CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210875Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	May 19, 2020
Requesting Office or Division:	Division of Neurology 1 (DN 1)
Application Type and Number:	NDA 210875
Product Name and Strength:	Kynmobi (apomorphine hydrochloride) film, 10 mg, 15 mg, 20 mg, 25 mg and 30 mg
Applicant/Sponsor Name:	Sunovion Pharmaceuticals Inc
OSE RCM #:	2019-2408-1
DMEPA Safety Evaluator:	Ebony Whaley, PharmD, BCPPS
DMEPA Team Leader:	Lolita White, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised carton labeling, Instructions for Use (IFU), and Integrated IFU received on May 18, 2020 for Kynmobi. The Division of Neurology 1 (DN 1) requested that we review the revised carton labeling, IFU, and Integrated IFU for Kynmobi (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The Applicant implemented our recommendations and we have no additional recommendations at this time.

10 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

[a] Whaley E. Human Factors Study Results and Label and Labeling Review for Kynmobi (NDA 210875). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 APR 20. RCM No.: 2019-2407 and 2019-2408.

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

/s/

EBONY A WHALEY
05/19/2020 12:01:41 PM

LOLITA G WHITE
05/19/2020 12:28:48 PM

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: May 13, 2020

From: Interdisciplinary Review Team for Cardiac Safety Studies

Through: Christine Garnett, PharmD
Clinical Analyst
DCN

To: Jack Dan, RPM
DN1

Subject: QT Consult to NDA 210875 (SDN 044)

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

This memo responds to your consult to us dated 5/11/2020 regarding the sponsor's QT related language in the proposed product label. We reviewed the following materials:

- Previous IRT reviews for NDA 210875 dated 09/25/2018 in DARRTS;
- Previous IRT reviews for NDA 21264 dated 07/09/2019 in DARRTS; and
- Proposed label (Submission 0044).

1 Responses for the Division

During our review of the TQT study (CTH-201), we found the results to be inconclusive and cannot be used to exclude a 10-ms mean increase in the QTc interval at the maximum recommended dose of 35 mg (QT-IRT review dated 09/25/2018 in DARRTS). The maximum therapeutic exposure in the current submission is comparable to that in the previous submission. Therefore, we disagree with the sponsor's proposed QT-related language in Section 12.2:

12 CLINICAL PHARMACOLOGY

12.2 Pharmacodynamics

Cardiac Electrophysiology

(b) (4)

One of the major issues with the TQT study was that the selected doses did not cover the exposures associated with clinical dosing regimen. The final dose levels were achieved through individual titrations based on tolerability rather than by randomized treatment assignment. The higher dose groups did not result in higher exposures compared to lower dose groups as would have been expected with linear PK. The mean Cmax across dose levels is ~4 ng/mL, which is inadequate to cover Cmax of the maximum recommended therapeutic dose of 30 mg (~9 ng/ml) [based on Clinical Pharmacology review in DARRTS dated 05/02/2020] that is being considered in the current resubmission. Furthermore, higher exposures are expected in patients with renal impairment (50% higher Cmax with renal impairment). Note that there were too few patients receiving 15 mg and doses above 20 mg (2 for 25 mg, 3 for 35 mg and 1 for 50 mg) to be able to adequately characterize the change in QTc interval at those dose levels.

We note that the RLD, APOKYN, was shown to prolong the QTc interval in a TQT study (see QT-IRT review under NDA 21264 dated 07/09/2019 in DARRTS) and has Warning and Precautions for QT Prolongation in the label. Even though a positive exposure-response was observed in the TQT study submitted under NDA 21264, ΔΔQTc at a given concentration may not be well predicted. Therefore, we cannot use TQT study submitted under APOKYN to exclude a small effect for KYNMOBI.

Thank you for requesting our input into the development of this product. We welcome more discussion with you now and in the future. Please feel free to contact us via email at cderdcrpqt@fda.hhs.gov

---

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

/s/

NAN ZHENG
05/13/2020 08:35:30 AM
Gopichand Gottipati is the primary clinical pharmacology reviewer.

GOPICHAND GOTTIPATI
05/13/2020 08:59:45 AM

CHRISTINE E GARNETT
05/13/2020 09:01:21 AM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: May 6, 2020

To: Dave Podskalny, M.D.
Division of Neurology I (DN I)

Jack Dan, Regulatory Project Manager

Tracy Peters, Associate Director for Labeling, DN I

From: Dhara Shah, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Aline Moukhtara, Team Leader, OPDP

Subject: OPDP Labeling Comments for TRADENAME™ (apomorphine hydrochloride) sublingual film

NDA: 210875

In response to the DN I consult request dated January 22, 2020, OPDP has reviewed the proposed product labeling (PI), Patient Prescribing Information (PPI), Instructions for Use (IFU), and carton and container labeling for the original NDA submission for TRADENAME™ (apomorphine hydrochloride) sublingual film.

PI, PPI, IFU: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DN I (Jack Dan) on April 24, 2020, and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed PPI and IFU was sent under separate cover on May 5, 2020.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on November 21, 2019, and our comments are provided below.

Thank you for your consult. If you have any questions, please contact Dhara Shah at (240) 402-2859 or Dhara.Shah@fda.hhs.gov.

61 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

---

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

/s/

DHARA SHAH
05/06/2020 03:05:30 PM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	May 4, 2020
To:	Jack Dan, Regulatory Project Manager **Division of Neurology I (DN1)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Marcia Williams, PhD Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Maria Nguyen, MSHS, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Dhara Shah, PharmD, RAC Regulatory Review OFficer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI) and Instructions for Use (IFU)
Drug Name (established name):	TRADENAME (apomorphine hydrochloride)
Dosage Form and Route:	sublingual film
Application Type/Number:	NDA 210875
Applicant:	Sunovion Pharmaceuticals, Inc.

1 INTRODUCTION

On November 21, 2019, Sunovion Pharmaceuticals, Inc., submitted for the Agency's review a Class 2 resubmission for New Drug Application (NDA) 210875 for TRADENAME (apomorphine hydrochloride) sublingual film. The proposed indication for TRADENAME (apomorphine hydrochloride) sublingual film is for the acute, intermittent treatment of "OFF" episodes associated with Parkinson's disease. The purpose of this submission is to review recommendations made by, and agreements reached with the Division of Neurology 1 (DN1) during milestone meetings, including the Type A meeting.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Neurology 1 (DN1) on January 23, 2020, for DMPP and on January 22, 2020 for OPDP to review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for TRADENAME (apomorphine hydrochloride) sublingual film.

2 MATERIAL REVIEWED

- Draft TRADENAME (apomorphine hydrochloride**)** PPI and IFU received on November 21, 2019, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on April 24, 2020.
- Draft TRADENAME (apomorphine hydrochloride**)** Prescribing Information (PI) received on November 21, 2019, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on April 24, 2020.
- Approved APOKYN (apomorphine hydrochloride) comparator labeling dated December 3, 2019.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the PPI and IFU document using the Arial font, size 10.

In our collaborative review of the PPI and IFU we:

- simplified wording and clarified concepts where possible
- ensured that the PPI and IFU are consistent with the Prescribing Information (PI)

- removed unnecessary or redundant information
- ensured that the PPI and IFU are free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI and IFU meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the PPI and IFU are consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The PPI and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI and IFU are appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI and IFU.

Please let us know if you have any questions.

14 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

---

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

/s/

MARIA T NGUYEN
05/04/2020 07:06:18 PM
DMPP-OPDP review of TRADENAME (apomorphine HCL) NDA 210875 PPI and IFU

DHARA SHAH
05/05/2020 09:46:49 AM

MARCIA B WILLIAMS
05/05/2020 09:51:26 AM

LASHAWN M GRIFFITHS
05/05/2020 10:14:36 AM

HUMAN FACTORS STUDY REPORT AND LABELS AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	April 20, 2020
Requesting Office or Division:	Division of Neurology 1 (DN1)
Application Type and Number:	NDA 210875
Product Type:	Single-ingredient
Drug Constituent Name and Strength	Apomorphine hydrochloride sublingual film, 10 mg, 15 mg, 20 mg, 25 mg and 30 mg
Rx or OTC:	Rx
Applicant/Sponsor Name:	Sunovion Pharmaceuticals Inc
Submission Date:	November 21, 2019; February 3, 2020; March 10, 2020
OSE RCM #:	2019-2407; 2019-2408
DMEPA Safety Evaluator:	Ebony Whaley, PharmD, BCPPS
DMEPA Team Leader:	Lolita White, PharmD
DMEPA Associate Director for Human Factors:	QuynhNhu Nguyen, MS
DMEPA Associate/Deputy Director:	Danielle Harris, PharmD

1. REASON FOR REVIEW

This review evaluates the human factors (HF) validation study results and labels and labeling submitted as part of the 505(b)(2) submission under NDA 210875 for apomorphine hydrochloride sublingual film for areas of vulnerability that may lead to medication errors.

1.1. PRODUCT DESCRIPTION

Apomorphine hydrochloride sublingual film is a single-ingredient product intended for acute, intermittent treatment of "OFF" episodes associated with Parkinson's disease (PD) including end-of-dose wearing "OFF" (including early morning "OFF"), partial/delayed/No-ON and unpredictable "OFF". Apomorphine hydrochloride sublingual film is intended for administration by patients, caregivers and healthcare providers (HCPs) in the home or healthcare setting. Apomorphine s hydrochloride sublingual film has been submitted under the 505(b)(2) pathway, and the reference product is Apokyn (NDA 21264).

The Applicant proposes the product be supplied in 30-count cartons and also as a titration kit for patient and caregiver use which will contain a total of 15 individually packaged films of: (3) 10 mg films, (3) 15 mg films, (3) 20 mg films, (3) 25 mg films, and (3) 30 mg films. Both packaging configurations will include child-resistant cartons (e.g. (b) (4) packaging). (See Appendices A and F).

1.2. REGULATORY HISTORY RELATED TO THE PROPOSED PRODUCT'S HUMAN FACTORS DEVELOPMENT PROGRAM

On March 29, 2018, the Applicant submitted an HF validation study results report as part of their initial 505(b)(2) submission for NDA 210875. We reviewed the HF validation study results and noted several use errors and close calls that occurred on critical tasks. We also noted that the Applicant implemented revisions to the labeling in response to the use errors and close calls but did not validate the revisions. Additionally, our review identified areas of vulnerability in the labels and labeling that may lead to medication errors, and we recommended additional labeling revisions. Our review of the HF validation study results also noted a study methodology concern: the user interface used in the HF validation study did not include the intend-to-market carton packaging (i.e. (b) (4) packaging). Overall, we determined the HF validation study methodology was deficient and the results did not demonstrate that the intended users can use the proposed product safely and effectively for the intended uses. As such, we recommended that the Applicant complete an additional HF validation study to support that the intended users can safely and effectively use the intend-to-market product.

Subsequently, NDA 210875 received a Complete Response (CR) on January 29, 2019 due to the aforementioned HF deficiencies and also due to clinical pharmacology, biopharmaceutics, and safety deficiencies.

On February 27, 2019, the Applicant submitted their HF validation study protocol for an additional HF validation study to address our previously identified concerns, and we provided recommendations to the Applicant.[a] On November 21, 2019, the Applicant submitted the results of the HF validation study testing as part of a Class 2 resubmission for NDA 210875 which is the focus of this review.

2. MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide our findings and evaluation of each material reviewed.

Table 1. Materials Considered for this Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Background Information Previous HF Reviews (DMEPA and CDRH)	B
Background Information on Human Factors Engineering (HFE) Process	C
Human Factors Validation Study Report	D
Information Requests Issued During the Review	E
Labels and Labeling	F

[a] Whaley E. Human Factors Protocol Review for apomorphine hydrochloride IND 110955. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 MAY 15. RCM No.: 2019-671.

3. OVERALL ASSESSMENT OF MATERIALS REVIEWED

The sections below provide a summary of the study design, errors, use difficulties, and close calls observed (Table 2), and our analysis to determine if the results support the safe and effective use of the proposed product.

3.1 SUMMARY OF STUDY DESIGN

The Applicant submitted the results from two HF validation studies as part of this NDA submission. The studies included similar use tasks; however, there was variability in the user interface.

In the first study, the Applicant provided the regular instructions for use (IFU) in the carton and an IFU specific to opening the child-resistant (CR) packaging was available on the study table. The HF validation study included 90 study participants: 30 patients with PD (15 untrained and 15 trained), 30 lay caregivers (15 untrained and 15 trained), and 30 healthcare providers (HCPs) (15 untrained and 15 trained). The HF validation study included the following scenarios: Use Scenario 1 (Opening CR packaging), Use Scenario 2 (full use of the product including opening packaging and administration), and knowledge task questions. Participants were not explicitly instructed to refer to or review either IFU during simulated use testing.

Following the completion of the first HF validation study and based on participant performance and root cause analysis, the Applicant reorganized content and revised the formatting of Steps 1, 6, and 7 of the regular IFU. Additionally, the Applicant determined that instead of supplying the product with a CR packaging IFU, they would supply the product with an Integrated IFU which combined the contents of the product IFU and the CR packaging IFU into one document. The Applicant intends that the Integrated IFU will be supplied as a tear sheet at the pharmacy level and that the regular product IFU will be supplied within the product carton.

In the second study, the goal was to validate the user interface changes implemented following the first study. The Applicant provided the regular IFU supplied in the carton and the Integrated IFU supplied on the study table. The second study (also referred to as the supplemental HF validation study) included 30 study participants: 10 patients with PD (5 untrained and 5 trained), 10 lay caregivers (5 untrained and 5 trained), and 10 HCPs (5 untrained and 5 trained). The supplemental HF validation study only included Use Scenario 2.

3.2 RESULTS AND ANALYSES

Table 2 describes the study results, Applicant's analyses of the results, and DMEPA's analyses and recommendations.

Table 2: Summary and analyses of errors/close calls/use difficulties with critical tasks during the HF validation study and supplemental study Participants: P – untrained patients, PT – trained patients, C – untrained caregivers, CT – trained caregivers, H – untrained HCPs, HT – trained HCPs				
Critical Tasks	**Number of, Description of, and Participant's Subjective Feedback on Use Errors, Close Calls, and Use Difficulties**	**Applicant's Root Cause Analysis**	**Applicant's Discussion of Mitigation Strategies**	**DMEPA's Analysis and Recommendations**
Use Scenario 1 – HF validation study only (patient participants only - ON state) HF validation study – CR packaging IFU/Quick Guide as tear sheet on the study table and regular IFU in carton				
Depresses child resistant (CR) tabs on carton's side – ON state	*Use difficulty* *n = 1* • One patient participant experienced difficulty simultaneously depressing the CR tabs on the carton's sides. The participant required assistance, explaining that they would cut the carton open with scissors. The participant indicated that that the tabs' offset position required them to stretch their fingers in an unnatural position, thereby compromising their grip strength. *Close call* *n = 1* • One patient participant experienced difficulty with simultaneously depressing the CR tabs on the carton's sides but was able to open the packaging within two minutes. The participant indicated that that the tabs' offset position required them to stretch their fingers in an unnatural position, thereby compromising their grip strength.	• Reliance on users to possess sufficient dexterity to depress tabs.	The Applicant states that despite the use difficulty and close call, both participants were able to open the CR carton and that both participants did not have difficulty opening the CR carton during Use Scenario 2, indicating that once users become familiar with the product, this difficulty is diminished. The Applicant determined that the level of residual risk associated with difficulty of opening the carton has been minimized to the extent possible and is outweighed by the clinical benefit of using the product. Therefore, the Applicant states that no additional mitigation is warranted and is unlikely to improve the level of residual risk.	Based on the Applicant's use-related risk analysis (URRA), failure to open the carton might result in delay in therapy resulting in the user remaining in OFF state or in the user removing the pouching from the carton in a manner that eliminates the child-resistant feature and could result in accidental exposure. Our review of the study results did not identify subjective feedback indicating that the labels and labeling should be improved. We note that two participants were able to open the packaging after initial difficulty. We also note that in Use scenario 1, participants had access to a CR packaging IFU. We note that dexterity concerns are a common clinical manifestation of Parkinson's disease. We also acknowledge and agree with the Applicant's assertion that users who have difficulty opening the CR packaging may seek alternative means to access the medication, such as caregiver assistance.

Table 2: Summary and analyses of errors/close calls/use difficulties with critical tasks during the HF validation study and supplemental study Participants: P – untrained patients, PT – trained patients, C – untrained caregivers, CT – trained caregivers, H – untrained HCPs, HT – trained HCPs				
Critical Tasks	**Number of, Description of, and Participant's Subjective Feedback on Use Errors, Close Calls, and Use Difficulties**	**Applicant's Root Cause Analysis**	**Applicant's Discussion of Mitigation Strategies**	**DMEPA's Analysis and Recommendations**
				Our review of the labels and labeling finds that the Integrated IFU includes instructions regarding how to open the CR packaging. We also note the Integrated IFU states "For assistance with the KYNMOBI child-resistant carton, please ask your care partner for help". However, we note that the CR packaging IFU is intended to be supplied as a tear sheet at the pharmacy level. As such, the user would need to receive and review the CR packaging IFU in order to access the instructions on how to open the CR packaging. To mitigate the risk of users not receiving or reviewing the CR packaging IFU, we recommend including instructions regarding how to open the CR packaging directly on carton itself. **As such, we provide carton labeling recommendation #1 in Section 3.4 below**. Given that this same information was provided to users in the CR packaging IFU in the study environment (e.g. instructions for how to open the CR packaging supplied on study table), in this particular instance, we find that this revision does not require additional HF validation data.

Table 2: Summary and analyses of errors/close calls/use difficulties with critical tasks during the HF validation study and supplemental study Participants: P – untrained patients, PT – trained patients, C – untrained caregivers, CT – trained caregivers, H – untrained HCPs, HT – trained HCPs				
Critical Tasks	**Number of, Description of, and Participant's Subjective Feedback on Use Errors, Close Calls, and Use Difficulties**	**Applicant's Root Cause Analysis**	**Applicant's Discussion of Mitigation Strategies**	**DMEPA's Analysis and Recommendations**
Store materials away from children (ON state)	*Use errors* *n = 2* • Two patient participants did not respond correctly to the associated question. One participant reported that they would store the pouches outside the carton in a box on the bedroom floor because opening the carton with their dexterity impairments was too challenging. The other participant, who required the carton to be cut open, reported that they would store the pouches out of the carton in a kitchen drawer about three feet from the floor. Both participants reported that they do not have young children in their homes, so they did not consider the need to keep the medication away from young children when deciding where they should store it.	• Habit – no children in home environment	The Applicant states that they have taken all reasonable measures to help ensure users understand to keep the proposed product out of the reach of children. The Applicant notes that the IFU includes instruction to keep the product and all medicines out of the reach of children.	Based on the Applicant's URRA, failure to store the product away from children might result in accidental exposure. Our review of the study results did not identify subjective feedback indicating that the labels and labeling should be improved. We note that the participants indicated they would manipulate the CR packaging in a manner that would pose risk to accidental exposure. However, we also note that the participants' incorrect responses may have been due to them not having children in their home environment. Our review of the labels and labeling finds that Integrated IFU and regular IFU include the instruction "Keep TRADENAME and all medicines out of the reach of children". Based on our overall assessment of the study results, participant subjective feedback, and review of the labels and labeling, we have no recommendations for revision to the user interface at this time.
Use Scenario 2 – HF validation study and supplemental validation study				

Table 2: Summary and analyses of errors/close calls/use difficulties with critical tasks during the HF validation study and supplemental study Participants: P – untrained patients, PT – trained patients, C – untrained caregivers, CT – trained caregivers, H – untrained HCPs, HT – trained HCPs				
Critical Tasks	**Number of, Description of, and Participant's Subjective Feedback on Use Errors, Close Calls, and Use Difficulties**	**Applicant's Root Cause Analysis**	**Applicant's Discussion of Mitigation Strategies**	**DMEPA's Analysis and Recommendations**
HF validation study – CR packaging IFU/Quick Guide as tear sheet on the study table and regular IFU in carton Supplemental study – Integrated IFU as tear sheet on the study table and regular IFU in carton				
Retrieves appropriate dose	***Validation study*** *Use errors* *n = 25/90 participants* • **12 participants administered both films at the same time.** Subjective feedback of note included: participants were familiar with taking multiple pills simultaneously; explained that when they need to take multiple pills, they simultaneously administer all of their pills and did not know to administer the films separately because they only read the CR packaging IFU. • **12 participants administered the 15 mg film before the 20 mg film,** rather than taking the film in the order instructed (20 mg then 15 mg). Subjective feedback of note included: participants did not think the administration order was important because it is not important when they administer other medications and did not notice the instruction. • **1 participant only administered the 15 mg film.** The participant chose to administer only the 15 mg film because it was a new medication and he did not want the patient to experience an adverse reaction.	***Validation study*** • Negative transfer – typical practice of administering multiple pills • Referred to CR packaging IFU but did not read IFU • Decoupled instructional materials • Reliance on user to know correct administration order • IFU Step 1 information density • Focus on images rather than text • Habit of looking at IFU • Unique administration order • Negative transfer – application of titration to new medication administration • Test artifact – nervousness	The Applicant states that administering both films at the same time to reach a 35 mg dose may result in a patient receiving their full dose with a slightly higher peak concentration (Cmax). The Applicant notes that the overall cumulative exposure (AUC) is not altered. Regarding administering the films in the incorrect order, the Applicant states the AUC will be similar regardless of the order of film administration. Therefore, the Applicant states the risk to the patient from administering films in the wrong order is negligible. The Applicant states that the residual risk associated with retrieving the appropriate dose is reasonably low in view of the medication's benefits.	Based on the Applicant's URRA, administering both films simultaneously instead of one at a time might result in more adverse events including nausea and vomiting. Additionally, based on the URRA, administering the 15 mg film before the 20 mg film might result in underdose and delay in therapy. During the previous review cycle, we confirmed with the clinical reviewer that the potential harm associated with administering two films at the same time is the increased risk of adverse events such as nausea, vomiting, orthostatic hypotension, and syncope. Regarding administration of the 15 mg film prior to the 20 mg film, the clinical reviewer does not find the clinical impact to be significant. Our review of the study results did not identify subjective feedback indicating that the labels and labeling should be improved. We note that following the validation study, the formatting of IFU Step 1
	Supplemental study *Use errors* *n = 4/30 participants* • **3 participants administered both films at the same time.** • **1 participant administered the 15 mg film before the 20 mg film**. • Subjective feedback of note included: participants explained that when they take multiple pills, they	***Supplemental study*** • Negative transfer – typical practice of administering multiple pills • Integrated IFU Step 4 amount of content • Reliance on user to read IFU regarding correct film administration order.		

Table 2: Summary and analyses of errors/close calls/use difficulties with critical tasks during the HF validation study and supplemental study Participants: P – untrained patients, PT – trained patients, C – untrained caregivers, CT – trained caregivers, H – untrained HCPs, HT – trained HCPs				
Critical Tasks	**Number of, Description of, and Participant's Subjective Feedback on Use Errors, Close Calls, and Use Difficulties**	**Applicant's Root Cause Analysis**	**Applicant's Discussion of Mitigation Strategies**	**DMEPA's Analysis and Recommendations**
	administer them simultaneously and thus did not think the administration order was important for this product. *Use difficulties* *n = 1/30 participants* • **1 participant experienced difficulty determining whether to administer both films at the same time**. The participant said that when they administer other sublingual medications (e.g., Saphris) to patients, she typically administers them simultaneously. Also, they did not notice the direction regarding the administration order due to the relatively large amount of text.	• Unique administration – specific dose administration order		was revised to improve information flow, density, and ease of reading. Our review of the Applicant's RCA and our independent review of the labels and labeling notes that the Integrated IFU Step 4 and regular IFU Step 1 could be revised to indicate that only one film should be administered at a time. **As such, we provide IFU recommendation #1 in Section 3.4 below.** In this particular instance, we find that this revision does not require additional HF validation data to be submitted.
Drinks water and swallows excess water before administering film	***Validation study*** *Use errors* *First film* *n = 27/90 participants* • **27 participants did not drink water or instruct the standard patient (SP) to drink water prior to administering the film**. Subjective feedback of note included: forgot to do so; unfamiliar with sublingual medication; did not think they needed to drink water; mouth already felt moist or SP's mouth was already moist; and did not refer to IFU. *Use errors* *Second film* *n = 25/90 participants* • **25 participants did not drink water or instruct the SP to drink water prior to administering the second film.**	***Validation study*** • IFU Step 1 information density • Placement of direction to repeat steps 2-7 • IFU Step 2 directions appear to be a suggestion • Information density – training • Unfamiliar administration method. • Concluded mouth was sufficiently moist. • Perceived risk of under dose. • Reliance on SP to know to drink water before	The Applicant determined that introducing any further modifications to the IFU might introduce additional errors related to safe and effective use. The Applicant states that while there is a minor underdose risk associated with not drinking water prior to taking the film, the outcome is more desirable compared to not administering product at all. The Applicant concludes that the level of residual risk is acceptable, and additional	Based on the URRA, failure to drink water before administering the film and failure to swallow that excess water before administering the film might result in underdose (e.g. dry mouth may impact the dissolution and absorption). Regarding the clinical impact of underdose, the clinical reviewer noted that errors of administration that would affect absorption (i.e. swallowing too soon, not letting the films dissolve, etc.) would likely result in an underdose, and that in this case, the drug would not be efficacious and would not result in an ON period for the patient.

