CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210730Orig1s000

PRODUCT QUALITY REVIEW(S)

Table of Contents

U.S. FOOD & DRUG ADMINISTRATION

RECOMMENDATION

☒ Approval
☐ Approval with Post-Marketing Commitment
☐ Complete Response

NDA 210730
Assessment 2

Drug Product Name	Oliceridine injection
Dosage Form	Intravenous injection
Strength	1 mg/mL (in 1 mL, 2 mL and 30 mL vials)
Route of Administration	Intravenous injection
Rx/OTC Dispensed	Rx
Applicant	Trevena, Inc.
US agent, if applicable	N/A

Submission(s) Assessed	Document Date	Discipline(s) Affected
Supporting document 46; eCTD 0047	7 Feb 20	Resubmission; drug product, drug substance, facilities
Supporting document 48; eCTD 0049	10 Mar 20	Facilities
Supporting document 56; eCTD 0057	15 Jun 20	Drug product

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance	Sukhamaya (Sam) Bain	Donna Christner
Drug Product	Eric Bow	Julia Pinto
Manufacturing	Cassandra Abellard	Frank Wackes
Microbiology	Denise Miller	Bryan Riley
Biopharmaceutics	N/A	N/A
Regulatory Business Process Manager	Anika Lalmansingh	
Application Technical Lead	Valerie Amspacher	
Laboratory (OTR)	N/A	N/A
Environmental	N/A	N/A

EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

Drug substance, drug product, process/facilities and microbiology all recommend approval.
Based upon review of the stability data provided, the proposed shelf-life of 48 months is acceptable for all product presentations.

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

This NDA was originally submitted 2 Nov 2017. A complete response was sent 2 Nov 2018 with one CMC deficiency. The application was resubmitted on 7 Feb 20.

Oliceridine injection, 1 mg/mL is a clear, colorless, sterile, preservative-free solution, supplied in a glass vial for intravenous administration in three product presentations, including 1 mL of solution in a 2 mL single-dose vial, 2 mL of solution in a 2 mL single-dose vial, and 30 mL of solution in a 30 mL single-dose vial.
The drug product formulation, and therefore the resultant solution concentration of 1 mg/mL, as well as the manufacturing unit operations and the materials of construction of the primary packaging, are consistent across all presentations.
Based upon review of the stability data provided, the proposed shelf-life of 48 months is acceptable for all product presentations.

Proposed Indication(s) including Intended Patient Population	Management of moderate to severe acute pain in adult patients for whom an intravenous (IV) opioid is warranted
Duration of Treatment	Acute
Maximum Daily Dose	40 mg
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

Drug Substance: Adequate

The resubmission does not change the drug substance CMC, except for updating the stability data. We also note that the resubmission does not involve any change in the drug substance manufacturing and testing facilities.
The updated stability data on the drug substance are satisfactory and support the revised retest period of (b) (4) months.

Drug Product: Adequate

The applicant has provided adequate additional leachables data and method verification to resolve the deficiency. The applicant has provided adequate evidence to support the drug product stability through 36 months. The proposed shelf-life of 48 months is acceptable given the trends in the stability data and statistical analysis provided by the applicant.

Labeling: Adequate

Manufacturing: Adequate

Process and Facilities were found to be adequate for NDA 210730-Orig-1. This was documented in separate templates for the Process and Facility IQA templates prior to the integrated review of these disciplines. Following assessment of the Resubmission, OPMA noted the following changes to the Facility Discipline:
1) (b) (4) has been Withdrawn. This site was for the storage of stability samples and was previously adequate.
2) (b) (4) has been Withdrawn. This site was listed for release testing of excipients and was therefore NEN (No Evaluation Necessary).
These changes do not impact the original Approve recommendation for the application, Furthermore, there are no status changes to any of the facilities listed in the Original submission and no further changes (additions/ deletions) of facilities listed per Resub-46.

Biopharmaceutics: Choose an item.

N/A

Microbiology (if applicable): Adequate

Resub 46 is a complete response addressing the deficiencies listed in the CR letter. There was no new information submitted affecting the (b) (4) manufacturing process in the response and the original DMA review remains applicable with an approve recommendation.

