

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

213189Orig1s000

OTHER REVIEW(S)

Clinical Inspection Summary

DATE	December 9, 2020
From	Jenn Sellers M.D. on behalf of John Lee, M.D., Medical Officer Phillip Kronstein, M.D., Team Leader Kassa Ayalew, M.D., M.P.H., Branch Chief Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	Jennifer Harmon, Regulatory Project Manager Roselyn Epps, M.D., Medical Officer David Kettl, M.D., Clinical Team Leader Division of Dermatologic and Dental Products (DDDP)
Application	NDA 213189
Applicant	Athenex, Inc.
Drug	Terbanibulin (proposed, (b) (4))
NME/Original NDA	Yes
Review Timeframe	Standard
Proposed Indication	Actinic Keratosis of the Face or Scalp
Consultation Date	February 18, 2020
CIS Goal Date	October 14, 2020 (original); December 10, 2020 (extended)
Action Goal Date	December 14, 2020
PDUFA Due Date	December 30, 2020

I. OVERALL ASSESSMENT OF FINDINGS

The clinical sites of Drs. Swinyer, Bukhalo, Bruce, and Forman were inspected in support of this NDA. Based on the results of these inspections, the studies (KX01-AK-003 and KX01-AK-004) appear to have been conducted adequately, and the data generated by these sites appear acceptable in support of the respective indication.

II. BACKGROUND

This NDA 213189 submitted by Athenex, Inc. is in support of the marketing approval of tirbanibulin, for the topical treatment of actinic keratosis (**AK**), an abnormal proliferation of superficial skin cells (intra-epidermal keratinocytes) that frequently progresses to cancer (squamous cell carcinoma, **SCC**).

Tirbanibulin (also referred to as KX2-391 or KX01 in study protocols) is a synthetic new molecular entity (NME) that appears to selectively inhibit cell tubulin polymerization to block the proliferation of abnormal (atypical) keratinocytes. Early studies indicate that the topical application of tirbanibulin to AK lesions (once daily for 5 days) is safe and effective in eliminating the (pre-cancerous) AK lesions. Tirbanibulin appears to be effective also against (frank) cancer, including (intra-oral) SCC. Up to 65% of SCC cases originate from AK (10% 10-year risk), and SCC currently ranks as the second most common cause of skin cancer deaths in the US.

To support the review of this new NME NDA, four CI sites were identified for GCP inspection, two sites for each of the two pivotal studies nearly identical in design and sharing the same study title (described together below).

Studies KX01-AK-003 and KX01-AK-004: *A Phase 3, Double-Blind, Vehicle-Controlled, Randomized, Parallel Group, Multicenter, Efficacy and Safety Study of KX2-391 Ointment 1% in Adult Subjects with Actinic Keratosis on the Face or Scalp*

These two double-blind randomized controlled trials were conducted between September 2017 and April 2019 in 351 adult subjects randomized at 31 US sites (identical for both studies). The (common) primary study objective was to evaluate the efficacy of topical KX2-391 (1% free-base ointment) relative to vehicle control (0% ointment), when applied once daily for five consecutive days to a contiguous 25 cm² area of skin containing AK lesions, in eliminating all lesions within the application area by Day 57.

The study consisted of screening, treatment, response assessment (Days 5, 8, 15, 29, and 57), and follow-up. Subject randomization (equal ratio, KX2-391 or vehicle) was stratified by skin region (face or scalp, 2/3 or 1/3 of subjects, respectively).

- Subjects were selected if determined to have an index 25 cm² skin area (face or scalp) containing 4-8 morphologically typical AK lesions (gross examination, no histopathologic confirmation). The intended index area was not permitted to contain any atypical and/or rapidly changing AK lesion.
- The subjects self-applied the topical study medication, the first application under staff supervision at the study site and the remaining four applications at home. The same physician dermatologist evaluated and tracked the lesions (including lesion count) within the index area, at baseline and for all study visits.

All subjects with any adverse event of the skin within the topically treated area (presumed skin reaction) were followed longer for safety (every 7-28 days) until the skin reaction resolved or stabilized. Subjects who cleared all lesions were also followed longer for efficacy (every 3 months) for AK recurrence up to 12 months.

III. RESULTS

1. Leonard J. Swinyer, M.D.

Site #320
4970 S Waimea Way,
Holladay, Utah 84117
Inspection dates: 04/14/2020 - 04/17/2020

At this site for Protocol KX01-AK-003, 24 subjects were screened, 20 were enrolled, and 14 of those enrolled completed the study.

