expressly prohibited from self-administration at visits (Study 300 protocol section 15.2 and Study 301 protocol section 14.2). In the maintenance phase, patients were instructed how to use the packet and handle the films and not released till clinic personnel "were satisfied" with the performance but there was no evaluation or recording of the success of the training or the ability to self-administer.

To infer that patients could correctly use the medication, one must then rely on the patients self-report diaries for two day before each maintenance phase clinic visit and the accounting of dispensed and returned medication by study personnel. It is relevant to again point out the missing and discrepant information regarding self-administered use of APL-130-277 in the out-patient period and returned medication counts at each outpatient visit as discussed previously. Even though the packaging used in the study was different than the intend to market package, they have some design elements is common. One can speculate (though it cannot be quantified) if difficulty in successfully opening the package or other wastage was in part related to the high rate of non-return of unused dispensed medication in the safety population. In the titration visits and clinic visits during maintenance treatment, thin films were opened and placed in the patient's mouth by the study staff. The patient was not observed as to their own ability to use the supplied pouches. Thus, I think the conclusions of the DMEPA review are quite valid. The uncertainty regarding ability to manipulate the packaging potentially increases the risk, for example, of the patient not being able to be dosed, or the patients/caregiver attempting solutions that may undermine the integrity of the thin film drug product.

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

This section is not applicable to this submission.

8.8.2. Human Reproduction and Pregnancy

This section is not applicable to this submission. There were no reproductive or developmental studies conducted in support of the clinical development of APL-130277. In clinical studies of APL-130277, pregnant and/or breastfeeding women were excluded, and no pregnancies were reported during or after treatment with APL-130277.

8.8.3. Pediatrics and Assessment of Effects on Growth

This section is not applicable to this submission. The RLD label indicates that adverse developmental effects in rats (increased neonatal deaths) and rabbits (increased incidence of malformation) occur when administered during pregnancy at clinically relevant doses.

8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

There were no reports of overdose with APL-130277 in the development program.
No studies evaluating drug abuse or withdrawal effects have been performed. The clinical studies in the submission give no indication of habituation, increasing use, or side effects indicative of withdrawal.

The SMQ for Drug Abuse and Dependence, and Drug Withdrawal in the safety population revealed that the most commonly reported events that met the criteria for drug abuse and dependence were somnolence and dizziness. These however are characteristic TEAEs related to APL-130277 use and there are no other associated TEAEs that would suggest that these are due to abuse potential.

8.9. Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through Postmarket Experience

This product is not currently commercially available.

8.9.2. Expectations on Safety in the Postmarket Setting

Beyond those discussed above, no additional safety concerns warrant consideration at this time.

8.9.3. Additional Safety Issues From Other Disciplines

The important contributions of DMEPA, OSE DPV, and the QT-IRT have been discussed above.

8.10. Integrated Assessment of Safety

Apomorphine hydrochloride delivered as a sublingual thin film has a side effect profile qualitatively like the reference listed drug delivered by subcutaneous injection.

The exception to this are hypersensitivity related events which appear to occur to a much greater extent than with APOKYN®. While the events attributed to hypersensitivity were generally mild and resolved quickly on drug cessation, there were several instances of a more severe reaction requiring a more targeted medical intervention.

The reviewer's understanding of this tendency to develop hypersensitivity to APL-130277 was hampered by the sponsor's poor recognition and reporting of such events during the progress of the studies. While it appears that longer duration of exposure is related to hypersensitivity, it is difficult to know whether it is also related to the total daily dose of APL-130277 because of the poor method employed in Studies 300 and 301 to record how many doses per day patients were taking during maintenance treatment.

The ability of the patient to effectively open the drug packaging intended for market and to successfully self-administer APL-130277 also remains in question.

The injectable form of apomorphine is available to PD patients (b) (4) but it is a clearly less convenient dosage form. The sublingual route is advantageous but comes at the cost of drug hypersensitivity, the extent and severity of which has not been fully defined. It makes sense to this reviewer that the occurrence of hypersensitivity for APL-130277 is the greatest differentiating factor for this drug when compared to the RLD and, should this agent become approvable, it should be so labeled.

