CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210875Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Office of Clinical Pharmacology Review

NDA Number	210875
Link to EDR	\\cdsesub1\evsprod\nda210875\0044
Submission Date	11/21/2019
Submission Type	NDA resubmission
Proprietary Name	To be determined
Dosage Form and Strength	Sublingual (SL) film 10 mg, 15 mg, 20 mg, 25 mg, and 30 mg
Proposed Dose/Regimen	The proposed dose range for APL-130277 is 10 mg (b) (4) mg. Dose titration should be initiated with 10 mg dose when patients are in an "OFF" state. Continue dose titration until an effective and tolerable dose is achieved. Do not administer more than 5 doses per day.
Proposed Indication	For the acute, intermittent treatment of "OFF" episodes associated with Parkinson's disease (b) (4) (b) (4) (b) (4)
Applicant	Sunovion Pharmaceuticals, Inc.
OCP Division	Division of Neuropsychiatric Pharmacology
Associated IND	110955
OCP Review Team	Mariam Ahmed Ph.D., Sreedharan Sabarinath Ph.D. and Mehul Mehta, Ph.D.

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1. Executive Summary

This is a resubmission to address the deficiencies outlined in the complete response letter (CRL) to the original NDA 210875 (CRL dated 29 January 2019) for apomorphine sublingual (SL) film (APL-130277). The CRL identified three major sources of deficiencies: human factors, clinical pharmacology and biopharmaceutics, and safety.

To address the clinical pharmacology and biopharmaceutics deficiency identified in the CRL, the division requested the applicant (Sunovion Pharmaceuticals, Inc.) to complete and provide the final report of Study CTH-203 to support the scientific appropriateness of reliance on FDA's finding of nonclinical safety and applicable clinical pharmacology information for the listed drug, APOKYN® (apomorphine hydrochloride injection). In addition, the CRL included additional comments and recommendations which were not approvability issues. These included recommendations to conduct in vitro studies to evaluate the drug-drug interaction (DDI) potential of two major metabolites of apomorphine from the proposed SL product (APL-130277): apomorphine glucuronide and norapomorphine glucuronide.

In this resubmission, the applicant included the complete study report of the relative bioavailability study (CTH-203) and in vitro DDI studies for apomorphine glucuronide. Study CTH-203 was 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 in patients with Parkinson's Disease (PD).

The primary focus of this review is to assess the acceptability of the bridge between APL-130277 and the listed drug. Although the applicant initially proposed [redacted] (b) (4) for APL-130277, the clinical review team is recommending approval of doses [redacted] (b) (4) up to 30 mg [redacted] (b) (4). This review also evaluates the in vitro DDI results for apomorphine glucuronide.

1.1 Recommendation

The Office of Clinical Pharmacology (OCP) has reviewed the information submitted in the NDA and recommends approval.

The SL route has lower bioavailability for apomorphine compared to subcutaneous (S.C.) injection. The bioavailability for APL-130277 relative to APOKYN is about 17% for AUC_{inf} and 12% for C_{max}. The doses of APL-130277 were adjusted for the difference in bioavailability of apomorphine for the proposed SL route of administration. The recommended dose range of the proposed SL product APL-130277 is 10-30 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.

Therefore, it is acceptable for the applicant to rely on FDA's finding of non-clinical safety and clinical pharmacology for APOKYN. The clinical safety and efficacy data for APL-130277 is available from their own clinical development program.

1.2 Post-Marketing Requirements and Commitments

The applicant should 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 in DARRTS dated 12/29/2018.

2. Background and Regulatory History

The applicant submitted the original NDA application on 29 March 2018 for APL-130277 (Sequence 0001). On 29 January 2019 the agency issued a Complete Response Letter (CRL) in which three main deficiencies that prevented approval were identified. These deficiencies were:

- Human Factors (HF): The HF study submitted in the original application did not provide adequate data to demonstrate that the proposed mitigations are effective and do not introduce new use-related risks. Furthermore, the HF study did not evaluate the final intend-to-market user interface, specifically the proposed (b) (4) packaging.
- Clinical Pharmacology and Biopharmaceutics: In order to justify the relevance of comparative data with APL-130277 and APO-go® (apomorphine hydrochloride injection) to support the scientific appropriateness of reliance on FDA's finding of safety for APOKYN® (apomorphine hydrochloride injection) the Division requested that Sunovion complete and provide the final report for Study CTH-203.
- Safety: Division requested further characterization of oral adverse events (AEs) associated with APL-130277 which was to also include an evaluation of oral adverse events by an expert. The Division also requested that Sunovion provide a safety update in accordance with 21 CFR 314.50(d)(5)(vi)(b).

The CRL also included additional comments and recommendations which did not constitute approvability issues. The office of clinical pharmacology recommended conducting in vitro studies to evaluate the DDI potential of two major metabolites from APL-130277: apomorphine glucuronide and norapomorphine glucuronide. These metabolites exposures significantly increased due to the change of administration route from S.C. to SL.

3. Summary of Pivotal Relative Bioavailability Study: CTH-203

Title: A Comparative Bioavailability Study to Evaluate the Single Dose Pharmacokinetic Properties of APL-130277 with Two Different Formulations of Subcutaneous Apomorphine in a Randomized, 3-Period Crossover Design in Subjects with Parkinson's Disease Complicated by Motor Fluctuations ("OFF" Episodes)

Primary Objectives:

To evaluate the PK and comparative bioavailability of a single dose of APL-130277 SL film with S.C. APO-go and S.C. APOKYN in subjects with PD complicated by motor fluctuations (OFF Episodes).

Secondary Objectives: To evaluate the safety and tolerability of the study drugs.

Reviewer's comment:

Although the study had 3 treatment arms (APL-130277, APOKYN and APO-go), the focus of this review is on the relative bioavailability of APL-130277 SL film compared to the US listed drug, APOKYN.

Methodology:

- This was as an open-label, randomized, 3-way, 6-sequece crossover study. Subjects were to receive all 3 treatment arms (APL-130277 SL, S.C. APO-go and S.C. APOKYN) with a minimum 1-day wash-out between each visit (excluding the Screening Visit).
- The dose of APOKYN was based on the subject's prescribed dose at the time of screening.

PK Sampling:

Blood samples from each subject were drawn prior to drug administration (pre-dose) and 0.25, 0.5, 0.75, 1, 1.5, 3, and 6 hours after dosing in each study period.

Reviewer's Comment:

Given that the T_{max} for APOKYN occurs between 10 minutes and 1 hours, this sampling scheme may miss the true C_{max} for APOKYN. This is not considered a major issue as it in fact would result in an over estimation (i.e. conservative estimate) of the relative bioavailability for C_{max} with APL-130277.

Number of Subjects (Planned and Analyzed):

Planned: 12; Screened: 8; Enrolled: 8; Completed: 7.

All 8 enrolled subjects were included in the Safety and PK Populations. There were data from 8 subjects included in the PK analysis for APL-130277 and APO-go and data from 7 subjects in the analysis for APOKYN. Subject (b) (6) was excluded from the summary statistics for all analytes in Period 1 (APOKYN) because all plasma concentrations for this subject were below the limit of quantification (BLQ). This was likely due to a malfunction of the APOKYN delivery system (either due to user error or malfunctioning device). Therefore, quantifiable PK data is only available from 6 subjects who received both APL-130277 and APOKYN in both periods.

Reviewer's Comment:

The study design, treatment assignment, washout period (1 day, given that apomorphine half-life is ~2 hours), sample size and PK sampling scheme are acceptable (see previous comment regarding the PK sampling scheme).

Test Products and Dose:

APL-130277 dosing was based on the subject's current prescribed dose of APOKYN, as shown in Table 1.

Table 1: Doses of APOKYN® and Corresponding Dose of APL-130277 and Number of Subjects at each Dose Level.

APOKYN Current Dose	APL-130277 Dose
2 (N=0)	15 (N=0)
3 (N=3)[a]	20 (N=3)
4 (N=2)	25 (N=2)
5 (N=2)[b]	30 (N=3)

[a] Although 3 subjects in the 3 mg dose levels received APOKYN dose, subject (b) (6) was excluded from the summary statistics for all analytes in Period 1 (APOKYN) because all plasma concentrations for this subject were below the limit of quantification (BLQ). This was likely due to a malfunction of the APOKYN delivery system (either due to user error or malfunctioning device). Therefore, data from 2 subjects are available for this dose level for APOKYN. [b] Subject (b) (6) terminated early and did not receive 5 mg APOKYN.
Source: CTH-203 study report, Table 10, Page 42.

Main Criteria for Inclusion and Exclusion:

The key inclusion criteria were male or female ≥ 18 years of age with clinical diagnosis of idiopathic PD, consistent with United Kingdom Brain Bank Criteria (excluding the "more than 1 affected relative" criterion). The subjects were required to have clinically meaningful response to levodopa with well-defined OFF episodes, as determined by the Investigator and be receiving APOKYN of ≤ 5 mg per dose for at least 4 weeks before the Screening Visit. The subjects were to be receiving stable doses of levodopa/carbidopa (immediate or sustained release) administered at least 4 times per day or RYTARY™ administered 3 times per day, for at least 4 weeks before the Screening Visit. Adjunctive PD medication regimens must have been maintained at a stable dose for at least 4 weeks prior to the Screening Visit with the exception that MAO-B inhibitors must have been maintained at a stable level for at least 8 weeks prior to the Screening Visit. Subjects were to have Stage III or less on the modified Hoehn and Yahr scale in the ON state and a Mini-Mental State Examination score > 23. There were to be no planned medication change(s) or surgical intervention anticipated during the study and the subjects must have experienced a well-defined OFF episode in the morning if they did not take their morning PD medications on schedule and must have been willing to delay morning doses on the 3 study dosing days.

Subjects were excluded from participation in the study if they had atypical or secondary parkinsonism; previous treatment with continuous S.C. apomorphine infusion, or

DUODOPA/DUOPA; or had contraindications to APO-go or APOKYN or hypersensitivity to apomorphine hydrochloride or any macrolide antibiotic or any of the ingredients of APO-go or APOKYN (notably sodium metabisulfite).

Criteria for Evaluation:

Main Criteria for Relative Bioavailability Assessment:

The PK parameters calculated were: maximum observed plasma concentration (C_{max}); observed time of the maximum concentration (T_{max}); terminal-phase half-life (t½); area under the concentration-time curve from time zero to the last measurable plasma concentration-time curve (AUC_{last}); area under the concentration-time curve from time zero extrapolated to infinity (AUC_{inf}). Relative bioavailability between the test and reference products was also evaluated.

Reviewer's Comment:

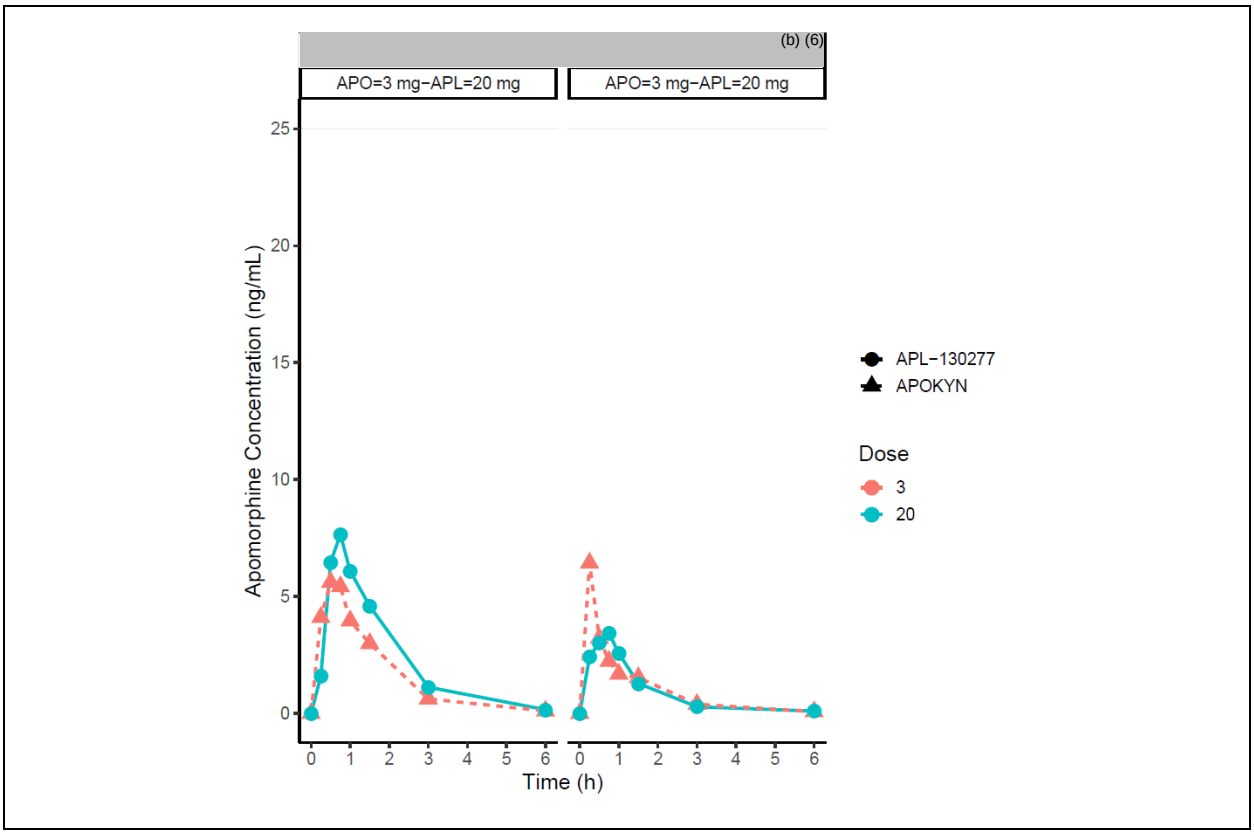
While the approved dose range for APOKYN is 2 to 6 mg, the applicant limited the inclusion criteria to subjects receiving doses between 2-5 mg and limited the dosing of APL-130277 to 30 mg. This could be due to the difficulty in recruiting subjects stabilized on the highest dose of APOKYN 6 mg. Although the applicant (b) (4) *APL-130277, the clinical review team is recommending approval of doses* (b) (4) *up to 30 mg* (b) (4) *.* ***Therefore, this review will focus on the acceptability of the PK bridge between the highest recommended dose of APL-130277 (30 mg) and the highest approved dose of APOKYN (6 mg).*** *The PK bridging between APL-130277 and the listed drug will be considered acceptable if apomorphine exposure from the 30 mg dose of APL-130277 is less than or equal to that from the maximum approved dose of APOKYN.*