Table 2: Summary and analyses of errors/close calls/use difficulties with critical tasks during the HF validation study and supplemental study Participants: P – untrained patients, PT – trained patients, C – untrained caregivers, CT – trained caregivers, H – untrained HCPs, HT – trained HCPs				
Critical Tasks	**Number of, Description of, and Participant's Subjective Feedback on Use Errors, Close Calls, and Use Difficulties**	**Applicant's Root Cause Analysis**	**Applicant's Discussion of Mitigation Strategies**	**DMEPA's Analysis and Recommendations**
	Eleven of these participants repeated the same failure as with the first film.	administering each film (study artifact) • Test artifact – nervousness or previous use scenario performance. • Negative transfer – application of knowledge from other dissolving medications	mitigation is not warranted and is unlikely to improve the level of residual risk.	Our review of the study results identified subjective feedback suggesting that the Integrated IFU is text dense and the associated IFU step might be overlooked. We note the Applicant implemented the Agency's previous user interface revisions regarding how to mitigate the risk of failures with this task. Our review of the labels and labeling also notes that the Integrated IFU Step 5 and regular IFU Step 2 include text and a graphic instructing the user to drink water prior to administering the film. However, we find the graphic could be revised to reiterate the intended step. **As such, we provide IFU recommendation #2 in Section 3.4 below.** Because the revision is a reiteration of existing text, we find that this revision does not require additional HF validation data to be submitted.
	Supplemental HF study *Use errors* *First film* *n = 4/30 participants* • **4 participants did not drink water or instruct the SP to drink water prior to administering the first film**. Subjective feedback of note included: forgot to do so; misinterpreted Integrated IFU Step 5's bold text to mean users should drink water prior to administering the film only if they are thirsty; and referred to experience with other similar products. *Use errors* *Second film* *n = 1/30 participants* • **1 participant did not instruct the SP to drink water prior to administering the second film only.**	***Supplemental HF study*** • Less conspicuous text - did not read the text in Integrated IFU Step 5 stating "this helps the film dissolve more easily" because it was not highlighted and seemed unimportant • Information density – training • Concluded mouth was sufficiently moist • Test artifact – nervousness • Negative transfer – application of knowledge from other dissolving medications or experience with Listerine strips		
Depresses CR tabs on carton's side – patients in OFF state	***Validation study*** *Use difficulties* *First film* *n = 15/90 participants*	***Validation study*** • Reliance on users to possess sufficient dexterity to depress tabs	The Applicant states that the residual risk of users experiencing difficulty depressing the tabs on the	Based on the Applicant's URRA, failure to open the carton might result in delay in therapy or in the user removing the pouch from the

Table 2: Summary and analyses of errors/close calls/use difficulties with critical tasks during the HF validation study and supplemental study Participants: P – untrained patients, PT – trained patients, C – untrained caregivers, CT – trained caregivers, H – untrained HCPs, HT – trained HCPs				
Critical Tasks	**Number of, Description of, and Participant's Subjective Feedback on Use Errors, Close Calls, and Use Difficulties**	**Applicant's Root Cause Analysis**	**Applicant's Discussion of Mitigation Strategies**	**DMEPA's Analysis and Recommendations**
	• 15 participants experienced difficulty depressing the CR tabs on the carton's side while opening the first carton. Specifically, 5 of these 15 participants reported that when attempting to depress the tabs, the carton's edges near the tabs become worn down (i.e., softened). As such, when they continued to attempt to open the CR packaging, the carton became continually worn down, so it was more challenging to open. *Use difficulties* *Second film* *n = 5/90 participants* • 4 participants experienced the same difficulty as with the first carton. • 1 participant experienced difficulty depressing the CR tabs on the carton's side while opening the second carton only.	• Participants said CR packaging carton edges become worn down under pressure. • Inconspicuous "Push" text and arrows. • Inconspicuous tabs. • CR packaging affords users to bend tabs along the carton's outer edge. • Reliance on users to know to depress tabs and pull the tray simultaneously.	CR carton's side is reasonably low in view of the medication's benefits. The Applicant noted the study results indicate that once the users are familiarized with the product, this difficulty is diminished. The Applicant also noted that all participants could open the CR carton within 2 minutes. In response to the Agency's March 4, 2020 Information Request, the Applicant indicated that "...packaging similar to that of the intend-to-market carton evaluated in the HF validation study and the HF supplemental study has been utilized in the real world for several years. At least 40 million (b) (4) packages have been distributed since 2014 of which one is a commercial prescription medication containing 56 dose units. To date, the packaging manufacturer has not received any negative feedback regarding an	carton in a manner that eliminates the child-resistant feature and could result in accidental exposure. We acknowledge that users were able to overcome initial difficulty with this task. We also note that user performance improved in the supplemental study as compared to the validation study. Additionally, we note that in Use Scenario 1 where users were in the ON state, there was improved user performance. This suggests that users who have difficulty opening the CR packaging in the OFF state may have improved performance in the ON state. Our review of the study results did not identify subjective feedback indicating that the labels and labeling should be improved. However, we note feedback indicating that the tabs on the carton can become worn after multiple uses, which may further complicate opening the packaging. Our review of the labels and labeling finds that the Integrated IFU includes instructions regarding how to open the CR packaging. We
	Supplemental study *Use difficulties* *First film* *n = 3/30 participants* • 3 participants experienced difficulty depressing the CR tabs on the carton's side while opening the first carton only. Two of the participants explained that the tabs' offset position compromised their grip strength and made it difficult to depress. Additionally, the third participant reported that when attempting to depress the tabs, the carton's edges near the tabs become worn down and more challenging to open. One of the three participants also thought Integrated IFU Figure C was instructing her to depress the sides of the carton rather than the tabs because the tabs are not visible in Figure	***Supplemental study*** • Reliance on users to possess sufficient dexterity to depress tabs • CR packaging carton edges become worn down under pressure • Inconspicuous tabs		

Table 2: Summary and analyses of errors/close calls/use difficulties with critical tasks during the HF validation study and supplemental study Participants: P – untrained patients, PT – trained patients, C – untrained caregivers, CT – trained caregivers, H – untrained HCPs, HT – trained HCPs				
Critical Tasks	**Number of, Description of, and Participant's Subjective Feedback on Use Errors, Close Calls, and Use Difficulties**	**Applicant's Root Cause Analysis**	**Applicant's Discussion of Mitigation Strategies**	**DMEPA's Analysis and Recommendations**
	C. Further, she reportedly did not notice the carton's tabs because of they are clear.		inability of the distributed packages to withstand multiple openings and reclosures for the duration the package requires." The Applicant determined that the residual risk associated with difficulty of opening the child resistant carton has been minimized to the extent possible and is outweighed by the clinical benefit of using the product. Therefore, the Applicant states that additional mitigation is not warranted and is unlikely to improve the level of residual risk.	note that the proposed (b) (4) packaging is also used for a currently marketed product (i.e. Mavenclad). However, as stated above, we find the CR packaging carton labeling could be revised by including instructions regarding how to open the CR packaging. **As such, we provide carton labeling recommendation #1 in Section 3.4 below**. As previously noted, we find that this revision does not require additional HF validation data. Additionally, we find that the Integrated IFU could be revised to depict the clear plastic tabs on the CR packaging. **As such, we provide IFU labeling recommendation #3 in Section 3.4 below.** In this particular instance, we find that this revision does not require additional HF validation data be submitted.
Removes film from pouch (OFF state)	***Validation study*** *Use difficulties* *First film* *n = 8/90 participants* • 8 participants experienced difficulty opening the pouch. Subjective feedback of note included: used their stronger hand to pull the pouch tab and tore the pouch down the center; dexterity impairments resulted in them having difficulty gripping the pouch tabs; and "Pull Here" text combined with the upward pointing arrows	***Validation study*** • Reliance on users to pull the right pouch tab away from their bodies. • Reliance on users to possess sufficient dexterity to pull the tabs apart • Ambiguous "Pull Here" text and arrows.	The Applicant states that the residual risk of users experiencing difficulty removing film from pouch is reasonably low. The Applicant notes that there was improved user performance with the second pouch, indicating that once the users are	Based on the Applicant's URRA, failure to open the pouch might result in delay in therapy. Our review of the study results identified subjective feedback indicating user confusion with the "Pull Here" text on the foil pouch. However, we note that users were able to overcome initial difficulty.

Table 2: Summary and analyses of errors/close calls/use difficulties with critical tasks during the HF validation study and supplemental study Participants: P – untrained patients, PT – trained patients, C – untrained caregivers, CT – trained caregivers, H – untrained HCPs, HT – trained HCPs				
Critical Tasks	**Number of, Description of, and Participant's Subjective Feedback on Use Errors, Close Calls, and Use Difficulties**	**Applicant's Root Cause Analysis**	**Applicant's Discussion of Mitigation Strategies**	**DMEPA's Analysis and Recommendations**
	on the tabs resulted in them thinking that they should peel open each pouch tab's top to access the medication *Use difficulties* *Second film* *n = 2/90 participants* • 2 participants experienced difficulty opening the pouch (also had difficulty with first film).		familiarized with the product, this difficulty is diminished. The Applicant also noted that during the supplemental study, the participant who failed the task tried to peel off the "Pull Here" sticker to access the medication. However, the marketed film pouch will have the "Pull Here" text printed on to the pouch instead of the "Pull Here" sticker; as such, they find that this issue will not occur in real world (study artifact). The Applicant determined that the level of residual risk associated with difficulty of removing film from pouch has been minimized to the extent possible and is outweighed by the clinical benefit of using the product and that additional mitigation is not warranted and is unlikely to improve the level of residual risk.	Our review of the labels and labeling finds that the Integrated IFU and regular IFU include instructions and a graphic regarding how to open the foil pouch. Based on our overall assessment of the study results, participant subjective feedback, and review of the labels and labeling, we have no recommendations for revision to the user interface at this time.
	Supplemental study *Use difficulties* *First film* *n = 1/30 participants* • 1 participant reported that the pouch tab's "Pull Here" text combined with the downward pointing arrows on the "Pull Here" sticker resulted in her thinking that she should peel off the "Pull Here" sticker to access the medication	***Supplemental study*** • Ambiguous "Pull Here" text and arrows		

Table 2: Summary and analyses of errors/close calls/use difficulties with critical tasks during the HF validation study and supplemental study Participants: P – untrained patients, PT – trained patients, C – untrained caregivers, CT – trained caregivers, H – untrained HCPs, HT – trained HCPs				
Critical Tasks	**Number of, Description of, and Participant's Subjective Feedback on Use Errors, Close Calls, and Use Difficulties**	**Applicant's Root Cause Analysis**	**Applicant's Discussion of Mitigation Strategies**	**DMEPA's Analysis and Recommendations**
Does not cut/break/chew film in half	***Validation study*** *Use errors* *n = 7/90 participants* • 4 participants broke the film in half when they tore the foil pouch open. Two of these participants did not administer all pieces of the film. • 1 participant broke the film while attempting to fit the first film under the SP's tongue. • 1 participant broke the first film when removing the film from the pouch. The participant picked up most pieces of the film but did not administer a 2 - 5mm wide piece. • 1 participant accidentally dropped the second film when opening the foil pouch, causing a small 2 - 5mm wide piece to break off of the film. The participant did not administer the piece that broke off the film.	• "Take whole" instructions decoupled from administration steps. • Reliance on user to understand ramifications of broken or incomplete film. • Reliance on user to know film size.	The Applicant states that there is an acceptably low residual risk associated with administering a ripped film and that the action itself poses no risk of personal injury. However, the Applicant notes that this use error can lead to underdose if the user does not administer all pieces of the ripped film. The Applicant states that not administering a small piece of the second film (estimated 2-5 mm) would result in ~5%-15% under dose and the patient would have received ~85%-95% of the prescribed 35 mg dose. The Applicant determined that they have taken all reasonable measures to help ensure users understand proper administration technique. The Applicant also determined that while there is a minor under dose risk associated with administering a ripped film, the outcome is more desirable compared to not	Based on the Applicant's URRA, cutting, breaking, or chewing the film in half might result in underdose. As previously noted, the clinical reviewer determined that in the case of underdose, the drug would not be efficacious and would not result in an ON period for the patient. Our review of the study results did not identify subjective feedback indicating confusion with the labels and labeling. Our review of the labels and labeling finds that the Integrated IFU and regular IFU include the statement "TRADENAME must be taken whole. Do not cut, chew, or swallow TRADENAME" in the Important Product Information section. We also note the film pouch label states "Do not cut, chew or swallow". However, we note the IFU could be improved to indicate that that users should administer the entire film and should administer a broken film. **As such, we provide IFU recommendations #4 and #5 in Section 3.4 below.** In this particular instance, we find that this revision
	Supplemental study *Use errors* *n = 1/30 participants* • 1 participant broke the second film when removing the film from the pouch. This participant did not administer a small piece (about 2-5 mm wide). The participant noticed the instruction to administer the film whole but was unconcerned with missing a small piece of the film because based on her clinical judgement, she reportedly determined that a small amount of missing medication would not significantly impact treatment.	***Supplemental study*** • Reliance on user to understand ramifications of incomplete film		

Table 2: Summary and analyses of errors/close calls/use difficulties with critical tasks during the HF validation study and supplemental study Participants: P – untrained patients, PT – trained patients, C – untrained caregivers, CT – trained caregivers, H – untrained HCPs, HT – trained HCPs				
Critical Tasks	**Number of, Description of, and Participant's Subjective Feedback on Use Errors, Close Calls, and Use Difficulties**	**Applicant's Root Cause Analysis**	**Applicant's Discussion of Mitigation Strategies**	**DMEPA's Analysis and Recommendations**
			administering any product. Accordingly, the Applicant concluded that the level of residual risk is acceptable and additional mitigation is not warranted and is unlikely to improve the level of residual risk.	does not require additional HF validation data.
Places film fully under tongue	***Validation study*** *Use errors* *First film* *n = 16/90 participants* • 8 participants placed the film on top of their tongue. Of note, a subset of these participants also administered two films simultaneously. • 8 participants did not place the first film fully under the tongue. • Subjective feedback of note included: were not looking in a mirror; area under the tongue too small; did not read the IFU; and familiar with other similar dosage forms. *Second film* *n = 10/90 participants* • 8 participants did not place the second film fully under the tongue (including 4 participants who repeated the same failure as with the first film) • 2 participants repeated same failure as with first film by placing film on top of tongue	• Mouth size impacts proper film placement • Dexterity impairments impact proper film placement • Reliance on users to determine proper film placement • Reliance on users to understand importance of keeping film under tongue • Reliance on users to know the film should be placed "close to the base" of the tongue • Test artifact – uncomfortable administering treatment to unfamiliar person.	The Applicant states that there is an acceptably low residual risk associated with not placing the film fully under the tongue. The Applicant noted that the user errors may result in under dose as it may impact the absorption of apomorphine. The Applicant noted that they have taken all reasonable measures to help ensure users understand proper administration technique. The Applicant also stated that introducing any further modifications to the IFU and integrated instructions might introduce additional errors related to safe and effective use. The Applicant determined that the level of residual risk is acceptable and additional	Based on the Applicant's URRA, failure to place the film fully under the tongue might result in underdose. As previously noted, the clinical reviewer determined that in the case of underdose, the drug would not be efficacious and would not result in an ON period for the patient. Our review of the study results did not identify subjective feedback indicating confusion with the labels and labeling or specific areas of the labels and labeling that could be improved upon. We also note that some participants indicated that that mouth size made it difficult for them to place the film fully under the tongue. Our review of the labels and labeling finds that the Integrated IFU Step 8 and regular IFU Step 5 includes instruction and a graphic
	Supplemental study *Use errors* *First film*	***Supplemental study*** • Mouth size impacts proper film placement		

Table 2: Summary and analyses of errors/close calls/use difficulties with critical tasks during the HF validation study and supplemental study Participants: P – untrained patients, PT – trained patients, C – untrained caregivers, CT – trained caregivers, H – untrained HCPs, HT – trained HCPs				
Critical Tasks	**Number of, Description of, and Participant's Subjective Feedback on Use Errors, Close Calls, and Use Difficulties**	**Applicant's Root Cause Analysis**	**Applicant's Discussion of Mitigation Strategies**	**DMEPA's Analysis and Recommendations**
	n = 6/30 participants • 3 participants did not place both films fully under the tongue • 2 participants did not keep both films fully under the tongue (i.e. moved the film with their tongue) • 1 participant placed both films on top of their tongue • Subjective feedback of note included: participants reported that the area under the tongue was too small so they were not able to accurately place the film in the correct position; moved the film with their tongue because they thought it would break up the film, helping it dissolve more quickly *Use errors* *Second film* *n = 7/30 participants* • 6 participants repeated the same error as with the first film • 1 participant did not place the second film fully under the tongue	• Negative transfer – experience with Listerine strips	mitigation is not warranted and is unlikely to improve the level of residual risk.	instructing users to place the film under the tongue. We also note the Applicant has revised these IFU steps since our previous review (e.g. implemented our recommendations for revision and validated their post-validation revisions). Based on our overall assessment of the study results, participant subjective feedback, and review of the labels and labeling, we have no recommendations for revision to the user interface at this time.
Does not swallow saliva	***Validation study*** *Use errors* *First film* *n = 50/90 participants* • **50 participants swallowed their saliva or did not instruct the SP not to swallow their saliva when administering the first film**. Regarding subjective feedback, several participants indicated that they relied on the SP to know not to swallow their saliva (study artifact). Other subjective feedback of note included: could not overcome natural reflex to swallow; referred to previous experience with similar dosage forms; and	• IFU Step 6's (b) (4) statement appears to be a suggestion • IFU Step 6's inconspicuous (b) (4) statement • IFU Step 5 appears as the final mechanical administration step • Film pouch instructions do not indicate not to swallow while the film dissolves	The Applicant states that the residual risk associated with users swallowing saliva while the film is dissolving is reasonably low. Th Applicant states the associated risk of swallowing saliva prematurely is that it might interfere with film dissolution and as a result the patient might not receive	Based on the Applicant's URRA, if the patient swallows their saliva before the film completely dissolves there is risk for underdose. As previously noted, the clinical reviewer determined that underdose, the drug would not be efficacious and would not result in an ON period for the patient. Our review of the study results identified subjective feedback the

Table 2: Summary and analyses of errors/close calls/use difficulties with critical tasks during the HF validation study and supplemental study Participants: P – untrained patients, PT – trained patients, C – untrained caregivers, CT – trained caregivers, H – untrained HCPs, HT – trained HCPs				
Critical Tasks	**Number of, Description of, and Participant's Subjective Feedback on Use Errors, Close Calls, and Use Difficulties**	**Applicant's Root Cause Analysis**	**Applicant's Discussion of Mitigation Strategies**	**DMEPA's Analysis and Recommendations**
	assumed that the (b) (4) statement in IFU Step 6 was not important to mention because it was not bold. *Use errors* *Second film* *n = 55/90 participants* • **55 participants swallowed their saliva or did not instruct the SP not to swallow their saliva when administering the second film**. Of these, 43 participants were repeat failures (i.e. committed same failure with first film). Of note, several participants indicated that they relied on the SP to know not to swallow or thought the SP would remember the instruction they gave with the first film (study artifact). ***Supplemental study*** *Use errors*	• Reliance on users to know not to swallow saliva • Clinical judgement – knowledge of PD patients • Judgement – SP did not have excess saliva. • Inherent difficulty of judging when the film is dissolved • Natural reflex to swallow when saliva pools in mouth. • Reliance on SP to know not to swallow based on instruction during first film administration or because medication is in sublingual form (study artifact) • Reliance on SP to know not to swallow based on instruction to let film dissolve in mouth (study artifact) • Negative transfer – application of knowledge from other dissolving medications, experience swallowing all other medications, or experience with Listerine strips • Test artifact – SP knew proper film administration • Test artifact – nervousness. ***Supplemental study***	the full dose but would not result in injury to the patient. The Applicant notes improvements that have been made to the corresponding IFU step over the course of HF development. Additionally, the Applicant states that patient swallowing saliva while waiting for the film to dissolve is beyond their control as swallowing saliva is a natural reflex and patients with PD are prone to have salivary problem including increased salivation and increased difficulty with controlling the involuntary urge to swallow. As such, the Applicant concludes that the residual risk associated with swallowing saliva while the film is dissolving is acceptable and that the IFU and integrated instructions have been modified to the most reasonable extent possible.	labels and labeling could be improved upon. Specifically, participants noted that certain information in IFU Step 5 and 6 could be improved to increased prominence or improve phrasing. We also note that several study failures may be attributed to study artifact and the use of the SP. We also note that these participants did not swallow the film. Our review of the labels and labeling finds that the Integrated IFU (b) (4) Based on the overall assessment of the study results, participant subjective feedback, and review of the labels and labeling, we have no recommendations for revision to the user interface at this time.

Table 2: Summary and analyses of errors/close calls/use difficulties with critical tasks during the HF validation study and supplemental study Participants: P – untrained patients, PT – trained patients, C – untrained caregivers, CT – trained caregivers, H – untrained HCPs, HT – trained HCPs				
Critical Tasks	**Number of, Description of, and Participant's Subjective Feedback on Use Errors, Close Calls, and Use Difficulties**	**Applicant's Root Cause Analysis**	**Applicant's Discussion of Mitigation Strategies**	**DMEPA's Analysis and Recommendations**
	First film *n = 10/30 participants* • 8 participants swallowed their saliva or did not instruct the SP not to swallow their saliva when administering the film. • 2 participants swallowed their saliva or did not instruct the SP not to swallow his or her saliva when administering both films at the same time. • Subjective feedback of note included: natural reflex to swallow and reliance on SP. *Use errors* *Second film* *n = 15/30 participants* • 8 participants repeated the same use error as with the first film. • 7 participants swallowed their saliva or did not instruct the SP not to swallow their saliva only when administering the second film.	• Reliance on SP to know not to swallow based on instruction during first film administration or instruction to keep tongue down and/or not to move mouth • Natural reflex to swallow when object is in mouth or when saliva pools in mouth • Personal judgement – personal knowledge of PD patient • Reliance on SP to know not to swallow because medication is in the form of sublingual film • Reliance on users to know how sublingual film is absorbed • Cognitive load – unfamiliar administration method • Test artifact – SP knew proper film administration; nervousness		
Does not drink water while the film is dissolving	***Validation study*** *Use errors* *First film* *n = 5/90 participants* • 3 participants drank water immediately after administering the film(s).	***Validation study*** • IFU Step 7 non-specific time range for film dissolution • Negative transfer – typical practice of drinking water after administering medication	The Applicant states that there is an acceptably low residual risk associated with drinking water before the film is completely dissolved and that the action itself poses no risk of personal	Based on the Applicant's URRA, if a user drinks water before the film fully dissolves, there is risk of underdose. As previously noted, the clinical reviewer determined that underdose, the drug would not

Table 2: Summary and analyses of errors/close calls/use difficulties with critical tasks during the HF validation study and supplemental study Participants: P – untrained patients, PT – trained patients, C – untrained caregivers, CT – trained caregivers, H – untrained HCPs, HT – trained HCPs				
Critical Tasks	**Number of, Description of, and Participant's Subjective Feedback on Use Errors, Close Calls, and Use Difficulties**	**Applicant's Root Cause Analysis**	**Applicant's Discussion of Mitigation Strategies**	**DMEPA's Analysis and Recommendations**
	• 2 participants drank water before the first film was dissolved, but at least two minutes after administering the film. • Subjective feedback of note included: film was taking longer than 2 minutes to dissolve and thought moistening their or the SP's mouth with water would help the film dissolve fully and applied their knowledge of drinking water immediately after administering their current medication. *Use errors* *Second film* *n = 4/90 participants* • 1 participant drank water immediately after administering the film. • 3 participants drank water before the second film was dissolved, but at least two minutes after administering the film.	• Decoupled instructional materials	injury. The Applicant indicates that as the patient swallows some drug with the water, the drug will travel to the stomach where it will have no appreciable biological effect due to first pass metabolism, the patient will not receive full dose. However, the Applicant notes that since the film still remains under the tongue, most of the drug will continue to be absorbed through the tongue. The Applicant states they have taken all reasonable measures to help ensure users understand proper administration technique. As such, the Applicant Sunovion asserts that they have modified the IFU and the integrated instructions to the most reasonable extent possible and concludes that the level of residual risk is acceptable.	be efficacious and would not result in an ON period for the patient. Our review of study results did not identify subjective feedback indicating user confusion with the labels and labeling. Our review of the labels and labeling finds that the Integrated IFU and regular IFU indicates that the instructions do not explicitly indicate that users should not drink water while the film is dissolving. However, we note the IFU labeling instructs users not to chew or swallow film or swallow their saliva and to keep the film in place until it has completely dissolved. Based on the overall assessment of the study results, participant subjective feedback, and review of the labels and labeling, we have no recommendations for revision to the user interface at this time.
	Supplemental study *Use errors* *First film* *n = 1/30 participants* • 1 participant drank water immediately after administering the film. The participant attributed the use error to unfamiliarity with sublingual medications due to lack of concentration during the product evaluation session as a result of their PD symptoms. *Use errors* *Second film* *n = 1/30 participants*	***Supplemental study*** • IFU Cognitive load – unfamiliar administration method		

Table 2: Summary and analyses of errors/close calls/use difficulties with critical tasks during the HF validation study and supplemental study Participants: P – untrained patients, PT – trained patients, C – untrained caregivers, CT – trained caregivers, H – untrained HCPs, HT – trained HCPs				
Critical Tasks	**Number of, Description of, and Participant's Subjective Feedback on Use Errors, Close Calls, and Use Difficulties**	**Applicant's Root Cause Analysis**	**Applicant's Discussion of Mitigation Strategies**	**DMEPA's Analysis and Recommendations**
	• 1 participant repeated the same use error as with the first film.			
Wait for film to dissolve	***Validation study*** *Use errors* *First film* *n = 56/90 participants* • 36 participants determined the first film was fully dissolved before it was actually dissolved. • 20 participants did not check for film to be dissolved. • Subjective feedback of note included: 16 participants explained that IFU Steps 6 and 7 do not explicitly state or show what "completely dissolved" looks like, 8 participants could not see any film in their mouth or the SP's mouth and determined the film was fully dissolved, and 9 patient participants explained that they determined that the film was dissolved based on what they could feel in their mouth and therefore did not think that they had to visually confirm the film was dissolved. *Use errors* *Second film* *n = 40/90 participants* • 28 participants repeated the error of prematurely determining the film was dissolved. • 18 participants repeated error of not checking check for film to be dissolved. • 8 participants determined the second film only was fully dissolved before it was actually dissolved. • 4 participants did not check for the second film only to be dissolved.	***Validation study*** • IFU Steps 6 and 7 ambiguity regarding mouth feel or appearance when film is completely dissolved • Reliance on training – incorrect description of "completely dissolved" from trainer • IFU Step 7 non-specific time range for film dissolution • Cognitive load – unfamiliar administration method • Negative transfer— experience with Listerine strips • Impression film was dissolved based on feeling • Confidence in personal judgement • IFU Step 7 non-specific time range for film dissolution • IFU Step 7 not associated with an image • Decoupled instructional materials • Personal judgement – expectation that film would continue to dissolve	The Applicant states that there is an acceptably low residual risk associated with users not waiting for the film to complete dissolve. The Applicant noted that the dissolution time of the proposed product was measured during CTH-300 in-clinic dosing. The results show that the film fully dissolved within 3 minutes 70% of the time. Therefore, most participants who waited for the film to dissolve for about 3 minutes would have received full dose or most of the prescribed dose. Following the supplemental study, the Applicant did not recommend additional mitigations.	Based on the Applicant's URRA, if a user does not wait for the film to fully dissolve, there is risk of underdose. As previously noted, the clinical reviewer determined that underdose, the drug would not be efficacious and potentially would not result in an ON period for the patient. Following the HF validation study, we note that the dissolution wait time was revised (b) (4) to 3 minutes and that the associated IFU step was revised to include bolding and reorganized content. These revisions were tested in the supplemental study. Our review of the labels and labeling finds that the Integrated IFU and regular IFU indicates that users are instructed to "Visually check if the film completely dissolves, if possible" and also that film dissolution can take "about 3 minutes". Based on the overall assessment of the study results, participant

