CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210730Orig1s000

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:	July 27, 2020
Requesting Office or Division:	Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)
Application Type and Number:	NDA 210730
Product Name and Strength:	Olinvyk (oliceridine) injection, 1 mg/ml
Total Product Strength:	1 mg/mL, 2 mg/2 mL, 30 mg/30 mL
Applicant/Sponsor Name:	Trevena, Inc. (Trevena)
OSE RCM #:	2017-2276-3
DMEPA Safety Evaluator:	Zahra Farshneshani, PharmD
DMEPA Team Leader:	Otto L. Townsend, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling, received on June 26, 2020 and July 22, 2020 for Olinvyk. The Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP) requested that we review the revised container label and carton labeling for Olinvyk (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] and in an information request (IR)[b] sent to the applicant.

1.1 BACKGROUND

The container label and carton labeling for the Oliceridine 30 mg/30 mL vial did not clearly indicate to the user that this vial strength is only intended for patient-controlled analgesia (PCA) use. The lack of instructions or statements that this presentation is for preparing PCA syringes may result in users incorrectly using this product as a multi-dose vial. Changes to the container label and carton labeling may further reduce the risk of medication errors (i.e., use as a MDV)

[a] Farshneshani Z. Label and Labeling Review for Olinvyk (NDA 210730). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 MAY 1. RCM No.: 2017-2276-2

[b] Yuan, E. Information Request for "FDA Communication: NDA 210730 - DMEPA Information Request. Silver Spring (MD): FDA, CDER, OND, DOP1 (US); 2020 JUL 20.

or potential diversion due the large amount of drug that would remain in the vial if erroneously selected instead of the more appropriate 1 mg/mL or 2 mg/mL presentations to administer a single dose. Thus, on July 20, 2020 we sent an IR to the applicant to request the addition of a warning statement to the carton and container labels for the 30 mg/30 mL drug product presentation indicating that this presentation is intended for PCA use only. We recommended that they add a warning statement to the container label and carton labeling for the 30 mg/30 mL presentation that warns the user that this presentation is intended for PCA use only.

2 CONCLUSION

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

APPENDIX

A.1 List of Labels and Labeling Reviewed

- Container label (submitted on July 22, 2020)
- Carton labeling (submitted on July 22, 2020)

A.2 IMAGES OF LABEL AND LABELING RECEIVED ON JULY 22, 2020

Container label

Carton labeling

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/s/

ZAHRA FARSHNESHANI
07/27/2020 04:25:54 PM

OTTO L TOWNSEND
07/28/2020 02:43:11 PM

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

Date: July 17, 2020

To: Rigoberto Roca, M.D., Director (Acting)
Division of Anesthesia, Addiction Medicine and Pain Medicine (DAAP)

Through: Dominic Chiapperino, Ph.D., Director
Chad Reissig, Ph.D., Supervisory Pharmacologist
Controlled Substance Staff

From: Katherine Bonson, Ph.D., Senior Pharmacologist
Controlled Substance Staff

Subject: NDA review of abuse potential
Oliceridine (Olinvyk), intravenous
NDA 210,730 (IND 113,537)
Indication: Treatment of moderate to severe pain
Sponsor: Trevena, Inc.
Resubmission PDUFA Goal Date: August 7, 2020

Materials reviewed:
- NDA submissions (11/20/17 and 2/7/20)
- Statistical Review of Human Abuse Potential Study with Oliceridine (Dr. Ling Chen, Office of Biostatistics, CDER/FDA, 7/11/18)

Table of Contents

I. BACKGROUND

This memorandum responds to a consult request from the Division of Anesthesia, Addiction Medicine and Pain Medicine (DAAP) to CSS regarding the resubmission of NDA 210730 for oliceridine (TRV-130, tradename Olinvyk) by Trevena, Inc. Oliceridine is formulated as a sterile aqueous solution (1.0 mg oliceridine free base equivalents/ml) for intravenous injection under inpatient hospital or clinic settings for the acute treatment of moderate to severe pain (b) (4).

The NDA for oliceridine received a Complete Response under its first submission on November 2, 2018, based on deficits in information related to QT prolongation, adequate sample size to demonstrate safety in humans, data evaluating animal embryo-fetal development, and control of leachable in the product.

During the first submission of NDA 210730, CSS conducted a full abuse potential assessment of the animal and human data from abuse potential-related studies that were submitted (DARRTS: Dr. Bonson, October 4, 2018).

In the present resubmission, the Sponsor did not submit any new abuse potential-related studies or information. Thus, the CSS conclusions and recommendations regarding the abuse potential of oliceridine are the same as those from 2018, which are shown below in *II. Conclusions* and *III. Recommendations.*

II. CONCLUSIONS

a) No new abuse potential-related data were submitted or reviewed in the present NDA resubmission for oliceridine.

b) CSS affirms our conclusion in our consult from the first review cycle (October 4, 2018), that oliceridine is a mu opioid agonist with abuse potential.

c) CSS provides recommendations for product labeling in this new review cycle in *Recommendation*s (below).

III. RECOMMENDATIONS

Based on the CSS evaluation of the preclinical and clinical abuse-related data, CSS concludes that if the NDA for oliceridine is approved:

a) Oliceridine should be recommended for placement in Schedule II of the Controlled Substances Act (CSA). The Sponsor also proposes that oliceridine should be recommended for Schedule II placement.

b) The text for Section 5.1 (Addiction, Abuse, and Misuse) and Section 9 (Drug Abuse and Dependence) of the drug label should reflect that oliceridine produced significant abuse signals. The text below is the most recent negotiated labeling, based on FDA

revisions of the Sponsor's original proposed label. Additional changes might be made prior to the NDA action.

5.1 ADDICTION, ABUSE, AND MISUSE

OLINVIK contains oliceridine (controlled substance schedule to be determined after review by the Drug Enforcement Administration). As an opioid, OLINVYK exposes users to the risks of addiction, abuse, and misuse [see Drug Abuse and Dependence (9)].

Although the risk of addiction in any individual is unknown, it can occur in patients appropriately prescribed OLINVYK. Addiction can occur at recommended dosages and if the drug is misused or abused [see Drug Abuse and Dependence (**Error! Reference source not found.**)].

Assess each patient's risk for opioid addiction, abuse, or misuse prior to prescribing OLINVYK, and monitor all patients receiving OLINVYK for the development of these behaviors or conditions. Risks are increased in patients with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depression). The potential for these risks should not, however, prevent the proper management of pain in any given patient. Patients at increased risk may be prescribed opioids such as OLINVYK, but use in such patients necessitates intensive counseling about the risks and proper use of OLINVYK along with intensive monitoring for signs of addiction, abuse, and misuse.

Opioids are sought by drug abusers and people with addiction disorders and are subject to criminal diversion. Consider these risks when prescribing or dispensing OLINVYK. Strategies to reduce these risks include prescribing the drug in the smallest appropriate quantity. Contact local state professional licensing board or state controlled substances authority for information on how to prevent and detect abuse or diversion of this product.

9 DRUG ABUSE AND DEPENDENCE

9.1 CONTROLLED SUBSTANCE

OLINVYK contains oliceridine. (Controlled substance schedule to be determined after review by the Drug Enforcement Administration.)

9.2 ABUSE

OLINVYK contains oliceridine, a substance with a high potential for abuse similar to other opioids including fentanyl, hydrocodone, hydromorphone, methadone, morphine, oxycodone, oxymorphone, and tapentadol. OLINVYK can be abused and is subject to misuse, abuse, addiction, and criminal diversion [see Warnings and Precautions (**5.1**)].

The abuse potential of oliceridine was evaluated in healthy, nondependent, recreational opioid users at doses of 1, 2, and 4 mg. Intravenous morphine was used as a positive control at doses of 10 and 20 mg. Statistically significant differences were observed between all doses of oliceridine and placebo on most subjective effects (e.g., Drug Liking VAS) and pupillometry endpoints (e.g., miosis). Intravenous administration of oliceridine demonstrated comparable subjective effects when compared to dose-matched levels of intravenously administered morphine.

All patients treated with opioids require careful monitoring for signs of abuse and addiction, because use of opioid analgesic products carries the risk of addiction even under appropriate medical use.

Prescription abuse is the intentional, non-therapeutic use of a drug, even once, for its rewarding psychological or physiological effects.

Drug addiction is a cluster of behavioral, cognitive, and physiological phenomena that may include a strong desire to take the drug, difficulties in controlling drug use (e.g., continuing drug use despite harmful consequences, giving a higher priority to drug use than other activities and obligations), and possible tolerance or physical dependence.

"Drug seeking" behavior is very common in persons with substance use disorders. Drug seeking tactics include emergency calls or visits near the end of office hours, refusal to undergo appropriate examination, testing, or referral, repeated "loss" of prescriptions, tampering of prescriptions, and reluctance to provide prior medical records or contact information for other treating health care provider(s). "Doctor shopping" (visiting multiple prescribers or healthcare prescribers to obtain additional prescriptions) is common among drug abusers and people suffering from untreated addiction. Preoccupation with achieving adequate pain relief can be appropriate behavior in a patient with poor pain control.
Abuse and addiction are separate and distinct from physical dependence and tolerance.

Healthcare providers should be aware that addiction may not be accompanied by concurrent tolerance and symptoms of physical dependence (b) (4). In addition, abuse of opioids can occur in the absence of true addiction.

OLINVYK injection, like other opioids, can be diverted for non-medical use into illicit channels of distribution. Careful record-keeping of prescribing information, including quantity and frequency, and renewal requests, as required by law, is strongly advised.

Proper assessment of the patient, proper prescribing practices, periodic reevaluation of therapy, and proper dispensing and storage are appropriate measures that help to limit abuse of opioid drugs.

There were no reports of diversion of OLINVYK during the clinical development program.
Risk Specific to Abuse of OLINVYK Injection.

Abuse of OLINVYK injection poses a risk of overdose and death. The risk is increased with concurrent use of OLINVYK with alcohol and other central nervous system depressants.

Parenteral drug abuse is commonly associated with transmission of infectious diseases such as hepatitis and HIV.

9.3 DEPENDENCE

Both tolerance and physical dependence can develop during chronic opioid therapy.

Tolerance is a physiological state characterized by a reduced response to a drug after repeated administration (i.e., a higher dose of a drug is required to produce the same effect that was once obtained at a lower dose).

Physical dependence is a state that develops as a result of physiological adaptation in response to repeated drug use, manifested by withdrawal signs and symptoms after abrupt discontinuation or a significant dose reduction of a drug. Withdrawal also may be precipitated through the administration of drugs with opioid antagonist activity (e.g., naloxone), mixed agonist/antagonist analgesics (e.g., pentazocine, butorphanol, nalbuphine), or partial agonists (e.g., buprenorphine). Physical dependence may not occur to a clinically significant degree until after several days to weeks of continued opioid usage.

OLINVYK should not be abruptly discontinued in a physically-dependent patient [see Dosage and Administration (2.X)]. If OLINVYK is abruptly discontinued in a physically-dependent patient, a withdrawal syndrome may occur. Some or all of the following can characterize this syndrome: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia, and mydriasis. Other signs and symptoms also may develop, including irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, or increased blood pressure, respiratory rate, or heart rate [see Nonclinical Toxicology (13.2)].

Infants born to mothers physically dependent on opioids will also be physically dependent and may exhibit respiratory difficulties and withdrawal signs [see Use in Specific Populations (8.1)].

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/s/

KATHERINE R BONSON
07/17/2020 02:57:56 PM

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DOMINIC CHIAPPERINO
07/20/2020 01:44:16 PM

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

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

Memorandum

Date: 7/15/2020

To: Eva Yuan, PharmD, RAC
Regulatory Health Project Manager
Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)

From: Nima Ossareh, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Sam Skariah, Team Leader, OPDP

Subject: OPDP Labeling Comments for OLINVYK (oliceridine) injection), for intravenous use,

NDA: 210730

In response to DAAAP consult request dated April 24, 2020, OPDP has reviewed the proposed product labeling (PI) for OLINVYK (oliceridine) injection), for intravenous use.

PI: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DAAAP on July 10, 2020, and are provided below.

Thank you for your consult. If you have any questions, please contact Nima Ossareh at (240) 402-2769 or nima.ossareh@fda.hhs.gov.

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/s/

NIMA OSSAREH
07/15/2020 03:55:08 PM

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:	July 2, 2020
Requesting Office or Division:	Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)
Application Type and Number:	NDA 210730
Product Name and Strength:	Olinvyk (oliceridine) injection, 1 mg/ml
Total Product Strength:	1 mg/mL, 2 mg/2 mL, 30 mg/30 mL
Applicant/Sponsor Name:	Trevena, Inc. (Trevena)
OSE RCM #:	2017-2276-2
DMEPA Safety Evaluator:	Zahra Farshneshani, PharmD
DMEPA Team Leader:	Otto L. Townsend, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling, received on June 26, 2020 for Olinvyk. The Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP) requested that we review the revised container label and carton labeling for Olinvyk (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].

On June 26, 2020, The Applicant also requested that we acknowledge their response to our second recommendation that they received in a discipline review letter (DRL) on June 17, 2020.

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time. We acknowledge and agree with their response to our second recommendation.

[a] Farshneshani Z. Label and Labeling Review for Olinvyk (NDA 210730). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 MAY 1. RCM No.: 2017-2276-1

APPENDIX

A.1 List of Labels and Labeling Reviewed

- Container label (submitted on June 26, 2020)
- Carton labeling (submitted on June 26, 2020)

A.2 IMAGES OF LABEL AND LABELING RECEIVED ON JUNE 26, 2020

Container labels

Carton labeling

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/s/

ZAHRA FARSHNESHANI
07/02/2020 02:28:41 PM

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07/02/2020 03:23:01 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: June 12, 2020

From: Interdisciplinary Review Team for Cardiac Safety Studies

Through: Christine Garnett, PharmD
Clinical Analyst
Division of Cardiology and Nephrology

To: Shelly Kapoor
DAAAP

Subject: QT Consult to NDA 210730 (SDN 046)

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 question related to a consult to us dated 2/14/2020 regarding the sponsor's thorough QT study. We reviewed the following materials:

- Previous IRT review(s) for NDA 210730 dated 04/16/2020 in DARRTS.

1 Responses for the Division

Question: Repeat dosing up to 27 mg daily appears to result in clinically significant QT-prolongation. Given that a clinical study showed that the QTc effect diminishes after 10 hours with repeat dosing, are there any safety concerns regarding QT effects if repeat dosing exceeds 27 mg/day?

IRT's response: The clinical QTc prolongation observed with oliceridine diminished despite continued dosing in the second thorough QT study, suggesting that further QTc prolongation with dosing beyond what was studied is unlikely (DARRTS 04/16/2020). However, given that the mechanism behind the observed QTc prolongation is unknown, it's not possible to extrapolate the QTc effects outside the observed dosing schedule.

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

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/s/

LARS JOHANNESEN
06/12/2020 09:21:18 AM

CHRISTINE E GARNETT
06/12/2020 09:25:09 AM

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 1, 2020
Requesting Office or Division:	Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)
Application Type and Number:	NDA 210730
Product Name and Strength:	Olinvyk (oliceridine) injection, 1 mg/ml
Total Product Strength:	1 mg/1 mL, 2 mg/2 mL, 30 mg/30 mL
Applicant/Sponsor Name:	Trevena, Inc. (Trevena)
OSE RCM #:	2017-2276
DMEPA Safety Evaluator:	Zahra Farshneshani, PharmD
DMEPA Team Leader:	Otto L. Townsend, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised prescribing information, container labels and carton labeling received on February 7, 2020 for Olinvyk. The Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP) requested that we review the revised prescribing information, container label and carton labeling for Olinvyk (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions to the container label and carton labeling are in response to recommendations that we made during a previous label and labeling review.[a]

1.1 REGULATORY HISTORY

Trevena, Inc. originally submitted their NDA on November 2, 2017. However, a Complete Response letter was issued to Trevena on November 2, 2018 due to clinical deficiencies. Trevena submitted their complete response to the clinical deficiencies on February 7, 2020.

[a] Johnson C. Label and Labeling Review for Olinvyk (NDA 210730). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 MAY 23. RCM No.: 2017-2276

2 CONCLUSION

The revised prescribing information, container labels and carton labeling is unacceptable from a medication error perspective. Tables 1 and 2 below include the identified medication error issues with the submitted revised prescribing information (PI), container labels and carton labeling, our rationale for concern, and the proposed recommendation to minimize the risk for medication error.

3 RECOMMENDATIONS FOR TREVENA, INC.

We recommend the following be implemented prior to approval of this NDA 210730:

Table 1. Identified Issues and Recommendations for Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)			
Prescribing Information			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
General Issues			
1.	In the Dosage and Administration sections of the Highlights of Prescribing Information (HPI) and Full Prescribing Information (FPI), the lower dosages of the dose ranges are not followed by a unit of measurement.	Confusion may occur if the unit of measurement for each dose is not explicitly expressed.	As previously recommended in our May 2018[b] review, add a unit of measurement after each number used to express dose to minimize the risk for confusion. Revise the dosage statement in the Dosage and Administration sections of the HPI and FPI by adding the unit of measurement, "mg", after each number. For example, change, "1 to 3 mg" to read, "1 mg to 3 mg".

Table 2. Identified Issues and Recommendations for Trevena, Inc. (entire table to be conveyed to Applicant)			
Container Label and Carton Labeling			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION

[b] Johnson C. Label and Labeling Review for Olinvyk (NDA 210730). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 MAY 23. RCM No.: 2017-2276

1.	For the 1 mg/mL product, we appreciate that you implemented our previous recommendation to present the strength statement as 1 mg/1 mL. However, we note our previous recommendation is not consistent with United States Pharmacopeia (USP) standards, which states, "For containers that hold a volume equal to 1 mL, the strength should be expressed as quantity per milliliter (quantity/mL), not quantity/1 mL."	Strength presentations that are inconsistent with standards may lead to confusion.	To align with USP standards, change the strength presentation for the 1 mg/mL product to read, "1 mg/mL".
Carton Labeling			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
1.	The human-readable and machine-readable (2D data matrix barcode) product identifier required under the Drug Supply Chain Security Act (DSCSA) is missing on the label.	In September 2018, FDA released draft guidance on product identifiers required under the Drug Supply Chain Security Act.[c] The Act requires manufacturers and repackagers, respectively, to affix or imprint a product identifier to each package and homogenous case of a product intended to be introduced in a transaction in(to) commerce beginning November 27, 2017, and November 27, 2018,	We recommend that you review the draft guidance to determine if the product identifier requirements apply to your product's labeling.

[c] The draft guidance is available from: https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm621044.pdf

		respectively. We recommend that you review the draft guidance to determine if the product identifier requirements apply to your product's labeling.	

APPENDIX

A.1 List of Labels and Labeling Reviewed

- Container label (submitted on 02/07/2020)
- Carton labeling (submitted on 02/07/2020)
- Prescribing Information (Image not shown) (submitted on 02/07/2020)

A.2 IMAGES OF LABEL AND LABELING RECEIVED ON FEBRUARY 7, 2020

Container labels

(b) (4)

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/s/

ZAHRA FARSHNESHANI
05/01/2020 06:19:07 PM

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Interdisciplinary Review Team for Cardiac Safety Studies

QT Study Review

Submission	NDA 210730
Submission Number	046 (Resubmission)
Submission Date	2/7/2020
Date Consult Received	2/14/2020
Drug Name	Oliceridine
Indication	The management of moderate to severe acute pain in adults severe enough to require an intravenous opioid analgesic and for whom alternative treatments are inadequate.
Therapeutic dose	Up to 27 mg total daily dose
Clinical Division	DAAAP

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

This review responds to your consult dated 2/14/2020 regarding the sponsor's QT evaluation. We reviewed the following materials:

- Previous QT-IRT review for IND 113537 dated 03/22/2019; 04/25/2019 in DARRTS;
- Study CP130-1014 Study Report (link); and
- Cardiac Statistical Analysis Plan (link)

1 SUMMARY

QTc prolongation was observed in this TQT study, which decreased with repeat dosing of oliceridine up to 27 mg (Figure 1). The underlying mechanism behind the observed QTc prolongation remains unknown but is unlikely to be mediated via direct inhibition of ion channels given that it is not observed with repeat dosing. The clinical relevance of the observed QTc prolongation is unknown but is unlikely to be important given that it is transient and not hERG-mediated.

Table 1: The Point Estimates and the 90% CIs (FDA Analysis)

ECG parameter	Treatment	Time	ΔΔ	90% CI
QTc	Repeat dosing up to 27 mg	9 h	10.7	(8.5 to 12.9)

For further details on the FDA analysis please see section 4.

1.1 RESPONSES TO QUESTIONS POSED BY SPONSOR

Not applicable.

1.2 COMMENTS TO THE REVIEW DIVISION

Not applicable.

2 RECOMMENDATIONS

2.1 ADDITIONAL STUDIES

Not applicable.

2.2 PROPOSED LABEL

Below are proposed edits to the label submitted to SDN 046 (link) from the CSS-IRT. *Our changes are highlighted (addition, ~~deletion~~). Each section is followed by a rationale for the changes made. Please note, that this is a suggestion only and that we defer final labeling decisions to the Division.*

12.2 Pharmacodynamics

Cardiac Electrophysiology

The effect of oliceridine on the QTc interval was evaluated in 2 dedicated t~~T~~horough QT/QTc studies.

A single-dose, randomized, positive- (moxifloxacin) and placebo-controlled 4 period crossover study evaluated the ECG effects of oliceridine at a therapeutic (3 mg IV infusion) and a supratherapeutic (6 mg IV infusion) dose in 62 healthy volunteers. Dose-dependent QTc prolongation was observed in this study (3 mg: 7 ms [upper 90% CI: 9 ms]; 6 mg: 12 ms [14 ms]), which occurred after peak oliceridine plasma concentration (b) (4)

(b) (4)

A multi-dose, randomized, positive- (moxifloxacin) and placebo-controlled 3-way crossover study in 65 healthy volunteers evaluated intermittent dosing over 24 hours to the maximum daily cumulative dose of 27 mg. The maximum mean ΔΔQTcI was 11.7 ms (two-sided 90% UCI 14.7 ms) at 9 hours. Thereafter, the QTc effect did not progressively increase with repeat dosing, and despite continued dosing began to diminish after 12 hours.

The clinical significance of the transient QTc changes seen in the single dose and multiple dose studies in healthy volunteers is unknown. (b) (4)

(b) (4)

We propose to use similar language for the first study as we proposed during the last review cycle for the first study and to remove (b) (4)

(b) (4)

3 SPONSOR'S SUBMISSION

3.1 OVERVIEW

3.1.1 Clinical

Oliceridine has been observed to cause delayed and dose-dependent prolongation of the QTc interval in a prior TQT study following a single dose of 3 and 6 mg (IND 113537, DARRTS 02/05/2016). The mechanism of the delayed QTc prolongation observed in this study is unknown.

Late clinical studies only collected post-dose ECGs at 1 h and at 24 h (DARRTS 03/08/2018) leaving it unknown whether or not the QTc effect could increase with the repeat dosing regimen proposed (total daily dose of 27 mg). Ultimately, this concern was included in the CR letter in the first review cycle for this NDA (DARRTS 11/02/2018).

The sponsor proposed a new thorough QT study to address the QT issue, which was previously reviewed to by the QT-IRT (IND 113537, DARRTS 03/22/2019). Issues were identified in the protocol review relating to the proposed dosing regimen, study design and sample size. The sponsor later addressed the issue of dosing (DARRTS 04/25/2019). The issues concerning the study design and sample size have been addressed in the design of the final study.

3.1.2 Nonclinical Safety Pharmacology Assessments

Detailed review of the nonclinical data is presented in section 5. The overall conclusions are:

- Results from experiments that conducted by sponsor suggest that oliceridine is a mixed ion channel blocking drug that also accumulates in cardiac tissue.
- The experiments did not provide a mechanism to explain why the QTc effect diminishes after 10 h with repeat dosing, and it is unclear why the QT effect of quinidine increased over time.
- The mechanisms of delayed QTc prolongation after 6 mg single dose and the transient QTc prolongation after repeat dosing remain unknown.

3.2 SPONSOR'S RESULTS

3.2.1 By Time Analysis

Oliceridine failed to exclude the 10 msec threshold at the proposed maximum daily dose level (total cumulative dose of 27 mg) for ΔΔQTcF. The primary analysis is based on QTcI. Analysis of QTcF are provided as secondary. The sponsor used mixed-effects model with unstructured covariance. The largest estimated mean for ΔΔQTcF is 10.1 msec (7.28, 13) at 5 hours post-dose.

Reviewer's comment: The largest estimated mean for ΔΔQTcF is 10.7 msec (8.5, 12.9) at 9 hours post-dose using a mixed-effects model with compound symmetry covariance. Please see Section 4.3 for details.

3.2.1.1 Assay Sensitivity

Assay sensitivity was established by the moxifloxacin arm by showing the lower 90% confidence bounds greater than 5 msec at all 4 pre-specified time points (1, 2, 3, and 4 hours) for both ΔΔQTcF and ΔΔQTcI in sponsor's by-time point analysis.

Reviewer's comment: The result is consistent with reviewer's analysis. Please see Section 4.3.1.1 for reviewer's assay sensitivity by-time point analysis based on QTcF.

3.2.1.1.1 QT Bias Assessment

Not applicable.

3.2.2 Categorical Analysis

There were no significant outliers per the sponsor's analysis for QTc (i.e., > 500 msec or > 60 msec over baseline, HR (<45 or >100 bpm), PR (>200 msec and 25% over baseline) and QRS (>120 msec and 25% over baseline) for oliceridine.

Reviewer's comment: The result is consistent with reviewer's analysis. Please see Section 4.4 for reviewer's analysis.

3.2.3 Exposure-Response Analysis

The primary analysis for this study was by-time analysis (see section 3.2.1). The sponsor performed C-QT analysis as a secondary analysis using a direct effect model and concluded that while the model fit the data reasonably well, that their model did not account for the observed hysteresis or the decrease in QTc prolongation with repeat dosing.

Reviewer's comment: A direct C-QT model for oliceridine is not appropriate because the QT effect is not correlated with time-matched oliceridine QTc concentration as we noted in our previous review (IND 113537, DARRTS 02/05/2016). Moreover, in the current study the observed delayed QTc effect decreased with repeat dosing. The reviewer did therefore not conduct C-QT analysis for this study.

3.2.4 Safety Analysis

A summary of TEAEs for Torsades de Pointes/QT Prolongation standard MedDRA query (SMQ) by PT and treatment is provided in Table 14.3.1.9. Overall, 2 subjects experienced TEAEs within the SMQ:

- Subject (b) (6) experienced a moderate TEAE of syncope 3 days following the last dose of oliceridine that was considered not related to study medication and was reported as resolved (a subject narrative is provided in Section 16).
- Subject (b) (6) experienced a TEAE of ventricular tachycardia that led to study discontinuation (a subject narrative is provided in Section 16).

Subject (b) (6) experienced moderate TEAE of somnolence and mild TEAE of euphoric mood and sinus tachycardia, following the first dose of 2 mg oliceridine at 07:45. After the second dose (3 mg at 09:45), the subject experienced a TEAE of decreased oxygen saturation (09:55) and sinus tachycardia (10:11, 113 bpm). At 10:12, the subject experienced asymptomatic 4 beats non-sustained ventricular tachycardia,

which resulted in study drug discontinuation. Laboratory results obtained at 10:35 showed hypokalemia (3.2 mEq/L).

The investigator considered the event of ventricular tachycardia to be probably related to oliceridine as a consequence of oliceridine-induced hypoxemia and the presence of low potassium.

Reviewer's comment: The observed ventricular tachycardia is likely drug-related and possibly secondary to oliceridine-induced hypoxemia. No subjects experienced significant QTc prolongation in this study (see section 4.4.1).

4 REVIEWERS' ASSESSMENT

4.1 EVALUATION OF THE QT/RR CORRECTION METHOD

The sponsor used QTcI for the primary analysis, however, as no large increases or decreases in heart rate (i.e. |mean| < 10 bpm) were observed (see Section 0) the reviewer used QTcF.

4.2 ECG ASSESSMENTS

4.2.1 Overall

Overall ECG acquisition and interpretation in this study appears acceptable.

4.2.2 QT Bias Assessment

Not applicable.

4.3 BY TIME ANALYSIS

The analysis population used for by time analysis included all subjects with a baseline and at least one post-dose ECG.

A total of 65 subjects received treatments. Subject (b) (6) received complete dose of placebo and moxifloxacin in the first two periods but stopped receiving oliceridine early at the third period due to side effect. Subject (b) (6) completed treatments for all 3 periods, but the subject did not have baseline QTcI assessment. Both subjects were excluded from sponsor's by-time analysis. The total sample size used in sponsor's analysis is 63.

Subject (b) (6) was excluded in reviewer's by-time analysis since the baseline information is not available. Subject (b) (6) was included in reviewer's by-time analysis as intention-to-treat analysis. The total sample size used in reviewer's analysis is 64.

The statistical reviewer used a linear mixed model to analyze the drug effect by time for each biomarker (e.g., ΔQTcF, ΔHR, etc.) independently. The model includes treatment, sequence, period, time (as a categorical variable), and treatment-by-time interaction as fixed effects and baseline as a covariate. The model also includes subject as a random effect and a compound symmetry covariance matrix to explain the associated between repeated measures within period.

4.3.1 QTc

Figure 1 displays the time profile of ΔΔQTcF for different treatment groups. The maximum ΔΔQTcF values by treatment are shown in Table 2. Upward arrows indicate dosing time points with strength labeled below individual arrows.