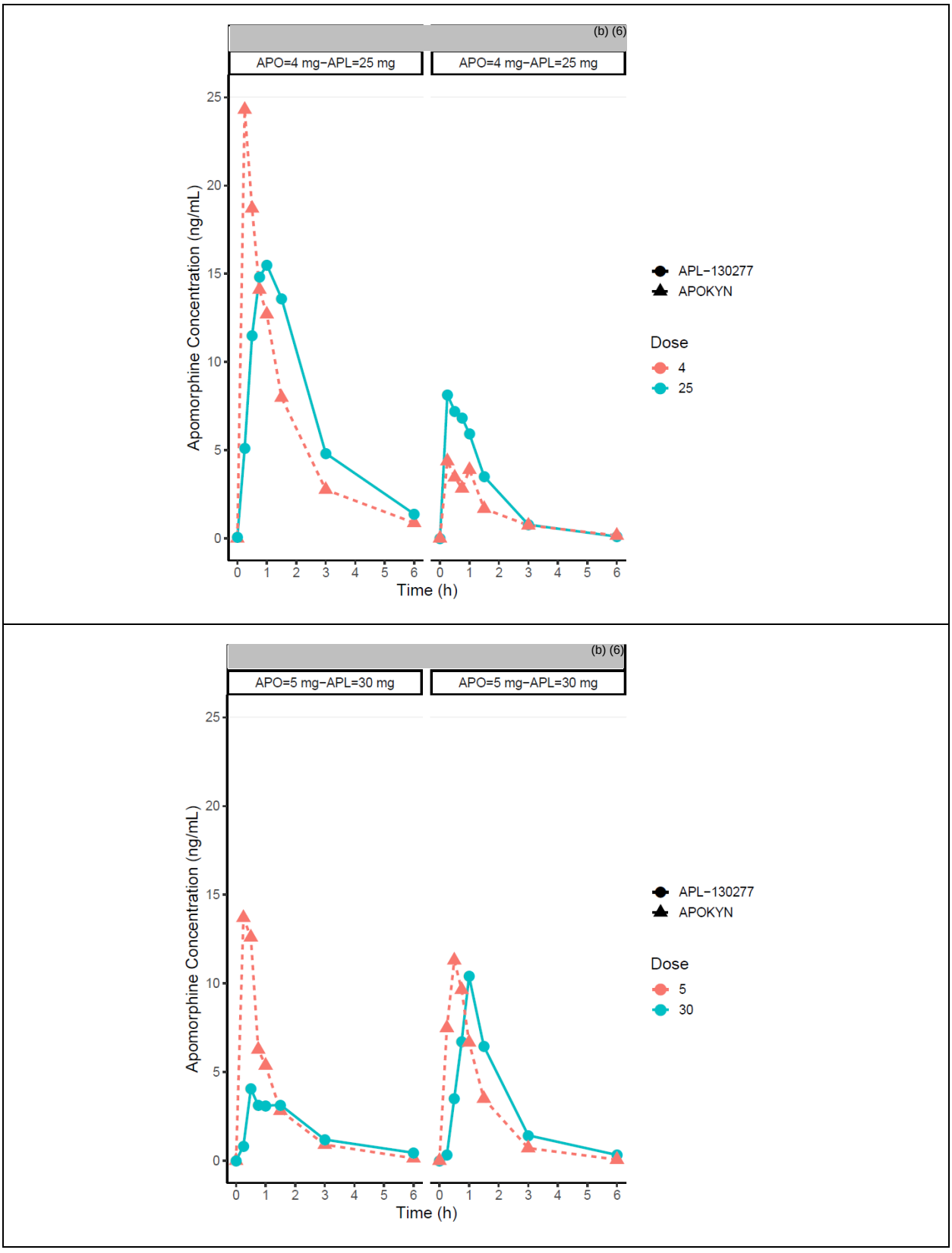
Results:

Relative Bioavailability Assessment:

Table 1 shows the number of dose groups/levels studied and the number of subjects at each dose level per treatment group. The applicant reported the individual subject plasma apomorphine concentration-time data. The plot for the apomorphine plasma concentrations over the sampling period are presented in Figure 1 below for each individual (N=6) who received both APL-130277 and APOKYN®. The descriptive statistics for the dose normalized PK parameters of APL-130277 (N=8) and APOKYN (N=6) as well as the least square mean ratios (i.e. relative bioavailability) of APL-130277 to APOKYN® are shown in Table 2 below.

Figure 1: Plasma Concentration Time Profile for Apomorphine for Each Subject who Received Both APL-130277 and APOKYN® (N=6, plasma profiles for each subject by treatment).





Source: Reviewer's analysis

Reviewer's Comment:

Note that the first scheduled PK sampling is at 15 minutes post dose in this study. The first point of the plasma concentration time curve is the highest concentration for APOKYN in 4 patients, suggesting that true C_{max} may have been missed because of insufficient early sampling times in those subjects. This happened for APL-130277 in only one subject (Subject ID: (b) (6)). Thus, there may be some under estimation of C_{max} for APOKYN and the relative bioavailability estimation for the C_{max} of APL-130227 relative to APOKYN would be considered conservative.

Table 2: Summary of Dose Normalized Pharmacokinetic Parameters for Apomorphine Following APL-130277™ and APOKYN® Treatment - PK Population

PK Parameter	APL-130277 (N=8) LSM (90% CI)	APOKYN (N=6) LSM (90% CI)	LSM Ratio (APL-130277 vs APOKYN (90% CI)
C_{max}/Dose (ng/mL)/(mg)	0.28 (0.191, 0.413)	2.29 (1.46, 3.59)	12.3 (7.5, 20.3)
AUC_{last} /Dose (h*ng/mL)/(mg)	0.50 (0.34, 0.73)	2.91 (1.97, 4.30)	17.2 (13.1, 22.5)
AUC_{inf} /Dose (h*ng/mL)/(mg)	0.52 (0.36, 0.76)	2.97 (2.02, 4.39)	17.6 (13.7, 22.5)

AUC: area under concentration-time curve; C_{max}: maximum concentration; CI: confidence interval; LSM: least square means.

Source: CTH-203 Clinical Study Report, Table 12 and 14, Page 51 and 60

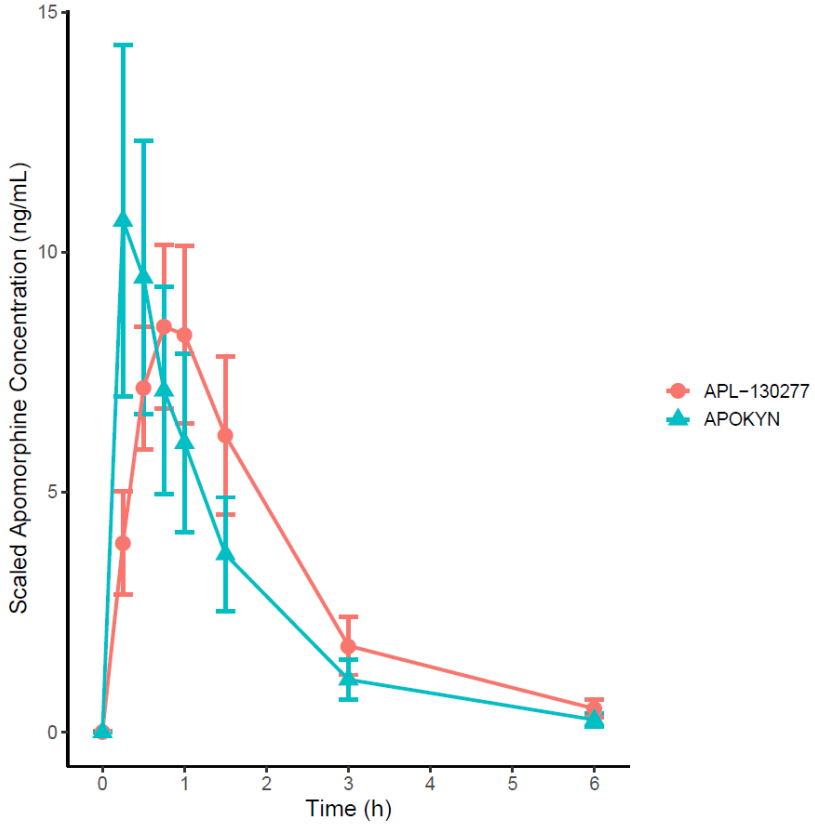
Reviewer's Comments and Additional Analyses:

- *Given that the study was conducted in PD patients who were already stabilized on APOKYN®, these patients were on different dose levels. The patients were then randomized to a dose of APL-130277 that would provide comparable exposure for apomorphine following APOKYN® dosing. Given the limited number of subjects in each dose level, it was not possible to naively pool the data from all individuals and assess the central tendency (i.e. geometric mean) and variability (i.e. 90% confidence interval) of aporphine exposures following APL-130277 and APOKYN® administration. Therefore, the sponsor chose to calculate the dose normalized ratios for C_{max} and AUC assuming dose proportionality for APL-130277 and APOKYN®. According to this assumption, the relative*

bioavailability of the proposed SL formulation was approximately 17% (AUC) and 12% (C_{max}) compared to APOKYN®. While APOKYN® has linear PK over the approved dose range of 2-6 mg (Ref. APOKYN USPI), APL-130277 has less than dose proportional PK over the range of 10-35 mg (Study CTH-201, please refer to the original clinical pharmacology review). Therefore, the relative bioavailability estimate reported here may be an over estimation and may be considered as a conservative estimate.

- *The review team aimed to understand if the exposure from the highest recommended dose of APL-130227 (30 mg) is covered by the exposure from APOKYN® highest approved dose (6 mg). Since there is limited number of subjects at this dose level (N=2 subjects administered both SL and S.C. products), the review team used superposition rule to predict apomorphine exposure following the highest recommended dose administration for the APL-130277 and the highest approved dose for the APOKYN® for all patients administered both SL and S.C. products in this study (N=6). This assumes linear/proportional PK for APL-130277. Figure 2 presents the mean (±SE) apomorphine plasma concentrations over the sampling period for the highest studied dose for both products in Study CTH-203.*
- *The least square mean for apomorphine exposure following the highest recommended dose for APL-130277 (30 mg) and APOKYN (6 mg) using the superposition rule is presented in Table 3. The recommended highest dose of APL-130277 (30 mg) has ~40 and 10% lower C_{max} and AUC_{inf} respectively as compared to the highest approved dose of APOKYN® (6 mg).*

Figure 2: Mean (±SE) Apomorphine Dose Normalized Plasma Concentration for Subjects Received Both APL-130277 (Normalized to 30 mg) and APOKYN® (Normalized to 5 mg) predicted using superposition principle, assuming linear/proportional PK for both products(N=6).



Source: Reviewer's analysis.

Table 3: Summary of Predicted Exposures for APL-130277 and APOKYN highest Recommended Dose for Subjects Treated with Both Products in Study CTH-203 (N=6).

PK Parameter	APL-130277 LSM (30 mg)	APOKYN LSM (6 mg)	LSM Ratio (APL-130277/APOKYN)
C_{max} (ng/mL)	8.76	14.05	0.6
AUC_{inf} (h*ng/mL)	16.04	18.21	0.9

AUC: area under concentration-time curve; C_{max}: maximum concentration; CI: confidence interval; LSM: least square means.

Source: Reviewer's analysis

Conclusion:

Study CTH-203 was 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 SL route has lower bioavailability for apomorphine compared to subcutaneous injection. The doses of APL-130277 were adjusted for the difference in bioavailability of apomorphine for the proposed SL route of administration; the dose range of the proposed SL product APL-130277 is 10-30 mg, while APOKYN's dose range is 2-6 mg. Based on Study CTH-203, the exposures of apomorphine from the highest dose of APL-130277 (30 mg) are approximately 40% and 10% lower C_{max} and AUC_{inf}, respectively, for APL-130277 compared to APOKYN. Therefore, it is acceptable for the applicant to rely on FDA's finding of non-clinical safety and applicable clinical pharmacology for APOKYN. The clinical safety and efficacy data for APL-130277 is from their own clinical development program.

4. Summary of Metabolite Exposures from Study CTH-203

The applicant measured apomorphine sulfate and norapomorphine in Study CTH-203 following both SL and S.C. route of administrations. Administration of APL-130277 led to increased exposure of apomorphine sulfate compared to administration of APOKYN. The geometric mean C_{max} and AUC_{last} values were roughly 3-fold higher after APL-130277 compared to APOKYN. On the other hand, norapomorphine was not detectable in any subject following the administration of both SL and S.C. products.

Reviewer's Comments:

The observations for these two metabolites from Study CTH-203 are in agreement with previous studies that were reviewed in the original submission. Please refer to the original OCP review in DARRTS dated 12/29/2018 for details.

