CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213189Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	NDA
Application Number(s)	213189
Priority or Standard	Standard
Submit Date(s)	12/30/2019
Received Date(s)	12/30/2019
PDUFA Goal Date	12/30/2020
Division/Office	Division of Dermatology and Dentistry/Office of Immunology and Inflammation
Review Completion Date	12/09/2020
Established/Proper Name	tirbanibulin
(Proposed) Trade Name	Klysiri
Pharmacologic Class	Microtubule Inhibitor
Code name	
Applicant	Athenex Inc.
Dosage form	Ointment
Applicant proposed Dosing Regimen	Apply sufficient ointment to evenly cover a 25 cm^2 treatment field on the face or scalp once daily for 5 consecutive days using 1 (b) (4) packet per application
Applicant Proposed Indication(s)/Population(s)	Actinic keratosis of the face or scalp in adults
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	For the treatment of actinic keratosis
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Indicated for the topical treatment of actinic keratosis of the face or scalp Adults
Recommended SNOMED CT Indication Disease Term for each Indication (if applicable)	201101007 |Actinic keratosis (disorder)
Recommended Dosing Regimen	Once daily for 5 consecutive days using 1 single-dose packet per application.

Table of Contents

Table of Tables

Table of Figures

Reviewers of Multi-Disciplinary Review and Evaluation

Regulatory Project Manager	Jennifer Harmon, PharmD
Nonclinical Reviewer	Norman See, PhD
Nonclinical Supervisor	Barbara Hill, PhD
Nonclinical Division Director	Andrew Goodwin, PhD
Office of Clinical Pharmacology Reviewer(s)	Liping (Cindy) Pan, PhD
Office of Clinical Pharmacology Team Leader(s)	Chinmay Shukla, PhD
Clinical Reviewer	Roselyn E. Epps, M.D., FAAD
Clinical Team Leader	David Kettl, MD
Statistical Reviewers	Guoying Sun, PhD Kathleen Fritsch, PhD
Statistical Team Leaders	Wanjie Sun, PhD Mohamed Alosh, PhD
Cross-Disciplinary Team Leader	David Kettl, MD
Division Director (DPT-II)	Andrew Goodwin, PhD
Division Director (OCP)	Chandrahas G Sahajwalla, PhD
Division Director (OB)	Laura Lee Johnson, PhD
Division Deputy Director (DDD)	Shari L. Targum, MD, MPH
Office Director (OII)	Julie Beitz, MD

Additional Reviewers of Application

OPQ	Application Technical Lead: Hamid Shafiei, Ph.D. Regulatory Business Process Manager: Melinda Bauerlien, M.S. Drug Substance Review: Jeffrey Medwid, Ph.D. / Donna Christner, Ph.D. Drug Product Review: Caroline Strasinger, Ph.D. / Moo-Jhong Rhee, Ph.D. Manufacturing Review: Rose Xu, Ph.D. / Vidya Pai, Ph.D. Biopharmaceutics Review: Tapash Ghosh, Ph.D. Microbiology Review: Koushik Paul, Ph.D. / Jesse Wells, Ph.D. Enviromental Assessment Review: Caroline Strasinger, Ph.D. / Moo-Jhong Rhee, Ph.D.
OND/DCN	IRTCSS: Christine Garnett, PharmD, Clinical Analyst
OMP/DMPP	Patient Labeling Reviewer: Susan Redwood, MPH, BSN, RN / Shawna Hutchins, MPH, BSN, RN /LaShawn Griffiths, MSHS-PH, BSN, RN
OPDP	Presciption Drug Promotion: Laurie Buonaccorsi, Regulatory Review Officer / Matthew Falter PharmD
OSE/DMEPA	Safety Evaluator: Madhuri Patel, PharmD / Sevan Kolejian, PharmD, MBA
OSE/DRM	Risk Management Analyst: Donnella Fitzgerald, PharmD / Lindsey Crist, PharmD, BCPS / Jacqueline Sheppard, PharmD / Doris Auth, PharmD
OSE/PMS	Safety Project Management: Tri Bui-Nguyen, PhD / Sue Kang, MS
OSI/DCCE	Reviewer: John Lee, MD / Phillip Kronstein, MD

OPQ=Office of Pharmaceutical Quality
OMP/DMPP=Office of Medical Policy / Division of Medical Policy Program
OND/DCN=Office of New Drugs / Divison of Cardiology and Nephrology
OPDP/DMPP=Office of Prescription Drug Promotion
OSE/DMEPA=Office of Surveillance and Epidemiology /Division of Medication Error Prevention and Analysis
OSE/DRM=Office of Surveillance and Epidemiology / Division of Risk Managment
OSI/DCCE=Office of Scientific Investigations / Division of Clincal Compliance Evaluation