Figure 1: Mean and 90% CI of ΔΔQTcF Timecourse (unadjusted CIs).

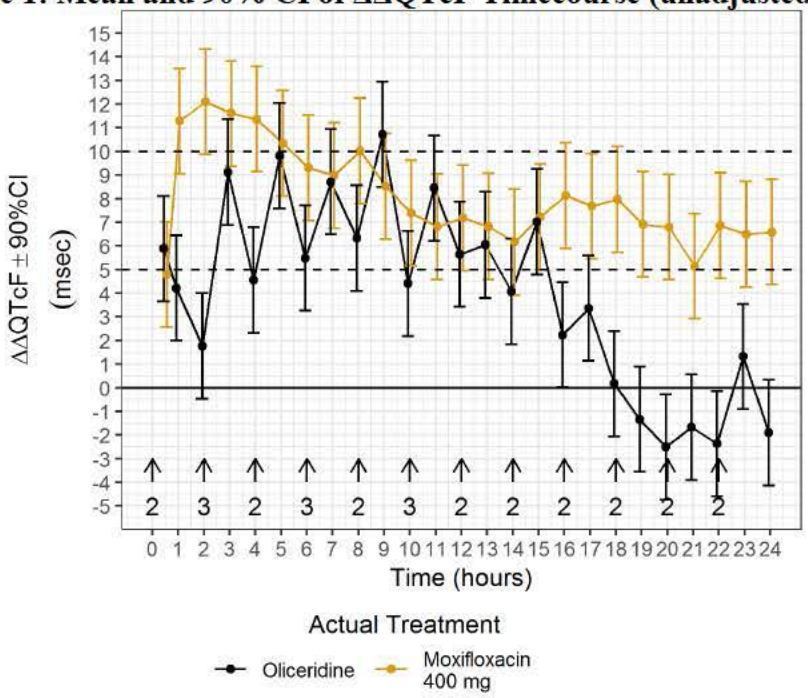


Table 2: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for ΔΔQTcF

N	Time (hours)	ΔΔQTcF (msec)	90.0% CI (msec)
64	9.000	10.7	(8.5 to 12.9)

4.3.1.1 Assay sensitivity

The time course of changes in ΔΔQTcF for moxifloxacin 400 mg is shown in Figure 1 with unadjusted CIs. After Bonferroni adjustment for 4 time points, the maximum lower limit of 90% CI for ΔΔQTcF was 9.1 msec at 2 hours post dose.

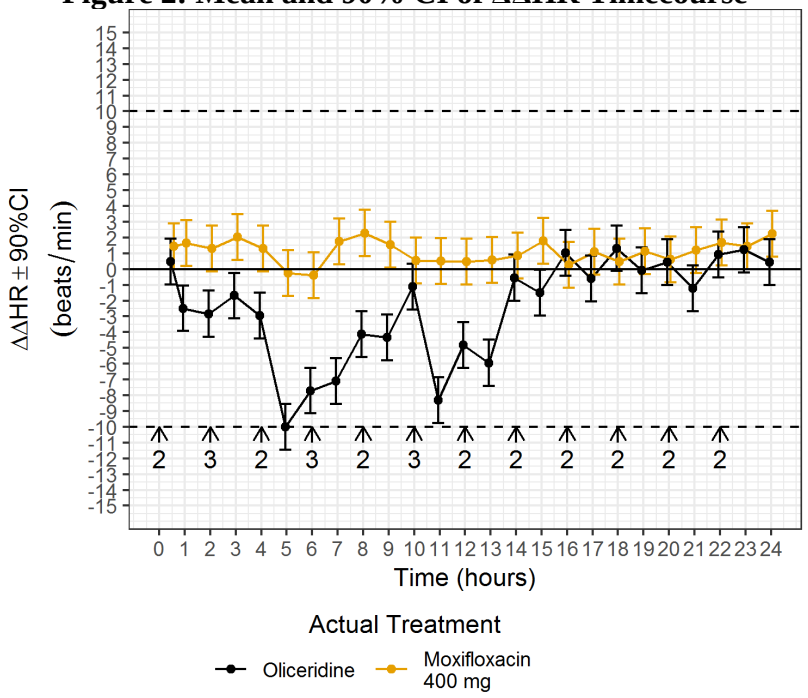
Table 3: The Point Estimates and the 90% CIs Corresponding to the Largest Lower Bounds for ΔΔQTcF

N	Time (hours)	ΔΔQTcF (msec)	90% CI (msec)	97.5% CI (msec)
64	2.000	12.1	(9.9, 14.3)	(9.1 to 15.1)

4.3.2 HR

Figure 2 displays the time profile of ΔΔHR for different treatment groups.

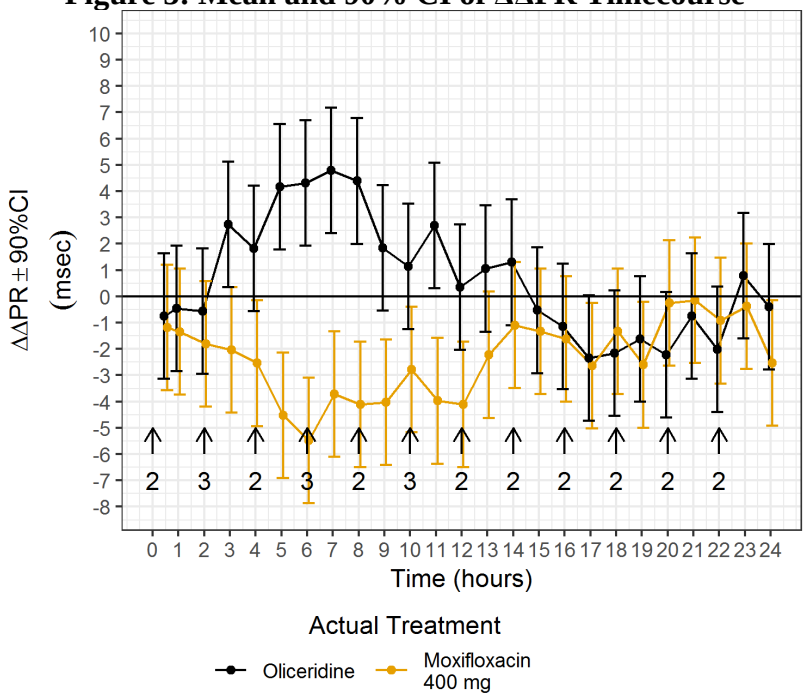
Figure 2: Mean and 90% CI of ΔΔHR Timecourse



4.3.3 PR

Figure 3 displays the time profile of ΔΔPR for different treatment groups.

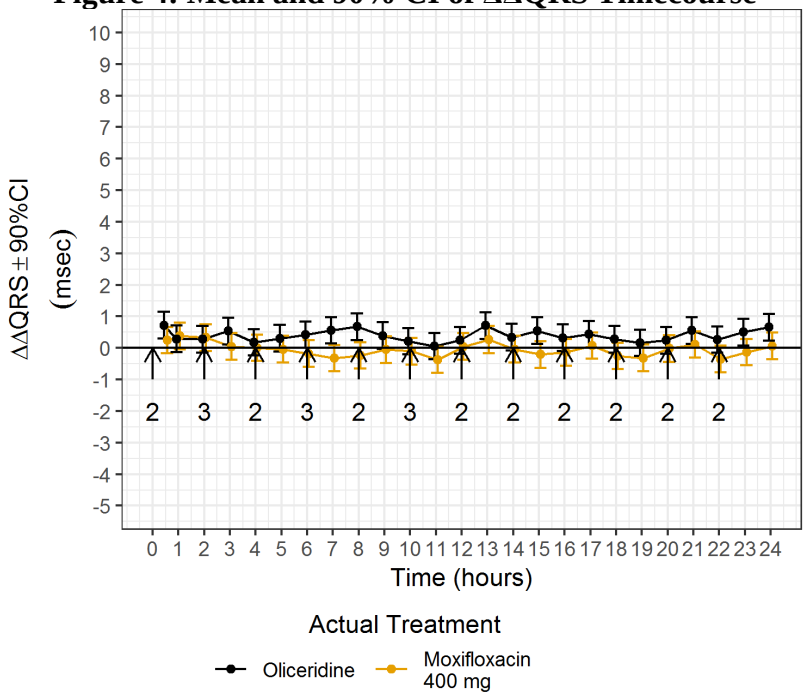
Figure 3: Mean and 90% CI of ΔΔPR Timecourse



4.3.4 QRS

Figure 4 displays the time profile of ΔΔQRS for different treatment groups.

Figure 4: Mean and 90% CI of ΔΔQRS Timecourse



4.4 CATEGORICAL ANALYSIS

Categorical analysis was performed for different ECG measurements either using absolute values, change from baseline or a combination of both. The analysis was conducted using the safety population and includes both scheduled and unscheduled ECGs.

4.4.1 QTc

No subject had QTcF above 500 msec. No subjects experienced ΔQTcF above 60 msec.

4.4.2 HR

No subject experienced HR>100 bpm after receiving oliceridine.

4.4.3 PR

No subject experienced PR > 220 msec after receiving oliceridine.

4.4.4 QRS

No subject experienced QRS > 120 msec with 25% increase over baseline after receiving oliceridine.

4.5 EXPOSURE-RESPONSE ANALYSIS

Exposure-response analysis was not conducted.

5 APPENDIX I: REVIEW OF SUPPORTING NONCLINICAL DATA

Oliceridine (TRV130) is a G protein-biased ligand at the μ-opioid receptor (MOR) and is developed for the management of moderate to severe acute pain in adult patients for whom an intravenous (IV) opioid is warranted.

5.1 SPONSOR'S SUBMISSION

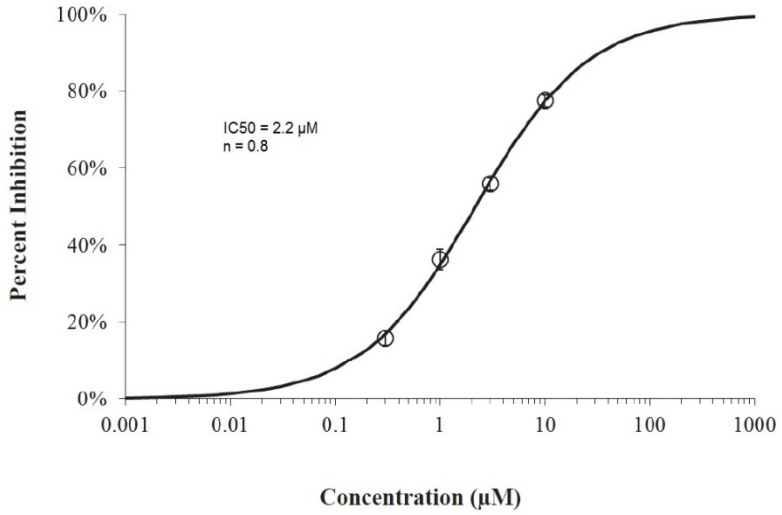
5.1.1 *In Vitro* patch clamp experiments

The sponsor has evaluated the effects of oliceridine and its metabolites on hERG currents, Nav1.5 peak and late currents, and Cav1.2 in HEK293 cells.

5.1.1.1 GLP hERG (manual) assay

There was one GLP study (110520.USF) evaluating the effects of oliceridine on hERG currents. Sponsor's voltage protocol is quite similar to the recommended hERG current protocol by the FDA (http://cipaproject.org/wp-content/uploads/sites/24/2018/06/CiPA-protocol-100918.pdf). Four concentrations of TRV130A (0.3, 1, 3 and 10 μM) were tested at near-physiological temperature (33-35 °C). The calculated IC50 value for the inhibitory effects of oliceridine on hERG current was 2.2 μM (Figure 5).

Figure 5. Dose-response curves of TRV130 on hERG currents.



Source: 110520.USF (Figure 3)

5.1.1.2 Automated patch clamp assay for hERG, Cav1.2 and Nav1.5 currents

The effects of oliceridine on hERG, Cav1.2 and Nav1.5 currents were evaluated at room temperature using the an automated patch clamp system (PatchXpress 7000A) in mammalian cell lines (TRV130-101110). Oliceridine concentration-dependently inhibited hERG, Cav1.2 and Nav1.5 currents. The IC50s values for oliceridine inhibited hERG, Cav1.2 , Nav1.5 (tonic) and Nav1.5(phase) currents were 6.2 μM, 39.6 μM , 19.5 μM and 9.0 μM, respectively (Table 4).

Table 4. Effects of oliceridine on cardiac ion currents

	IC50 (μM)			
	hERG	Cav1.2	Nav1.5 (tonic)	Nav1.5 (phasic)
TRV130	6.2	39.6	19.5	8.8

5.1.1.3 Automated patch clamp assay for hERG, Cav1.2 and Nav1.5 currents

The sponsor evaluated the effects of oliceridine (TRV130) and its two major metabolites TRV0109662 (CML-353) and TRV0306954 (M22) on hERG, Cav1.2 and Nav1.5 (peak and late) currents using automated patch clamp system (QPatch) at room temperature (180724-usf). The calculated IC50s for oliceridine inhibited hERG and late Nav1.5 currents were 4.3 μM and 8.8 μM. respectively. Oliceridine had no significant effects on Cav1.2 and peak Nav1.5 currents at concentrations up to 10 μM. Two major metabolites TRV0109662 and M22 had no effect on hERG, hCav1.2, peak hNav1.5 or late hNav1.5 ion channel currents when tested at concentrations up 300 μM, resulting in IC50's > 300 μM at all channels (Table 5).

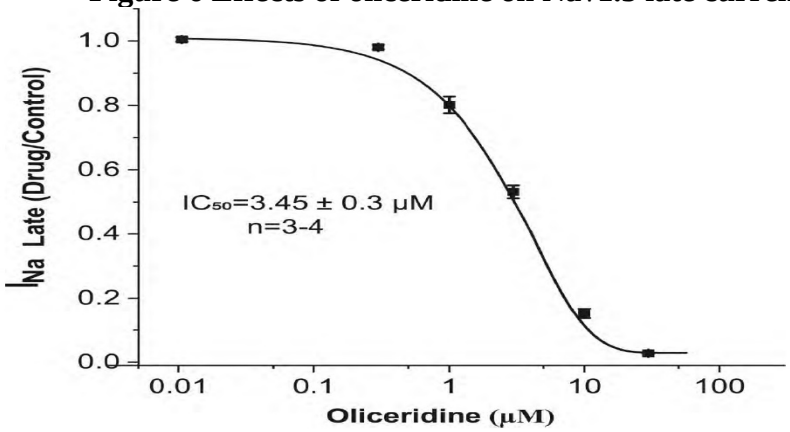
Table 5. Effects of oliceridine and two major metabolites on cardiac ion channels

	IC50 (μM)			
	hERG	Cav1.2	Nav1.5 peak	Nav1.5 late
TRV130	4.3	>10	>10	8.8
TRV0109662	>300	>300	>300	>300
M22	>300	>300	>300	>300

5.1.1.4 Late Nav1.5 assay (manual)

The sponsor also evaluated the effects of oliceridine on Nav1.5 late currents in CHO cells expressing SCN5A and SCN1B using whole cell patch clamp techniques at a temperature of 35°C (TRV130-29). Nav1.5 late currents were measured at the end of a 300 ms depolarizing pulse from a holding potential of −120 mV to – 20 mV in the presence of ATX-II (5 nM). Oliceridine concentration-dependently inhibited the Nav1.5 late currents with an estimated IC50 of 3.5 μM (Figure 6).

Figure 6 Effects of oliceridine on Nav1.5 late currents



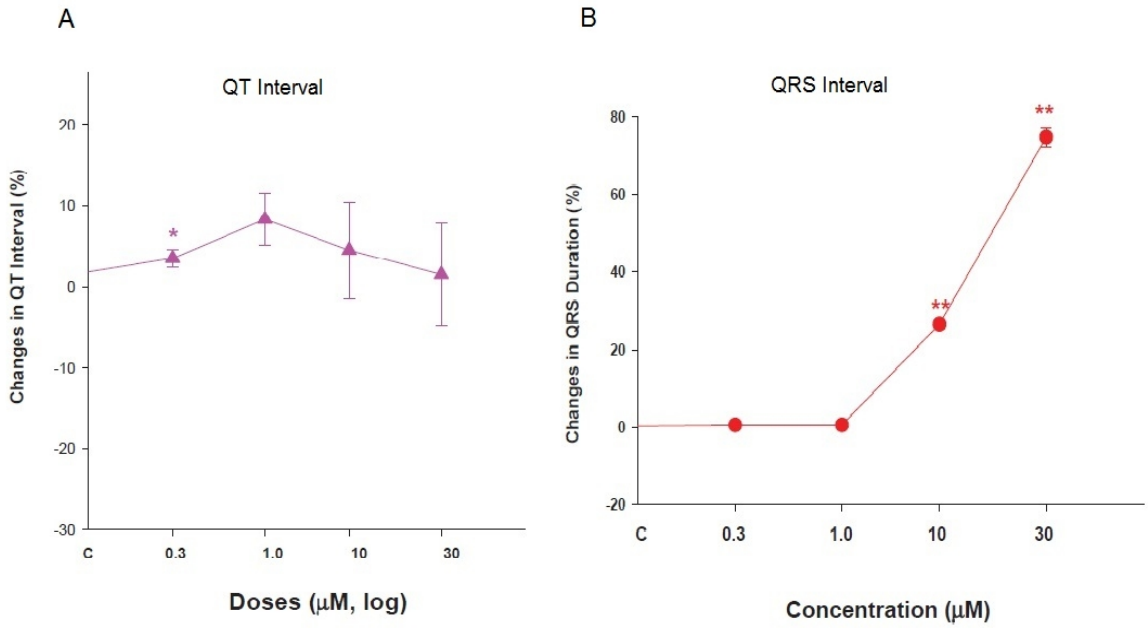
Source: TRV130-29 (Figure 2)

5.1.2 Effects of oliceridine on QT and QRS intervals in the rabbit left ventricular wedge preparations.

The effects of oliceridine on pseudo-ECG parameters including QT, QRS and Tp-Te intervals in rabbit left ventricular wedge preparation were evaluated in two separated studies (limrrwmu04 and TRV130-26).

In the first study (limrrwmu04), the sponsor evaluated the effects of oliceridine on QT, QRS intervals at four concentrations (0.3, 1.0 3.0 and 3 µM). Oliceridine produced a small increase in QT interval at 0.3 and 1 µM, and QT prolongations were attenuated at concentrations of 10 and 30 µM (Figure 7A). In addition, Oliceridine caused significant QRS prolongations at 10 and 30 µM (Figure 7B).

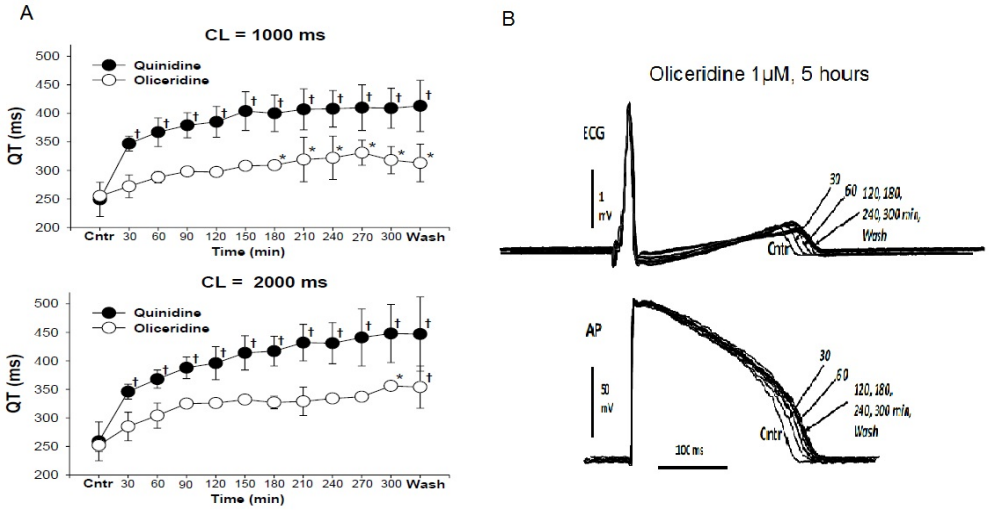
Figure 7 Effects of oliceridine on QT and QRS intervals in rabbit wedge preparation



Source: limrrwmu04 (Figure 3 and Figure 4)

In the second wedge preparation study (TRV130-26), the sponsor evaluated the time course (up to 5 hours) of oliceridine and quinidine (positive control) to prolong the QT at a frequency of 0.5 Hz, 1 Hz and 2 Hz. Both oliceridine (1 µM) and quinidine (3.3 µM) produced time-dependent prolongations of QT interval at all tested frequencies. The degrees of QT prolongations were much greater during the initial 30-60 minutes of exposure to the drug (Figure 8). In addition, washout (10 minutes) of oliceridine and quinidine caused no significant change of QT intervals. At a higher concentration of 10 µM, oliceridine produced a significant prolongation of QT interval. QT prolongations were greater at 30 mins than at 120 mins of exposure to the drug.

Figure 8 Time-dependent prolongation of QT and APD intervals by oliceridine (1µM) and quinidine (3.3 µM).

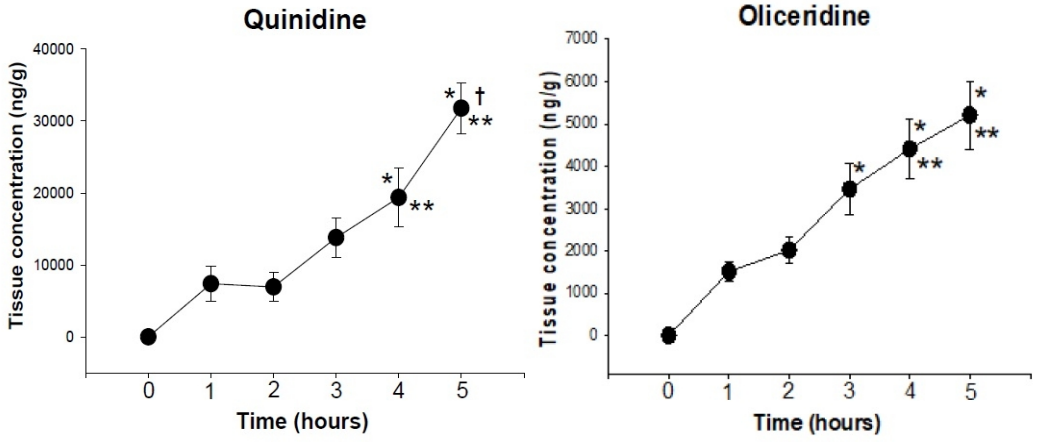


Source: TRV130-26 (Figure 1 and Figure 4).

5.1.3 Analysis of intracellular concentrations of oliceridine and quinidine in ventricular tissues from rabbit ventricular wedge preparation.

The sponsor also measured oliceridine and quinidine concentrations in homogenized cardiac tissues following completion of wedge preparation experiments. Those wedge preparations were cut into two sections (left and right) and frozen at -80 °C. On the day of evaluation, samples were thawed, homogenized in PBS, extracted with acetonitrile, spiked with an internal standard and analyzed for oliceridine or quinidine concentration using the LC-MS/MS methods. Results showed that both oliceridine and quinidine displayed progressive tissue accumulation (intracellular uptake) over a period of 5 hours without achieving a steady-state (Figure 9).

Figure 9. Accumulation of oliceridine and quinidine in rabbit left ventricular tissues



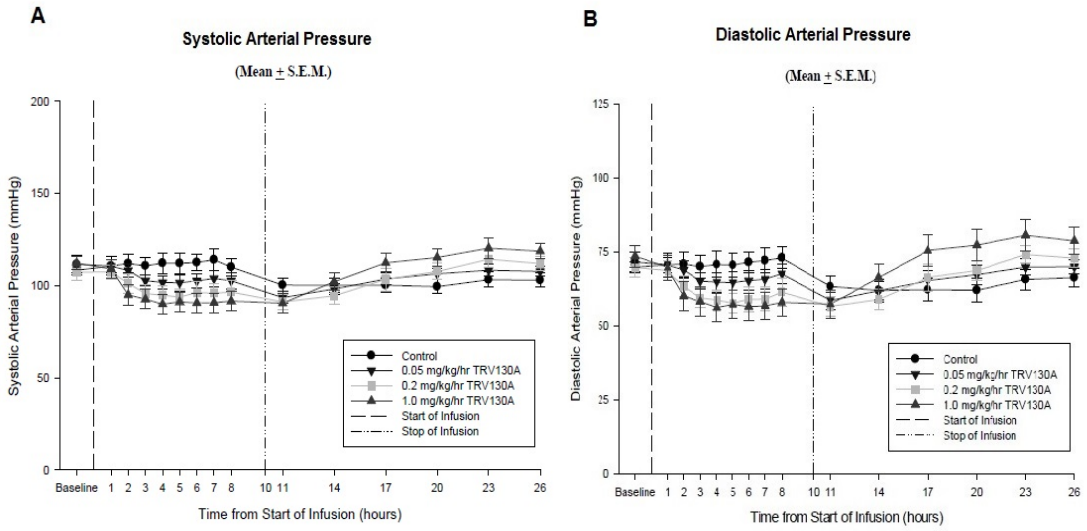
* - p<0.05 vs. respective 1-hour value. ** - p<0.05 vs. respective 2-hour value. † - p<0.05 vs. respective 3-hour value.
Mean ± SE. n=8 for all except the quinidine 3-hour value which included an n=10.

Source: TRV130-26 (Figure 12).

5.1.4 Effects of oliceridine on cardiovascular function in male monkey.

The potential cardiovascular effects of a 10 hours continuous IV infusion of oliceridine at doses at 0.05 mg/kg/hr (Css was 30.7 ng/ml), 0.2 mg/kg/hr (Css was 143 ng/ml) and 1 mg/kg/hr (C_{ss} was 710 ng/ml) were evaluated in cynomolgus monkeys (8242813). Administration of TRV130A caused notable, dose-dependent decreases (up to 25%) in systolic, diastolic, and mean arterial pressures (Figure 10). However, TRV130A did not have significant effect on QRS, PR, QT, or corrected QT (QTc) interval.

Figure 10 Effects of oliceridine on systolic and diastolic arterial pressures in male monkeys



Source: 8242813 (Figure 6 and Figure 7)

5.1.5 Sponsor's interpretation for the disconnection between peak plasma concentration of oliceridine and changes of QT intervals

The sponsor suggested that the disconnect between peak plasma concentration of oliceridine and the ECG effects (QT prolongation) observed in Study CP130-1008 at a dose of 6 mg is due to gradual accumulation of oliceridine in the myocardial cells.

Our results provide support for the hypothesis that the mismatch between Cmax and IC50 for inhibition of IKr as well as the delayed peak of QT prolongation observed in Study CP130-1008 are due to gradual accumulation of oliceridine intracellularly in the myocardial cells. In a heterologous expression system (HEK) transfected with KCNH2, which encodes hERG, the IKr channel protein, oliceridine blocks IKr with an IC50 of 2.2 μM. Although the mean clinical oliceridine unbound Cmax following a supratherapeutic dose is a small fraction of this (0.145 μM), with progressive accumulation of the drug intracellularly, and with preferential accessibility to the IKr channel from inside the cell, myocardial oliceridine concentrations can reasonably approach levels capable of reducing repolarization reserve, thus prolonging APD and the QT interval. Oliceridine also blocks cardiac sodium (NaV1.5, peak INa, IC50=9.023 μM; late INa, IC50 =3.45 μM) and calcium (ICa, CaV1.2, IC50=39.6 μM) channel currents. At erapeutic concentrations, the effect of oliceridine on these currents is likely to be small and is expected to have little effect on repolarization. Because the IC50 for inhibition of late INa is generally much

lower that that of peak INa, inhibition of this current is expected to counter the effect of the drug to prolong APD and QT interval. The accumulation of oliceridine intracellularly is expected to significantly inhibit both inward (late INa) and outward (IKr) currents, which likely explains the plateau in QT and APD prolongation observed in this study.

5.2 REVIEWER'S ASSESSMENT

5.2.1 Potencies of oliceridine and its metabolites on cardiac ion channels

The results from in vitro manual and automated patch clamp experiments demonstrated that oliceridine inhibits several cardiac ionic currents using recombinant cell lines.

Two major metabolites TRV0109662 and TRV0306954 (M22) had no effect on hERG, hCav1.2, peak hNav1.5 or late hNav1.5 ion channel currents (IC50's > 300 µM at all channels). The estimated safety margins against hERG channel for TRV0109662 (molecular weight is 261.1 g/mol, Cmax was 4.68 ng/ml, considered a 4.5 % PPB) and M22 (molecular weight is 578.68 g/mol, Cmax was 177 ng/ml, considered a 15 % PPB) are greater than 17525 X and 1151 X, respectively.

The ratios of potency of cardiac ion channel inhibition to human therapeutic free plasma concentration IC50/Cmax(free) are shown in Table 6. This data suggests that oliceridine inhibits multiple cardiac ionic currents, including hERG and Nav1.5, at therapeutic drug levels.

Table 6. Ion channel profile of oliceridine and safety margin against specific ion channels

	hERG	Nav1.5 late	Nav1.5 peak	Cav1.2
Lowest IC_{50} (µM)	2.2	3.5	8.8	39.6
IC50/Cmax-free	46	73	183	823

The molecular weight of oliceridine is 459.47 g/mol, and the Cmax was 94.3 ng/ml using a maximum PCA dosing regimen. Considering the 76.6 % protein bound (23.4 % free fraction of oliceridine in human serum), then the free Cmax is 22.1 ng/ml.