Table 2: Summary and analyses of errors/close calls/use difficulties with critical tasks during the HF validation study and supplemental study Participants: P – untrained patients, PT – trained patients, C – untrained caregivers, CT – trained caregivers, H – untrained HCPs, HT – trained HCPs				
Critical Tasks	**Number of, Description of, and Participant's Subjective Feedback on Use Errors, Close Calls, and Use Difficulties**	**Applicant's Root Cause Analysis**	**Applicant's Discussion of Mitigation Strategies**	**DMEPA's Analysis and Recommendations**
		• Test artifact – SP instead of actual patient, discomfort, discretion. • Negative transfer – application of knowledge of similar medication. • Habit – reliance on pharmacy or reliance on patient.		subjective feedback, discussion with the clinical reviewer, and review of the labels and labeling, we have no recommendations for revision to the user interface at this time.
	Supplemental study *Use errors* *First film* *n = 16/30 participants* • 14 participants determined the first was fully dissolved before it was actually dissolved • 2 participants did not check for the first film to be dissolved. • Subjective feedback of note included that some participants stated that the film should be "completely dissolved," but it does not explicitly state or show what "completely dissolved" looks like and that Integrated IFU Step 10's "about 3 minutes" text indicates that it should not take much more than 3 minutes for the film to dissolve, resulting in them not waiting more than 3 minutes for the film to dissolve. *Use errors* *Second film* *n = 13/30 participants* • 12 participants repeated the same failure of determining the film was dissolved before it actually was.	***Supplemental study*** • Integrated IFU Steps 9 and 10 ambiguity regarding mouth feel or appearance when film is completely dissolved – participants either though remaining residue was acceptable or could not see any remaining film/residue • Integrated FU Step 10 non-specific time range for film dissolution – participants did not wait more than 3 minutes for the film to dissolve • Impression film was dissolved based on feeling – could no longer feel the film • IFU Step 10 not associated with an image - did not see the instruction in Integrated IFU Step 10 to visually check		

Table 2: Summary and analyses of errors/close calls/use difficulties with critical tasks during the HF validation study and supplemental study Participants: P – untrained patients, PT – trained patients, C – untrained caregivers, CT – trained caregivers, H – untrained HCPs, HT – trained HCPs				
Critical Tasks	**Number of, Description of, and Participant's Subjective Feedback on Use Errors, Close Calls, and Use Difficulties**	**Applicant's Root Cause Analysis**	**Applicant's Discussion of Mitigation Strategies**	**DMEPA's Analysis and Recommendations**
	• 1 participant repeated the failure of not checking if the film was dissolved.	that the film was dissolved because he focused on the images • Assumed test administrator was timing film dissolution (study artifact)		
Store material away from children (OFF State) Also assessed in Use scenario 1	***Validation study*** *Use error* *n = 1* • 1 participant reported that she would store the pouches outside the carton in a box on her bedroom's floor because opening the carton with her dexterity impairments was too challenging.	• Habit – No children in home environment. Participant explained that she does not have children in her home, so she did not consider the risk of children accessing the films.	The Applicant states that they have taken all reasonable measures to help ensure users understand to keep the proposed out of the reach of children. Specifically, the Applicant noted that the IFU includes instruction to keep the product and all medicines out of the reach of children. The Applicant also noted that the results for Knowledge Task 1 show that all participants clearly understood the product's labelling related to storing the medication out of the reach of children. As such, the Applicant concludes that the level of residual risk associated with not storing the product away from children is acceptable and additional mitigation is not warranted and is unlikely to	Based on the Applicant's URRA, failure to store the product away from children might result in accidental exposure. Our review of the study results did not identify subjective feedback indicating that the labels and labeling should be improved. Our review of the labels and labeling finds that Integrated IFU and regular IFU include the instruction "Keep TRADENAME and all medicines out of the reach of children". Based on the overall assessment of the study results, participant subjective feedback, and review of the labels and labeling, we have no recommendations for revision to the user interface at this time.

Table 2: Summary and analyses of errors/close calls/use difficulties with critical tasks during the HF validation study and supplemental study Participants: P – untrained patients, PT – trained patients, C – untrained caregivers, CT – trained caregivers, H – untrained HCPs, HT – trained HCPs				
Critical Tasks	**Number of, Description of, and Participant's Subjective Feedback on Use Errors, Close Calls, and Use Difficulties**	**Applicant's Root Cause Analysis**	**Applicant's Discussion of Mitigation Strategies**	**DMEPA's Analysis and Recommendations**
			improve the level of residual risk.	

3.3 ANALYSIS OF NON-CRITICAL TASKS

We observed use errors and use difficulties with the following non-critical tasks:

- Removes pouch from tray (ON state)
- Does not drop/place film on table, floor, or contaminated area
- Ensures films are not expired

After evaluating the use errors and use difficulties pertaining to these tasks, we agree with the Applicant that no additional mitigation strategies are necessary, and we determined that the residual risk is acceptable.

3.4 LABELS AND LABELING

Tables 3 and 4 below include the identified medication error issues with the submitted label and labeling, our rationale for concern, and the proposed recommendation to minimize the risk for medication error.

Table 3: Identified Issues and Recommendations for Division of Neurology 1			
	Identified Issue	**Rationale for Concern**	**Recommendation**
Highlights of Prescribing Information			
1.	The dosing range and administration information is not specified.	The Dosage and Administration section does not provide the specific dosing information which might contribute to wrong dose errors.	Consider revising the Dosage and Administration section to include the dose range and administration information (e.g. "The dose range for TRADENAME is 10 mg (b) (4) per dose as needed.").
Full Prescribing Information			
1.	The dosing information in Section 2 Dosage and Administration lacks clarity regarding the frequency of administration.	We are concerned the dosing information poses the risk of incorrect frequency of administration errors.	We recommend revising the statement "The dose range for TRADENAME is 10 mg (b) (4)" to "The dose range for TRADENAME is 10 mg (b) (4) per dose as needed. ".
2.	The administration instructions in Section 2.1 Important Administration Instructions lack clarity.	We are concerned the administration instructions should poses the risk of users administering (b) (4)	We recommend including the statement (b) (4) in Section 2.1 Important Administration Instructions.
3.	Section 3 incorrectly contains administration information.	We are concerned that the administration information may be overlooked because it is placed in Section 3 Dosage Forms and Strengths.	(b) (4)

Table 4: Identified Issues and Recommendations for Sunovion Pharmaceuticals Inc (entire table to be conveyed to Applicant)			
	Identified Issue	**Rationale for Concern**	**Recommendation**
Instructions for Use (IFU)			
1.	Integrated IFU Step 4 and regular IFU Step 1 could be improved (b) (4)	(b) (4)	
2.	Integrated IFU Step 5 and regular IFU Step 2 could be revised to clarify important administration instructions.	We are concerned that in the HF validation study and supplement study, 65 participants did not drink water or instruct the standard patient to drink water prior to administering the film. If users do not drink water prior to administering the film, there is risk of underdose.	Revise the graphic in Integrated IFU Step 5 and regular IFU Step 2 to include a text label, such as "Drink water".
3.	Integrated IFU Step 1 should be clarified to identify or label the clear plastic tabs.	We are concerned that in the HF validation study and supplemental study, 19 participants experienced difficulty depressing the plastic tabs on the CR packaging. Difficulty opening the packaging might result in delay in therapy or in the user removing the foil	Revise Integrated IFU Step 1 and/or Figure C to depict or label the clear plastic tabs (e.g. include text label to identify the clear plastic tabs).

		pouch from the carton in a manner that eliminates the CR feature from the packaging.	
4.	Integrated IFU Step (b) (4) should be clarified to indicate that users should administer the entire film.	In the HF validation study and supplemental study, 7 participants who broke the film did not administer all the pieces of the film. Failure to administer the entire film could result in underdose.	Revise the statement (b) (4) to "Place the entire film close to the base of your tongue…".
5.	Integrated IFU Step 7 and regular IFU Step 4 do not provide instructions regarding how to handle broken films.	In the HF validation study and supplemental study, 7 participants who broke the film did not administer all the pieces of the film. Failure to administer the entire film could result in underdose.	Revise Integrated IFU Step 7 and regular IFU Step 4 to include the statements "TRADENAME must be taken whole. Throw away film if it is broken or missing pieces. Use a new film for your dose."
Container Labels			
1.	The "Rx Only" statement is overly prominent.	We are concerned the prominence of the "Rx Only" statement competes in size and prominence with important information listed on the principal display panel (PDP) such as the route of administration statement.[b]	Decrease the prominence of the statement "Rx Only" as this information appears equally prominent to the route of administration on the PDP.
Carton Labeling			
(b) (4)			

[b] Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf

[c] Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf

4. CONCLUSION AND RECOMMENDATIONS

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

Upon review of the subjective feedback from study participants and the root cause analyses, we identified some recommendations to revise the Instructions for Use (IFU) and carton labeling to improve prominence, clarity, and understanding of important information. These recommendations are based on our review of the subjective feedback and root cause analysis of the use-related issues as well as our expert review of the proposed product user interface. In this particular instance, we have determined that these changes can be implemented without submission of additional HF validation testing data for the Agency's review. Additionally, our evaluation of the proposed label and labeling identified areas of vulnerability that may lead to medication errors. Above, we have provided recommendations in Table 3 for the Division and Table 4 for the Applicant. We ask that the Division convey Table 4 in its NDA 210875.

4.1 RECOMMENDATIONS FOR THE SUNOVION PHARMACEUTICALS INC

The human factors (HF) validation study results identified use errors, close calls, and use difficulties with critical and non-critical tasks. Upon review of the subjective feedback from study participants and the root cause analyses, we identified recommendations to revise the Instructions for Use (IFU) and carton labeling to improve prominence, clarity, and understanding of important information. These recommendations are based on our review of the subjective feedback and root cause analysis of the use-related issues as well as our expert review of the proposed product user interface. In this particular instance, we have determined that these changes can be implemented without submission of additional HF validation testing data for Agency's review. Additionally, our evaluation of the proposed label and labeling identified areas of vulnerability that may lead to medication errors. We have provided recommendations in Table 4 and we recommend that you implement these recommendations for your NDA 210875.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. DRUG PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 5 presents relevant product information for apomorphine hydrochloride film that Sunovion Pharmaceuticals Inc submitted on November 21, 2019.

Table 5. Relevant Product Information	
Initial Approval Date	N/A
Therapeutic Drug Class or New Drug Class	non-ergoline dopamine agonist
Active Ingredient	apomorphine hydrochloride
Indication	acute, intermittent treatment of OFF episodes associated with Parkinson's disease (b) (4)
Route of Administration	sublingual
Dosage Form	film
Strength	10 mg, 15 mg, 20 mg, 25 mg, 30 mg
Dose and Frequency	The dose range is 10 mg (b) (4). Doses should be separated by at least 2 hours. Do not administer more than 5 doses per day. Dose titration should be initiated with 10 mg when patients are in an OFF state. (b) (4) Continue to titrate in a similar manner until an effective and tolerable dose is achieved. (b) (4)

<table>
<tr><td>How Supplied</td><td>Apomorphine hydrochloride film is supplied as a blue rectangular single film with a white printed number identifying the strength (e.g.., “10” is 10 mg). Each sublingual film is individually packaged in a sealed foil pouch. Films are supplied in the following strengths and package configurations (Table 3):
<table>
<tr><th>Single Film Strength (NDC Code)</th><th>Package Configuration</th><th>NDC Code</th></tr>
<tr><td colspan="3">Trade Titration Kit</td></tr>
<tr><td>10 mg (63402-010-01)
15 mg (63402-015-01)
20 mg (63402-020-01)
25 mg (63402-025-01)
30 mg (63402-030-01)</td><td>Each titration kit carton will contain a total of 10 individually packaged films of:
2 – single 10 mg films
2 – single 15 mg films
2 – single 20 mg films
2 – single 25 mg films
2 – single 30 mg films</td><td>63402-088-10</td></tr>
<tr><td colspan="3">Trade Product</td></tr>
<tr><td>10 mg (63402-010-01)</td><td>30 films per carton</td><td>63402-010-30</td></tr>
<tr><td>15 mg (63402-015-01)</td><td>30 films per carton</td><td>63402-015-30</td></tr>
<tr><td>20 mg (63402-020-01)</td><td>30 films per carton</td><td>63402-020-30</td></tr>
<tr><td>25 mg (63402-025-01)</td><td>30 films per carton</td><td>63402-025-30</td></tr>
<tr><td>30 mg (63402-030-01)</td><td>30 films per carton</td><td>63402-030-30</td></tr>
</table></td></tr>
<tr><td>Storage</td><td>Store at 20°–25°C (68°–77°F); excursions permitted between 15°–30°C (59°–86°F). Keep in the foil pouch until ready to use.</td></tr>
</table>

Container Closure	(b) (4)
Intended Users	Patients, caregivers, HCPs
Intended Use Environment	Home, clinical

APPENDIX B. BACKGROUND INFORMATION

B.1 PREVIOUS HF REVIEWS

B.1.1 Methods

On March 13, 2020, we searched the L:drive and AIMS using the term, apomorphine, to identify reviews previously performed by DMEPA or CDRH.

B.1.2 Results

Our search identified four previous reviews[defg] pertinent to this review, and we confirmed that our previous recommendations were implemented or are addressed in the current review.

B.2 PREVIOUS FDA/SPONSOR INTERACTIONS PERTAINING TO HF

On April 2, 2019, the Agency held a Type A meeting with the sponsor to discuss the Complete Response deficiencies for NDA 210875.[h] In the meeting, we discussed the responses to the HF-related questions. The Applicant sought advice on alternative mitigations, including caregiver assistance and additional training, to address concerns that users might be unable to open the CR packaging. The Agency clarified that ultimately, it is a review issue whether the data collected through the HF validation study support safe and effective use by the intended users, in the intended uses, and use environments. Additionally, with regard to training as a mitigation, the Agency informed the sponsor that without a REMS, it is not possible to ensure that routine and consistent training would be provided.

[d] Whaley, E. Human Factors Protocol Review for Kynmobi (apomorphine) IND 110955. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 JUN 26. RCM No.: 2017-637.

[e] Whaley, E. Human Factors Report and Label and Labeling Review for Kynmobi (NDA 210875). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 NOV 8. RCM No.: 2018-1341 and 2018-2080.

[f] Whaley, E. Human Factors Memorandum for Kynmobi (NDA 210875). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 JAN 14. RCM No.: 2018-1341-1 and 2018-2080-1.

[g] Whaley, E. Human Factors Protocol Review for Kynmobi (apomorphine) IND 110955. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 MAY 15. RCM No.: 2019-671.

[h] Meeting Preliminary Comments for Kynmobi (apomorphine) NDA 210875. Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Drug Evaluation I, Division of Neurology Products (US); 2019 MAR 29.

APPENDIX C. BACKGROUND INFORMATION ON HUMAN FACTORS ENGINEERING PROCESS

The background information can be accessed in EDR via:
\\cdsesub1\evsprod\nda210875\0044\m5\53-clin-stud-rep\535-rep-effic-safety-stud\parkinsons\5354-other-stud-rep\hf-summative-test\hf-validation-test-plan-20sep2019-hf-validation-test-oct2019.pdf

APPENDIX D. HUMAN FACTORS VALIDATION STUDY RESULTS REPORT

The HF study results report can be accessed in EDR via:
\\cdsesub1\evsprod\nda210875\0044\m5\53-clin-stud-rep\535-rep-effic-safety-stud\parkinsons\5354-other-stud-rep\hf-summative-test\human-factors-engineering-report-15nov2019.pdf

APPENDIX E. INFORMATION REQUESTS ISSUED DURING THE REVIEW

On January 29, 2020, we sent an Information Request to request the Sponsor provide justification that the education levels of the patient and caregiver participants are representative of the demographics of the intended users for this product. The Sponsor responded on February 3, 2020. See EDR link:

\\cdsesub1\evsprod\nda210875\0049\m1\us\111-info-amend\resp-fda-req-04mar2020.pdf

On March 4, 2020, we sent an Information Request to the Sponsor to obtain more detail regarding user difficulty opening the child-resistant carton. The Sponsor responded on March 10, 2020. See EDR link:

\\cdsesub1\evsprod\nda210875\0049\m1\us\111-info-amend\resp-fda-req-04mar2020.pdf

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[i] along with postmarket medication error data, we reviewed the following apomorphine film labels and labeling submitted by Sunovion Pharmaceuticals Inc.

- Container label (pouch label) received on November 21, 2019
- Carton labeling received on November 21, 2019
- Professional Sample container label (pouch label) received on November 21, 2019
- Professional Sample carton labeling received on November 21, 2019
- Demonstration container label (pouch label) received on November 21, 2019
- Demonstration carton labeling received on November 21, 2019
- Instructions for Use (Image not shown) received on November 21, 2019
    - \\cdsesub1\evsprod\nda210875\0044\m1\us\114-label\1141-draft-label\kynmobi-ifu.pdf
    - \\cdsesub1\evsprod\nda210875\0044\m1\us\114-label\1141-draft-label\kynmobi-cr-ifu-ifu.pdf
- Prescribing Information (Image not shown) received on November 21, 2019
    - \\cdsesub1\evsprod\nda210875\0044\m1\us\114-label\1141-draft-label\draft-labeling-text-pi.pdf

25 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

[i] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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

/s/

EBONY A WHALEY
04/20/2020 05:45:55 PM

LOLITA G WHITE
04/20/2020 06:15:22 PM

QUYNHNHU T NGUYEN
04/21/2020 10:13:26 AM

DANIELLE M HARRIS
04/21/2020 10:34:43 AM

M E M O R A N D U M

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: April 6, 2020

To: Eric Bastings, MD, Director (Acting)
Division of Neurology I

Through: Dominic Chiapperino, PhD, Director
Chad Reissig, PhD, Supervisory Pharmacologist
Controlled Substance Staff

From: Edward Hawkins, PhD, Pharmacologist
Controlled Substance Staff

Subject: **Product name:** Kynmobi (Apomorphine Hydrochloride)
Dosages, formulations, routes: sublingual film 30 mg sublingual
NDA number: 210875
IND Number: 110955
Indication(s): An adjunctive for the acute, intermittent management of OFF episodes in patients with Parkinson's disease
Applicant: Sunovion
PDUFA Goal Date: May 21, 2020

Materials Reviewed:

- NDA 210875 for Kynmobi, submitted November 21, 2019, and subsequent amendments

Table of Contents

I. SUMMARY

1. Background

This memorandum responds to a consult request by the Division of Neurology I (DNP I) to evaluate abuse-related preclinical and clinical data submitted by Sunovion (Applicant) under NDA 210875 and IND 110955 for Kynmobi (apomorphine hydrochloride).

Apomorphine was removed from control in the Controlled Substances Act (CSA) in 1976 based on its lack of abuse potential (41 FR 26568). The Applicant is using the 505(b)(2) pathway utilizing Apokyn (NDA 021264) as the reference listed drug which was approved by FDA in April 2004. Apomorphine was not scheduled at that time. CSS was not consulted during the IND phase, however, during the NDA filing stage it was deemed unnecessary for the Applicant to complete a full abuse potential assessment as outlined in the FDA's guidance for industry, Assessment of Abuse Potential for Drugs.

In the NDA submission, the Applicant proposes to not control apomorphine in the CSA. After evaluating the nonclinical and clinical data in the NDA or referenced data, CSS concludes that apomorphine does not have abuse potential and should not be controlled in the CSA. However, there are reports in the literature of people trying to use apomorphine for abuse. In some of the cases, this appears to be because it contains 'morphine' in the name and individuals believe it will produce opioid-like effects. Apomorphine is actually a non-specific dopamine agonist and many individuals stop using the drug when it does not produce the desired effects.

2. Conclusions

CSS has reviewed the nonclinical and clinical abuse-related data submitted in NDA 210875 for Kynmobi (apomorphine hydrochloride) and concludes that the drug does not have abuse potential and should not be recommended for placement in the Controlled Substances Act. This conclusion is based on the following data:

- In receptor binding and functional studies, apomorphine was determined to be a non-selective dopamine agonist, with antagonist activity at serotonergic and adrenergic receptors.

- The Applicant did not conduct animal or clinical studies to determine the abuse potential of apomorphine.

    - Apokyn (NDA 021264) was approved by FDA in April of 2004 and was not scheduled.

- In Phase 1 studies, healthy subjects did not report adverse events that strongly correlate to abuse potential. There were two reports of hallucinations in Phase 2 and 3 studies, however, that was in subjects with Parkinson's Disease who may have neurological and physical deficits. The two reports of hallucinations account for 0.3% of the people given drug treatment in phase 2/3 studies.

3. Recommendations

Based on the CSS determinations that apomorphine does not have abuse potential and does not appear to produce physical dependence, CSS concludes that:

1. Apomorphine should not be recommended for control under the Controlled Substances Act.

2. Section 5 includes a section (5.5) on hallucinations and psychotic-like behavior. This statement is consistent with previous labels and indicates the low levels of hallucinations (0.2%) associated with apomorphine.

3. Section 9 (Drug Abuse and Dependence) should reflect the abuse-related data submitted in the NDA and presented consistently with respect to the listed drug's (Apokyn) labeling. CSS recommends the following changes to the Applicant's label, where additions are indicated in bold, underlined text and deletions have been stricken through:

5.5 Hallucinations / Psychotic-Like Behavior

Patients with a major psychotic disorder should not be treated with apomorphine because of the risk of exacerbating psychosis. In addition, certain medications used to treat psychosis may exacerbate the symptoms of Parkinson's disease and may decrease the effectiveness of KYNMOBI [*see Drug Interactions (7.3)*].

In pooled clinical studies, 0.2% of KYNMOBI-treated patients experienced hallucinations during titration and 4% had hallucinations and/or psychotic-like behavior during maintenance treatment. Events experienced during maintenance treatment were considered serious for two patients, one of whom discontinued the study.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

KYNMOBI is not a controlled substance.

9.2 Abuse

In premarketing clinical experience, KYNMOBI did not reveal any tendency for a withdrawal syndrome or drug-seeking behavior. However, there are rare postmarketing reports of abuse of medications containing apomorphine (b) (4). In general, these reports consist of patients taking increasing doses of medication in order to achieve a euphoric state.

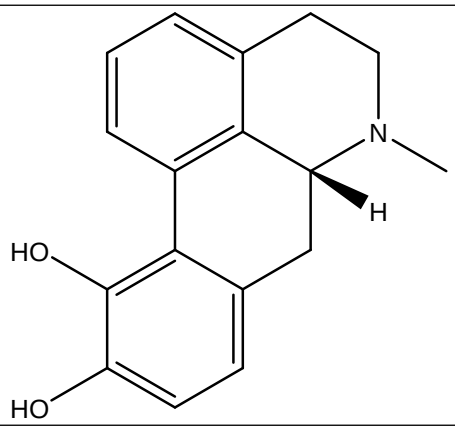
II. DISCUSSION

1. Chemistry

1.1 Drug Substance Information

Apomorphine HCl is also known by the nonproprietary name of 4H-Dibenzo [de, g] quinoline-10, 11-diol, 5, 6, 6a, 7-tetrahydro-6-methyl hydrochloride, hemihydrate. Apomorphine HCl has a molecular weight of (b) (4) g/mol, a chemical formula of C17 H17 NO2 • HCl • ½ H2O (salt), and a CAS # of 314-18-2 (TABLE 1).

Table 1: General Chemical Properties of Apomorphine

Nomenclature	
International Non-proprietary Name (INN)	Apomorphine HCl
Chemical Abstract Number (CAS)	314-18-2
Chemical Name (IUPAC)	4H-Dibenzo [de, g] quinoline-10, 11-diol, 5, 6, 6a, 7-tetrahydro-6-methyl hydrochloride, hemihydrate
Substance codes	APL-130277
Structure	
Molecular Formula	C17 H17 NO2 • HCl • ½ H2O (salt)
Molecular mass	(b) (4) g mol^{-1}
Structure	

1.2 Drug Product Information

Apomorphine hydrochloride is the active pharmaceutical ingredient in Kynmobi. Kynmobi, also known as APL-130277, is designed as a sublingual film able to deliver apomorphine through sublingual administration. Kynmobi is manufactured as single strips that can be cut into dose strengths of 10, 15, 20, 25, and 30 mg which are individually packaged.

Excipients in the tablet

(b) (4) Inactive ingredients in the tablets include pyridoxine hydrochloride, sodium hydroxide, sodium metabisulfite, disodium EDTA, dihydrate (b) (4) (b) (4) glyceryl monostearate, (b) (4) sucralose, (b) (4) hydroxyethyl cellulose, (b) (4) FD&C Blue #1 (b) (4) and white ink.