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Application Technical Lead	Hamid Shafiei, PhD	Office of Pharmaceutical Quality (OPQ) / Division of New Drug Products	Sections: 4.2	Select one: ___ Authored _✓_ Approved
	Signature: *{See appended electronic signature page}*			
Nonclinical Reviewer	Norman See, PhD	Office of Immunology and Inflammation (OII)/Division of Pharmacology Toxicology for Immunology and Inflamation (DPTII)	Sections: 5, 19.3	Select one: _✓_ Authored ___ Approved
	Signature: *{See appended electronic signature page}*			
Nonclinical Supervisor	Barbara Hill, PhD	OII/DPTII	Sections: 5, 19.3	Select one: ___ Authored _✓_ Approved
	Signature: *{See appended electronic signature page}*			
Nonclinical Division Director	Andrew Goodwin, PhD	OII/DPTII	Sections: 5, 19.3	Select one: ___ Authored _✓_ Approved
	Signature: *{See appended electronic signature page}*			
Clinical Pharmacology Reviewer	Liping Cindy Pan, PhD	Office of Clinical Pharmacology (OCP) Division of Immunology and Inflammation Pharmacology (DIIP)	Sections: 6 and 19.4	Select one: _✓_ Authored ___ Approved
	Signature: *{See appended electronic signature page}*			
Clinical Pharmacology Team Leader	Chinmay Shukla, PhD	OCP/DIIP	Sections: 6 and 19.4	Select one: ___ Authored _✓_ Approved
	Signature: *{See appended electronic signature page}*			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Pharmacology Division Director	Chandrahas G Sahajwalla, PhD	OCP/DIIP	Sections: 6 and 19.4	Select one: ___ Authored ✓ Approved
	Signature: *{See appended electronic signature page}*			
Clinical Reviewer	Roselyn Epps, MD, FAAD	Office of Immunology and Inflammation (OII) / Division of Dermatology and Dentistry (DDD)	Sections: 1, 2, 3, 4.1, 7.1, 7.2, 8.1, 8.2, 9, 10, 11, 12, 13, 19.2	Select one: ✓ Authored ___ Approved
	Signature: *{See appended electronic signature page}*			
Clinical Team Leader	David Kettl, MD, FAAP	OII/DDD	Sections: 1, 2, 3, 4.1, 7.1, 7.2, 8.1, 8.2, 9, 10, 11, 12, 13, 19.2	Select one: ___ Authored ✓ Approved
	Signature: *{See appended electronic signature page}*			
Deputy Division Director (Clinical)	Shari Targum, MD, MPH, FACC, FACP	OII/DDD	Section: ALL	Select one: ___ Authored ✓ Approved
	Signature: *{See appended electronic signature page}*			
Office Direector (Clinical)	Julie G. Beitz, MD	OII	Sections: ALL	Select one: ___ Authored ✓ Approved
	Signature: *{See appended electronic signature page}*			
Statistical Reviewer	Guoying Sun, PhD	Office of Biostatistics (OB) / Division of Biostatistics VII (DBVIII)	Sections: 8.1, 8.3, and 19.4.4	Select one: ✓ Authored ___ Approved
	Signature: *{See appended electronic signature page}*			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Statistical Team Leader	Wanjie Sun, PhD	OB/DBVIII	Sections: 8.1, 8.3, and 19.4.4	Select one: ___ Authored ✓ Approved
	Signature: *{See appended electronic signature page}*			
Statistical Reviewer	Kathleen Fritsch, PhD	Office of Biostatistics (OB) / Division of Biostatistics III (DBIII)	Sections: 8.1, 8.3, and 19.4.4	Select one: ✓ Authored ___ Approved
	Signature: *{See appended electronic signature page}*			
Statistical Team Leader	Mohamed Alosh, PhD	OB/DBIII	Sections: 8.1, 8.3, and 19.4.4	Select one: ___ Authored ✓ Approved
	Signature: *{See appended electronic signature page}*			
Division Director (Statistical)	Laura Lee Johnson, PhD	OB/DBIII	Sections: 8.1, 8.3, and 19.4.4	Select one: ___ Authored ✓ Approved
	Signature: {See appended electronic signature page}			

Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AESI	adverse event of special interest
AK	actinic keratosis
ALT	alanine aminotransferase
AR	adverse reaction
AST	aspartate aminotransferase
AUC	area under the curve
BCC	basal cell carcinoma
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
BSA	body surface area
BW	body weight
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CI	confidence interval
CMC	chemistry, manufacturing, and controls
CMH	Cochran-Mantel-Haenszel
COA	clinical outcomes assessment
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
CYP	cytochrome P450
DHOT	Division of Hematology Oncology Toxicology
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice

GD	gestation day
GRMP	good review management practice
hERG	human Ether-à-go-go-Related Gene
ICH	International Conference on Harmonisation
IND	Investigational New Drug
IP	investigational product
IRT	Interdisciplinary Review Team
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent-to-treat
KM	Kaplan-Meier
LOAEL	low observed advese effect level
LLOQ	lower limit of quantitation
LSR	local skin reaction
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
MM	malignant melanoma
MPE	micronucleated polychromatic erythrocytes
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
NOAEL	no observed adverse effect level
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert (also known as Patient Information)
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
PWCBP	patients who can become pregnant
RBC	red blood cell
REMS	risk evaluation and mitigation strategy
RIPT	repeat insult patch test
RFU	recurrence follow-up
Rxn	reaction

SAE	serious adverse event
SAP	statistical analysis plan
SCC	squamous cell carcinoma
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event
TK	toxicokinetics
WBC	white blood cell

1 Executive Summary

1.1. Product Introduction

Klisyri® (tirbanibulin) ointment, 1% is a synthetic, small molecule, new molecular entity (NME). The single-dose 250 mg packets contain 2.5 mg of tirbanibulin, to be applied daily to a 25 cm^2 area of the face or scalp for five consecutive days. For the purpose of this review, tirbanibulin, KX2-391, and "study drug" will be used interchangeably.

1.2. Conclusions on the Substantial Evidence of Effectiveness

This multidisciplinary review recommends approval for KLISYRI (tirbanibulin) ointment 1%, for the indication of multiple actinic keratoses of the face or scalp in adults.

Athenex has provided sufficient evidence that tirbanibulin ointment treats actinic keratoses of the face or scalp superiorly to vehicle in adults. Athenex submitted two randomized, double-blind, vehicle-controlled clinical trials to support the safety and efficacy for this new drug application. Tirbanibulin was demonstrated to be superior to vehicle in the randomized vehicle-controlled trials. Tirbanibulin ointment demonstrated an acceptable benefit-risk safety profile, as local skin reactions were the predominant adverse events.

The benefits of tirbanibulin ointment 1% treatment are that the treatment is nonsurgical, outpatient, and multiple lesions may be treated at once. The drug is topical and administered by the patient at home. Although other FDA-approved products are available for the treatment of actinic keratosis of the face or scalp, tirbanibulin ointment 1% is another therapeutic option for consideration by prescribers.

1.3. Benefit-Risk Assessment

[Do not insert text here. Use the table]

Benefit-Risk Summary and Assessment

Klisyri® (tirbanibulin) ointment, 1% is a small molecule, new molecular entity microtubule inhibitor.

The benefits of tirbanibulin ointment 1% treatment are that the treatment is nonsurgical, outpatient, and multiple lesions may be treated at once with a five-day therapy. The drug is topical and administered by the patient at home. Other FDA-approved products are available for actinic keratosis of the face or scalp, and tirbanibulin ointment 1% is another therapeutic option for treatment for prescribers.