5.2.2 Effects of oliceridine on cardiac repolarization in rabbit left ventricular wedge preparation

Results from study limrrwmu04 showed that oliceridine prolonged QT interval (ΔQT) at frequency of 0.5 Hz by 11 ms, 27 ms, 13 ms and 3 ms at concentrations of 0.3, 1, 10 and 30 µM, respectively. In addition, it prolonged QRS interval by 10 ms and 19 ms at concentrations of 10 and 30 µM (Table 7). These results demonstrated that oliceridine dominantly inhibited hERG current at lower concentration (0.3 and 1.0 µM), and inhibited both hERG and late Nav1.5 at higher concentrations (10 and 30 µM).

Table 7. Effects of oliceridine on QT and QRS intervals in rabbit wedge preparation

	0.3 µM	1.0 µM	10 µM	30 µM
ΔQT (mean), ms	11	27	13	3
ΔQRS (mean), ms	0.2	0.2	10	19

Source: limrrwmu04 Table 2

In another wedge preparation study (TRV130-26), the sponsor observed that oliceridine at 1 µM produced time-dependent prolongation of the QT interval over a period of 5 hours, without achieving a steady-state at frequencies of 0.5 and 1 Hz. The sponsor also discovered that there was a gradual and progressive accumulation of oliceridine in the cardiac tissues over 5 hours (Table 8). Although the amount of oliceridine increased over a period of 5 hours in the homogenized cardiac tissues, the sponsor cannot determine whether the progressive accumulation of oliceridine occurred intracellularly or extracellularly. In addition, the sponsor cannot determine exact intracellular concentrations of oliceridine and if the intracellular concentration at highest measuring point (at 5 hour) was greater than the perfusion concentration (1 µM).

Table 8. Time course of QT prolongation and oliceridine accumulation in wedge preparation

	1 hour	2 hour	3 hour	4 hour	5 hour
ΔQT (mean), ms at 1 Hz	33	42	54	67	63
oliceridine, ng/mg	1510	2015	3459	4410	5209

Source: TRV130-26, Table 5

5.2.3 Effects of oliceridine on hemodynamic parameters in male monkeys

Oliceridine was administered to eight male cynomolgus monkeys at dose levels of 0.05, 0.2, and 1.0 mg/kg/hr by 10-hour intravenous infusion. Administration of oliceridine caused dose-dependent decreases (< 25%) in mean systolic, diastolic, and mean arterial pressures in monkey. The decrease in mean systolic, diastolic, and mean arterial pressures could be due to the inhibition of peak sodium channel by oliceridine.

5.3 SUMMARY

Overall, results from the *in vitro* experiments showed that oliceridine inhibited multiple cardiac ion channels including hERG, Nav1.5 peak and late and Cav1.2, suggesting that oliceridine is a multi-ion channel blocking drug that also accumulates in cardiac tissue.

However, the experiments did not provide a mechanism to explain why the QTc effect diminishes after 10 h with repeat dosing, and it is unclear why the QT effect of quinidine increased over time.

The mechanisms of delayed QTc prolongation after 6 mg single dose and the transient QTc prolongation after repeat dosing remain unclear.

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/

LARS JOHANNESEN
04/16/2020 02:27:01 PM

JANELL E CHEN
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YU YI HSU
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DONGLIN GUO
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MICHAEL Y LI
04/16/2020 04:15:27 PM

CHRISTINE E GARNETT
04/16/2020 04:16:21 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: April 25, 2019

From: CDER DCRP QT Interdisciplinary Review Team

Through: Christine Garnett, Pharm.D.
Clinical Analyst
Division of Cardiovascular and Renal Products /CDER

To: Shelly Kapoor, RPM
DAAAP

Subject: QT-IRT Consult to IND 113537 (NDA 210730) (SDN 123)

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 4/8/2019 regarding the sponsor's QT related question. The QT-IRT reviewed the following materials:

- Sponsor's revised dosing proposal (IND 113537 / SDN 123; link); and
- Previous QT-IRT review(s) for IND 113537 dated 03/29/2019 in DARRTS.

1 QT-IRT Responses

Question 1: Based on the results of the simulations detailed above, and taking into account FDA's requests around using a bolus dose regimen in Study CP130-1014 that is more consistent with the demand dose utilization seen in the Phase 3 clinical studies, Trevena proposes that the bolus dosing regimen in Study CP130-1014 be modified as follows:

- Initial oliceridine loading dose of 2 mg, followed by oliceridine 2 mg every two hours, except at 2, 6, and 10 hours where 3 mg will be administered, for a total of 27 mg over 24 hours.

Does the FDA agree that this revised dosing regimen is an acceptable alternative to the originally proposed regimen?

QT-IRT's response: Yes, the revised dosing regimen is acceptable.

Please send the following responses to the sponsor's questions in the previous submission to IND 113537 (SDN 121). We have revised some of our responses revised since our review to you dated 03/29/2019.

Protocol Question 1: Does the Agency agree that [redacted] is acceptable for this study?
QT-IRT's response: No, we recommend that you use the 3-way Williams Square crossover as you did in your previous TQT study.

Protocol Question 2: Does the Agency agree that the study population (healthy male or female volunteers who are CYP2D6 extensive metabolizers) is acceptable for this study?
QT-IRT's response: Yes, it is reasonable to only include extensive metabolizers in your study because the primary objective of this study is to characterize the effects at the highest proposed dosing regimen. However, given that the mechanism of the observed QT prolongation with your product is poorly understood it might not be possible to extrapolate findings from this study to poor metabolizers taking your drug without dose adjustment.

Protocol Question 3: Does the Agency agree with the proposed criteria for inclusion in the evaluable QT Population and the overall Safety Population?
QT-IRT's response: Your proposed criteria appear reasonable; however, the proposed minimum number of subjects to be included (N=20) is lower than the proposed sample size in your SAP (N=54), which could impact the interpretation of your study.

Protocol Question 4: Does the Agency agree that the dose regimen proposed in this study provides an appropriate dosing regimen to allow the necessary conclusions to be drawn regarding the potential effects of oliceridine on measures of cardiac repolarization?
QT-IRT's response: Yes, the proposed dosing regimen appears reasonable to evaluate the effect of repeat doses of oliceridine, up to a total daily dose of 27 mg, on cardiac repolarization.

Question 5: Does the Agency agree that [redacted]
QT-IRT's response: See our response to Question 1.

Protocol Question 6: Does the overall design of Study CP130-1014 meet the Division's needs to address the deficiencies identified in the November 2, 2018 Complete Response Letter regarding the Division's request for additional QT interval data for oliceridine?
QT-IRT's response: The protocol should address our comments to Protocol Questions 1-5, as well as the following comments:

1) In your protocol you are proposing to use QTcI as the primary endpoint, which will be derived based on data collected on day -1 in period 1. However, it is not clear from your protocol if you are proposing to use only ECGs collected at rest during matched time-points on day -1 (section 2.6) or if you are intending on using the entire baseline recording (section 3.1). Please clarify how you intend to collect QT/RR data within each subject to support QTcI.

2) Instead of pre-specifying QTcI as the primary endpoint you could define the change in HR triggering the need for QTcI. For example, if the change in HR greater than the predefined threshold is observed you could then re-analyze the baseline data to support QTcI or otherwise use QTcF for the primary.
3) It is also important to account for QT/RR hysteresis prior to deriving the individual QT/RR relationship to avoid bias when estimating the individual QT/RR relationship.
4) Please clarify the order of procedures for time-points with several procedures and holter ECG extraction.
5) When evaluating the performance of a QT correction methodology it is not appropriate to use on-treatment data (Dang, et al. Ther Innov Regul Sci 2013;47:256-60 and Malik et al. Drug Saf 2018;doi: 10.1007/s40264-018-0735-2).
6) For exposure-response analysis, we recommend the analysis and reporting of results follow the recommendations described in "*Scientific white paper on concentration-QTc modeling"* (Garnett, C. et al., J Pharmacokinet Pharmacodyn 2017; doi 10.1007/s10928-017-9558-5) and "*Correction to: Scientific white paper on concentration-QTc modeling*" (Garnett, C. et al., J Pharmacokinet Pharmacodyn 2018; doi 10.1007/s10928-017-9565-6).
7) When you submit your QT study report, please include the following items
   a) Study report(s) for any other clinical studies of the effect of product administration on the QT interval that have been performed
   b) Study report
   c) Statistical analysis plan
   d) Clinical study protocol
   e) Investigator's Brochure
   f) A completed Highlights of Clinical Pharmacology and Cardiac Safety Table
   g) Annotated CRF
   h) A data definition file which describes the contents of the electronic data sets
   i) Electronic data sets as SAS.xpt transport files (in CDISC SDTM and ADAM format – if possible) and all the SAS codes used for the primary statistical and exposureresponse analyses. Please make sure that the ECG raw data set includes at least the following: Subject ID, treatment, period, ECG date, ECG time (down to second), nominal day, nominal time, replicate number, heart rate, intervals QT, RR, PR, QRS and QTc (including any corrected QT, e.g., QTcB, QTcF, QTcN, QTcI, along with the correction factors for QTcN and QTcI), Lead, and ECG ID (link to waveform files, if applicable).
   j) Data set whose QT/QTc values are the average of the above replicates at each nominal time point
   k) Adverse Event analysis using the MedDRA SMQ "Torsade de pointes/QT Prolongation" and include the preferred term "Seizure" by treatment and dose level.
   l) Narrative summaries and case report forms for any
      i) Deaths
      ii) Serious adverse events
      iii) Episodes of ventricular tachycardia or fibrillation
      iv) Episodes of syncope
      v) Episodes of seizure
      vi) Adverse events resulting in the subject discontinuing from the study
8) Submit all related ECG waveforms to the ECG warehouse (www.ecgwarehouse.com)

2 BACKGROUND

Oliceridine is a small molecule G protein μ-opioid receptor agonist, which has been observed to cause dose-dependent prolongation of the QTc interval in a single dose thorough QT study occurring ~1 h after peak concentration. The sponsor has proposed a new thorough QT study to characterize the effects after multiple doses to address a deficiency in the CR letter. We refer the reader to our previous review dated 03/22/2019 for a review of the study protocol and summary of the information available for oliceridine.

The proposed dosing regimen was a major protocol review issue, because the sponsor had not provided a comparison to the proposed maximum dosing regimen. After completing our review, a teleconference was scheduled with the sponsor to discuss this issue further and based on the teleconference discussion the sponsor has now submitted a revised proposal, which is the focus of this review.

The information submitted by the sponsor supports that the originally proposed dosing regimen would yield a Cmax comparable to the PCA dosing regimen simulated (Table 1).

Table 1: Comparison of Cmax between previous proposal and maximum PCA

Dosing Regimen	Median C_{max} (ng/mL)	5^{th}, 95^{th} Percentiles (ng/mL)
Bolus dosing: Study CP130-1014 Protocol Simulation (N=100)	75.2	18.8, 297
Maximum PCA Dosing PCA Simulation (N=100)	94.3	26.4, 393

Source: Sponsor's revised dosing proposal, Table 1

At the teleconference the FDA proposed using a maximum PCA dosing regimen in the thorough QT study, which would result in meeting the 27 mg total daily dose limit before the 24 h. In response to this the sponsor has proposed to revise the dosing regimen to redistribute the hours with 3 mg dosing to be at 2, 6 and 10 h instead of 6, 12 and 18 h. To support this revised proposal the sponsor has provided a comparison based on more frequent PK samples showing, as expected, comparable Cmax.

Overall, the information provided addresses the concern noted in our previous review about lack of support for the proposed dosing regimen and both the revised proposal and the previous proposed dosing regimen are acceptable.

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

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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/

LARS JOHANNESEN
04/25/2019 09:15:37 AM

CHRISTINE E GARNETT
04/25/2019 09:23:56 AM

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: March 22, 2019

From: CDER DCRP QT Interdisciplinary Review Team

Through: Christine Garnett, Pharm.D.
Clinical Analyst
Division of Cardiovascular and Renal Products /CDER

To: Shelly Kapoor, RPM
DAAAP

Subject: QT-IRT Consult to IND 113537 (SDN 121)

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 2/21/2019 regarding the sponsor's QT related question. The QT-IRT reviewed the following materials:

- Design rationale for CP130-1014 (IND 113537 / SDN 121; link);
- Study protocol for CP130-1014 (IND 113537 / SDN 121; link);
- SAP for CP130-1014 (IND 113537 / SDN 121; link);
- Meeting minutes from 12/19/2019 meeting (NDA 210730 dated 01/18/2019);
- Clinical pharmacology review for NDA 210730 (DARRTS 10/23/2018);
- Study report for CP130-3001 (NDA 210730 / SDN 1; link);
- Study report for CP130-3002 (NDA 210730 / SDN 1; link);
- Population-PK model for oliceridine (NDA 210730 / SDN 1; link);
- Previous QT-IRT review(s) for IND 113537 dated 02/05/2016;
- Previous QT-IRT review(s) for NDA 210730 dated 06/06/2018; 09/27/2018; 12/10/2018;
- hERG report 110520.USF (NDA 210730 / SDN 1; link);
- Patch report for oliceridine (NDA 210730 / SDN 1; link);
- Patch report for oliceridine and its major metabolites (NDA 210730 / SDN 35; link); and
- Rabbit Left Ventricular Wedge Preparation study report (NDA 210730 / SDN 1; link).

1 QT-IRT Responses

Question 1: Does the Agency agree that a two-sequence design (Table 1) in which the positive control arm is fixed as the last period, knowing that the central reading cardiologist is blinded to study treatment, is acceptable for this study?

QT-IRT's response: No, we recommend that you use the 3-way Williams Square crossover as you did in your previous TQT study.

Question 2: Does the Agency agree that the study population (healthy male or female volunteers who are CYP2D6 extensive metabolizers) is acceptable for this study?

QT-IRT's response: Yes, it is reasonable to only include extensive metabolizers in your study because the primary objective of this study is to characterize the effects at the highest proposed dosing regimen. However, given that the mechanism of the observed QT prolongation with your product is poorly understood it might not be possible to extrapolate findings from this study to poor metabolizers taking your drug without dose adjustment.

Question 3: Does the Agency agree with the proposed criteria for inclusion in the evaluable QT Population and the overall Safety Population?

QT-IRT's response: Your proposed criteria appear reasonable; however, the proposed minimum number of subjects to be included (N=20) is lower than the proposed sample size in your SAP (N=54), which could impact the interpretation of your study.

Question 4: Does the Agency agree that the dose regimen proposed in this study provides an appropriate dosing regimen to allow the necessary conclusions to be drawn regarding the potential effects of oliceridine on measures of cardiac repolarization?

QT-IRT's response: Yes, the proposed dosing regimen appears reasonable to evaluate the effect of repeat doses of oliceridine, up to a total daily dose of 27 mg, on cardiac repolarization.

Question 5: Does the Agency agree that this dose regimen is consistent with the proposed labeled dose administration for oliceridine?

QT-IRT's response: No, you have not provided a comparison to the proposed labeled dose and the provided justification suggests that the Cmax in the previous phase 3 trials exceeds the expected Cmax for the dosing regimen proposed in your thorough QT study.

Question 6: Does the overall design of Study CP130-1014 meet the Division's needs to address the deficiencies identified in the November 2, 2018 Complete Response Letter regarding the Division's request for additional QT interval data for oliceridine?

QT-IRT's response: The protocol should address our comments to Questions 1–5, as well as the following comments:

1. In your protocol you are proposing to use QTcI as the primary endpoint, which will be derived based on data collected on day -1 in period 1. However, it is not clear from your protocol if you are proposing to use only ECGs collected at rest during matched time-points on day -1 (section 2.6) or if you are intending on using the entire baseline recording (section 3.1). Please clarify how you intend to collect QT/RR data within each subject to support QTcI.
2. Instead of pre-specifying QTcI as the primary endpoint you could define the change in HR triggering the need for QTcI. For example, if the change in HR greater than the predefined threshold is observed you could then re-analyze the baseline data to support QTcI or otherwise use QTcF for the primary.
3. It is also important to account for QT/RR hysteresis prior to deriving the individual QT/RR relationship to avoid bias when estimating the individual QT/RR relationship.
4. When evaluating the performance of a QT correction methodology it is not appropriate to use on-treatment data (Dang, et al. Ther Innov Regul Sci 2013;47:256-60 and Malik et al. Drug Saf 2018;doi: 10.1007/s40264-018-0735-2).
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6. When you submit your QT study report, please include the following items
    a. Study report(s) for any other clinical studies of the effect of product administration on the QT interval that have been performed
    b. Study report
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    d. Clinical study protocol
    e. Investigator's Brochure
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    g. Annotated CRF
    h. A data definition file which describes the contents of the electronic data sets
    i. Electronic data sets as SAS.xpt transport files (in CDISC SDTM and ADAM format – if possible) and all the SAS codes used for the primary statistical and exposure-response analyses. Please make sure that the ECG raw data set includes at least the following: Subject ID, treatment, period, ECG date, ECG time (down to second), nominal day, nominal time, replicate number, heart rate, intervals QT, RR, PR, QRS and QTc (including any corrected QT, e.g., QTcB, QTcF, QTcN, QTcI, along with the correction factors for QTcN and QTcI), Lead, and ECG ID (link to waveform files, if applicable).
    j. Data set whose QT/QTc values are the average of the above replicates at each nominal time point
    k. Adverse Event analysis using the MedDRA SMQ "Torsade de pointes/QT Prolongation" and include the preferred term "Seizure" by treatment and dose level.

l. Narrative summaries and case report forms for any
    i. Deaths
    ii. Serious adverse events
    iii. Episodes of ventricular tachycardia or fibrillation
    iv. Episodes of syncope
    v. Episodes of seizure
    vi. Adverse events resulting in the subject discontinuing from the study

7. Submit all related ECG waveforms to the ECG warehouse (www.ecgwarehouse.com)

2 BACKGROUND

2.1 Product Information

Oliceridine is a small molecule G protein μ-opioid receptor agonist, which has been observed to cause dose-dependent prolongation of the QTc interval in a thorough QT study, which included two single doses of 3 and 6 mg. The peak QTc effect occurred ~1 h after peak oliceridine concentration, which suggests that the observed dose-proportional QTc increase is not mediated via direct inhibition of the hERG potassium channel by oliceridine (DARRTS 02/05/2016). Additional nonclinical assessments by the sponsor suggests that the delayed QTc prolongation is not mediated via direct inhibition of hERG by any major metabolite of oliceridine (DARRTS 09/27/2018).

The oliceridine NDA received a complete response due to the inadequacies of the clinical ECG data submitted to characterize the QT effects in patients. The complete response letter included the following description of the data required to resolve the inadequacies of the available data:

Information Needed to Resolve the Deficiency
To address the safety concern of QT prolongation at the maximum proposed daily dose, provide data from a randomized active-controlled study that will include 24-hour Holter monitoring and replicate QT measurements extracted every hour from the Holter monitors and compared to the control group. The study should be of adequate duration and sample size to allow reliable

In December of 2018, the sponsor requested a meeting to discuss a study in patients to address the deficiency stated above. A principal concern of the study was that it might not result in an adequate number of patients receiving the maximum proposed daily dose as well as how to interpret the results of the study when it included a titration scheme (DARRTS 12/10/2018).

After the meeting, the sponsor requested clarification about if a healthy volunteer study would be adequate. A post meeting note was included in the meeting minutes to address this question (DARRTS 01/18/2019):

Agency Post Meeting Note:
The evaluation of the effects of oliceridine on the QT interval may be performed in a healthy volunteer population, if it is possible to conduct a multiple-dose study covering the maximum proposed total daily dose in healthy subjects. A healthy volunteer study should also include a placebo- and positive-control arm, and, based on the findings of the thorough QT study for oliceridine, the primary analysis should reflect a by-time analysis.

If you choose to conduct the study in a post-surgical population, consider surgical procedures where collection of 12-lead ECGs can be tolerated post surgically

The sponsor has now submitted a study protocol for a multiple-dose study in healthy volunteers and the details of our review can be found in Appendix 3.

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

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/s/

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DALONG HUANG
03/22/2019 12:05:11 PM

MOHAMMAD A RAHMAN
03/22/2019 12:15:15 PM

CHRISTINE E GARNETT
03/22/2019 12:18:16 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: December 10, 2018

From: CDER DCRP QT Interdisciplinary Review Team

Through: Christine Garnett, Pharm.D.
Clinical Analyst
Division of Cardiovascular and Renal Products /CDER

To: Shelly Kapoor, RPM
DAAAP

Subject: QT-IRT Consult to NDA 210730 (SDN 043)

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 11/20/2018 regarding the sponsor's QT related questions. The QT-IRT reviewed the following materials:

- Sponsor's briefing material (NDA 210730 / SDN 043; link);
- Complete response letter (NDA 210730 / SDN 043; link); and
- Previous QT-IRT review(s) for NDA 210730 dated 03/08/2018; 06/06/2018; 07/11/2018 and 09/27/2018 in DARRTS.

1 QT-IRT Responses

Question 1: Does the Agency agree with the general study design proposed, including the treatment arms, number of patients per treatment arm, the minimum duration of opioid therapy, and the randomized open-label nature of the design?

QT-IRT's response: No, see our responses to questions 2 - 9.

Question 2: Does the Agency agree with the proposed dosing regimens?

QT-IRT's response: We are concerned that with the variable titration dosing regimen, there may not be an adequate number of patients receiving the highest proposed label dose. Would it be possible to specify that enrollment continues until there are at least 20 evaluation patients who have received the highest proposed label total daily dose of oliceridine?

Question 3: Does the Agency agree that patients in this study should be permitted to receive multi-modal analgesic therapy in addition to the specified opioid therapy?

QT-IRT's response: If possible, we recommend that other QT prolonging analgesics and antiemetics are not used.

Question 4: Does the Agency agree that the proposed study requirement of a minimum duration of exposure to oliceridine or active comparator treatment to extend for at least the first 21-24 hours of postoperative care (with the proposed treatment window interval of 3 hours) will provide a sufficient safety exposure population to characterize the cardiac safety of oliceridine?

QT-IRT's response: The study requirement should have a dose and duration component.

Question 5: Does the Agency agree with the proposed study population main inclusion and exclusion criteria?

QT-IRT's response: Excluding patients who have increased risk of QT prolongation at baseline appears reasonable.

Question 6: Does the Agency agree with the specified minimal time of treatment exposure (24 ± 3 hours) for the primary endpoint?

QT-IRT's response: Yes.

Question 7: Does the Agency agree with the overall ECG collection plan and time-points to be collected?

QT-IRT's response: The ECG sampling schedule appears appropriate; however, you have not provided adequate information for us to comment on the ECG acquisition and measurement plan.

Question 8: Does the Agency believe that the proposed statistical analysis of the QT interval data will provide adequate data to mitigate the potential risk of QT prolongation with oliceridine in product labeling?

QT-IRT's response: You have not provided adequate information to allow us to comment on your proposed statistical analysis plan.

Question 9: Does the Agency agree that, for the purposes of this study, patients receiving either morphine or hydromorphone may be analyzed together as a single treatment group?

QT-IRT's response: Yes.

2 Internal Comments to the Division

- *The proposed dosing in the study might not result in an adequate number of patients in the study receiving the maximum proposed daily dose, which will impact study interpretability.*

3 BACKGROUND

3.1 Product Information

Oliceridine is a small molecule G protein μ-opioid receptor agonist, which has been observed to cause dose-dependent prolongation of the QTc interval with a peak effect occurring ~1 h after peak plasma concentration of parent drug in a thorough QT study. The mechanism of the observed delayed QTc prolongation is unknown. The proposed dosing regimen in the last review cycle consisted of a titration phase and a maintenance phase. In the titration phase, patients receive 1 to 2 mg doses as needed. During the maintenance phase, patients receive 1 to 2 mg every 1 to 3 hours as needed with 3 mg available to patients with more severe pain. For patient-controlled analgesia (PCA) demand doses of 0.1 to 0.35 mg with a 6-minute lock-out may be given as needed based on initial patient response. Supplemental 1 mg doses as often as every hour can also be used in conjunction with demand doses. The maximum daily dose was initially proposed as 100 mg and subsequently lowered to 40 mg.

The oliceridine NDA received a complete response due to the inadequacies of the clinical ECG data submitted to characterize the QT effects in patients. The complete response letter included the following description of the data required to resolve the inadequacies of the available data:

Information Needed to Resolve the Deficiency
To address the safety concern of QT prolongation at the maximum proposed daily dose, provide data from a randomized active-controlled study that will include 24-hour Holter monitoring and replicate QT measurements extracted every hour from the Holter monitors and compared to the control group. The study should be of adequate duration and sample size to allow reliable evaluation of oliceridine's QT prolongation effects.

The sponsor has proposed a new clinical study to address the inadequacies noted in the complete response letter. The sponsor is also proposing to lower the maximum daily dose to 27 mg.

3.2 Sponsor's proposed clinical study

Proposed Study Design
To address the Clinical issue #1 described by the Agency in the Complete Response Letter, we propose to conduct a randomized, open-label, two-arm parallel group study in patients reporting moderate to severe pain post-surgery, and for whom IV opioid analgesia is warranted, and where opioid use is anticipated to be required for at least 24 hours during the post-surgical period.

Study Population
Eligible patients will be between the ages of 18 - 75 years undergoing specified surgical procedures anticipated to result in moderate to severe post-operative pain of sufficient magnitude to indicate the use of IV opioid analgesia for clinical management of pain. In addition, surgical types will be specified that are anticipated to require the use of IV opioid analgesia for at least 24 hours during the patient's post-operative care. Identification of specific surgical types to meet these requirements will be determined using data from several sources, including inspection of

cumulative dose and duration of oliceridine use in the Phase 3 open-label ATHENA safety study, and from expert clinical consultation from prospective study site principal investigators.

Key exclusion criteria will include a known QT interval prolongation (whether due to underlying heart disease, congenital Long QT Syndrome or current use of QT prolonging medications) or history of ventricular tachycardia or cardiac arrest. Patients with QT prolongation or ECG findings that would interfere with QT interval assessments on screening or baseline ECG will be excluded from the study. In addition, a history of any past or present disease which, in the opinion of the investigator, may affect the outcome of the study will result in the exclusion of that patient.

A patient will be eligible for inclusion in the evaluable, primary analysis study population if they have received their final dose of oliceridine no earlier than 21 hours into their post-operative care period. A time window of 3 hours or less in advance of the 24-hour exposure minimum will be specified in the protocol. Please refer to clinical issue #2 regarding Trevena's proposal of the maximum daily dose for oliceridine.

Study Treatments

Oliceridine:

Oliceridine will be specified by clinician choice at the point of randomization to be administered as either patient-controlled analgesia (PCA) or clinician-administered bolus dosing after an initial titration phase.

Titration will consist of an initial loading dose of 1-2 mg given as a bolus injection. As multiple doses may be needed during titration, subsequent doses of 1-2 mg may be given as soon as 10 minutes after the previous dose based upon patient need and previous response to oliceridine.

PCA dosing will be provided as 0.35 mg on-demand dosing, with a PCA lockout interval of 6 minutes. Supplemental bolus doses of 1 mg may be administered in conjunction with demand doses hourly, as needed.

Clinician administered bolus dosing will consist of doses of 1-2 mg every 1 to 3 hours as needed. Doses of 3 mg may be used in patients with more severe pain. Dose selection and interval for clinician-administered bolus dosing will be based on clinician assessment of pain intensity and the patient's clinical status.

Standard of Care:

For patients randomized to standard-of-care therapy, morphine or hydromorphone will be specified by clinician choice at the point of randomization to be administered as either PCA or clinician-administered bolus dosing. Dose selection and dosing regimen will be determined and specified in the protocol prior to study initiation.

Concomitant Treatments

Multimodal treatment:

Multimodal treatment with use of non-opioid analgesic therapy will be permitted as specified in the study protocol and will be standardized by convention across all study sites.

Antiemetic treatment:

Prophylactic antiemetic treatment, using a protocol-specified regimen without QT prolonging effects, will be permitted. Additional antiemetics may be added in a tiered sequence to be specified in the protocol for any patient still experiencing moderate or severe nausea, or who is vomiting.

Antibiotic treatment:
Prophylactic antibiotic therapy will be permitted as determined by clinician assessment and need, and within protocol-specified guidelines for concomitant medication. Antibiotics with known QT prolonging effects will not be permitted (e.g. fluoroqiunolones).

ECG Assessments
Post-surgery, patients will recover in the PACU according to the individual institutional guidelines. Before the administration of any opioid (either standard of care or oliceridine), each patient will be fitted with a 12-lead Holter ECG device and an ECG will be obtained in triplicate which will be used as the baseline for the analyses. Patients will be able to receive non-opioid therapy as multimodal treatment specified above, antiemetic treatment as specified above, and prophylactic antibiotic therapy as determined by clinician assessment and need, and within protocol-specified guidelines for concomitant medication. Patients will continue with Holter monitoring for a minimum of 24 hours post initiation of intravenous opioid therapy, and until 2-4 hours post-discontinuation of intravenous opioid therapy. Only patients who complete at least 24 hours of oliceridine or standard-of-care therapy and who have had a minimum of 21 hours of continuous 12 lead ECG monitoring will be included in the evaluable study population for the primary analysis dataset. Patients who complete less than 21 hours of opioid therapy for reasons other than QT prolongation will be dropped from the primary analysis dataset, but will be included in safety population analysis.