Screenshot of Panorama taken 10 Jul 20 showing approval of facilities

QUALITY ASSESSMENT DATA SHEET

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	III	(b) (4)		4		
	III			4		
	III			4		

Action codes for DMF Table:
1 – DMF Reviewed.
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

B. OTHER DOCUMENTS: *IND, RLD, RS, Approved NDA*

Document	Application Number	Description
IND	113537	

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics				
Pharmacology/Toxicology				
CDRH-ODE				
CDRH-OC				
Clinical				
Other				

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

CHAPTER IV: LABELING

IQA NDA Assessment Guide Reference

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information:

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	Yes	
Established name(s)	Yes	
Route(s) of administration	Yes	
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	Yes	
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	n/a	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	Yes	

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	n/a	

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Yes	
Strength(s) in metric system	Yes	
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance		
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	n/a	
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	n/a	
For injectable drug products for parental administration, use appropriate labeling term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	No	Should include "single-dose"

1.2.3 Section 11 (DESCRIPTION)

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	Yes	
Dosage form(s) and route(s) of administration	Yes	
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.		
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	Yes	
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	n/a	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	n/a	
Statement of being sterile (if applicable)	Yes	
Pharmacological/ therapeutic class	No	Needs mention of opioid agonist class
Chemical name, structural formula, molecular weight	Yes	
If radioactive, statement of important nuclear characteristics.	n/a	
Other important chemical or physical properties (such as pKa or pH)	No	Needs pH

Section 11 (DESCRIPTION) Continued

Item	Information Provided in the NDA	Assessor's Comments
For oral prescription drug products, include gluten statement if applicable	n/a	
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity"	n/a	

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

Item	Information Provided in the NDA	Assessor's Comments
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	Yes	
Strength(s) in metric system	Yes	
Available units (e.g., bottles of 100 tablets)	Yes	
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Yes	
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	n/a	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	Yes	

Section 16 (HOW SUPPLIED/STORAGE AND HANDLING) (Continued)

Item	Information Provided in the NDA	Assessor's Comments
Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g. to protect from light or moisture, to maintain stability, etc.)	Yes	
If the product contains a desiccant, ensure the size and shape differ from the dosage form and desiccant has a warning such as "Do not eat."	n/a	
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Yes	
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: "Not made with natural rubber latex. Avoid statements such as "latex-free."	n/a	
Include information about child-resistant packaging	n/a	

1.2.5 Other Sections of Labeling

There may be other sections of labeling that contain product-quality related information. For example, there are specific required/recommended warnings for certain inactive ingredients [e.g., aspartame, aluminum in large and small volume parenterals, sulfites, FD&C Yellow Number 5 (tartrazine), and benzyl alcohol]. Please notify the prescription drug division if the product contains any of these inactive ingredients.

Please include your comments about other sections of labeling if they contain product quality information.

1.2.6 Manufacturing Information After Section 17 (for drug products)

Item	Information Provided in the NDA	Assessor's Comments
Manufacturing Information After Section 17		
Name and location of business (street address, city, state and zip code) of the manufacturer, distributor, and/or packer	Yes	

2.0 PATIENT LABELING

Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guide, Patient Information, Instructions for Use):

Any deficiencies should be listed at the end in the "ITEMS FOR ADDITIONAL ASSESSMENT."

3.0 CARTON AND CONTAINER LABELING

3.1 Container Label

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

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Proprietary name, established name, and dosage form (font size and prominence	Yes	
Dosage strength	Yes	
Route of administration	Yes	
If the active ingredient is a salt, include the equivalency statement per FDA Guidance		
Net contents (e.g. tablet count)	Yes	
"Rx only" displayed on the principal display	Yes	
NDC number	Yes	
Lot number and expiration date	Yes	
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	Yes	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	Yes	
Other package terms include pharmacy bulk package and imaging bulk package which require "Not for direct infusion" statement.	n/a	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	n/a	
Bar code	Yes	

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Name of manufacturer/distributor	Yes	
Medication Guide (if applicable)	Yes	
No text on Ferrule and Cap overseal	Yes	
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	n/a	
And others, if space is available		

Assessment of Carton and Container Labeling: *{Adequate }*

Any deficiencies should be listed at the end in the "ITEMS FOR ADDITIONAL ASSESSMENT."

ITEMS FOR ADDITIONAL ASSESSMENT

Overall Assessment and Recommendation:

Primary Labeling Assessor Name and Date: Eric Bow

Secondary Assessor Name and Date (and Secondary Summary, as needed): Julia Pinto

Eric Bow

Digitally signed by Eric Bow
Date: 7/07/2020 01:17:47PM
GUID: 5df160d800320e19970e198e30e1cc2e

Julia Pinto

Digitally signed by Julia Pinto
Date: 7/07/2020 02:21:27PM
GUID: 5050dbcb00001294a888a4bdc20a3a58

M E M O R A N D U M

DATE: 20 May 2020

TO: NDA 210-730

FROM: Denise Miller
Sr. Microbiologist, OPMA/DMA Branch 5

THROUGH: Bryan Riley Ph.D.
Branch Chief, OPMA/DMA Branch 5

SUBJECT: Complete Response to NDA 210-730 (Resub 46)
Sponsor: Trevena
Product: Oliceridine

The original application was reviewed by the Division of Microbiological Assessment which was completed on 08/29/2018 with a recommendation for approval; there were no DMA deficiencies identified. The sponsor received a Complete Response on 02 November 2018 for deficiencies from other disciplines.