Two identical phase 3 trials for efficacy demonstrated a clinically significant difference between study drug and vehicle control. The clearance rate was 44% and 54% for trials 003 and 004, respectively. The majority of 100% Clear subjects who continued to the follow up period dropped out during the open observation period due to AK recurrence. The risks were local adverse events, including local irritation and redness. No other signal was identified, including allergic reactions or ocular adverse events. Therefore, the benefits, a convenient, brief treatment regimen for treatment of multiple AKs for five days appears to outweigh the risk of the observed adverse events.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Actinic keratosis (AK) is a common skin lesion related to sun damage which is considered precancerous in certain cases. The natural history of AKs can be variable. Spontaneous resolution has been reported to occur in 15 to 63% of lesions after one year. Importantly, AKs have been reported to progress to squamous cell carcinoma (SCC); the rates of progression of a single AK to SCC have been estimated to be 0.075% per year. The frequency of AK progression to invasive SCC is unknown. AKs are seen in the adult population.	Actinic keratosis is a precancerous lesion which should be treated, due to unpredictable progression to squamous cell carcinoma.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current Treatment Options	• Multiple AK treatment options are available. Topical drug products have been approved since 1970, including 5-flurouracil, diclofenac, and imiquimod. Combination therapy with topical aminolevulinic acid and ultraviolet light is available for field treatment of multiple lesions. Additionally, laser devices have been cleared to treat actinic keratoses, including carbon dioxide and thulium laser systems. Destructive surgical treatments are used to treat AKs, such as liquid nitrogen treatment (cryotherapy) and surgical removal.	Multiple AK treatments are available. Treatment options are necessary due to variable patient AK characteristics including size, location, and number of AKs. These characteristics are evaluated to determine the best treatment, e.g., local vs. field treatment, forehead vs. scalp, head vs. arms. Past treatment response is also a factor in treatment choice.
Benefit	• Tirbanibulin topical ointment 1%, an NME with a microtubule inhibitor mechanism of action, is proposed for topical application to a 25 cm^2 area of the face or scalp. The regimen is once daily for five days. • Given the evidence from the two identical Phase 3 studies enrolling 702 subjects total, tirbanibulin ointment 1% demonstrated superiority to vehicle for the primary endpoint of complete (100%) clearance rate at Day 57 and the key secondary endpoint of partial (75%) clearance rate at Day 57 in the treatment of adults with AKs on the face or scalp.	Tirbanibulin ointment demonstrated efficacy in the treatment of multiple AKs of the face or scalp.
Risk and Risk Management	• Local skin reactions (LSR) were reported in over 50% with study drug more frequently compared to vehicle, primarily erythema, scaling and flaking, peaking Day 8 or Day 15. The LSRs were tolerable and diminished in frequency by Day 57. • No serious AEs or deaths were reported due to tirbanibulin. One skin cancer was reported in the treatment area, unlikely related to study drug. • With long-term follow up, AKs recurred in 73% of subjects who reported 100% clearance at Day 57 and entered the long-term follow up study.	The treatment was well tolerated and the side effects were generally well tolerated with no serious or permanent advese effects or events. Tirbanibulin ointment does not permanently treat AKs in those with a history of multiple AKs. New lesions can occur over time with or without prior treatment Monitoring for recurrence and skin cancer is warranted, and is acknowledged as the standard of care.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Tirbanibulin is intended for short term use. Repeat or chronic tirbanibulin ointment treatment was not evaluated.	

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

				Section of review where discussed, if applicable
☐	**The patient experience data that were submitted as part of the application include:**			
	☐	Clinical outcome assessment (COA) data, such as		
		☐	Patient reported outcome (PRO)	
		☐	Observer reported outcome (ObsRO)	
		☐	Clinician reported outcome (ClinRO)	
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify):		
☐	**Patient experience data that were not submitted in the application, but were considered in this review:**			
	☐	Input informed from participation in meetings with patient stakeholders		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Other: (Please specify):		
X	**Patient experience data was not submitted as part of this application.**			

2 Therapeutic Context

2.1. Analysis of Condition

Actinic keratosis (AK) is a common skin lesion related to sun induced skin damage, also known as senile keratosis or solar keratosis. AKs are typically considered precancerous, intraepithelial lesions featuring keratinocyte dysplasia. The natural history of AKs can be variable. Spontaneous resolution has been reported to occur in 15 to 63% of lesions after one year. Importantly, AKs have been reported to progress to squamous cell carcinoma (SCC); the rates of progression of a single AK to SCC have been estimated to be 0.075% per year. The frequency of AK progression to invasive SCC is unknown. Additionally, the AK recurrence rates one year after regression range between 15 to 53%.[1]

2.2. Analysis of Current Treatment Options

Drug products approved for the treatment of actinic keratoses in adult patients are listed in the table below. Multiple laser devices have been approved to treat actinic keratoses, including carbon dioxide and thulium laser systems. Additionally, destructive surgical treatments are used to treat AKs, such as liquid nitrogen treatment (cryotherapy) and surgical removal.

[1] Werner RN, Sammain A, Erdmann R, et al. Br J Dermatol 2013 Sep;169(3):502-18.

Table1: Currently Available FDA-Approved Treatments for Actinic Keratoses

Product (s) Name	Year of Approval	Relevant Indication	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
FDA Approved Treatments [Combine by Pharmacologic Class, if relevant]						
5-Fluorouracil (Efudex®)	1970	Treatment of multiple actinic or solar keratoses	Solution 2% Solution 5% Cream 5%	Original Trials not available	Local inflammation (burning, crusting, allergic contact dermatitis, erosions, erythema, pain, irritation, pruritus, photosensitivity, scarring, rash, ulceration; symptoms of DPD deficiency. Teratogenic.	Contraindicated: Pregnancy; Dihydropyrimidine dihydrogenase (DPD) deficiency
5-Fluorouracil (Fluoroplex®)	1971	Topical treatment of multiple actinic (solar) keratoses	Cream 1%	Original Trials not available	Inflammatory Rxn in adjacent normal skin w/occlusive dressing. Delayed hypersensitivity potential. Teratogenic.	Contraindicated: Pregnancy; Dihydropyrimidine dihydrogenase (DPD) deficiency
Aminolevulinic acid HCL with BLU-U Blue Light Photodynamic Therapy (Levulan® Kerastick®)	1999	Treatment of moderate AKs of the face or scalp	Solution 20%	Two R, VC, investigator-blinded trials. CCR Levulan® 69% vs. 14% VEH at 12 weeks. p< 0.001	Photosensitivity; irritation to eyes, or mucous membranes. Contraindicated with cutaneous photosensitivity at wavelengths	Pregnancy Category C: Animal reproduction studies have not been conducted.