Analysis Plan
For those patients who meet minimum time for opioid treatment (with either oliceridine or active comparator treatment), ECGs will be extracted in triplicate hourly, starting 1-hour post-administration of the first dose of opioid. The primary endpoint will be defined as the mean change in the Fridericia-corrected QT (QTcF) interval from baseline by treatment and by time-point. Secondary endpoints include an outlier analysis, which will evaluate the number and proportion of patients with QTcF change from baseline >30 msec, >60 msec, and those with QTcF intervals >450 msec, QTcF >480 msec, and QTcF >500 msec. A time averaged analysis will also be performed, evaluating the mean QTcF change from baseline across the entire 24-hour period as well as in 6-hour quartiles.

The proportion of patients in either treatment group who discontinue due to QT prolongation will be provided as a descriptive summary.

The sample size of the QT sub-study is not based on a formal power calculation but is based on what is deemed feasible in a patient population. An estimate of the power can be obtained by looking at one test (one sided, one group), with a threshold of the QT effect (ΔQTcF) of 15 (or 20) msec and variability of ΔQTcF that is assumed to be substantially higher than in healthy volunteer studies. The table below gives the number of patients per arm needed to achieve 90% power of a test for non-inferiority (single group) against a threshold of 15 (or 20) msec at a one-sided 5% level assuming various values for the SD of the change from baseline and an underlying effect of 6 msec. The threshold of 15 (or 20) msec was selected based on other patient programs conducted by the Sponsor's expert consultant. To achieve 90% power that the upper bound of the 90% confidence interval is less than 15 (or 20) msec, the needed sample size as a function of SD of the ΔQTcF is provided in Table 1, which shows high precision in evaluating potential QTc prolongation.

Table 1: Sample size to exclude a QT effect (ΔQTcF) exceeding 15 or 20 msec

SD of ΔQTcF	Size of effect to exclude	Number of patients /arm needed for 90% power
10 msec	15 msec	12
10 msec	20 msec	6
15 msec	15 msec	25
15 msec	20 msec	11
20 msec	15 msec	44
20 msec	20 msec	19

In Thorough QT/QTc trials conducted in patients which used a by timepoint central tendency analysis for the primary endpoint (such as trials of atypical antipsychotics), a sample size of 60 subjects has generally proven sufficient. The planned trial is not expected to provide a wider variability in measurement as seen in such studies. A sample size of 60 patients per arm has therefore been selected to ensure adequate power.

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

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/s/

LARS JOHANNESEN
12/10/2018

CHRISTINE E GARNETT
12/10/2018

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

Date: October 4, 2018

To: Sharon Hertz, M.D., Director
Division of Anesthesia, Analgesia and Addiction Products

Through: Dominic Chiapperino, Ph.D., Director
Silvia Calderon, Ph.D., Senior Pharmacologist
Controlled Substance Staff

From: Katherine Bonson, Ph.D., Pharmacologist
Controlled Substance Staff

Subject: NDA review of abuse potential
Oliceridine (Olinvyk), intravenous
NDA 210,730 (IND 113,537)
Indication: Treatment of moderate to severe pain
Sponsor: Trevena, Inc.
PDUFA Goal Date: November 2, 2018

Materials reviewed:

- NDA submission (11/20/17)
- Statistical Review of Human Abuse Potential Study with Oliceridine (Dr. Ling Chen, Office of Biostatistics, CDER/FDA, 7/11/18)

Table of Contents

I. Background

This memorandum responds to a consult request from the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) to CSS to evaluate abuse-related preclinical and clinical data submitted by Trevena, Inc. in NDA 210730 for oliceridine (TRV-130, tradename Olinvyk). Oliceridine is formulated as a sterile aqueous solution (1.0 mg oliceridine free base equivalents/ml) for intravenous injection under inpatient hospital or clinic settings for the acute treatment of moderate to severe pain (b) (4)

According to the Sponsor, the dosing should be determined individually for each patient and titrated to a dose that provides adequate analgesia and minimizes adverse reactions: "The initial dose of oliceridine should typically be 1 to 3 mg. Onset of analgesic effect is expected within 5 minutes of the initial dose. Subsequent doses may be given approximately 10 minutes following the initial dose and should be based on individual patient need and previous response to oliceridine. Multiple doses may be needed during titration. Maintenance of analgesia is generally achieved with oliceridine at approximately 1 mg per hour administered as doses of 1 to 3 mg every 1 to 3 hours as needed (PRN), or patient-controlled analgesia (PCA) demand doses of 0.1 to 0.5 mg, PRN."

The Sponsor states that, "The development rationale for oliceridine stemmed from the finding that β-arrestin-2 knock-out mice treated with morphine demonstrated enhanced analgesia while reducing respiratory and gastrointestinal dysfunction compared with wild-type animals. Oliceridine is a full agonist for G protein coupling at the mu-opioid receptor, but exhibits lower β-arrestin2 recruitment to the mu-opioid receptor than morphine or other conventional opioid full agonists. In nonclinical models, this biased signaling profile resulted in potent analgesic efficacy, with less respiratory depression, less slowing of GI motility, and less sedation compared with morphine." A failure to recruit β-arrestin2 has also been predicted to reduce the ability of an opioid to produce the rewarding properties that underlie abuse potential (Crowley et al, 2016), or withdrawal signs indicative of physical dependence (Hales, 2011).

The search for an opioid that can produce analgesia without the risk of addiction, or overdose resulting in death from respiratory depression, has been a research and drug development goal for over a century. Numerous candidate compounds that act as mu opioid agonists, but have reduced recruitment of β-arrestin2 compared to G-protein, have been proposed to fulfill this role. In addition to oliceridine, these compounds include herkinorin (Groer et al, 2007), kurkinorin (Crowley et al, 2016), mitragynine and 7-hydroxymitragynine (Kruegel et al., 2016), and PZM21 (Hill et al., 2018).

However, oliceridine is the only drug that has been thoroughly evaluated in FDA-vetted clinical trials for its ability to produce analgesia, respiratory depression, abuse potential, and physical dependence. The data from these large-scale human studies will help inform whether the lack of interaction with β-arrestin2 predicts an improved safety profile for a mu opioid agonist.

The following review evaluates the abuse potential of oliceridine based on the abuse-related data from preclinical studies, which include chemistry, receptor binding, functional, and animal behavioral studies, and from Phase 1 and Phase 2/3 clinical studies, which include a human abuse potential study and analyses of abuse-related adverse events in all clinical studies conducted with oliceridine.

II. CONCLUSIONS

CSS has reviewed the nonclinical and clinical abuse-related data submitted in NDA 210730 for oliceridine. We are in agreement with the Sponsor that oliceridine is a mu opioid agonist with high abuse potential, based on abuse-related data showing that oliceridine:

- Has high affinity at mu opioid receptors in receptor binding studies, similar to other mu opioid agonists
- Acts as a mu opioid agonist that preferentially recruits G-protein rather than β-arrestin2
- Produces overt behaviors in animals similar to those produced by mu opioid agonists
- Produces full generalization to morphine in drug discrimination studies in animals, showing that it produces effects similar to mu opioid agonists
- Produces self-administration in animals, suggesting it has rewarding properties like mu opioid agonists
- Produces physical dependence in animals, similar to mu opioid agonists
- Produces positive subjective responses and euphoric effects in opioid abusers who participated in a human abuse potential study, similar to mu opioid agonists
- Produces euphoria and other abuse-related adverse events in Phase 1 clinical studies conducted with healthy subjects, similar to mu opioid agonists

Additionally, CSS has considered the effects of oliceridine on respiratory depression observed in Phase 1 and Phase 2/3 clinical studies as an indicator of the risks associated with overdose. Based on the clinical assessment conducted by the medical officers in DAAAP, there was no clear advantage for oliceridine over morphine in relation to respiratory safety.

Thus, an overall assessment of the abuse-related data from preclinical and clinical studies leads to the finding that oliceridine is a mu opioid agonist with an abuse potential, risk of

respiratory depression in the context of an overdose, and ability to produce physical dependence that is similar to other mu opioid agonists.

Therefore, it does not appear that the biased agonism of oliceridine with regard to preferential recruitment of G-protein over β-arrestin2 translates into a human safety advantage for oliceridine compared to traditional mu opioid agonists.

III. RECOMMENDATIONS

Based on the CSS evaluation of the preclinical and clinical abuse-related data, CSS concludes that if the NDA for oliceridine is approved:

a) Oliceridine should be recommended for placement in Schedule II of the Controlled Substances Act (CSA). The Sponsor also proposes that oliceridine should be recommended for Schedule II placement.

b) The text for Section 9 (Drug Abuse and Dependence) of the drug label should reflect that the preclinical and clinical abuse-related studies with oliceridine produced significant abuse signals.

IV. DISCUSSION

A. Chemistry of Oliceridine

Drug Substance

Oliceridine fumarate (USAN name) a new molecular entity identified by CAS registry number: 1467617-09-9. It is chemically known as [(3-Methoxythiophen-2-yl)methyl]({2-[(9*R*)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine fumarate. It has a molecular formula of $C_{22}H_{30}N_2O_2S.C_4H_4O_4$ and a molecular weight of (b) (4). It is a white to lightly colored solid with a melting point of 179-181^{0}C. It is sparingly soluble in water.

The drug product is a 1 mg/ml clear, colorless, sterile, preservative-free solution in a glass vial for intravenous use.

Oliceridine injection is formulated as a sterile aqueous solution (1.0 mg oliceridine [free base equivalents]/mL) in a solution of approximately pH (b) (4) containing L-histidine and mannitol. Oliceridine injection, 1 mg/mL is filled into a clear USP Type (b) glass vial with a (b) (4) rubber stopper, topped with an aluminum seal with plastic flip-off cap. It will be available in vials containing 1, 2, and 30 mg of oliceridine.

B. Preclinical Abuse-Related Studies with Oliceridine

1. Receptor Binding and Functional Studies

a. Receptor Binding Studies with Oliceridine (Study #797915, TRV130-01, TRV130-02, and 100022039).

In receptor binding studies with oliceridine, there was high affinity of oliceridine for the mu opioid receptor (Ki = 1, 18, and 6 nM in mouse, rat and human sites, respectively). There was no significant affinity of oliceridine for 101 other receptors, channels, and transporters, and to inhibit activity of 29 different enzymes, including abuse-related and CNS active sites such as: opioids (kappa, delta), GABA/ benzodiazepine, dopamine (D1 and D2), serotonin (1B, 2A, 3, 5A, 6, and 7), NMDA/glutamate, channels (calcium, potassium, sodium, chloride), transporters (dopamine, norepinephrine), acetylcholine (muscarinic and nicotinic), adenosine, norepinephrine (alpha and beta), histamine, and neurokinin. Oliceridine did show some affinity for the σ receptor and 5-HT1A receptor (Ki = 1-7 μM), but this was 180-fold less than the affinity for the mu opioid receptor and neither of these sites are associated with abuse potential.

TRV0109662 and M22 were identified as major metabolites of oliceridine in humans (17.4% and 61.9% of total ^{14}C drug-related material, respectively). TRV0109662, the primary amine metabolite, has very weak affinity for mu opioid receptors (half-maximal effective concentration [EC_{50}]=5 μM. The M22 metabolite is a non-acyl glucuronide of hydroxylated oliceridine that does not have affinity for mu opioid receptors.

b. Functional Studies (Study #TRV130-02, TRV130-01, TRV130-18, and TRV130-17)

Mu opioid receptor agonists have second messenger functioning that typically involves activation of both G-protein and β-arrestin2 pathways. However, oliceridine has been shown in published studies to preferentially recruit only G-protein. In this way, oliceridine is described as a biased agonist.

In vitro functional studies were conducted in human embryonic kidney (HEK-293) cells expressing recombinant human mu opioid receptors. Oliceridine produced inhibition of

forskolin-stimulated cAMP accumulation (a measure of G-protein activation). This occurred with an efficacy slightly greater that of morphine. As shown in Table 1 (below), oliceridine has a potency that is slightly less than that of fentanyl, but 2 times greater than that of hydromorphone and 6 times greater than that of morphine (EC_{50} of ~8 nM vs. ~6 nM, ~16 nM, and ~50 nM, respectively).

HEK-293 cells were also stably transfected to overexpress β-arrestin2 fused to a β-galactosidase (PathHunter β-arrestin assay). In this assay, oliceridine did not produce a measurable recruitment of β-arrestin2. However, fentanyl, hydromorphone, and morphine all recruited β-arrestin2 with an EC_{50} ranging from 126 to 501 nM.

Table 1: Functional Activity in Human Cells of Oliceridine, Fentanyl, Hydromorphone, and Morphine (from Study #TRV130-02)

	cAMP		β-arrestin2	
Compound	**EC50 (nM)**	**pEC50**	**EC50 (nM)**	**pEC50**
oliceridine	7.9	8.1	N.Q.	N.Q.
fentanyl	6.3	8.2	251	6.6
hydromorphone	15.8	7.8	126	6.9
morphine	50.1	7.3	501	6.3

N.Q.: not quantifiable

These data suggest that oliceridine acts as a mu opioid agonist that preferentially recruits G-protein rather than β-arrestin2.

The two major metabolites of oliceridine, TRV0109662 and M22 (glucuronidated metabolite) were also tested in these assays and shown to be 500- and 800-fold less potent at activating either cAMP or β-arrestin2 than TRV130, respectively.

C. Pharmacokinetics (Study #CPB-P10-1373M01, CPB-P10-1311R01, CPB-P10-1348K01, CP130-1003, and CP130-1004)

In humans, oliceridine has a very low oral bioavailability (~6% from a 100 microgram oral solution). This suggests it is unlikely that a drug abuser would seek out oliceridine for abuse via the oral route of administration.

The pharmacokinetics of intravenous oliceridine in animals (mice, rats, and monkeys) was compared to humans in Table 2, shown below.

Table 2: Comparison of Animal and Human Pharmacokinetics Following Intravenous Oliceridine

Species	Dose (mg/kg)	Cmax (ng/ml)	AUC0-∞ (ng*hr/ml)	Half-Life t½ (hr)
C57 BL/6 Mice	0.3	93	36.3	0.4
Sprague-Dawley Rat	0.5	75	73.3	0.7
Cynomolgus Monkey	0.3	206	167	1.1
Human	0.06	117	108	1.7

D. Animal Behavioral Studies

1. General Behavioral Observations (Study #8242814 and TRV 130-19)

An Irwin test of general behavior was conducted in rats (n = 6/dose) at doses of 0.25, 0.5, and 1.0 mg/kg/hour (i.v.), administered over a 6 hour period. The Sponsor states that, "The low dose of 0.25 mg/kg/hour was predicted to produce a steady state maximum exposure (C_{ss}) that is a small multiple of the exposure in rats that produces a positive effect in pharmacology studies in response to various pain stimuli." At the lower dose of 1.0 mg/kg/hour, oliceridine decreased forelimb grip strength over the 24-hour monitoring period. There were no other changes in overt behavior, excretion of urine or fecal boli, or body temperature relative to vehicle in response to oliceridine at any of the three doses.

However, when a higher dose of oliceridine (1.5 mg/kg/hour, i.v.) was administered over a 24 hour period in a toxicity study, it produced behavioral impairment as well as reduced food consumption and reduced body weight.

In a rotorod test (which measures ability of a rat to hold onto a slowly rotating rod), oliceridine (0.3 mg/kg, s.c.) and morphine (3 mg/kg, s.c.) produced a statistically similar impairment in motor ability (43 seconds to fall vs. 27 seconds, respectively). These doses were selected on the premise of producing equianalgesic responses (based on a previously conducted hot plate test in rats), so it would be expected that similar impairment would be observed..

These general behavioral tests demonstrate that oliceridine produces sedative and motor effects, as would be expected from a mu opioid agonist.

2. Abuse-Related Animal Behavioral Studies

a. Drug Discrimination Study with Oliceridine (Study #8317098)

In a drug discrimination study, rats (n = 15) were trained to discriminate morphine (3.0 mg/kg, s.c.) from vehicle using a fixed ratio (FR) 10 schedule of reinforcement. When rats could stably discriminate morphine from vehicle (with a generalization of >90%),

challenge sessions with oliceridine began at doses of 0.1, 0.3, and 1.0 mg/kg (s.c.). These oliceridine doses represent exposures that are 0.72-fold, 2-fold, and 10-fold the exposure "expected" by the Sponsor from human therapeutic doses. Morphine was also tested as a positive control at doses of 0.3, 1.0, 1.7, 3.0, and 10.0 mg/kg (s.c.). Vehicle sessions were interspersed between morphine and oliceridine sessions. All treatments were administered 30 min prior to behavioral testing. For regulatory purposes, a test drug is said to have "full generalization" to the training drug when the test drug produces bar pressing ≥75% on the bar associated with the training drug.

As expected, morphine (3-10 mg/kg) produced full generalization (98%) to the morphine cue. Similarly, oliceridine (0.3 and 1.0 mg/kg) produced full generalization (75-99%) to the morphine cue. Partial generalization to the morphine cue was seen for morphine at the lower dose of 1.7 mg/kg (67%). The 0.3 and 1.0 mg/kg doses of morphine and the 0.1 mg/kg dose of oliceridine did not produce generalization to morphine.

Based on the results, the discriminative stimulus effects of oliceridine are similar to those produced by morphine, with differences in potency consistent with those observed for analgesic responses.

b. Self-Administration Study (Study #8317099)

A self-administration study was conducted in rats to evaluate whether oliceridine produces reward sufficient enough to be reinforcing. Animals were initially trained to press a lever to receive morphine (0.56 mg/kg/infusion, i.v.), using a fixed ratio (FR)5 final schedule of reinforcement. Once responding for morphine was stable, animals were allowed to lever press to receive a range of doses of oliceridine (0.00125, 0.0125, 0.04, and 0.125 mg/kg/infusion, i.v.), morphine (the positive control; 0.01, 0.10, 0.30, 0.56, and 1.0 mg/kg/infusion), or vehicle (i.v.) over a one-hour session. The 0.125 mg/kg/infusion high dose of oliceridine was selected because it is one-fourth of the dose that produced transient muscle rigidity (e.g., 0.5 mg/kg/infusion). Animals were allowed access to each treatment for 3 consecutive days in 1 hour test sessions.

As expected, morphine produced a high degree of self-administration (~12-27 infusions/session at doses of 0.10-0.56 mg/kg/infusion), while vehicle produced a low degree of self-administration (<5 infusions/session). Oliceridine also produced a high degree of self-administration (~13-19 infusions/session at doses of 0.0125 and 0.04 mg/kg/infusion) compared to vehicle. The morphine and oliceridine doses above produced self-administration that was statistically significantly greater than vehicle ($p<0.001$ and 0.05, respectively). The two rewarding doses of oliceridine produced cumulative oliceridine plasma levels that represent 3-8 times the human EC_{50}.

These self-administration data show that oliceridine produces sufficiently rewarding effects to be reinforcing. Since these effects are similar to those produced by morphine, this indicates that oliceridine produces rewarding effects similar to that of morphine.

3. Animal Physical Dependence Study (Study #8317097)

An animal physical dependence study was conducted in which rats received a continuous intravenous infusion of oliceridine (0.05, 0.15, 0.5 mg/kg/hr), morphine (the positive control; 4 mg/kg/hr), or vehicle for 14 days. The 0.5 mg/kg/hr dose of oliceridine was selected because it was the highest dose that was well-tolerated in a previous 14-day study and because it is 9 times the human EC_{50} (10.1 ng/ml). Observations were taken daily during drug administration and during the 7-day drug discontinuation phase.

During the drug discontinuation phase, both oliceridine and morphine produced dose-dependent decreases in food consumption, body weight, and classic opioid withdrawal signs including behaviors such as piloerection, hunched posture, vocalizing, aggression, squinting, twitching, soft feces, decreased locomotion, decreased muscle tone and grasp strength, and tremor.

This data shows that similar to morphine oliceridine produces physical dependence, as would be expected of a mu opioid agonist.

Although CSS informed the Sponsor on September 20, 2016, that an animal study would suffice for evaluation of physical dependence, given that oliceridine is a classic mu opioid agonist, the Sponsor informed us that they were including the Subjective Opioid Withdrawal Scale (SOWS) for assessments at the end of their Phase 3 clinical studies (see below).

E. Clinical Abuse-Related Studies

1. Subjective Responses to Oliceridine in Healthy Individuals (Study #CP130-1001 and CP130-1003)

In a Phase 1 ascending dose study, the subjective effects of a 1-hour infusion of oliceridine (0.15, 0.25, 0.4, 0.7, 1.2, 2.2, 4, and 7 mg) or placebo was tested in 8 separate groups of healthy adult men. At the time this study was conducted, the Sponsor was proposing a therapeutic dose of 1 mg, so the Sponsor considered these doses of oliceridine to be less than, equal to, and 2X, 4X, and 7X greater than the therapeutic dose proposed at that time. Prior to and throughout the drug infusion, subjects were asked to fill out questionnaires about their feelings of sedation, anxiety, and dysphoria using the Bond-Lader mood rating scale. Oliceridine did not produce any changes on these subjective measures except at the 7 mg dose (7X therapeutic dose), where there were increases in sedation, anxiety, and dysphoria responses compared to baseline.

In a second Phase 1 study, oliceridine (1.5, 3.0, and 4.5 mg, equal to 1.5X, 3X, and 4.5X the proposed therapeutic dose) was compared to morphine (10 mg) and placebo during a 2-minute intravenous infusion in healthy adult men using the Drug Effects Questionnaire (DEQ). At the time this study was conducted, the Sponsor was proposing a therapeutic dose of 1 mg, so the Sponsor considered these doses of oliceridine to be 1.5X, 3X, and

4.5X greater than the therapeutic dose proposed at that time. Although the DEQ is validated for use with individuals who have a history of drug abuse, use of this questionnaire in healthy subjects can provide information about whether persons without a history of drug use will experience effects that suggest the test drug has abuse potential. In this study, 10 mg morphine produced subjective responses on DEQ subscales (Drug Liking, High, Good Effects, Any Effects, Sleepy, Dizzy, Bad Effects, Nausea, and Feel Sick) that were intermediate to those produced by 1.5 and 3 mg oliceridine. The 4.5 mg oliceridine dose produced the highest scores on all measures compared to morphine and placebo. The time course of the effects for oliceridine peaked for the positive subjective measures 30-120 min and returned to baseline 4 hours after drug administration.

These results in healthy individuals show that oliceridine can produce subjective responses that would be expected from a mu opioid agonist, such as morphine.

2. Human Abuse Potential Study with Oliceridine (Study #CP130-1011)

This was a randomized, double-blind, placebo- and active-controlled, crossover study that evaluated the intravenous abuse potential, safety, tolerability, and PK of oliceridine compared to morphine and placebo in healthy nondependent recreational opioid users. The study consists of a Screening Phase, the Main Study (Qualification Phase and Treatment Phase), and a Follow-Up Visit.

Subjects

Number of Subjects

During the Qualification Study, 52 subjects participated. During the Main Study, 42 adult subjects (age 18-55 years; 30 men, 12 women) who passed the Qualification Phase were randomized from the Qualification Phase into the Treatment Phase. There were 40 study completers. Subjects had to have a body mass index (BMI) within 18.0 to 32.0 kg/m^2.

Inclusion Criteria for participation in either study are standard but include the following criteria that are relevant for a human abuse potential study:

- The subject had a history of recreational opioid use at least 10 times in the last year and at least on 1 occasion within the 8 weeks before screening.
- The subject reported intranasal use on at least 3 occasions in the year prior to screening or intravenous use on at least 1 occasion in the year prior to screening.

Exclusion Criteria are standard but include the following criteria that are relevant for a human abuse potential study:

- The subject had a positive urine drug screen or a positive alcohol test at screening.

- The subject was physically dependent on opioids, as demonstrated by successful completion of a naloxone challenge; i.e., subject did not exhibit signs or symptoms of opioid withdrawal (as assessed by a Clinical Opiate Withdrawal Scale score of <5) following administration of intravenous naloxone in the Naloxone Challenge.
- Drug or alcohol dependence in the 12 months prior to screening (except nicotine), as defined by the Diagnostic and Statistical Manual of Mental Disorders, 4th edition, Text Revision (DSM-IV-TR), or any self-reported dependence or "addiction" within the subject's lifetime (except nicotine or caffeine).
- Subjects who had ever been in treatment for substance use disorders (except smoking cessation).
- Subjects who smoked greater than 20 cigarettes per day on average, in the month prior to Screening, or inability to abstain from smoking (or use of any nicotine-containing substance) for at least 8 hours.
- History or presence of any clinically significant psychiatric, neurologic, or pulmonary disease at screening.

Naloxone Challenge Test

All subjects passed the Naloxone Challenge Test prior to the administration of study drug in the Qualification Phase using the Clinical Opiate Withdrawal Scale (COWS).

A total of up to 0.8 mg naloxone HCl was administered. An initial dose of 0.2 mg naloxone HCl was administered as an intravenous (IV) bolus, followed by another IV bolus dose of 0.6 mg naloxone HCl for subjects who displayed no signs of withdrawal after the initial dose (COWS score of <5).

Intravenous Drug Doses

Qualification Phase

The following treatments were administered through a 1 minute intravenously infusion:

- 10 mg morphine
- placebo

The 10 mg morphine dose was also used in the Treatment Phase as a positive control. There was a washout period of at least 24 hours in between treatments and 48 hours between the end of the Qualification Phase and the start of the Treatment Phase.

Treatment Phase

The following treatments were administered through a 1 minute intravenously infusion:

- Oliceridine 1 mg
- Oliceridine 2 mg
- Oliceridine 4 mg

- Morphine 10 mg
- Morphine 20 mg
- Placebo

At the time this study was conducted, the Sponsor was proposing a therapeutic dose of 1 mg, so the Sponsor considered these doses of oliceridine to be equal to, 2X, and 4X greater than the therapeutic dose proposed at that time.

According to the Sponsor, "These doses were selected to represent a range of oliceridine and morphine doses that could safely be administered over a 1-minute infusion. The 4 mg dose of oliceridine was dose-matched based on relative potency to morphine 20 mg; the 2 mg dose of oliceridine was dose-matched based on relative potency to morphine 10 mg, and the 1 mg dose of oliceridine represents a proposed therapeutic dose."

There was a washout period of 48 hours in between treatments.

Qualification Criteria

Subjects must pass the following criteria in the Qualification Phase to be eligible to enter the Treatment Phase:

1. Emax score in response to intravenous morphine greater than that of placebo on the bipolar Drug Liking VAS (difference $\geq$15 points)

2. Emax score $\geq$65 points for intravenous morphine within 1 hour post-dose

3. Acceptable overall responses to morphine on all other subjective measures

4. Acceptable placebo response based on Drug Liking VAS (score between 40 and 60 points, inclusive). Acceptable placebo response on all other subjective measures.

5. Subject was able to tolerate the dose of intravenous morphine, including ability to complete all pharmacodynamic assessments within 1 hour postdose.

Pharmacodynamic Variables

All subjective endpoints and pupillometry were assessed at baseline, 5, 15, and 30 minutes, and 1, 1.5, 2, 3, 4, 6, 8, and 12 hours after drug administration, with three exceptions: VAS for Overall Drug Liking and Take Drug Again were assessed at 8 and 12 hours, and Drug Similarity was assessed at 8 hours.

Primary Measure:

Drug Liking VAS (Emax)

Secondary Measures:

Balance of effects:
- Drug Liking VAS
- Overall Drug Liking VAS
- Take Drug Again VAS

Positive effects:
- Good Effects VAS
- High VAS

Negative effects:
- Bad Effects VAS

Sedative effects:
- Alert/Drowsy VAS

Other drug effects:
- Any Effects VAS

Objective Measures:
- Pupillometry

Safety Variables
- Adverse events
- Vital signs
- Clinical laboratory results
- 12-lead ECGs
- Physical examinations
- Concomitant medications
- Continuous pulse oximetry/telemetry monitoring

Safety measures were evaluated at the same time as subjective measures.

Results

Subjective Responses

Responses on the primary measure of Drug Liking, and the secondary measures of High, and Good Drug Effects VAS, were evaluated for statistically significance following administration of oliceridine, morphine, and placebo by both the FDA Office of Biostatistics as well as by the Sponsor. An evaluation of all other secondary measures was only conducted by the Sponsor.

On the primary measure of Drug Liking, morphine at both doses (20 and 40 mg, i.v.) produced statistically significant increases in response compared to placebo (81-89 points vs. 51 points, respectively; $p < 0.0001$), as shown in Table 3 (below). On a bipolar scale like Drug Liking, 50 points out of 100 is considered a neutral response. These results validate the study.

Similarly, oliceridine at all 3 doses also produced a statistically significant increase in Drug Liking compared to placebo (72-88 points vs. 51 points, respectively; $p < 0.001$). The 1 mg dose of oliceridine produced responses on Drug Liking that were statistically less than that produced by the 20 mg dose of morphine (72 points vs. 81 points; $p < 0.001$). In contrast, the 2 mg dose of oliceridine was statistically indistinguishable from the 20 mg dose of morphine on Drug Liking (83 points vs. 81 points). Similarly, the 4 mg dose of oliceridine was statistically indistinguishable from the 40 mg dose of morphine on Drug Liking (88 points vs. 89 points). Each of the responses to oliceridine and morphine were far outside the acceptable placebo range on a bipolar scale (40-60 points).