Note: Two manufacturing sites were originally proposed for Oliceridine and both were acceptable. (b) (4) manufacturing information was provided in DMF (b) (4) and was acceptable (DMA review D (b) (4) M07R01.docx dated 07/30/2018). There were no manufacturing changes submitted to DMF (b) (4) since the 07/30/2018 review and the DMF remains acceptable. The second proposed manufacturing site, (b) (4) has been withdrawn.

Resub 46 is a complete response addressing the deficiencies listed in the CR letter. **There was no new information submitted affecting the** (b) (4) **manufacturing process in the response and the original DMA review remains applicable with an approve recommendation.**

END

Denise Miller

Digitally signed by Denise Miller
Date: 5/20/2020 06:45:53AM
GUID: 508da7280002a5d546459b998253d1aa

Bryan Riley

Digitally signed by Bryan Riley
Date: 5/20/2020 08:36:01AM
GUID: 503450f200004f5816a1d3ae902b5e91

CDER/ OPMA/ DPMIV

DATE: March 11, 2020

FROM: Cassandra Abellard, CSO, OPMA/ DPMIV/B11

SUBJECT: NDA-210730-ORIG-1-RESUB-46

THROUGH: Frank Wackes, QAL, OPMA/ DPMIV/B11

TO: Anika Lalmansingh, RBPM
Valerie Amspacher, ATL

The Office of Pharmaceutical Manufacturing Assessment (OPMA) has completed their assessment of the Resubmission for NDA 210730 (Resub-46).

Process and Facilities were found to be adequate for NDA 210730-Orig-1. This was documented in separate templates for the Process and Facility IQA templates prior to the integrated review of these disciplines. Following assessment of the Resubmission, OPMA noted the following changes to the Facility Discipline:

1) (b) (4) has been Withdrawn. This site was for the storage of stability samples and was previously adequate.
2) (b) (4) has been Withdrawn. This site was listed for release testing of excipients and was therefore NEN (No Evaluation Necessary).

These changes do not impact the original Approve recommendation for the application, Furthermore, there are no status changes to any of the facilities listed in the Original submission and no further changes (additions/ deletions) of facilities listed per Resub-46.

Sincerely,

CDER/OPQ/OPMA/ DPMIV-B11

U.S. Food and Drug Administration
CDER Office of Pharmaceutical Quality
Office of Pharmaceutical Manufacturing Assessment
10903 New Hampshire Avenue
Silver Spring, MD 20903
www.fda.gov

Cassandra Abellard

Digitally signed by Cassandra Abellard
Date: 3/13/2020 01:15:48PM
GUID: 564f42da0022c9f20052124ea8956e48

Frank Wackes

Digitally signed by Frank Wackes
Date: 3/13/2020 01:22:47PM
GUID: 53b5aba70000559b0ef1af4e030aa45a

Recommendation: Complete Response

NDA 210730
Review # 1

Drug Name/Dosage Form	Olinvo® (Oliceridine) injection
Strength	1mg/ml
Route of Administration	Injection
Rx/OTC Dispensed	Rx
Applicant	Trevena, Inc.
US agent, if applicable	

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Submission Type	Submission Date/SD Number	Location
Original NDA	02-NOV-2017/SD_01	DARRTS/EDR
Amendment*	11-DEC-2017/SD_03	DARRTS/EDR
Amendment**	13-DEC-2017/SD_04	DARRTS/EDR
Amendment	27-FEB-2018/ SD_09	DARRTS/EDR
Amendment	Feb 5, 2018 SD_7	DARRTS/EDR
Amendment	March 7 2018/ SD 12	DARRTS/EDR
Amendment	March 30, 2018 SD_13	DARRTS/EDR
Amendment	June 1, 2018 SD_20	DARRTS/EDR
Amendment	July 20 2018 SD_29	DARRTS/EDR
Amendment	July 30 2018 SD_30	DARRTS/EDR
Amendment	Oct 2018	DARRTS/EDR

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Sam Bain	OPQ/ONDP/DNDPAPI/BII
Drug Product	Xinghua Wu	OPQ/ONDP/DNDPII/BIV
Process	Cassandra Abellard	OPQ/OPF/DPAII/BVI
Microbiology	Denise Miller	OPQ/OPF/DMA/BI
Facility	Cassandra Abellard/Christina Capacci-Daniel	OPQ/OPF/DIA/BII CDRH/OC
Biopharmaceutics	Peng Duan/Kelly Kitchens	OPQ/ONDP/DB/BII
Regulatory Business Process Manager	Steven Kinsley	OPQ/OPRO/RBPMI/BI
Application Technical Lead	Julia Pinto	OPQ/ONDP/DNDPII/BIV
Laboratory (OTR)	St. Louis Labs	
ORA Lead	N/A	
Environmental Analysis (EA)	Raanan Bloom	OPQ/ONDP/DNDPII/BIV

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	III		(b) (4)	4		Currently in use in approved products
	V			4		
	V			4		

B. Other Documents: *NONE*

2. CONSULTS: NONE

Executive Summary

I. Recommendations and Conclusion on Approvability

Adequate data is provided to ensure the identity, quality and purity of the drug substance and drug product manufactured as described in this NDA. Drug substance, process, facilities, microbiology and biopharmaceutic teams recommend approval. However, the HPLC method validation for detection of leachables in the drug product is a deficiency not currently resolved. Therefore the overall CMC recommendation is a Complete Response.