2. Nonclinical Pharmacology

Receptor binding and activity assays can give an indication as to whether or not a substance affects a receptor pathway that is known to be associated with abuse potential. For substances that are CNS active, the Applicant is required to determine if their active pharmaceutical ingredient and any major metabolites will bind to and have activity at these receptors.

2.1 Receptor Binding and Functional Assays

The Applicant did not conduct, and were not required to conduct, in vitro binding or functional assays on apomorphine. It is well-established in the literature that apomorphine is a partial agonist at the dopamine receptors with greater activity at D2, D3, and D4, than D1 and D5. It is also an antagonist at several serotonin and norepinephrine receptors. Independently, these mechanisms of action are not typically associated with abuse potential.

2.2 Safety Pharmacology/Metabolites

Absorption

Sublingual apomorphine is rapidly absorbed followed by a distribution and elimination phase. Apomorphine's metabolism happens via auto-oxidation, O-glucuronidation, O-methylation, N-demethylation, and sulfation with only 3-4% being renally eliminated unmetabolized. Apomorphine produces an abundant number of metabolites which are not well characterized.

Study # CTH-200 was conducted to determine the PK parameters of a single dose of sublingual apomorphine in healthy adults. The data are presented in Table 5 and indicate that the drug is rapidly

absorbed with a tmax of 1.75 hours. The relative bioavailability was calculated to be approximately 19% after sublingual administration.

Table 2: PK Parameters of a Single 15 mg Dose of Sublingual Apomorphine in Healthy Adults

Dose	15 mg
C_{max} (ng/mL)	4.95
t_{max} (h)	0.85
AUC_{24} (µg*h/mL)	113
$t_{1/2}$ (h)	1.75
AUC (h*ng/mL)	10.4

2.3 Animal Behavioral Studies

Two toxicokinetic studies were conducted in rats given oral doses of apomorphine ranging from 3 to 30 mg/kg. There were no significant changes in body weight, food consumption, or clinical signs. The study determined a no observed effect level (NOEL) of 30 mg/kg.

4. Clinical Studies

4.1 Human Abuse Potential Studies

The Applicant did not conduct a human abuse potential (HAP) study to assess the abuse potential of apomorphine.

The Applicant did conduct a search for treatment related adverse events related to abuse in their single and repeat dose clinical studies. However, subjects with Parkinson's disease may have severe neurological deficits that can impact the overall evaluation of adverse events in this population.

4.2 Adverse Event Profile Through all Phases of Development

The Applicant conducted seven Phase 1 Studies and six Phase 2/3 studies during the clinical development program for Kynmobi. All adverse events (AEs), including abuse-related AEs were coded to a Medical Dictionary for Regulatory Activities (MedDRA) and the MedDRA system organ class (SOC) and preferred term (PT). The following is a description of, and analysis of abuse-related AEs found during different phases of clinical development.

Phase1 studies:

The AEs related to CNS/abuse-associated effects from the seven phase 1 studies are presented in **Table 3**. The most prevalent of these AEs were headache, dizziness, nausea, and giddiness. Although present in more than 2% of the population, these AEs do not necessarily indicate that a substance has abuse potential. There were no reports of hallucinations, euphoria, feeling good, or other AEs typical of drugs with abuse potential. In all of these studies there was one report of an intentional overdose, however, no

further information was provided. The AEs reported in these studies are consistent with those reported in clinical studies conducted with Apokyn (apomorphine).

Phase 2/3 Studies

In these studies, a total of 425 subjects with Parkinson's Disease were given doses between 10 and 60 mg apomorphine. In total there were two hallucinations reported in the phase 2 and phase 3 studies, and these were the only adverse events considered to be abuse-associated; however, these reports are 0.47% of the total number of subjects exposed to drug in these studies.

In conclusion, apomorphine, at the doses tested, did not produce any meaningful abuse-related effects in phase 1, 2, or 3 studies.

4.3 Tolerance and Physical Dependence Studies in Humans

No studies were conducted to assess the tolerance or physical dependence of apomorphine in humans. Furthermore, an analysis of reported AEs following drug discontinuation in Phase 2/3 studies did not produce a profile of AEs indicative of physical dependence or withdrawal.

5. Regulatory Issues

Based on the analysis of all submitted and referenced data and information pertaining to abuse potential, we conclude that apomorphine does not have abuse potential. We will not be recommending drug scheduling of apomorphine under the Controlled Substances Act. The Applicant has proposed drug product labeling that includes section 9 Drug Abuse and Dependence. This labeling is consistent with the listed drug's (Apokyn) labeling and, thus, is found to be acceptable.

Table 3: Abuse Related Adverse Events from Phase 1 Studies

Study #	CTH-101	CTH-102	CTH-103		CTH-104	CTH-106	CTH-107			CTH-200		Total
	N = 15	N = 12	N = 16	N = 16	N = 13	N = 12	N = 10	N = 10	N = 20	N = 19	N = 19	N = 162
Dose of Kynmobi	3 mg	8 mg	10	15	25 mg	15	4.5 mg Nunavut	9 mg Nunavut	15 mg	2 mg APO-GO	15 mg	--
Headache	1 (6.7)	0	0	0	0	1 (8.3)	0	0	0	2 (10.5)	0	4 (2.5)
Dizziness	5 (33.3)	3 (25)	3 (30)	7 (43.8)	9 (69.2)	5 (41.7)	0	1 (10)	2 (10)	7 (36.8)	7 (36.8)	49 (30.2)
Nausea	2 (13.3)	5 (41.7)	1 (10)	3 (18.8)	4 (30.7)	2 (16.7)	0	0	4 (20)	2 (10.5)	5 (26.3)	28 (17.3)
Giddiness	0	2 (16.7)	0	0	0	1 (8.3)	0	0	0	2 (10.5)	0	5 (3.1)

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

/s/

EDWARD G HAWKINS
04/06/2020 01:09:29 PM

CHAD REISSIG
04/08/2020 07:02:37 AM

DOMINIC CHIAPPERINO
04/08/2020 07:43:17 AM

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: March 20, 2020

TO: Eric Bastings, MD
Director (Acting)
Division of Neurology I (DN I)
Office of Neuroscience (ON)

FROM: Xingfang Li, MD, RAC
Division of Generic Drug Study Integrity (DGDSI)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: John A. Kadavil, Ph.D.
Deputy Director
DGDSI, OSIS

SUBJECT: Routine inspection of clinical sites supporting clinical study CTH-203 (NDA 210875)

1 Inspection Summary

The Office of Study Integrity and Surveillance (OSIS) arranged inspections of the following sites:

- Parkinson's Disease Treatment Center of Southwest Florida, Port Charlotte, FL
- Quest Research Institute, Farmington Hills, MI
- Parkinson's Disease and Movement Disorders Center, Boca Raton, FL

No objectionable conditions were observed, and Form FDA 483 was not issued at the inspection close-outs. The final inspection classifications are No Action Indicated (NAI).

1.1. Recommendation

After reviewing the inspectional findings, I conclude that data from the audited study CTH-203 (NDA 210875) are reliable to support regulatory decisions.

To date (3/19/2020), OSIS has received finalized EIRs from the inspections at Parkinson's Disease Treatment Center of Southwest Florida, and Parkinson's Disease and Movement Disorders Center of Boca Raton, and an inspection summary from the inspection at Quest Research Institute. If the finalized EIR from the inspection at Quest Research Institute provides new information that will affect OSIS' current recommendations, an addendum to this review will be provided to the Division of Neurology I.

2 Inspected Study:

NDA 210875

Study Number: CTH-203
Study 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)"
Dates of conduct: Aug 2017 – Mar 2019

Clinical sites:

Parkinson's Disease Treatment Center of Southwest Florida (1006)
4235 Kings Hwy Unit 102
Port Charlotte, FL 33980
FEI: 3016250970

Quest Research Institute (1008)
28595 Orchard Lake Rd Ste 301
Farmington Hills, MI 48334
FEI: 3010405786

Parkinson's Disease and Movement Disorders Center (1012)
951 NW 13th St. Ste 5E
Boca Raton, FL 33486
FEI: 3010475540

3 Inspectional Findings

Parkinson's Disease Treatment Center of Southwest Florida (1006) Port Charlotte, FL

ORA investigator Ladislav Kermet (FLA-DO) inspected Parkinson's Disease Treatment Center of Southwest Florida from February 06 to 11, 2020.

The inspection included a thorough examination of study records (paper-based), subject records, informed consent process, protocol compliance, institutional review board approvals, sponsor and monitor correspondence, test article accountability and storage, randomization, adverse events, and case report forms.

At the conclusion of the inspection, investigator Kermet did not observe any objectionable conditions and did not issue Form FDA 483 to the clinical site. However, investigator Kermet did discuss the following items with management at the closeout meeting.

1. The site does not conduct operational activities within the quality assurance system to verify that quality requirements for the study-related activities have been fulfilled.

Site's response: The site will establish a systematic process to verify collected and reported data.

OSIS Evaluation: This OSIS reviewer finds this response acceptable.

2. Study personnel did not use a log book when entering the drug room, where controlled substances were stored.

Site's response: The site will create a pharmacy room log book and will educate all personnel to sign in with a signature, date, and purpose.

OSIS Evaluation: This OSIS reviewer finds this response acceptable.

3. The site did not have written standard operating procedures to facilitate consistency in the of handling complaints and recall procedures.

 Routine inspections of the following sites: Parkinson's Disease Treatment Center of Southwest Florida, Port Charlotte, FL; Quest Research Institute, Farmington Hills, MI; Parkinson's Disease and Movement Disorders Center, Boca Raton, FL

Site's response: The site will update their SOPs to include handling recalls and complaints.

OSIS Evaluation: This OSIS reviewer finds this response acceptable. There is no demonstrable impact on the study outcomes.

During reviewing EIR and exhibits, this OSIS reviewer learned that subject (b) (6) had a history of melanoma, which is listed as an exclusion criterion. However, a protocol waiver was granted for subject (b) (6) to be enrolled in this study by the sponsor and medical monitor (**ATTACHMENT 1, page 5**).

Quest Research Institute, Farmington Hills, MI (1008)

ORA investigator Andrace Deyampert (DET-DO) inspected Quest Research Institute from March 11 to 13, 2020.

Based on the inspection summary, nine subjects were screened, six accounted as screen failures, and three enrolled. All enrolled subjects completed the study. There were no significant objectionable conditions observed, or evidence of under-reporting of safety events and data in the CSR.

At the conclusion of the inspection, investigator Deyampert did not observe any objectionable conditions and did not issue Form FDA 483 to Quest Research Institute. However, investigator Deyampert did discuss the following item with management at the closeout meeting.

1. Ms. Deyampert discussed the importance of ensuring source records are attributable, legible, original, accurate, contemporaneous, and complete, as centrifugation times and sample preparation information lacked documentation. However, interviews with individuals directly involved with these tasks were completed to capture their involvement and practices implemented in the study.

Site's response: The team agreed to update their procedures to ensure all steps pertaining to study related activities are captured.

 Routine inspections of the following sites: Parkinson's Disease Treatment Center of Southwest Florida, Port Charlotte, FL; Quest Research Institute, Farmington Hills, MI; Parkinson's Disease and Movement Disorders Center, Boca Raton, FL

OSIS Evaluation: This OSIS reviewer finds this response acceptable. Please also note that protocol waivers were granted for two of the three subjects enrolled by the sponsor prior to randomization.

Parkinson's Disease and Movement Disorders Center, Boca Raton, FL (1012)

ORA investigator Angelica Chica (FLA-DO) inspected Parkinson's Disease and Movement Disorders Center from March 9 to 12, 2020.

The inspection included a thorough examination of study records (paper-based), subject records, informed consent process, protocol compliance, institutional review board approvals, sponsor and monitor correspondence, test article accountability and storage, randomization, adverse events, and case report forms.

At the conclusion of the inspection, investigator Chica did not observe any objectionable conditions and did not issue Form FDA 483 to the clinical site. However, investigator Chica did discuss the following item with management at the closeout meeting.

1. Subject (b) (6) had a discrepancy between the source records and the data listing for an AE documented on the screening laboratory report. The sub-investigator (SI) documented that the lab results were clinically significant (CS) and made a note, that the subject had experienced a fever and UTI, the day after the blood specimens were drawn (**ATTACHMENT 2, page 13**). However, the SI did not document how the information on fever and UTI was obtained nor was it documented in an AE log for this subject (there was no AE log for this subject in the source records). Additionally, the subject was screened on 10/11/2017 but the SI wrote the incorrect date (10/9/2017) on the lab requisition form. Per the SI, she called the lab and had the incorrect date changed and a new lab report was faxed to the site with the correct date of 10/11/2017 (**ATTACHMENT 2, page 13-23**).

 Routine inspections of the following sites: Parkinson's Disease Treatment Center of Southwest Florida, Port Charlotte, FL; Quest Research Institute, Farmington Hills, MI; Parkinson's Disease and Movement Disorders Center, Boca Raton, FL

Site's response: Dr. Isaacson understood the verbal discussion item and agreed. Dr. Isaacson stated that moving forward, all CS lab results will require a separate treatment note, and all CS events will be captured as an AE.

OSIS Evaluation: This OSIS reviewer finds this response acceptable.

4. Conclusion:

After reviewing the inspectional findings, I conclude the data from study CTH-203 (NDA 210875) are reliable.

Based on the inspectional findings, studies of similar design conducted between the previous inspections and the end of the current surveillance interval should be considered reliable without an inspection for each of the study sites.

Xingfang Li, MD, RAC
Pharmacologist
DGDSI, OSIS

Final Classification:

NAI- Parkinson's Disease Treatment Center of Southwest Florida
4235 Kings Hwy Unit 102
Port Charlotte, FL 33980
FEI: 3016250970

NAI- Quest Research Institute
28595 Orchard Lake Rd Ste 301
Farmington Hills, MI 48334
FEI: 3010405786

NAI- Parkinson's Disease and Movement Disorders Center
951 NW 13th St. Ste 5E
Boca Raton, FL 33486
FEI: 3010475540

Email cc:

ORA BIMO Inspection POC
ORAFLABIMO@fda.hhs.gov
ORADETBIMO@fda.hhs.gov
OSIS/Kassim/Folian/Fenty-Stewart/Johnson/CDER-OSIS-BEQ@fda.hhs.gov
OSIS/DNDSI/Bonapace/Dasgupta/Biswas/Ayala
OSIS/DGDSI/Cho/Kadavil/Choi/Skelly/Au/Li

Draft: XFL 03/17/2020; 03/19/2020
Edits: MFS 03/20/2020; JAK 03/20/2020

ECMS: Cabinets/CDER_OTS/Office of Study Integrity and Surveillance/INSPECTIONS/BE Program/CLINICAL/Parkinson's Disease Treatment Center of Southwest Florida Street, Port Charlotte, FL, USA

ECMS: Cabinets/CDER_OTS/Office of Study Integrity and Surveillance/INSPECTIONS/BE Program/CLINICAL/Quest Research Institute, Farmington Hills, MI, USA

ECMS: Cabinets/CDER_OTS/Office of Study Integrity and Surveillance/INSPECTIONS/BE Program/CLINICAL/Parkinson's Disease and Movement Disorders Center, Boca Raton, FL, USA

OSIS file #: BE #8815
FACTS: 11983906

32 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

---

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

/s/

XINGFANG LI
03/20/2020 03:57:43 PM

MICHAEL F SKELLY
03/20/2020 03:59:50 PM

JOHN A KADAVIL
03/20/2020 04:12:12 PM

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 2/20/2020

TO: Division of Neurology I (DN I)
Office of Neuroscience (ON)

FROM: Division of New Drug Study Integrity (DNDSI)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Decline to conduct an on-site inspection**

RE: NDA 210875

The Division of New Drug Study Integrity (DNDSI) within the Office of Study Integrity and Surveillance (OSIS) determined that an inspection is not warranted at this time for the site listed below. The rationale for this decision is noted below.

Rationale

OSIS inspected the site in September 2017, which falls within the surveillance interval. The inspection was conducted under the following submission: (b) (4).

The final classification for the inspection was Voluntary Action Indicated (VAI) for the following observation:

(b) (4)

(b) (4)

In addition, 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 (OSIS EIR review-September 2017 Inspection).

Therefore, based on the rationale described above, an inspection is not warranted at this time.

Inspection Site

Facility Type	Facility Name	Facility Address
Analytical	(b) (4)	

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

/s/

JAMES J LUMALCURI
02/20/2020 12:29:14 PM

HUMAN FACTORS MEMORANDUM

REVIEW OF SPONSOR'S RESPONSE TO DISCIPLINE REVIEW LETTER

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	January 14, 2019
Requesting Office or Division:	Division of Neurology Products (DNP)
Application Type and Number:	NDA 210875
Product Type:	Single-ingredient
Product Name and Strength:	Kynmobi (apomorphine) sublingual film 10 mg, 15 mg, 20 mg, 25 mg and 30 mg
Rx or OTC:	Rx
Applicant Name:	Sunovion Pharmaceuticals Inc.
Submission Date:	December 7, 2018
OSE RCM #:	2018-1341-1; 2018-2080-1
DMEPA Safety Evaluator:	Ebony Whaley, PharmD, BCPPS
DMEPA Team Leader:	Lolita White, PharmD
DMEPA Associate Director for Human Factors:	Quynh Nhu Nguyen, MS
DMEPA Deputy Director:	Danielle Harris, PharmD, BCPS

1 PURPOSE OF MEMORANDUM

The Division of Neurology Products (DNP) requested that we review the sponsor's response[a] to the Discipline Review (DR) letter issued by the Agency on November 21, 2018 to determine if the response adequately addresses our concerns outlined in the DR letter. The DR letter comments were related to our review of the sponsor's human factors (HF) validation study results report, labels and labeling, and packaging design.[b] The sponsor submitted their response to the DR letter to address our recommendations to: (1) implement our modifications to the labels and labeling and provide results of another HF validation study to show that the

[a] Sponsor's response to the Discipline Review letter can be accessed via \\cdsesub1\evsprod\nda210875\0037\m1\us\111-info-amend\resp-fda-discipline-review-letter-21nov2018.pdf

[b] Whaley, E. Human Factors Report and Label and Labeling Review for Kynmobi (NDA 210875). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 NOV 8. RCM No.: 2018-1341 and 2018-2080.

mitigations are effective without introducing new risks and (2) to address our recommendation to evaluate the [redacted] packaging in the intended user population in the HF validation study.

1.1 REGULATORY HISTORY

On March 29, 2018, the sponsor submitted a HF validation study results report as part of NDA 210875 for Kynmobi (apomorphine) sublingual film. Kynmobi (apomorphine) sublingual film is a single-ingredient product intended for acute, intermittent treatment of "OFF"[c] episodes associated with Parkinson's [redacted] We reviewed the HF validation study results included in the submission and noted several use errors and close calls that occurred on critical tasks.[d] We noted that the sponsor implemented revisions to the Instructions for Use (IFU) and container label in response to the user errors and close calls, but did not validate the revisions. Additionally, our review identified areas of vulnerability in the labels and labeling that may lead to medication errors and we recommended additional labels and labeling revisions. Our review of the HF validation study results also noted a study methodology concern: the user interface used in the HF validation study did not include the intend-to-market carton packaging (i.e. [redacted] packaging). We are concerned that the [redacted] packaging requires a push-pull technique to open, which may pose use difficulty for the intended user population (i.e. patients with Parkinson's disease) to open or close the packaging due to dexterity and motor impairments that occur in the OFF period. Thus, we determined the HF validation study methodology was deficient and the results do not demonstrate that the intended users can use the proposed product safely and effectively for the intended uses.[e] DNP agreed with our assessment and communicated our recommendations in a DR letter to the sponsor on November 21, 2018.[f]

---

[c] "Off" periods describe those times when a Parkinson's disease patient's symptoms have returned, commonly experienced just prior to taking the next dose of medication, and this experience is called "wearing off." The "off" periods may also occur unpredictably without a consistent relation to the timing of medication.

[d] Whaley, E. Human Factors Report and Label and Labeling Review for Kynmobi (NDA 210875). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 NOV 8. RCM No.: 2018-1341 and 2018-2080.

[e] Whaley, E. Human Factors Report and Label and Labeling Review for Kynmobi (NDA 210875). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 NOV 8. RCM No.: 2018-1341 and 2018-2080.

[f] Discipline Review Letter for Kynmobi (apomorphine) NDA 210875. Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Drug Evaluation I, Division of Neurology Products (US); 2018 NOV 21. https://darrts.fda.gov//darrts/faces/ViewDocument?documentId=090140af804c660e&_afrRedirect=3257201447333262

On November 27, 2018, we held an informal teleconference with the sponsor to discuss the DR letter. The sponsor indicated that they did not agree with the Agency's conclusion regarding the need for additional HF validation testing. The Agency requested that the sponsor submit their rationale as a formal submission to the NDA. The sponsor submitted a formal response to the NDA on December 7, 2018.[g]

2 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Table 1 below provides our assessment of the sponsor's response to the DR letter (see Appendix A).

[g] Sponsor's response to the Discipline Review letter can be accessed via \\cdsesub1\evsprod\nda210875\0037\m1\us\111-info-amend\resp-fda-discipline-review-letter-21nov2018.pdf

	Table 1. Original Recommendations/Sponsor's Response/Subsequent Agency Response		
No.	Original DMEPA Recommendations[h]	Summary of Sponsor's Response (12/7/2018)	DMEPA's Analysis of Sponsor's Response
1.	*DMEPA recommendation regarding the HF validation study results*: Your study results showed several use errors and close calls that occurred on critical tasks. We note that you implemented revisions to the Instructions for Use (IFU) and film pouch (container label) to address the use errors and close calls. However, you did not validate the revisions to the user interface. We are concerned with these issues because of the clinical significance of failures with critical tasks, including underdose and risk of adverse events. Furthermore, our evaluation of the proposed user interface, label and labeling identified areas of vulnerability that may lead to medication errors and we provide additional recommendations below for labels and labeling revisions. We recommend you implement your	The sponsor stated that they do not believe an additional HF validation study is necessary "as the potential risks and issues associated with self-administration of APL-130277 [Kynmobi] by patients experiencing OFF episodes in packaging that is nearly identical to the intended commercial product has adequately been addressed". In addition, they summarized the results from the HF validation study and other supporting data (see below): • Human Factor study results • Clinical Trial Study Data • Clinical Trial Product Complaints Regarding the child resistant (CR) packaging (i.e. (b) (4) packaging), the sponsor stated that	The sponsor's response indicates their intent to forego the need for additional human factors validation data by leveraging data from existing clinical trial data and human factors data. We acknowledge that the sponsor has evaluated the proposed product in the clinical environment; however, it is important to note that there are differences in how the product is used in the clinical trial versus how the product will be evaluated in the HF validation study, which is intended to mimic real-world use. For example, in the clinical trials, participants typically are provided oversight, training, and the study is conducted under tight controls as compared to what can be expected to occur once a product is marketed. Moreover, the purposes of the two tests are different (e.g. in the clinical trial, the focus is on the safety and efficacy of the drug, vs. in the HF validation study, the focus is on how intended users interact with the product user interface, and whether the user interface can be improved to support safe and effective use). We discussed with the clinical review team, and they noted that study personnel administered Kynmobi to

[h] Whaley, E. Human Factors Report and Label and Labeling Review for Kynmobi (NDA 210875). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 NOV 8. RCM No.: 2018-1341 and 2018-2080.

	Table 1. Original Recommendations/Sponsor's Response/Subsequent Agency Response		
No.	Original DMEPA Recommendations[h]	Summary of Sponsor's Response (12/7/2018)	DMEPA's Analysis of Sponsor's Response
	proposed modifications, implement our, and provide results of another human factors validation study to demonstrate that the mitigations are effective and that they do not introduce new risks.	the primary packaging used in the HF validation study and the clinical studies is similar in design and composition to the intend-to-market primary packaging. (b) (4)	study participants during clinical visits and that study participants received training regarding how to administer the product. The clinical review team disagreed with the sponsor's determination that the clinical studies data supports the usability of the product.
2.	*DMEPA recommendation regarding the* (b) (4) *packaging:* We note that the (b) (4) packaging requires a push-pull technique to open, which may pose concerns for the intended user population (i.e. patients with Parkinson's disease) due to dexterity and motor impairments that occur in the OFF period. We also note that Kynmobi is intended for the acute use; therefore, delay in therapy (e.g. due to difficulty opening the (b) (4) packaging) would cause the user to remain in the OFF state. We are concerned that if users experience difficulty opening or closing the (b) (4) packaging, they might attempt to remove the foil pouches from the packaging permanently, or	Overall, the sponsor believes that conducting "an additional Human Factor study will not further mitigate any identified or potential risks related to the packaging for APL-130277 [Kynmobi], but will significantly delay the availability of a safe and effective, easy to administer treatment for OFF episodes in Parkinson's disease (PD) patients".	Therefore, we do not agree with the approach to leverage data from clinical trials. We remain concerned about the lack of additional HF validation data to demonstrate that intended users can use the product safely and effectively for its intended uses and in the intended use environments. As stated in our previous review, the HF validation study results identified use errors and close calls that occurred on critical tasks, which could result in compromised medical care, including risks of dosing errors (e.g. underdose). Regarding the sponsor's determination that the Kynmobi packaging used in the HF validation study is nearly identical to the intend-to-market product, we note their determination was based on the primary container (film pouch) packaging only. However, we note that the intend-to-market outer carton (i.e. (b) (4) packaging) was not part of the user interface evaluated in the HF validation study. Additionally, we note the intended user population has

	Table 1. Original Recommendations/Sponsor's Response/Subsequent Agency Response		
No.	Original DMEPA Recommendations[h]	Summary of Sponsor's Response (12/7/2018)	DMEPA's Analysis of Sponsor's Response
	otherwise manipulate the packaging in a manner that eliminates the child-resistant features, which may increase the risk of secondary exposure. Given that the (b) (4) packaging was not part of the user interface evaluated in the HF validation study and the intended user population has clinical manifestations that might impact interaction with the (b) (4) packaging, we find that the study results are not representative of real-world use. We recommend your additional HF validation study evaluates the intend-to-market packaging (i.e. (b) (4) packaging).		clinical manifestations that might impact their interaction with the (b) (4) packaging (e.g. ability to open and close the packaging). As such, we do not have data to demonstrate that the intended user population can safely and effectively use the proposed packaging. (b) (4) We expect the sponsor to provide data to support that the intended user is able to access the product in the intend-to-market packaging prior to Agency approval of the proposed product. Regarding the sponsor's statement that an additional HF validation would delay the availability of the product for treatment of OFF episodes in Parkinson's disease (PD) patients, we defer to DNP to determine if whether from a public health perspective, the benefit of having product available for use on the market outweighs the concerns that we identified.
3.	We recommended several revisions to the Instructions for Use (IFU), container labels, and carton labeling	The sponsor's submitted revised IFU and samples of container labels and carton labeling. We note the sponsor	We acknowledge the sponsor implemented our proposed label and labeling revisions and we note the sponsor determined that validation of the revisions is

	Table 1. Original Recommendations/Sponsor's Response/Subsequent Agency Response		
No.	Original DMEPA Recommendations[h]	Summary of Sponsor's Response (12/7/2018)	DMEPA's Analysis of Sponsor's Response
	in the Identified Issues and Recommendations table.	implemented our recommendations; however, the sponsor states they do not agree that the label and labeling revisions require additional HF validation.	not needed. We disagree and continue to find that based on close calls and use errors that occurred on critical tasks, the label and labeling revisions should be validated as part of the user interface in an additional HF validation study to demonstrate that the mitigations are effective and that they do not introduce new use risks.