Table 3: Effects of Intravenous Placebo, Morphine, and Oliceridine on Subjective Measures (mean and standard deviation) (n = 40)

Measure	Placebo	Morphine 10 mg	Morphine 20 mg	Oliceridine 1 mg	Oliceridine 2 mg	Oliceridine 4 mg
Drug Liking VAS bipolar	51 ± 2	81 ± 15 ^	89 ± 13 ^	72 ± 15 ^	83 ± 15 ^	88 ± 13 ^
Overall Drug Liking VAS bipolar	50 ± 1	76 ± 17 ^	75 ± 27 ^	65 ± 16 ^	72 ± 21 ^	79 ± 18 ^
Take Drug Again VAS bipolar	49 ± 8	79 ± 17 ^	74 ± 29 ^	64 ± 19 ^	72 ± 23 ^	77 ± 20 ^
Good Drug Effects VAS	2 ± 5	69 ± 27 #	85 ± 19 ^	48 ± 30 ^	71 ± 25 ^	84 ± 18 ^
High VAS	2 ± 6	70 ± 27 #	87 ± 18 ^	47 ± 29 ^	72 ± 26 ^	86 ± 16 ^
Bad Drug Effects VAS	1 ± 4	14 ± 21 #	29 ± 31 ^	3 ± 7	11 ± 24 *	23 ± 31 ^
Alert/Drowsy VAS bipolar	48 ± 17	33 ± 17 ^	23 ± 18 ^	39 ± 16 #	33 ± 15 ^	25 ± 16 ^
Any Drug Effect VAS	2 ± 7	75 ± 26 ^	55 ± 38 ^	47 ± 29 ^	74 ± 25 ^	87 ± 15 ^
Maximum Pupillary Constriction (mm)	0.7 ± 0.6	2.3 ± 0.8 ^	3.0 ± 0.7 ^	1.2 ± 0.5 ^	2.0 ± 0.7 ^	2.6 ± 0.8 ^

Scales are unipolar (0-100, with 0-20 acceptable placebo range) unless noted as bipolar (0-100, with 40-60 acceptable placebo range) * $p < 0.05$; # $p < 0.01$, ^ $p < 0.0001$ compared to placebo

Morphine and oliceridine at each dose tested produced statistically significant increases compared to placebo on the other positive subjective measures of Good Drug Effects and High, as well as on measures taken at the end of the study, Overall Drug Liking and Take Drug Again.

Each dose of oliceridine and morphine also produced statistically significant increases compared to placebo on Bad Effects (with the exception of 1 mg oliceridine), Drowsiness, and Any Drug Effects.

When oliceridine was compared to 10 mg morphine, the 1 mg oliceridine dose produced statistically significantly lower scores on all of the subjective measures (except for Drowsiness) compared to morphine, while the 2 mg dose was statistically similar to 10 mg morphine on all subjective measures. When the 4 mg dose of oliceridine was compared to 20 mg morphine, there were no statistically significant differences between the two drugs at these doses.

These data show that oliceridine produces positive and negative subjective responses at therapeutic and supratherapeutic doses that are similar to those produced by morphine, when the doses are matched for potency.

Pupillometry

When pupil size was measured following administration of oliceridine and morphine, all doses of the two drugs produced miosis.

The degree of miotic response was statistically significantly less for oliceridine at 1 and 2 mg compared to 10 mg morphine. Miosis was also statistically significantly less for 4 mg oliceridine compared to 20 mg morphine.

Drug Similarity Questionnaire

As shown below in Table 4, on the Drug Similarity question, oliceridine and morphine were both identified as an “opioid” (72-84 points vs. 88-99 points, respectively) on the opioid VAS (evaluating similarity to morphine, hydrocodone, oxycodone, or hydromorphone; n = 39-40).

Oliceridine and morphine also were identified as “codeine” (53-57 points vs. 11-34 points, respectively; n=2) and “heroin” (37-40 points vs. 51-71 points, respectively; n=3).

Table 4: Effects of Intravenous Placebo, Morphine, and Oliceridine on Drug Similarity Measures

Measure	Placebo	Morphine 10 mg	Morphine 20 mg	Oliceridine 1 mg	Oliceridine 2 mg	Oliceridine 4 mg
Drug ID: Opioids (n = 39-40)	0	82	99	49	72	84
Drug ID: Codeine (n = 2)	0	11	34	57	57	53
Drug ID: Heroin (n = 3)_	0	71	51	40	40	37

Abuse-Related Adverse Events

As shown in Table 5 (below), the most frequently-reported abuse-related adverse event resulting from administration of any dose of oliceridine or any dose of morphine was euphoric mood (38-58% vs. 50-69%, respectively). A high rate of somnolence was also reported in response to administration of oliceridine (8-20%) and morphine (15-33%). Paresthesia was also reported at a high rate for both oliceridine (3-8%) and morphine (8-19%). Placebo administration did not produce any of these abuse-related adverse events.

Table 5: Abuse-Related Adverse Events in Human Abuse Potential Study with Oliceridine, Morphine, and Placebo

Preferred Term	Oliceridine (N[%])			Morphine (N[%])		Placebo (N[%]) N=40
	1 mg N=40	2 mg N=40	4 mg N=40	10 mg N=40	20 mg N=42	
Euphoric mood	15 (38%)	20 (50%)	23 (58%)	20 (50%)	29 (69%)	0
Somnolence	3 (8%)	8 (20%)	7 (18%)	6 (15%)	14 (33%)	0
Paresthesia	1 (3%)	3 (8%)	2 (5%)	3 (8%)	8 (19%)	0

The ability of oliceridine to produce euphoria, somnolence, and paresthesia at rate similar to that of morphine show that oliceridine produces classic mu opioid agonists effects.

Overall Conclusions from Human Abuse Potential Study

Oliceridine at therapeutic and supratherapeutic doses produced increases on positive subjective measures such as Drug Liking, High, Good Drug Effects, and Take Drug Again similar to that produced by morphine. Oliceridine also produced miosis as well as

adverse events that included a high rate of euphoric effects. These drug responses parallel those produced by morphine.

Thus, this human abuse potential study shows that oliceridine produces classic opioid responses in healthy individuals with a history of opioid abuse.

3. Abuse-Related Adverse Events in Clinical Studies

Trevena conducted the following clinical studies with oliceridine: 8 Phase 1 studies in healthy subjects as well as two Phase 2 studies and two Phase 3 studies in patients undergoing bunionectomy and abdominoplasty. The following details the abuse-related adverse events reported in these studies.

Phase 1 Clinical Safety Studies (Excluding HAP Study) (Study # CP130-1001, CP130-1002, CP130-1003, CP130-1005, CP130-1006, CP130-1007, and CP130-1008)

In Phase 1 clinical studies conducted with 0.15 to 7.0 mg intravenous oliceridine in healthy subjects, there was a high rate of abuse-related adverse events (Table 6, below).

These included ~12% euphoria, 13% relaxation, and 29% somnolence, with a ~2-5% rate of feeling abnormal, feeling drunk, fatigue, lethargy, hypoaesthesia, and paresthesia.

Administration of 10 mg intravenous morphine produced many of the same abuse-related adverse events, but at an incidence that was lower than that reported for oliceridine.

Table 6: Abuse-Related Adverse Events in Phase 1 Studies

Preferred Term	Overall (N [%])		
	Placebo (N=114)	Morphine 10 mg (N=30)	Oliceridine 0.15-7.0 mg (N=221)
Euphoric mood	1 (0.9%)	1 (3.3%)	26 (11.8%)
Somnolence	3 (2.6%)	8 (26.7%)	65 (29.4%)
Feeling of relaxation	0	0	29 (13.1%)
Fatigue	0	2 (6.7%)	12 (5.4%)
Lethargy	1 (0.9%)	1 (3.3%)	9 (4.1%)
Hypoaesthesia	0	0	8 (3.6%)
Paraesthesia	0	1 (3.3%)	7 (3.2%)
Feeling abnormal	0	0	5 (2.3%)
Feeling drunk	0	0	7 (3.2%)

When the abuse-related adverse events produced by oliceridine are analyzed on the basis of dose (Table 7, below), there is a dose-dependent response for only certain adverse events such as euphoric mood, fatigue, lethargy, sluggishness, and hypoaesthesia.

For some adverse events, such as somnolence, feeling abnormal, and paresthesia, there was little difference dependent on dose. When relaxation was evaluated, there was a higher incidence at moderate doses compared to low or higher doses.

Table 7: Abuse-Related Adverse Events in Phase 1 Studies, Reported by Oliceridine Dose Level

Preferred Term	Oliceridine by Dose Level (N [%])		
	<2.0 mg (N=42)	2.0-4.5 mg (N=148)	>4.5 mg (N=66)
Euphoric mood	6 (14.3%)	22 (14.9%)	17 (25.8%)
Somnolence	15 (35.7%)	57 (38.5%)	26 (39.4%)
Fatigue	0	8 (5.4%)	8 (12.1%)
Lethargy	0	8 (5.4%)	7 (10.6%)
Hypoaesthesia	1 (2.4%)	7 (4.7%)	7 (10.6%)
Feeling of relaxation	2 (4.8%)	21 (14.2%)	5 (7.6%)
Feeling abnormal	2 (4.8%)	5 (3.4%)	2 (3.0%)
Sluggishness	0	2 (1.4%)	2 (3.0%)
Paraesthesia	1 (2.4%)	7 (4.7%)	2 (3.0%)

Overall, the abuse-related adverse events reported in Phase 1 clinical studies show that oliceridine produces classic opioid-related effects such as euphoria and sedation, which often occurred on a dose-dependent basis.

Phase 2/3 Clinical Efficacy Studies (Study # CP130-2001, CP130-2002, CP130-2004, CP130-3001, CP130-3002, and CP130-3003).

In Phase 2/3 clinical efficacy studies conducted with intravenous oliceridine, morphine, and placebo for the treatment of pain, oliceridine produced some abuse-related adverse events, but the rate was similar to that produced by placebo (see Table 8 below).

Oliceridine dosing in Phase 2/3 studies included:

- 0.5 to 4 mg q 3 or 4 h (Study #CP130-2001)
- 1.5 mg loading dose, then 0.1 to 0.35 mg Q6 minutes PRN (Study CP130-2002)

- 1.5 mg loading dose, 0.1 to 0.5 mg Q6 minutes PRN demand dose (Studies #CP130-3001 and CP130-3002)
- 1-3 mg bolus dose, 1-3 mg supplemental doses PRN, 1.5 mg loading dose, 0.5 mg Q6 min PRN demand dose (CP130-3003)
- 2 mg loading dose, then 1 mg Q5 minutes (CP130-2004; 1 subject only)

Morphine dosing in Phase 2/3 studies included:

- 4 mg Q4H (CP130-2001)
- 4 mg loading dose, then 1 to 1.5 mg q 6 min PRN (Study CP130-2002)
- 4 mg loading dose, then 1 mg Q6 minutes PRN (CP130-3001 and CP130-3002)

Euphoric responses were reported at a low rate for oliceridine (~1%) and morphine (~1%), but were not observed for placebo (0%). This 1% rate of euphoria from oliceridine in Phase 2/3 studies is much lower than the 14-26% rate of euphoria in response to oliceridine (depending on dose) that was observed in Phase 1 studies with healthy individuals. However, a lack of a euphoria response following administration of opioids with known abuse potential is common when abuse-related adverse events are assessed in a subject population being treated for pain conditions.

Somnolence was the most frequently reported adverse event for oliceridine and saline (~5% vs. 4%, respectively), followed by sedation (~3% both), anxiety (~2% vs. 1%, respectively), restlessness (~1% vs. 2%, respectively), and paraesthesia (~1% both). Morphine produced similar rates of anxiety, restlessness and paresthesia (2%, 2% and 1%, respectively), but a higher rate of somnolence (13%) and sedation (8%) compared to oliceridine and placebo.

Table 8: Abuse-Related Adverse Events in Phase 2/3 Studies with Oliceridine, Morphine, and Placebo

Preferred Term	Placebo (N=252)	Morphine (N=305)	Oliceridine (N=1535)
Euphoria/Drunk/Abnormal	0	2 (0.7%)	20 (1.3%)
Somnolence	10 (4.0%)	41 (13.4%)	79 (5.1%)
Sedation	8 (3.2%)	24 (7.9%)	41 (2.7%)
Anxiety	3 (1.2%)	6 (2.0%)	36 (2.3%)
Restlessness	5 (2.0%)	5 (1.6%)	14 (1.2%)

Overall, oliceridine produced abuse-related adverse events in Phase 2/3 clinical studies that were similar to those produced by placebo.

4. Compliance and Diversion

The Sponsor reports that, "To date, no diversion of oliceridine or morphine has been reported during the clinical development program. All clinical studies completed have been conducted within a controlled clinical research or hospital setting, and as such, there were no opportunities for subjects or patients to take the study medication to their homes."

5. Assessment of Human Physical Dependence (Study # CP130-3001 and CP130-3002)

During the End of Phase 2 meeting with the Sponsor on March 29, 2016, CSS informed the Sponsor that it would not be necessary to conduct a human assessment of physical dependence following oliceridine discontinuation, since the animal physical dependence study had already shown classic opioid withdrawal signs upon drug discontinuation.

However, the Sponsor informed CSS that they intended to provide all patients in Phase 3 studies (Studies #CP130-3001 and CP130-3002) with the Subjective Opioid Withdrawal Scale (SOWS) questionnaire to assess withdrawal symptoms during the day of their last dose of oliceridine, at the end of the study.

The Sponsor describes the studies as follows:

> Two Phase 3 pivotal efficacy and safety studies evaluated oliceridine administered PRN... to provide primary evidence that the demonstration of efficacy and safety of oliceridine was replicated across studies:
>
> - one with a 48-hour Randomized Treatment Period after bunionectomy (hard tissue model; APOLLO 1) and
> - one with a 24-hour Randomized Treatment Period after abdominoplasty (soft tissue model; APOLLO 2)

During the Phase 3 studies, the loading dose for oliceridine was 1.5 mg with a demand dose of 0.1 mg, 0.35 mg, or 0.5 mg PRN, and a supplemental dose of 0.75 mg q1h PRN. For morphine, the loading dose was 4 mg with a demand dose of 1 mg PRN and a supplemental dose of 2 mg q1h PRN.

During the drug discontinuation period, placebo produced a very low SOWS score of 2.5 $\pm$ 4.2 (n = 162). Similarly, morphine produced a SOWS score of 3.5 $\pm$ 5.8 (n = 158), while oliceridine produced a SOWS score of 3.1 $\pm$ 5.1 (n = 470). On the SOWS, a total score of <17 out of 64 was considered to represent no to mild withdrawal symptoms, 17 to 32 was considered to represent moderate symptoms, and >32 was considered to represent severe symptoms.

These data suggest that neither morphine or oliceridine produce a classic opioid withdrawal syndrome upon drug discontinuation. This result is suspect, however, because morphine has a well-characterized ability to produce physical dependence.

This strongly suggests that the design of this study is inadequate to fully assess the ability of an opioid to produce physical dependence.

First, the Sponsor states in the study protocol that, "If clinically indicated, analgesic treatment according to standard medical practice may have continued after treatment with study medication." This included the administration of opioids, since the patients in these studies had recently undergone serious surgical procedures that may have produced lingering pain even after the study was completed. Allowing subjects access to opioids will obviate any withdrawal symptoms since the subject would not be undergoing opioid discontinuation. This may explain why the positive control drug, morphine, failed to produce withdrawal symptoms.

Second, the assessment of withdrawal symptoms begins on the same day as the last dose of oliceridine or morphine, and this is the sole self-report available. The Sponsor states that they believe this single evaluation on the same day as the last drug administration conforms with the 2017 *Guidance for Industry: Assessment of the Abuse Potential of Drugs*, because withdrawal is assessed for at least 5 half-lives after drug discontinuation. However, the Sponsor did not submit the protocol for this physical dependence evaluation to CSS prior to data collection at the end of the Phase 3 studies. If they had, we would have informed them that it would have been necessary to ask subjects to provide SOWS data for at least several days to ensure there were no residual opioid effects.

Third, the limited duration of drug administration in Phase 3 studies may inherently prevent the development of physical dependence from either morphine or oliceridine. Indeed, the Sponsor states in the study report that, "These relatively low scores are expected, given the relatively short duration of study drug administration."

In summary, this is not an ideal design for determining whether oliceridine produces physical dependence in humans. However, since oliceridine was shown to produce physical dependence in rats, it is clear that the drug can produce a withdrawal syndrome.

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/s/

KATHERINE R BONSON
10/03/2018

SILVIA N CALDERON
10/04/2018

DOMINIC CHIAPPERINO
10/23/2018

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: September 27, 2018

From: CDER DCRP QT Interdisciplinary Review Team

Through: Christine Garnett, Pharm.D.
Clinical Analyst
Division of Cardiovascular and Renal Products /CDER

To: Eva Yuan, RPM
DAAAP

Subject: QT-IRT Consult to NDA 210730 (SDN 35)

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 8/16/2018 regarding the sponsor's QT related question. The QT-IRT reviewed the following materials:

- Supplementary ion channel and ECG analysis (NDA 210730 / SDN 35; link);
- Study report for the effects of oliceridine and its major metabolites on hERG, Cav1.2 and Nav1.5 (NDA 210703, SDN 35, link);
- Meeting minutes for "AC discussion" for NDA 210730 dated 07/18/2018 in DARRTS;
- Request for raw data from preclinical experiments for NDA 210730 dated 08/20/2018 in DARRTS;
- Previous QT-IRT review(s) for IND 113537 dated 02/08/2016 in DARRTS; and
- Previous QT-IRT review(s) for NDA 210730 dated 03/08/2018;07/11/2018 in DARRTS.

1 QT-IRT Responses

We have reviewed the additional reports submitted by the sponsor to support the assessment of proarrhythmic risk of OLINVO, which contained additional preclinical information (results of the assessment of oliceridine and major metabolites on hERG, $Ca_V1.2$ and $Na_V1.5$) and clinical information (assessment of changes in QTcF, QTcI and J-T_{peak}C). We agree with the sponsor that the additional preclinical data collected for the two major metabolites support that the metabolites do not inhibit hERG or $Ca_V1.2$. However, we cannot comment on the conclusions based on the data for the late $Na_V1.5$ current. The sponsor used an experimental protocol that

differs from our experience, and we requested submission of the raw data to confirm drug effects. We still have not received the raw data. Data aside, it is important to bear in mind that any potential effects of oliceridine on the late $Na_V1.5$ current are unlikely to impact the QTc observations. This is because oliceridine is rapidly cleared. Moreover, the submitted results for the QTc and J-T_{peak}c interval are not consistent with the drug being a mixed ion channel blocker as the changes in J-T_{peak}c tracks with QTc changes. The information reviewed in this consult request suggests that the mechanism behind the delayed and dose-proportional QTc prolongation is not explained by direct inhibition of the hERG potassium channel by oliceridine or any of its major metabolites. Due to the uncertainty about the mechanism causing the observed QTc prolongation it is not possible to predict the QTc prolongation with the currently proposed dosing paradigm, which results in exposures of the major metabolites that exceeds the exposures following the highest dose in the thorough QT study (~2.4-fold for M22 and ~2.8-fold for TRV9198662).

2 BACKGROUND

We have previously reviewed the thorough QT study for OLINVO, which showed a delayed dose-proportional increase in QTc, which did not coincide with peak parent drug concentration (DARRTS 02/08/2016). At present the mechanism for the observed QTc prolongation is unknown and possible mechanisms include inhibition of the hERG potassium channel by a hERG active metabolite or non-hERG mediated mechanisms (DARRTS 03/08/2018).

The sponsor submitted a proposal to (b) (4) and evaluate J-T_{peak}c and T_{peak}-T_{end}. We reviewed the proposal and concluded that we did not agree with the approach to use (b) (4) (b) (4) With regards to the use of J-T_{peak}c and T_{peak}-T_{end}, we concluded that it was unclear how this analysis would be helpful, because the role of new ECG biomarkers (such as J-T_{peak}c and T_{peak}-T_{end}) is to confirm the preclinical observations and at this point in time the sponsor had not done a complete preclinical characterization of oliceridine and all the major metabolites and the mechanism for the observed QTc prolongation is unknown. We therefore proposed that the sponsor conducted additional preclinical experiments to attempt to identify the mechanism behind the delayed and dose-proportional increase in QTc (DARRTS 07/11/2018).

The sponsor agreed to conduct additional preclinical experiments and study report on the effects of oliceridine and its major metabolites (M22 and TRV9198662) on hERG, $Ca_V1.2$ and $Na_V1.5$ (DARRTS 07/18/2018).

The sponsor submitted has now a summary of the preclinical findings, which included information on J-T_{peak}c and T_{peak}-T_{end} as well as a preclinical study report on 08/14/2018, which will be the focus of this review.

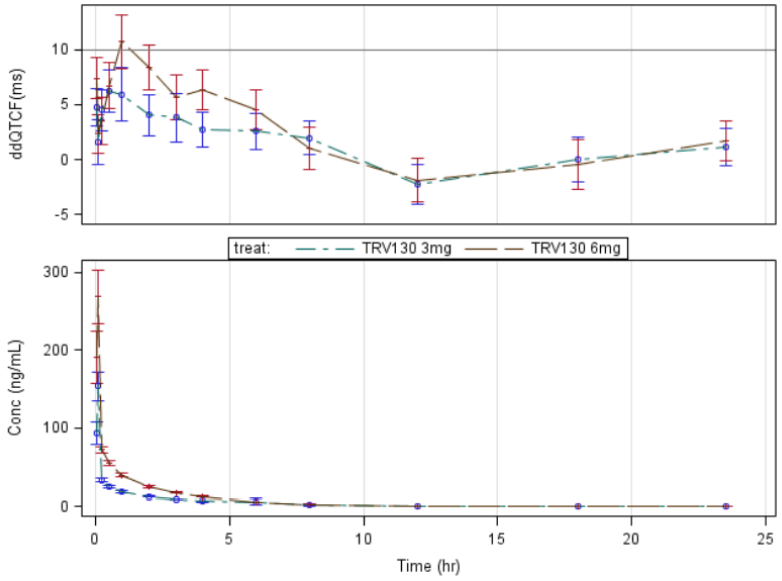
2.1 Preclinical data

We have reviewed the study report, which documented the effects of OLINVO (oliceridine; TRV-130 fumarate) and its two major metabolites (M22 and TRV0109662) at room temperature on hERG, $Ca_V1.2$, and $Na_V1.5$ current (peak and late components) obtained using automated patch clamp equipment QPatch. The two major metabolites (M22 and TRV0109662) appear to not inhibit hERG current at clinically relevant concentrations, suggesting that they are unlikely to contribute to QTc prolongation by blocking hERG channels. Oliceridine and its metabolites do

not appear to block $Ca_V1.2$ channels at clinically relevant concentrations. However, oliceridine appears to suppress late $Na_V1.5$ current. Suppression of late $Na_V1.5$ current may mitigate the proarrhythmia risk associated with QTc prolongation. Given that the experimental protocols used in these experiments differed from our experience (recommendations currently posted on HESI's website), we requested the raw data associated with this nonclinical study report to be submitted for in-house analysis to confirm drug effects (DARRTS 08/20/2018). Due to the size of the raw data files, the sponsor has not been unable to upload the data to the gateway. The sponsor did submit the data files on DVDs; however, the format of the contents of the DVD does not permit uploading it to the EDR. Therefore, we were unable to perform data analysis to confirm drug effects on cardiac ion channels.

It is important to bear in mind that the sponsor's data showed that OLINVO-associated QTc prolongation is delayed with respect to PK profile (QT max: ~1 hr; PK max: ~5 min; Figure 1) and at the time of peak QTc the plasma level of oliceridine is already reduced to ~11% of peak concentration. Therefore, one should be concerned that at the time of QTc prolongation, the effect of possible late $Na_V1.5$ current inhibition may be gone due to the rapid clearance of oliceridine.

Figure 1: ΔΔQTcF Time-course vs Concentration course for oliceridine



Source: QT-IRT review under IND 113537 dated 02/08/2016

2.2 Clinical data

The sponsor also submitted information on J-T_{peak} and T_{peak}-T_{end} to support their conclusion that the parent drug is a mixed ion channel blocker. There are two concerns with this conclusion: 1) we have not received the raw data from the preclinical experiments and we are therefore unable to comment on the results (see preclinical section for additional details) and 2) the time-course of the observed QTc and J-T_{peak}c changes do not appear consistent with our expectations for drugs that are mixed ion channel blockers. The latter is because the changes in J-T_{peak}c over time tracks the changes in QTc (Table 1), which differs from our experience with another mixed ion channel

blocker (ranolazine) for which an increased QTc was observed without changes in J-T_{peak}c over time (Figure 2).

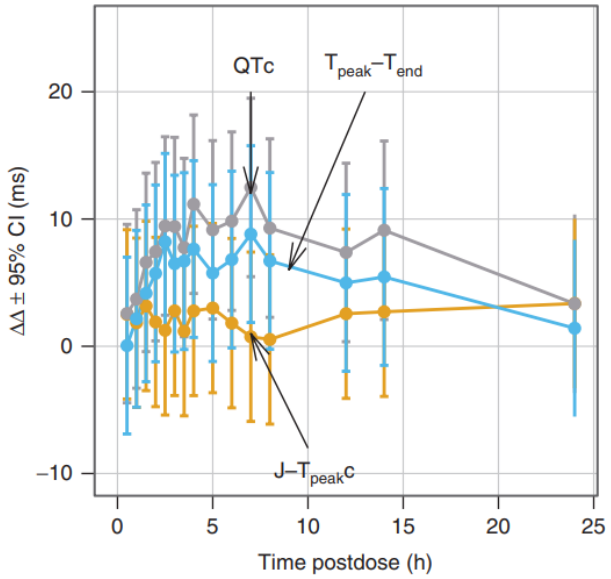
Because of the limitations with the available clinical data, a clinical study is necessary to characterize the effects of oliceridine on the QTc interval at the therapeutically relevant exposures to all major moieties. We propose that the clinical QT study is a multiple dose study with the maximum proposed dosing regimen in healthy volunteers, if feasible. If it is not feasible to administer the maximum proposed dosing regimen in healthy volunteers, a clinical QT study in patients who can tolerate the maximum proposed dosing regimen.

Table 1: By-timepoint analysis of QTcI, QTcF and J-T_{peak}c

Timepoint	ΔΔQTcI	ΔΔQTcF	ΔΔJ-Tpeakc
2.5 min	7.5 (9.7)	8.0 (10.2)	7.9 (10.0)
5 min	1.9 (4.1)	2.4 (4.6)	2.1 (4.2)
15 min	4.0 (6.2)	4 (6.2)	2.8 (4.9)
30 min	7.5 (9.7)	7.4 (9.6)	4.6 (6.7)
1 hr	11.5 (13.7)	11.6 (13.8)	7.2 (9.3)
2 hr	9.2 (11.5)	9.1 (11.3)	5.9 (8.0)
3 hr	6.4 (8.6)	6.3 (8.5)	4.2 (6.3)

Source: Supplementary ion channel and ECG analysis, Table 1

Figure 2: Time-course of changes in QTc, J-T_{peak}c and T_{peak}-T_{end} following administration of a single dose of ranolazine (mixed ion channel blocker)



Source: Johannesen et al., Clin Pharmacol Ther 2014

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

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CHRISTINE E GARNETT
09/28/2018

Clinical Inspection Summary

Date	July 30, 2018
From	Damon Green, M.D., M.S., Reviewer Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations (OSI)
To	Shelly Kapoor, Regulatory Project Manager Elizabeth Kilgore, M.D., Clinical Reviewer Janet Maynard, M.D., Clinical Team Leader Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
NDA #	NDA 210730
Applicant	Travena, Inc.
Drug	Olinvo™ (Oliceridine Injection)
NME	Yes
Therapeutic Classification	Opioid analgesic
Proposed Indication	Treatment for moderate to severe acute pain
Consultation Request Date	December 13, 2017
Summary Goal Date	August 1, 2018
Action Goal Date	November 2, 2018
PDUFA Date	November 2, 2018

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical sites of Drs. Gimbel and Nazarian were inspected in support of this NDA. Based on the results of these inspections, the study appears to have been conducted adequately, and the data generated by these sites appear acceptable in support of the respective indication.

The final classification of the inspections of Drs. Gimbel and Nazarian was No Action Indicated (NAI).

II. BACKGROUND

Trevena, Inc. is seeking approval of Olinvo™ (oliceridine) Injection for the management of moderate to severe acute pain in adult patients for whom an intravenous opioid is warranted. Conventional opioid analgesics like morphine, fentanyl, and hydromorphone are mainstays of acute pain management; however, their use is hampered by well-known adverse events. Oliceridine selectively binds to the μ-opioid receptor (MOR) with high affinity. In particular, oliceridine is a G protein-biased ligand at the MOR in that it stimulates G protein coupling with markedly reduced β-arrestin2 recruitment compared to conventional opioids like morphine, hydromorphone, and fentanyl. According to the sponsor, this results in potent analgesic efficacy, with less respiratory depression, less slowing of gastrointestinal motility, and less sedation compared with morphine.

The following protocols were inspected in support of this application:

Protocol CP130-3001: "A Phase 3, Multicenter, Randomized, Double-blind, Placebo- and Active-controlled Study of Oliceridine (TRV130) for the Treatment of Moderate to Severe Acute Pain After Bunionectomy"

This was a Phase 3, multicenter, randomized, double-blind, placebo- and active-controlled study to evaluate the efficacy, safety, and tolerability of multiple regimens of oliceridine compared with morphine, and safety and tolerability compared with placebo, in patients with moderate to acute postoperative pain after bunionectomy.