The study records reviewed records included, but were not limited to, informed consent; inclusion/exclusion criteria; randomization, dosing, and study drug administration; the primary efficacy endpoints; adverse event reporting; protocol compliance; and other documents: IRB approvals and communication letters; IRB approved advertisement; follow up letters from study monitors; email and letter communication from the sponsor; investigational product shipping records; site training records; investigational brochure and contact information from the sponsor.

The primary efficacy endpoint data were verified against the data line listings provided by the sponsor; no discrepancies were noted. There was no evidence of underreporting of adverse events.

2. Michael Bukhalo, M.D.

Site #323
5301 Keystone Court
Rolling Meadows, Illinois 60008
Inspection dates: 07/13/2020 - 07/16/2020

At this site for Protocol KX01-AK-003, 21 subjects were screened, 20 subjects were enrolled, and all enrolled have completed the study.

Study records reviewed for this protocol included (but were not limited to): IRB approvals; monitoring reports; site signature and responsibility logs; and site training logs. All informed consent forms were reviewed. The primary efficacy endpoint was the number of actinic keratosis (AK) lesions at Day 57. The AK lesions reported for the baseline visit and Day 57 were reviewed for all subjects enrolled. Six enrolled subject records were audited for protocol adherence, adverse event reporting, test article accountability, and concomitant medications.

There was no evidence of under-reporting of adverse events. No discrepancies were noted. There was no evidence of underreporting of adverse events.

3. Suzanne Bruce, M.D.

Site #407
1900 St. James Place
Suite 650
Houston, Texas 77056
Inspection dates: 06/09/2020 - 06/11/2020

At this site for Protocol KX01-AK-004, 23 subjects were screened, 20 were enrolled, and all of whom enrolled completed the study.

Twenty subject records were reviewed during this inspection which included, but not limited to, subject medical records, source documents, Independent Review Board (IRB)/CI correspondences, and drug accountability logs, training records, delegation of authority logs, financial disclosures, drug accountability, randomization scheme, study eligibility criteria, the primary efficacy endpoint data, adverse events, and protocol deviations.

The primary efficacy endpoint data were verified against the data line listings provided by the sponsor; no discrepancies were noted. There was no evidence of underreporting of adverse events.

4. Seth Forman, M.D.

Site #411
15416 N Florida Ave
Tampa, Florida 33613
Inspection dates: 08/03/2020 - 08/06/2020

At this site for Protocol KX01-AK-004, 20 subjects were screened and enrolled. All subjects completed the study.

The study records for all 20 screened were reviewed during the inspection including the procedures and records related to the authority and administration of the clinical trial, the protocol and amendment, IRB submissions and documentation, subject records, financial disclosures, investigational product controls, and the monitoring of the study. The inspection also reviewed all available relevant records as follows: informed consent forms, protocol and amendment, signed investigator agreements, financial disclosure statements, IRB submissions and correspondence, adverse event reporting, clinical source data, study test article accountability, concomitant medication, data listings, and sponsor monitoring activities.

The primary efficacy endpoint data were verified against the data line listings provided by the sponsor; no discrepancies were noted. There was no evidence of underreporting of adverse events.

{See appended electronic signature page}

Jenn Sellers, M.D.
John Lee, M.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

{See appended electronic signature page}

Phillip D. Kronstein, M.D.
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Office of Scientific Investigations

CC:

Central Document Room / NDA 213189

DDDP / Clinical Team Leader / David Kettl

DDDP / Medical Officer / Roselyn Epps

DDDP / Regulatory Project Manager / Jennifer Harmon

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OSI / DCCE / GCPAB / Program Analyst / Yolanda Patague

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/s/

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12/09/2020 04:49:51 PM

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

Date of This Memorandum:	September 10, 2020
Requesting Office or Division:	Division of Dermatology and Dentistry (DDD)
Application Type and Number:	NDA 213189
Product Name and Strength:	Klisyri (tirbanibulin) ointment, 1%
Applicant/Sponsor Name:	Athenex, Inc.
OSE RCM #:	2019-2686-1
DMEPA Safety Evaluator:	Madhuri R. Patel, PharmD
DMEPA Team Leader:	Sevan Kolejian, PharmD, MBA

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received on September 1, 2020 for Klisyri. Division of Dermatology and Dentistry (DDD) requested that we review the revised container labels and carton labeling for Klisyri (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a

2 CONCLUSION

The Applicant implemented all of our recommendations. The carton labeling is acceptable from a medication error perspective. However, we note the net quantity statement on the container label has been removed from the Principal Display Panel (PDP) and we recommend adding the net quantity statement back.

