CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213189Orig1s000

PRODUCT QUALITY REVIEW(S)

U.S. FOOD & DRUG ADMINISTRATION

RECOMMENDATION

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

NDA 213189
Assessment # 1

Drug Product Name	KLISYRI
Dosage Form	Ointment
Strength	1%
Route of Administration	Topical
Rx/OTC Dispensed	Rx
Applicant	Athenex, Inc.
US agent, if applicable	N/A

Submission(s) Assessed	Document Date	Discipline(s) Affected
Original Submission	12/30/2019	All
Proprietary Name Request	01/28/2020	All
Multiple Categories	03/16/2020	All
Paten Exclusivity	04/27/2020	All
Response to Information Request – Clinical	05/14/2020	Clinical
Response to Information Request – Quality	05/18/2020	ONDP and OPMA
Response to Information Request – Clinical	06/05/2020	Clinical Pharmacology
Response to Information Request – Quality	06/19/2020	OPMA
Response to Information Request – Clinical	08/14/2020	Clinical
Labeling	09/01/2020	All

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance	Jeffrey Medwid, Ph.D.	Donna Christner, Ph.D.
Drug Product	Caroline Strasinger, Ph.D.	Moo-Jhong, Rhee, Ph.D.
Manufacturing	Rose Xu, Ph.D.	Vidya Pai, Ph.D.
Microbiology	Koushik Paul, Ph.D.	Jesse Wells, Ph.D.
Biopharmaceutics	Tapash Ghosh, Ph.D.	N/A

Regulatory Business Process Manager	Melinda Bauerlien, MS	
Application Technical Lead	Hamid Shafiei, Ph.D.	
Laboratory (OTR)	N/A	N/A
Environmental	Caroline Strasinger, Ph.D.	Moo-Jhong Rhee, Ph.D.

FDA U.S. FOOD & DRUG ADMINISTRATION

EXECUTIVE SUMMARY

IQA NDA Assessment Guide Reference

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

- The applicant of this 505(b)(1) new drug application has provided **sufficient CMC information** to assure the identity, purity, strength, and quality of the drug substance (tirbanibulin) and the drug product, KLISYRI® (tirbanibulin) Ointment, 1%.
- Labels/labeling issues have been **satisfactorily** addressed.
- The Office of Process and Facility has made an overall "**Acceptable**" recommendation regarding the facilities involved in this NDA.
- The claim for categorical exclusion from the preparation of environmental assessment has been granted.

Therefore, from the OPQ perspective, this NDA is recommended for **APPROVAL** with expiration dating period of **24 months**.

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

Athenex, Inc. has submitted this 505(b)(1) application for KLISYRI® (tirbanibulin) Ointment, 1% for topical administration. KLISYRI® is indicated for the treatment of actinic keratosis of face or scalp.

The active ingredient, tirbanibulin is a new molecular entity that has been shown to exhibit potent antiproliferative activity against immortalized human keratinocytes and several cancer cell lines in vitro. Tirbanibulin is a white to off white solid which is insoluble in water.

Each gram of KLISYRI ointment contains 10mg of tirbanibulin as the active ingredient and mono- and di-glycerides and polypropylene glycol as inactive ingredients.

KLISYRI ointment is packaged as 250mg units equivalent to 2.5mg of tirbanibulin in single-dose packet (b) (4) (b) (4) for a single application. KLISYRI ointment is to be applied evenly to cover up to 25cm^2 treatment field on the face or scalp once daily for 5 consecutive days using one packet per administration. KLISYRI is offered in a package containing 5 packets to cover the recommended duration of use.

KLISYRI ointment should be stored at room temperature and should not be refrigerated or frozen.

Proposed Indication(s) including Intended Patient Population	Treatment of actinic keratosis of face or scalp
Duration of Treatment	5 consecutive days
Maximum Daily Dose	One single-dose packet of 250mg ointment for topical application once daily
Alternative Methods of Administration	None

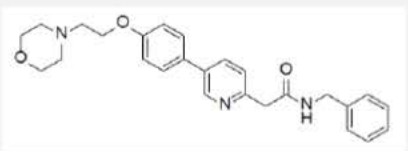
B. Quality Assessment Overview

Drug Substance: Adequate

The active ingredient, tirbanibulin is a synthetic potent antiproliferative showing activity against immortalized human keratinocytes and several cancer cell lines in vitro. It is the active ingredient of KLISYRI (tirbanibulin) ointment indicated for the treatment of actinic keratosis of face or scalp.

Tirbanibulin is a white to off-white solid. It is freely soluble in dimethyl sulfoxide, slightly soluble in ethanol and ethyl acetate, and insoluble in water. Tirbanibulin is an achiral molecule with no stereocenter. It has UV absorption maxima (b) (4). It is not hygroscopic and exhibits (b) (4) a melting range of (b) (4) °C (b) (4) (b) (4)

Tirbanibulin has the chemical name, N-benzyl-2-(5-4-(2-morpholinoethoxy)phenyl)pyridin-2-yl)acetamide, a molecular formula of $C_{26}H_{29}N_3O_3$, a molecular weight of 431 (b) (4) g/mol, and the chemical structure below:



Tirbanibulin is produced (b) (4) It is manufactured in accordance to current Good Manufacturing Practices

(cGMP) requirement [redacted]. The drug substance is packaged [redacted] for shipping and handling. It is tested and release against a specification that assures the identity, strength, purity, and quality of the drug substance at release and throughout its assigned retest date o [redacted] months when stored [redacted]. Sufficient stability data in support of the proposed retest date of [redacted] months has been submitted

The drug substance module of this application has been reviewed by the Drug Substance Reviewer Dr. Jeffrey Medwid. Dr. Medwid has found the drug substance information provided in the application adequate to support the approval of this application from the drug substance perspective. Dr. Medwid's review is provided in the Drug Substance Chapter of the Integrated Quality assessment (IQA).

Drug Product: Adequate

The drug product, KLISYRI® (tirbanibulin) Ointment, 1% for topical administration has been developed for the treatment of actinic keratosis of face or scalp. It is packaged as 250mg units equivalent to 2.5mg of tirbanibulin in a single-dose packet [redacted] for a single application. KLISYRI ointment is to be applied evenly to cover up to 25cm^2 treatment field on the face or scalp once daily for 5 consecutive days using one packet per administration. KLISYRI is offered in a package containing 5 packets to cover the recommended duration of use.

KLISYRI ointment is formulated a creamy white to off-white ointment, each gram containing 10mg of tirbanibulin as the active ingredient and mono- and di-glycerides and polypropylene glycol as inactive ingredients. Inactive ingredients used in the composition of KLISYRI are all compendial materials and the amount each inactive ingredient in the formulation of the drug product is below the approved amount listed in the FDA inactive ingredients database (IID) for topical drug products.