					of 400-450 nm, or porphyrins.	
5-Fluorouracil (Carac®)	2000	Topical treatment of multiple actinic or solar keratoses of the face and anterior scalp	Cream 0.5%	Two R, DB, VC, studies Pts w/ ≥ 5 AKs of face or scalp, Tx for 1, 2, or 4 wks.Tx up to 4 weeks showed higher clearing and ↓ lesions vs vehicle.	Local inflammation and ulceration; potential for delayed hypersensi-tivity; symp-toms of Dihydropyr-imidine dehydrogenas e (DPD) deficiency, which may include systemic toxicity, stomatitis, diarrhea, neutropenia and neuro-toxicity.	Contraindica ted: Pregnancy; Dihydropyr-imidine dihydrogen-ase (DPD) deficiency
Diclofenac (Solaraze®)	2000	Topical treatment of actinic keratoses (AK).	Gel 3%	Three trials, SD vs vehicle. Scalp, forehead, face, forearm, or hand; up to 3 areas Tx. Complete clear at 30 days: all areas- 14% vs 4% VEH; scalp 40% vs 0%; forehead 14% vs 7%; face 21% vs 11%. No recurrence evaluation.	W & P: Local dermal adverse Rxns. Anaphylac-toid reactions may occur w/o prior exposure. Avoid eye exposure, open wounds, infections, exfoliative dermatitis, oral NSAIDs. Give w/ caution to patients with aspirin triad, severe HF, active GI ulcer/bleed, renal failure. Sun avoid-ance during Tx.	Pregnancy: Category B. Contraindi-cated: known hypersensi-tivity; w/CABG surgery.

Imiquimod (Aldara®)	2004	Typical AKs of the face or scalp in immuno-competent adults	Cream 5%	Two DB, VC trials, Tx Biweekly for 16 Wks. Clear in 44-46% vs 3-4% VEH 8 weeks after Tx.	W&P: Use in healed skin. Avoid ex-posure to sun/lamps, eyes, lips, nostrils. Local skin Rxns.	Pregnancy: Category C. No adequate and well-controlled trials in pregnant women
Methyl amino-levulinate HCl (Metvixia®)	2004	Treatment of thin and moderately thick, non-hyperkerato tic, non-pigmented AKs of the face and scalp	Gel 3% plus CureLight BroadBand Model CureLight 01 (red light 570-670 nm)	Two R, DB trials. US Study #1 drug+PDT cleared 83% vs 32% VEH+PDT at 12 wks. Study #2 cleared face & scalp drug+PDT 85% vs. 38% VEH+PDT	Photosensi-tivity; hypersensi-tivity; irritation to mucous membranes. Contraindi-cated w/ allergies to porphyrins, peanut and/or almond oil.	Pregnancy: Category C. Unknown effects on fetus and maternal reproduc-tion capacity; Animal studies not done.
Imiquimod (Zyclara®)	2010	AKs, full face or balding scalp	Cream 3.75%	Two R, DB, VC trials; daily for 2-weeks x 2 cycles, w/ 2 week rest. Clearance in 25.9-45.6% vs 2.5-10.1% VEH at 8 weeks	Local skin Rxns (e.g. skin weeping, erosion), systemic Rxns, flu-like signs & symptoms (fever, malaise, nausea, myalgia, rigors).	Pregnancy: Category C. No adequate and well-controlled trials in pregnant women
Ingenol Mebutate (Picato®)	2012	AKs of face or scalp; trunk or extremities	Gel 0.015% (face) 0.05% (trunk & extremities)	Two DB, VC trials. CCR at Day 57: study drug 28 to 42% vs 5% for VEH.	W&P: Eye disorders w/exposure. Local skin Rxn, appl. site pigment change, scarring. Hypersensi-tivity and allergic Rxns w/ hospital-ization reported Postmarket-ing. SCC risk under review	Pregnancy: Category C. No adequate and well-controlled trials in pregnant women