The study was conducted at 7 sites in the United States beginning 05/13/2016 and ending on 10/19/2016. A total of 418 subjects were randomized.

The primary efficacy endpoint was the proportion of patients who responded to study medication vs placebo at the 48-hour NRS assessment.

Protocol CP130-3002: "A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-and Active-controlled Study of Oliceridine (TRV130) for the Treatment of Moderate to Severe Acute Pain After Abdominoplasty"

This was a Phase 3, multicenter, randomized, double-blind, placebo- and active-controlled study to evaluate the efficacy, safety, and tolerability of multiple regimens of oliceridine compared with morphine, and safety and tolerability compared with placebo, in patients with moderate to acute postoperative pain after abdominoplasty.

The study was conducted at 5 sites in the United States beginning 05/27/2016 and ending on 12/15/2016. A total of 407 subjects were randomized.

The primary efficacy endpoint was the proportion of patients who responded to study medication vs placebo at the 48-hour NRS assessment.

Rationale for Site Selection

The inspections of Drs. Gimbel and Nazarian were requested due to high enrollment.

III. RESULTS (by site):

Site #/ Name of CI/ Address	Protocol #/ # of Subjects Enrolled	Inspection Dates	Classification
Site #10030 **Joseph S. Gimbel, MD** Arizona Research Center 20414 N. 27th Ave., Suite 200 Phoenix, AZ 85027	CP130-3001 Subjects: 54 CP130-3002 Subjects: 104	04-12 Apr 2018	NAI
Site #10001 **Artin Nazarian, MD** Lotus Clinical Research 100 W. California Blvd., Unit 25 Pasadena, CA 91105	CP130-3002 Subjects: 158	14 May to 04 Jun 2018	NAI

Key to Compliance Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations; Data unreliable.

1. Dr. Joseph S. Gimbel

At this site for Protocol CP130-3001, 128 subjects were screened and 54 subjects were enrolled. Of the enrolled subjects, 49 completed the study. For Protocol CP130-3002, 150 subjects were screened and 104 subjects were enrolled. Of the enrolled subjects, 103 completed the study.

A total of 39 subject study records were reviewed for Protocol CP130-3001, and 96 subject study records were reviewed for Protocol CP130-3002. Study and subject-specific records reviewed for both protocols included, but were not limited to, informed consent forms, source patient records, drug accountability, IRB/monitor correspondence, training records, adverse event reporting, financial disclosures, and electronic case report forms.

The primary efficacy endpoint data was verifiable, and there was no evidence of under-reporting of adverse events.

2. Dr. Artin Nazarian

At this site for Protocol CP130-3002, 378 subjects were screened and 158 subjects were enrolled. Of the enrolled subjects, 152 completed the study. Dr. Paulette Saddler was the clinical investigator at the start of the study on 5/27/2016, followed by Dr. Kjell Hult starting 6/27/2016. Dr. Nazarian became the clinical investigator on 8/9/2016.

A total of 11 subject records received a complete review for the entire clinical investigator compliance program, while 34 subject records were reviewed for the primary efficacy endpoint, and 28 records were reviewed for informed consent. Study and subject-specific records reviewed included, but were not limited to, informed consent forms, source patient records, drug accountability, IRB/monitor correspondence, training records, adverse event reporting, financial disclosures, and electronic case report forms.

The primary efficacy endpoint data was verifiable. Concerning adverse events, the clinical site discovered during an internal quality control audit, completed after data-lock, that the MRPSS sedation scores for 3 patients were assessed at 2 (i.e. mild), though were not captured as adverse events of "mild sedation." The clinical investigator (CI) notified the IRB and the sponsor. According to the CI, these events resolved with no safety concerns. These events took place before Dr. Nazarian became the clinical investigator for this protocol. Also, the FDA field investigator noted that for subject 303 (morphine treatment group) the NRS score at T45 was entered as 5 on the source document, though it was recorded as 6 in the EDC.

Reviewer Comment: These findings appear limited in scope and would have minimal impact on the overall safety and efficacy results.

{See appended electronic signature page}

Damon Green, M.D., M.S.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
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cc:

Central Doc. Rm.
DAAAP /Division Director/Hertz
DAAAP/Medical Team Leader/Maynard
DAAAP /Project Manager/Kapoor
DAAAP/Medical Officer/Kilgore
OSI/Office Director/Burrow
OSI/DCCE/ Division Director/Khin
OSI/DCCE/Branch Chief/Ayalew
OSI/DCCE/Team Leader/Kronstein
OSI/DCCE/GCPAB Reviewer/Green
OSI/ GCP Program Analysts/Patague
OSI/Database PM/Dana Walters

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/s/

DAMON C GREEN
07/30/2018

PHILLIP D KRONSTEIN
07/30/2018

KASSA AYALEW
07/30/2018

Hepatology Consultation

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF SURVEILLANCE AND EPIDEMIOLOGY
OFFICE OF PHARMACOVIGILANCE AND EPIDEMIOLOGY

DATE: 7 July 2018

FROM: John R. Senior, M.D.
Associate Director for Science
Office of Pharmacovigilance and Epidemiology (OPE)
Office of Surveillance and Epidemiology (OSE)

TO: Shelly Kapoor, RPM, Division of Analgesia, Anesthesia, and Addiction (DAAAP)
Elizabeth Kilgore, M.D., Medical Reviewer, DAAAP
Sharon Hertz, M.D., Director, (DAAAP)

SUBJECT: Is there a liver signal for oliceridene?
Documents reviewed:

1) Consultation request from DAAAP dated 9 May 2018 asking for expert review of oliceridene, NDA 210730, received 2 November 2017.
2) Letter of initial submission dated 31 October 2017, sequence 0001, describing oliceridene injection 1 mg/ml (OLINVO™), by Paul M. Kirsch, Vice President for Regulatory Affairs, Trevena, Inc., Chesterbrook PA 19087
3) Published (PubMed) literature on oliceridine, 17 articles to 30 June 2018.

Oliceridine is novel molecular entity discovered by Trevena scientists and first reported in 2013 (Chen et al, J Med Chem 2013, PMID 24063433) as a G-protein-biased mu-opioid receptor agonist for relief of acute severe pain. It was originally termed TRV130 by the sponsor, and prior to submission of the NDA 210730 on 2 November 2017 had a tentatively approved trade name of OLINVO™. Oliceridine is reported by the sponsor to elicit robust G-protein signaling, with potency and efficacy similar to that of morphine, but with less beta-arestin 2 recruitment and receptor internalization, thus displaying fewer adverse effects than morphine. It is proposed for intravenous administration in patients expected to have moderate-to-severe acute pain, and the model chosen was bunionectomy. It was granted breakthrough therapy status in February 2016.. Search of PubMed for "oliceridine" yields 17 publications, the majority (see references 1-9)) of which were submitted by the sponsor, and 8 were published by other authors commenting and speculating on its possible future (see references 10-17).

The request for consultation of 9 May 2018 focused on whether oliceridine has potential to cause drug-induced liver injury ("a liver signal"), as shown by our eDISH program (**e**valuation of **D**rug-**I**nduced **S**erious **H**epatotoxicity) analyses. DAAAP had requested on 14 May 2018 that the sponsor submit liver test data in eDISH format for safety and efficacy studies in the development program and address the potential of oliceridine to cause drug-induced liver injury. Trevena submitted on 11 June 2018 its safety and efficacy summary responses, in data from several studies that Dr. Ted Guo entered into eDISH.

Even before looking at the data submitted, it should be realized that some liver injury is likely to occur in all or nearly all patients who undergo surgical trauma (in these studies bone resection, bunionectomy), anesthesia, and administration of multiple drugs. The eDISH program was developed 15 years ago particularly to help medical reviewers with the very difficult problem of probable causal estimations, of whether the newly administered drug or something else probably caused the effect on the liver. It depends on finding evidence of liver injury serious enough to cause hepatocellular injury with leakage of intracellulart aminotransferase enzymes into the plasma and/or whole liver dysfunction (reduction in clearing bilirubin from plasma). Then the problem is to determine the probable cause of the effect by eliminating as many alternative causes as possible, to reduce the uncertainty so that drug-induction remains as the most probable (>50%) cause, more than all other possible causes combined. To do this, two methods are employed:

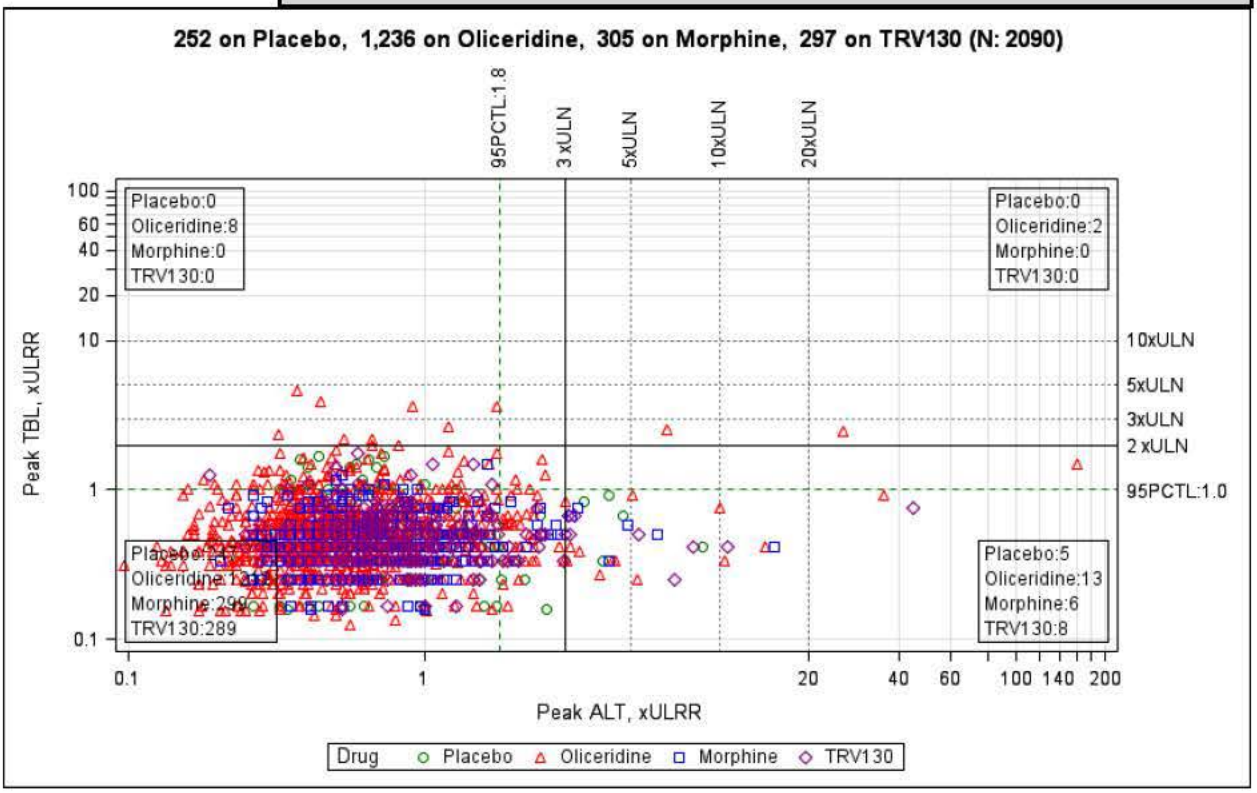
1. time course of principal liver test measures, serum activities of alanine and aspartate aminotransferase, alkaline phosphatase, and concentration of total serum bilirubin:
2. clinical narrative, describing the patient in the manner of a physician seeking to make the most like cause, in preparation to act by starting specific treatment.

It must be conceded that these steps, while helpful, are not always sufficient to get the correct answer, despite the process of investigating and reporting on clinical trial subjects being costly in time and money. If well carried out, the process may reduce the uncertainty enough to allow judicious initiation of treatment but that needs to be followed up to find out if it was correct. Stopping the drug in question is an obvious and quick solution to see if prompt improvement occurs. If so, recurrence on re-administration is powerful evidence that the drug had been causing the worsening of liver injury and function, but is seldom done because of concerns that such re-administration may lead to irreversible worsening and even death, based on reports from the literature. Oliceridene has not been approved anywhere yet, and there are no post-marketing reports. So, let's see what we have received from Trevena from their clinical trials.

Shown below is the initial graph based on information and data sent by the sponsor for Dr. Guo's inspection regarding formatting as directed for eDISH analyses. A total of 2090 subjects were included: 1533 given oliceridine (of them 297 received the early version TRV130), 305 given morphine, and mercifully only 252 given placebo after having their bunion bone resected. These data were gathered from 17 studies, with exposure claimed by the sponsor in the for 221 healthy subjects, 97 from special populations termed "hepatic and renal", and 1535 patients in phase 2 and 3 studies, totaling 1853 individuals exposed to the various drugs. It is unclear why the sponsor's total of 1853 is 237 fewer than the 2090 whose data were sent to Dr. Guo, or why healthy subjects were mixed in with patients undergoing surgical bunionectomy.

It is obvious at a glance that only those receiving oliceridine (red triangles) showed peak serum bilirubin above twice the upper limit of normal (ULN), of whom 2 of the 10 also showed peak elevated alanine aminotransferase (ALT) greater than 3xULN. It is also evident at a glance that there was no relative preponderance of ALT elevations compared to the numbers exposed:

oliceridine	15/1236 = 1.21%		
TRV130	8/297 = 2.69%	both olicerine and TRV130	23/1533 = 1.50%
morphine	3/305 = 1.97%		
placebo	5/252 = 1.98%		



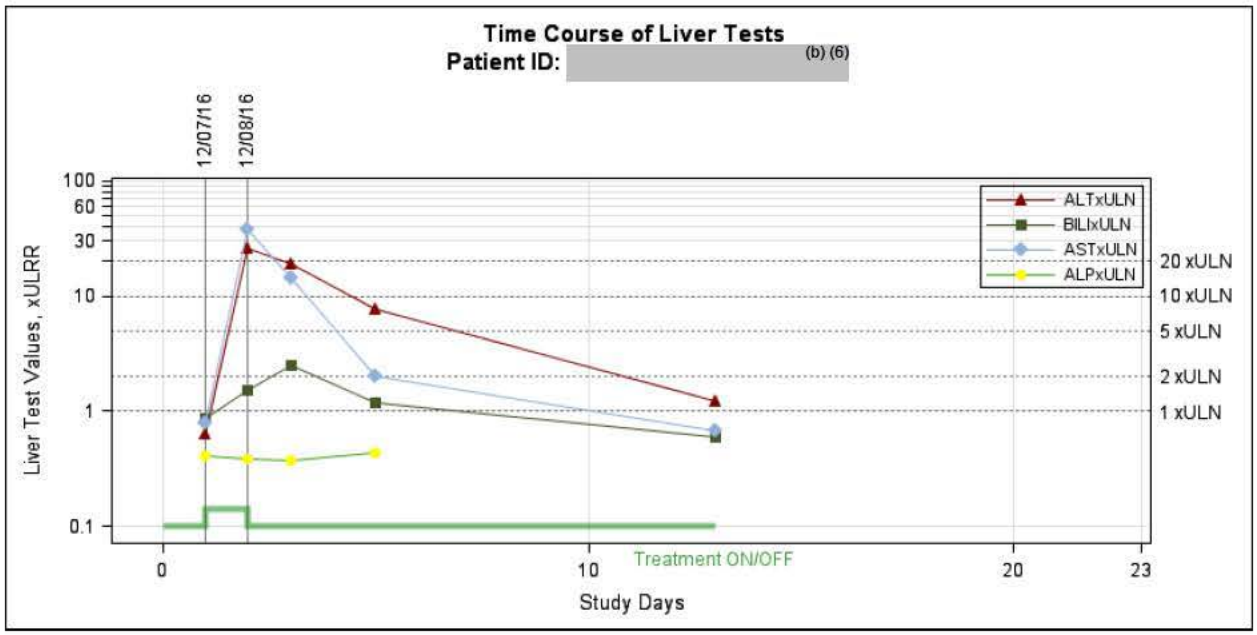
For the two subjects in the right upper quadrant ("northeast"), both from the ATHENA study CP130-3003, narrative clinical information was provided that was very helpful in diagnosing the probable cause of the liver test abnormalities observed.

Patient [redacted] (b) (6) showed peak ALT 26xULN and TBL 3.7xULN. The narrative information showed:

ATHENA Patient [redacted] (b) (6) is a 70-year-old white male (101.9 kg, 182.9 cm) in the oliceridine >4 to 8 mg cumulative dose group (Listing 16.2.2.1). He was enrolled in the ATHENA study to treat acute pain following hiatal hernia repair (Listing16.2.2.3) with general anesthesia. The patient received a loading dose of oliceridine (1 mg) on Relative Day 1 at 15:37 and subsequently received 5 bolus administrations of oliceridine 1 mg (for a cumulative dose of 6 mg) over the 15-hour Treatment Period (Listing 16.2.3.1). An LFT time course plot for this patient is provided in Figure 14.3.5.1 of the CSR . The patient experienced a high, clinically significant (by the investigator) ALT >26 xULN (1043 U/L [normal range: 10-40 U/L]) and AST >37xULN (1281 U/L [normal range: 5-34 U/L]) during the End of Treatment Period on Relative Day 2 with high but not clinically significant bilirubin >1xULN (2.3 mg/dL [normal range 0-1.5 mg/dL]). The ALT, AST and bilirubin values had been within the normal range at Baseline (25 and 27 U/L, and 1.3 mg/dL, espectively). On Relative Day 3, AST and ALT remained clinically significant by the investigator (758 and 480 U/L, respectively), bilirubin was high ≥2xULN (3.7 mg/dL) but not considered clinically significant by the investigator. By relative Day 5 the ALT, AST and bilirubin were 305 (clinically significant by the investigator), and 69 U/L, and 1.8 mg/dL, respectively. On Day 13 ALT continued to decline, remaining high ≥1xULN (49U/L) while AST and bilirubin were within normal range (23 U/L and 0.9 mg/dL, respectively) ALP remained within normal range during the study (Listing 16.2.7.1). His elevant

past medical history included coronary artery disease, dyslipidemia, hypertension, hypothyroidism, sleep apnea syndrome, and colon cancer (Listing 16.2.2.4). He received heparin, cefazolin, propofol, desflurane, ondansetron, and labetalol as relevant perioperative medications. Other concomitant medications included docusate, acetylsalicylic acid, metoprolol, levothyroxine, lisinopril, oxycodone, and pravastatin (Listing 16.2.2.2). Other than the laboratory AEs of hepatic enzyme increased (nonserious, moderate, unlikely related, resolved; no treatment was received) and blood LDH increased (1359 U/L on Day 2; nonserious, moderate, unlikely related, resolved; no treatment was received), no relevant clinical AEs were reported (Listing 16.2.5.1) On Day 13 Final ALT was 1xULN and AST,ALPand total bilirubin values were within normal range. Sponsor assessment: The sponsor has assessed the relationship of the study medication to the elevation in ALT and AST as unlikely related. This patient has no history of pre-existing liver disease with normal LFT measurements at aseline. He has a history pertinent for ischemic heart disease and use of a statin (pravastatin) for hypercholesterolemia. His anesthetic regimen included propofol and desflurane. The cumulative exposure of study medication was 6 mg over a 15 -hour treatment period. Post-surgery on Day 2 he experienced marked elevations of ALT, AST and LDH and an increase in total bilirubin ≥2xULN (3.7mg/dL) on Day 3. All LFT levels declined and were no longer clinically significant by Day 13. The differential diagnosis for a pattern of laboratory abnormalities such as these might include an ischemic etiology with the concomitant LDH rise, medication reaction to the anesthetic regimen, for which there are case reports of LFT abnormalities, or other medication with adverse hepatic effects (eg. Pravastatin, Lisinopril).With a low level of exposure to the study medication (6mg) and a variety of other potential etiologies an unlikely relationship to the study medication was determined by the investigator and agreed by the sponsor.

The time course of the liver tests for this patient showed:

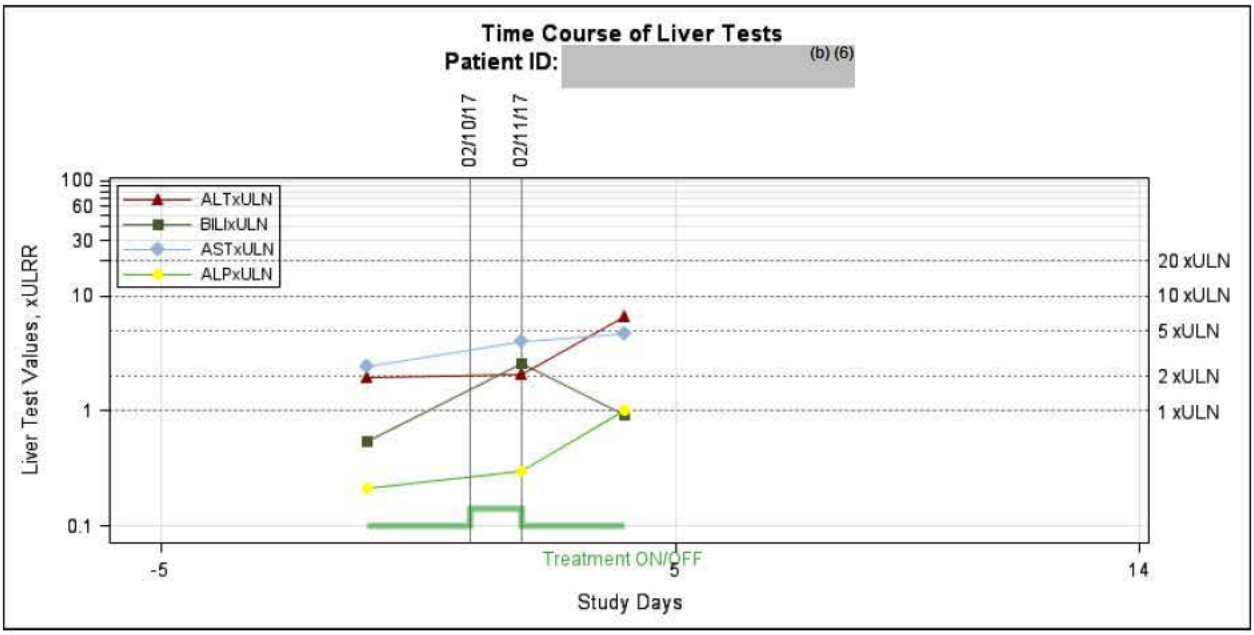


Note that the peak AST was even higher than the ALT immediately post-operatively (and aftyer anesthesia), which is a possible indication of vascular injury to the liver, and that the bilirub peak occurred a day later, then all abnormalities subsided within a few days.

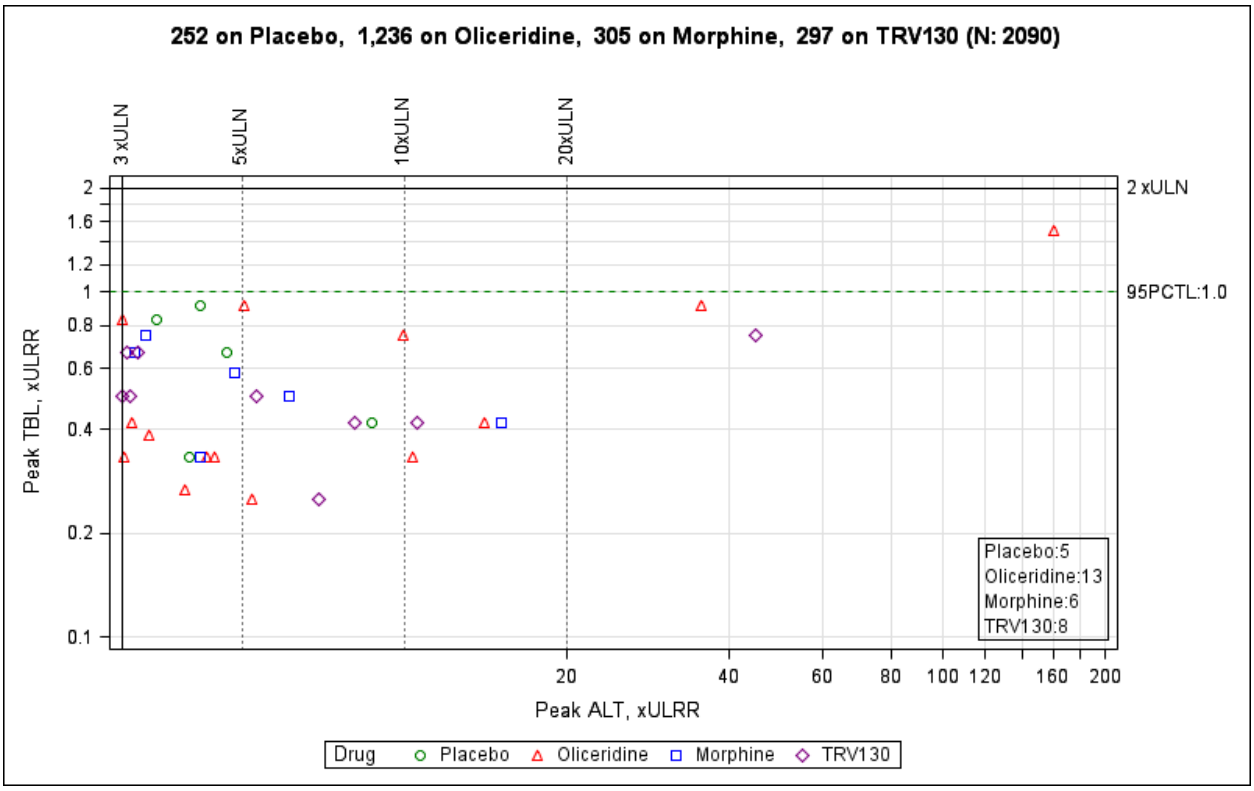
The other patient whose data placed him in the right upper (NE) quadrant had a rather similar history but somewhat less dramatic findings:

ATHENA Patient (b) (6) is a 54-year-old white male (105.4 kg, 181.6 cm) in the oliceridine >16 to 36 mg umulative dose group (Listing 16.2.2.1). He was enrolled in the ATHENA study to treat acute pain following aortic arch repair (Listing 16.2.2.3) with general anesthesia. The patient received a loading dose of oliceridine (0.5 mg) on Relative Day 1 at 08:01and subsequently self-administered 50 demand doses of oliceridine 0.5 mg (for a cumulative dose of 25.5mg) over the 28 hour Treatment Period (Listing 16.2.3.1).An LFT time course plot for this patient is provided in Figure 14.3.5.1 of

the CSR . The patient experienced abnormal, not clinically significant by the investigator ALT ≥1xULN (114 U/L [normal range: 0-59 U/L]), ALP (28 U/L [normal range: 40-130 U/L]) and AST ≥2xULN(95 U/L [normal range: 0-39 U/L]) during Baseline on Relative Day 1 while bilirubin was within normal range (0.7 mg/dL [normal range: 0-1.3 mg/dL]). On elative Day 2, ALT and ALP were ificant by the investigator (123 and 39 U/L, respectively) while AST and bilirubin were high, clinically significant by the investigator (154 U/L, and 3.3 mg/dL, respectively). On Relative Day 4, ALT, ALP and AST remained high (389, 131 and 184 U/L, respectively [ALT and AST clinically significantby the investigator, ALP not clinically significant by the investigator), while bilirubin was within normal range (1.2 mg/dL).Additional laboratory esults were not provided (Listing 16.2.7.1). His relevant past medical history included aortic coarctation, atrial fibrillation, atrial flutter, and hypertension (Listing 16.2.2.4 He received acetylsalicylic acid, atorvastatin, eplerenone, lisinopril, amlodipine, metoprolol, propofol, sevoflurane, cefazolin, vancomycin, heparin, amiodarone, famotidine, and as relevant perioperative medications. Of note, the patient had received a concomitant medication containing acetaminophen (p aracetamol 650 mg QID [between Relative Day -1 and Day 3]). Other concomitant medications included docusate, furosemide, insulin, oxycodone, and oxygen (Listing 16.2.2.2). His lowest observed SBP was 85mmHg and his lowest observed DBP was 49 mmHg (Listing 16.2.6.1). In addition to the TEAEs of ALT increased, AST increased, and hyperbilirubinemia (all nonserious, mild, and not related; no treatment received), he experienced the relevant clinical TEAEs of post procedural haemorrhage (nonserious, severe, not related, resolved; aminocalproic acid and red blood cells were administered as treatment), blood pressure decreased (nonserious, moderate, not related, resolved; no treatment received), metabolic acidosis (nonserious, moderate, not related, resolved; sodium bicarbonate administered as treatment), and hypokalemia (nonserious, moderate, not related, resolved; potassium chloride administered as treatment), all occurring on Day -1 (Listing 16.2.5.1). No subsequent ALT, AST, or bilirubin values were reported after Day 4. This patient also experienced a TEAE leading to early discontinuation of QT prolongation (nonserious, moderate, unlikely related, resolving) and is described in Section 17.2.1 of the CSR .Sponsor assessment: The sponsor has assessed the relat ionship of the study medication to the elevation in ALT, AST, and bilirubin as unlikely related.This patient has significant cardiovascular disease and no reported history of underlying liver disease, though his baseline ALT and AST levels were above normal. There is no hepatitis screening serology data. He underwent a complicated surgical procedure where it appears he may have experienced transient ischemia judging from the references to hemorrhage, hypotension,and metabolic acidosis. The patient was given propofol and sevoflurane as anesthetic agents. Post surgery he received a total of 25.5 mg of study medication over a 28-hour treatment period with discontinuation for QT prolongation. ALT ncreased from baseline to ≥2xULN on Day 2, further rising to ≥6xULN on Day 4. AST and ALP were also elevated on Day 4. The bilirubin level was ≥2xULN on Day 2 and then returned to normal0by Day 4. Some of the complications noted as TEAEs during surgery,the extensive list of perioperative medications and anesthetics,some of which have known hepatic effects, and potential for unrecognized underlying hepatic disease at baseline, could be associated with this pattern of laboratory abnormalities. Also of note, the patient received acetaminophen 650 mg PO QID between Days 1 and 3 There are many confounding variables to be considered in causation , which lead the investigator to conclude that the study medication was not related to the increase in transaminases and bilirubin.