KLISYRI is manufactured in accordance to cGMP requirements by Athenex Pharma Solutions, LLC. It is tested and released against a specification that assures the identity, strength, purity, and quality of the drug product at release and throughout its proposed shelf-life of 24 months [redacted] this drug product should be store at room

temperatures, 20ºC – 25ºC (68ºF – 77ºF). The drug product is labelled with the statements "do not refrigerat (b) (4) freeze". Sufficient stability data in support of the proposed expiration dating period of 24 months has been submitted.

The drug product module of this application has been reviewed by the Drug Product Reviewer, Dr. Caroline Strasinger. Dr. Strasinger has concluded that the information provided in the drug product module is adequate to support the approval of this application from the drug product perspective. Dr. Strasinger's review is provided in the Drug Product Chapter of the IQA.

The applicant's request for categorical exclusion from the preparation environmental assessment has also been reviewed by Dr. Strasinger. Dr. Strasinger has found the applicant's request valid and has recommended granting the categorical exclusion for this application. The review of the categorical exclusion is also captured in the Drug Product Chapter of the IQA.

Labeling: Adequate

The CMC sections of the Prescribing Information (PI) as well as the immediate container and carton labels have been reviewed by the Drug Product Reviewer, Dr. Caroline Strasinger. Dr. Strasinger has found that the final PI as well as immediate container and carton labels submitted to this application satisfactory and recommended the approval of this application from the labeling/label perspective. Dr. Strasinger labeling/label review is provided in the Labeling Chapter of the IQA.

Manufacturing: Adequate

The manufacturing process for KLISYRI (tirbanibulin) ointment consists of (b) (4)

(b) (4) The currently proposed scale for the commercial drug product is the same scale as the primary registration stability batches. However, the applicant has stated that based on the commercial demands if needed, the batch size for the commercial production may be scaled up to (b) (4) the scale used for the primary registration stability batches.

Pre-approval inspections of the drug product manufacturing facility, Athenex Pharma Solutions, LLC. (FEI 3008876196) and the testing facility (b) (4) (FE (b) (4)) were conducted. No FDA 483 Form was issued to any of the two firms.

The manufacturing process as well as the facilities involved in this application were reviewed by the OPMA Reviewer, Dr. Rose Xu. Dr. Xu has found both the manufacturing process and facilities adequate to support the approval of this application. Dr. Xu's review is provided in the Manufacturing Chapter of the IQA.

Biopharmaceutics: Adequate

The applicant has successfully developed and validated an in vitro release testing (IVRT) method for KLISYRI (tirbanibulin) Ointment, 1%. The applicant has used this method to monitor developmental and clinical batches of drug product and to bridge the clinical batches to the batches manufactured at the proposed commercial site. The applicant has committed to test the three validation batches of drug product manufactured by the proposed commercial process at the intended commercial manufacturing site at release and during stability using this IVRT method. The applicant will provide the IVRT data in the annual reports.

The biopharmaceutics section of this application has been reviewed by the Biopharmaceutics Reviewer, Dr. Tapash Ghosh. Dr. Ghosh has found the IVRT method and the acceptance criterion adequate from the biopharmaceutics perspective. Dr. Ghosh's review is provided in the Biopharmaceutics Chapter of the IQA.

Microbiology (if applicable): Adequate

KLISYRI (tirbanibulin) Ointment, 1% is a white to off-white non-aqueous ointment. It is nonsterile and intended for topical administration.

As a non-sterile drug prdoct it is tested for bioburden using USP <61> and USP <62>. The applicant has performed method suitability for this drug product and has tested multiple batches of drug product at release and during stability for up 24 months. The applicant has committed to continue the stability testing of the 3 registration primary stability batches through the proposed expiration dating period and to provide the data in annual reports. Furthermore, testing and acceptance limits for bioburden according USP <61> and USP <62> is included in the drug product release stability specification (b) (4)

(b) (4)

The Microbiology section of this application has been reviewed by the Microbiology Reviewer, Dr. Koushik Paul. Dr. Paul has found the information provided in the microbiology section this application adequate and has recommended the approval of this application from the

Microbiology perspective. Dr. Paul's review is provided in the Microbiology Chapter of the IQA.

C. Risk Assessment

From Initial Risk Identification			Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**
Assay and related substances	Amounts of components (active and inactive ingredients) input in the formulation as well as degradation of the active in the formulation over time.	M	Stability data indicate that assay and related substances will not significantly change during proposed shelf-life.	Acceptable	None

D. List of Deficiencies for Complete Response

None

Application Technical Lead:

Hamid Shafiei, Ph.D.
Branch IV/DNDP 2/ONDP/OPQ

Hamid Shafiei

Digitally signed by Hamid Shafiei
Date: 9/23/2020 02:24:21PM
GUID: 507d824300005f344cf8b5e5989f0057

U.S. FOOD & DRUG ADMINISTRATION

QUALITY ASSESSMENT DATA SHEET

IQA NDA Assessment Guide Reference

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	III	(b) (4)		----------	----------	Sufficient information is provided in the NDA

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

Document	Application Number	Description
N/A	N/A	N/A

2. CONSULTS

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

44 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

The below information and labeling deficiencies were agreed to by the Applicant on 01-SEP-2020. The deficiencies are presented below only for completeness of review. The Label and Labeling is now ADEQUATE from the ONDP perspective.

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	TRADENAME	ADEQUATE Location established, name pending approval
Established name(s)	(tirbanibulin) ointment	ADEQUATE
Route(s) of administration	For topical use	ADEQUATE
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	Ointment: 1% tirbanibulin	ADEQUATE
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.	(b) (4) packets	INADEQUATE: Although not an injection, revis (b) (4) to single-dose throughout PI This was **satisfactorily** resolved on 9/1/20

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)

3 DOSAGE FORMS AND STRENGTHS

Ointment: (b) (4) 1% (b) (4) -white to off-white ointment in a (b) (4) single-dose (b) (4) packet (2.5 mg tirbanibulin in 250 mg).

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	ointment	Revise for formatting
Strength(s) in metric system	1%	Revise to include (2.5 mg tirbanibulin in 250 mg). This was **satisfactorily** resolved on 9/1/20
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	Not applicable	N/A
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	Ointment in a (b) (4) packet	INADEQUATE: Include white to off-white in a single-dose packet This was **satisfactorily** resolved on 9/1/20
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.	(b) (4) packet	INADEQUATE: Single-dose packet This was **satisfactorily** resolved on 9/1/20

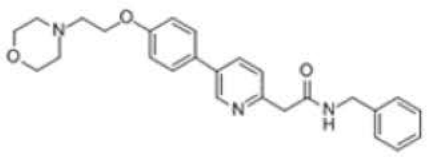
11 DESCRIPTION

TRADENAME(tirbanibulin) ointment is a microtubule inhibitor for topical use. (b) (4)

(b) (4)

The chemical name of tirbanibulin is *N*-benzyl-2-(5-(4-(2-morpholinoethoxy)phenyl)pyridin-2-yl)acetamide. (b) (4)

(b) (4) Tirbanibulin's structural formula is:



Tirbanibulin ointment 1% contains 10 mg of tirbanibulin per gram of white to off-white ointment containing mono- and di-glycerides and propylene glycol.