3 RECOMMENDATIONS FOR ATHENEX, INC.

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

- A. For the container label, consider adding back the net quantity statement (e.g. 0.25 g). This may be located above the tear line if needed.

^a Patel, M. Label and Labeling Review for Klisyri (NDA 213189). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 MAY 26. RCM No.: 2019-2686.

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/s/

MADHURI R PATEL
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SEVAN H KOLEJIAN
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**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: July 30, 2020

To: Jennifer Harmon, PharmD
Regulatory Project Manager
Division of Dermatology and Dentistry (DDD)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Shawna Hutchins, MPH, BSN, RN
Senior Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

From: Susan Redwood, MPH, BSN, RN
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Laurie Buonaccorsi, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Patient Package Insert (PPI)

Drug Name (established name): KLISYRI (tirbanibulin)

Dosage Form and Route: ointment, for topical use

Application Type/Number: NDA 213189

Applicant: Athenex, Inc.

1 INTRODUCTION

On December 30, 2019, Athenex, Inc., submitted for the Agency's review an original New Drug Application (NDA) 213189 for KLISYRI (tirbanibulin) ointment, for topical use indicated for the treatment of actinic keratosis (AK) of the face or scalp.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Dermatology and Dentistry (DDD) on January 23, 2020, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for KLISYRI (tirbanibulin) ointment, for topical use.

2 MATERIAL REVIEWED

- Draft KLISYRI (tirbanibulin) ointment PPI received on December 30, 2019, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on July 23, 2020.
- Draft KLISYRI (tirbanibulin) ointment Prescribing Information (PI) received on December 30, 2019, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on July 23, 2020.

3 REVIEW METHODS

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

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

In our collaborative review of the PPI we:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

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

Please let us know if you have any questions.

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/s/

SUSAN W REDWOOD
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LAURIE J BUONACCORSI
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SHAWNA L HUTCHINS
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LASHAWN M GRIFFITHS
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**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

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

Memorandum

Date: July 29, 2020

To: Roselyn Epps, Clinical Reviewer,
Division of Dermatology and Dentistry (DDD)
Jennifer Harmon, Regulatory Project Manager, DDD

From: Laurie Buonaccorsi, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Matthew Falter, Team Leader, OPDP

Subject: OPDP Labeling Comments for KLISYRI (tirbanibulin) ointment, for topical use

NDA: 213189

In response to DDD's consult request dated April 8, 2020, OPDP has reviewed the proposed product labeling (PI), patient package insert (PPI), and carton and container labeling for the original NDA submission for KLISYRI (tirbanibulin) ointment, for topical use (tirbanibulin).

PI and PPI: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DDD on July 23, 2020 and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed PPI will be sent under separate cover.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on December 30, 2019, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Laurie Buonaccorsi at (240) 402-6297 or laurie.buonaccorsi@fda.hhs.gov.

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/s/

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

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

Date of This Review:	May 26, 2020
Requesting Office or Division:	Division of Dermatology and Dentistry (DDD)
Application Type and Number:	NDA 213189
Product Name, Dosage Form, and Strength:	Klisyri (tirbanibulin) ointment, 1%
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Athenex, Inc.
FDA Received Date:	December 30, 2019
OSE RCM #:	2019-2686
DMEPA Safety Evaluator:	Madhuri R. Patel, PharmD
DMEPA Team Leader:	Sevan Kolejian, PharmD, MBA

1 REASON FOR REVIEW

As part of the approval process for Klisyri (tirbanibulin) ointment, 1%, the Division of Dermatology and Dentistry (DDD) requested that we review the proposed labels and labeling for areas that may lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B – N/A
Human Factors Study	C – N/A
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review

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

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We reviewed the Prescribing Information (PI), Patient Package Insert (PPI), container labels and carton labeling and noted that the label and labeling can be improved to prevent wrong dose errors and to facilitate product identification. We note the placeholder “TRADENAME” should be replaced with the name “Klisyri”, which was found conditionally acceptable on March 31, 2020^a.

4 CONCLUSION & RECOMMENDATIONS

We conclude that the proposed label and labeling can be improved to facilitate product identification and prevent wrong dose errors. We provide recommendations below in Section 4.1 for the Division and Section 4.2 for the Applicant to address our concerns.