5. Bioanalytical Method Validation

Plasma concentrations of apomorphine and two of its metabolites (norapomorphine and apomorphine sulfate) were determined utilizing a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) method with a linearity range of 0.02 to 20 ng/mL for apomorphine; 10 to 1000 ng/mL for apomorphine-sulfate; and 0.50 to 20 for norapomorphine (Method Validation Report APL-MV-03). This method was reviewed previously was found to be acceptable.

Additionally, in this resubmission, the applicant submitted detailed plasma apomorphine, norapomorphine and apomorphine sulfate concentration results and assay performance (see Report APL-SA-203). In this analytical report a total of 183 human plasma samples from 8 completed patients have been analyzed for apomorphine, norapomorphine and apomorphine-sulfate concentrations using the validated LC-MS/MS method. Incurred sample reanalysis (ISR)

reproducibility was performed for 46 samples for all three analytes. The ISR met the acceptance criteria with overall acceptance of (b) (4)% for apomorphine ISR samples that had the repeat and original results within 20% of each other. All sample analyses were completed within the established frozen sample storage stability period of 517 days at ≤-60°C (APL-MV-03-Addendeum-2).

6. Summary of OSIS inspection for Study CTH-203

The Office of Clinical Pharmacology consulted the Office of Study Integrity and Surveillance (OSIS) to inspect the analytical and the clinical sites for Study CTH-203. The three clinical sites for this study were inspected, and the final inspection classification is No Action Indicated (NAI). For more information please refer to the review by Dr. Xingfang Li (available in DARRTS dated 03/20/2020).

OSIS concluded that no inspection is warranted for the analytical site as the same site was inspected recently under (b) (4) with an inspection classification of Voluntary Action Indicated (VAI) (b) (4) . However, OSIS stated that the observations did not impact the reliability of other studies conducted at the site and recommended that other studies conducted using similar methods of analysis (LC-MS/MS) be accepted for Agency review. For more information, please refer to the review by Dr. James J Lumalcuri (available in DARRTS dated 02/20/2020).

7. In Vitro Studies

Due to the change in the route of administrations, apomorphine SL administration results in 3 major inactive metabolites: apomorphine sulfate, apomorphine glucuronide and norapomorphine glucuronide (Study CTH-200). In the original submission, the applicant submitted the in vitro DDI potential for apomorphine sulfate. In this resubmission, the in vitro DDI studies for apomorphine glucuronide were included and are reviewed below. The applicant should also conduct in vitro DDI studies for norapomorphine glucuronide post-marketing.

Apomorphine glucuronide

The applicant evaluated the potential of apomorphine glucuronide to inhibit human cytochrome P450 (CYP) CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4/5 catalytic activity in pooled human liver microsomes over a concentrations range of 0.06 - 60 µM using human liver microsomes (HLM) (Document No. 277-512A). The maximum direct inhibition by apomorphine glucuronide was observed for CYP3A4 (20%). Therefore, the IC_{50} of apomorphine glucuronide associated with inhibition of major transporters is greater than 60 µM. Likewise, no significant time-dependent and co-factor-dependent loss of initial product formation was observed for any CYP enzyme indicating absence of any time-dependent inhibition.

The applicant studied the induction potential of apomorphine glucuronide with major CYP enzymes (Document No. 277-513A). Induction was measured by catalytic activity and mRNA expression assays selective for isoforms CYP1A2, CYP2B6, and CYP3A4 in cultured primary human hepatocytes from 3 separate donors at apomorphine glucuronide concentrations range of 0.06 - 60 µM. Apomorphine glucuronide caused no increases of CYP1A2, CYP2B6 and CYP3A4 mRNA or enzyme activity that were greater than 2.0-fold, and that were 20% or greater than the positive control response for all three lots of hepatocytes.

The applicant conducted a study to investigate the interaction of apomorphine glucuronide with human ABC (efflux) transporters: BCRP, BSEP, MDR1, MRP2, MRP3, MRP4, and human SLC (uptake) transporters: MATE1, MATE2-K, OATP1B1, OATP1B3, OAT1, OAT3, OCT1, OCT2 (Document No. 277-511A). According to this study, apomorphine glucuronide inhibited the BCRP and MRP3 mediated probe substrate accumulation at the applied concentrations with a maximum inhibition of 22% and 50% at 50 µM, respectively. Additionally, apomorphine glucuronide inhibited the MATE1-, OAT1- and OAT3-mediated probe substrate accumulation by 28%, 22% and 40% at 50 µM, respectively. Apomorphine glucuronide did not influence the BSEP, MDR1, MATE2-K, OATP1B1-, OATP1B3-, OCT1- and OCT2-mediated probe substrate accumulation at concentrations up to 50 µM.

Reviewer's Comments:

- *The mean C_{max} (total) of apomorphine glucuronide observed after a single sublingual dose of 35 mg is 182 ng/mL or 0.4 µM (N=5, Study CTH-301 reviewed in the original submission). Given the half-life is approximately 3 hours for this metabolite, the projected C_{max} of apomorphine glucuronide at steady state (assuming administration 5 times daily every 2 hours) is ~1 µM). Given that the IC_{50} was greater than the maximum concentration tested in vitro (i.e. >60 µM which is at least 60-fold higher than the maximum concentration following the maximum recommended dose), the potential for apomorphine glucuronide to interfere with the metabolism of concomitant medications by CYP inhibition or induction is considered low.*
- *Apomorphine glucuronide was not an in vitro inducer of CYP1A2, CYP2B6 and CYP3A4 mRNA or enzyme activity at the concentrations tested in human hepatocytes. Therefore, the potential for apomorphine glucuronide to affect the metabolism of concomitant medications by CYP induction is considered low.*
- *The DDI potential due to inhibition of major transporters is considered minimal.*

- *The applicant also studied the potential for apomorphine glucuronide as a substrate for major transporters. However, this is not considered relevant as the metabolite is pharmacologically inactive and of no toxicological concern.*

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Office of Clinical Pharmacology
Review Addendum

NDA Number	210875
Link to EDR	\\cdsesub1\evsprod\nda210875\0001
Submission Date	03/29/2018
Submission Type	505 (b)(2)
Brand Name	KYNMOBI™
Generic Name	Apomorphine hydrochloride sublingual film (APL-130277)
Dosage Form and Strengths	Sublingual Film 10 mg, 15 mg, 20 mg, 25 mg and 30 mg
Route of Administration	Sublingual
Proposed Indication	For the acute, intermittent treatment of "OFF" episodes associated with Parkinson's disease (b) (4)
Proposed Dose/Regimen	The dose range for KYNMOBI is 10 mg (b) (4). Dose titration should be initiated with 10 mg dose when patients are in an "OFF" state. Continue dose titration until an effective and tolerable dose is achieved. Do not administer more than 5 doses per day
Applicant	Sunovion Pharmaceuticals, Inc.
Associated IND	110955
OCP Review Team	Mariam Ahmed, PhD., Kevin Krudys, PhD., and Sreedharan Sabarinath, PhD.
OCP Final Signatory	Ramana Uppoor, PhD.

BACKGROUND

The purpose of this addendum is to update the previous OCP review (DARRTS dated 12/29/2018) based on the revised findings of Biopharmaceutics review team on the adequacy of the bridging between the proposed product and the listed drug, Apokyn (apomorphine subcutaneous injection) (Ref. OPQ review signed off in Panorama on 1/25/2019).

The applicant bridged the proposed drug product with a European drug product, Apo-go (apomorphine subcutaneous injection) using a relative bioavailability study (CTH-200). The US approved listed drug Apokyn and Apo-go were to be bridged based on "sameness" of the two

products. However, based on the recent Biopharmaceutics review, the provided composition and in vitro data are insufficient and in vivo PK data becomes relevant to verify the “sameness” between Apokyn and Apo-go.

There is an ongoing relative bioavailability study CTH-203 with Apokyn, Apo-go and the proposed drug product. The final report of this study is not available for review at this time.

RECOMMENDATION:

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.

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/s/

SREEDHARAN N SABARINATH
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RAMANA S UPPOOR
01/29/2019 12:49:09 PM

Office of Clinical Pharmacology Review

NDA Number	210875
Link to EDR	\\cdsesub1\evsprod\nda210875\0001
Submission Date	03/29/2018
Submission Type	505 (b)(2)
Brand Name	KYNMOBI™
Generic Name	Apomorphine hydrochloride sublingual film (APL-130277)
Dosage Form and Strengths	Sublingual Film 10 mg, 15 mg, 20 mg, 25 mg and 30 mg
Route of Administration	Sublingual
Proposed Indication	For the acute, intermittent treatment of "OFF" episodes associated with Parkinson's disease (b) (4)
Proposed Dose/Regimen	The dose range for KYNMOBI is 10 mg (b) (4) Dose titration should be initiated with 10 mg dose when patients are in an "OFF" state. Continue dose titration until an effective and tolerable dose is achieved. Do not administer more than 5 doses per day
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1. EXECUTIVE SUMMARY

The Applicant, Sunovion Pharmaceuticals Inc., submitted a New Drug Application (NDA) for APL-130277 (KYNMOBI™, apomorphine hydrochloride sublingual film) through the 505(b)(2) regulatory pathway. The proposed indication is treatment of acute, intermittent "OFF" episodes associated with Parkinson's disease (PD) (b) (4) KYNMOBI is intended to be used at proposed doses of 10, 15, 20, 25, 30 (b) (4) up to a maximum of 5 times per day. The available dosing strengths are 10, 15, 20, 25, and 30 mg sublingual films. (b) (4)

The applicant is relying on FDA's findings on safety of the approved prescription product APOKYN® (NDA 021264) subcutaneous (SC) injection as the reference listed drug (RLD) approved for the same indication. Apomorphine hydrochloride for SC injection is marketed as APOKYN® in the United States, APO-go® in most of Europe, and MOVAPO® in Canada and Australia.

The applicant conducted 13 clinical studies with KYNMOBI to support the new formulation and route of administration. These included seven Phase 1 studies in healthy volunteers (CTH-101-104, CTH-106-107, and CTH-200), three Phase 2 studies in PD patients (CTH-105, CTH-201, and an ongoing study: CTH-203), and three Phase 3 studies (pivotal efficacy study: CTH-300, an ongoing long-term safety study: CTH-301, and an ongoing Phase 3 study: CTH-302 to demonstrate the preference of KYNMOBI compared with subcutaneous apomorphine). All Phase 3 studies used the to-be-marketed product.

The pivotal Phase 3 study (CTH-300) was a 12-week, prospective, multicenter, randomized, double-blind, placebo-controlled study that evaluated the efficacy and safety of KYNMOBI over a dose range of 10-35 mg titrated based on efficacy and tolerability in levodopa (L-Dopa)-responsive subjects with PD complicated by motor fluctuations ("OFF" episodes). The study met its primary endpoint, which was the change from pre-dose on the Movement Disorder Society-Unified Parkinson's Disease Rating Scale Part III (MDS-UPDRS III) score at 30 minutes at Week 12 as compared to the placebo group.

In this application, the applicant is proposing to establish a pharmacokinetic (PK) bridge to the RLD (APOKYN®) by relying on Study CTH-200 in healthy subjects using Apo-go® SC injection, interim data from 5 patients with PD from the ongoing Study CTH-203, and the sameness of APOKYN® and APO-go® products. Study CTH-200 was a Phase 1, single dose relative bioavailability study that compared 15 mg KYNMOBI with 2 mg APO-go® SC injection. The ongoing Study CTH-203 is a 3-period crossover, comparative bioavailability study that evaluated

the single dose PK of KYNMOBI, APO-go®, and APOKYN® in PD patients. The Biopharmaceutics review team is evaluating the sameness of APOKYN® and APO-go® products.

The primary objectives of this review are:

- to evaluate the PK bridging of the proposed product to the RLD (APOKYN® SC injection) and,
- to assess the adequacy of the proposed dosing recommendations for general and special populations.

1.1 Recommendations

The Office of Clinical Pharmacology has reviewed this NDA and the application is acceptable from an OCP perspective.

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness:	Primary evidence of effectiveness was established in a pivotal Phase 3 efficacy study CTH-300, based on change in MDS-UPDRS III from pre-dose to 30 minutes post-dose at Week 12.
General dosing instructions:	The dose range for KYNMOBI is 10 mg (b) (4). The dose is titrated based on tolerability and efficacy. Dose titration should be initiated with 10 mg KYNMOBI sublingual film when patients are in an "OFF" state. If the patient tolerates the dose but does not respond adequately, the next dose strength can be increased at the next observed "OFF" period by 5 mg increments until an effective and tolerable dose is achieved. Doses should be separated by at least 2 hours and the maximum number of doses is 5 doses per day.
Dosing in patient subgroups (intrinsic and extrinsic factors):	The effects of renal and hepatic impairments were not studied with KYNMOBI™. Based on available information, the review team recommends no dosing adjustment for patients with mild/ moderate renal impairment and mild/moderate hepatic

	impairment. KYNMOBI is not recommended for patients with severe renal impairment or severe hepatic impairment. KYNMOBI can be administered without regard to food.
Labeling:	The proposed labeling in general is adequate. (b) (4) [redacted]
Bridge between the to-be-marketed and clinical trial formulations:	The to-be-marketed formulation is the same as the formulation used in the completed and ongoing Phase 3 efficacy and safety trials and in the PK bridging studies (CTH-200 and the ongoing CTH-203).
Bridge between the to-be-marketed formulation and the RLD:	To establish the PK bridge between KYNMOBI and the RLD, APOKYN®, the applicant is relying on the totality of evidence from Study CTH-200 (used Apo-go® and KYNMOBI), the interim PK data from 5 subjects with PD from the ongoing Study CTH-203 (used APOKYN®, Apo-go® and KYNMOBI), and the sameness of APO-go® and APOKYN®. Please refer to the Biopharmaceutics review by Dr. Gerlie Gieser for the evaluation of sameness between the RLD, Apokyn®, and APO-go®.