9. Advisory Committee Meeting and Other External Consultations

No external advisory opinion was sought in the evaluation of this 505 (B)(2) application.

10. Labeling Recommendations

10.1. Prescription Drug Labeling

The label for this product with it reliance on the label for the RLD, will substantially include the referenced sections as described in the sponsor's amended response to an information request (1.11.4 Response to IR, May 18, 2018). Sections in labeling specific to this product will include 2 Dosing and Administration, 6 Adverse Reactions, and 14 Clinical Studies using information as reviewed here. Because of the non-approvable nature of this application, final prescribing information has not been agreed upon with the sponsor.

10.2. Nonprescription Drug Labeling

This section does not apply.

11. Risk Evaluation and Mitigation Strategies (REMS)

No REMS are anticipated at this time.

12. Postmarketing Requirements and Commitments

No PMR or PMC are recommended at this time.

13. Appendices

13.1. Clinical Studies in APL-130277 Development Program (sponsor's tabular listing)

Study No.; Phase; Country	Objective(s) of Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Dosed Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status
Studies in Healthy Subjects							
CTH-101 Phase 1 Malaysia	Evaluate the PK, safety, and tolerability of a single 3-mg dose of APL in a crossover design	Pilot study; double-blind, placebo-controlled, randomized crossover	**Products:** APL (3 mg; prototype formulation) or placebo **Regimen:** Single dose. Part 1: subjects received 3 mg APL with drug layer facing down, (T-Down). Part 2: same subjects received 3 mg APL with drug layer facing up, (T-Up). **Route**: Sublingual	15 Completed (receiving APL [12] or matching placebo [3])	Healthy male subjects	Single dose, Part 1 and Part 2 separated by a 24-hour washout period	Completed and reported

Study No.; Phase; Country	Objective(s) of Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Dosed Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status
CTH-102 Phase 1 Malaysia	Evaluate the PK, safety, and tolerability of a single 8-mg dose and 12-mg dose of APL in a crossover design	Pilot study; double-blind, placebo-controlled, 2-dose, randomized crossover	**Products:** APL (8 or 12 mg; prototype formulation) or placebo **Regimen:** Single dose. Cohort 1 - Part 1: subjects receive 8 mg APL T-Down. Part 2: same subjects receive 8 mg APL T-Up. Study halted at conclusion of Cohort 1. **Route:** Sublingual	12 Completed Cohort 1 (receiving APL [10] or matching placebo [2]) Note: Cohort 2 was not completed	Healthy male subjects	Single dose, Part 1 and Part 2 separated by a 24-hour washout period	Completed and reported

Study No.; Phase; Country	Objective(s) of Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Dosed Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status
CTH-103 Phase 1 Malaysia	Evaluate the PK, safety, and tolerability of a single 10-mg, 15-mg, and 25-mg dose of APL as compared with a 2-mg, 3-mg, and 4-mg dose of subcutaneous apomorphine in a crossover design of 3 cohorts of 16 healthy volunteers.	Double-blind, 3-dose, active comparator, placebo-controlled, randomized	**Products:** APL (10, 15, or 25 mg; prototype formulation), subcutaneous apomorphine (2, 3, or 4 mg), or placebo **Regimen:** Single dose. **Route**: Sublingual or subcutaneous	32 Completed Cohort 1 (16) (receiving APL [13 or comparator] or matching placebo [2]) Cohort 2 (16) (receiving APL [14] or comparator or matching placebo [2]) Note: Study halted at the conclusion of Cohort 2.	Healthy male subjects	Up to 2 days of APL, 10 mg, 15 mg and 25 mg, subcutaneous apomorphine, or placebo, administered once daily.	Completed and reported
CTH-104 Phase 1 Malaysia	Evaluate the PK, safety, and tolerability of a single 25-mg dose of APL	Double-blind, single-dose, placebo-controlled, randomized	**Products:** APL (25 mg), or placebo **Regimen:** Single dose **Route**: Sublingual	13 Completed (receiving APL [11] or matching placebo [2])	Healthy male subjects	Single dose	Completed and reported