^a Patel, M. Proprietary Name Review for Klisyri (NDA 213189). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 MAR 31. Panorama No. 2020-37451349

4.1 RECOMMENDATIONS FOR DIVISION OF DERMATOLOGY AND DENTISTRY (DDD)

A. Prescribing Information

1. General Comments

- a. Replace the name, "TRADENAME", with the conditionally acceptable proprietary name, "Klisyri" throughout the label and labeling.
- b. We note the use of the term (b) (4) to describe the product in the Prescribing Information and carton labeling. We defer to the Office of Pharmaceutical Quality (OPQ) to determine the package type term for this product. Ensure that the OPQ determined package type term is used throughout the labels and labeling.

2. How Supplied/Storage and Handling Section

- a. We note the total net quantity for the carton is not listed. We recommend adding the total net quantity for the 5 packets. Ensure the units used for the net quantity is consistent throughout the label and labeling.

4.2 RECOMMENDATIONS FOR ATHENEX, INC.

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

B. General Comments (Container labels & Carton Labeling)

1. Replace "Tradename" with the conditionally accepted proprietary name, Klisyri.
2. The cartons containing 5 packets use the same NDC on the carton and container labels. The container label of one packet and the carton labeling of 5 packets should have different NDC package codes (last 2 digits of the NDC). Revise the NDC numbers so that the carton labeling and container labels use a different NDC package code. Please note, the professional sample carton and container labels would also need different package codes.

C. Container Labels

1. To facilitate product identification, we recommend relocating the product proprietary name below the tear lines for the packet as they currently appear above the point to separation.
2. If space permits, consider adding: Discard unused portion.

D. Carton Labeling

1. To ensure consistency with the Prescribing Information, revise the statement, (b) (4) to read "Recommended Dosage: See prescribing information."

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Klisyri received on December 30, 2019 from Athenex, Inc..

Table 2. Relevant Product Information for Klisyri	
Initial Approval Date	N/A
Active Ingredient	tirbanibulin
Indication	topical treatment of actinic keratosis of the face or scalp
Route of Administration	topical
Dosage Form	ointment
Strength	1%
Dose and Frequency	(b) (4)
How Supplied	(b) (4)
Storage	Store 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
Container Closure	packet

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^b along with postmarket medication error data, we reviewed the following Klisyri labels and labeling submitted by Athenex, Inc..

- Container label received on December 30, 2019
- Carton labeling received on December 30, 2019
- Professional Sample container label received on December 30, 2019
- Professional Sample Carton Labeling received on December 30, 2019
- Prescribing Information and Patient Package Insert (Image not shown) received on December 30, 2019, available from <\\cdsesub1\evsprod\nda213189\0001\m1\us\labelv36dec2019.pdf>

G.2 Label and Labeling Images

(b) (4)



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

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/s/

MADHURI R PATEL
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SEVAN H KOLEJIAN
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Memorandum

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

Date: May 7, 2020

From: Interdisciplinary Review Team for Cardiac Safety Studies

Through: Christine Garnett, Pharm.D.
Clinical Analyst, DCN

To: Jennifer Harmon, RPM
DDDP

Subject: IRT Consult to NDA # 213189 (SDN # 001)

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

This memo responds to your consult to us dated 2/21/2020 regarding the sponsor's QT assessment. We reviewed the following materials:

- Sponsor's cardiac safety report (SN0001 / SDN001; [link](#));
- Sponsor's QT assessment (SN0001 / SDN001; [link](#));
- Sponsor's proposed product label (SN0001 / SDN001; [link](#)); and
- Highlights of clinical pharmacology and cardiac safety (SN0001 / SDN001; [link](#)).

1 Internal Comments to the Division

At the sub-nanomolar systemic exposures with the topical application (as ointment 1% w/w) of tirbanibulin at the proposed therapeutic dose, clinically relevant QT/QTc prolongation are unlikely and large increases in QTc were not observed in subjects undergoing routine safety ECGs assessments in phase 2 and 3 clinical studies. A thorough QT study is not usually necessary for topical drugs with low systemic bioavailability.

2 Recommendations

We propose (b) (4) a thorough QT study is not necessary for this product and such an assessment was not conducted. Section 12.2 is for the results of a thorough QT study and not for the results from routine safety ECGs. Please note, that this is a suggestion only and that we defer final labeling decisions to the Division.