1.2.3 Section 11 (DESCRIPTION)

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	TRADENAME	INADEQUATE: TRADENAME (tirbanibulin) ointment This was **satisfactorily** resolved on 9/1/20
Dosage form(s) and route(s) of administration	(b) (4)	INADEQUATE: Topical use and revise for formatting This was **satisfactorily** resolved on 9/1/20
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	N/A	N/A
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	containing mono- and di-glycerides and propylene glycol	ADEQUATE
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	N/A
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	N/A
Statement of being sterile (if applicable)	N/A	N/A
Pharmacological/ therapeutic class	Not present	INADEQUATE: Add microtubule inhibitor This was **satisfactorily** resolved on 9/1/20
Chemical name, structural formula, molecular weight	present	ADEQUATE
If radioactive, statement of important nuclear characteristics.	N/A	N/A
Other important chemical or physical properties (such as pKa or pH)	N/A	N/A

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	N/A
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity"	(b) (4)	INADEQUATE: Remove (b) (4) This was **satisfactorily** resolved on 9/1/20

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)	ointment	
Strength(s) in metric system	1%	
Available units (e.g., bottles of 100 tablets)	5 (b) (4) packets	INADEQUATE: 5 single dose packets This was **satisfactorily** resolved on 9/1/20
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	(b) (4)	ADEQUATE
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	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.	(b) (4) packet	INADEQUATE: Revise to single-dose packet This was **satisfactorily** resolved on 9/1/20

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.)	Each packet should be discarded after single use.	ADEQUATE
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	N/A
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Store at 20°C-25°C (68°F-77°F), excursions permitted to 15°C-30ºC (59°F-86ºF) [see USP Controlled Room Temperature]. Do not refrigerate or freeze.	ADEQUATE
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	N/A
Include information about child-resistant packaging	N/A	N/A

1.2.5 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	Manufactured for: XXXXXXX.	Include information including street address, city, state zip code of the manufacturer This was **satisfactorily** resolved on 9/1/20

ASSESSMENT OF THE PI: *INADEQUATE*

The following Items should be addressed for the PI. Refer to screen shots above for specifics of text and format.

Highlights

- Revise all uses o [redacted] (b) (4) packet to single-dose packet

Section 3

- Revise section for clarity as indicated above
  - Include white to off-white ointment
  - 2.5 mg tirbanibulin per 250 mg of ointment
  - single-dose packet

Section 11

- Include therapeutic class, microtubule inhibitor
- Revis [redacted] (b) (4) to "for topical use"
- Adjust significant figures on molecular weight
- Revise section for clarity as indicated above

Section 16

- Remove the wor [redacted] (b) (4)
- Modify [redacted] (b) (4) to single dose

On SEPTEMBER 1, 2020 the Applicant agreed to all OPQ related deficiencies. The Labeling of NDA 213189 is ADEQUATE.

2.0 CARTON AND CONTAINER LABELING

2 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	TRADENAME (tirbanibulin) ointment	ADEQUATE
Dosage strength	1%	ADEQUATE
Route of administration	Topical Use Only	ADEQUATE
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	N/A	N/A
Net contents (e.g. tablet count)	Container: 0.25 grams Carton: Contains (b) (4) Packet (b) (4) (b) (4)	INADEQUATE: Modify carton to read contains 5 Single-Dose Packets, and remove (b) (4) This was **satisfactorily** resolved on 9/1/20
"Rx only" displayed on the principal display	Present on Carton	ADEQUATE
NDC number	Present on Container and Carton	ADEQUATE
Lot number and expiration date	Present	ADEQUATE
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	Store at 20°C-25°C (68°F-77°F), excursions permitted to 15°C-30ºC (59°F-86ºF) [see USP Controlled Room Temperature]. Do not refrigerate or freeze.	ADEQUATE
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	(b) (4)	INADEQUATE: Modify to Single-Dose This was **satisfactorily** resolved on 9/1/20

Other package terms include pharmacy bulk package and imaging bulk package which require "Not for direct infusion" statement.	N/A	N/A
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	N/A
Bar code	Present	ADEQUATE

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Name of manufacturer/distributor	Manufactured for: Almirall, LLC Exton, PA 19341	ADEQUATE
Medication Guide (if applicable)	N/A	N/A
No text on Ferrule and Cap overseal	N/A	N/A
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	N/A
And others, if space is available	N/A	N/A

Assessment of Carton and Container Labeling: *INADEQUATE*

For the Carton

- Modify carton to read contains 5 Single-Dose Packets
- Remove (b) (4)
- Remove (b) (4)

On SEPTEMBER 1, 2020 the Applicant agreed to all OPQ related deficiencies. The Label of NDA 213189 is ADEQUATE.

Overall Assessment and Recommendation:

On September 1, 2020 the Applicant agreed to all OPQ related deficiencies. The Label and Labeling of NDA 213189 is ADEQUATE.

This application is deemed ready for APPROVAL from the OPQ/ONDP label/labeling perspective.

Primary Labeling Assessor Name and Date:
Caroline Strasinger, PhD
OPQ, ONDP, DNDP II, B4

Secondary Reviewer Name and Date (and Secondary Summary, as needed):

I agree with Dr. Strasinger's assessment of the labeling and labels and concur with her recommendation that this application is ready for approval once all deficiencies noted are satisfactorily resolved.

Moo-Jhong Rhee, Ph.D.
Chief, Branch 4
DNDP II/ONDP

Caroline Strasinger

Digitally signed by Caroline Strasinger
Date: 9/02/2020 03:17:47PM
GUID: 5051dfdd000013b995075b4d54108ed8

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

BIOPHARMACEUTICS

NDA: NDA 213189-ORIG-1 (505(b)(1))

Drug Product Name / Strength: Tirbanibulin Topical Ointment (1%)

Indication: For the topical treatment of actinic keratosis of the face or scalp

Route of Administration: Topical

Applicant Name: Athenex, Inc. dba Kinex Pharmaceuticals, Inc., Buffalo, NY 14203

Review Summary: The sponsor developed and validated an IVRT method and used that to monitor the stability of the bulk and finished products. The method has also been used successfully to bridge pre-approval product and manufacturing sites. Overall, ORIG-1 (505(b)(1)) NDA 213189 for Tirbanibulin Topical Ointment (1%) is **ADEQUATE** from Biopharmaceutics perspective.

List Submissions being reviewed (table):

- Application Type/Number: NDA 213189 (Sequence No. 0001, 30 December 2019)
- Supporting Document (Sequence No. 0008, 19 June 2020)
- Supporting Document (Sequence No. 0009, 14 August 2020)

Highlight Key Outstanding Issues from Last Cycle: N/A

Concise Description Outstanding Issues Remaining: None.