II. Summary of Quality Assessments

A. Product Overview

Proposed Indication(s) including Intended Patient Population	Management of moderate to severe acute pain in adult patients for whom an intravenous opioid is warranted
Duration of Treatment	
Maximum Daily Dose	
Alternative Methods of Administration	None

B. Quality Assessment Overview

OLINVO injection is a clear, colorless, sterile, preservative-free solution stored in a glass vial for intravenous use. OLINVO is manufactured in a single strength of 1 mg/mL, containing 1.0 mg of oliceridine free base (1.3 mg of oliceridine fumarate salt), as well as L-histidine and mannitol, in water for injection. OLINVO injection solution is provided with three presentations, 1 mL in a 2-mL vial, 2 mL in a 2-mL vial and 30 mL in a 30-mL vial.

The drug product is filled in a clear USP Type (b) (4) glass vial plugged with a (b) (4) (b) (4) rubber stopper and sealed by an aluminum seal with a flip-off cap. The 13-mm gray cap is used for 1-mL fill, the 13-mm orange cap is for 2-mL fill and the 20-mm purple cap is for 30-mL fill. Sufficient stability data is provided to support the proposed and granted expiry of 24 months for the product stored in vials 25 °C/60% RH.

The analytical methods used for release and stability testing are well described and validated for the intended uses. Method verification is being carried out by the (b) (4) labs. The HPLC method used to detect leachables in the drug product has not been

adequately validated. Therefore a leachable assessment of the container closure system could be not be determined.

Microbiology and Biopharmaceutics review of the drug product also recommend approval.

The drug substance, Oliceridine fumarate, as a new molecular entity, and is manufactured (b) (4)

Drug substance and drug product facilities have been inspected. The (b) (4) included in the NDA filing, and recommended as inadequate by the Office of Facilities, has been withdrawn from the NDA by the Sponsor. The remaining manufacturing facilities for the drug substance and drug product are adequate.

This NDA is recommended as Complete Response.

Application Technical Lead Signature:

Julia C. Pinto, Ph.D.
Branch Chief(Acting)
ONDP/Division II/Branch IV

NDA 210730
Table of Contents

115 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

BIOPHARMACEUTICS

Product Background:

NDA: 210730

Drug Product Name / Strength: Oliceridine 1 mg/mL

Indication: For the management of moderate to severe acute pain in patients 18 years of age or older for whom an IV opioid is warranted.

Route of Administration: Injection

Applicant Name: Trevena, Inc.

Review Summary:

The proposed drug product is an intravenous injection. There is no dissolution data submitted. During the drug development program, the Applicant first developed HCL salt of oliceridine (TRV130A), which was used in IND and early phase of clinical studies. Later, due to difficulty in scalable for later clinical development, the Applicant developed a formulation with the fumarate salt of oliceridine (TRV130), which was used in later Phase 1 and Phase 3 studies. The Biopharmaceutics review focused on the evaluation of formulation bridging between TRV130A and TRV130. The Applicant submitted solubility data to support that the difference in excipients and different salt forms of oliceridine would not affect the solubility of drug product. From Biopharmaceutics perspective, the difference in excipients and different salt forms of API unlikely affect the solubility of drug product and unlikely would result in any precipitation. Furthermore, by compared AUC of TRV130A in Study CP130-1001 and AUC of TRV130 in Study CP130-1002, the dose corrected AUC_{0-t} and AUC_{0-inf} was similar, suggesting that the difference in formulations unlikely affected the drug absorption.

Overall, from Biopharmaceutics perspective, formulation TRV130A and TRV130 was appropriately bridged, and we recommend the approval of NDA 210730.

Dissolution Method and Acceptance Criteria

Reviewer's Assessment: N/A

{Assess method development, method robustness, and criteria; modeling approach}

The proposed drug product is an intravenous (IV) injection (1 mg/mL provided in 1 mL, 2mL, and 30 mL fill volume) indicated for the management of moderate to severe acute pain in patients 18 years of age or older for whom an IV opioid is warranted. Dissolution review is not needed.

Bridging of Formulations

Reviewer's Assessment: Adequate

An early formulation TRV130A was developed and used in early clinical studies (Table 1). Compared to the be-marketed formulation TRV130, which was used in all Phase 3 studies, the formulations were different in the API (different salt form Hydrochloride in TRV130A vs. Fumarate in TRV130) and the excipients ((b) (4) in TRV130A vs. L-histidine and mannitol in TRV130 was different).