1.2 Post-Marketing Requirements and Commitments

In vitro studies to evaluate drug-drug interaction (DDI) potential of the two major metabolites from KYNMOBI, apomorphine glucuronide and norapomorphine glucuronide are required, based on current in vitro DDI FDA guidance[1].

The systemic exposure of apomorphine glucuronide and norapomorphine glucuronide after sublingual administration of KYNMOBI was about 9.6 and 10.4-fold higher than the parent drug apomorphine, respectively. Per the current in vitro DDI guidance, the DDI potential of a more polar metabolite than the parent needs to be evaluated when the metabolite has systemic exposure similar to or higher than the parent. The elimination half-lives of these two metabolites (3.1 h for apomorphine glucuronide and 4.1 h for norapomorphine glucuronide)

[1] https://www.fda.gov/downloads/Drugs/Guidances/UCM581965.pdf

are slightly longer than that of apomorphine. KYNMOBI is expected to be used multiple times a day. The average dosing frequency was 2 to 3 times daily in the pivotal efficacy study[2].

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Pharmacology and Clinical Pharmacokinetics

Apomorphine is a non-ergoline, dopamine agonist. While the precise mechanism of action of apomorphine as a treatment for Parkinson's disease (PD) is unknown, it is believed to be due to stimulation of post-synaptic dopamine D1 and D2 type receptors within the caudate-putamen in the brain. Apomorphine is currently available in the US as a SC formulation APOKYN® (apomorphine hydrochloride injection; NDA 021264) and is currently the only product in the US approved for acute, intermittent treatment of "OFF" episodes associated with advanced PD.

Following sublingual (SL) administration, the time to maximum concentration (T_{max}) ranged from 0.5 to 1 hour (with 15 mg dose, Study CTH-200) in healthy subjects. Compared with the SC formulation, the relative bioavailability of KYNMOBI is approximately 19%. Apomorphine exposure increased with increasing KYNMOBI dose; however, the increase in C_{max} and AUC was less than dose proportional over the dose range 10-50 mg.

After SL administration of KYNMOBI 15 mg (Study CTH-200), 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 KYNMOBI is sulfation and glucuronidation by multiple sulfotransferase (SULT) and glycosyltransferase (UGT) 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 9.1fold greater following SL administration compared to SC administration.

[2] Sponsor claimed that the exposure to these metabolites is transient and therefore there is no need to conduct the DDI studies (response to the Information Request letter dated 15 August 2018).

2.2 Dosing and Therapeutic Individualization

The recommended range for KYNMOBI is 10 mg (b) (4) per dose. Doses should be separated by at least 2 hours and the maximum number of doses is 5 times per day.

The dose should be titrated based on tolerability and efficacy. Dose titration should be initiated with 10 mg KYNMOBI sublingual film when patients are in an "OFF" state. If the patient tolerates the dose but does not respond adequately, the next dose strength can be increased at the next observed "OFF" period by 5 mg increments until an effective and tolerable dose is achieved.

2.2.2 Therapeutic individualization

No dose adjustment is necessary in patients with mild or moderate renal impairment or patients with mild or moderate hepatic impairment. However, slower dose titration and careful monitoring is recommended in these subjects. KYNMOBI is not recommended in subjects with severe hepatic impairment or severe renal impairment. Please refer to Section 3.3.3 for more information.

2.3 Outstanding Issues

None.

2.4 Summary of Labeling Recommendations

The Office of Clinical Pharmacology has reviewed the package insert for KYNMOBI™ and finds it generally acceptable. The following changes are proposed:

1) For subjects with renal and hepatic impairment:
   - No dose adjustment is required in subjects with mild/moderate renal impairment or mild/moderate hepatic impairment. Careful monitoring during dose titration is necessary.
   - KYNMOBI™ is not recommended in subjects with severe renal impairment or severe hepatic impairment.
2) For Section 12 renal and hepatic impairment:
   - Qualitative description of the results from Argiolas et al.[3] describing the effect of hepatic and renal impairment on apomorphine exposure following sublingual route of administration will be described.

[3] BJU International 2001; 88(Suppl. 3), 18-21

3) Information on the 3 major metabolites from KYNMOBI, apomorphine sulfate, apomorphine glucuronides, and norapomorphine glucuronides will be included.

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Overview of the Product and Regulatory Background

KYNMOBI is a near square (b) (4) film containing apomorphine hydrochloride for SL administration for the on-demand treatment of "OFF" episodes associated with Parkinson's disease. KYNMOBI (b) (4) is composed of cellulose-ether based film, containing drug substance, (b) (4) (pyridoxine hydrochloride) (b) (4) (glyceryl monostearate). KYNMOBI is available in 5 strengths: 10 mg, 15 mg, 20 mg, 25 mg, and 30 mg films.

The product is intended to be an alternative to the SC injectable form of apomorphine hydrochloride, which is marketed as APO-go® in most of Europe, APOKYN® in the United States, and MOVAPO® in Canada and Australia. APOKYN® is the RLD upon which this 505(b)(2) application is based.

Currently, there is no approved apomorphine drug product for SL use either for the proposed indication or for any other indication in the US. An apomorphine hydrochloride SL tablet was (b) (4) approved in Europe. Apomorphine hydrochloride SL tablets were marketed as IXENSE in Austria, Germany, France, and Italy and were marketed as UPRIMA in Ireland, UK, Spain, France, Sweden, and Norway. However, both IXENSE and UPRIMA are currently withdrawn for commercial reasons.

Prior to submission of an Investigational New Drug (IND) application for KYNMOBI, a pre-IND meeting was held on 20 April 2011. During this meeting the agency provided guidance on CMC, Clinical and Pharmacology/Toxicology strategies to support a 505(b)(2) application. During the End-of-Phase 2 meeting, held on February 4th, 2015, a general agreement was reached on the Phase 3 clinical development program and the design elements of the pivotal Phase 3 Study CTH-300. Additionally, in a written response dated May 26th, 2015, the Division informed the applicant the need for evaluating drug-drug interaction potential of major metabolites because the exposure to these metabolites are significantly higher from the SL route of administration relative to the RLD.

During the pre-NDA meeting on February 6th, 2018, the agency commented on the applicant's approach to bridge KYNMOBI to APOKYN® utilizing data from the relative bioavailability study (CTH-200 which compared KYNMOBI 15 mg to APO-go® 2mg) and indicated that demonstration of "sameness" (physiochemical assessment) between current APO-go® and APOKYN® products would be required.

3.2 General Pharmacology and Pharmacokinetic Characteristics

Following SL administration, apomorphine exposure increased with increasing KYNMBOI dose; however, the increases in C_{max} and AUC were less than dose proportional over the dose range of 10-50 mg (Please refer to Section 4.2). The median terminal $t_{½}$ was estimated to be 1.7 h for apomorphine after 15 mg of KYNMBOI in healthy subjects (Study CTH-200). The T_{max} ranged from 0.5 to 1 hour. The geometric mean C_{max} was about 5 ng/mL.

The geometric mean of the apparent volume of distribution was 3630 L based on noncompartmental analysis results.

The major metabolic pathway for apomorphine from KYNMOBI is sulfation and glucuronidation by multiple sulfotransferase (SULT) and glycosyltransferase (UGT) enzymes with limited N-demethylation catalyzed by multiple enzymes, including CYP2B6, CYP2C8 and CYP3A4/5, followed by conjugation.

There is a change in the metabolic profile of apomorphine after SL administration as compared to the SC administration. There are four metabolites associated with apomorphine: apomorphine-sulfate, norapomorphine, apomorphine glucuronide and norapomorphine glucuronide. Of these, apomorphine sulfate, apomorphine glucuronide and norapomorphine glucuronide were considered major metabolites from KYNMOBI. The ratio of $AUC_{0-\infty}$ of the metabolite to $AUC_{0-\infty}$ of parent (M/P) were 9.6, 131, and 10.4 for apomorphine glucuronide, apomorphine sulfate, and norapomorphine glucuronide, respectively. Following 15 mg of KYNMOBI, the half-lives of these three major metabolites are: 3.1, 2.6, and 4.1 h for apomorphine glucuronide, apomorphine sulfate, and norapomorphine glucuronide, respectively. Plasma levels of norapomorphine were not quantifiable after administering 15 mg of KYNMOBI (Study CTH-200).

The geometric mean of the apparent clearance is 1440 L/h based on noncompartmental analysis (15 mg, Study CTH-200). Only limited amount of drug is excreted through renal elimination after SL administration. The percent of unchanged apomorphine recovered in urine was about 0.03%of apomorphine dose.

3.3 Clinical Pharmacology Review Questions

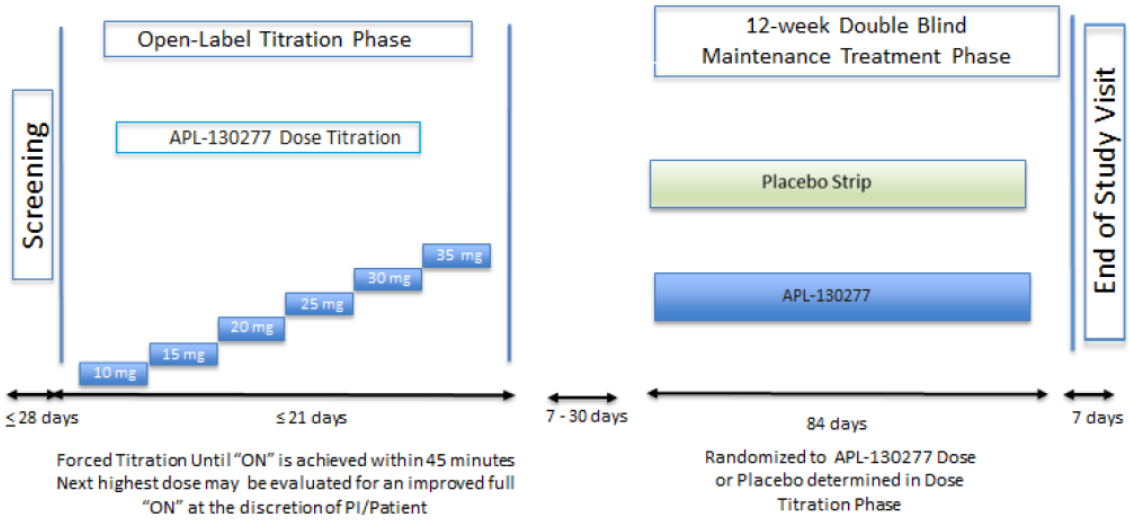
3.3.1 To what extent does the available clinical pharmacology information provide pivotal or supportive evidence of effectiveness?

The primary evidence of efficacy for KYNMOBI was demonstrated in the pivotal efficacy Study CTH-300. This was a 12-week, prospective, multicenter, randomized, double-blind, placebo-controlled, Phase 3 study that evaluated the efficacy and safety of KYNMOBI in L-Dopa-responsive subjects with PD complicated by motor fluctuations ("OFF" episodes). The study consisted of 2 phases: a Titration Phase of 3 weeks and a Maintenance Phase of 12 weeks duration.

During the Titration Phase, individual responses to single doses of KYNMOBI were evaluated. The dose of KYNMOBI was titrated based on tolerability and effect, beginning at 10 mg, in 5-mg dose increments up to a dose of 35 mg. Dose titration to next dose level occurs within 3 days of the previously administered dose. The 35 mg dose was administered using 2 films (20 mg followed by 15 mg KYNMOBI). Dose selection during the Titration Phase was based on assessment of tolerability and efficacy, as determined by the investigator's and subject's assessment of a full "ON" response.

Subjects who successfully completed the Titration Phase of the study were randomized 1:1 to either KYNMOBI or placebo and moved to the Maintenance Phase of the study, where they self-administered study medication for up to 5 "OFF" episodes per day over a 12-week period. Subjects returned to the clinic at 4-week intervals in a defined "OFF state" for efficacy and safety assessments. The efficacy assessment included MDS-UPDRS III and the subject's self-rating of "ON" response at post-dose timepoints of 15, 30, 45, 60, and 90 minutes. In addition, subjects were required to complete an at-home dosing diary for the two days before each maintenance visit. The schematic illustration of the study design is presented in Figure 1.

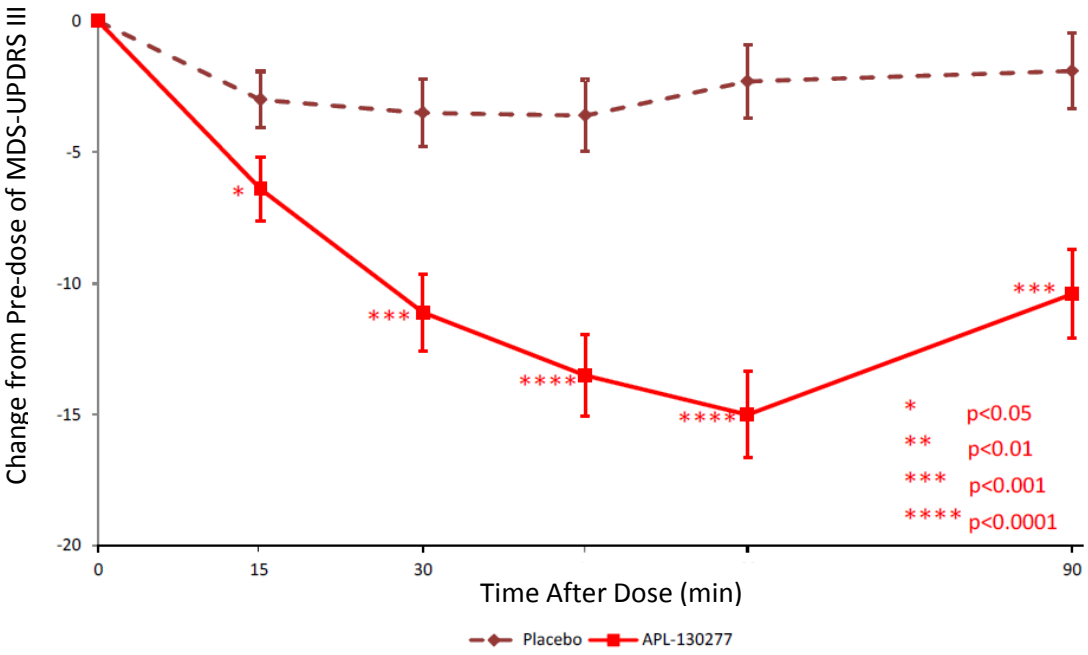
Figure 1: Overall Study Design: Study CHT-300.