However, as per the sponsor's statement, IVR testing has been included in the full stability testing program for the three commitment batches (i.e. process validation batches). The results will be provided during the annual report period after approval. This ongoing program includes a total of 10 batches using the proposed commercial manufacturing process with monitoring at both release and throughout stability. The Agency will be looking forward to the IVR testing report in the Annual report.

BCS Designation : N/A

Dissolution Method and Acceptance Criteria: *N/A*

Clinical relevance of dissolution method & acceptance criteria (e.g., IVIVR, IVIVC, In Silico Modeling, small scale in vivo): *N/A*

Application of dissolution/IVIVC in QbD: *N/A*

MODIFIED RELEASE ORAL DRUG PRODUCTS –In-Vitro Alcohol Dose Dumping: *N/A*

In-Vitro Soft-food Interaction Study: *N/A*

In-Vitro Release Testing (IVRT) for Semi-Solid Products:

IVRT is not reported/considered as a Critical Quality Attribute (CQA). IVRT is considered as a Quality Attribute with the target set that release rate comparable to reference drug product batch during product development.

According to the applicant, the IVRT is used to compare formulations during development and will be continued for stability testing of the registration lots of the drug product and release of the process validation batches. IVRT provides a discriminatory method evaluating release profile that allows evaluation of the impact of various formulation and manufacturing process changes on product performance. Beyond the process validation batches, the IVRT test will only be employed to establish comparability per SUPAC-SS guidance and not for routine analysis.

IVRT Method Development

The IVRT method development is described in detail in section 3.2.P.2.2.3.1. Release rate experiments are performe (b) (4) (b) (4) (b) (4) The method development included the following:

(b) (4)

Final IVRT Conditions: The final method conditions for the IVRT method are shown in Table 7.

Table 7 IVRT Method Conditions for the determination of tirbanibulin release

Parameter	Condition
Apparatus	Six vertical diffusion cells per sample per run
Surface Area	1.767 cm^2
Sampling Intervals	20, 40, 60, 90, 120, 150 minutes
Temperature	32°C ± 0.5°C
Application Method	Wet mount
Application Amount	Approximately 800 mg*
Sample Aliquot	200 µL
Membrane	Nylon membranes, 0.45 µm, 25-32 mm
Receiving Medium	0.1 *N* HCl
Receptor Volume	Approximately 15 mL
Stirring Speed	600 rpm

*Sufficient test material is applied to the membrane covering the surface area defined by the double thick 15 mm x 3 mm thick wafer (1.767 cm^2) such that no exposed membrane remains, and infinite dose is maintained throughout the test period.

IVRT Method Validation Summary: The IVRT validation study included assessment of precision, inter-day intermediate precision, inter-analyst intermediate precision, discrimination and robustness. The summary of the IVRT method validation was performed on tirbanibulin ointment 1% bulk product and is presented in 3.2.P.2.2.

A bridging study was performed to evaluate the IVRT method (validated on bulk product) for the release rate of tirbanibulin ointment 1% finished product packets. The bridging study included assessments for precision, inter-day intermediate precision and inter-analyst intermediate precision. All acceptance criteria were met.

The summary of the IVRT method bridging study performed on tirbanibulin ointment 1% finished product packets is presented in 3.2.P.2.2, Table 23.

Table 23 IVRT Method Bridging Summary (Finished Packed Product, TER-062-19.01)

Parameter	Criteria	Result
Precision Determined using (b) (4) (b) (4)		(b) (4)
Inter-day Precision Determined (b) (4)		
Inter-analyst Intermediate Precision Determined using two analysts		

Reviewer's Assessment:

APPEARS THIS WAY ON ORIGINAL

The IVRT method is considered suitable for analysis of IVRT samples from studies performed with tirbanibulin ointment 1% finished packet product.

In-Vitro Permeation Testing (IVPT) for Transdermal/Topical Products: *N/A*

In-Vitro Dissolution Testing for Abuse-deterrent Products : *N/A*

In-Vitro BE Evaluation for Pulmonary Products: *N/A*

EXTENDED RELEASE DOSAGE FORMS –Extended Release Claim: *N/A*

Bridging of Formulations:

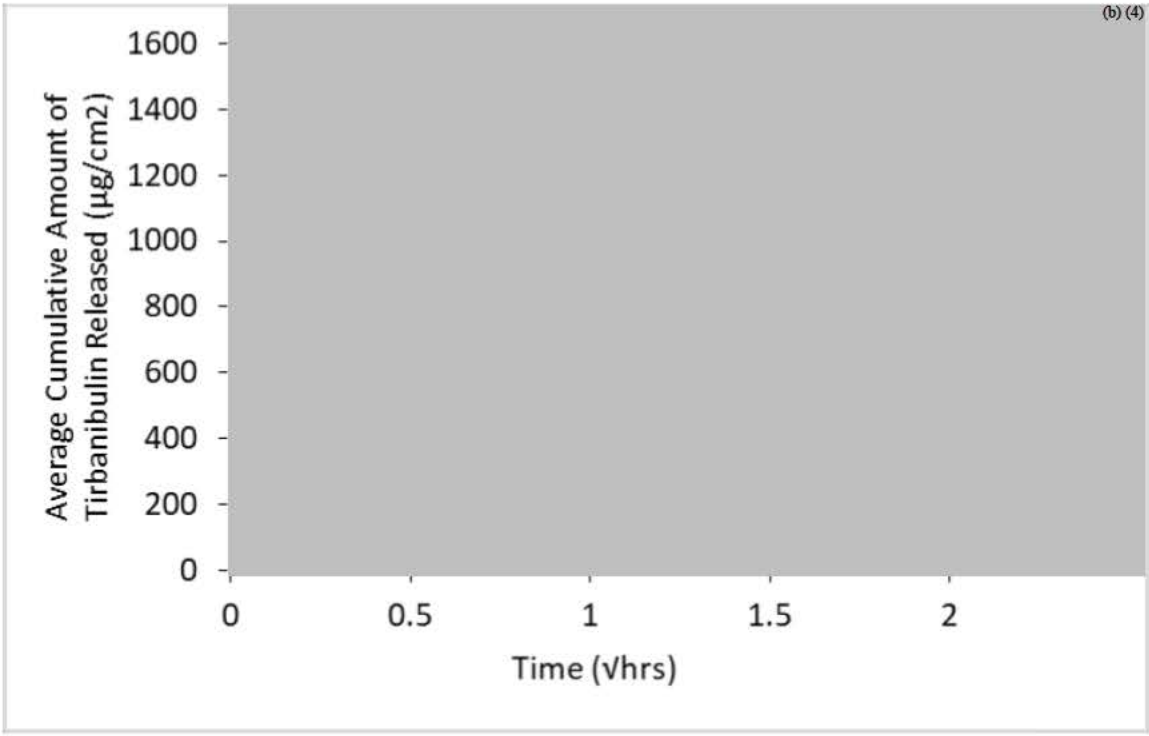
The following describe changes to drug product through clinical development and manufacture of registration batches, which needed bridging.