Table 1: Comparison of TRV130 A and TRV130 Drug Products

Ingredient	Amount	Units	Primary Function	(Associated Batch Number(s)) in which the Oliceridine HCl Formulation was Used
Oliceridine hydrochloride salt ⇔ Oliceridine free base	(b) (4)	mg/mL	Active ingredient	**Phase 1** - CP130-1001 (P05311) - CP130-1002 (P06412) - CP130-1003 (P06412) - CP130-1004 (P06412) - CP130-1005 (P06412) - CP130-1006 (P06412) **Phase 2** - CP130-2001 (P06813, P06913)
		(b) (4)	(b) (4)	

Ingredient	Amount	Units	Primary Function	Number(s)) in which the Oliceridine Fumarate Formulation was Used
Oliceridine fumarate salt ⇔ Oliceridine free base	1.3 (salt) ⇔ 1.0 (free base)	mg/mL	Active ingredient	**Phase 1** - CP130-1007 (P06814) - CP130-1008 (P06814) - CP130-1010 (P03115) - CP130-1011 (B150620) - CP130-1012 (B150620) **Phase 2** - CP130-2002 (P06814) **Phase 3** - CP130-3001 / APOLLO 1 (B150620) - CP130-3002 / APOLLO 2 (B150620) - CP130-3003 /ATHENA (B150417, B160121, B160285, B160286, B160287, B160288, B160289, B160290, B160636)
L-histidine, USP	(b) (4)			
Mannitol, USP				
Water for Injection, USP	q.s. to batch volume			
NOTE: This same oliceridine fumarate drug product formulation was also used for all primary (registration) stability batches and is the intended commercial formulation				

1. Impact of formulation difference on solubility of API

Although the proposed drug product is a clear, colorless solution for IV administration and it is immediately systemic available, the difference in the salt form of API might affect its solubility and subsequently affect its bioavailability due to precipitation.

Aqueous solubility of oliceridine fumarate was assessed across a pH range of 5.0 to 8.8 in an (b) (4) As the solubility shown in Table 2, the solubility of oliceridine fumarate is high.

Table 2: Oliceridine Fumarate pH Solubility in Aqueous Organic Buffer Systems

pH	Solubility (mg/mL)
4.98	125.5
5.48	185.2
5.86	182.6
7.57	128.3
8.06	18.2
8.77	3.8

The Applicant also evaluated the potential impact of different (b) (4) in two formulations on solubility of oliceridine fumarate (Table 3). As seen in Table 3, the change of (b) (4) in TRV130A to L-histidine in TRV130 would not result in precipitation of oliceridine fumarate.

Table 3. **Oliceridine Fumarate Solubility in Different (b) (4) at pH (b) (4) (the pH of the proposed drug product is 6.4-7.4)**

(b) (4)	Solubility (mg/mL)
	130.0
	107.2
	76.2
	84.7

Similarly, the Applicant also evaluated the impact of (b) (4) mannitol on solubility of oliceridine fumarate, and as seen in Table 4, the addition of mannitol in formulation would not result in precipitation of the API.

Table 4: Oliceridine Fumarate Solubility in Different (b) (4)

(b) (4)	Solubility (mg/mL)
	82.9
	78.6
	69.1

2. PK of TRV130A and TRV130

Study CP130-1001 is a multipart, randomized, single-blind, placebo-controlled, parallel-group, single ascending dose study in healthy adult males with formulation TRV 130A. The PK parameters of TRV130A in different treatment groups were shown in Table 5.

Table 5. Summary of TRV130A PK parameters in Study CP130-1001

Part	Dose (mg)	Infusion Duration (min)	C_{max}* (ng/mL)	t_{max}** (hr)	AUC_{0-t}* (ng*h/mL)	$AUC_{0-\infty}$* (ng*h/mL)	AUC_{extr}* (%)	$t_{½}$* (h)	CL* (L/h)
A	0.15	60	1.0375 (28.32) n = 6	0.98 (0.98-1.22) n = 6	2.264 (27.33) n = 6	2.515 (28.55) n = 6	9.4948 (37.51) n = 6	1.628 (27.79) n = 6	59.63 (28.68) n = 6
	0.25	60	2.2858 (22.66) n = 5	0.98 (0.98-0.98) n = 5	5.123 (13.55) n = 5	5.292 (12.30) n = 5	2.9795 (42.61) n = 5	1.564 (12.42) n = 5	47.24 (12.21) n = 5
	0.4	60	3.5461 (21.07) n = 6	0.98 (0.98-1.17) n = 6	8.461 (12.98) n = 6	8.735 (11.56) n = 6	2.7483 (60.26) n = 6	1.721 (23.56) n = 6	45.82 (11.48) n = 6