The primary endpoint was the mean change from pre-dose to 30 minutes post-dose in MDS-UPDRS III score at the 12-week visit (maintenance visit 4; MV4) of the Maintenance Phase. As per the applicant analyses, the KYNMOBI treatment group showed a least square mean improvement from pre-dose to 30 minutes post-dose in MDS-UPDRS III score of -11.1 points (95% confidence interval [CI]: -14.0, -8.2) versus -3.5 points for the placebo group (95% CI: -6.1, -0.9). Figure 2 presents the mean change from pre-dose in MDS-UPDRS III score over time for KYNMOBI and placebo at MV4.

Additionally, the key secondary endpoint of the study, the percentage of subjects with a subject-rated full "ON" response within 30 minutes at MV4, showed a significant difference favoring KYNMOBI (per applicant analyses, adjusted odds ratio: 2.81 [95% CI: 1.036, 7.644]; p = 0.0426). For more details, please refer to statistics review by Dr. Xiangmin Zhang.

Figure 2: Change from Pre-dose in the MDS-UPDRS III Score at Week 12 (Study CTH-300).



3.3.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes, the applicant's proposal of dose titration based on tolerability and efficacy, initiated with 10 mg dose and titrated up to 35 mg per dose for the treatment of up to 5 OFF periods per day is acceptable. This is as per the pivotal efficacy study CTH-300.

Selection of starting dose:

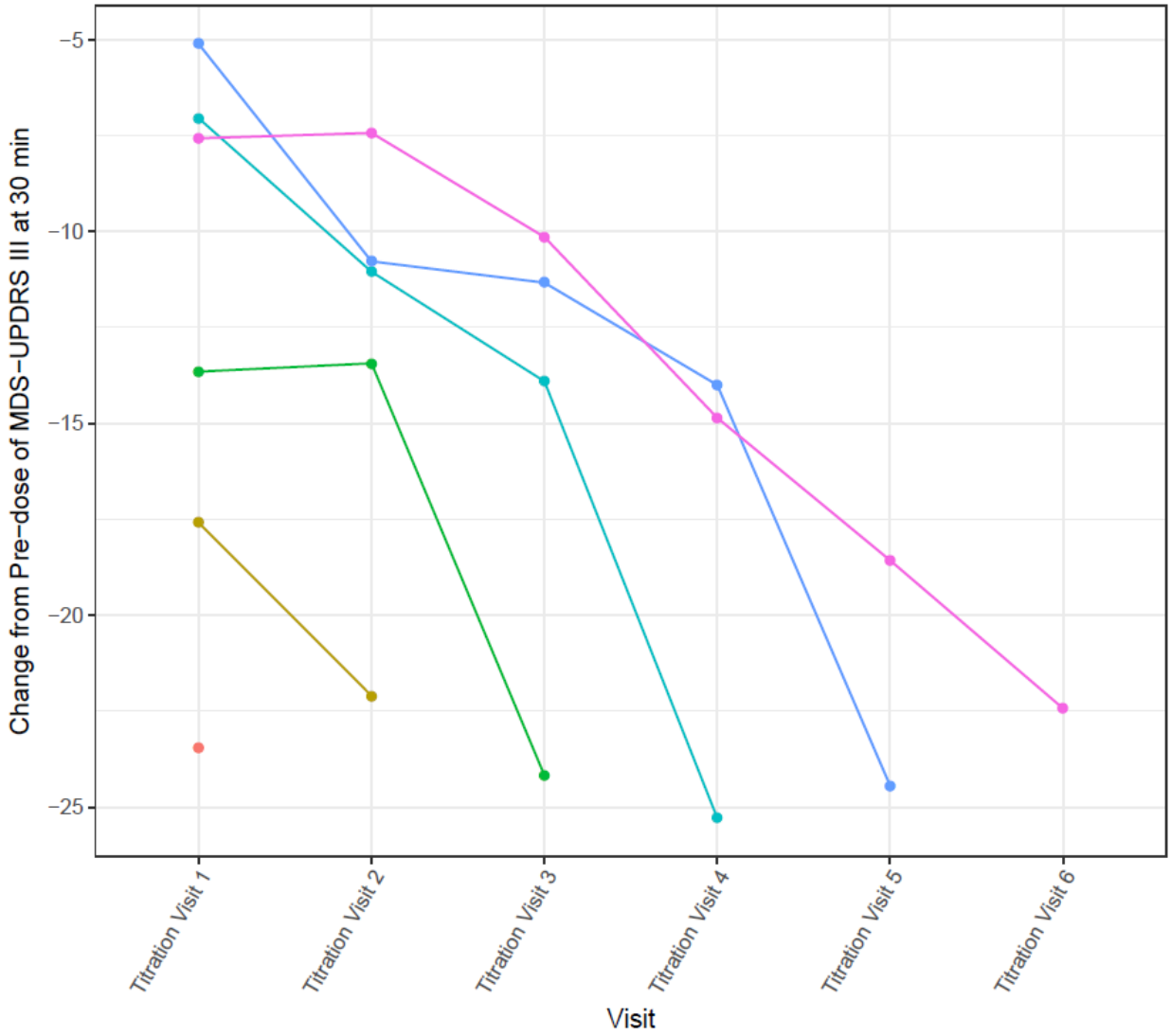
In the pivotal Phase 3 efficacy study, starting dose of 10 mg was used during the Titration Phase. This starting dose was selected based on the comparison of apomorphine exposure following SC administered apomorphine and KYNMOBI evaluated in healthy volunteers. The bioavailability of KYNMOBI is ~19% relative to SC apomorphine. Therefore, a starting dose of 10 mg was chosen to provide exposures similar to that with the approved 2 mg starting dose of SC apomorphine.

Dose titration scheme:

Dosing during the Titration Phase of the pivotal Phase 3 efficacy study was based on assessment of tolerability and efficacy, as determined by the investigator's and subject's assessment of a full "ON" response. If the subject tolerated the dose but did not respond adequately (i.e. did not convert from the "OFF" state to a full "ON" state), the KYNMOBI dose was increased in a 5-mg dose increment to the next dose strength, and the subject was dosed again at the next observed "OFF" period. Titration continued in a similar manner until an effective and tolerable dose was achieved. The maximum KYNMOBI dose was 35 mg (which was achieved by administering a 20 mg film first, and then after 3 minutes had elapsed, a 15 mg film was administered). In this study, the most common doses selected during dose titration were 15 mg and 20 mg (24.8% and 22.0% of subjects, respectively).

Individual dose-response relationships over the proposed dose range (10-35 mg) was seen during the Titration Phase of Study CTH-300 (please see Figure 1 for the overall study design). Figure 2 presents the mean change from pre-dose in MDS-UPDRS III score at 30 min at each titration visit. Subjects were grouped by the highest dose received during the Titration Phase and the mean change in the MDS-UPDRS III score at 30 min was calculated for each group at each titration visit. Figure 3, shows that within each dose group, as the dose was increased during the titration visits by 5 mg increments, an improvement in response (i.e., reduction in MDS-UPDRS III score at 30 min) was evident. While some patients show response on MDS-UPDRS III score at the starting dose of 10 mg itself, some patients required up to 35 mg dosing to get similar response. Eventually, subjects in all dosing groups attained similar effect on the reduction of the MDS-UPDRS III score as the dose was titrated up. For more details on study design, please refer to Section 4.3.

Figure 3: Individual Dose-Response Relationships: Effect of Increasing KYNMOI Dose on Mean Change from Pre-dose of MDS-UPDRS III at 30 min versus Titration Visit, Stratified by the Highest Dose Received.



Dose Level	10 mg	15 mg	20 mg	25 mg	30 mg	35 mg
N (%)	18 (12.8)	35 (24.8)	31 (22.0)	21 (14.9)	16 (11.3)	20 (14.2)

PMaximum number of doses per day and maximum unit dose:

In studies CTH-300 (pivotal efficacy study) and CTH-301 (open label extension study), based on the home dosing diary for the 2 days prior to each visit, the mean number of daily doses per subjects was 2.2 and 2.5, respectively. A total of 7.4% and 6.8% of subjects administered 5 doses per day for at least 1 day, in these studies, respectively. There is very limited clinical experience with the maximum unit dose of 35 mg administered 5 times daily (1 subject in CTH-300 and 1 subject in CTH-301).

3.3.3 Is an alternative dosing regimen and/or management strategy required for subpopulations based on intrinsic/extrinsic factors?

As per APOKYN® prescribing information, APOKYN® starting dose should be reduced to half in subjects with mild and moderate renal impairment. APOKYN® is not recommended for subjects with severe renal impairment. No change of APOKYN® dosing is recommended for subjects with mild and moderate hepatic impairment, however, the patients should be closely monitored. APOKYN® is not recommended for subjects with severe hepatic impairment.

Changing apomorphine route of administration from SC to SL results in increasing the first pass effect as evidenced by the low relative bioavailability and increase in metabolites to parent ratio (M/P). Since hepatic[4, 5] and renal[6] impairment can affect drug clearance and first pass effect, it is expected that the effect of hepatic and renal impairment on apomorphine exposures can be higher after SL administration as compared to SC route. Therefore, the ability to extrapolate dosing recommendations for these populations from the RLD is limited.

Effect of renal impairment

Dedicated renal and hepatic impairment studies were not conducted using KYNMOBI. However, the clinical studies of KYNMOBI included subjects with mild renal impairment (baseline creatinine clearance [CLcr] of >50 to <80 mL/min; N=24). There were no differences in apomorphine exposure after administration of KYNMOBI in patients with mild renal impairment as compared to normal subjects (baseline CLcr of ≥ 80 mL/min; N=43). There was no experience in subjects with moderate or severe renal impairment with KYNMOBI.

[4] Clinical Pharmacokinetics1979 December; 4(6): 423–432
[5] Gastroenterology. 1979 Jul; 77(1):96-102.
[6] Kidney Int. 2014 Mar; 85(3): 522–528.

Argiolas and Hedlund published a review summarizing the clinical pharmacokinetics of apomorphine after administration of IXENSE SL[7]. IXENSE SL (apomorphine hydrochloride sublingual tablets) received a marketing authorization in 2001 from the European Commission for the treatment of erectile dysfunction but was later voluntarily withdrawn based on commercial reasons in 2004[8]. According to this publication, the mean $AUC_{0-\infty}$ of apomorphine SL tablet was increased by 4% in male subjects with mild renal impairment (CLcr 40-80 mL/min/1.73 m2), by 52% in moderate renal impairment (CLcr 10-40 mL/min/1.73 m2) and by 67% in severe renal impairment (CLcr <10 mL/min/1.73 m2). There was no significant change in mean C_{max}[9].

Data from the abovementioned renal impairment study was not published and there was no information on the adequacy of the bioanalytical method used in this study. It is also noted that the reported classification for renal impairment categories based on creatinine clearance is different from the current FDA guidance. Without subject level data it is not possible to recategorize and reanalyze the study results based on current FDA guidance. However, it is expected that re-classification of the subjects according to the current FDA guidance classification for moderate renal impairment (i.e. CLcr>30-<60 mL/mL) would have lesser increase in the exposure than the reported in this publication.

Based on this publication, the applicant proposed no dose adjustment for patients with mild renal impairment taking KYNMOBI. It should be noted that there is no dose strength available for KYNMOBI to reduce the starting dose by 50% as per the RLD label. Additionally, the applicant proposed that (b) (4) patients with severe renal impairment is not recommended[10].

This review team agree with the applicant's dosing recommendation for subjects with mild and severe renal impairment. Not recommending KYNMOBI in subjects with severe renal impairment is based on the absence of experience with APOKYN® and KYNMOBI in this population. Since KYNMOBI dose is titrated based on both efficacy and tolerability under medical supervision, no dose capping is necessary in subjects with moderate renal impairment.

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[7] BJU International 2001; 88(Suppl. 3), 18-21

[8] https://www.ema.europa.eu/documents/public-statement/public-statement-ixense-apomorphine-hydrochloride-withdrawal-marketing-authorisation-european-union_en.pdf

[9] It is noted that this classification cut-off for renal impairment group is different than the current FDA guidance classification. Unfortunately, the subject level data is not available. Therefore, it is expected that re-classification of the subjects according to the current FDA guidance classification for moderate renal impairment (i.e. CLcr>30 (b) (4) mL/mL) would have less increase in the exposure than the reported exposure increase.