- **Formulation Change** [redacted] (Commercial Formulation).
- **API manufacturer change:** Drug substance manufacturer changed from [redacted] for early clinical studies t [redacted] (intended commercial supplier) for Phase 3 and Registration batches.
- **DP manufacturer change:** Drug product manufacturer was changed from [redacted] (up to late stage Phase 1 and Phase 3 clinical trials) to APS (registration batches and intended commercial supplier). This comparison is detailed in 3.2.P.2.3.

An IVRT method was developed and validated as described above to support the above changes in compliance with the requirements of US FDA guidance "*Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls; In Vitro Release Testing and In Vivo Biocomparability Documentation*" (May 1997). Each change is described separately in the following section:

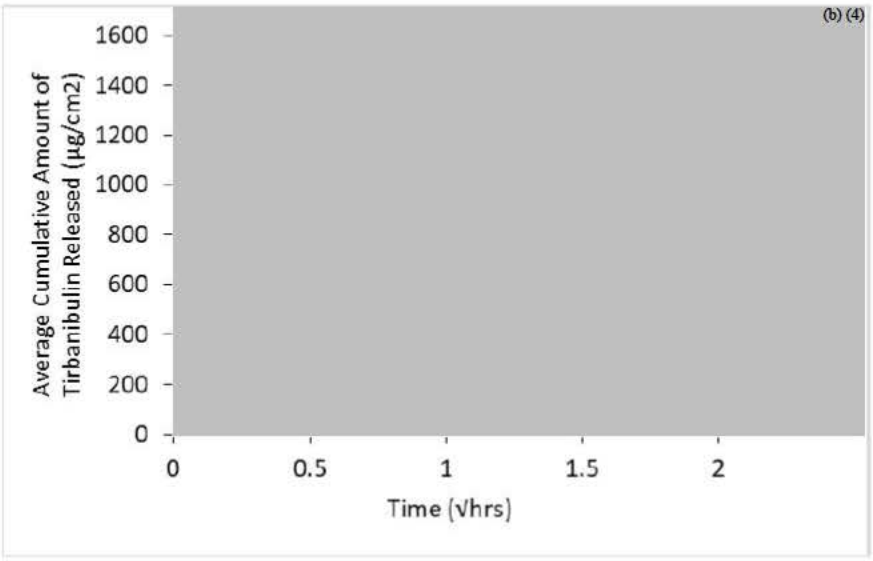
Formulation Change: Drug product batches IVRT evaluations (3.2.P.2.2, Figure 1) of drug product representing Formulation 1 (batch F001-16- 0042) and the Commercial Formulation (batch F001-17-0068) demonstrate that the changes in composition yielded comparable formulations. Figure 1 depicts the IVRT data for the two formulations.

Figure 1 **Average Cumulative Amounts of Tirbanibulin Released from Tirbanibulin Ointment 1 % – Formulation 1 and Commercial Formulation**



Drug substance manufacturer change: Another study comparing the effect of changing drug substance supplier on the quality and performance of the commercial formulation was conducted. The data are presented (3.2.P.2.2, Figure 2) show that the source of the drug substance had no impact on the quality or performance of the formulation.

Figure 2 **Average Cumulative Amounts of Tirbanibulin Released from Drug Product Batches Manufactured with Drug Substance from** (b) (4)



Drug Product Manufacturer Change: Comparability of drug **product manufacturing site** change is described in 2.3.P.2.3 and 3.2.P.2.3.

The performance of the bulk formulations from the two different manufacturing sites (b) (4) (lot AXC2018080901) and APS (lot S1800099), was compared through an assessment of IVRT. The release rates and a comparison by Wilcoxon Rank Sum/Mann- Whitney rank test are shown in 3.2.P.2.3 (Tables 11, Table 12 and Figure 3).

The performance of the bulk formulations from the two different manufacturing site (b) (4) APS, was compared through an assessment of IVRT. The release rates for th (b) (4) lot AXC2018080901, and APS lot S1800099 are shown in Table 11.

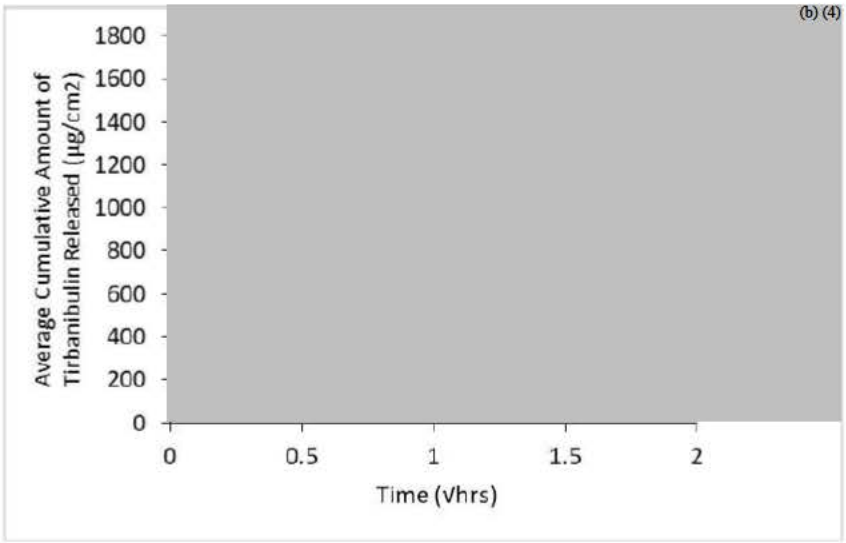
Table 11 Release Rates (Slope) for Tirbanibulin Ointment 1% w/w Bulk Formulation Manufactured at (b) (4) and APS

Manufacturer	(b) (4)		APS	
Lot Number →	AXC2018080901		S1800099	
Parameter	Release Rate (µg/cm2/√hr)	Correlation Coefficient	Release Rate (µg/cm2/√hr)	Correlation Coefficient
Cell 1	(b) (4)			
Cell 2				
Cell 3				
Cell 4				
Cell 5				
Cell 6				
Average	**1018.85**	N/A[1]	**1006.06**	N/A
% RSD	3.5	N/A	6.0	N/A

[1] Not Applicable

Average cumulative amounts of tirbanibulin released from all six cells for the (b) (4) and APS lots are presented in Figure 3.

Figure 3: Average Cumulative Amounts of Tirbanibulin Released from Tirbanibulin Ointment 1 % – (b) (4) and APS batches



The release results for the two formulation batches were compared using the Wilcoxon Rank Sum/Mann-Whitney rank test. The ratios of release rates for the two formulations were determined and are presented in Table 12. Release rates (slopes) fo (b) (4) and APS batches are shown in the first row and first column, respectively. The ratios of the release rates for the two formulations are then calculated and multiplied by 100%.