3 Background

3.1 Product Information

Athenex, Inc. is developing tirbanibulin for the topical treatment of actinic keratosis of the face or scalp. Tirbanibulin (KX2-391, KX01; MW: 431.5 g/mol, freebase) is actinic keratosis agents (keratolytic/ antiproliferative). Tirbanibulin is expected to bind to tubulin resulting in inhibition of tubulin polymerization and disruption of Src signaling. The sponsor claims that tirbanibulin exerts antiproliferative effects in multiple cancer cell lines and immortalized human keratinocytes in vitro via induction of cell cycle arrest and apoptosis. The product is formulated as ointment containing 1% w/w tirbanibulin (10 mg per gram) for topical administration. The proposed dose is once daily topical application for 5 consecutive days using 1 (b) (4) packet per application (250 mg ointment; 2.5 mg tirbanibulin per unit). Tirbanibulin exhibits a low systemic absorption following topical administration (Study # KX01-AK-007).

The sponsor conducted maximal use pharmacokinetics study using to-be marketed formulation (Study # KX01-AK-007). This was a phase 1, open-label, uncontrolled, non-randomized, parallel group study evaluating the systemic exposure and safety of tirbanibulin in subjects with actinic keratosis lesions. The primary objective of this study was to determine the pharmacokinetics of tirbanibulin following topical administration of 1% ointment under maximal use conditions (MUSE). The study consisted of screening, treatment, and follow-up periods. The subjects (n=18) were randomized (1:1) in 2 groups to receive once daily treatment for 5 consecutive days (25 cm² on face in group-1 and on scalp in group-2; self-application in the morning using (b) (4) (b) (4) packets). The actinic keratosis lesion counts for subjects enrolled in this study were higher than the phase 3 studies (median: 8.4 versus 6.0 lesions).

Pharmacokinetic samples for the determination of tirbanibulin (LLOQ: 0.01 ng/mL) and its metabolites (LLOQ: 0.05 ng/mL) were collected on Days 1, 3, and 4 at 0 (pre-dose), and on Day 5 at 0 (pre-dose), at 2, 4, 6, 8, 10, 12, 16, and 24 hours post-the Day 5 application. ECGs were collected during screening, treatment (Days 1 and 5), and follow-up visit (Day 29 or early termination).

The peak concentrations of 0.34 ± 0.29 ng/mL and 0.18 ± 0.1 ng/mL were observed for group 1 (on face) and group 2 (on scalp), respectively. The average peak concentrations for KX2-391 across both groups 0.258 ng/mL (0.598 nM). One subject had a peak concentration of 1.09 ng/mL (~2.53 nM) and all other 17 subjects had peak concentrations at or lower than 0.428 ng/mL. The sponsor's analysis indicates that the metabolites (KX2-5036 and KX2-5163) concentrations were mostly below limit of quantification (LC-MS/MS method). The sponsor claims lack of association between steady-state exposure (Day 5; C_{min}) and time-matched QTcF or ΔQTcF in 18 subjects. Overall, minimal systemic exposure of tirbanibulin was observed after topical application under maximal use conditions.

3.2 Sponsor's Position related to the Question

The sponsor claims that there is a low risk of QT prolongations associated with topical administration of tirbanibulin based on the data from their non-clinical and clinical studies (# KX01-AK-003 and KX01-AK-004). In addition, minimal systemic exposure of tirbanibulin was observed following its topical application under maximal use conditions (Study # KX01-AK-007).

The absence of nonclinical cardiac findings in the dog telemetry study are consistent with the lack of a QT interval prolongation observed in the clinical program for KX2-391 in humans. In addition, the lack of potential for tirbanibulin to delay cardiac repolarization in the hERG assay with an exposure margin of >9700 (based upon total individual maximum plasma concentration of 1.09 ng/mL at steady-state from the MUSE study), and the lack of association between post-dose time (at steady-state and Tmax) and $\Delta QTcF$ from Phase 3 ECG monitoring (ERT Cardiac Safety Report), all point to the cardiac safety of tirbanibulin ointment 1%.

In conclusion, the collected data demonstrated sub-nanomolar exposure and did not show mean increases in QTcF to the level of clinical or regulatory concern with the topical use of tirbanibulin ointment 1% once daily for 5 days in adult recipients with AK. There was also no observed effect on other ECG parameters in patients (PR, QRS, HR, RR, T wave morphology). These data support tirbanibulin as low risk for causing effects associated with prolongation of the QT interval. These data support the Sponsor's conclusion that a thorough QT clinical study is not justified.