Study No.; Phase; Country	Objective(s) of Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Dosed Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status
CTH-106 Phase 1 Malaysia	Evaluate the safety, efficacy, and tolerability, of a single 15-mg dose of two formulations of APL in a 3-way crossover design. Evaluate the effects of film orientation on PK	Pilot study, randomized, 3-way crossover	**Products:** APL (15 mg; 2 different formulations) **Regimen:** Single dose; three-way crossover. Subject received APL (CTH-105 formulation [T-Up]), APL (scaled-up formulation[a] [T-Down]), and APL (scaled-up formulation[a] [T-Up]). **Route**: Sublingual	12 completed all phases of the 3-way crossover	Healthy male subjects	Up to 3 single doses over 3 days	Completed and reported

Study No.; Phase; Country	**Objective(s) of Study**	**Study Design and Type of Control**	**Test Product(s); Dosage Regimen; Route of Administration**	**Number of Dosed Subjects**	**Healthy Subjects or Diagnosis of Patients**	**Duration of Treatment**	**Study Status**
CTH-107 Phase 1 Malaysia	Evaluate the PK, safety, and tolerability of a single dose of Nunavut formulation of apomorphine compared with a 15-mg dose of APL in a crossover design	Pilot study, randomized, crossover	**Products:** APL (15 mg) or Nunavut[b] (4.5 mg or 9 mg) **Regimen:** Cohort 1: 10 subjects received either APL or Nunavut (4.5 mg) Cohort 2: 10 subjects received either APL or Nunavut (9 mg) **Route**: Sublingual	20 Completed (10 per cohort)	Healthy subjects	Each cohort dose on 2 separate study days, separated by a 24-hour washout period.	Completed and reported

CTH-200 Phase 1 Malaysia	Comparative bioavailability study to examine the single-dose PK properties of APL and subcutaneous apomorphine (APO-go®)	Single-dose, randomized, 2-way crossover	**Products:** APL (15 mg) or subcutaneous apomorphine (2 mg; APO-go) **Regimen:** Up to 2 single doses of study medication (APL and APO-go) over 2 separate treatment days **Route**: Sublingual or subcutaneous	19 Completed both phases of the 2-way crossover	Healthy subjects	Up to 2 single doses over 2 days	Completed and reported

Study No.; Phase; Country	Objective(s) of Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Dosed Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status
Studies in Subjects with PD							
CTH-105 Phase 2 US	Examine the safety, tolerability and efficacy of single treatments of APL in PD patients	Open-label	**Products:** APL (10 mg, 15 mg, 20 mg, 25 mg, and 30 mg) **Regimen:** starting dose of 10 mg and titrated upwards **Route**: Sublingual	19 completed (receiving APL 10 mg [3], 15 mg [4], 20 mg [2], 25 mg [5], 30 mg [5] up to a dose of APL needed to induce an "ON" response)	Subjects with PD and "OFF" episodes	From screening until Day 7 (study completion), the study took a maximum of 28 days. Dosing was completed within 7 days	Completed and reported
CTH-300 Phase 3 North America and Europe	Evaluate the efficacy and safety of APL versus placebo in PD patients over a 12-week period	Randomized, double-blind, placebo-controlled, parallel-group	**Products:** Titration with APL (10, 15, 20, 25, 30, and 35 mg, as tolerated) **Regimen:** 12-week maintenance phase, randomized to the effective dose of APL or matching placebo **Route**: Sublingual	141 enrolled / 109 randomized	Subjects with PD and "OFF" episodes	Approximately 135 days	Completed and reported