Table 12: (b) (4) /APS Drug product Slope Ratios for the Comparison

(b) (4)

Per USP <1724> and the 1997 Guidance for Industry: *Non-sterile Semisolid Dosage Forms. Scale-Up and Post-Approval Changes: Chemistry, Manufacturing, and Controls; In Vitro Release Testing and In Vivo Bioequivalence Documentation* using the Wilcoxon Rank Sum/Mann-Whitney rank test, results for two data sets are considered equivalent if the 8th and 29th ranked ratios fall within the range 75 to 133.33%.

The 8th and 29th ranked ratios for this study are (b) (4)% and (b) (4)%, respectively indicating that the in-vitro release performance of drug product batches manufactured at APS and (b) (4) are comparable.

Reviewer's Assessment: In summary, the IVRT results successfully bridge the formulation change, API manufacturer changes and comparability of drug product manufactured at the two sites per USP <1724> and the 1997 Semi Solid Guidance for Industry.

Biowaiver Request: *N/A*

R Regional Information

Comparability Protocols: *N/A*

Post-Approval Commitments: *N/A*

Lifecycle Management Considerations

The Sponsor received the following Information Request for NDA 213189, on June 12, 2020 from FDA.
Biopharmaceutics: We acknowledge that you have performed a thorough investigation for development of the In vitro drug release testing (IVRT) method for the proposed drug product. The IVRT method is currently under our review; however, it appears to be adequately developed. While IVRT test/specification is not required for routine

batch release and stability program, inclusion of IVRT specification can provide an improved quality control for the determination of batch to batch uniformity. Therefore, we suggest that you include IVRT testing as a quality control (QC) measure at minimum for batch release and possibly for annual time-points during stability, at least for the first few batches after approval of your application. IVRT can also be used as a useful tool to compare product quality in the event of SUPAC related manufacturing changes post-approval.

Sponsor's Response received on June 19, 2020: The applicant acknowledges the Agency's suggestion to include IVRT testing as a quality control (QC) at minimum for batch release and possibly for annual time-points during stability, at least for the first few batches after approval of this application.

The applicant agrees that a comprehensive IVRT data set can provide valuable product characterization and process understanding. To ensure a suitable repository of IVRT data was available prior to the commercial phase, an IVRT characterization program was proactively implemented throughout phase 3, primary registration and process validation activities. IVR testing has been included in the full stability testing program for the three commitment batches (i.e. process validation batches) as stated in section 3.2.P.8.2. The results will be provided during the annual report period after approval. This ongoing program includes a total of 10 batches using the proposed commercial manufacturing process with monitoring at both release and throughout stability, as summarized in Table 11. Since the process is qualified and adequately controlled, the implementation of the IVRT for an additional few batches after the completion of process validation studies will not contribute new information on the determination of batch to batch uniformity. IVRT will be considered to discriminate the effect of process variability in the production of proposed drug product per FDA SUPAC guideline.

Table 11 Summary of IVRT Target Data Set (Studies In-Progress and Planned)

Bulk Batch # (Finished Good Batch)	Type (Bulk / FG)	Batch Use	IVRT Study Duration	Status
ACX2017042803	Bulk Release and Bulk Stability	Phase 3	Initial Release through 12 Months Stability	Complete
AXC2017050101	Bulk Release and Bulk Stability	Phase 3	Initial Release through 12 Months Stability	Complete
AXC2018080901 (F1800673)	Bulk Release and Finished Good Stability	Site Transfer Comparability	Initial Release through 36 Months Stability	In-Progress (18 Months Stability)
S1800097 (F1800591)	Bulk Release and Finished Good Stability	Primary Registration #1	Initial Release through 36 Months Stability	In-Progress (18 Months Stability)
S1800098 (F1800596)	Bulk Release and Finished Good Stability	Primary Registration #2	Initial Release through 36 Months Stability	In-Progress (18 Months Stability)
S1800099 (F1800605)	Bulk Release and Finished Good Stability	Primary Registration #3	Initial Release through 36 Months Stability	In-Progress (18 Months Stability)
S2000039 (F2000468)	Bulk Release, Hold and Finished Good Stability	Bulk Hold carried to Finished Good	Initial Release/60 Day Bulk Hold through 36 Months Stability	In-Progress (Bulk Hold Complete)
Process Validation Batch #1	Bulk Release and Finished Good Stability	Process Validation	Initial Release through 36 Months Stability	Planned
Process Validation Batch #2	Bulk Release and Finished Good Stability	Process Validation	Initial Release through 36 Months Stability	Planned
Process Validation Batch #3	Bulk Release and Finished Good Stability	Process Validation	Initial Release through 36 Months Stability	Planned

In response to the above response, the FDA issued the following Information Request on August 5, 2020.
Biopharmaceutics: In your response to Biopharmaceutic information request, you have mentioned that in vitro release testing (IVRT) has been included in the full stability testing program for the three commitment batches (i.e. process validation batches) and that the ongoing program includes testing of a total of 10 batches using the proposed commercial manufacturing process with monitoring at both release and throughout stability. You have also mentioned that the results from IVRT will be provided during the annual report after the approval of your application. We acknowledge that IVRT control is currently in place and you plan to submit the IVRT results in the annual report post-approval. To facilitate our CMC/ Biopharmaceutic review of your application, please submit the currently available IVRT data. You can submit any additional data produced after the approval of your application in the annual reports as you have planned.

Sponsor's Response received on August 14, 2020:
The currently available IVRT data at both release and throughout stability is summarized in Table 1. The Excel file containing release rates for each of the 6 replicate cells per lot per timepoint of these IVRT data is also provided for demonstration purposes. A summary of a Bulk versus Finished Good drug product IVRT bridging study is presented in Table 2. This bridging study demonstrated that IVRT results are not impacted by storage containe (b) (4) (b) (4) The cumulative IVRT data collected thus far (up to 18 months, studies planne nsistent in vitro drug substance release rates across batches and over time on batches manufactured using the proposed commercial manufacturing process. Drug product produced a (b) (4) (e.g., Phase 3 and Site Transfer Comparison batch) and Athenex Pharma Solutions (APS; the proposed commercial manufacturer) have equivalent release profiles. Details of a manufacturing site comparison IVRT study are presented in 3.2.P.2.3.1.3.2.

Additionally, IVRT data support a suitable bulk hold period in the proposed bulk storage containe (b) (4) (b) (4). The applicant is committed to continuing the current IVRT stability studies, and performing similar IVRT stability studies on three process validation batches.