5-Fluorouracil (Tolak®)	2015	Multiple AKs, face, scalp, and ears	Cream 4%	Two multicenter, DB, VC trials. Clear in 24-54% Tolak vs 4% VEH at 4 weeks	W&P: application site Rxn; hypersensi-tivity;photo-sensitivity; eye adverse Rxn; embryo-fetal toxicity.	Contraindicated: Pregnancy; Dihydropyr-imidine dihydrogen-ase (DPD) deficiency
5-Amino-levulinic Acid HCl (Ameluz®)	2016	Mild to moderate severity AKs, face and scalp	Gel 10% plus BF-RhodoLED lamp (≈635 nm)	Three R, DB, VC trials. Clearance w/PDT for 84-91% vs. 13-22% VEH at Weeks.	W&P: transient amnestic episodes reported. Use protective eyewear; photosensi-tivity; mucous membrane irritation; risk of bleeding. Local skin Rxns +99%; 92% reported erythema, pain/ burning.	No available data reg. use in pregnancy and lactation

CCR=complete clearance rate; R=randomized; DB=double-blind; VC=vehicle-controlled; VEH=vehicle
W&P=Warnings & Precautions; Tx=treatment; Rxn=reaction; PDT=photodynamic therapy; CABG=coronary artery bypass grafting
Source: Clinical reviewer's table.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Because tirbanibulin ointment, 1% is not currently marketed in the United States, this section is not applicable.

3.2. Summary of Presubmission/Submission Regulatory Activity

The Applicant developed tirbanibulin ointment, 1% under investigational new drug (IND) application 122464 using the 505(b)1 regulatory pathway.

On June 27, 2014, the Division received correspondence to open IND 122464 for investigational drug KX2-391 ointment topical formulation intended for the treatment of actinic keratosis. (b) (4) Study KX2- 001 was considered safe to proceed on July 31, 2014.

An End-of-Phase 2 (EOP2) Meeting was held December 12, 2016. Outcomes of the meeting included the following:

1. The sponsor's proposal to conduct two identical phase 3 clinical trials appeared reasonable, and the NDA application should be complete, including the 12-month follow up period data, at the time of submission.

2. The proposed size of the safety database/number of subjects may be acceptable depending on the safety experience.

3. The proposed safety evaluation plan appeared to be adequate.

4. The dermal safety studies could be conducted in parallel with Phase 3 clinical trials and with the final, to-be-marketed formulation. Cumulative irritation studies may be waived in cases where the product formulation has already been shown to be significantly irritating in early phase clinical studies and identified as such in proposed labeling. Provocative studies to evaluate photoallergy would be needed prior to marketing if the product absorbs light in the range of approximately (b) (4) nm.

5. The PK parameters of the dosing regimen had not been completely characterized; therefore, the Agency recommended adequate cardiovascular screening and monitoring during future trials of the product to ensure safety of subjects. The Agency recommended that ECG evaluations include baseline, at Tmax, at steady state, and periodically during the treatment.

6. A waiver for pediatric subjects appeared reasonable. The initial PSP should be supported with incidence and prevalence data for actinic keratoses, or lack thereof, in pediatric populations.

7. The Phase 2 program did not appear to be sufficient to identify a dose/dosing regimen optimized for Phase 3 development. Prior to conducting Phase 3 trials, the Agency recommended conducting a vehicle-controlled, dose-ranging study to investigate safety and efficacy at ranges in concentration, frequency, duration of therapy and also obtain estimates of the treatment effect for designing future Phase 3 trials. Without reasonable estimates for the product there is the risk of conducting underpowered trials.

8. The Agency did not agree that the PK of KX2-391 ointment, 1% was adequately characterized. Therefore, the Agency recommended conducting a maximal use PK trial during development, and encouraged the sponsor to capture the worst-case scenario.
9. The Agency recommended that the sponsor address drug interaction potential during development.

10. KX2-391 is a new molecular entity and the Agency recommended that every effort be made to completely characterize its disposition in humans, including:

    a. Conduct in vitro studies to characterize metabolism and protein binding properties of KX2-391

    b. Conduct in vitro studies to evaluate the drug-drug interaction potentials for KX2-391 and its major metabolites.

    Additionally, based on the in vitro study findings, it may become necessary to further assess the PK of the major metabolites of KX2-391 in clinical trials using validated bioanalytical assays.

11. The ongoing nonclinical studies were summarized in the briefing package but not submitted for review, and therefore of unclear utility and acceptability. It was unclear to the Agency whether or not the completed and ongoing nonclinical studies would fully satisfy the requirements to support Phase 3 testing and marketing registration of KX2-391 ointment 1%.