Study No.; Phase; Country	**Objective(s) of Study**	**Study Design and Type of Control**	**Test Product(s); Dosage Regimen; Route of Administration**	**Number of Dosed Subjects**	**Healthy Subjects or Diagnosis of Patients**	**Duration of Treatment**	**Study Status**
CTH-301 Phase 3 North America and Europe	Evaluate the long-term safety, tolerability, and efficacy of APL in PD patients	Open-label	**Products:** APL 10, 15, 20, 25, 30, and 35 mg **Regimen:** APL – starting dose of 10 mg and titrated upwards **Route**: Sublingual	As of the cutoff date (19 Jan 2018), 272 subjects have enrolled (57 rollover subjects and 215 *de novo* subjects) A total of 257 subjects have received at least 1 dose of APL (55 rollover subjects and 202 *de novo* subjects)	Subjects with PD and "OFF" episodes	Subjects may participate in the study until the Sponsor terminates the study, or until commercial availability of APL in the subject's country	Ongoing

Study No.; Phase; Country	Objective(s) of Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Dosed Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status
CTH-201 Phase 2 North America and Europe	Evaluate the effect of APL compared with placebo on QTc intervals in PD patients	Randomized, double-blind, placebo controlled, 3-period crossover, positive control, QT evaluation	**Products:** APL (10, 15, 20, 25, 30, 35, 40, 50, and 60 mg [starting dose of 10 mg and titrated upwards]); moxifloxacin (400 mg); placebo **Regimen:** Single doses; APL and placebo administered in a double-blind fashion and moxifloxacin administered open-label in a 3-way balanced crossover. **Route**: Sublingual (APL and placebo) or oral (moxifloxacin)	48 enrolled / 41 randomized to crossover assessment phase 40 subjects were dosed in the crossover assessment phase and completed the study	Subjects with PD	Maximum duration: 46 days (from Screening to End of Study visit)	Completed and reported

Study No.; Phase; Country	**Objective(s) of Study**	**Study Design and Type of Control**	**Test Product(s); Dosage Regimen; Route of Administration**	**Number of Dosed Subjects**	**Healthy Subjects or Diagnosis of Patients**	**Duration of Treatment**	**Study Status**
CTH-203 Phase 2 US	Comparative bioavailability study to examine the single-dose PK properties of APL with 2 different formulations of subcutaneous apomorphine (APO-go and APOKYN®)	Randomized, 3-period crossover	**Products:** APL (15 mg, 20 mg, 25 mg, or 30 mg) or subcutaneous apomorphine (APO-go [2 mg, 3 mg, 4 mg, or 5 mg] or APOKYN [2 mg, 3 mg, 4 mg, or 5 mg]) **Regimen:** Single dose. Randomized, 3-Period Crossover Design **Route**: Sublingual or subcutaneous	Approximately 12 planned	Subjects with PD	From screening until final study completion approximate duration 37 days	Ongoing

Study No.; Phase; Country	**Objective(s) of Study**	**Study Design and Type of Control**	**Test Product(s); Dosage Regimen; Route of Administration**	**Number of Dosed Subjects**	**Healthy Subjects or Diagnosis of Patients**	**Duration of Treatment**	**Study Status**
CTH-302 Phase 3 Europe	Demonstrate the preference of APL compared with subcutaneous apomorphine as a therapy for the acute and intermittent management of "OFF" episodes in subjects with PD in the titration period and in an open-label crossover period	Open-label randomized, crossover, and double-observer, single-blind, superiority	**Products:** APL: starting dose of 10 mg, with further titration at home up to 30 mg subcutaneous apomorphine: starting dose of 2 mg, with further titration in the clinic up to 6 mg **Regimen:** 4-week crossover maintenance phase **Route**: Sublingual or subcutaneous	Approximately 85 randomized planned	Subjects with PD and "OFF" episodes	Approximately 106 days	Ongoing

13.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): CTH-300 Efficacy Trial

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 33		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 1		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 1 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in S Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

KENNETH J BERGMANN
01/27/2019 04:36:47 PM

GERALD D PODSKALNY
01/28/2019 05:20:09 PM