Table 2. Bulk versus Associated Finished Good IVRT Bridging Study Summary

	Run #1 / Day #1			Run #2 / Day #2	
Batch	Bulk (S1800097)	Finished Good (F1800591)		Bulk (S1800097)	Finished Good (F1800591)
Average Release Rate ($\mu g/cm^2/\sqrt{hr}$) [a]	(b) (4)				
%RSD [a]					
(b) (4)					

Table 1. Average IVRT tirbanibulin release rate data at both release and throughout stability

Bulk Batch # (Finished Good Batch)	Type (Bulk /FG)	Batch Use	IVRT Study Duration	Status	Average Release Rate (µg/cm²/√hr) and (%RSD) per 6 Cells [a,b]									
					T0	1 Month	2 Months	3 Months	6 Months	9 Months	12 Months	15 Months	18 Months	>18 Months
ACX2017-042803	Bulk Release and Bulk Stability	Phase 3	Initial Release through 12 Months Stability	Complete	(b) (4)									
AXC2017-050101	Bulk Release and Bulk Stability	DS Source Comparison (parallel to Phase 3)	Initial Release through 12 Months Stability	Complete										
AXC2018-080901	Bulk Release and	Site Transfer Comparison	Initial Release through 36 Months Stability	In-Progress										
(F1800673)	Finished Good Stability			(18 Months Stability)										
S1800097	Bulk Release and	Primary Registration #1	Initial Release through 36 Months Stability	In-Progress										
(F1800591)	Finished Good Stability			(18 Months Stability)										
S1800098	Bulk Release and	Primary Registration #2	Initial Release through 36 Months Stability	In-Progress										
(F1800596)	Finished Good Stability			(18 Months Stability)										
S1800099	Bulk Release and	Primary Registration #3	Initial Release through 36 Months Stability	In-Progress										
(F1800605)	Finished Good Stability			(18 Months Stability)										

Bulk Batch # (Finished Good Batch)	Type (Bulk /FG)	Batch Use	IVRT Study Duration	Status	Average Release Rate (µg/cm²/√hr) and (%RSD) per 6 Cells [a,b]									
					T0	1 Month	2 Months	3 Months	6 Months	9 Months	12 Months	15 Months	18 Months	>18 Months
S2000039	Bulk Release, Hold and	Bulk Held carried to Finished Good	Initial Release/60 Day Bulk Hold through 36 Months Stability	In-Progress	(b) (4)									
(F2000468)	Finished Good Stability			(Bulk Hold Complete)										
Process Validation Batch #1	Finished Good Release and Finished Good Stability	Process Validation	Initial Release through 36 Months Stability	Planned										
Process Validation Batch #2	Finished Good Release and Finished Good Stability	Process Validation	Initial Release through 36 Months Stability	Planned										
Process Validation Batch #3	Finished Good Release and Finished Good Stability	Process Validation	Initial Release through 36 Months Stability	Planned										
					(b) (4)									

List of Deficiencies: *None*

Biopharmaceutics Reviewer Name and Date: *Tapash Ghosh, Ph.D., September 1, 2020*

Tapash Ghosh

Digitally signed by Tapash Ghosh
Date: 9/02/2020 03:05:54PM
GUID: 508da7230002a2433ddcef616ca190df

MICROBIOLOGY

Product Background: Actinic Keratosis of the face or scalp.

NDA: 213189

Drug Product Name / Strength: Tirbanibuli (b)(4)(1% strength).

Route of Administration: Topical Ointment.

Applicant Name: Athenex, Inc.

Manufacturing Site: Athenex Pharma Solutions, LLC, 11342 Main Street, Clarence, NY 14031, USA. FEI# 3008876196.

Method of Sterilization: This is a nonsterile product.

Review Recommendation: **Adequate**

Theme (ANDA only): **N/A**

Justification (ANDA only): N/A

Review Summary (b) (4)

(b) (4)

List Submissions Being Reviewed: 12/30/2019.

Highlight Key Outstanding Issues from Last Cycle: N/A

Remarks: The submission is **recommended** for approval on the basis of sterility assurance.

Concise Description Outstanding Issues Remaining: None.

Supporting Documents: Microbiology review N212321MR01.doc, dated 06/26/2019.

List Number of Comparability Protocols (NDA only): Comparability Protocol is not included with the application.

S Drug Substance – non-sterile

Reviewer's Assessment: The drug substance is not the subject of this review.

P.1 Description of the Composition of the Drug Product

Description of the Composition of the Drug Product
(*3.2.P.1 Description and Composition of the Drug Product.pdf)*

The Drug Product is an ointment, which is intended for topical use. The drug product is provided in a single strength (1% w/w) and intended for only one single application. The composition of the drug product is provided below.

Table 1 Composition of tirbanibulin ointment 1%

Components	Function	Quality	Unit Formula	
			% w/w	Unit (mg)
Tirbanibulin	API	In-house	1.0	2.5[1]
Mono- and Di-glycerides	(b) (4)	USP-NF		(b) (4)
Propylene Glycol		USP		
	Total Nominal Weight		100.0	250.0
(b) (4)				

Description of container closure system –
(*3.2.P.7 Container Closure System.pdf)*

(b) (4)

Reviewer's Assessment: Based on the above information the reviewer has concluded that the applicant has provided adequate description of the drug product composition and the packaging system to support the manufacturing process for the drug product.

Acceptable

P.2 Pharmaceutical Development

P.2.5 Microbiological Attributes:

Container/Closure and Package Integrity – Not Applicable

Antimicrobial Effectiveness Testing– Not Applicable

P.3 Manufacture

P.3.1 Manufacturers

(3.2. P.3.1 Manufacturer(s).pdf)

Athenex Pharma Solutions, LLC, 11342 Main Street, Clarence, NY 14031, USA.
FEI# 3008876196.

All manufacturing activities related to the drug product manufacturing, including packaging, storage, release testing, and stability testing are performed in the above facility.

Reviewer's Assessment: The applicant has provided satisfactory manufactures information to support the manufacturing process of the non-sterile drug product.

Acceptable

P. 3.3 Description of the Manufacturing Process and Process Controls

(3.2.P.3.3 Description of Manufacturing Process and Process Controls.pdf)

Overall Manufacturing Operation

A detailed description and flowchart of the manufacturing process were provided in *3.2.P.3.3 Description of Manufacturing Process and Process Controls.pdf.* Briefly (b) (4)

(b) (4)

(b) (4) are proposed for the Tirbanibulin drug product.

Reviewer's Assessment: Based on the above information the reviewer has concluded that the applicant has provided satisfactory description of the overall manufacturing operation to support the manufacturing process of the non-sterile drug product.

Acceptable

Environmental Monitoring

Reviewer's Assessment: The environmental monitoring information could not be located. This (b) (4) drug product is low risk hence environmental monitoring information is not necessary.

Acceptable

P. 3.5 Process Validation and/or Evaluation

Reviewer's Assessment: Process validation is not reviewed since the drug product is a non-sterile product.