12. The Agency agreed that data from repeated-dose toxicity studies of greater than 28-days duration, or from carcinogenicity assays conducted with KX2-391, were not necessary to support development or marketing of this product for this indication. However, acceptable data which address effects of the drug substance on prenatal and postnatal development, including maternal function (nonclinical peri/post- natal development data), should be included in the initial submission to a NDA. The Agency

suggested that these data be obtained in studies that involve oral or parenteral administration (as supported by preliminary dose-range finding studies and comparative pharmacokinetic data) in order to achieve adequate systemic exposure.

13. The Agency mentioned that ICH documents indicate that peri/postnatal development data are typically considered to be appropriate in support of an NDA. If final evaluation of the embryo-fetal development study results confirmed KX2-391 as fetotoxic, and the need to conduct a peri/postnatal study of KX2-391 was established, the labeling for KX2-391 ointment would contain precautions for use in women of childbearing potential. The Agency would consider a request for a waiver if final embryofetal development data were submitted with a scientific rationale to support the waiver request, and include an example of the proposed labeling.

The June 8, 2020 Midcycle Communication conveyed that the disciplines identified no significant review issues to date, while the application review was ongoing. As no major safety concerns were identified, a REMS is not required, and there is no recommendation for a RMP/RiskMAP. There were no novel or complex regulatory issues identified during the review.

At the September 28, 2020, Late-Cycle meeting, no substantive review issues related to Product Quality, Nonclinical, Clinical Pharmacology, or Clinical/Biostatistics elements of the application were identified. No Advisory Committee meeting was held, or REMS program planned. Routine pharmacovigilance and labeling should be adequate to communicate risks to prescribers and patients.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

Four clinical study sites were recommended for inspection by OSI. Study sites were selected primarily for high site enrollment and/or higher reported efficacy rates.

Table 2: Clinical Study Sites Recommended for Inspection

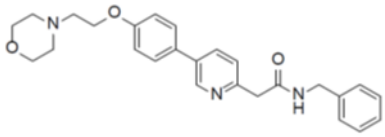
(Name, Address, Phone number, email, fax#)	Site #	Protocol ID	Number of Subjects (SAFPOP)
Bruce, MD, Suzanne 1900 St. James Place, Suite 650 Houston, TX 77056 USA United States phone:713-985-0210 fax:713-961-2730 email: sbruce@sbaskincar.com	407	2. KX01-AK-004	20
Bukhalo, MD, Michael 5301 Keystone Ct. Rolling Meadows, IL 60008 USA United States phone:847-392-5440 fax:847-392-8439 email: bukhalom@hotmail.com	323	1. KX01-AK-003	20
Forman, MD, Seth 4915 Ehrlich Road Tampa, FL 33624 USA United States phone:813-264-2155 fax:813-264-2156 email: sforman@forwardclinicaltrials.com	411	2. KX01-AK-004	20
Swinyer, MD, FAAD, Leonard 1548 East 4500 South, Suite 201 Salt Lake City, UT 84117 USA United States phone:801-269-0135 fax:801-288-0170 email: doc@dermatologyresearch.net	320	1. KX01-AK-003	20

Investigator Stephen T. Hansen inspected Site 320 and reviewed conduct of clinical Protocol KX01-AK-003 between April 14, 2020 and April 17, 2020. On November 20, 2020, OSI reported that after review of the FDA Establishment Inspection Report and the documents submitted with that report, no objectionable conditions or practices were identified that would justify enforcement action by the Office of Compliance.

4.2. Product Quality

1) Drug Substance

The drug substance, tirbanibulin is a synthetic potent antiproliferative showing activity against immortalized human keratinocytes and several cancer cell lines in vitro. Tirbanibulin has not been previously marketed or approved as an active ingredient in the United States and therefore, it has been classified as a new molecular entity (NME). 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 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:



It is manufactured in accordance to current Good Manufacturing Practices (cGMP) requirements (b) (4) It is tested and released against a specification that assures the identity, strength, purity, and quality of the drug substance at release and throughout its assigned retest date of (b) (4) months when stored (b) (4) The drug substance information provided in this application has been reviewed and found to be adequate.

2) 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, (b) (4) for a single application. KLISYRI ointment is to be applied evenly to cover up to 25cm2 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 is 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.

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 month (b) (4) this drug product should be stored at room temperatures, 20ºC – 25ºC (68ºF – 77ºF). The drug product is labelled with the statements "do not refrigerate" and " (b) (4) freeze". The applicant has submitted sufficient stability data that support the proposed expiration dating period of 24 months.

3) The OPQ Recommendation

- 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.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

Tirbanibulin is a new-molecular-entity small-molecule drug substance that, when topically applied in an ointment formulation, inhibits proliferation of keratinocytes through inhibition of tubulin polymerization and disruption of Src tyrosine kinase signaling. This results in disruption of the intracellular microtubule network, resulting in cell cycle arrest and apoptosis of keratinocytes. The drug product under NDA 213189, for which tirbanibulin is the API, has been proposed for treatment of actinic keratosis of the face and scalp.