[10] Sunovion Response to FDA Request for Information (27 September 2018)

Given the limitation of the available dosing strengths for KYNMOBI (lowest dose strength is 10 mg), it is not practical to reduce the starting dose. Additionally, the maximum observed increase in the exposure is ~50% in either C_{max} (per APOKYN® label)[11] or $AUC_{0-\infty}$ (per Argiolas and Hedlund publication). $AUC_{0-\infty}$ and C_{max} achieved after 10 mg of KYNMOBI is ~10 and ~30% lower than that achieved after 2 mg apomorphine SC administration. Moreover, $AUC_{0-\infty}$ and C_{max} achieved after 35 mg of KYNMOBI is ~20 and ~70% lower than that achieved after 6 mg apomorphine SC administration. Please refer to Section 4.2 for more details.

Therefore, no dose adjustment is necessary for subjects with mild or moderate renal impairment. However, careful monitoring for signs and symptoms of orthostatic hypotension, especially during dose escalation, is necessary. Additionally, KYNMOBI is not recommended in subjects with severe renal impairment.

Effect of hepatic impairment

Studies in subjects with hepatic impairment have not been conducted with KYNMOBI. However, according to the published literature[12], patients with mild, moderate or severe hepatic insufficiency[13], had 16%, 36%, and 62% higher C_{max} and 59%, 35%, and 68% higher $AUC_{0-\infty}$, respectively, than the subjects with normal hepatic function[14], following SL administration of apomorphine.

(b) (4)

The use of KYNMOBI in patients with severe hepatic impairment is not recommended.

The review team recommends administration of KYNMOBI in mild/moderate hepatic impairment with careful monitoring. No dose capping is recommended for this population for the same reasons listed for mild/moderate renal impairment. Not recommending KYNMOBI in subjects with severe hepatic impairment is based on the absence of clinical experience with APOKYN® and KYNMOBI in this population.

[11] In a study with subcutaneous apomorphine, after APOKYN® administration, the $AUC_{0-\infty}$ and C_{max} values were increased by approximately 16% and 50%, respectively, following a single administration in subjects with moderate renal impairment as compared to normal renal impairment. The mean time to peak concentrations and the mean terminal $t_{1/2}$ of apomorphine were unaffected by the renal status of the individual.

[12] BJU International 2001; 88(Suppl. 3), 18-21

[13] Based on the Child-Pugh classification

[14] Note: Per the RLD APOKYN® prescribing information, the $AUC_{0-\infty}$and C_{max} values increased by approximately 10% and 25%, respectively, in subjects with moderate hepatic impairment (as determined by the Child-Pugh classification method) as compared to normal matched healthy volunteers following a single administration.

Food Effect

No food effect study was conducted with KYNMOBI. However, in the pivotal efficacy study, KYNMOBI was administered without regard to food. Therefore, KYNMOBI can be dosed without regard to food as it was studied in Phase 3.

3.3.4 Is the PK bridging information provided in the application adequate?

Bridging between the clinical trial formulations and the to-be-marketed formulation:

The formulations used in the clinical studies CTH-200, CTH-200, CTH-203, CTH-300, and CTH-301 supporting this application are same as the to-be-marketed formulation. Therefore, no PK bridging study is necessary.

Bridging between the to-be-marketed formulation and the RLD APOKYN®:

The applicant conducted Study CTH-200 to establish the PK bridge between the to-be-marketed formulation and APO-go® (the European apomorphine product for SC injection). This 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 SL film and 2 mg of SC APO-go®. The apomorphine exposure following KYNMOBI was approximately 19% compared to APO-go®. The dose normalized C_{max} following KYMOBI was ~11% relative to Apo-go®.

Study CTH-203, is a supportive comparative bioavailability study that is currently ongoing. This study aims to evaluate the PK and comparative bioavailability of a single dose of KYNMOBI with APO-go® and APOKYN® in subjects with PD (planned N=12). The study was designed as an open-label, randomized, three-way crossover study. KYNMOBI and APO-go® dosing in the three-way crossover is based on the subjects' current prescribed dose of APOKYN. The sponsor submitted interim PK analysis of the first 5 subjects who completed the study. Based on this interim analysis, the relative bioavailability of apomorphine exposure following KYNMOBI is approximately 19% compared to APOKYN®. The dose normalized C_{max} following KYMOBI was ~15% relative to APOKYN®.

Since Study CTH-200 was conducted using APO-go® and not the RLD APOKYN®, the applicant is relying on both the sameness of APO-go® and APOKYN® products and on the interim PK data from the ongoing Study CTH-203 to support the bridge between KYNMOBI and the RLD APOKYN®.

The sameness of the APO-go® and APOKYN® drug components was assessed by the biopharmaceutics review team and it was concluded as adequate. Please refer to the review by Dr. Gerlie Gieser for more details. 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. APPENDICES

4.1 Summary of Bioanalytical Method Validation and Performance

This review focused on the review of the bioanalytical validation reports: APL-MV-03, and APL-MQ-04. These methods were used to determine apomorphine, apomorphine-sulfate, apomorphine glucuronide, norapomorphine, and norapomorphine-glucuronide concentrations in human plasma samples from study CTH-200, CTH-201, CTH-203, and CTH-301. Summary of bioanalytical method validation studies and supported clinical studies is provided in Table 1.

Table 1: Summary of Bioanalytical Method Validation Studies and Supported Clinical Studies.

Bioanalytical Validation Report	Analytes	Method Description	Supported Clinical Study
APL-MV-03	Apomorphine Apomorphine-sulfate Norapomorphine	A liquid chromatography-tandem mass spectrometry (LC-MS/MS) method for the simultaneous measurement of apomorphine (0.0200 – 20.0 ng/mL), norapomorphine (0.500 – 20.0 ng/mL) and apomorphine sulfate (10.0 – 1,000 ng/mL) in human K2EDTA plasma. This method is modified from a previously validated LC-MS/MS method, APM 01 to better meet the higher metabolite concentrations observed in the clinical studies. The validation report comprises the validation results obtained on two different LC-MS/MS instruments (APM 02, Version 01, Agilent G6490 and APM 02, Version 02, Agilent G6495). Analytical procedures were the same for two versions, and only differences were injection volume (5-µL vs. 3-µL) and internal standards (Version 01 used (b) (4) as the internal standard for all three analytes, while Version 02 had corresponding stable isotope-label internal standard for each of three analytes).	CTH-200 CTH-201 CTH-203 CTH-301
APL-MQ-04	Total apomorphine (apomorphine glucuronides included) Total norapomorphine (norapomorphine glucuronides	LC-MS/MS method was developed and qualified for the simultaneous measurement of total apomorphine (apomorphine + apomorphine glucuronides) and total norapomorphine (norapomorphine + Norapomorphine glucuronides) in human K2EDTA plasma. An enzymatic hydrolysis procedure using Escherichia coli β-glucuronidase Type IX-A was used for study	CTH-200 CTH-301

	included)	sample preparation. Corresponding stable isotope labeled internal standard was used for each analyte.	

Summary of the performance characteristics and validation attributes for plasma apomorphine are provided in Table 2.

Table 2: Validation Study Summary for Method APL-MV-03.

Method	APL-MV-03/ APM 02, version 01[15] (Agilent G6490)	APL-MV-03/ APM 02, version 02[16] (Agilent G6495)
Apomorphine		
Methodology	LC-MS/MS	
Biological Matrix	Human plasma	
Internal Standard (IS)	(b) (4)	
Calibration Curve	0.0200 - 20.0 ng/mL	
QC concentrations	0.0200, 0.0600, 6.00, 10.0, 15.0 ng/mL	
Accuracy, and Precision		
Inter-run accuracy, range	93.2105.4%;	96.0- 106.0%
Inter-run precision, range	5.3- 8.5%	3.3-7.3%
Intra-run accuracy, range	92.2-102.1%	92.7-101.6%
Intra-run precision, range	4.2-14.1%	2.4-4.7%
Selectivity and Specificity	Inferences at LLOQ: 1.1% Inferences at IS: 0.0%	NA
Stability		

[15] APM 02 (version 01) is the same procedure as that in the validated method APM 01 except for three analytes having different calibration ranges (Apomorphine 0.0200 – 20.0 ng/mL), Norapomorphine (0.500 – 20.0 ng/mL) and Apomorphine-Sulfate (10.0 – 1000 ng/mL) by using 0.200-mL of plasma. A partial validation including selectivity, linearity, precision and accuracy (inter-run and intra-run), and carry-over were performed to validate these modified curve ranges and sample volume.

[16] The bioanalytical method (APM 02, version 02) was for setting this APM 02 method on Agilent G6495 LC-MS/MS system with improvement of each analyte having its own (b) (4) internal standard.

Short term stability in biological matrix at room temperature, accuracy	Up to 24 hours: QC low: 111.2% and QC high: 101.1%	
Long term stability in biological matrix,	UP to 504 days at -20°C: QC low: 93.1%; QC high: 95.3%	
Freeze and thaw stability	6 cycles at -60°C: The CV for QC low and QC high was 5.5% and	
Apomorphine Sulfate		
Methodology	LC-MS/MS	
Biological Matrix	Human plasma	
Internal Standard (IS)	(b) (4)	
Calibration Curve	10.0 to 1,000 ng/mL	
QC concentrations	10.0, 30, 200, 500, 750 ng/mL	
Accuracy, and Precision		
Inter-run accuracy, range	95.6- 104.0%	99.5-104.4%
Inter-run precision, range	4.8-9.8%	2.2-3.6%
Intra-run accuracy, range	91.6-101.1%	94.4-99.1%
Intra-run precision, range	5.4- 14.6%	2.6-5.1%
Selectivity and Specificity	Inferences at LLOQ: 2.2% Inferences at IS: 0.0%	NA
Stability		
Short term stability in biological matrix at room temperature, accuracy	Up to 24 hours: QC low: 103.2% and QC high: 108.7%	
Long term stability in biological matrix, accuracy	UP to 504 days at -20°C: QC low: 93.1%; QC high: 95.3%	
Freeze and thaw stability, accuracy	6 cycles at -60°C: QC low: 100% and QC high: 100%	
Norapomorphine		
Methodology	LC-MS/MS	
Biological Matrix	Human plasma	

Internal Standard (IS)	(b) (4)	
Calibration Curve	0.500 to 20.0 ng/mL	
QC concentrations	0.500, 1.50, 6.00, 10.0, 15.0 ng/mL	
Accuracy, and Precision		
Inter-run accuracy, range	98.1-103.6%	100.4%-100.7%
Inter-run precision, range	5.7-10.2%	3.4-3.7%
Intra-run accuracy, range	97-105.4%	95.3-98.6%
Intra-run precision, range	3.4-12%	2.7-4.8%
Selectivity and Specificity	Inferences at LLOQ: 0.1% Inferences at IS: 0.0%	NA
Stability		
Short term stability in biological matrix at room temperature	Up to 24 hours: QC low: 99.5% and QC high: 102.1%	
Long term stability in biological matrix,	UP to 504 days at -20°C: QC low: 93.1%; QC high: 95.3%	
Freeze and thaw stability	6 cycles at -60°C: QC low: 99% and QC high: 99.2%	

Reviewer's Comments:

- *The methods satisfied the criteria for method validation and application to routine analysis as per the FDA Guidance for Industry: Bioanalytical Method Validation*[17]*, and hence are acceptable.*

[17] Available from: [https://www.fda.gov/downloads/drugs/guidances/ucm070107.Pdf].

Table 3: Validation Study Summary for Method APL-MQ-04.

Method	APL-MV-04 (Agilent G6495)
Total Apomorphine (Apomorphine + Apomorphine Glucuronides)	
Methodology	LC-MS/MS
Biological Matrix	Human plasma
Internal Standard (IS)	(b) (4)
Calibration Curve	1 - 150 ng/mL
QC concentrations	1.00, 2, 6, 75, 120 ng/mL
Accuracy, and Precision	
Inter-run accuracy, range	96.4-98.2%
Inter-run precision, range	1.8-5.4%
Intra-run accuracy, range	97.5-99.9%
Intra-run precision, range	0.9-2%
Selectivity and Specificity	Inferences at LLOQ: 0.4% Inferences at IS: 0.0%
Stability	
Short term stability in biological matrix at room temperature, accuracy	Up to 24 hours: QC low: 111.2% and QC high: 101.1%
Long term stability in biological matrix, accuracy	UP to 337 days at -20°C: QC low: 106%; QC high: 100.5%
Freeze and thaw stability	6 cycles at -20°C: QC low: 101.7% and QC high: 97.2%.
Total Norapomorphine (Norapomorphine+ Norapomorphine Glucuronides)	
Methodology	LC-MS/MS
Biological Matrix	Human plasma
Internal Standard (IS)	(b) (4)
Calibration Curve	1 to 150 ng/mL
QC concentrations	1, 2, 6, 75, 120 ng/mL
Accuracy, and Precision	

Inter-run accuracy, range	96.5-98.5%
Inter-run precision, range	2.1-6.7%
Intra-run accuracy, range	97.4-99.3%
Intra-run precision, range	1.3-2.9%
Selectivity and Specificity	Inferences at LLOQ: 0.8% Inferences at IS: 0.0%
Stability	
Short term stability in biological matrix at room temperature	Up to 24 hours: QC low: 99.5% and QC high: 102.1%
Long term stability in biological matrix, accuracy	UP to 337 days at -20°C: QC low: 100.4%; QC high: 103.0%
Freeze and thaw stability	UP to 6 cycles at -20°C: QC low: 101.8%; QC high: 95.1%

Reviewer's Comments:

- *The longest possible storage duration of the study samples for total apomorphine (apomorphine + apomorphine glucuronides) and total norapomorphine (norapomorphine + norapomorphine glucuronides) was 448 days at ≤ -20^{0}C. However, the longest duration samples were stored was 504 days. As per the bioanalytical method validation guidance, "the sponsor should determine the long-term stability of the sample over a period of time equal to or exceeding the time between the date of first sample collection and the date of last sample analysis".*
- *This issue with long term stability data is not considered significant because labeling decisions will not be affected by these deficiencies. Based on the data from study CTH-200, it was determined that both apomorphine glucuronide and norapomorphine glucuronide are major metabolites since they exceeded the threshold determined in the drug-drug interaction guidance[18].*

[18] https://www.fda.gov/downloads/Drugs/Guidances/UCM581965.pdf

4.2 Bridging to the RLD and Dose Proportionality of the To-be-marketed Product

Bridging Studies

Study CTH-200

Title of Study:

A Comparative Bioavailability Study to Examine the Single Dose Pharmacokinetic Properties of 15 mg Sublingual Thin Film of APL-130277 and 2 mg subcutaneous APO-go® in Healthy Volunteers

Objectives:

The primary objective is to evaluate the PK and comparative bioavailability of a single dose of 15 mg KYNMOBI SL film with 2 mg APO-go® SC injection in healthy volunteers in a crossover design. The secondary objective is to establish the safety and tolerability of the 2 study drugs.