Part	Dose (mg)	Infusion Duration (min)	C_{max} (ng/mL)	t_{max} (hr)	AUC_{0-t} (ng*h/mL)	$AUC_{0-\infty}$ (ng*h/mL)	AUC_{extr} (%)	$t_{½}$ (h)	CL (L/h)
A	0.7	60	6.4314 (18.05) n = 6	0.98 (0.98-1.08) n = 6	13.639 (14.90) n = 6	13.968 (13.97) n = 6	2.0012 (65.77) n = 6	1.773 (33.15) n = 6	50.11 (14.13) n = 6
	1.2	60	11.5285 (27.01) n = 6	0.98 (0.98-1.08) n = 6	22.536 (19.54) n = 6	22.861 (19.20) n = 6	1.3547 (39.42) n = 6	1.809 (21.38) n = 6	52.48 (19.21) n = 6
	2.2	60	28.275 (27.75) n = 6	0.99 (0.98-1.25) n = 6	52.632 (14.73) n = 6	53.037 (14.86) n = 6	0.5386 (104.00) n = 6	1.957 (40.45) n = 6	41.5 (14.83) n = 6
	4	60	47.9208 (19.12) n = 6	0.98 (0.98-1.00) n = 6	104.285 (22.82) n = 6	104.918 (23.01) n = 6	0.3455 (33.31) n = 6	1.975 (47.49) n = 6	38.15 (22.97) n = 6
	7	60	102.3563 (24.45) n = 6	0.98 (0.98-1.05) n = 6	204.405 (19.12) n = 6	205.965 (19.38) n = 6	0.2797 (176.51) n = 6	2.66 (39.03) n = 6	34 (19.55) n = 6
B	0.25	60	3.0914 (14.44) n = 4	1.03 (0.98-1.08) n = 4	10.494 (14.01) n = 4	11.145 (16.03) n = 4	5.0853 (70.68) n = 4	2.815 (24.6) n = 4	22.43 (16.24) n = 4
C	1.5	30	23.9867 (27.45) n = 6	0.505 (0.25-0.57) n = 6	35.186 (9.46) n = 6	35.506 (9.30) n = 6	0.8911 (45.94) n = 6	1.834 (17.25) n = 6	42.18 (9.25) n = 6
	1.5	15	35.4574 (30.92) n = 6	0.28 (0.20-0.28) n = 6	37.908 (13.18) n = 6	38.276 (13.10) n = 6	0.8797 (37.86) n = 6	2.235 (38.58) n = 6	39.17 (13.12) n = 6
	1.5	5	32.2802 (34.46) n = 6	0.13 (0.12-0.17) n = 6	32.535 (9.31) n = 6	32.939 (9.07) n = 6	1.1629 (42.36) n = 6	1.853 (14.97) n = 6	45.54 (9.13) n = 6
	1.5	1	34.8001 (32.77) n = 6	0.075 (0.05-0.10) n = 6	31.757 (14.26) n = 6	32.103 (14.28) n = 6	0.8968 (61.39) n = 6	1.863 (11.50) n = 6	46.73 (14.32) n = 6

Abbreviations: mg = milligram, min = minute
*Geometric Mean (Coefficient of variation for the geometric mean)
**Median (minimum - maximum)
Source: Table 14.2.1.4

A summary of the statistical assessment of dose proportionality in Part A is presented in the table below:

Study CP130-1002 was an open-label, non-randomized, 4-day single ascending dose crossover study conducted in healthy adult males and females with formulation TRV130 (2-minute infusion). The PK parameters of TRV130 in different doses were summarized in Table 6.

Table 6. Summary of Oliceridine Formulation TRV130 PK Parameters (Study CP130-1002)

Dose (mg)	C_{max} [a] (ng/mL)	t_{max} [b] (h)	AUC_{0-t} [a] (ng*h/mL)	$AUC_{0-\infty}$ [a] (ng*h/mL)	$t_{½}$ [a] (h)	CL [a] (L/h)
2.0	31.94 (39.04)	0.08 (0.08 - 0.08)	44.07 (41.28)	44.69 (41.30)	2.21 (32.03)	44.75 (41.31)
2.5	59.77 (38.09)	0.08 (0.03 - 0.08)	58.42 (41.42)	59.03 (41.44)	2.92 (47.98)	42.35 (41.44)
3.0	55.56 (12.27)	0.08 (0.03 - 0.08)	72.75 (40.39)	73.40 (40.47)	3.14 (41.54)	40.88 (40.46)
3.5	75.06 (39.62)	0.08 (0.08 - 0.08)	87.64 (42.56)	88.34 (42.73)	2.62 (45.52)	39.62 (42.74)

$AUC_{0-\infty}$=area under the plasma concentration-time curve from time 0 extrapolated to infinity; AUC_{0-t}=area under the plasma concentration-time curve from time 0 to time of last measurable plasma concentration; CL=clearance; C_{max}=maximum observed plasma concentration; GeoCV=coefficient of variation for the geometric mean; PK=pharmacokinetics; $t_{½}$=apparent terminal half-life; t_{max}=time to peak concentration

[a] Geometric Mean (GeoCV%).