3 CONCLUSION AND RECOMMENDATIONS

We reviewed the sponsor's submission dated December 7, 2018 and concluded that the provided information does not adequately address the concerns we conveyed in the November 21, 2018 DR letter about the HF validation study results and the (b) (4) packaging. Thus, we maintain our conclusion that the human factors validation study does not provide sufficient evidence to demonstrate that the proposed product can be used safely and effectively by intended users for its intended users and use environments. We discussed our conclusion with the DNP review team and note the division intends to issue a complete response for NDA 210875 based on a quality issue identified with the application as well as the human factors deficiencies identified above. Thus, we provide letter-ready deficiencies in Section 3.1 below that we recommend DNP convey to the sponsor.

3.1 COMMENTS FOR SUNOVION

We acknowledge your December 7, 2018 formal response to the Agency's Discipline Review letter dated November 21, 2018. We note that your submission provided additional information and your plan to address the Agency's concerns about your human factors (HF) validation study results and the (b) (4) packaging.

We acknowledge that you have evaluated this product in the clinical environment. However, given the oversight, training, and tight controls provided in your clinical study, we are not assured that those factors would be provided consistently and routinely to users in real-world use. Thus, we do not find the data obtained from your clinical study would be representative of a real-world interaction with your proposed user-interface. Additionally, the intend-to-market outer carton (i.e. (b) (4) packaging) was not part of the user interface evaluated in the HF validation study. (b) (4) Furthermore, we expect that the product is safe and effective for use at the time of approval.

Thus, we maintain that the HF validation study does not provide sufficient evidence to demonstrate that the proposed product can be used safely and effectively by intended users for its intended users and use environments. The following deficiencies listed in our Discipline Review letter dated November 21, 2018 remain outstanding:

The HF validation study methodology is deficient and the results do not demonstrate that your proposed product can be used safely and effectively by the intended users for its

intended uses and use environments. Your HF study results identified several use errors and close calls that occurred on critical tasks. Additionally, you have not provided data to demonstrate that your proposed mitigations are effective and do not introduce new use-related risks. Furthermore, your HF study did not evaluate the final intend-to-market user interface, i.e., your proposed (b) (4) packaging. Thus, you have not provided sufficient data to demonstrate whether the intended users can open and close the packaging.

To address these concerns, we recommend you evaluate the use-related errors observed in the HF study, employ additional mitigation strategies, update your use-related risk analysis, and conduct another HF validation study using the intend-to-market user interface (i.e., (b) (4) packaging) to demonstrate that the mitigations are effective and don't introduce new risks.

We recommend you consider the following prior the conducting another HF validation study:

1. HF validation study results

   Your study results showed several use errors and close calls that occurred on critical tasks. We note that you implemented revisions to the Instructions for Use (IFU) and film pouch (container label) to address the use errors and close calls. However, you did not validate the revisions to the user interface. We are concerned with these issues because of the clinical significance of failures with critical tasks, including underdose and risk of adverse events. Furthermore, our evaluation of the proposed user interface, label and labeling identified areas of vulnerability that may lead to medication errors and we provided additional recommendations in our November 21, 2018 letter. We acknowledge that you have implemented our IFU, container label, and carton labeling recommendations. We recommend you provide results of another human factors validation study using the final intend-to-market user interface to demonstrate that the mitigations are effective and that they do not introduce new risks.

2. (b) (4) packaging

   A. We note that the (b) (4) packaging requires a push-pull technique to open, which may pose concerns for the intended user population (i.e. patients with Parkinson's disease) due to dexterity and motor impairments that occur in the OFF period. We also note that Kynmobi is intended for the acute, intermittent

treatment of "OFF" episodes associated with Parkinson's disease; therefore, delay in therapy (e.g. due to difficulty opening the [redacted] packaging) would cause the user to remain in the OFF state. We are concerned that if users experience difficulty opening or closing the [redacted] packaging, they might attempt to remove the foil pouches from the packaging permanently, or otherwise manipulate the packaging in a manner that eliminates the child-resistant features, which may increase the risk of secondary exposure. Given that the [redacted] packaging was not part of the user interface evaluated in the HF validation study and the intended user population has clinical manifestations that might impact interaction with the [redacted] packaging, we find that the study results are not representative of real-world use. We recommend your additional HF validation study evaluates the intend-to-market packaging (i.e. [redacted] packaging).

We recommend you submit your HF validation study protocol for feedback from the Agency before commencing your study. Note that submission of a protocol for review is not a requirement. If you decide not to submit a protocol, this approach carries some risk to you because prospective Agency review is not possible, but this is a business decision for your company.

Please refer to our draft guidance titled "Contents of a Complete Submission for Threshold Analyses and Human Factors Submissions to Drug and Biologic Applications" for the content of a human factors validation study protocol submission. The guidance is available online at https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM621902.pdf

Place the requested information in eCTD Section 5.3.5.4 – Other Study reports and related information.

Guidance on human factors procedures to follow can be found in:

Applying Human Factors and Usability Engineering to Medical Devices, available online at:
http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm259760.pdf

Guidance on Safety Considerations for Product Design to Minimize Medication Errors and can be found online at:

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM331810.pdf

Note that we recently published two draft guidance documents that, while not yet finalized, might also be useful in understanding our current thinking and our approach to human factors for combination products, product design, and labeling:

Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development and can be found online at:

http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM484345.pdf

Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors and can be found online at:

http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm349009.pdf

APPENDIX A. Sponsor's Response to Discipline Review letter

Full DR letter response accessible in EDR via:

\\cdsesub1\evsprod\nda210875\0037\m1\us\111-info-amend\resp-fda-discipline-review-letter-21nov2018.pdf

APPENDIX B. LABELS AND LABELING

B.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[i] along with postmarket medication error data, we reviewed the following Kynmobi labels and labeling submitted by Sunovion Pharmaceuticals Inc. on December 7, 2018.

- Container labels
- Carton labeling
- Instructions for Use (not pictured)

- Container label (trade)

(b) (4)

6 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

[i] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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

/s/

EBONY A WHALEY
01/14/2019 03:44:31 PM

LOLITA G WHITE
01/14/2019 03:50:41 PM

QUYNHNHU T NGUYEN
01/14/2019 03:53:46 PM

DANIELLE M HARRIS
01/15/2019 09:40:57 AM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs

REVIEW DEFERRAL MEMORANDUM

Date:	January 8, 2019
To:	Billy Dunn, MD Director Division of Neurology Products (DNP)
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Marcia Williams, PhD Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Nyedra Booker, PharmD, MPH Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
Subject:	Review Deferred: Patient Package Insert (PPI) and Instructions for Use (IFU)
Drug Name (established name):	KYNMOBI (apomorphine hydrochloride)
Dosage Form and Route:	sublingual film
Application Type/Number:	NDA 210875
Applicant:	Sunovion Pharmaceuticals, Inc.

1 INTRODUCTION

On March 29, 2018 Sunovion Pharmaceuticals, Inc. submitted for the Agency's review, an Original New Drug Application (NDA)-Request for Priority Review Designation for KYNMOBI (apomorphine hydrochloride) sublingual film. The proposed indication for KYNMOBI (apomorphine hydrochloride) sublingual film is for the acute, intermittent treatment of "OFF" episodes associated with Parkinson's disease (PD) (b) (4)

On April 3, 2018, the Division of Neurology Products (DNP) requested that the Division of Medical Policy Programs (DMPP) review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for KYNMOBI (apomorphine hydrochloride) sublingual film.

This memorandum documents the DMPP review deferral of the Applicant's proposed PPI and IFU for KYNMOBI (apomorphine hydrochloride) sublingual film.

2 CONCLUSIONS

Due to outstanding product quality and Division of Medication Error Prevention and Analysis (DMEPA)/Human Factor (HF) deficiencies, DNP plans to issue a Complete Response (CR) letter. Therefore, DMPP defers comment on the Applicant's patient labeling at this time. A final review will be performed after the Applicant submits a complete response to the CR letter. Please send us a new consult request at such time.

Please notify us if you have any questions.

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

/s/

NYEDRA W BOOKER
01/08/2019 12:04:40 PM

MARCIA B WILLIAMS
01/08/2019 12:06:25 PM

LASHAWN M GRIFFITHS
01/09/2019 12:12:12 PM

Clinical Inspection Summary

Date	11/26/2018
From	Cara Alfaro, Pharm.D., Clinical Analyst Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Jack Dan, Regulatory Project Manager Kenneth Bergmann, M.D., Medical Officer Division of Neurology Products
NDA #	210875
Applicant	Sunovion Pharmaceuticals
Drug	Apomorphine sublingual film
NME	No
Proposed Indication	Acute, intermittent treatment of "OFF" episodes associated with Parkinson's disease (b) (4)
Consultation Request Date	5/29/2018
Summary Goal Date	11/29/2018
Action Goal Date	1/29/2019
PDUFA Date	1/29/2019

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical sites of Drs. Truong and Liang were inspected in support of this NDA. The studies appear to have been conducted adequately, and the data generated by these sites appear acceptable in support of the respective indication. In particular, adverse events submitted by the sponsor were verified against source documents at the sites, with a focus on adverse events consistent with hypersensitivity reactions. Source document review verified adverse events, with no evidence of under-reporting of adverse events.

As requested by the review division (DNP), study drug dosing diaries were collected during these inspections. Two of four subjects at Dr. Liang's site completed the forms incorrectly and recorded dosing information for a concomitant medication rather than the study drug. There was no documentation at the site that these subjects had been retrained on how to complete the diaries correctly or any clarification of the dosing of study medication. Therefore, study drug dosing information for Subjects # (b) (6) and # (b) (6) is not considered reliable. Dosing diaries were collected for four of five subjects enrolled at Dr. Truong's site, and these diaries appear to have been completed correctly.

The final compliance classification of the inspection of Dr. Truong was No Action Indicated (NAI). The final compliance classification of Dr. Liang was Voluntary Action Indicated (VAI).

II. BACKGROUND

Apomorphine sublingual film is being developed by Sunovion Pharmaceuticals, under NDA 210875 (IND 110,955), for the acute intermittent treatment of "OFF" episodes associated with Parkinson's Disease (PD) (b) (4) These "OFF" episodes are periods in which patients have greater difficulty with movement with regard to mobility, slowness, and stiffness.

Approval for apomorphine sublingual films is being sought through a 505(b)(2) pathway with Apokyn®, apomorphine subcutaneous injection, as the reference listed drug. Apokyne® is the only product in the U.S. approved for the acute, intermittent treatment of "OFF" episodes associated with advanced PD. Apomorphine sublingual film is being developed as an alternative dosage form that is reportedly easier to administer.

The sponsor has submitted one Phase 3 study, CTH-300, in support of the efficacy and safety of apomorphine sublingual film for the acute, intermittent treatment of "OFF" episodes associated with PD. The sponsor also submitted one open-label extension study, CTH-301, to support long-term safety of apomorphine sublingual film in this population. De novo subjects and subjects completing prior protocols, including CTH-300, could enroll in Protocol CTH-301.

Protocol CTH-300

Title: "A Phase 3, randomized, double-blind, placebo-controlled, parallel-group study to examine the efficacy, safety and tolerability of APL-130277 [apomorphine] in levodopa responsive patients with Parkinson's Disease complicated by motor fluctuations ("OFF" episodes)"

Subjects: 141

Sites: 32 sites in the U.S. and 1 site in Canada

Study Initiation and Completion Dates: 6/18/2015 to 12/11/2017

Database Lock: 12/21/2017

This was a 12-week, randomized, double-blind, placebo controlled study in levodopa responsive PD subjects with motor fluctuations. Included were subjects with Parkinson's disease who had a clinically meaningful response to levodopa, receiving stable doses of levodopa/carbidopa for at least 4 weeks before screening, experienced at least one well defined "OFF" episode per day, with a total daily "OFF" time duration of ≥2 hours (waking hours), and a Mini Mental State Examination (MMSE) score >25.

The study was comprised of three phases:

- **Screening Phase** (≤28 days)
- **Dose Titration Phase** (open-label, ≤21 days): Subjects were administered single escalating doses of apomorphine (10 to 35 mg) at intervals of every 3 days to determine the dose for treating "OFF" episodes. Once an effective dose was determined, defined as a full "ON" response within 45 minutes, no further dose escalations occurred.
- **Maintenance Treatment Phase** (double-blind, 12 weeks): The initial Maintenance Treatment Phase visit occurred between 7 and 30 days after the final Dose Titration Phase Visit. Subjects were randomized in a 1:1 ratio to receive apomorphine or placebo at the dose determined in the Dose Titration Phase. Subjects self-administered the study drug in up to 5 "OFF" episodes per day for 12 weeks. Subjects returned to the clinic at 4-week intervals for safety and efficacy assessments. Between each study visit, subjects were contacted by telephone at 2-week intervals. Subjects could return to the clinic for an unscheduled Dose Adjustment Visit if a dose reduction was needed for safety and tolerability.

Subject were given a home dosing diary at the first visit (TV1) of the Dose Titration Phase (for training purposes) and at each visit during the Maintenance Treatment Phase of the study. The following information was to be collected: date, subject number, the time study treatment was self-administered, "ON"/"OFF" status at 30 minutes following dosing.

The *primary efficacy endpoint* was the mean change from pre-dose in the Movement Disorders Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part III Motor Examination score at 30 minutes after dosing at Week 12 of the Maintenance Treatment Phase.

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

Protocol CTH-301

Title: "An open-label, Phase 3 study examining the long-term safety, tolerability and efficacy of APL-130277 [apomorphine] in levodopa responsive patients with Parkinson's Disease complicated by motor fluctuations"

Subjects: Subjects completing prior studies (CTH-201, CTH-203, CTH-300, CTH-302) and approximately 100 *de novo* subjects

Sites: 32 sites in the U.S. and 1 site in Canada

Study Initiation and Completion Dates: Study is ongoing

Database Cut-Off Date: 1/19/2018

This is an ongoing, open-label study to evaluate the long-term safety and tolerability of apomorphine in levodopa responsive subjects with PD. Enrolled are subjects completing prior protocols, including CTH-300, as well as *de novo* subjects. Inclusion criteria are similar to Protocol CTH-300. This open-label study includes a Dose Titration Phase (similar to Protocol

CTH-300) and a Long-Term Safety Phase. Subjects enrolling from Protocol CTH-300 enter into the Long-Term Phase and do not repeat the Dose Titration Phase. Similar to Protocol CTH-300, the maximum dose of apomorphine in this study is 35 mg and can be self-administered up to 5 times per day for treatment of "OFF" episodes. During the first year of the Long-Term Phase, study visits occur at 4 weeks, 12 weeks, and every 12 weeks thereafter. For years 2 through 5, subjects will return to the clinic every 16 weeks. Subjects may continue to participate in the study until the sponsor terminates the study or until study drug becomes commercially available.

Rationale for Site Selection

The clinical sites were chosen primarily based on numbers of protocol violations, adverse events of interest (hypersensitivity), and prior inspectional history.

III. RESULTS

Site #/ Name of CI Address	**Protocol # # of Enrolled Subjects**	**Inspection Dates**	**Final Compliance Classification**
Site #1007 **Daniel Truong, M.D.** 9940 Talbert Avenue Suite 204 Fountain Valley, CA 92708	CTH-300 Subjects: 5 CTH-301 Subjects: 5	27-31 Aug 2018	NAI
Site #1029 **Tsao-Wei Liang, M.D.** 909 Walnut Street, 2nd Floor Philadelphia, PA 19107	CTH-300 Subjects: 4 CTH-301 Subjects: 4	6-10 Aug 2018	VAI

Compliance Classifications
NAI = No Action Indicated, no deviation from regulations.
VAI = Voluntary Action Indicated, deviation(s) from regulations.
OAI = Official Action Indicated, significant deviations from regulations. Data may be unreliable.

1. Daniel Truong, M.D.

At this site for Protocol CTH-300, 20 subjects were screened, 5 subjects were enrolled and randomized, and 4 subjects completed the study. One subject discontinued due to an adverse event (urticaria).

At this site for Protocol CTH-301, 6 subjects were screened and 5 subjects were enrolled (3 had participated in Protocol CTH-300 and 2 were *de novo* subjects). Two subjects completed this study, two subjects discontinued the study due to inability to travel to site/other personal issues and an adverse event (throat tightness, pharyngeal edema; Subject # (b) (6)). One subject remains active in this ongoing study.

Signed informed consent forms, dated prior to participation in the study, were present for all subjects who were screened. An audit of the study records of all subjects enrolled was conducted. Records reviewed included, but were not limited to, source documents, monitoring documents, IRB/sponsor communications, financial disclosure, test article accountability, inclusion/exclusion criteria, adverse event reports, laboratory results, concomitant medications, protocol deviations, key secondary efficacy endpoint (subject-rated ON response), and primary efficacy endpoint (MDS-UPDRS Part III scores).

The primary efficacy endpoint was the mean change from pre-dose in the MDS-UPDRS Part III Motor Examination score at 30 minutes after dosing at Week 12. For each subject, the MDS-UPDRS Part III scores at pre-dose and at 30 minutes after dosing at Week 12 were verified, and no discrepancies were identified. The key secondary efficacy endpoint was the percentage of subjects with a subject-rated full "ON" response within 30 minutes at Week 12. Subject-rated full "ON" response within 30 minutes at Week 12 was verified, and no discrepancies were identified.

The FDA field investigator collected dosing diaries for four of the five randomized subjects; the dosing diary for Subject # (b) (6) was inadvertently not collected. Per protocol, subjects were to complete dosing diaries for the two days prior to each study visit. The dosing diaries appeared to have been completed correctly. As requested by the review division (DNP), the frequency of daily dosing of study drug is provided in Table 1 on the following page.

Table 1. CTH-300 Study Drug Dosing Diary (Site #1007)

Subject #	Date	Visit	Number of Study Drug Doses
(b) (6)	9/22/15	MV2	3
	9/23/15	MV2	3
	10/20/15	MV3	3
	10/21/15	MV3	2
	12/1/15	MV4	3
	12/2/15	MV4	4
	11/21/15	MV2	2
	11/22/15	MV2	2
	12/14/15	MV3	1
	12/15/15	MV3	1
	1/23/16	MV4	2
	1/24/16	MV4	2
	2/29/16	MV2	3
	3/1/16	MV2	3
	4/4/16	MV3	3
	4/5/16	MV3	3
	4/26/16	MV4	3
	4/27/16	MV4	3
	9/25/17	MV2	3
	9/26/17	MV2	2
	10/24/17	MV3	2
	10/25/17	MV3	2
	11/20/17	MV4	2
	11/21/17	MV4	3

Adverse events were reviewed, with a focus on events consistent with a hypersensitivity reaction (as requested by the review division):

- Subject # (b) (6), participating in Protocol CTH-300 and randomized to apomorphine SL prn, experienced adverse events consistent with a hypersensitivity reaction. Per sponsor line listings, these adverse events included lip swelling (9/28 – 10/6/15), oral mucosal blistering (9/28 – 10/6/2015), swelling face (9/28 – 10/6/15), and urticaria (11/13/15 - ongoing). The subject was randomized to apomorphine 15 mg on 9/23/2018. Study drug was withdrawn on 9/28/15 due to these adverse events. A narrative was provided for this subject in the NDA submission. In general, the adverse events described in the narrative were consistent with the source documents available at the site. Email correspondence between the clinical research coordinator and the Chief Medical Officer (CMO) for Cynapsus Therapeutic Inc. was available at the site. In this correspondence, dated 10/14/2015, the CMO requested that the site consider rechallenging the subject at the EOS visit due to the confounding factor that the subject had received a flu vaccine around the time of the hypersensitivity reactions. The FDA field investigator did not collect data to determine whether a rechallenge was attempted. However, the narrative

states that study drug was withdrawn on 11/13/2015, after the subject had developed urticaria, which would indicate that this rechallenge had been performed. An oropharyngeal examination on 11/13/2015 did not reveal any abnormalities. The adverse event log at the site indicates that "hives all over body" resolved on 11/16/2015.

- Subject # (b) (6), participating in CTH-301 and taking apomorphine SL prn, experienced the adverse events pharyngeal edema (6/14 – 6/16/2017), throat tightness (6/14 – 6/16/2017), and oral discomfort [burning sensation in mouth] (6/14/2017). The EOS visit notes for 7/7/2017 state that the subject wished to end study participation and "reports progressively worsening burning sensation and swelling of tongue with investigational product" and "also reports difficulty swallowing." A physical examination and oropharyngeal examination did not note abnormalities. The adverse event log at the site included resolution dates as above (e.g. 6/14/2017, 6/16/2017).

- Subject # (b) (6), participating in CTH-301 and taking apomorphine SL prn, experienced the adverse events swelling of gums (3/3/2016 – 6/23/2016), multi foci redding under tongue (3/3/2016 – 6/23/2016), and tongue swelling (3/3/2016 – 6/23/2016). All adverse events were described as mild, and no action was taken with respect to study drug. This subject completed the study.

- Subject # (b) (6), participating in CTH-301 and taking apomorphine SL prn, experienced the adverse event multi foci reddening right cheek (12/11/2017 – 12/12/2017). At 12/11/2017 visit (TV2), the post-dose oropharyngeal examination noted multi foci reddening inside the right cheek, while the pre-dose examination had been normal. In notes for this visit, the findings were described as small, pinpoint marks arranged in a linear fashion with very mild erythema, suggestive of bite marks. Per the SAE/AESI form, the subject was dosed at their next visit (LTS V1) with no recurrence of this adverse event.

Reviewer Comments: The adverse events provided in the sponsor line listings were verified using source documents at the site. There was no evidence of under-reporting of adverse events.

2. Tsao-Wei Liang, M.D.

At this site for Protocol CTH-300, 8 subjects were screened, 4 subjects were randomized, and 3 subjects completed the study. One subject (Subject # (b) (6)) discontinued the study due to adverse events of abdominal muscle spasms, difficulty concentrating, dyskinesia, and loss of appetite.

At this site for Protocol CTH-301, 5 subjects were screened and enrolled in the study, three of whom had participated in Protocol CTH-300. Two of the five enrolled subjects discontinued the study due to adverse events (mouth swelling and ulceration; nausea, dyskinesia, and fatigue), one subject withdrew due to health issues (kidney stones), one subject completed the study, and one subject is currently enrolled in this ongoing study.

Signed informed consent forms, dated prior to participation in the study, were present for all subjects who were screened. Per protocol, all enrolled subjects had documented approval for enrollment from the Enrollment Adjudication Committee. An audit of the study records of all subjects enrolled was conducted. Records reviewed included, but were not limited to, source documents, monitoring documents, study staff training, IRB/sponsor communications, financial disclosure, test article accountability, inclusion/exclusion criteria, adverse event reports, concomitant medications, protocol deviations, key secondary efficacy endpoint (subject-rated ON response), and primary efficacy endpoint (MDS-UPDRS Part III scores).

The primary efficacy endpoint was the mean change from pre-dose in the MDS-UPDRS Part III Motor Examination score at 30 minutes after dosing at Week 12. For each subject, the MDS-UPDRS Part III scores at dose and at 30 minutes after dosing at Week 12 were verified, and no discrepancies were identified. The key secondary efficacy endpoint was the percentage of subjects with a subject-rated full "ON" response within 30 minutes at Week 12. Subject-rated full "ON" response within 30 minutes at Week 12 was verified, and no discrepancies were identified.

The FDA field investigator collected dosing diaries for all four randomized subjects. Per protocol, study drug dosing diaries were completed for the two days prior to each study visit. Subjects # (b) (6) and # (b) (6) did not complete the study drug dosing diaries correctly. These subjects entered dose times for the concomitant medication, carbidopa/levodopa, rather than for the study drug. There was no documentation at the site that these subjects had been retrained on how to complete the diaries correctly or any clarification of the dosing of study medication.

Table 2. CTH-300 Study Drug Dosing Diary (Site #1029)

Subject #	Date	Visit	Number of Study Drug Doses
(b) (6)	7/19/2016	MV2	2
	7/20/2016	MV2	2
	Completed incorrectly		
	7/5/2017	MV1	5
	7/6/2017	MV1	5
	8/9/2017	MV2	0
	8/10/2017	MV2	3
	9/5/2017	MV3	2
	9/6/2017	MV3	3
	9/20/2017	MV4	0
	9/21/2017	MV4	0
	Completed incorrectly		

A Form FDA 483 was not issued at the conclusion of the inspection. However, based on the incorrectly completed study drug dosing diaries in two of four subjects, failure to provide documentation of retraining of subjects, and failure to clarify study drug dosing information, the inspection was upgraded from NAI to VAI.