3.3 Nonclinical Cardiac Safety

Refer to the sponsor's highlights of clinical pharmacology and clinical safety. The expected highest concentrations of ~1 ng/mL (Study # KX01-AK-007; PPB: 88%) at steady-state with proposed dosing offers >10000-fold margin (hERG IC50 ~ 24.67 μ M or ~10600 ng/mL).

In a functional hERG patch-clamp study (Study YY91QH) the IC50 for KX2-391 was 24.67 μ M. A hERG patch-clamp study with the metabolite KX2-5036 (Study XV31HF) showed no significant inhibition of the hERG potassium current up to the highest concentration tested (30 μ M).

3.4 Clinical Cardiac Safety

Refer to the sponsor's highlights of clinical pharmacology, clinical safety and the sponsor's clinical summary of safety ([m2.7.4](#)), and the sponsor's cardiac safety report.

This was a Phase 3, double-blind, vehicle-controlled, randomized, parallel group, multicenter, efficacy and safety study of KX2-391 Ointment 1% in adult subjects with actinic keratosis on the face or scalp.

There were 348 subjects treated with KX2-391 while 343 received vehicle in the QT/QTc population. Single ECGs were recorded at Day 1 pre-dose (baseline), Day 5, and Day 15. Changes from baseline in cardiac intervals were small in both treatment arms. Vehicle-corrected changes from baseline were also minimal. Mean $\Delta\Delta QTcF$ was 0.6 msec on Day 5 and 1.1 msec on Day 15 (10-day washout) with an upper bound of the 2-sided 90% CI < 3 msec at both time points. Mean HR, PR, and QRS changes from baseline and vehicle-corrected were small and not clinically significant. Outliers were infrequent and evenly distributed between treatment groups. Morphological analysis and diagnostic interpretation did not show evidence of an adverse cardiac effect of KX2-391 treatment.

In conclusion, the collected data did not show mean increases in QTcF to the level of clinical or regulatory concern with the topical use of KX2-391 ointment 1% once daily for 5 days in adult recipients with actinic keratosis. There is also no observed effect on other ECG parameters (PR, QRS, HR, RR, T wave morphology).

3.5 Summary Results of Prior QTc Assessments

As a substitution request for thorough QT study, the sponsor proposed to use the QT analysis performed using data from their 2 identical phase-3 studies (Study # KX01-AK-003 & KX01-AK-004).

Study # KX01-AK-003 was a phase-3, double-blind, vehicle-controlled, randomized, parallel group, multicenter, efficacy and safety study in adult subjects with actinic keratosis on the face or scalp. The study consisted of screening, treatment, response assessment (up to day 57), and recurrence follow-up periods. Subjects (n=351) were randomized to treatment on Day 1 in a 1:1 (ointment 1% or vehicle) ratio in each treatment area subgroup (2:1 - face: scalp). Tirbanibulin ointment 1% (250 mg of ointment in single use packets) was applied topically once daily for 5 consecutive days to the 25 cm² treatment area.

Study # KX01-AK-004 was a phase-3, double-blind, vehicle-controlled, randomized, parallel group, multicenter, efficacy and safety study in adult subjects with actinic keratosis on the face or scalp. The study consisted of screening, treatment, response assessment (up to day 57), and recurrence follow-up periods. Subjects (n=351) were randomized to treatment on Day 1 in a 1:1 (ointment 1% or vehicle) ratio in each treatment area subgroup (2:1 - face: scalp). Tirbanibulin ointment 1% (250 mg of ointment in single use packets) was applied topically once daily for 5 consecutive days to the 25 cm² treatment area.

Both studies included 12-lead safety ECGs on Day 1 pre-dose (baseline), Day 5 (collected after administration of the final dose of this 5-day treatment regimen) and Day 15 (10 days post dose).

The collected data did not show mean increases in QTcF to the level of clinical or regulatory concern with the topical use of KX2-391 ointment 1% once daily for 5 days in adult recipients with actinic keratosis. There is also no observed effect on other ECG parameters (PR, QRS, HR, RR, T wave morphology).

Reviewer's comments: Submitted data by the Sponsor do not indicate a clinically relevant effect of tirbanibulin on the QTc interval at the proposed therapeutic dose.

3.6 Relevant Details of Planned Phase 3 Study

Not applicable.

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

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

/s/

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