[b] Median (minimum - maximum).

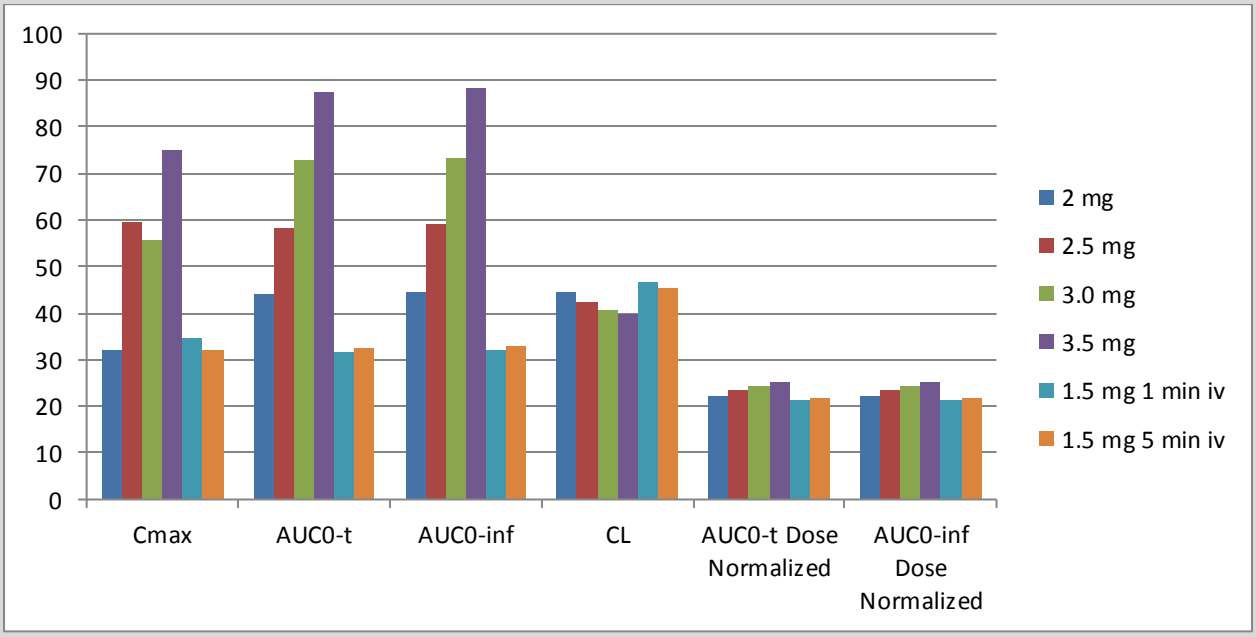
Data source: CP130-1002, CSR Table 14.2.1.3

In study CP130-1002, TRV130 was given intravenous with 2 min infusion, while the closest comparison in study CP130-1001 was 1.5 mg of TRV130 given intravenous with 1 min infusion or 5 min infusion. Figure 1 summarized the PK parameters of different strengths (2 mg, 2.5 mg, 3.0 mg, and 3.5 mg) of TRV130 and 1.5 mg of TRV130A with 1 min or 5 min intravenous infusion. As shown in Figure 1, the Cmax of 2.0 mg with 2 min infusion was in the middle of the Cmax of 1.5 mg with 1 min infusion and 1.5 mg with 5 min infusion, which was reasonable, since for injection at similar doses, Cmax was affected mostly by the diffusion time. The dose normalized AUC_{0-t} and AUC_{0-inf} of TRV130 and TRV130A were similar. Therefore, despite the formulation difference between TRV130 and TRV130A, the drug exposure of these two formulations was similar.

TRV130A was applied in the early clinical development, and TRV130 was used in later Phase 1 and Phase 3 clinical studies.

Overall, formulation TRV130A and TRV130 is appropriately bridged.

Figure 1. Comparison of PK parameters of different strengths of TRV130 (2 mg, 2.5 mg, 3.0 mg, and 3.5 mg) and TRV130A (1.5 mg with 1 min infusion and 1.5 mg with 5 min infusion)



Primary Biopharmaceutics Reviewer Name and Date: Vincent (Peng) Duan, Ph.D. 2/18/2018

Secondary Reviewer Name and Date (and Secondary Summary, as needed):
Kelly M. Kitchens, Ph.D., March 26, 2018

MICROBIOLOGY

Product Background: The drug product is an opioid product indicated for the management of moderate to severe acute pain in adults. The drug is for intravenous administration only and may be administered in doses of 1 to 3 mg every 1 to 3 hours or as patient-controlled analgesia demand doses of 0.1 to 0.5 mg as needed.

NDA: 210-730

Drug Product Name / Strength: Olinvo 1 mg/mL
Supplied at 1 mL/2mL vial, 2 mL/2mLvial, and 30 mL/30 mL vial

Route of Administration: intravenous

Applicant Name: Trevena Inc.