Reviewer Comments: Two of four subjects did not complete the study drug dosing diaries correctly. Study drug dosing information for Subjects # (b) (6) *and #* (b) (6) *is not considered reliable.*

Adverse events were reviewed, with a focus on events consistent with a hypersensitivity reaction (as requested by the review division):

- Subject # (b) (6), participating in Protocol CTH-301 and taking apomorphine SL prn, experienced adverse events consistent with a hypersensitivity reaction. Per sponsor line listings, these adverse events included mouth swelling (3/25 – 4/4/17) and mouth ulceration (3/25 – 4/4/17; 5/14 – ongoing). Study drug was interrupted in March 2017, after the first hypersensitivity adverse events, and withdrawn in May after the second mouth ulceration adverse event occurred. The adverse event logs at the site were consistent with adverse events in the sponsor line listing. The adverse event log noted that the mouth ulceration adverse event was ongoing at the end of study visit on 5/20/2017.

- Subject # (b) (6), participating in Protocol CTH-301 and taking apomorphine SL prn, experienced adverse events consistent with a hypersensitivity reaction. Per sponsor line listings, these adverse events included small, focal, closed vesicle right-center of soft palate (12/21/17 – ongoing) and erythema of posterior pillar of fauces (12/21/17 – ongoing). The sponsor provided a narrative summary for this subject in the NDA submission. The subject was continuing in the study at the time the narrative was submitted, with the last study visit date in the narrative being 12/21/2017. Source documents at the site show that on 6/28/2018 (Long-term Safety Visit 4) the pre-dose oropharyngeal cavity examination noted a small focal, white ulceration of the right posterior pillar of mild severity. Upon query from the sponsor in July 2018, the site stated that the subject "was not using the strips very often (~1x/week), and she had reported no symptoms relevant to the mouth." She was on the 30 mg dose of study drug at the time the ulcerations were noted. According to the site, this subject was due to return to the clinic in August 2018 to determine the stop date/final outcome of the adverse event and rechallenge details, if applicable.

Reviewer Comments: The adverse events provided in the sponsor line listings were verified using source documents at the site. There was no evidence of under-reporting of adverse events. The review division may wish to contact the sponsor for an update on the adverse events for Subject # (b) (6)*, including the results of a possible rechallenge.*

{See appended electronic signature page}

Cara Alfaro, Pharm.D.
Clinical Analyst
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Phillip Kronstein, M.D.
Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Kassa Ayalew, M.D., M.P.H
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

cc:

Central Document Room/NDA #210875
DNP/Division Director/Billy Dunn
DNP/Medical Team Leader/Gerald Podskalny
DNP/Medical Officer/Kenneth Bergmann
DNP/Project Manager/Jack Dan
OSI/Office Director/David Burrow
OSI/DCCE/ Division Director/Ni Khin
OSI/DCCE/GCPAB/Branch Chief/Kassa Ayalew
OSI/DCCE/GCPAB/Team Leader/Phillip Kronstein
OSI/DCCE/GCPAB/Reviewer/Cara Alfaro
OSI/GCPAB Program Analyst/Yolanda Patague

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

/s/

CARA L ALFARO
11/26/2018

PHILLIP D KRONSTEIN
11/26/2018

KASSA AYALEW
11/26/2018

Interdisciplinary Review Team for QT Studies Consultation: Thorough QT Study Review

NDA	NDA 210875
Brand Name	KYNMOBI™
Generic Name	Apomorphine sublingual film (APL-130277)
Sponsor	Sunovion Pharmaceuticals Inc.
Indication	Acute, intermittent treatment of "OFF" episodes associated with Parkinson's diseas (b) (4)
Dosage Form	Sublingual film
Drug Class	Non-ergot dopamine agonist
Therapeutic Dosing Regimen	Dose titration should be initiated with 10 mg sublingual film when patients are in an "OFF" state. If the patient tolerates the dose but does not respond adequately, increase to the next dose strength at the next observed "OFF" period. (b) (4) Doses should be separated by at least 2 hours. Do not administer more than 5 doses per day. The average frequency of dosing in the development program was 2-3 times per day.
Duration of Therapeutic Use	Acute intermittent use
Maximum Tolerated Dose	Not known
Submission Number and Date	SDN 001; 29 Mar 2018
Review Division	DNP

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

1 SUMMARY

1.1 OVERALL SUMMARY OF FINDINGS

The TQT Study CTH-201 is inconclusive to exclude a 10-ms mean increase in the QTc interval at recommended clinical dosing regimen (10 mg starting dose with titration up to

a highest dose of 35 mg, with a maximum of 5 doses per day and the consecutive doses separated by at least 2 hours).

The rationale for our conclusion is as follows:

- **Doses evaluated do not cover the exposures associated with clinical dosing regimen**. Based on the design, the final dose levels were achieved through individual titrations based on tolerability rather than by randomized treatment assignment. The higher dose groups did not result in higher exposures compared to lower dose groups as would have been expected with linear PK. The mean Cmax across dose levels is ~4 ng/mL, which is inadequate to cover C_{max} of the maximum recommended therapeutic dose of 35 mg (~9 ng/ml). Furthermore, higher exposures are expected in patients with renal impairment (50% higher C_{max} with renal impairment).
- **Lack of dose-response for QTc prolongation**. In central tendency analysis for pooled dose levels (10-50 mg), the largest upper bound of the 2-sided 90% CI for the mean ΔΔQTcF was 9.8 ms, with the corresponding mean of 6.3 ms. When the same analysis was used to assess dose-response, the QTc effects for 10- and 20-mg dose levels were different despite having similar exposures: the largest mean ΔΔQTc exceeded 10 ms at 4 timepoints for the 10 mg dose whereas it was below 10 ms for the 20 mg dose at all timepoints. These discrepant findings could be caused by the small number of subjects within each dose level and the study was not powered to detect dose-response. Furthermore, there were too few patients receiving 15 mg and doses above 20 mg (2 for 25 mg, 3 for 35 mg and 1 for 50 mg) to be able to adequately characterize the change in QTc interval at those dose levels.
- **Lack of ability to adequately characterize concentration-QTc relationship.** A concentration-QTc analysis would have been the more appropriate analysis for this titration study design to project the QTc effects at dose/exposures of interest. However, the data did not support a direct effect linear C-QTc model. Potential reasons for the poor fit is narrow range of exposures (higher doses did not provide higher concentrations); and possible time delay between peak QTc effects and peak concentrations.

1.2 QT INTERDISCIPLINARY REVIEW TEAM'S COMMENTS

- Besides the above major issues, there was a minor data quality issue identified with the submitted data: subjects (b) (6) and (b) (6) received placebo during period 2 and period 3 respectively, but non-zero (quantifiable) APL-130277 concentrations were reported on this placebo treatment in the dataset.
- The *in vitro* safety margin for hERG channel inhibition (IC_{50} / $C_{max, free}$) is 38-fold for the therapeutic C_{max} at maximum clinical dose of 35 mg; thereby supporting a mechanism for QTc prolongation at clinical exposures.
- The reference listed drug for this 505(b)(2) application, Apokyn® (first approved in 2004), carries Warning and Precautions language for QTc prolongation in the label. The data for the Apokyn submission was submitted to the Agency in paper format and are not easily accessible for further evaluation of PK-QTc effects to draw inference about the QTc prolongation potential of APL-130277 based on comparison of exposures.

- Lastly, ECG data were collected in the pivotal phase 3 study CTH-300, which had similar study design as Study CTH-201 and the distribution of doses were similar between the two studies. Triplicate ECGs were collected 50 minutes post dose during the double-blind placebo-controlled maintenance phase visits. There were 54 subjects on APL-130277 in CTH-300 and none of the subjects had a post-dose QTcF >500 ms or ΔQTcF >60 ms (See Appendix 6.3).

2 PROPOSED LABEL

The sponsor provided the following QT-related language in their current proposed label:

(b) (4)

Reviewer's comments: We have the following recommendations for labeling. We defer final labeling decisions to the Division.

- *We recommend removing language from section* (b) (4)
- (b) (4)
- *As per the clinical pharmacology guidance for labeling, change the Section 12.2 subheading from "* (b) (4) *" to "Cardiac Electrophysiology" and change the units from "msec" to "ms" wherever applicable.*

3 BACKGROUND

3.1 PRODUCT INFORMATION

Apomorphine is a non-ergot dopamine agonist that binds to D1-like and D2-like receptors. The product under development, APL-130277, is a soluble thin film for sublingual

administration. APL-130277 is designed to deliver apomorphine systemically through absorption from the oral cavity mucosa, thus bypassing the extensive first pass metabolism associated with gastrointestinal absorption of the compound.

The product is intended to be an alternative to the injectable form of apomorphine hydrochloride, which is marketed in North America as APOKYN® and in most of Europe and Asia as APO-go® and MOVAPO® in Canada and Australia.

This product is submitted as a 505(b)(2) application with APOKYN® as the reference listed drug.

3.2 MARKET APPROVAL STATUS

Apomorphine sublingual film is not approved for marketing in any country.

3.3 PRECLINICAL INFORMATION

Multiple studies assessing proarrhythmic risk by apomorphine have been performed by different investigators with varying results. Apomorphine blocked hERG mediated K+ channel currents in Chinese hamster ovary cells with an IC_{50} value of 2.4 μM using the whole-cell patch clamp technique. In a study supporting APOKYN, the IC_{50} for apomorphine inhibition of cloned hERG channels was determined to be 0.127 μM.

Apomorphine significantly prolonged repolarization action potential duration at 90% re-polarization (APD90) by 20 msec at a concentration of 1.5 μM in a canine Purkinje fiber assay. In a study supporting APOKYN, no effects on action potential duration in dog purkinje fibers were seen at doses up to 1 μM.

In conscious adult female beagle dogs, intravenous apomorphine (25 μg/kg) increased QT_c (+ 15 milliseconds) at a mean concentration of 3.4 ng/ml.

See Appendix 6.1 for more information.

Reviewer's comment: hERG IC_{50} of 0.127 μM quoted above translates to a safety margin (IC_{50} / $C_{max, free}$) of 38-fold considering the therapeutic C_{max} of 9 ng/mL at the maximum clinical dose, 90% protein binding and molecular weight of 267.3 g/mol.

3.4 CLINICAL CARDIAC SAFETY

See Appendix 6.1 for more information.

Clinical cardiac safety is provided for the single Phase 3 placebo-controlled study (CTH-300). Cardiac safety events as defined per ICH E14 guidance that were observed during the maintenance / treatment phase in the single Phase 3 placebo-controlled study CTH-300 are included in sponsor's table below. There were no events of syncope, seizures, ventricular arrhythmias, ventricular tachycardia, ventricular fibrillation, flutter, torsade de pointes, or sudden death observed during the maintenance / treatment phase of study CTH-300.

Table 4: Cardiac Safety Events Observed During Maintenance / Treatment Phase in Placebo-controlled Study CTH-300 (ISS Analysis Pool 1)

Preferred Term	APL-130277 N = 54 n (%)	Placebo N = 55 n (%)
Cardiac arrest	1 (1.9%)	0
Electrocardiogram QT prolonged	1 (1.9%)	0

Given that APL-130277 uses the same active pharmaceutical ingredient (API) as APOKYN® and APO-go®, and the pharmacokinetic profile is comparable between the sublingual thin film and the s.c. injection, the risks associated with the drug will be the same as those seen in the APOKYN® and APO-go®.

The approved label for APOKYN® has the following labeling language related to QTc prolongation and AEs that are typically listed under MedDRA SMQ "Torsade de pointes/QT Prolongation":

5 WARNINGS AND PRECAUTIONS

5.4 Syncope

In clinical studies, approximately 2% of APOKYN-treated patients experienced syncope.

5.10 Coronary Events

In clinical studies, 4% of patients treated with APOKYN experienced angina, myocardial infarction, cardiac arrest and/or sudden death; some cases of angina and myocardial infarction occurred in close proximity to APOKYN dosing (within 2 hours), while other cases of cardiac arrest and sudden death were observed at times unrelated to dosing. APOKYN has been shown to reduce resting systolic and diastolic blood pressure and may have the potential to exacerbate coronary (and cerebral) ischemia in patients with known cardiovascular and cerebrovascular disease. If patients develop signs and symptoms of coronary or cerebral ischemia, prescribers should re-evaluate the continued use of APOKYN.

5.11 QTc Prolongation and Potential for Proarrhythmic Effects

There is a small dose related prolongation of QTc interval with doses of APOKYN greater than 6 mg *[See Clinical Pharmacology (12.2)]*. Doses greater than 6 mg do not provide additional clinical benefit and are not recommended.

Drugs that prolong the QTc interval have been associated with torsades de pointes and sudden death. The relationship of QTc prolongation to torsades de pointes is clearest for larger increases (20 msec and greater), but it is possible that smaller QTc prolongations may also increase risk, or increase it in susceptible individuals, such as those with hypokalemia, hypomagnesemia, bradycardia, concomitant use of other drugs that prolong the QTc interval, or genetic predisposition (e.g., congenital prolongation of the QT interval). Although torsades de pointes has not been observed in association with the use of APOKYN at recommended doses in clinical studies, experience is too limited to rule out an increased risk. Palpitations and syncope may signal the occurrence of an episode of torsades de pointes.

The risks and benefits of APOKYN treatment should be considered prior to initiating treatment with APOKYN in patients with risk factors for prolonged QTc.

7 DRUG INTERACTIONS

7.4 Drugs Prolonging the QT/QTc Interval

Caution should be exercised when prescribing APOKYN concomitantly with drugs that prolong the QT/QTc interval *[see Warnings and Precautions (5.11)]*.

12 CLINICAL PHARMACOLOGY

12.2 Pharmacodynamics

Prolongation of the QTc Interval: In a placebo-controlled study in which patients received increasing single doses of APOKYN from 2 mg to up to 10 mg, the mean difference in QTc (measured by Holter monitor) between APOKYN and placebo was 0 msec at 4 mg, 1 msec at 6 mg, and 7 msec at 8 mg. Too few patients received a 10 mg dose to be able to adequately characterize the change in QTc interval at that dose.

In a controlled trial in which patients were administered placebo or a single dose of APOKYN (mean dose of 5.2 mg; range of 2 mg to 10 mg), the mean difference between APOKYN and placebo in the change in QTc was about 3 msec at 20 minutes and 90 minutes. In the entire database, 2 patients (one at 2 mg and 6 mg, one at 6 mg) exhibited large QTc increments (> 60 msecs from pre-dose) and had QTc intervals greater than 500 msecs acutely after dosing. Doses of 6 mg or less thus are associated with minimal increases in QTc.

3.5 CLINICAL PHARMACOLOGY

Appendix 6.1 summarizes the key features of clinical pharmacology of apomorphine sublingual film.

4 SPONSOR'S SUBMISSION

4.1 OVERVIEW

The QT-IRT reviewed the protocol prior to conducting this study under IND 110955 on 7 Jun 2016. Higher dose and a three-way balanced crossover design were recommended in the protocol review. In response to the protocol review, the sponsor modified the study design with a highest tolerated dose finding phase and a three-way crossover phase. the sponsor submitted the study report CTH-201 for APL-130277, including electronic datasets and waveforms to the ECG warehouse.

4.2 TQT STUDY

4.2.1 Title

A Phase 2, Randomized, Double-blind, Placebo Controlled, 3-period Crossover, Positive Control, QT-evaluation Study of APL-130277 in Subjects with Parkinson's Disease Complicated by Motor Fluctuations ("OFF" Episodes)

4.2.2 Protocol Number

CTH-201

4.2.3 Study Dates

26 Apr 2017 – 21 Dec 2017

4.2.4 Objectives

The primary objective was to evaluate the effect of APL-130277 compared to placebo on QTc intervals in subjects with Parkinson's disease (PD) complicated by motor fluctuations.

The secondary objectives included the evaluation of safety and pharmacokinetics of APL-130277.

4.2.5 Study Description

4.2.5.1 Design

The study consists of an open-label dose titration phase and a crossover assessment phase. The open-label dose titration phase was to determine the highest tolerated APL-130277 dose for the randomized crossover assessment phase.

The crossover assessment phase is a randomized, 6-sequence, crossover design with three dosing occasions. Each dosing occasion was followed by a 3-day washout period.

This review focused on the crossover thorough QT part.

4.2.5.2 Controls

The Sponsor used both placebo and positive (moxifloxacin) controls.

4.2.5.3 Blinding

The positive (moxifloxacin) control was not blinded. APL-130277 and placebo arms were administered blinded using a double dummy approach.

4.2.6 Treatment Regimen

4.2.6.1 Treatment Arms

There were 3 treatments in the crossover TQT part:

- A: APL-130277 sublingual film at the dose determined in the Dose Titration Phase
- B: Placebo (matched APL-130277) sublingual film
- C: Moxifloxacin 400 mg tablet

4.2.6.2 Sponsor's Justification for Doses

APL-130277 doses of 10 mg to 35 mg were included in the Randomized Crossover Assessment Phase to mimic the exposure in the target population. Where possible, subjects were titrated to a supratherapeutic dose (up to 60 mg) which was 1 or 2 levels above the initial dose producing an "ON" response. These doses met the ICH E14 criteria of being above the intended clinical dose with an acceptable level of adverse events commonly associated with apomorphine.

Reviewer's Comment: The protocol review had stated, "The highest dose to be studied in this study is 40 mg and it is also the highest proposed therapeutic dose. The Sponsor has not provided a comparison of Cmax expected with 40 mg dose vis-à-vis Cmax with 6 mg s.c. dosing of Apokyn®. Moreover, similar to Apokyn®, the Cmax values are expected to increase by 25% in hepatic impairment and 50% in renal impairment subjects. Also, the Apokyn label states that the average frequency of dosing in the clinical development program was 3 times per day. Thus, a single dose of 40 mg may be inadequate to cover the high clinical exposures due to effect of intrinsic/extrinsic factors and possible accumulation under real dosing scenario. We recommend the Sponsor includes a dose higher than 40 mg if not prevented by safety". Accordingly, the sponsor had planned to initiate dosing at 10 mg and titrate the doses to up to 60 mg based on titration to response and tolerability. However, very few patients received doses above 20 mg (n=2 for 25 mg, n=3 for 35 mg and n=1 for 50 mg).

See Section 5.3 for the details of limitations of this study from the perspective of adequacy of exposure margin.

4.2.6.3 Instructions with Regard to Meals

Reviewer's comment: Not applicable, as the drug product is a sublingual film.

4.2.6.4 ECG and PK Assessments

See Appendix 6.2 for details of ECG and PK assessments. Briefly,

ECG: Triplicate ECGs collected at t=0 (pre-dosing), 15, 30, 45, 60 minutes and at 2, 3, 4, 8, 12, 24 hours after dosing during each period.

PK:

Apomorphine: t=0 (pre-dosing), 30, 45, 60 minutes and at 2 and 4 hours after dosing. Moxifloxacin: t=0 (pre-dosing), 30, 60 minutes, 2, 3, 4, 6, 8 hours after dosing.

Reviewer's Comment: As per the protocol review, ECG/PK sampling time was acceptable for capturing potential effects near T_{max} and delayed effects up to 24 hours.

4.2.6.5 Baseline

The average of redoes QT/QTc values in Period 1 was used as baseline for all periods.

4.2.7 ECG Collection

Intensive 12-Lead Holter monitoring was used to obtain digital ECGs. Standard 12-Lead ECGs were obtained while subjects were recumbent.

4.2.8 Sponsor's Results

4.2.8.1 Study Subjects

A total of 48 subjects with Parkinson's disease complicated by motor fluctuations enrolled in the Dose Titration Phase of the study and received at least one dose of APL-130277 study medication. Forty-one of the 48 subjects (41/48, 85.4%) completed the Dose Titration Phase and entered the Crossover Assessment Phase. One subject

discontinued prior to receiving any of the three study treatments. Thus, a total of 40 subjects were included in the Crossover Assessment Phase.

The average age (SD) of the 40 subjects was 63.7 years (8.7), ranging from 46 to 88 years. Twenty-six subjects (26/40, 65.0%) were males and 14 subjects (14/40, 35.0%) were females. Most of the subjects (37/40, 92.5%) were White, with the remaining 3 subjects (3/40, 7.5%) being Black or African American. Fourteen subjects (14/40, 35.0%) were of ethnicity Hispanic or Latino.

All 40 subjects were included in the safety, ECG, and PK populations. A total of 31 subjects (31/40, 77.5%) were included in the completer population.

4.2.8.2 Statistical Analyses

4.2.8.2.1 Primary Analysis

Reviewer's Comments: The sponsor's primary analysis was based on data up to 4 hours; results showed that the largest mean QTc difference between APL130277 and placebo was below 10 ms. We agree with the sponsor's conclusions for primary analysis. Please see the reviewer's independent analysis up to 24 hours in Section 5.2.

4.2.8.2.2 Assay Sensitivity

Reviewer's Comments: The sponsor conducted assay sensitivity analysis based on data up to 4 hours; results showed that the assay sensitivity was established for the study. We agree with the sponsor that the assay sensitivity was demonstrated in the study. Please see the reviewer's independent analysis based on data up to 24 hours in Section 5.2.

4.2.8.2.3 Categorical Analysis

Reviewer's Comments: The sponsor listed outliers by time point up to 24 hours. Overall, there were no subjects who experienced QTcF >500 ms and mean change from baseline in QTcF >60 ms. Findings from the reviewer's independent analysis were consistent with the sponsor's results. Please see the reviewer's categorical analysis in Section 5.2.

4.2.8.3 Safety Analysis

No deaths or serious treatment emergent adverse events (serious TEAEs, SAEs) were reported. Five subjects discontinued study treatment during Dose Titration Phase due to dopaminergic TEAE(s). All these TEAEs were resolved.

Orthostatic hypotension was reported in 3 subjects (6.3%). Bundle branch block (left and right), ECG QT prolongation, nodal arrhythmia and glossodynia were each reported once (2.1%;). Of these, Bundle branch block (left: subject (b) (6) and right: subject (b) (6)), ECG QT prolongation (subject (b) (6)) and nodal arrhythmia (subject (b) (6)) were not assessed by the Investigator as drug-related event.

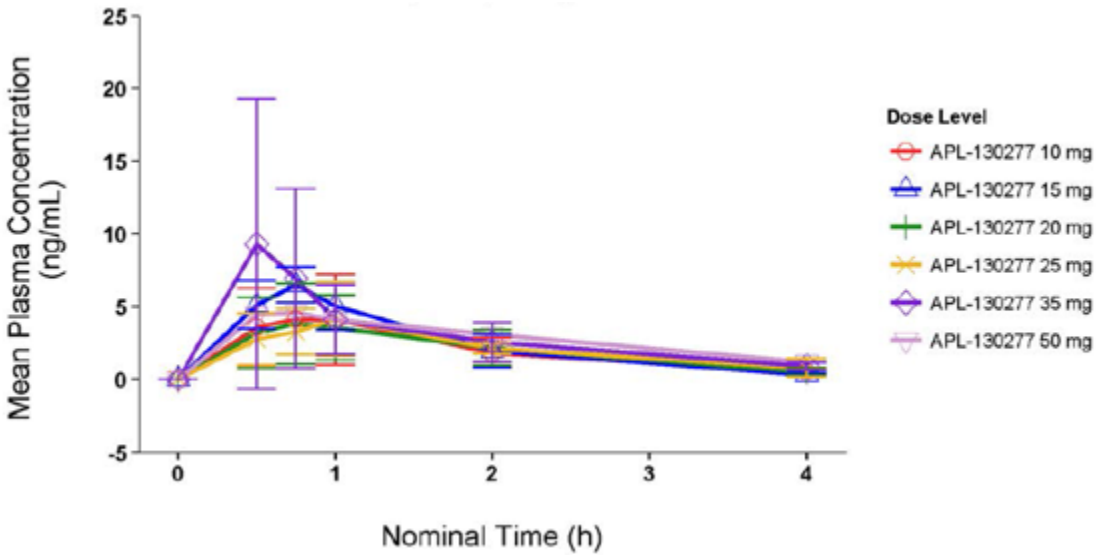
4.2.8.4 Clinical Pharmacology

4.2.8.4.1 Pharmacokinetic Analysis

Apomorphine concentration-time profiles are presented in Figure 1 and the PK results are summarized in Table 1. Following the administration of different doses of apomorphine

sublingual films, the C_{max} values showed considerable variability (%CV > 60%) and the number of subjects were too few for appropriate interpretation (Table 1).

Figure 1: Mean [SD] Apomorphine Plasma Concentration vs Time Plot by Dose Level



Source: Study CTH-201, Amended Pharmacokinetics Report – Figure 4.1 on Page 20-21

Table 1: Arithmetic Mean Apomorphine Plasma PK Parameters by Dose Level

Parameter	Arithmetic Mean Plasma Apomorphine PK					
	10 mg (N=14)	15 mg (N=4)	20 mg (N=15)	25 mg (N=2)	35 mg (N=3)	50 mg[c] (N=1)
Cmax (ng/mL)[a]	5.14 (63.8)	6.57 (18.6)	4.23 (66.3)	4.16 (61.1)	9.29 (107)	4.61
Cmax/Dose (ng/mL/mg)	0.514 (63.8)	0.438 (18.6)	0.212 (66.3)	0.166 (61.1)	0.265 (107)	0.0922
Tmax (h)[b]	0.75 (0.50 - 1.02)	0.75 (0.50 - 0.75)	1.00 (0.50 - 2.07)	1.50 (1.00 - 2.00)	0.58 (0.50 - 0.88)	0.78
AUCinf (h*ng/mL)	7.88 (50.7)	9.70 (35.8)	8.62 (47.4)	NC	17.0 (14.8)	13.6

Source: Study CTH-201, Amended Pharmacokinetics Report, Table on Page 5

4.2.8.4.2 Exposure-Response Analysis

The sponsor did not perform exposure-response analysis.

Reviewer's comment: The reviewer's independent analysis and interpretation is described in Section 5.3. The peak QTc effects showed some delay compared to the T_{max} and a direct effect model for exposure-response relationship did not seem appropriate for describing this relationship.