No other narrative reports were received by Dr. Guo, but we were later informed on 15 June by Dr Janet Maynard of the DAAAP that the sponsor had sent narratives for the 14 subjects with serum transaminase elevations more than 5xULN in the right lower (southeast, SE) quadrant, shown below:



It may be seen that 13 + 8, 23/(1236 + 297) of subjects given oliceridine or TRV130 (1.37%) had shown peak serum transaminases over 5xULN, compared to the 6/305 given morphine and 5/252 given placebo .both 1.5%. Inspection of those narratives again showed no reason other than the surgical operation-anesthesia-other drugs to explain the liver test abnormalities observed.

None of the "liver signals" were associated with clinical symptom or findings, and would have been missed except for the close monitoring. None resulted in any serious (disabling, causing hospitalization, life-threatening, or fatal) whole liver dysfunction, and were transient, immediate post-operative findings that quickly disappeared.

The ponsor sent on 11 June (DARRTS NDA 210739, submission 0023) narratives for the 14 subjects in the RLQ plus 8 more "new"subjects, in response to the DAAAP request for more information, but as .xpt files that I could not open. Dr. Maynard sent on 15 June a copy of the 52-apge submission that may be seen in the attachment immediately below:

Response to
Question 1 - Ammend

For those who have the patience to read all 52 pages, review all 22 case narratives, and look at the time course of liver test finding for the 14 in eDISH, there are no additional "smoking guns" to raise further alarms about a "liver signal."

Whether DAAAP finds that oliceridine is enough better that morphine to justify what may very likely to be an astronomical price for the drug is beyond the scope of this consultation. You are encouraged to read what others have said about Trevena's new drug in the 8 references attached (10-17, below), to which I have appended links and PMID numbers to facilitate your finding them in PubMed. Oliceridine is not listed in the NIH program called LiverTox as a drug that causes serious liver injury or dysfunction.

/s/

John R. Senior, MD
7 July 2018

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_____^_*published by Trevena*_^_____

---------- comments by others about oliceridine ----------

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/s/

SONAM S KAPOOR
07/12/2018
Checked in on behalf of Dr. John Senior OPE/OSE

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: July 10, 2018

From: CDER DCRP QT Interdisciplinary Review Team

Through: Christine Garnett, Pharm.D.
Clinical Analyst
Division of Cardiovascular and Renal Products /CDER

To: Shelly Kapoor, RPM
DAAAP

Subject: QT-IRT Consult to NDA 210730

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 06/08/2018 regarding the sponsor's response to Mid-Cycle Communication Agenda. The QT-IRT reviewed the following materials:

- Sponsor's response document submitted to Sequence # dated 06/08/2018;
- Midcycle Communication dated 06/18/2018 in DARRTS;
- Sponsor's response to previous information request submitted to Sequence #0014 dated 04/04/2018;
- Previous QT-IRT review for NDA 210730 dated 03/08/2018 and 06/06/2018 in DARRTS; and
- Previous QT-IRT review for IND 113537 dated 02/05/2016 in DARRTS.

1. QT-IRT Responses

Question 1: To evaluate the mechanism of a delayed effect: (b) (4)

(b) (4)

Does the Agency agree that this would be a [redacted] (b) (4) ?

QT-IRT's response: No, [redacted] (b) (4) (b) (4)

Question 2: To evaluate the clinical significance of the QT effects observed: [redacted] (b) (4) (b) (4)

Does the Agency agree that [redacted] (b) (4) (b) (4)

QT-IRT's response: No, [redacted] (b) (4) (b) (4)

2. BACKGROUND

We have previously reviewed the thorough QT study for OLINVO, which showed a delayed dose-proportional increase in QTc, which did not coincide with peak oliceridine concentration (QT max ~1 h) (DARRTS 02/05/2016). At present the mechanism is unknown and possible mechanisms include inhibition of the hERG potassium channel by a hERG active metabolite; inhibition of hERG potassium channel trafficking or non-hERG mediated mechanisms (DARRTS 03/08/2018).

Based on the concern for QTc prolongation, the sponsor was requested to provide a mechanism (03/19/2018). We have previously reviewed the response from the sponsor, which did not offer a mechanism (06/08/2018). Of note, in the response letter the sponsor did provide average PK data for two major metabolites TRV0306954 (M22) and TRV019662, which account for 62% and 17% of plasma AUC respectively and the provided PK results suggest that the Tmax is between 0.5 and 3 h. It is therefore possible that either (or both) of these metabolites could contribute to

the observed QTc prolongation, however, no in vitro hERG assay analysis for either has been performed or exposure-response using clinical QTc data.

The QT issue was also included in the Midcycle communication dated 06/18/2018 in DARRTS and the current submission is a review of two follow-up analyses proposed by the sponsor to address the QT issue, which are addressed below.

(b) (4)

[redacted]

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

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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/

LARS JOHANNESEN
07/11/2018

CHRISTINE E GARNETT
07/11/2018

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: June 6, 2018

From: CDER DCRP QT Interdisciplinary Review Team

Through: Christine Garnett, Pharm.D.
Clinical Analyst
Division of Cardiovascular and Renal Products /CDER

To: Shelly Kapoor, RPM
DAAAP

Subject: QT-IRT Consult to NDA 210730

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 04/05/2018 regarding the sponsor's response to a previous information request. The QT-IRT reviewed the following materials:

- Sponsor's response to the information request submitted to Sequence #0014 dated 04/04/2018;
- Information request dated 03/19/2018 in DARRTS;
- Previous QT-IRT reviews under NDA 210703 dated 03/08/2018; and
- IND 113537 dated 02/08/2016 in DARRTS.

1. QT-IRT Comments to the Division

The submitted information suggests that OLINVO has QTc prolongation; however, the time course of the QTc effects does not follow the PK profile for oliceridine and the potential for the major metabolites of oliceridine, M22 or TRV0109662, to inhibit hERG and prolong the QTc interval has not been evaluated. We, therefore, recommend that the QT prolongation potential for OLINVO is described in the label as suggested below. If the division would like to have the sponsor evaluate the mechanism further, we recommend a more comprehensive nonclinical work-up for oliceridine and all major metabolites.

In the ATHENA study, there were 6 patients with ΔQTcF > 60 ms, 11 patients with QTcF > 500 ms and 5 patients that met both criteria. Drug effects cannot be excluded in some of these cases. Furthermore, the timing of the ECGs was limited to baseline 1 h and every 24 hours which does not capture the maximum QTc effect at the proposed dosing regimen.

The following is QT-IRT's proposed labeling language, which is a suggestion only. We defer final labeling decisions to the Division. Of note, we used xx to denote the maximum hourly dose that would exceed 2x of the highest dose in the thorough QT study and yy to denote the highest daily dose – these doses will need to be further discussed with the clinical and clinical pharmacology review teams.

5.x QT Prolongation

Dose-dependent prolongation of the QTc interval has been observed for OLINVO [see 12.2 Pharmacodynamics]. Avoid OLINVO in patients with congenital long QT syndrome. ECG monitoring is recommended in patients receiving doses greater than xx mg/h or in patients with electrolyte abnormalities (e.g., hypokalemia or hypomagnesemia), congestive heart failure, bradyarrhythmias, or patients taking other medicinal products that lead to QT prolongation.

12.2 Pharmacodynamics

Cardiac Electrophysiology

The effects of OLINVO (single dose 3 and 6 mg each infused IV over 5 minutes) on the QT interval was evaluated in a thorough QT study in 58 healthy subjects. These doses are lower than the maximum recommended daily dose of yy mg. Dose-dependent QTc prolongation was observed (3 mg: 7 ms [upper 90% CI: 9 ms]; 6 mg: 12 ms [14 ms]) and occurred after peak oliceridine plasma concentration.

2. BACKGROUND

We reviewed the TQT study for oliceridine under IND 113537 (review dated 02/08/2016) and concluded that OLINVO prolongs the QTc in a dose-dependent manner, but that maximum QTc effect occurred post peak plasma concentration of oliceridine due to an unknown mechanism.

In a subsequent consult request, the review division requested that we review the QT study and other studies, and provided our comments on QT findings. In the review associated with that consult (dated 03/08/2018), we re-stated our previous conclusion and further elaborated that the mechanism of QT prolongation is unknown and provided some potential reasons: 1) inhibition of hERG by a hERG active metabolite; 2) inhibition of hERG potassium channel trafficking or 3) non-hERG mediated mechanism. We further stated, that a hERG active metabolite could be possible as the peak QT effect coincided with the time of peak total radioactivity in a mass balance study, but that no definitive conclusion could be drawn based on limited data. Furthermore, we raised concerns about interpretation of the data in late phase trials as only limited ECG collection was included (1, 24 and 48 h post-dose).

Based on these limitations, we proposed revisions to section 12.2 to more accurately reflect the results of the TQT study and language for section 5.

Subsequently, an information request (dated 03/19/2018) the concerns about the limited information on the mechanism was conveyed to the sponsor and the sponsor was asked to:

a) Provide a proposed mechanism for the delayed onset of the QTcF prolongation observed with oliceridine. In addition, provide data to support this hypothesized mechanism.

b) Taking into consideration the proposed clinical dose (including the range and frequency of dosing), provide additional data to adequately evaluate the QT effects of oliceridine, such as a multiple dose tQT study.

The purpose of this memo is to review the response from the sponsor to this information requested (NDA 210730, Seq 0014).

Sponsor's Response to information request

a) Proposed mechanism

Nonclinical studies with oliceridine failed to identify any non-hERG mediated effects on cardiac signaling. The IC50 for oliceridine in a hERG assay (Study 110520.USF) was 2.2 μM, equivalent to a plasma concentration of 1110 ng/mL, a plasma concentration that is 5-fold higher than the mean Cmax (240 ng/mL) observed following the 6 mg IV dose of oliceridine in Study CP130-1008. Oliceridine's major metabolites, TRV0109662 and M22, were not tested in a hERG assay due to the lack of electrophysiologic changes in a monkey cardiovascular safety study (described below). In this monkey study, TRV0109662 and M22 plasma concentrations exceeded maximum expected clinical concentrations.

The effect of oliceridine on cardiac ion channel current amplitude was evaluated in an in vitro pharmacology study using an automated patch clamp platform and cell line expression systems (Study 101110.USF). Oliceridine IC50 values were 6.2 μM, 36.6 μM, 19.5 μM and 9 μM for the human hERG, human Cav1.2 L-type calcium channel, and human Nav1.5 sodium channel (tonic and phasic inhibition), respectively. The potential effects of oliceridine on cardiac electrical activity were also tested in an ex vivo isolated rabbit left ventricular wedge preparation (Study LIMRRWMU04), an assay evaluating multi-channel effects. Oliceridine was a weak hERG inhibitor with additional multi-ion channel effects that could mitigate any potential inhibition of hERG. In this assay, oliceridine did not cause any proarrhythmic events and had a composite torsadogenic (TdP) risk score of zero or lower at all tested concentrations (0.3 to 30 μM). A TdP score of >2.5 in this model correlates with risk of Torsade de Pointes.

Reviewer's Comment: The preclinical hERG data suggests that oliceridine has a potential for inhibition of hERG as the safety margin is less than 30.

Oliceridine, as well as metabolites TRV0109662 and M22, were tested for their ability to displace radioligand binding at a large number of receptors, channels and transporters, including cardiac active channels. Tested at a concentration of 10 μM, the only significant off-target interactions (inhibition >50%) of oliceridine were at the κ and nociceptin opioid receptors, the human 5-HT1A receptor, and rat σ receptors (Study 797915). Binding affinities at these receptors were more than 180-fold lower than the binding affinity at the human μ opioid receptor. TRV0109662 and M22 produced no significant interactions at any of the evaluated targets, other than weak interactions (500- to 800-fold less potent than oliceridine) at the μ opioid receptor (Studies 100022039 and 100040220).

In vivo data collected from a monkey cardiovascular safety pharmacology study identified no evidence that oliceridine or the primary metabolites, TRV0109662 and M22, affected cardiac signaling. Oliceridine was administered as a 10 hr continuous IV infusion in telemetered

cynomolgus monkeys (Study 8242813). Administration of oliceridine caused dose-dependent decreases in mean systolic, diastolic, and mean arterial pressures, mean arterial pulse pressure, and body temperature during infusion. No effect on QRS, PR, QT or corrected QT (QTc) intervals, and no abnormal ECG waveforms or arrhythmias were identified. In addition to high levels of oliceridine, plasma concentrations of TRV0109662 and M22 in monkeys administered the top dose of 1 mg/hr in this study significantly exceed expected human concentrations (Table 5).

Table 5: Mean Peak (C_{max}) TRV0109662 and M22 Plasma Concentrations (ng/mL) in Monkeys and Humans

Species/Oliceridine Dose	TRV0109662	M22
Monkeys (1 mg/hr)	22.0[a]	596[b]
Humans (3 mg/hr)	4.68[c]	177[d]

[a]8242809/XT150020; [b]8242809/TRE-R7676; [c]QS130-3001; [d]QS130-3004

These *in vivo* data, combined with the *in vitro* studies on cardiac ion channels including hERG, provide no evidence that oliceridine or its major human metabolites produce QT prolongation at plasma exposures (Cmax and AUC) observed after high doses of oliceridine.

Reviewer's Comment: While, the monkey study did not appear to suggest a potential for QT prolongation, it is worth noting that the highest exposure evaluated is ~3-5x the maximum dose proposed in the label (3 mg/hr).

b) Additional data

The primary study objective of the thorough QT study was to assess the ECG effects of oliceridine relative to placebo at a single therapeutic (3 mg) and supratherapeutic (6 mg) dose infused IV over 5 minutes in healthy male and female subjects.

First, regarding the 1-hour and 2-hour time points at the supratherapeutic dose, the observed changes in QTcF are rather modest increases for a supratherapeutic dose, particularly for a drug which is to be used in the hospital, under close medical observation, and for short-term use.

Reviewer's Comment: The reviewer's concern is whether the increase could be greater, if its due to a metabolite that could accumulate with repeat dosing, or if the patients are receiving other drugs, e.g. antiemetics with a QT prolonging potential (e.g. ondansetron).

Second, if the observed changes were due to a metabolite, the ΔΔQTcF data suggest that the putative metabolite is cleared at a similar rate as parent; thus, accumulation with repeat dosing is unlikely.

Finally, ECGs performed in the thorough QT study at 6, 8, 12, 18, and 23.5 hours did not demonstrate significant QTc prolongation, which would be expected if there was accumulation of a QTc-prolonging metabolite.

Reviewer's Comment: The thorough QT study was a single dose study and if the QT effect was due to direct inhibition of hERG by a metabolite, then one would expect the QT prolongation to follow the course of that metabolite, e.g. M22.

A similar lack of effect over time was noted in the APOLLO 1 study, in which median changes from baseline QTcF at 1, 24 and 48 hours were 4, -2.5 and -2 milliseconds, respectively, in the

quartile of patients who had the greatest cumulative exposure to oliceridine (61.6 mg - 159.8 mg oliceridine cumulative dose; N=59; see APOLLO 1 CSR Table 14.3.5.3), suggesting no accumulation of a QTc-prolonging metabolite under conditions of protracted clinical use. Notably, these high cumulative exposures were incurred steadily over the 48-hour treatment period (APOLLO 1 CSR Figure 14.3.1); therefore, if a QTcF-prolonging metabolite was accumulating in these patients, its effect would be observed in the 24- and 48- hour ECGs. Additionally, in this highest exposure quartile, there were no changes from baseline QTcF at 24 or 48 hours of >30 msec or increases to >= 500 msec (APOLLO 1 CSR Table 14.3.5.4).

Reviewer's Comment: Neither APOLLO1, APOLLO2 or ATHENA were designed to characterize the QT prolonging effect of oliceridine.

Controlled Phase 3 Population

As noted in Table 6 below and in the Integrated Summary of Safety (ISS) Section 4.3.2.1.1, a similar percentage of patients in the placebo, oliceridine, and morphine treatment regimens had QT interval and QTcF changes >30 msec: 13.8%, 11.3%, and 13.4%, respectively, and 7.5%, 8.3%, and 8.3%, respectively. One patient (0.2%) in the oliceridine treatment regimen had a QTcF change from Baseline >60 msec; there were no TEAEs associated with QTcF for this patient (APOLLO 1 Patient 10016-054; see narrative in APOLLO 1 CSR Section 11.10.2.2). No patient in the placebo or morphine treatment regimens had a QTcF change from Baseline >60 msec.

The percentage of patients in the placebo, oliceridine, and morphine treatment regimens with a QT interval >450 msec was similar (13.0%, 9.6%, and 8.9%, respectively). No patients in any treatment regimen had a QTcF >500 msec.

Table 6: QT-related Potentially Clinically Significant ECG results by Treatment Regimen (Controlled Phase 3 Safety Analysis Set)

PCSA Criterion	Placebo N=162 n (%)	Oliceridine 0.1 mg N=153 n (%)	Oliceridine 0.35 mg N=158 n (%)	Oliceridine 0.5 mg N=159 n (%)	Oliceridine Total N=470 n (%)	Morphine N=158 n (%)
QT Interval change from Baseline >30 msec	22 (13.8)	25 (16.3)	10 (6.3)	18 (11.4)	53 (11.3)	21 (13.4)
QTcF change from Baseline >30 msec	12 (7.5)	15 (9.8)	11 (7.0)	13 (8.2)	39 (8.3)	13 (8.3)
QTcF change from Baseline >60 msec	0	1 (0.7)	0	0	1 (0.2)	0
QTcF change from Baseline >60 msec	0	1 (0.7)	0	0	1 (0.2)	0
QT Interval >450 msec	21 (13.0)	19 (12.4)	9 (5.7)	17 (10.7)	45 (9.6)	14 (8.9)
QTcF >500 msec	0	0	0	0	0	0

ECG = electrocardiogram; PCSA = potentially clinically significant abnormality
Note: Patients summarized by actual treatment. Percentages were based on the number of patients in each treatment group within the ECG result of interest.
Data source: ISS Table 14.6.1.1

ATHENA Study Population

ATHENA patients who met predefined QTcF criteria of either a change from Baseline in QTcF >60 msec, and/or QTcF >500 msec post-Baseline are summarized in ATHENA CSR Section 10.9.2.1. ATHENA CSR In-text Table 22 describes each patient using parameters relevant to QT interval. All post-Baseline values meeting at least one of these criteria were included in this analysis.

Twenty-two patients (2.9%) met one or both pre-defined QTcF criteria. Of these 22 patients; 6 patients met the criteria for a change from Baseline in QTcF >60 msec, 11 patients met criteria for QTcF >500 msec post-Baseline, and 5 patients met both criteria. Given that torsadagenic drugs would, in general, demonstrate greater QTc prolongation with higher dose and exposure, it is important to note that there was no relationship with cumulative dose - patients were distributed across all oliceridine cumulative dose groups: 3 (1.9%) patients, 1 (1.2%) patient, 5 (4.1%) patients, 6 (3.6%) patients, and 7 (2.9%) patients in the oliceridine ≤4 mg, >4 to 8 mg, >8 to 16 mg, >16 to 36 mg, and >36 mg cumulative dose groups, respectively.

Of the 22 patients who met at least one of the pre-defined QTcF criteria, 11 patients had at least one identified potential confounding factor that may have prolonged the QT interval (eg, prior or concomitant medication with a propensity to increase the QT interval; TEAEs of electrolyte abnormalities that are associated with increases in the QT interval).

In 10 patients, the QTcF abnormality resolved at the time of the final ECG assessment. In 2 patients, although the post-Baseline QTcF was >500 msec, it was less than Baseline. In the remaining patients, resolution was not documented.

Most importantly, none of these patients had any TEAE or ECG assessment of ventricular extrasystoles, premature ventricular complexes, or ventricular tachycardia.

Treatment-emergent AEs of ECG QT prolonged were reported in 3 ATHENA patients (ATHENA CSR Table 14.3.2.2.1). Patient (b) (6) (nonserious, mild, unlikely related, outcome unknown) met the QTcF criterion for a change from Baseline of >60 msec, and Patient (b) (6) (nonserious, moderate, unlikely related, resolving, led to early study medication discontinuation) met both QTcF criteria (see narrative in ATHENA CSR Section 17.2.2 and ATHENA CSR In-text Table 22). Patient (b) (6) did not actually meet QTcF criteria and is discussed in ATHENA CSR Section 10.9.2.2).

Reviewer's Comment: The reviewer conducted an independent assessment of the outliers which is presented below.

Reviewer's Assessment of ECG findings in ATHENA

ATHENA (CP130-3003) was a multicenter, open-label study of oliceridine in patients with acute pain for which parenteral opioid therapy is warranted. The dosing utilized in this study consisted of an initial dose of 1 to 2 mg with a supplemental dose of 1 mg PRN as early as 15 min afterwards followed by 1 to 3 mg every 1 to 3 hours PRN. ECGs were collected at baseline at 1 hour after the first dose and every 24 h of oliceridine treatment, like APOLLO-1 and APOLLO-2.

In ATHENA, there were 6 patients with ΔQTcF > 60 ms, 11 patients with QTcF > 500 ms and 5 patients that met both criteria (Table 1). Per the Sponsor, 11 patients had at least one identified

potential confounding factor that may have contributed to QTc prolongation; however, drug effect could not be excluded in some of these cases.

1. (b) (6) /F/73y/>16 to 36 mg (QTc >500 ms and ΔQTc>60 ms): Moderate hypokalemia and administration of sevoflurane or ondansetron could have contributed to QTc prolongation. Time course of QTc interval does not support drug effect.
2. (b) (6) /M/54y/>16 to 36 mg (QTc >500 ms and ΔQTc>60 ms): Concomitant use of amiodarone and dofetilide (administered on day 1) most likely contributed to QTc prolongation. QTc prolongation occurred at 24 h and end of treatment. Drug effect cannot be excluded.
3. (b) (6) (QTc>500 ms and ΔQTc>60 ms): Concomitant use of levofloxacin on day 1 could have contributed to QTc prolongation at 3 min and 60 min post dose. Levofloxacin IV infusion completed within 2 h prior to ECG collection on day 1. Drug effect cannot be excluded.
4. (b) (6) / F/39y />8 to 16 mg (ΔQTc>60 ms): QTc prolongation confounded with co-administration of levofloxacin IV on day 1. Drug effect cannot be excluded.
5. (b) (6) /F/36y/>16 to 36 mg (QTc>480 ms and ΔQTc >60 ms): The sponsor attributed QTc prolongation to vasopressin; however, the vasopressin label does list QTc prolongation as an adverse drug reaction. However, the patient also received other medication with a potential for QT prolongation: famotidine, metoclopramide, sevoflurane and ondansetron. Drug effect cannot be excluded.
6. (b) (6) /F/41y/>16to 36 mg (ΔQTc >60 ms): The sponsor attributed QTc prolongation to vasopressin; however, the vasopressin label does list QTc prolongation as an adverse drug reaction. However, the patient also received other medication with a potential for QT prolongation: famotidine, metoclopramide, sevoflurane and ondansetron. Drug effect cannot be excluded.
7. (b) (6) /F/34y/>36mg (ΔQTc >60 ms): The sponsor attributed QTc prolongation to RBBB. However, the QTc increased from 404 ms at baseline to 476 ms after oliceridine administration. The patient also received several other potentially QT prolonging medication such as famotidine, metoclopramide and ondansetron. Drug effect cannot be excluded.
8. (b) (6) /F/79y/≤4mg (QTc >500 ms): QTc prolongation observed at baseline, but not at screening. The QTc prolongation observed at baseline could potentially be attributed to other QT prolonging medication including famotidine, ondansetron, sevoflurane and metoclopramide.
9. (b) (6) /M/28y/>8 to 16 mg (QTc >500 ms): QTc prolongation observed at baseline, but not at screening. The QTc prolongation observed at baseline could potentially be attributed to other QT prolonging medication including: famotidine and ondansetron.
10. (b) (6) / F/45y/>16to 36 mg (QTc >500 ms): The sponsor attributed QTc prolongation to vasopressin; however, the vasopressin label does list QTc prolongation as an adverse drug reaction. Amitriptyline and hypokalemia could prolong the QTc interval. Drug effect cannot be excluded.
11. (b) (6) / F/73y/>36 mg (QTc>500 ms): The sponsor attributed QTc prolongation to AV pacemaker. However, the patient also received several other potentially QT prolonging medication such as famotidine and ondansetron. Drug effect cannot be excluded.

It is worth noting that the ECG monitoring was sparse (baseline, 1 h and every 24 h) and the absence of observed QTc prolongation is therefore not particularly reassuring. Furthermore, 2 subjects had adverse events (1 subject with syncope and 1 subject with ventricular tachycardia). These subjects did not have prolonged QTc intervals.

Adverse Events Associated with MedDRA SMQ Torsade de Pointes/QT Prolongation

Subject ID	Adverse event	Severity	Serious	AE action	AE outcome
(b) (6)	Syncope[1]	Severe	Y	Not applicable	Recovered/resolved
	Electrocardiogram QT prolonged	Moderate	N	Drug withdrawn	Recovering/resolving
	Ventricular tachycardia[2]	Mild	N	Dose not changed	Recovered/resolved
	Electrocardiogram QT prolonged	Mild	N	Dose not changed	Unknown
	Electrocardiogram QT prolonged	Mild	N	Not applicable	Unknown

[1]Largest QTcF interval (440 ms) occurred at baseline. [2]Largest QTcF interval (436 ms) occurred 65 minutes after treatment. Source: Reviewer's MAED analysis using adae.xpt

Overall, the reviewer considers it possible that several of the cases of QTc prolongation observed in ATHENA could be related to oliceridine and QTc prolongation was also observed in the thorough QT study. However, the interpretation of the ATHENA ECG data is complicated by lack of ECG replicates at each nominal timepoint and the study did not include a control arm to understand the background rates of QTc prolongation in the patient population due to concomitant medications and comorbid conditions.