Manufacturing Site:

(b) (4)

Method of Sterilization: (b) (4)

Review Recommendation: Recommendation is to approve the application from a quality microbiology perspective.

Review Summary: The sponsor provided information supporting the (b) (4) manufacturing process for two manufacturing sites. The (b) (4) site's manufacturing information was referenced in the (b) (4) DMF and the (b) (4) site's manufacturing information was provided in the NDA submission. Both sites were reviewed for the (b) (4) manufacturing process and found to be adequate.

List Submissions Being Reviewed:

Submit	Received	Review Request	Assigned to Reviewer
11/02/2017	11/02/2017	N/A	11/09/2017
02/16/18	02/16/18	N/A	NA

Highlight Key Outstanding Issues from Last Cycle: NA

Remarks: NA

Concise Description Outstanding Issues Remaining: None

Supporting Documents:

DMF (b) (4) **LOA Dated 05/12/17 provided. The DMF was reviewed in support of NDA 210-730 on (insert date) and found to be acceptable.**

DMF (b) (4) **LOA dated 05/09/17 Reviewed by DMA on 02/03/17 (D** (b) (4) **M33R01.doc) Adequate.**

DMA review (b) (4) **MR01 dated 14 July 2017**

List Number of Comparability Protocols (ANDA only): NA

S Drug Substance: NA

Reviewer's Assessment: ***NA,*** Drug substance is not sterile.

P Drug Product

P.1 Description of the Composition of the Drug Product

- **Description of drug product** – Oliceridine is a clear, colorless sterile preservative-free solution supplied at 1 mg/mL. The drug product is supplied in three presentations
  - 1 mL fill in a 2 mL vial
  - 2 mL fill in a 2 mL vial
  - 30 mL fill in a 30 mL vial
- **Drug product composition** – composition table 1 below was copied from 3.2.P Oliceridine 1 mg/mL – common section 3.2.P.1**:**

Table 1: Composition of the Drug Product Dosage Form				
Ingredient	**Amount**	**Units**	**Primary Function**	**Reference to Standards**
Oliceridine fumarate salt ⇔ Oliceridine free base	1.3 (salt) ⇔ 1.0 (free base)	mg/mL	Active ingredient	Internal Monograph[a]
L-histidine	(b) (4)		(b) (4)	USP
Mannitol				USP
(b) (4)				NF
				NF
Water for Injection	q.s. to batch volume			USP
(b) (4)	(b) (4)			NF
a Proposed commercial specifications for oliceridine fumarate drug substance are provided in Section 3.2.S.4.1.				

- **Description of container closure system –**
  - Vials
    - 2mL Clear Type (b) (4) glass vials with a 13 mm neck (for the 1 and 2 mL product)
    - 30 mL Clear Type (b) (4) glass vials with a 20 mm neck(for the 30 mL product)
  - Stopper
    - 13 mm (b) (4) rubber stopper (b) (4)
    - 20 mm (b) (4) rubber stopper (b) (4)

Reviewer's Assessment: ***Adequate***

P.2 Pharmaceutical Development

P.2.5 Microbiological Attributes

Container/Closure Integrity (CCI)

The CCI was demonstrated using a dye ingress method. The method uses a 0.1% methylene blue solution for the challenge and ingress was assessed with a UV-VIS spectrophotometer to a sensitivity of 10^{-3}% dye ingress. Positive controls were included.

The testing was performed on all container presentations from both proposed manufacturers (b) (4) using the stopper and seal validated compression force limits for the two vial sizes.

30 mL presentation: (b) (4)

(b) (4)

2 mL presentation:

1 mL presentation:

Note: the 2 mL and 1 mL presentations are the same container closure – only change is in the fill volume.

Acceptance Criteria:

All test containers must show no evidence of dye ingression

The positive controls must contain detectable levels of methylene blue

All lots demonstrated passing results of no dye ingress detected for all container closures at each manufacturer.

Reviewer's Assessment: ***Adequate,*** drug product lots from both proposed manufacturers were tested by the dye ingress method. The data provided supports the initial integrity of the container closures. The long term CCI is demonstrated in the stability program.

Antimicrobial Effectiveness Testing: NA

Reviewer's Assessment: NA, Product is single use and not preserved.

P.3 Manufacture

(b) (4)

14 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

Denise Miller

Digitally signed by Denise Miller
Date: 8/28/2018 04:56:45PM
GUID: 508da7280002a5d546459b998253d1aa

Bryan Riley

Digitally signed by Bryan Riley
Date: 8/28/2018 05:44:06PM
GUID: 503450f200004f5816a1d3ae902b5e91

Julia
Pinto

Digitally signed by Julia Pinto
Date: 10/22/2018 01:20:57PM
GUID: 5050dbcb00001294a888a4bdc20a3a58