5 REVIEWERS' ASSESSMENT

5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

The sponsor used QTcF for their primary analysis, which is acceptable since no large changes in heart rate were observed, i.e., mean changes were ≤10 bpm (Section 5.2.2). Therefore, no assessment of the QT/RR correction methodology is necessary and QTcF is used for all reviewers' assessments.

5.2 STATISTICAL ASSESSMENTS

5.2.1 QTc Analysis

5.2.1.1 The Primary Analysis for APL-130277

The statistical reviewer used mixed model to analyze the ΔQTcF effect up to 24 hours. The model includes treatment, sequence, period, time point, treatment by time point, and region as fixed effects and subject as a random effect. Baseline values are also included in the model as a covariate. The analysis results are listed in Table 2.

Table 2: Analysis Results of ΔQTcF and ΔΔQTcF for Treatment Group = A: APL-130277

	ΔQTcF (ms) APL-130277 (N=39)	ΔQTcF (ms) Placebo (N=40)	ΔΔQTcF (ms) APL-130277	
Time (hour)	LSmean	LSmean	LSmean	90% CI
0.25	0.6	-3.4	4.0	(0.5, 7.5)
0.5	0.7	-2.4	3.0	(-0.5, 6.5)
0.75	0.4	-3.4	3.7	(0.2, 7.3)
1	3.0	-3.2	6.3	(2.7, 9.8)
2	2.1	-2.7	4.9	(1.3, 8.4)
3	0.5	-1.3	1.8	(-1.7, 5.3)
4	-0.6	0.1	-0.6	(-4.2, 2.9)
8	-3.8	-3.5	-0.3	(-3.9, 3.3)
12	-0.2	-0.5	0.4	(-3.3, 4.1)
24	-3.8	-6.8	3.0	(-1.9, 7.8)

The largest upper bound of the 2-sided 90% CI for the mean differences between APL-130277 and placebo was 9.8 ms.

The analysis was repeated for the completer population for sensitivity analysis, results from which won't change the interpretation for the primary endpoint.

In addition to sensitivity analysis, the statistical reviewer conducted further analyses using data based on period specific baseline and applying different covariance structures for the MMRM model. Conclusions drawn from these analyses were consistent with the above findings (the reviewer's sensitivity analysis and additional analysis results are not shown).

5.2.1.2 Assay Sensitivity Analysis

The statistical reviewer used the same statistical model to analyze moxifloxacin and placebo data. The results are presented in Table 3. The largest unadjusted 90% lower confidence interval was 8.8 ms. By considering Bonferroni multiple endpoint adjustment, the largest lower confidence interval was 7.5 ms, which indicates that an at least 5 ms QTcF effect due to moxifloxacin can be detected from the study.

About 50% of the subjects were missing at hour 24 in the placebo arm, which might contribute to the unexpected upward trend at later time points. Assay sensitivity can be deemed established for the study.

Table 3: Analysis Results of ΔQTcF and ΔΔQTcF for Moxifloxacin

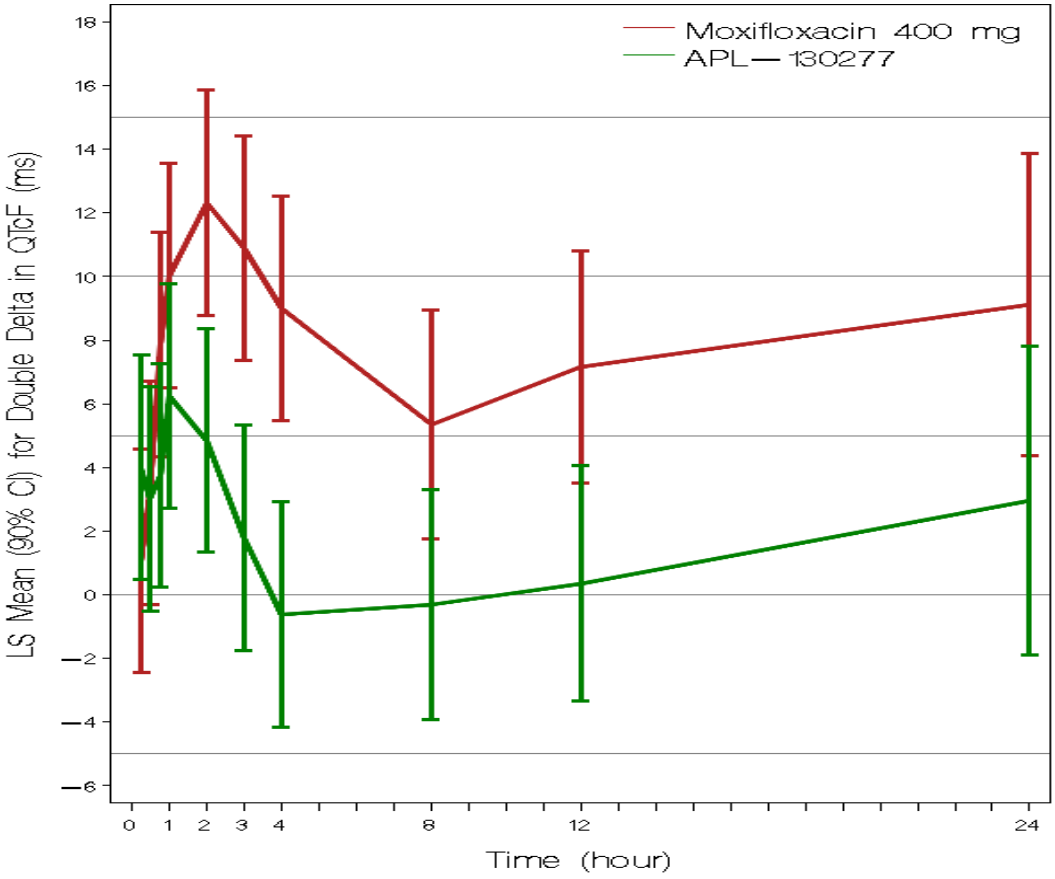
	ΔQTcF (ms) Moxifloxacin 400 mg (N=39)	**ΔQTcF (ms) Placebo (N=40)**	**ΔΔQTcF (ms) Moxifloxacin 400 mg**		
Time (hour)	**LSmean**	**LSmean**	**LSmean**	**90% CI**	**Adjust 90% CI***
0.25	-2.3	-3.4	1.1	(-2.4, 4.6)	(-3.7, 5.9)
0.5	0.9	-2.4	3.2	(-0.3, 6.7)	(-1.6, 8.0)
0.75	4.5	-3.4	7.9	(4.4, 11.4)	(3.1, 12.7)
1	6.8	-3.2	10.0	(6.5, 13.5)	(5.2, 14.8)
2	9.6	-2.7	12.3	(8.8, 15.9)	(7.5, 17.2)
3	9.6	-1.3	10.9	(7.4, 14.4)	(6.1, 15.7)
4	9.1	0.1	9.0	(5.5, 12.5)	(4.2, 13.8)
8	1.9	-3.5	5.3	(1.8, 8.9)	(0.5, 10.2)
12	6.6	-0.5	7.2	(3.5, 10.8)	(2.2, 12.1)
24	2.4	-6.8	9.1	(4.4, 13.9)	(2.7, 15.6)

* Bonferroni method was applied to all time points to adjust for multiple endpoint evaluation at 4 time points around moxifloxacin C_{max}.

5.2.1.3 Graph of ΔΔQTcF Over Time

The following figure displays the time profile of ΔΔQTcF for different treatment groups. It should be noted that CIs are all unadjusted, including moxifloxacin.

Figure 2: Mean and 90% CI ΔΔQTcF Timecourse



5.2.1.4 Categorical Analysis

Categorical analysis was based on safety population and data up to 24 hours.

Table 4 lists the number of subjects as well as the number of observations whose QTcF values were ≤ 450 ms, between 450 ms and 480 ms, and between 480 ms and 500 ms. No subject's QTcF was above 500 ms.

Table 4: Categorical Analysis for QTcF

	Total N		QTcF<=450 ms		450<QTcF<= 480 ms		480<QTcF<= 500 ms	
Treatment Group	**Subj. #**	**Obs. #**	**Subj. #**	**Obs. #**	**Subj. #**	**Obs. #**	**Subj. #**	**Obs. #**
Baseline / Predose	40	108	37 (92.5%)	103 (95.4%)	2 (5.0%)	4 (3.7%)	1 (2.5%)	1 (0.9%)

	Total N		QTcF<=450 ms		450<QTcF<= 480 ms		480<QTcF<= 500 ms	
Treatment Group	**Subj. #**	**Obs. #**	**Subj. #**	**Obs. #**	**Subj. #**	**Obs. #**	**Subj. #**	**Obs. #**
Placebo	40	373	36 (90.0%)	355 (95.2%)	4 (10.0%)	18 (4.8%)	0 (0.0%)	0 (0.0%)
Moxifloxacin 400 mg	39	371	33 (84.6%)	343 (92.5%)	5 (12.8%)	22 (5.9%)	1 (2.6%)	6 (1.6%)
APL-130277	39	367	34 (87.2%)	344 (93.7%)	5 (12.8%)	23 (6.3%)	0 (0.0%)	0 (0.0%)

Table 5 lists the categorical analysis results for ΔQTcF. No subject's change from baseline in QTcF was above 60 ms.

Table 5: Categorical Analysis of ΔQTcF

	Total N		ΔQTcF<=30 ms		30<ΔQTcF<=60 ms	
Treatment Group	**Subj. #**	**Obs. #**	**Subj. #**	**Obs. #**	**Subj. #**	**Obs. #**
Placebo	40	373	38 (95.0%)	370 (99.2%)	2 (5.0%)	3 (0.8%)
Moxifloxacin 400 mg	39	371	32 (82.1%)	359 (96.8%)	7 (17.9%)	12 (3.2%)
APL-130277	39	367	37 (94.9%)	364 (99.2%)	2 (5.1%)	3 (0.8%)

* For outlier analysis based on data from period specific baseline, all numbers are the same except that instead of 2 subjects with 3 observations whose ΔQTcF were between 30 to 60 ms, 1 subject with 2 observations whose ΔQTcF were between 30 to 60 ms.

5.2.2 HR Analysis

The same statistical analysis was performed based on HR. The point estimates and the 90% confidence intervals are presented in Table 6. The largest upper limit of 90% CI for the HR mean differences between APL-130277 and placebo was 7.3 bpm.

The outlier analysis results for HR are presented in Table 7.

Table 6: Analysis Results of ΔHR and ΔΔHR for Treatment Group = A: APL-130277

	ΔHR (bpm) APL-130277 (N=39)	ΔHR (bpm) Placebo (N=40)	ΔΔHR (bpm) APL-130277	
Time (hour)	**LSmean**	**LSmean**	**LSmean**	**90% CI**
0.25	1.9	1.5	0.5	(-2.6, 3.5)

	ΔHR (bpm) APL-130277 (N=39)	ΔHR (bpm) Placebo (N=40)	ΔΔHR (bpm) APL-130277	
Time (hour)	**LSmean**	**LSmean**	**LSmean**	**90% CI**
0.5	0.9	1.5	-0.6	(-3.7, 2.4)
0.75	-0.5	0.1	-0.7	(-3.7, 2.4)
1	-3.7	-0.5	-3.2	(-6.2, -0.1)
2	2.7	2.2	0.6	(-2.5, 3.6)
3	7.0	3.9	3.0	(-0.0, 6.1)
4	8.9	5.5	3.4	(0.3, 6.4)
8	13.2	9.0	4.2	(1.1, 7.3)
12	4.7	3.9	0.8	(-2.4, 3.9)
24	8.7	11.5	-2.8	(-7.0, 1.4)

Table 7: Categorial Analysis for HR

	Total N	HR<=100 bpm	HR>100 bpm	HR>45 bpm	HR<=45 bpm
Treatment Group	**Subj. #**	**Subj. #**	**Subj. #**	**Subj. #**	**Subj. #**
Baseline / Predose	40	38 (95.0%)	2 (5.0%)	40 (100%)	0 (0.0%)
Placebo	40	28 (70.0%)	12 (30.0%)	40 (100%)	0 (0.0%)
Moxifloxacin 400 mg	39	32 (82.1%)	7 (17.9%)	39 (100%)	0 (0.0%)
APL-130277	39	29 (74.4%)	10 (25.6%)	38 (97.4%)	1 (2.6%)

5.2.3 PR Analysis

The same statistical analysis was performed based on PR interval. The point estimates and the 90% confidence intervals are presented in Table 8. The largest upper limit of 90% CI for the PR mean differences between APL-130277 and placebo was 6.0 ms.

The outlier analysis results for PR are presented in Table 9. No subjects had PR >220 ms.

Table 8: Analysis Results of ΔPR and ΔΔPR for Treatment Group = A: APL-130277

	ΔPR (ms) APL-130277 (N=39)	ΔPR (ms) Placebo (N=40)	ΔΔPR (ms) APL-130277	
Time (hour)	LSmean	LSmean	LSmean	90% CI
0.25	0.8	-1.5	2.3	(-0.7, 5.2)
0.5	-1.2	0.2	-1.4	(-4.3, 1.5)
0.75	1.6	0.5	1.1	(-1.8, 4.0)
1	2.9	0.2	2.8	(-0.2, 5.7)
2	0.2	-1.3	1.4	(-1.5, 4.4)
3	-1.0	-1.8	0.7	(-2.2, 3.7)
4	-3.2	-2.6	-0.6	(-3.5, 2.4)
8	-4.9	-4.7	-0.2	(-3.2, 2.8)
12	2.2	2.8	-0.6	(-3.7, 2.5)
24	-2.6	-4.6	2.0	(-2.1, 6.0)

Table 9: Categorical Analysis for PR

	Total N		PR<=200 ms		200<PR<=220 ms	
Treatment Group	Subj. #	Obs. #	Subj. #	Obs. #	Subj. #	Obs. #
Baseline / Predose	40	108	40 (100%)	108 (100%)	0 (0.0%)	0 (0.0%)
Placebo	40	373	38 (95.0%)	371 (99.5%)	2 (5.0%)	2 (0.5%)
Moxifloxacin 400 mg	39	371	38 (97.4%)	370 (99.7%)	1 (2.6%)	1 (0.3%)
APL-130277	39	364	36 (92.3%)	359 (98.6%)	3 (7.7%)	5 (1.4%)

5.2.4 QRS Analysis

The same statistical analysis was performed based on QRS interval. The point estimates and the 90% confidence intervals are presented in Table 10. The largest upper limit of 90% CI for the QRS mean differences between APL-130277 and placebo was 4.2 ms.

The outlier analysis results for QRS are presented in Table 11.

Table 10: Analysis Results of ΔQRS and ΔΔQRS for Treatment Group = A: APL-130277

	ΔQRS (ms) APL-130277 (N=39)	ΔQRS (ms) Placebo (N=40)	ΔΔQRS (ms) APL-130277	
Time (hour)	LSmean	LSmean	LSmean	90% CI
0.25	-0.4	-1.0	0.6	(-1.2, 2.4)
0.5	-0.1	-0.7	0.6	(-1.2, 2.4)
0.75	-0.9	0.1	-1.1	(-2.9, 0.7)
1	-0.5	-1.2	0.6	(-1.1, 2.4)
2	1.3	-1.1	2.4	(0.6, 4.2)
3	0.1	-0.7	0.8	(-1.0, 2.6)
4	0.8	-0.4	1.1	(-0.7, 2.9)
8	0.1	0.4	-0.3	(-2.1, 1.6)
12	0.6	0.4	0.2	(-1.7, 2.1)
24	-0.1	-1.0	1.0	(-1.5, 3.4)

Table 11: Categorical Analysis for QRS

	Total N		QRS<=110 ms		QRS>110 ms	
Treatment Group	Subj. #	Obs. #	Subj. #	Obs. #	Subj. #	Obs. #
Baseline / Predose	40	108	39 (97.5%)	106 (98.1%)	1 (2.5%)	2 (1.9%)
Placebo	40	373	39 (97.5%)	367 (98.4%)	1 (2.5%)	6 (1.6%)
Moxifloxacin 400 mg	39	371	38 (97.4%)	368 (99.2%)	1 (2.6%)	3 (0.8%)
APL-130277	39	367	38 (97.4%)	363 (98.9%)	1 (2.6%)	4 (1.1%)

5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

The objective of the clinical pharmacology analysis is to assess the relationship between drug concentration and ΔΔQTcF effects. Prior to evaluating the relationship using a prespecified linear model, the following key assumptions for the model were evaluated: 1) absence of significant changes in heart rate (more than a 10 bpm increase or decrease in mean HR); 2) no delay between plasma concentration and ΔQTcF and 3) absence of

non-linear relationship. There were no large changes in heart rate (>10 bpm) with treatment as described earlier in Section 5.2.2.

An evaluation of the time-course of drug concentration and changes in ΔΔQTcF by each dose level is shown in Figure 3. Amongst the dose levels used in the study (10, 15, 20, 25, 35 and 50 mg), the profiles for 15 mg (n=4), 25 mg (n=2), 35 mg (n=3) and 50 mg (n=1) are not shown because these had too few patients for any interpretation. The geometric mean C_{max} for each of these dose levels is shown in Table 12.

Figure 3: Time-course of mean drug concentration (top) and QTcF changes (bottom) following single doses of apomorphine sublingual film

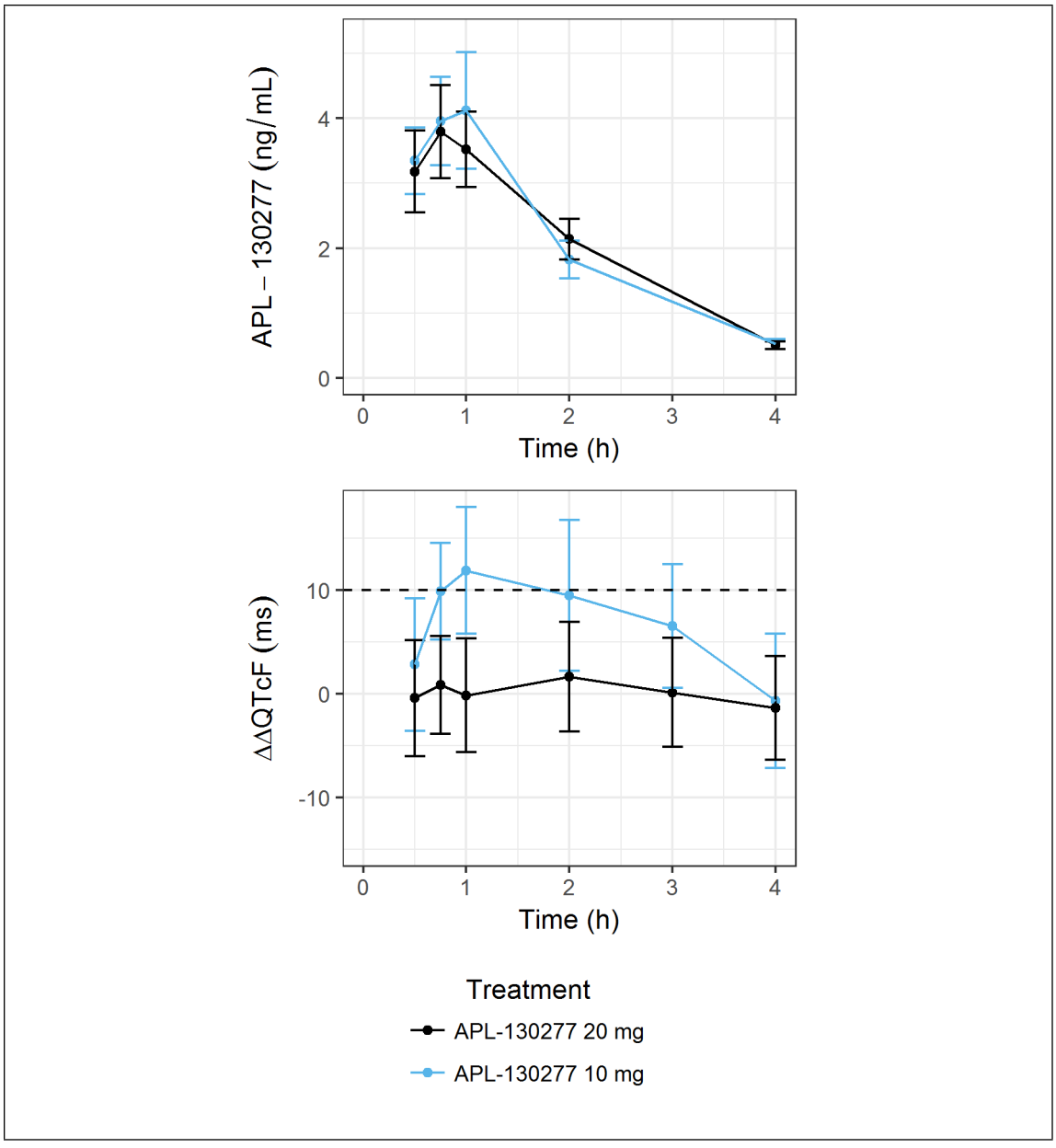


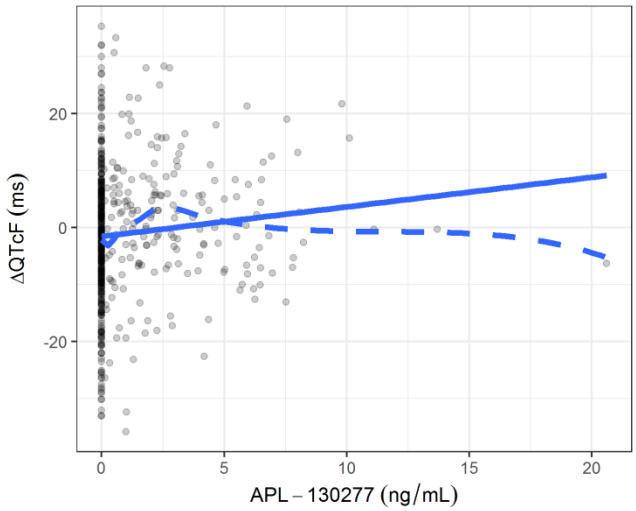
Table 12: Geometric mean C_{max} by dose level

Dose level	10 mg	15 mg	20 mg	25 mg	35 mg	50 mg
N	13	4	15	2	3	1
Geo. Mean Cmax (ng/mL)	3.85	6.48	3.44	3.75	5.85	4.61

The 90% confidence interval for mean QTc effect at each time point seem to include 10 ms at four time points for 10 mg dose. The drug has a short half-life (as per the sponsor, the terminal elimination half-life is about 1.89 hours with a range of 0.72 hour to 2.96 hours) and the time of maximum QTc effect seem to be at 1 h which is later than the T_{max} of ~0.75 h (see Table 1). Either this signal could be due to random variability in the assay (since 20 mg dose group does not show such a peak) or it could be a valid signal showing a delay between PK and QTc effects. Assuming it is a valid signal, it is unknown whether the 1 h timepoint was able to capture the peak QTc effects or there could be further potential for higher effect at an intermediate later time point which is not captured by the current ECG/PK assessment scheme (next time point after 1 h was 2 h). Because the doses were arrived at by individual titrations rather than the randomized assignment, the higher dose groups did not necessarily result in higher drug exposures (Table 12) and this precluded preliminary assessments using dose-response.

Figure 4 shows the relationship between drug concentration and ΔQTcF. However, this assessment of linearity would be confounded by delay in QTc effect as observed above.

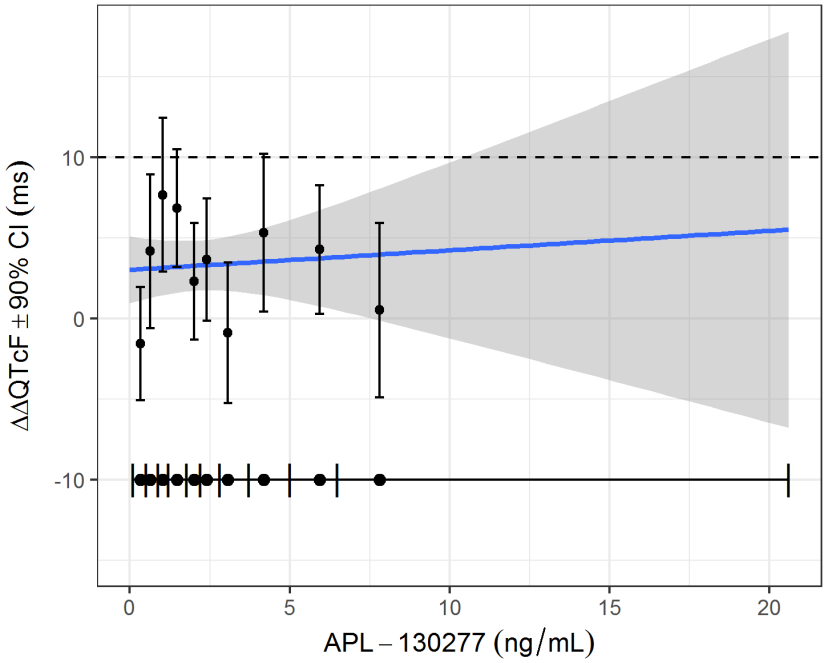
Figure 4: Assessment of linearity of concentration-QTc relationship



Exposure-Response Relationship

An exploratory concentration-QTc relationship was assessed using the prespecified white paper recommended linear mixed effects model. The slope for the relationship was not statistically significant (mean estimate = 0.12 ms per ng/mL; p = 0.8). The relationship between ΔΔQTcF and apomorphine concentrations is visualized in Figure 5. At the expected C_{max} of 9.3 ng/mL following maximum recommended therapeutic dose (35 mg), the mean predicted ΔΔQTcF is 4.2 ms with an upper bound of 90% CI of 9.6 ms.