Table 1: Overview of patients with significant QTc prolongation in ATHENA

Patient ID/Sex/Age	Cumulative Oliceridine Dose Group	Reason for Receiving Oliceridine	Relevant Medical History	Relevant Prior/ Concomitant Medications	Electrolytes (sodium, potassium, calcium)	QTcF Change from BL >60 msec	QTcF >500 msec post-BL	Other Temporally Relevant TEAEs	Comment
Patients with QTcF change from Baseline >60 msec									
(b) (6) F/39y	>8 to 16 mg	Abdominal myomectomy	Cardiac murmur 1977-1987	Levofloxacin 500 mg IV x 1 dose (Day 1; 12:12)	Calcium: BL: 8.2 mg/dL; Day 1: 7.3 mg/dL No FU	BL: 385 msec 60 min: 465 msec No FU ECG	No	None	Electrolyte abnormality / levofloxacin may increase QT interval
(b) (6) F/31y	>8 to 16 mg	Bilateral breast augmentation	None	None	Normal	BL: 359 msec EoT: 426 msec	No	None	None
(b) (6) F/36y	>16 to 36 mg	Hysterectomy	MVP (ongoing)	Vasopressin 20 U SC x 1 dose (Day 1; no time reported)	Normal	BL: 357 msec 60 min: 497 msec No FU ECG	No	None	Vasopressin: may increase QT interval
(b) (6) F/41y	>16 to 36 mg	Hysterectomy	Hypothyroidism (2005; ongoing) MVP (2016; ongoing)	Vasopressin 20 U SC x 1 dose (Day 1; no time reported)	BL and FU normal except: FU calcium 8.0 mg/dL on Day 2	BL: 347 msec 6 hrs: 418 msec No FU ECG	No	None	Vasopressin: may increase QT interval

Patient ID/Sex/Age	Cumulative Oliceridine Dose Group	Reason for Receiving Oliceridine	Relevant Medical History	Relevant Prior/ Concomitant Medications	Electrolytes (sodium, potassium, calcium)	QTcF Change from BL >60 msec	QTcF >500 msec post-BL	Other Temporally Relevant TEAEs	Comment
(b) (6) M/54y	>36 mg	Lumbar fusion	Hypertension (1999; ongoing)	None	BL and FU normal except: FU calcium 8.4 mg/dL on Day 2	BL: 341 msec 60 mins: 474 msec No FU ECG	No	ECG QT Prolonged (Day 1; nonserious, mild, unlikely related, unknown)	None
(b) (6) F/34y	>36 mg	Pancreatitis	Hypertension (ongoing)	None	Normal	BL: 404 msec 48 hour: 476 msec (RBBB) 72 hour: 477 msec (RBBB) No FU ECG	No	None	RBBB may increase QT interval
Patients with post-Baseline QTcF >500 msec									
(b) (6) /F/79y	≤4 mg	Hemi-colectomy	Cardiomegaly (ongoing) CVA (2014) COPD (2016; ongoing)	None	BL and FU normal except: FU calcium 7.6 mg/dL on Day 2 Serum potassium within normal range.	No	BL: 487 msec 60 mins: 501 msec EoT: 392 msec	Hypokalemia (Days 2 to 3; not serious, mild, not related, resolved).	Electrolyte abnormalitics may increase QT interval; QTcF outlier resolved

Patient ID/Sex/Age	Cumulative Oliceridine Dose Group	Reason for Receiving Oliceridine	Relevant Medical History	Relevant Prior/ Concomitant Medications	Electrolytes (sodium, potassium, calcium)	QTcF Change from BL >60 msec	QTcF >500 msec post-BL	Other Temporally Relevant TEAEs	Comment
(b) (6) M/84y	≤4 mg	Femoral-popliteal Bypass	Coronary artery disease (ongoing) Peripheral vascular disorder (ongoing) Hypercholesterolemia (ongoing) COPD (ongoing) Hypertension (ongoing) Aortic valve replacement (2015) Coronary artery bypass graft (2015) Femoral aneurysm (2016)	None	BL and FU normal except: FU calcium 7.1 mg/dL on Day 2	No	BL: 559 msec; 60 min: 549 msec	None	Post-Baseline QTcF less than Baseline
(b) (6) M/64y	≤4 mg	Laparoscopic low anterior resection	Hypertension (ongoing)	None	Normal	No	BL: 503 msec 60 min: 507 msec 6 hr: 469 msec	None	Post Baseline QTcF 4 msec increase over BL; QTcF outlier resolved
(b) (6) F/62y	>4 to 8 mg	Total hip arthroplasty	Hypothyroidism (1976; ongoing) Sleep apnea syndrome (1990; ongoing) Hypertension (2016; ongoing)	None	Normal	No	BL: 494 msec 60 mins: 510 msec 6 hr: 480 msec	None	QTcF outlier resolved

Patient ID/Sex/Age	Cumulative Oliceridine Dose Group	Reason for Receiving Oliceridine	Relevant Medical History	Relevant Prior/ Concomitant Medications	Electrolytes (sodium, potassium, calcium)	QTcF Change from BL >60 msec	QTcF >500 msec post-BL	Other Temporally Relevant TEAEs	Comment
(b) (6) F/47y	>8 to 16 mg	Hysterectomy with bilateral salpingo-oophorectomy	Hypotension (2015; ongoing)	None	Normal	No	BL: 514 msec; 60 min: 506 msec	None	Post-Baseline QTcF less than Baseline
(b) (6) F/34y	>8 to 16 mg	Medial meniscec-tomy	Right bundle branch block (2004; ongoing) Lyme disease (2014; ongoing)	None	BL and FU normal except: FU calcium 8.2 mg/dL 5 hrs post BL	No	BL: 493 msec 60 mins: 540 msec No FU ECG	None	None
(b) (6) M/28y	>8 to 16 mg	Closure of Patent Foramen Ovale	Atrial septal defect (1988; ongoing) Ventricular septal defect (1988) Right ventricular hypertrophy (2016; ongoing) Tricuspid valve incompetence (2016; ongoing) heart valve incompetence (1997; ongoing) heart valve stenosis (1997; ongoing)	None	BL and FU normal except: BL potassium 3.0 mmol/L; FU potassium 3.4 mmol/L and calcium 7.9 mg/dL on Day 5	No	BL: 542 msec; 6 hr: 543 msec; 24 hr: 456 msec	Hypomagne saemia (Days -2 to 2; not serious, moderate, not related, resolved)	Electrolyte abnormality may increase QT interval; QTcF outlier resolved

Patient ID/Sex/Age	Cumulative Oliceridine Dose Group	Reason for Receiving Oliceridine	Relevant Medical History	Relevant Prior/ Concomitant Medications	Electrolytes (sodium, potassium, calcium)	QTcF Change from BL >60 msec	QTcF >500 msec post-BL	Other Temporally Relevant TEAEs	Comment
(b) (6) F/45y	>16 to 36 mg	Pulmonary Valve Replacement	Scoliosis cardiac failure congestive (2016; ongoing) hypertension (2004; ongoing) pulmonary valve incompetence (2016; ongoing) restrictive pulmonary disease (2016; ongoing)	Vasopressin 0.1 U/kg/ mn IV x 60 mins (Day -1) Amitriptyline 10 mg QD (Day 2)	BL and FU normal except: BL calcium 7.9 mg/dL; FU calcium 8.2 mg/dL on Day 3	No	BL: 478 msec; 60 min: 503 msec 48 hr: 507 msec No FU ECG	Metabolic acidosis (Days -1 to 1; not serious, moderate, not related, resolved) Hypokalemia (Days -1 to 2; not serious, mild, not related, resolved) Hypomagnesemia (Days 1 to 2; not serious, mild, not related, resolved) Hypocalcemia (Day 2; not serious, moderate, not related, ongoing) Hypophosphatemia (Days 2 to 6; not serious, moderate, not related, resolved)	Vasopressin and amitriptyline may increase QT interval. Electrolyte abnormalities may increase QT interval.

Patient ID/Sex/Age	Cumulative Oliceridine Dose Group	Reason for Receiving Oliceridine	Relevant Medical History	Relevant Prior/ Concomitant Medications	Electrolytes (sodium, potassium, calcium)	QTcF Change from BL >60 msec	QTcF >500 msec post-BL	Other Temporally Relevant TEAEs	Comment
(b) (6) F/78y	>16 to 36 mg	Total right knee replacement	Cardiomyopathy (ongoing) Mitral valve calcification (ongoing) Atrial fibrillation (ongoing) Aortic arteriosclerosis (ongoing) Blood cholesterol increased (ongoing) Cardiac failure congestive (ongoing) Hypertension (ongoing)	Amiodarone 200 mg PO QD	Normal	No	BL: 526 msec All post-BL values <BL (459-503 msec) 48 hr: 459 msec (final)	None	QTcF outlier resolved
(b) (6) F/51y	>36 mg	Hernia Repair	None	None	Normal	No	BL: 500 msec; 60 min: 543 msec; 72 hr: 431 msec	None	QTcF outlier resolved

Patient ID/Sex/Age	Cumulative Oliceridine Dose Group	Reason for Receiving Oliceridine	Relevant Medical History	Relevant Prior/ Concomitant Medications	Electrolytes (sodium, potassium, calcium)	QTcF Change from BL >60 msec	QTcF >500 msec post-BL	Other Temporally Relevant TEAEs	Comment
(b) (6) F/73y	>36 mg	Right knee replacement	Bradycardia (2005) Hypertension (ongoing) LBBB (ongoing) Sleep apnea syndrome (ongoing) Cardiac pacemaker insertion (ongoing)	None	Normal	No	BL: 461 msec 60 min: 503 msec (AV pacemaker) 24 hr: 446 msec 48 hr: 478 msec (AV pacemaker)	None	AV Pacemaker; QTcF outlier resolved
Patients with QTcF change from Baseline >60 msec and post-Baseline QTcF >500 msec									
(b) (6) F/73y	>16 to 36 mg	Laparoscopic descending colon resection	Hypertension (1987; ongoing) Type 2 diabetes mellitus (ongoing) Aortic aneurysm (ongoing)	None	Normal except EOT sodium 153 mmol/L	BL: 419 msec 48 hr: 530 msec (RBBB) 72 hr: 432 msec	BL: 419 msec 48 hr: 530 msec (RBBB) 72 hr: 432 msec	Hypokalemia (Day 2; not serious, moderate, not related, ongoing) Hypophosphatemia (Day 3; not serious, mild, not related, ongoing)	Electrolyte abnormality / RBBB may increase QT interval; QTcF outlier resolved

Patient ID/Sex/Age	Cumulative Oliceridine Dose Group	Reason for Receiving Oliceridine	Relevant Medical History	Relevant Prior/ Concomitant Medications	Electrolytes (sodium, potassium, calcium)[a]	QTcF Change from BL >60 msec	QTcF >500 msec post-BL	Other Temporally Relevant TEAEs	Comment
(b) (6) M/54y	>16 to 36 mg	Aortic arch repair	Hypertension (ongoing) Coarction of Aorta (ongoing) Angioplasty (2008) Atrial fibrillation / flutter (2012)	Amiodarone 5 µg/kg/min (continuous; Day -1) Dofetilide 500 µg BID (Day 1)	Calcium 8.3 mg/dL (Day 2)	BL: 394 msec (LBBB) 24 hr: 528 msec (assessed as ABCS) Day 3: 492 msec (LBBB)	BL: 394 msec (LBBB) 24 hour: 528 msec (assessed as ABCS) Day 3: 492 msec (LBBB)	ECG QT prolonged (nonserious, moderate, unlikely related, resolving, drug withdrawn)	Amiodarone / Dofetilide / LBBB may increase QT interval; TEAE of ECG QT Prolongation led to early discon-tinuation. No ventricular dysrhythmias on ECGs. No FU ECG.
(b) (6) F/40y	>36 mg	Total abdominal hysterectomy	None	Azelastine 1 spray intranasal BID Levofloxacin 500 mg IV x 1 dose (Day 1)	Calcium 8.4 mg/dL (Day 2)	BL: 414 msec 60 mins: 505 msec 24 hr: 444 msec	BL: 414 msec 60 mins: 505 msec 24 hr: 444 msec	None	Azelastine and levofloxacin may increase QT interval; QTcF outlier resolved

Patient ID/Sex/Age	Cumulative Oliceridine Dose Group	Reason for Receiving Oliceridine	Relevant Medical History	Relevant Prior/ Concomitant Medications	Electrolytes (sodium, potassium, calcium)[a]	QTcF Change from BL >60 msec	QTcF >500 msec post-BL	Other Temporally Relevant TEAEs	Comment
(b) (6) M/71y	>36 mg	Total knee replacement	Hyperlipidemia (2011; ongoing) Hypertension (2012; ongoing)	None	Normal	BL: 400 msec 48 hrs: 551 msec No FU ECG	BL: 400 msec 60 min: 422 msec 24 hrs: 396 msec 48 hrs: 551 msec No FU ECG	None	None
(b) (6) F/69y	>36 mg	Hysterectomy	Post-surgical hypothyroidism (2014; ongoing) Adrenalectomy (2014) thyroidectomy (2014)	None	BL and FU normal except: FU calcium 8.2 mg/dL on Day 3	BL: 428 msec 24 hrs: 530 msec 48 hrs: 427 msec	BL: 428 msec 24 hrs: 530 msec 48 hrs: 427 msec	None	QTcF outlier resolved

ABCS=abnormal clinically significant; AV=atrioventricular; BID=twice a day; BL=baseline; CVA=cerebral vascular accident; COPD=chronic obstructive pulmonary disease; ECG=electrocardiogram; EoT=end of treatment; F=female; FU=follow-up; ID=identification; IV=intravenous; LBBB=left bundle branch block; M=male; MVP=mitral valve prolapse; NA=not applicable; PO=per oral; QD=once per day; QTcF=QT interval corrected for heart rate by Fridericia's formula; RBBB=right bundle branch block; SC=subcutaneous; TEAE=treatment-emergent adverse event; U=units; Y=yes; y=years

[a] Normal ranges provided in Listing 16.2.7.1.

Data sources: Listing 16.2.1.1, Listing 16.2.2.2, Listing 16.2.2.4, Listing 16.2.5.1, Listing 16.2.7.1, Listing 16.2.8

Source: ATHENA final study report, Table 22

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

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/s/

LARS JOHANNESEN
06/06/2018

CHRISTINE E GARNETT
06/06/2018

LABEL 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:	May 23, 2018
Requesting Office or Division:	Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Application Type and Number:	NDA 210730
Product Name and Strength:	Oliceridine injection 1 mg/mL
Total Product Strength:	1 mg/1 mL, 2 mg/2 mL, 30 mg/30 mL
Product Type:	Single Ingredient Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Trevena, Inc.
Submission Date:	11/2/2017 and 3/5/2018
OSE RCM #:	2017-2276
DMEPA Safety Evaluator:	Cameron Johnson, PharmD
DMEPA Team Leader:	Otto L. Townsend, PharmD

1 PURPOSE OF REVIEW

As part of the approval process for Oliceridine injection, 1 mg/mL, the Division of Anesthesia, Analgesia and Addiction Products (DAAAP) requested that we review the proposed packaging, label and labeling for areas that may lead to medication errors.

2 REGULATORY HISTORY AND MATERIALS REVIEWED

2.1 REGULATORY HISTORY

The Applicant originally submitted their NDA on November 2, 2017. On December 11, 2017 the applicant submitted a request to review the proprietary name Olinvo. On March 9, 2018 the proprietary name, Olinvo, was found to be unacceptable because it may be confused with the currently marketed proprietary name, [redacted] (b) (4) The labels and labeling that were evaluated for this review contain the proprietary name Olinvo, because the proprietary name was found to be unacceptable after the labels and labeling were submitted by Trevena, Inc.

2.2 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
ISMP Newsletters	C – N/A
FDA Adverse Event Reporting System (FAERS)*	D – N/A
Other	E – N/A
Labels and Labeling	F

N/A=not applicable for this review

*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 FINDINGS AND RECOMMENDATIONS

Tables 2 and 3 below include the identified medication error issues with the submitted packaging, label and labeling, DMEPA's rationale for concern, and the proposed recommendation to minimize the risk for medication error.

Table 2: Identified Issues and Recommendations for Division of Anesthesia, Analgesia and Addiction Products

Prescribing Information			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
General Issues			
1.	We note that the proprietary name (b) (4) is included throughout the Prescribing Information.	(b) (4)	Revise all references to "(b) (4) and replace with the placeholder "TRADENAME" until a proprietary name is found conditionally acceptable and can be added.
2.	In the Dosage and Administration sections of the Highlights of Prescribing Information (HPI) and Full Prescribing Information (FPI), the lower dosages of the dose ranges are not followed by a unit of measurement.	Confusion may occur if the unit of measurement for each dose is not explicitly expressed.	Add a unit of measurement after each number used to express dose to minimize the risk for confusion. Revise the dosage statement in the Dosage and Administration sections of the HPI and FPI by adding the unit of measurement, "mg", after each number. For example, change, "1 to 3 mg" to read, "1 mg to 3 mg".
Full Prescribing Information			
1.	In the How Supplied Section 16 of the FPI, the National Drug Code (NDC) for the container label has the same package code portion as the NDC for the carton for all the product strengths. For example, for the 1 mg/mL product strength the NDC is 71308-011-**10** for both	The package code portion of the NDC on the container and carton are usually different if the quantity within the carton differs from the quantity within the container. During distribution, dispensing and administration the NDC is often used to confirm a drug product.	We have provided a recommendation in Table 3 below for the Applicant to revise the NDC's so that the package codes are different for each container label and its corresponding carton labeling.

	the container label and carton labeling.		

Table 3: Identified Issues and Recommendations for Trevena (entire table to be conveyed to Applicant)

Container Label and Carton Labeling			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
1.	The proprietary name, "(b) (4) is included on the container label and carton labeling.	We reference our March 9, 2018 letter informing you that the proprietary name, "(b) (4) was found unacceptable.	Please remove all references to "(b) (4) If you intend to have a proprietary name for your product, you could include a placeholder, such as, "TRADENAME" until a proprietary name is found conditionally acceptable. Thereafter, you can add the conditionally acceptable name to the label and labeling and submit for our review.
2.	The container label has the same package code portion of the National Drug Code (NDC) as the carton for all the product strengths. For example, for the 1 mg/1 mL product strength the NDC is 71308-011-**10** for both the container label and carton labeling.	The package code portion of the NDC on the container and carton are usually different if the quantity within the carton is greater than one unit (i.e., 1 vial). During distribution, dispensing and administration the NDC is often used to confirm a drug product.	Revise the NDC's for the carton labeling for each strength so that the package code for each carton labeling is different from its corresponding container label.
3.	On all container labels and carton labeling the statement "Discard unused portion" is located several lines away from the	There is a risk that the user may be unaware that there may be overfill in each vial that should be discarded after a single dose. Failure to discard this unused	Revise each container label and carton labeling so that the statement "Discard unused portion" appears directly after the statement "Single dose vial" to minimize

	statement "Single-dose vial".	portion could result in an overdose.	the risk of the entire contents of the vial being given as a single dose. For example: "Single Dose Vial. Discard unused portion."
4.	All container labels and carton labeling contain the statement (b) (4)	Post-marketing reports have shown that negative statements may have the opposite of the intended meaning because the word (b) (4) can be overlooked and misinterpret the warning as an affirmative action[a]. Warning statements should be written in affirmative language.	On container labels and carton labeling, revise the statement (b) (4) to read, "Protect from freezing."
5.	The format of the expiration date has not been defined on the container labels or carton labeling.	Expiration dates have been misinterpreted and led to deteriorated drug medication errors based on confusing formats.	As currently presented, the format for the expiration date is not defined. To minimize confusion and reduce the risk for deteriorating drug medication errors, identify the format you intend to use. We recommend using a format like either DDMMMYYYY (e.g., 31JAN2013) MMMYYYY (e.g., JAN2013) YYYY-MM-DD (e.g., 2013-JAN-31) YYYY-MM-DD (e.g., 2013-01-31)
6.	For the 1 mg/1 mL container label and	Since the total product strength per volume is the	Remove the concentration per mL (1 mg/mL) statement

[a] Institute for Safe Medication Practices. Affirmative warnings (do this) may be better understood than negative warnings (do not do that". ISMP Med Saf Alert Acute Care. 2010;15(16):1-2.

	carton labeling the product strength (1 mg/1 mL) is displayed as well as the concentration per mL (1 mg/mL).	same as the concentration per mL (1 mg/mL), the concentration per mL is not necessary.	from the container label and carton labeling.
Container Label			
1.	The abbreviation "IV" is used to represent "intravenous" in the statement "FOR IV USE ONLY" on the 1 mg/1 mL and 2 mg/2 mL container labels.	The use of abbreviations can potentially lead to prescribing or administration errors.	Revise the statement (b) (4) (b) (4) to "FOR INTRAVENOUS USE ONLY" OR "FOR INTRAVENOUS USE". To accommodate this change, consider relocating the "Sterile" and "Rx only" statements.
2.	On the 2 mg/2 mL container label, the concentration per mL statement (1 mg/mL) is located two lines away from the strength per total volume statement (2 mg/2 mL).	The concentration per mL should follow the strength per total volume in close proximity.	Revise the 2 mg/2 mL label so that concentration per mL, "1 mg/mL", is enclosed by parentheses and is located directly after the strength per total volume, "2 mg/2 mL". Ensure that "2 mg/2 mL" is still more prominent than the concentration per mL. For example: **2 mg/2 mL** (1mg/mL) OR **2 mg/2 mL** (1 mg/ml).
3.	The 30 mg/30 mL container label contains the warning statement: "WARNINGS: MAY BE HABIT FORMING. MAY BE HARMFUL IF GIVEN TO SOMEONE FOR WHOM IT WAS NOT PRESCRIBED."	The warning statement on the 30 mg/30 mL label is not a required statement and is not consistent with the 1 mg/1 mL and 2 mg/2 mL container labels which do not have the warning statement.	To maintain consistency with the 1 mg/1 mL and 2 mg/2 mL container labels and because this information is present on the carton labeling, consider removing the warning statement from the 30 mg/30 mL container label.

4 CONCLUSION

DMEPA's evaluation of the proposed packaging, label and labeling identified areas of vulnerability that may lead to medication errors. We have provided recommendations in Table 2 above for the Division. We also have provided recommendations in Table 3 above and ask that the Division conveys the entire table to the Applicant so that recommendations are implemented prior to approval of this NDA.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for oliceridine that Trevena, Inc. submitted on 11/2/2017 and 3/5/2018.

Table 4. Relevant Product Information for oliceridine	
Initial Approval Date	N/A
Active Ingredient	oliceridine
Indication	Management of moderate to severe acute pain in adult patients for whom an intravenous opioid is warranted
Route of Administration	intravenous
Dosage Form	injection
Strength	1 mg/mL
Dose and Frequency	initial dose of 1 mg to 3 mg with subsequent doses given every 10 minutes as needed based on patient need; maintenance doses of 1 mg to 3 mg every 1 to 3 hours as needed or as patient-controlled analgesia (PCA) demand doses of 0.1 mg to 0.5 mg as needed
How Supplied	available as 1 mg/mL in a 2 mL glass vial; 2 mg/2 mL in 2 mL glass vial; 30 mg /30 mL in 30 mL glass vial
Storage	room temperature; do not freeze; protect from light
Container Closure	1 mg /1 mL vials: carton of 10 vials 2 mg/ 2 mL vials: carton of 10 vials 30 mg/30 mL vials: carton of 10 vials

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On 4/2/2018, we searched the L:drive and AIMS using the terms, Olinvo and oliceridine to identify reviews previously performed by DMEPA.

B.2 Results

Our search did not identify any previous reviews that were applicable to this review.

APPENDIX C.: N/A

APPENDIX D.: N/A

APPENDIX E.: N/A

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,[b] along with postmarket medication error data, we reviewed the following oliceridine labels and labeling submitted by Trevena, Inc.

- Container label (submitted on 11/2/2017)
- Carton labeling (submitted on 11/2/2017)
- Prescribing Information (Image not shown) (submitted on 3/5/2018)

F.2 Label and Labeling Images

(b) (4)

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

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

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/s/

CAMERON D JOHNSON
05/23/2018

OTTO L TOWNSEND
05/23/2018

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: March 8, 2018

From: CDER DCRP QT Interdisciplinary Review Team

Through: Christine Garnett, Pharm.D.
Clinical Analyst
Division of Cardiovascular and Renal Products /CDER

To: Shelly Kapoor, RPM
DAAAP

Subject: QT-IRT Consult to NDA 210730

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 11/27/2017 regarding a request to review ECG data from study CP130-008. The QT-IRT reviewed the following materials:

- Previous QT-IRT review under IND 113537 dated 02/08/2016 in DARRTS;
- Study report for APOLLO-1 (CP130-3001) submitted to NDA 210730 under sequence 0001 dated 10/31/2017;
- Study report for APOLLO-2 (CP130-3002) submitted to NDA 210730 under sequence 0001 dated 10/31/2017;
- Study report for CP130-1007 submitted to NDA 210730 under sequence 0001 dated 11/1/2017;
- Annotated labeling submitted to NDA 210730 under sequence 0001 dated 10/31/2017;
- Clinical overview submitted to NDA 210730 under sequence 0001 dated 11/2/2017; and
- Nonclinical overview submitted to NDA 210730 under sequence 0001 dated 11/2/2017.

1. QT-IRT Responses

Question: We are requesting QT-IRT assist in reviewing this new NDA for oliceridine (NDA 210730). Please review Study CP130-1008 and others as necessary and provide any comments to the Division.

QT-IRT's response: We previously reviewed CP130-1008 (DARRTS 02/08/2016) and concluded that oliceridine prolongs the QTcF interval in a dose-dependent manner with a delayed onset (3 mg: 6.8 ms [upper 90% CI: 8.9 ms]; 6 mg: 11.6 ms [13.7 ms]). The delayed onset of QTcF prolongation suggests that the QTcF prolongation is not mediated via direct inhibition of the hERG potassium channel by oliceridine, consistent with the sponsor's *in vitro* pharmacology safety studies. Alternative explanations to the delayed onset include: (1) a hERG active metabolite of oliceridine, (2) inhibition of hERG potassium channel trafficking or (3) a non-hERG mediated mechanism. Given that oliceridine undergoes extensive metabolism and that the time of maximum effect is like that of total radioactivity in blood, it is possible that the QTcF effect observed could be due to inhibition of hERG by a metabolite of oliceridine, however, given the available data no definitive conclusions can be drawn concerning the mechanism of the observed QTcF prolongation.

Because of the observed delayed onset of QTcF prolongation in the thorough QT study, the QT-IRT recommended additional ECG collection in patients to characterize the QTcF prolongation in patients. However, only limited ECG monitoring was obtained in patients (1 and 24 h post-loading dose) and it is not known if the timing of ECG collection is adequate.

Thus, the risk for QTcF prolongation with oliceridine remains unknown and we are proposing edits to the labeling to more appropriately reflect the findings of the thorough QT study. In addition, we are recommending to avoid use in patients receiving other QT prolonging medication.

Proposed labeling

The sponsor included the following language in the proposed label:

12.2 Pharmacodynamics

(b) (4)

[redacted]

The following is QT-IRT's proposed labeling language, which is a suggestion only. We defer final labeling decisions to the Division.

5.x QT Prolongation

(b) (4)

12.2 Pharmacodynamics

Cardiac Electrophysiology

(b) (4)

2. BACKGROUND

Product Information

Oliceridine (TRV130) is a G protein-biased ligand at the μ-opioid receptor (MOR) and is developed for the management of moderate to severe acute pain in adult patients for whom an intravenous (IV) opioid is warranted.

The sponsor is proposing an initial dose of oliceridine of 1 to 3 mg followed by 1 to 3 mg as needed on a 1 to 3 h interval or patient-controlled analgesia demand doses of 0.1 to 0.5 mg as needed.

Preclinical cardiac safety

Potential effects of oliceridine on the cardiovascular system were evaluated in a GLP in vitro hERG assay, an ex vivo rabbit left ventricular wedge preparation and a GLP in vivo monkey cardiovascular safety study. The IC50 for oliceridine in the hERG assay (Study No. 110520.USF) was 2.2 μM, approximately 367-fold higher than the predicted therapeutic protein free plasma concentration (2.3 ng/mL or 6 nM). In the rabbit wedge preparation (Study No. LIMRRWMU04), oliceridine did not cause any proarrhythmic events and had a composite torsadogenic risk score (TdP score) of zero or negative when tested up to 30 μM.

Reviewer's Comment: The sponsor has only evaluated the potential for inhibition of the hERG potassium channel current of the parent and not for any of the metabolites.

Clinical cardiac safety

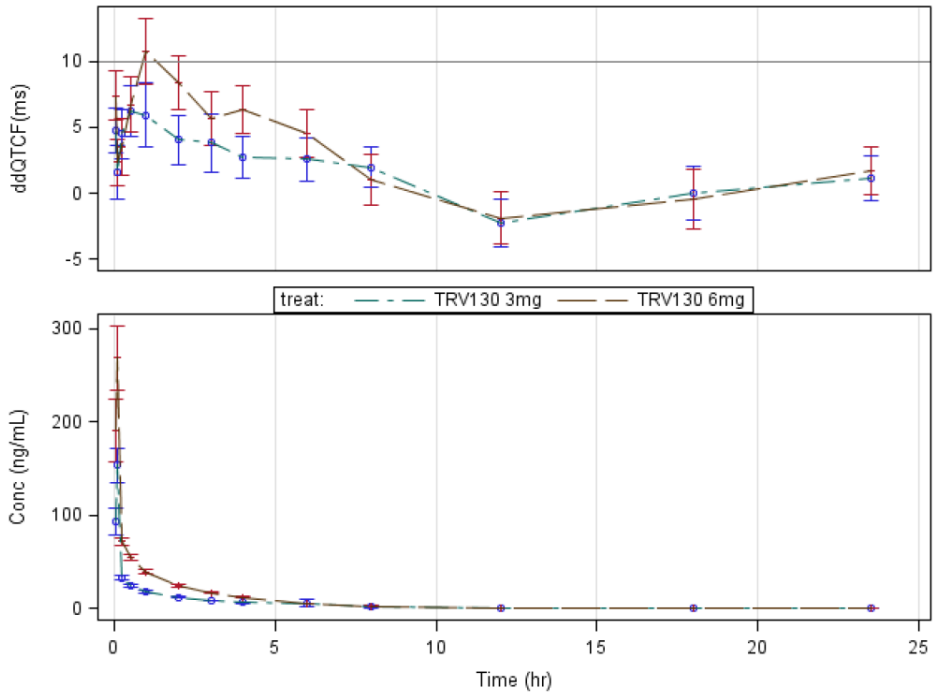
The sponsor has conducted a thorough QT study (CP130-1008) and collected ECGs in two phase 3 trials (APOLLO-1 and APOLLO-2).

Thorough QT study

We have previously reviewed the thorough QT study (CP130-1008) and concluded that oliceridine is a QTcF prolonger (DARRTS 02/08/2016). In our review, we also noted that the observed QTcF prolongation was dose-dependent and occurred after peak oliceridine plasma concentration (Figure 1). Because of the observed QTcF prolongation we proposed ECG monitoring, monitoring of electrolytes as well as discontinuation criteria based on ECGs. It was

also proposed that the timing of ECG monitoring should consider the delayed onset of the QTcF effect.

Figure 1: ΔΔQTcF time-course (top) and oliceridine PK time-course (bottom)



Source: QT-IRT review under IND 113537 dated 02/08/2016

APOLLO-1 and APOLLO-2

The two phase 3 trials (APOLLO-1 and APOLLO-2) were multi-center, randomized, double-blind, placebo and active-controlled studies with three oliceridine arms, placebo and morphine. The oliceridine arms all had the same loading dose of 1.5 mg and 0.1, 0.35 or 0.5 mg as demand doses or 0.75 mg q1h as a supplemental dose. ECGs were collected in both studies at baseline and at 1 and 24 h post-loading dose. In APOLLO-1 and ECG was also collected 48 h post-loading dose. However, as noted in the response it is uncertain if the timing of ECG collection is adequate.

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

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/s/

LARS JOHANNESEN
03/08/2018

CHRISTINE E GARNETT
03/08/2018