Methodology:

This was a single-center, pivotal, comparative bioavailability trial in healthy subjects designed to assess the PK, safety and tolerability of a single dose of 15 mg KYNMOBI SL film and 2 mg SC APO-go®.

On Day 1, the subjects were randomized to receive a dose of either 15 mg KYNMOBI or 2 mg APO-go® and then were crossed over to the other treatment on the subsequent treatment day. On both Day 1 and Day 2, pharmacokinetic and safety assessments were to be evaluated at various time points from 0 to 12 hours post-dose. Subjects were to return on Day 3 for a follow-up assessment for safety and to complete their participation in the study. All subjects were administered 10 mg domperidone twice a day from Day -3 to Day 2.

Study Population:

Healthy male or female volunteers 21 to 60 years of age with a body mass index (BMI) of 18 to 28 kg/m2 (± 10%). A total of 22 subjects were enrolled and 19 subjects were randomized and dosed.

Pharmacokinetics:

Blood samples were collected for measurement of apomorphine concentrations and metabolite concentrations, pre-dosing, and in regular intervals up to 12 hours post-dosing. Plasma PK parameters for apomorphine included: C_{max}, T_{max}, AUC_{last}, $AUC_{0-\infty}$, and $t_{½}$.

Statistical Methods:

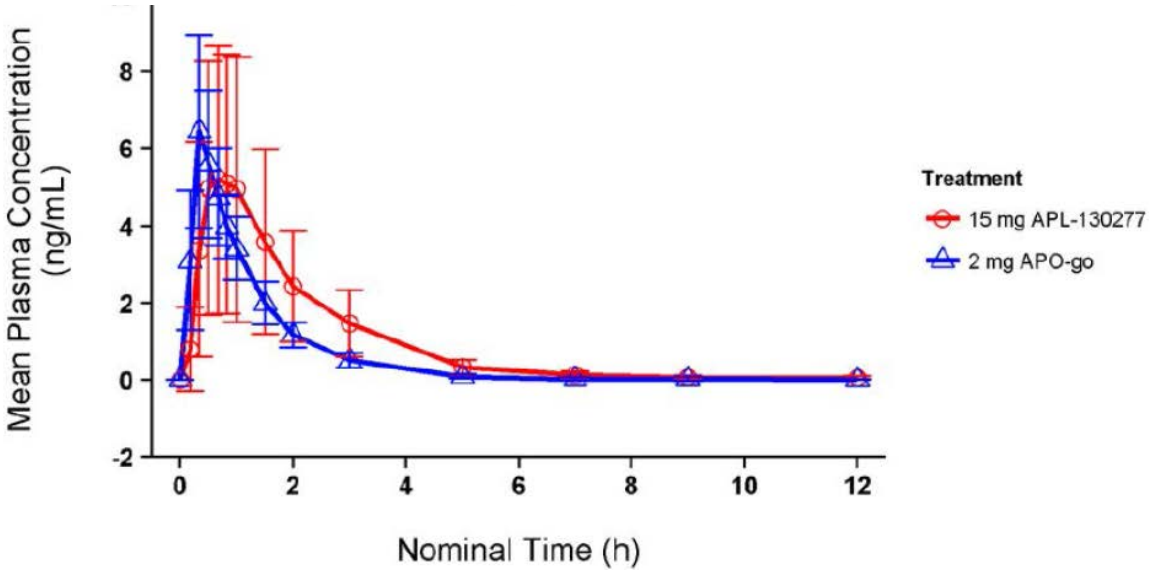
For the primary objective, a mixed effects model with fixed effects for treatment, sequence and period, with subject nested in sequence as a random effect, was used to analyze the natural log-transformed, dose-normalized AUC_{last}, $AUC_{0-\infty}$, and C_{max}. For the treatment comparison, a point estimate and 90% confidence interval (CI) was provided for the geometric mean ratio upon back-transformation.

For the secondary objective, urinary parent and metabolite profiles were assessed and quantified.

Results:

Plasma apomorphine PK parameters following administration of 15 mg KYNMOBI resulted in a lower C_{max}, higher AUC when compared to plasma apomorphine PK parameters following administration of 2 mg APO-go®. Mean apomorphine plasma concentration-time data are displayed by treatment on linear scales in Figure 4.

Figure 4: Mean (± SD) Apomorphine Plasma Concentration vs Time Plot with Treatments Overlaid (Linear Scale).



Source: CTH-200 Study Report

Mean noncompartmental PK parameter estimates for apomorphine following treatment with 15 mg KYNMOBI or 2 mg APO-go are presented with descriptive statistics in Table 4.

Table 4: Summary of Key Apomorphine Plasma Pharmacokinetics: 15 mg KYNMOBI and 2 mg APO-go®.

Treatment	C_{max} (ng/mL) (%CV)	T_{max} (h) (min, max)	AUC_{last} (h*ng/mL) (%CV)	$AUC_{0-\infty}$ (h*ng/mL) (%CV)	$t_{1/2}$ (h) (%CV)	CL/F (L/h) (%CV)	Vz/F (L) (%CV)
15 mg KYNMOBI	n=19 4.95 (73.2%)	n=19 0.85 (0.52, 1.05)	n=19 9.79 (63.7%)	n=16 10.4 (68.1%)	n=16 1.75 (43.6%)	n=16 1440 (68.1%)	n=16 3630 (66.4%)
2 mg APO-go®	n=19 6.15 (40.7%)	n=19 0.38 (0.35, 1.02)	n=19 7.61 (22.3%)	n=16 7.87 (20.4%)	n=16 0.904 (50.7%)	n=16 254 (20.4%)	n=16 331 (58.3%)

CV = coefficient of variation; h = hour; max = maximum; min = minimum; n = number of subjects.
Note: Data reported as geometric mean (Geometric %CV) except for T_{max} reported as median (minimum, maximum).
Reference: CTH-200 PK Report Table 8-5.

The ratio (KYNMOBI/APO-go®) of the geometric LSM for apomorphine C_{max}, AUC_{last}, and $AUC_{0-\infty}$ are presented in Table 5.

Table 5: Results from Statistical Assessment of Apomorphine Comparative Bioavailability Following Sublingual and Subcutaneous Administration.

Parameter	n	GM APL-30277	GM APO-go®	KYNMOBI/ APO-go® (%)	90% CI
C_{max} (ng/mL)	19	4.96	6.10	81.2	(65.94, 100.01)
$AUC_{0-\infty}$ (h*ng/mL)	16	10.2	7.24	141	(116.15, 172.04)
AUC_{last} (h*ng/mL)	19	9.77	7.61	128	(107.65, 153.31)

CI = confidence interval; GM = geometric mean; n = number of subjects. Source: CTH-200 PK Report Table 4-5

The relative bioavailability results, based the ratio of $AUC_{0-\infty}$, indicated that apomorphine exposure was 18.8% and suggested that a 15-mg dose of KYNMOBI was approximately equal to a 2.82 mg dose of APO-go® (Table 6).

Table 6: Results from Statistical Assessment of Relative Bioavailability of KYNMOBI Dose-adjusted Pharmacokinetic Parameters.

Parameter	n	GM KYNMOBI	GM APO-go®	KYNMOBI/ APO-go® (%)	90% CI
C_{max}/ D (ng/mL/mg)	19	0.330	3.05	10.8	(8.79, 13.33)
$AUC_{0-\infty}$/D (h*ng/mL/mg)	16	0.682	3.62	18.8	(15.49, 22.94)
AUC_{last}/D (h*ng/mL/mg)	19	0.652	3.80	17.1	(14.35, 20.44)

CI = confidence interval; C_{max}/ D = dose normalized C_{max}; $AUC_{0-\infty}$/ D =-dose normalized AUC0-oo; AUC_{last}/ D = dose normalized AUC_{last}; GM = geometric mean; n = number of subjects.
Source: CTH-200 PK Report Table 4-6

Analysis of apomorphine metabolites in plasma indicates exposure ($AUC_{0-\infty}$) was higher in subjects dosed with 15 mg KYNMOBI compared to 2 mg APO-go®. Apomorphine sulfate was approximately 4.35-fold higher following dosing with 15 mg KYNMOBI compared to 2 mg APO-go® (1550 versus 356 h*ng/mL). Apomorphine glucuronide was approximately 15.76-fold higher following dosing with 15 mg KYNMOBI compared to 2 mg APO-go® (140 versus 8.88 h*ng/mL). Norapomorphine glucuronide was approximately 9.1-fold higher following dosing with 15 mg KYNMOBI compared to 2 mg APO-go® (169 versus 18.6 h*ng/mL). Norapomorphine plasma concentrations were not quantifiable.

Mean noncompartmental PK parameter estimates for apomorphine glucuronide, apomorphine sulfate and norapomorphine glucuronide following treatment with 15 mg KYNMOBI or 2 mg APO-go® are presented with descriptive statistics in Table 7, Table 8, and Table 9, respectively.

Table 7: Summary of Key Apomorphine Glucuronide Plasma Pharmacokinetics: 15 mg KYNMOBI and 2 mg APO-go®.

Treatment	C_{max} (ng/mL) (%CV)	T_{max} (h) (min, max)	AUC_{last} (h*ng/mL) (%CV)	$AUC_{0-\infty}$ (h*ng/mL) (%CV)	$t_{1/2}$ (h) (%CV)
15 mg KYNMOBI	n=19 52.3 (79.8%)	n=19 0.53 (0.35, 3.03)	n=19 139 (60.8%)	n=10 140 (91.3%)	n=10 3.13 (49.9%)
2 mg APO-go®	n=19 3.97 (33.4%)	n=19 0.70 (0.35, 1.02)	n=19 8.36 (38.1%)	n=17 8.88 (33.5%)	n=17 1.40 (59.4%)

CV = coefficient of variation; h = hour; max = maximum; min = minimum; n = number of subjects.

Note: Data reported as geometric mean (Geometric %CV) except for T_{max} reported as median (minimum, maximum).
Source: CTH-200 PK Report Table 4-2.

Table 8: Summary of Key Apomorphine Sulfate Plasma Pharmacokinetics: 15 mg KYNMOBI and 2 mg APO-go®.

Treatment	C_{max} (ng/mL) (%CV)	T_{max} (h) (min, max)	AUC_{last} (h*ng/mL) (%CV)	$AUC_{0-\infty}$ (h*ng/mL) (%CV)	$t_{1/2}$ (h) (%CV)
15 mg KYNMOBI	n=19 432 (66.1%)	n=19 0.85 (0.35, 3.03)	n=19 1570 (63.1%)	n=15 1550 (63.9%)	n=15 2.56 (53.7%)
2 mg APO-go®	n=19 158 (42.5%)	n=19 1.02 (0.52, 2.02)	n=19 368 (48.8%)	n=16 356 (25.5%)	n=16 1.38 (23.6%)

CV = coefficient of variation; h = hour; max = maximum; min = minimum; n = number of subjects.
Note: Data reported as geometric mean (Geometric %CV) except for T_{max} reported as median (minimum, maximum).
Source: CTH-200 PK Report Table 4-3.

Table 9: Summary of Key Norapomorphine Glucuronide Plasma Pharmacokinetics: 15 mg KYNMOBI and 2 mg APO-go®.

Treatment	C_{max} (ng/mL) (%CV)	T_{max} (h) (min, max)	AUC_{last} (h*ng/mL) (%CV)	$AUC_{0-\infty}$ (h*ng/mL) (%CV)	$t_{1/2}$ (h) (%CV)
15 mg KYNMOBI	n=19 19.2 (75.3%)	n=19 3.02 (1.10, 5.02)	n=19 104 (75.2%)	n=5 169 (52.5%)	n=5 4.14 (38.4%)
2 mg APO-go®	n=19 3.80 (40.8%)	n=19 2.02 (1.02, 3.02)	n=19 17.3 (47.6%)	n=9 18.6 (40.1%)	n=9 3.02 (64.6%)

CV = coefficient of variation; h = hour; max = maximum; min = minimum; n = number of subjects.
Note: Data reported as geometric mean (Geometric %CV) except for T_{max} reported as median (minimum, maximum).
Source: CTH-200 PK Report Table 4-4.

Geometric mean percent recovery of apomorphine in urine was low (< 0.10% recovered) following treatment with either 15 mg KYNMOBI or 2 mg APO-go®. The predominant metabolite in urine was apomorphine sulfate for both routes of administration, with 23.4% of

the 15 mg dose recovered after SL administration and 40.0% after 2 mg administered SC. Recoveries of the glucuronide metabolites were similar but lower as evidenced by 1.72% and 1.87% (SL and SC, respectively) for apomorphine glucuronide and 2.19% and 2.55% for norapomorphine glucuronide (SL and SC, respectively). As expected, renal clearances were very low for apomorphine and higher for the conjugated metabolites.