Figure 5: ΔΔQTcF vs. Apomorphine Concentrations



There are several limitations for these assessments as noted below:

- Too few patients received doses above 20 mg (n=2 for 25 mg, n=3 for 35 mg and n=1 for 50 mg). Thus, the exposure coverage is limited to ~ 4 ng/mL, which is inadequate to cover C_{max} of ~9 ng/mL corresponding to maximum recommended therapeutic dose of 35 mg. Furthermore, similar to Apokyn®, the C_{max} is expected to increase by 50% in renal impairment subjects (highest clinically relevant exposure scenario).
- There seemed to be a delay in QTc effects compared to T_{max} with observed data and it is likely that the maximum QTc effect may not have been captured with the ECG/PK sampling scheme employed in the study. Due to this possibility of delay, a linear mixed effects concentration-QTc model for direct effect could not be used to estimate the QTc effects at relevant drug concentrations.
- There were a few data quality issues identified in the analysis dataset. For instance, subjects (b) (6) and (b) (6) received placebo during period 2 and period 3 respectively, but non-zero (quantifiable) APL-130277 concentrations were reported on this placebo treatment in the dataset.

5.4 CLINICAL ASSESSMENTS

5.4.1 Safety assessments

None of the events identified to be of clinical importance per the ICH E14 guidelines (i.e. syncope, seizure, significant ventricular arrhythmias or sudden cardiac death) occurred.

5.4.2 ECG assessments

Overall ECG acquisition and interpretation in this study appears acceptable.

5.4.3 PR and QRS Interval

No clinically meaningful effects on the PR an QRS intervals were detected in the pooled dose analysis.

6 APPENDIX

6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

<table>
<tr><td>Therapeutic dose and exposure</td><td>The proposed therapeutic doses for APL-130277 include 10, 15, 20, 25, 30 (b) (4) The maximum daily dose proposed for APL-130277 is (b) (4) (b) (4) up to 5 times per day).
The mean (%CV) Cmax and AUC at the single maximum proposed clinical dose is:
• Cmax: 9.29 ng/mL (107%CV)
• AUC: 17.0 h* ng/mL (14.8%CV)
The mean (%CV) Cmax and AUC at the steady state with the maximum proposed clinical dosing regimen is:
• Steady state not applicable as this is an acute intermittent use product</td></tr>
<tr><td>Maximum tolerated dose</td><td>APL-130277 was not formally studied to determine a maximum tolerated dose. Given this is a 505(b)(2) application, and that APOKYN® is the referenced listed drug (RLD), the highest dose of 35 mg APL-130277 was selected, based on the maximum dose (6 mg) of APOKYN.[a]</td></tr>
<tr><td>Principal adverse events</td><td>In general, adverse events were not related to dose.
Safety data for APL-130277 is summarized Table 2 and is based on one randomized, double blind, placebo-controlled, 12-week study in patients with Parkinson's disease (Study CTH-300).
Table 2: Adverse Reactions in 5% or More APL-130277 Treated Patients
<table>
<tr><th>Adverse Reaction</th><th>APL-130277
(N = 54)
n (%)</th><th>PLACEBO
(N = 55)
n (%)</th></tr>
<tr><td>Nausea</td><td>15 (28)</td><td>2 (4)</td></tr>
<tr><td>Somnolence</td><td>7 (13)</td><td>1 (4)</td></tr>
<tr><td>Dizziness</td><td>5 (9)</td><td>0 (0)</td></tr>
<tr><td>Oral mucosal erythema</td><td>4 (7)</td><td>2 (4)</td></tr>
<tr><td>Vomiting</td><td>4 (7)</td><td>0 (0)</td></tr>
<tr><td>Fatigue</td><td>4 (7)</td><td>0 (0)</td></tr>
<tr><td>Rhinorrhoea</td><td>4 (7)</td><td>0 (0)</td></tr>
<tr><td>Hyperhidrosis</td><td>3 (6)</td><td>2 (4)</td></tr>
<tr><td>Falls</td><td>3 (6)</td><td>1 (2)</td></tr>
<tr><td>Headache</td><td>3 (6)</td><td>0 (0)</td></tr>
<tr><td>Dry Mouth</td><td>3 (6)</td><td>0 (0)</td></tr>
<tr><td>Laceration</td><td>3 (6)</td><td>0 (0)</td></tr>
</table></td></tr>
</table>

Maximum dose tested	Single Dose	The maximum single dose tested was 50 mg in the cardiac conduction study (CTH-201).[a]
	Multiple Dose	Repeat dosing of APL-130277 on a regular schedule is not used. The maximum dose tested was 35 mg, which may be used if needed up to 5 times daily, each separated by at least 2 hours. On average subjects took 1-3 doses per day in clinical studies. Duration: The NDA includes data on 100 subjects using APL-130277 for ≥ 6months. Additional long-term safety data is provided in the 120-day update. Proposed Dosing Interval: APL-130277 is taken up to 5 times per day as needed and no sooner than 2 hours between doses.
Exposures Achieved at Maximum Tested Dose	Single Dose	Exposures achieved at the maximum single dose tested (35 mg (proposed maximum dose) and 50 mg (highest maximum single dose administered), Mean (%CV) Cmax and AUC) is provided below: [35 mg] • Cmax: 9.29 ng/mL (107%CV) • AUC: 17.0 h*ng/mL (14.8%CV) [50 mg; n=1] (single supratherapeutic exposure tested in cardiac conduction study CTH-201[a]) • Cmax: 4.61 ng/mL (NA) • AUC: 13.6 h*ng/mL (NA)

Exposures Achieved at Maximum Tested Dose	Multiple Dose	Repeat dosing of APL-130277 on a regular schedule is not used. The maximum dose tested was 35 mg which may be used if needed up to 5 times daily, each separated by at least 2 hours. On average subjects took 1-3 doses per day in clinical studies. Exposures achieved at the maximum dose tested (35 mg (proposed maximum dose)), Mean (%CV) Cmax and AUC) is provided below: Model predicted exposure of 35 mg taken every 2 hours for 5 doses (the maximum recommended): 50^{th} (5^{th} , 95^{th}) percentiles. • C_{max}: 8.99 (4.28, 19.25) ng/mL • AUC_{0-24}: 72.07 (35.69, 150.30) h*ng/mL
Range of linear PK	The dosing regimen for APL-130277 is as follows: • 10, 15, 20, 25, 30, 35 mg taken up to 5 times per day as needed and no sooner than 2 hours between doses. In studies involving patients, exposure increased with increase in dose but in a less than proportional manner.	
Accumulation at steady state	Steady state not applicable, as APL-130277 is used as needed.	
Metabolites	Apomorphine-sulfate; inactive Apomorphine-glucuronide; Phase II conjugate Norapomorphine; below the limit of quantitation Norapomorphine-sulfate; Phase II conjugate Norapomorphine-glucuronide; Phase II conjugate	

Absorption	Absolute/Relative Bioavailability	Mean (%CV) • Rel. BA to subcutaneous apomorphine 0.192 – 0.208 (27.5 – 35.2 %CV)
	Tmax	Median (range) for parent • 0.442 – 1.50 h (0.335 – 2.00) Median (range) for metabolites • Apomorphine-sulfate: 0.85 - 2.25 (0.33 – 4.08) • Apomorphine-glucuronide: 0.53 – 2.0 (0.35 – 3.03) • Norapomorphine: Not applicable (plasma concentrations were mostly BLQ) • Norapomorphine-sulfate: 1.5 (0.5 - 4.08) • Norapomorphine-glucuronide: 2.0 – 3.02 (1.10 – 5.02)
Distribution	Vd/F or Vd	Mean (%CV) • Vd/F: 1750 – 4780 L (30.8 – 65.6%CV)
	% bound	Mean (%CV) • Ultrafiltration, equilibrium dialysis, and ultraviolet spectrophotometric methods have been used to study the reversible plasma binding of apomorphine to rat, swine, bovine, and human plasma proteins (Smith 1985). The degree of binding was generally greater than 90%.
Elimination	Route	Primary route; percent dose eliminated • Hepatic Metabolism; sulfation and glucuronidation with limited N-demethylation. Other routes • Urinary; <0.10%

Elimination	Terminal t½	Mean (%CV) for parent • 0.721– 2.96 h (9.91 - 109 %CV) Mean (%CV) for metabolites • Apomorphine-sulfate: 0.85 - 2.25 (0.33 – 4.08 %CV) • Apomorphine-glucuronide: 0.53 – 2.0 (0.35 – 3.03 %CV) • Norapomorphine: Not applicable (plasma concentrations were mostly BLQ) • Norapomorphine-sulfate: 1.5 (0.5 - 4.08 %CV) • Norapomorphine-glucuronide: 2.0 – 3.02 (1.10 – 5.02 %CV)
	CL/F or CL	Mean (%CV) • CL/F: 1310 - 3790 L/h (31.9 – 75.4 %CV)
Intrinsic Factors	Age	Specify mean changes in Cmax and AUC: Clearance not influenced by age
	Sex	Specify mean changes in Cmax and AUC: Clearance not influenced by sex
	Race	Specify mean changes in Cmax and AUC: Clearance not influenced by race
	Hepatic & Renal Impairment	The mean changes in Cmax and AUC for hepatic and renal impairment is provided below: • Hepatic and Renal studies with APL-130277 were not conducted. • A PK model evaluating the impact of renal impairment on the PK of sublingual apomorphine was evaluated in mild-renally impaired patients compared to patients having normal renal function. Results indicated the exposure estimates were similar.

Extrinsic Factors	Drug interactions	No DDI studies were conducted with APL-130277. DDI information is provided by reference for the RLD APOKYN (Sequence 0001, Module 1.14.1.2 Annotated Draft Labeling Text). In vitro DDI and transporter studies were conducted with apomorphine sulfate (metabolite) suggesting a low risk
	Food Effects	No food effect studies with APL-130277 were conducted.
Expected High Clinical Exposure Scenario	Model predicted exposure following administration of APL-130277 35 mg every 2 hours for a total of 5 doses per day (ie, 175 mg/day). 50^{th} (5^{th}, 95^{th}) percentiles • Cmax : 8.99 (4.28, 19.25) ng/mL • AUC0-24: 72.07 (35.69, 150.30) h*ng/mL Insufficient data is available to cover supra-therapeutic dose. The 50mg dose administered in Study CTH-201 was a single dose.	
Preclinical Cardiac Safety	No preclinical cardiac safety studies have been conducted with APL-130277. Multiple studies assessing proarrhythmic risk by apomorphine have been performed by different investigators with varying results. Apomorphine blocked human ether-a-go-go related gene (hERG) mediated K^+ channel currents in Chinese hamster ovary cells with an IC_{50} value of 2.4 µM using the whole-cell patch clamp technique. In a study supporting APOKYN, the IC_{50} for apomorphine inhibition of cloned hERG channels was determined to be 0.127 µM . When evaluated in an action potential duration assay, apomorphine significantly prolonged repolarization action potential duration at 90% re-polarization (APD_{90}) by 20 msec at a concentration of 1.5 µM in a canine Purkinje fiber assay. However, in another study, there was no effect of apomorphine at concentrations of 10^{-9} to 10^{-5}M on the action potential characteristics of Purkinje fibers isolated from beagle dogs, whereas action potential duration at 90% re-polarization was prolonged at approximately 10-12% in isolated endocardial ventricular fibers from beagle dogs at concentrations of 10^{-6}M and greater. In a study supporting APOKYN, no effects on action potential duration in dog purkinje fibers were seen at doses up to 1 µM. The proarthymic potential of apomorphine has been evaluated in the chronic atrioventricular block canine model. In this model, 1 mg/kg apomorphine iv neither prolonged the QT interval nor induced torsade de pointes. This study indicates that apomorphine at approximately 10-1000 times therapeutic concentration will not induce repolarization delay or torsade de pointes.	

Preclinical Cardiac Safety (cont'd)	In vivo electrophysiological and hemodynamic evaluations were conducted for up to 1 hour after an iv apomorphine dose of 0.05 mg/kg or 0.5 mg/kg in anesthetized and instrumented male and female beagle dogs. There was no effect on QT interval at the doses examined. In another study, ECG effects of 3 dopamine agonists including apomorphine were evaluated in conscious adult female beagle dogs. Intravenous apomorphine (25 µg/kg) increased QT_c (+ 15 milliseconds) at a mean concentration of 3.4 ng/ml.
Clinical Cardiac Safety	To date, 3 clinical studies in Parkinson's disease subjects have been completed (CTH-105, CTH-201 and CTH-300) and 3 remain ongoing (CTH-301, CTH-203 and CTH-302). As of 10 May 2018, 451 unique subjects with PD received at least 1 dose of APL-130277 in the integrated dataset. As of this cutoff date, no subjects had enrolled into CTH-302 (EU registration study) and five in CTH-203. Subjects from CTH-203 were not included in the integrated total given difference in study design. Table 3 summarizes the extent of exposure calculated for each estimated total daily dose category for repeat dosing studies CTH-300 and CTH-301.

Table 3: Number of Subjects Exposed to APL-130277 in Studies CTH-300 and CTH-301 by Categorical Extent of Exposure and Overall Average Total Daily Dose Category During Maintenance/Treatment Phase (Maintenance/Treatment Phase Safety Population) Extent of Exposure Category (months)

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

Note: Extent of exposure calculated as date of last dose received in the study - date of first dose received in the study + 1. For subjects who participated in both studies, the duration of exposure is calculated as the total number of days over both studies, excluding the gap time between studies.
Note: Subjects missing overall average total daily dose are not represented in this table.
Note: For each subject, the overall average total daily dose is calculated by weighted averages, with weights equal to the number of days exposed during the available interval using the study drug accountability data.
Reference: ISS Table 7.26_SU.

Clinical Cardiac Safety (cont'd)	Clinical cardiac safety is provided for the single Phase 3 placebo-controlled study (CTH-300). For this study, total exposure during maintenance period, in subject years, was 10.2 and 11.3 in the APL-130277 and Placebo groups respectively. Cardiac safety events as defined per ICH E14 guidance that were observed during the maintenance / treatment phase in the single Phase 3 placebo-controlled study CTH-300 are included in Table 4. Table 4: Cardiac Safety Events Observed During Maintenance / Treatment Phase in Placebo-controlled Study CTH-300 (ISS Analysis Pool 1)

Preferred Term	APL-130277 N = 54 n (%)	Placebo N = 55 n (%)
Cardiac arrest	1 (1.9%)	0
Electrocardiogram QT prolonged	1 (1.9%)	0

There were no events of syncope, seizures, ventricular arrhythmias, ventricular tachycardia, ventricular fibrillation, flutter, torsade de pointes, or sudden death observed during the maintenance / treatment phase of study CTH-300.

The effects of APL-130277 on the QTc interval were evaluated in a randomized, double-blind, positive- and placebo- controlled 3-period crossover study in 40 subjects with PD (Study CTH-201). Subjects were titrated to an effective and tolerable dose of APL-130277, ranging from 10 mg to 50 mg, prior to entering the 3-way crossover period. Moxifloxacin 400 mg was used as a positive control for assay sensitivity. There were no clinically meaningful effects on QTc interval following administration of APL 130277. The upper limits of the 90% CIs for the time-matched and placebo adjusted mean changes from baseline in APL-130277 QTcF ($\Delta\Delta$QTcF) were below the regulatory threshold of 10 ms at all pre-specified time points (15, 30, 45, and 60 minutes, 2, 3, and 4 hours post-dose). The peak effect of 6.2 ms was observed at 60 minutes post-dose (90% CI from 2.7 to 9.7 ms). These results show that APL-130277 did not have a clinically meaningful effect on QTcF. For the evaluation of assay sensitivity, the lower limits of the 90% (Bonferroni-corrected) CIs for the positive control moxifloxacin compared to placebo ($\Delta\Delta$QTcF) were above the threshold of 5 ms at the 1, 2 and 3 hour post-dose time points, confirming that a QTcF prolongation could be detected in the study.

Clinical Cardiac Safety (cont'd)	Findings from the exposure analysis were consistent with QTc being nondependent on the apomorphine concentration up to the observed concentration range (maximum of 20.6 ng/mL). Additional analysis showed that if PD patients were to experience 5 "OFF" periods during a 10 hour period, and consequently administered a 35 mg dose of APL-130277 every 2 hours for a total of 5 doses, the Cmax is predicted to be 8.99 ng/mL. At a concentration of 10 ng/mL apomorphine (administered as APL-130277), the upper bound of the 95% CI for difference-from-baseline in QTcP was 6 ms, remaining below the 10 ms threshold of regulatory concern. Combined these results show that APL-130277 had no effect on the QT interval or any other conduction parameters as well no effect on EKG morphology.

[a] In cardiac conduction study (CTH-201) 1 subject received a supratherapeutic dose of 50 mg. Highest dose administered was determined during titration in which patients were titrated to tolerance.

6.2 ECG AND PK ASSESSMENTS [STUDY CTH-201]

Procedures	Screening Visits[a]		Titration Visit 1[b]	Titration Visit 2[b]	Titration Visit 3[b, c]	Titration Visit 4[b, c]	Titration Visit 5[b, c]	Titration Visit 6[b, c]	Titration Visit 7[b]	Titration Visit 8[b]	Titration Visit 9[b]	Randomization Procedures[d]	Period 1 Dosing Visit	Period 2 Dosing Visit	Period 3 Dosing visit	End of Study Visit
Study Visit	SV1	SV2	TV1	TV2	TV3	TV4	TV5	TV6	TV7	TV8	TV9		P1V1	P2V2	P3V3	EOS
Day	-14 to -3		1	2	3	4	5	6	7	8	9		1	3 days after P1V1	3 days after P2V2	3-5 days after P3V3
Maximum Study Duration (days)	1 to 14		15 to 28										35	38	41	44 to 46
Outpatient Visit[e]	X	X	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X	X	X		X	X	X	X
Written Informed Consent	X															
Reconfirmation of Consent		X	X	X	X	X	X	X	X	X	X		X	X	X	X
Review Entry Criteria	X	X														
Review Restriction Criteria			X	X	X	X	X	X	X	X	X		X	X	X	
Medical History/Demographics		X[a]														
Complete Physical Exam, including Oropharyngeal Exam[f]		X[a]														X
Abbreviated Physical Exam, including Oropharyngeal Exam[g]			X	X	X	X	X	X	X	X	X		X	X	X	
BMI, Weight and Height[h]		X[a]											X	X	X	X
Vital Signs (BP, HR, RR and Temp)[i, j]		X[a]	X	X	X	X	X	X	X	X	X		X	X	X	X
12-Lead ECG (Holter)[j, k]													X	X	X	
12-Lead ECG (Resting)[j, l]		X[a]	X	X	X	X	X	X	X	X	X		X	X	X	X

Procedures	Screening Visits[a]		Titration Visit 1[b]	Titration Visit 2[b]	Titration Visit 3[b,c]	Titration Visit 4[b,c]	Titration Visit 5[b,c]	Titration Visit 6[b,c]	Titration Visit 7[b]	Titration Visit 8[b]	Titration Visit 9[b]	Randomization Procedures[d]	Period 1 Dosing Visit	Period 2 Dosing Visit	Period 3 Dosing visit	End of Study Visit
Study Visit	SV1	SV2	TV1	TV2	TV3	TV4	TV5	TV6	TV7	TV8	TV9		P1V1	P2V2	P3V3	EOS
Day	-14 to -3		1	2	3	4	5	6	7	8	9		1	3 days after P1V1	3 days after P2V2	3-5 days after P3V3
Maximum Study Duration (days)	1 to 14		15 to 28										35	38	41	44 to 46
Clinical Laboratory Tests[e]		X														X
PK[j,f]													X	X	X	
MMSE		X														
Modified Hoehn and Yahr		X														
MDS-UPDRS Part III[j,g]		X	X	X	X	X	X	X	X	X	X					
Confirmation of L-Dopa Responsiveness		X														
Clinical Confirmation of "OFF" or full "ON"		X	X	X	X	X	X	X	X	X	X		X	X	X	
Subject Confirmation of "OFF" or full "ON"		X	X	X	X	X	X	X	X	X	X		X	X	X	
Subject "OFF" versus "ON" Training		X														
In-Clinic Dosing			X	X	X	X	X	X	X	X	X		X	X	X	
AEs/Serious AEs (SAEs)	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X

[a] All screening procedures were to be conducted within 14 days prior to Titration Visit 1 (TV1). If required by the Investigator, and following receipt of subject consent, the Investigator could review the subjects' medical history, BMI, height, weight, vital signs, 12-Lead ECG (in triplicate) and perform a complete physical examination at SV1 to determine if the subject was eligible for study participation. Procedures performed on SV1 were not repeated at SV2.

[b] Dosing days in the Dose Titration Phase were to be scheduled the following business day of the previous visit and all visits had to be completed within 14 days. A maximum of 2 days between visits could be permitted with Medical Monitor approval.

[c] Optional Dosing Regimen: For TV3, TV4, TV5 and TV6 only, subjects could be dosed with the next highest dose of study medication within 4 hours of the previous dose, as long as the subject achieved another "OFF" state that day.

[d] Following completion of the Dose Titration Phase of the study, Sponsor approval was required prior to randomization in the Three-Way Balanced Crossover Phase. Additional details were available in the Enrollment and Randomization Adjudication Process document, which is contained in a separate document.

[e] Subjects could be monitored in the clinic overnight before Dose Titration Visits if such facilities existed and the subject consented.

[f] Physical examination included the following: head-eyes-ears-nose and throat; respiratory system; cardiovascular system; gastrointestinal system, including mouth – oral cavity; musculoskeletal system; central and peripheral nervous system; and skin. The oropharyngeal cavity examination included a visual inspection of the inside of each cheek, the inside of the upper and lower lip, the surface of the tongue, and under the tongue.

[g] Abbreviated physical exam included head-eyes-ears-nose and throat; heart; lungs; abdomen; and skin; done at t = 0 (just prior to dosing) and 120 minutes after dosing at TV1 to TV9, Period 1, Period 2, and Period 3. The oropharyngeal cavity examination included a visual inspection of the inside of each cheek, the inside of the upper and lower lip, the surface of the tongue, and under the tongue.

[h] Both height and weight captured at the Screening Visit (SV2) to calculate BMI; only weight captured at all other indicated visits.

[i] Vital signs were assessed at the Screening (SV2) and End of Study (EOS) Visits; TV1 to TV9 and during Period 1, 2 and 3 at t = 0 minutes (just prior to dosing), 15, 45 and 60 minutes. Blood pressure was measured supine and standing (measured within 3 minutes of standing) at all time points.

[j] Suggested Sequence of Assessments at Pre-Dose: ECG – PK – Vitals – Efficacy. Sequence of Assessments after dosing (where applicable): MDS-UPDRS Part III - Subject "OFF"/"ON" status – ECG – PK – Vitals.

[k] 12-lead ECG (Triplicate; Holter): Period 1: Three (3) sets of triplicate ECGs were obtained over approximately 1-hour (prior to dosing) as the baseline assessment; and triplicate ECG were obtained at t = 15, 30, 45, 60 minutes and 2, 3, 4, 8, 12, 24 hours after dosing. Period 2 and Period 3: triplicate ECG at t = 0 (just prior to dosing), 15, 30, 45, 60 minutes and 2, 3, 4, 8, 12, 24 hours after dosing.

[l] 12-lead ECG (Single; Resting): Screening Visit (SV2): A triplicate ECG was obtained. TV1 to TV9: ECG at t = 0 (just prior to dosing) and 45 minutes after dosing. Period 1, Period 2 and Period 3 at 60 minutes after dosing. EOS: A triplicate ECG was obtained. ECGs were assessed by the Investigator at each visit.

[m] Blood and urine collection for clinical laboratory tests occurred at Screening Visit (SV2) and at the End of Study Visit (EOS). In addition, serum pregnancy test was performed on all females of childbearing potential.

[n] PK was assessed for APL-130277 and placebo dosing days at t = 0 (just prior to dosing), 30, 45, 60 minutes and 2, 4 hours after dosing. PK was assessed on the moxifloxacin dosing day at t = 0 (just prior to dosing), 30, 60 minutes and 2, 3, 4, 6, 8 hours after dosing.

[o] MDS-UPDRS Part III (Motor Function) was assessed at t = 0 (just prior to dosing), 30, 60 and 90 minutes after L-Dopa administration at the second Screening Visit (SV2); the modified Hoehn and Yahr was used during the Screening Visit (SV2). Assessments during the Titration Phase at t = 0 (just prior to dosing), 30, 60 and 90 minutes after dosing; these assessments excluded the "Dyskinesia Impact on Part III Ratings" and the Hoehn and Yahr staging.

[p] "Screening" scale was used at the Screening Visit (SV2); "Since Last Visit" was used at all other visits.

6.3 ELECTROCARDIOGRAM OUTLIER ANALYSIS IN THE PLACEBO-CONTROLLED POOL [PHASE 3 STUDY CTH-300]

TITRATION PHASE SAFETY POPULATION

Parameter (unit)	Assessment	APL-130277 N = 141 n (%)
QTcF Interval (msec)	n	140
	Normal (<=450 msec)	125 (89.3)
	>450 - 480 msec	14 (10.0)
	>480 - 500 msec	1 (0.7)
	>500 msec	0
	Increases > 30 - 60 msec	4 (2.9)
	Increases > 60 msec	1 (0.7)

Source: ISS-TFL, Table 11.2.1, Page 3078 of 13947

MAINTENANCE/TREATMENT PHASE SAFETY POPULATION

Parameter (unit)	**Assessment**	**APL-130277 N = 54 n (%)**	**Placebo N = 55 n (%)**
QTcF Interval (ms)	Normal (≤ 450 ms)	50 (92.6)	49 (89.1)
	> 450 - 480 ms	3 (5.6)	6 (10.9)
	> 480 - 500 ms	1 (1.9)	0
	> 500 ms	0	0
	Increases > 30 - 60 ms	1 (1.9)	1 (1.8)
	Increases > 60 ms	0	0

Source: ISS Report, Table 108, Page 297 of 382

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

/s/

DHANANJAY D MARATHE
09/18/2018
Gopichand Gottipati was the primary reviewer.

GOPICHAND GOTTIPATI
09/24/2018

JANELL E CHEN
09/24/2018

DALONG HUANG
09/24/2018

MOHAMMAD A RAHMAN
09/24/2018

MICHAEL Y LI
09/25/2018

CHRISTINE E GARNETT
09/25/2018