P.5 Control of Drug Product

P. 5.1 Specification

Release specifications for this drug product include:

Microbial Limits	Method (Analytical protocol number)	Specification
Total aerobic microbial count	USP <61> and <62> (APS-QCMETHOD-0033)	< (b) (4) cfu/g
Total yeast and mold count		< cfu/g
S. aureus		Absence of *S. aureus* i (b) (4)
P. aeruginosa		Absence of *P. aeruginosa* i (b) (4)

Reviewer's Assessment: The applicant provided satisfactory microbial limit specifications as per USP<1111> to support the manufacturing process for the drug product. Please note that (b) (4) is not necessary. Please note that the applicant has provide (b) (4) specifications for the excipients and the information can be found in *3.2. P.4.1 Specification(s).pdf*. Based on the information the Propylene Glycol and Mono- and Di-glycerides ha (b) (4) specifications of NMT (b) (4)% and NMT (b) (4)% respectively. Please note that the finish drug product does not have th (b) (4) specification.

Acceptable

P.5.2 Analytical Procedures

- Endotoxin and sterility– Not applicable for a non-sterile, topical product.
- Microbial Limits – USP <61> and USP <62>

P.5.3 Validation of Analytical Procedures

(Described in *3.2. P.5.3: Validation of Analytical Procedures.pdf)*

Microbial Limits assay is performed as per the USP <61> and USP <62>. The Protocol number is stated to be (APS-QCMETHOD-0033). The applicant has provided the actual results of the method suitability studies for USP <61> and USP <62> and the data are summarized below:

Table 7 Results of the (b) (4) TAMC/TYMC Verification: Microbial Enumeration Test USP <61>

Test	Limits	Organism	Average CFU Product Test Control	Average CFU Positive Control	% Recovery	Pass /Fail
Suitability Total Aerobic Microbial Count (TAMC) and Total Yeast and Mold Count (TYMC)	% Recovery (b) (4)	*S. aureus*	(b) (4)			Pass
		P. aeruginosa				Pass
		B. subtilis				Pass
		E. coli				Pass
		A. brasiliensis				Pass
		C. albicans				Pass

(b) (4)

Table 8 Verification Results for Tests for Specified Organisms (USP <62>): *S. aureus* and *P. aeruginosa*

Test	Limits	Organism	Presence/ Absence Product Inoculated Test Control	Presence/ Absence Positive Control	Test Unit	Media Negative Control	Pass / Fail
S. aureus Presence / Absence Test Dilution (b) (4)	(b) (4)	*S. aureus*				(b) (4)	Pass
P. aeruginosa Presence / Absence Test Dilution (b) (4)		*P.aeruginosa*					Pass

Reviewer's Assessment: Microbiological specifications for the non-sterile drug product release and stability is performed using USP <61> and USP <62>. Please note that since the method suitability studies are performed as per the USP <61> and USP <62>, the applicant does not require to submit the test procedures. Please note tha (b) (4) it is low risk. Moreover, adequate microbial quality testing will also be performed (similar product has been approved in (b) (4) MR01.doc, date (b) (4)). Therefore, microbial proliferation during manufacturing or storage is very unlikely. Hence, based on the above information the reviewer has concluded that the applicant has provided satisfactory specifications as per USP<1111> and enumeration data to support the manufacturing process for the drug product.

Acceptable

P.7 Container Closure

Reviewer's Assessment: Please refer to Section P.1 above.

P.8 Stability

P. 8.1 Stability Summary and Conclusion

(3.2.P.8.1: Stability Summary and Conclusion.pdf)

The proposed drug product is stored at 20°C-25°C. The stability testing schedule for the long-term storage condition (25°C ± 2°C/60% ± 5% RH) is captured below:

Stability Protocol:

Stability Test*	Initial	1M	3M	6M	9M	12M	18M	24M	36M
Microbial limit testing Total Aerobic Microbial Count Total combined yeast and mold count Specific Pathogens *S. aureus* *P. aeruginosa*	X	-	-	X	-	X	-	X	X

Proposed Expiry: 24 months

Proposed stability specifications: Same as finished product release specifications.

Reviewer's Assessment: Based on the above information the reviewer has concluded that the applicant has provided satisfactory stability information to support the manufacturing process of the non-sterile drug product.

Acceptable

P. 8.2 Post-Approval Stability Protocol and Stability Commitment

(3.2.P.8.2 Post-approval Stability Protocol and Stability Commitment.pdf)

Post Approval Stability Commitment:

The Applicant commits to continue stability studies on the three-primary registration batches over the entire proposed shelf life period per the proposed protocol provided. Updated Stability data and shelf life extension (if applicable) of Tirbanibulin ointment 1% will be provided in the Annual Report.

Reviewer's Assessment: Based on the above information the reviewer has concluded that the applicant has provided satisfactory post-approval information to support the manufacturing process of the non-sterile drug product.

Acceptable

P.8.3 Stability Data

[Data are provided in *3.2.P.8.3 Stability Data.pdf]*

Stability data has been provided for multiple batches (#F1800591, #F1800596, #F1800605, #F0001-17-0068, #F0001-17-0086, #F0001-17-0047, and #F0001-17-00673) for up to 24 months. The results from long-term stability were reviewed, all the data met the minimum specification for microbial limits.

Reviewer's Assessment: The applicant provided adequate stability data to support the manufacturing of the non-sterile drug product.

Acceptable

A Appendices

A.2 Adventitious Agents Safety Evaluation

Reviewer's Assessment: Not applicable

A.2.1 Materials of Biological Origin

Reviewer's Assessment: Not applicable

A.2.2 Testing at Appropriate Stages of Production

Reviewer's Assessment: Not applicable

A.2.3. Viral Testing of Unprocessed Bulk

Reviewer's Assessment: Not applicable

A. 2.4 Viral Clearance Studies

Reviewer's Assessment: Not applicable

R Regional Information

Executed Batch Records

Reviewer's Assessment: Not applicable

Comparability Protocols- No CP was included in the application.

2. REVIEW OF COMMON TECHNICAL DOCUMENT – QUALITY (CTD-Q) MODULE 1

2.A. Package Insert

Storage temperature: The drug product is proposed to be stored at 20°C-25°C (68°F-77°F), excursions permitted to 15°C-30°C (59°F-86°F). Do not refrigerate or freeze.

Route of administration (b) (4) (b) (4) for topical use only; not for oral or ophthalmic use.

Reviewer's Assessment: The applicant provided satisfactory package insert information to support the manufacturing of the non-sterile drug product.

Acceptable

List of Deficiencies: *None*

Primary Microbiology Reviewer Name and Date:

Koushik Paul, Ph.D. and 03/09/2020

Secondary Reviewer Name and Date (and Secondary Summary, as needed):

Jesse Wells, Ph.D. and 03/09/2020

Jesse Wells

Digitally signed by Jesse Wells
Date: 3/09/2020 12:41:36PM
GUID: 508da70b00028ea901ac6652677f7d00

Koushik Paul

Digitally signed by Koushik Paul
Date: 3/09/2020 10:16:57AM
GUID: 5600522e0069b02f59c7bd85b6b54742

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/

HAMID R SHAFIEI
09/24/2020 10:57:53 AM