Reviewer Comments:

- *Plasma apomorphine PK parameters following administration of 15 mg KYNMOBI resulted in a lower C_{max}, and higher AUC when compared to plasma apomorphine PK parameters following administration of 2 mg APO-go®.*
- *The bioavailability of KYNMOBI relative to APO-go® is 19%. This value agrees with literature reports for apomorphine administered sublingually[19,20,21].*
- *The difference in route of administration resulted in difference in C_{max} values being 2.7, 13.2, and 5.1-fold greater for SL versus SC administration for apomorphine sulfate, apomorphine glucuronide, or norapomorphine glucuronide, respectively. Similarly, $AUC_{0-\infty}$ values were 4.4, 15.8, and 9.1-fold greater for SL administration compared with SC administration. Apomorphine that is not absorbed sublingually is most likely swallowed. Orally administered apomorphine undergoes first pass metabolism in the gastrointestinal tract and in the liver[22]. According to literature, orally administered apomorphine has bioavailability of less than 4%[23].*

Study CTH-203 (Interim Analysis)

Title of Study:

A Comparative Bioavailability Study to Evaluate the Single Dose Pharmacokinetic Properties of APL-130277 with Two Different Formulations of Subcutaneous Apomorphine in a Randomized, 3- Period Crossover Design in Subjects with Parkinson's Disease Complicated by Motor Fluctuations ("OFF" Episodes)

Objectives:

The primary objective of this study was to evaluate the PK and comparative bioavailability of apomorphine and its metabolites (apomorphine sulfate and norapomorphine) following single

[19] Mov Disord. 1991;6(3):212-6.
[20] Mov Disord. 1996;11(6):633-8.
[21] BJU International 2001; 88(Suppl. 3), 18-21.
[22] Eur J Pharmacol. 1980; 67: 139-142.
[23] Mov Disord. 1991; 6(3):212-6.

doses of KYNMOBI sublingual thin film with APO-go® and APOKYN® in subjects with PD with motor fluctuations ("OFF" Episodes).

Methodology:

This is ongoing multi-center, phase 2, open-label, randomized, three-way crossover study. Patients in the study underwent an initial screening visit, followed by open-label, randomized, three-way crossover treatment visits (Periods 1, 2, and 3). A washout interval of at least 1 day was required before each treatment period visit.

KYNMOBI and APO-go® dosing in the three-way crossover treatment periods were based on the subjects' current prescribed dose of APOKYN®. APO-go® was administered at the same dose as APOKYN®, and KYNMOBI was administered at an approximate equivalent dose based on PK information from previous studies. The dosing algorithm is depicted in Table 10.

Table 10: Dosing Algorithm.

APOKYN® Current Prescribed Dose (mg)	APO-go® Study Dose (mg)	KYNMOBI Study Dose (mg)
2	2	15
3	3	20
4	4	25
5	5	30

Study Population:

Planned: 12 patients with PD who are currently receiving APOKYN®.
Enrolled and analyzed: a total of 5 subjects have been enrolled and analyzed.

Pharmacokinetics and Statistical Analysis:

Blood draws for PK analyses occurred at t = 0 (just prior to dosing), 15, 30, 45, 60 minutes and at 1.5, 3, and 6 hours after dosing. Plasma PK parameters calculated for apomorphine plasma concentration profiles were calculated using non-compartmental analysis and included: C_{max}, T_{max}, AUC_{last}, $AUC_{0-\infty}$, and t½.

Interim Results:

Interim results from the study are included in this submission and data from 5 out of a planned 12 subjects was available. Based on these 5 subjects, the PK parameters of apomorphine

following the 2 SC formulations were similar (Table 11). The relative bioavailability of KYNMOBI was ~19% (Table 12).

Table 11: Apomorphine Pharmacokinetic Parameters (Interim Data).

Sublingual Apomorphine (KYNMOBI)				**Subcutaneous Apomorphine (APO-go® or APOKYN®)**			
Dose	**C_{max} (ng/mL)**	**T_{max} (h)**	**$AUC_{0-\infty}$ (h*ng/m L)**	**Dose**	**C_{max} (ng/mL)**	**T_{max} (h)**	**$AUC_{0-\infty}$ (h*ng/mL)**
20 mg N=2	5.12	0.75	8.06	**APOKYN® 3 mg N=2**	6.01	0.38	7.35
				Apo-go® 3mg N=2	6.95	0.38	7.97
25 mg N=2*	11.2	0.62	22.5	**APOKYN® 4 mg N=2**	10.3	0.25	16.3
				Apo-go® 3mg N=2	11.5	0.25	15.7
30 mg N=1	10.4	1	15.8	**APOKYN® 5 mg N=1**	11.3	0.5	13.9
				Apo-go® 5 mg N=1	7.18	0.5	11

* Geometric mean. Source: CTH-203 PK report.
Source: CTH-203 PK report.

Table 12: Dose-normalized Comparative Bioavailability (Interim Data).

Test	**Reference**	**C_{max} (N=5)**	**$AUC_{0-\infty}$ (N=5)**
KYNMOBI	APOKYN®	0.15 (56.4%)	0.19 (25%)
KYNMOBI	APO-go®	0.148 (63.1%)	0.196 (34%)
APO-go®	APOKYN®	1.01 (29.7%)	0.972 (13.7%)

AUC: area under concentration-time curve; C_{max}: maximum concentration; CV: coefficient of variation.
Note: Geometric mean (geometric %CV) for both parameters.
Source: CTH-203 interim PK report

Reviewer Comments:

The aim of this study is to establish a bridge between KYNMOBI and the RLD, APOKYN®. While the sponsor conducted study CTH-200 to establish the bridge to the SC APO-go®, a bridge to the

US RLD (APOKYN®) is required. The sponsor is relying on the totality of evidence of the sameness between APOKYN® and APO-go®. The sponsor submitted this interim analysis to support the sameness argument. While no definitive conclusion on the bioequivalence of APOKYN® and APO-go® or the relative bioavailability of the KYNMOBI to APOKYN® could be reached, these interim results together with the results of study CTH-200 and the sameness of APOKYN® and APO-go® (evaluated by the biopharmaceutics review team), could support the PK bridging.

Dose Proportionality

Dose proportionality was evaluated in Study CTH-201. Study CTH-201 was a Phase 2, randomized, double-blind, placebo controlled, 3-period crossover, positive control, QT-evaluation study of KYNMOBI in subjects with PD complicated by motor fluctuations ("OFF" episodes). For more details, please refer to the QT-IRT review for this study. Summary of key apomorphine plasma pharmacokinetic parameters following KYNMOBI SL administration stratified by dose level is presented in Table 13.

Table 13: Summary of Key Apomorphine Plasma Pharmacokinetic Parameters.

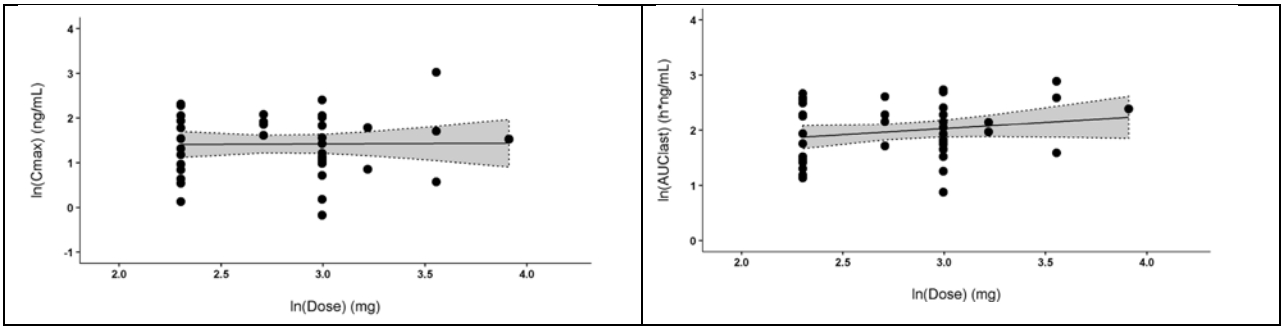
Dose Level	N	C_{max}	AUC_{last}	$AUC_{0-\infty}$
10	14	4.12 (82.9%)	6.67 (61.1%)	7.08 (51.3%)[1]
15	4	6.48 (19.4%)	8.94 (38.1%)	9.21 (38.9%)
20	15	3.44 (78.3%)	6.72 (54%)	7.99 (41.8%)[2]
25	2	3.75 (73%)	NC	7.81 (12.5%)
35	3	5.85 (188%)	10.5 (76.8%)	16.9 (15%)[3]
50	1	4.61 (NC)	10.9 (NC)	13.6 (NC)

[1]N=9; [2]N=6; [3]N=2; NC= not computed.

The sponsor investigated the relationship between apomorphine PK parameters (C_{max}, AUC_{last}, and $AUC_{0-\infty}$) and KYNMOBI dose using the power model. Following natural log-transformation, exposure and dose data were fit by linear regression, with slope representing the power model exponent.

Plots of natural log-transformed C_{max}, AUC_{last}, versus natural log dose of KYNMOBI are presented in Figure 5 .Based on this study, the relationship between plasma apomorphine exposure and KYNMOBI dose was less than dose proportional over the 10 to 50 mg dose range. The point estimates [90% CI] for the exponent were 0.0191 [0.146-0.805] for C_{max} and 0.222 [-0.0951-0.540] for AUC_{last}.

Figure 5: Ln-Ln Plot of Apomorphine Exposure (C_{max}, AUC_{last}) versus KYNMOBI Dose to Assess Dose Proportionality.



Source: CTH-201 PK report

Reviewer Comments:

- *The data suggests that the exposure of apomorphine following KYNMOBI administration (10- 35 mg) is covered by the exposures from APOKYN® (2- 6 mg)[24]. Based on the results of Study CTH-200 and CTH-203, the C_{max}, and $AUC_{0-\infty}$ of apomorphine following KYNMOBI 10 mg is 69%, and 90%, respectively relative to APO-go® 2 mg. Likewise, the C_{max}, and $AUC_{0-\infty}$ of apomorphine following KYNMOBI 35 mg is 33-35%%[25], and 63-78%[26], respectively[27] relative to APO-go® 6 mg.*

4.3 Dose Response

Evidence of dose-efficacy can be concluded based on the dose-response observed in APOKYN® over the dose range of 2-6 mg. Since KYNMOBI exposure over the dose range 10-35 mg does not exceed APOKYN® exposure over the approved dose range, a dose-response is also expected for KYNMOBI®. Additionally, dose-response can be driven from the Titration Phase of Study CTH-300.

[24] The applicant assessed the PK of APO-go® 2 mg (Study CTH-200; N= 19). There is very limited information in this submission regarding the PK of APOKYN®. However, given the sameness of APO-go® and APOKYN® and the dose proportionality of APOKYN®, which was established in the original APOKYN® NDA, the reviewer was able to establish that the lowest and highest dose of KYNMOBI (i.e. 10 and 35 mg, respectively) is capped by APOKYN® lowest and highest approved dose (i.e. 2 and 6 mg, respectively).
[25] Based on Studies CTH-203 and CTH-301
[26] Based on Studies CTH-203 and CTH-301
[27] Assumed a C_{max}, and $AUC_{0-\infty}$ of apomorphine following APO-go® 6 mg to equal 3 times the observed C_{max}, and $AUC_{0-\infty}$ of apomorphine following 2 mg in Study CTH-200.

Study CTH-300 was a randomized, placebo-controlled efficacy study, with initial Screening Visits, followed by an initial Dose Titration Phase in which individual responses (subjects were to be titrated to effect and tolerability) to single doses of KYNMOBI (10 mg to 35 mg) were evaluated in order to determine the initial starting dose for treating "OFF" episodes in an outpatient setting.

Once complete, subjects were randomized to either KYNMOBI or placebo (ratio 1:1) and moved to the Maintenance Treatment Phase of the study, where they self-administered study medication in up to 5 "OFF" episodes per day for 12 weeks in the at-home portion of the study. Subjects returned to the clinic in 4-week intervals for safety and efficacy assessments (including the primary endpoint in-office assessments). The schematic illustration of the study design is presented in Figure 1 (Section 3.3.1).

A total of 141 subjects were exposed to increasing single doses of KYNMOBI (10 mg to 35 mg) in the Dose Titration Phase. The extent of exposure during the Dose Titration Phase is presented in Table 14. The most common highest doses received were 15 mg and 20 mg (24.8% and 22.0% of subjects, respectively).

Table 14: Summary of Extent of Exposure During Titration Phase (Safety Population).

Number of Subjects (%)	Safety Population (N = 141)					
	10 mg	**15 mg**	**20 mg**	**25 mg**	**30 mg**	**35 mg**
Exposed to titration dose[a]	141 (100)	123 (87.2)	88 (62.2)	57 (40.4)	36 (25.5)	20 (14.2)
Highest dose received during dose titration	18 (12.8)	35 (24.8)	31 (22.0)	21 (14.9)	16 (11.3)	20 (14.2)

[a]Each titration dose was given as a single dose.
Source: Study CTH-300 report. Table 14.1.5.1.

Figure 3 (see Section 3.3.2) presents the mean change from pre-dose in MDS-UPDRS III score at 30 min at each titration visit stratified by the highest dose received. Note that for the group that received 10 mg as the highest dose level (N=18), the maximum drop in MDS-UPDRS III score was observed at the first titration visit. For the group that required dose increase, similar drop in MDS-UPDRS III score was eventually achieved at the subsequent visit(s). In other words, within each dose level, as the dose titrated throughout the visits, the reduction in MDS-UPDRS III score at 30 min increases. Some patients require up to 35 mg dosing to reach adequate response.

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