Tirbanibulin has been evaluated in a battery of nonclinical studies that included evaluation of ADME, pharmacology, safety pharmacology, repeat-dose toxicity (via both the oral and topical routes), genetic toxicology, reproductive toxicology, and evaluation for potential to induce ocular irritation or sensitization.

Safety pharmacology studies conducted with tirbanibulin included an Irwin test (functional battery for neural/behavioral effects), a hERG assay (in vitro assay for effects on cardiac potassium channels), and an in vivo assay for cardiovascular and respiratory effects in dogs. The Irwin and hERG assay were negative. No cardiovascular effects were observed in dogs following intravenous dosing at clinically relevant levels of systemic exposure. No effects on the ECG were observed in dogs dosed orally with tirbanibulin for 4 weeks.

Tirbanibulin was evaluated in repeat-dose general toxicity studies involving topical administration to the skin of rats and minipigs for up to 4 weeks, as well as in studies that involved oral dosing of rats and dogs for up to 4 weeks. The most relevant studies are summarized below.

5-Day Topical Minipig study:
Once daily topical administration of materials containing tirbanibulin in the vehicle of the clinical formulation at concentrations of 0, 0.1%, 0.5%, or 1.0% to minipigs on 5 consecutive days was well tolerated; treatment-related effects were limited to slight irritation of skin at the application site. The no adverse effect level (NOAEL) for systemic effects was the highest dose tested, 2 mL/kg/day of 1.0% tirbanibulin ointment, which resulted in a mean $AUC_{0\text{-}24h}$ on day 5 of 100 ng•h/mL in males and 46 ng•h/mL in females. The NOAEL for local effects was the low-dose, 2 mL/kg/day of 0.1% tirbanibulin ointment.

4-Week Oral Rat study:
In a general toxicity study conducted with rats, the animals were orally dosed with tirbanibulin at dosages of 0, 2.5, 5, and 10 mg/kg/day in males and 0, 1.25, 2.5, and 4 mg/kg/day in females (administered in two equal daily doses). Toxicity in this study was largely limited to high-dose animals and included mortality (1/15 female dosed at 4 mg/kg/day and 2/15 males dosed at 10

mg/kg/day), minimally to mildly lower RBC count, hemoglobin, and hematocrit in both sexes, and, in males, reduced reticulocyte count and WBC count, and minimally elevated aspartate aminotransferase. Reduced mean absolute weight of the thymus was observed in mid-dose and high-dose males, and reduced mean absolute weight of the testes was observed in high-dose males only. Treatment-related histopathological lesions in animals that survived to scheduled sacrifice were limited to males at ≥5 mg/kg/day and females at ≥2.5 mg/kg/day, and included findings in the thymus (lymphocyte deletion), testes (germ cell degeneration and depletion, sperm granuloma), epididymis (cellular debris, oligospermia), and bone marrow (hypocellularity). These effects tended to reverse during the recovery period. The NOAEL for orally administered tirbanibulin in rats for 28 days is considered to have approximated 2.5 mg/kg/day (administered in two divided daily doses) in both males and females. This dosage was associated with a mean AUC_{0-24} of 295 ng•hr/mL in males and 620 ng•hr/mL in females.

4-Week Oral Dog study:
In a general toxicology study conducted with dogs, the animals were orally dosed with tirbanibulin at dosages of 0, 0.5, 1.0, and 2.0/1.5 mg/kg/day in both sexes (administered in two equal daily doses). High-dose animals were dosed twice daily at 1.0 mg/kg/dose for the first 5 days, only dosed once on day 6, were not dosed on days 7-14, and were dosed twice daily at 0.75 mg/kg/dose on days 15-28. Toxicity in this study was largely limited to high-dose animals and included mortality in one high-dose male. Treatment-related adverse effects observed in the high-dose group included red, mucoid and liquid feces, vomiting, reduced mean body weight, and reduced food consumption. No treatment-related clinical signs or effects on mean body weight or food consumption were observed at ≤1.0 mg/kg/day. No effects on ophthalmology or ECG were observed in any group. Tirbanibulin administration at 0.5 mg/kg/day had no effect on clinical pathology test results. The only clinical pathology finding considered possibly test article-related at 1.0 mg/kg/day was minimally to mildly increased alanine aminotransferase. High-dose animals exhibited reversible suppression of RBC and WBC parameters. Microscopic lesions, including hypocellularity of the bone marrow, epithelial degeneration, hyperplasia, and mucosal edema in the small and large intestines, and epithelial degeneration in the gallbladder were found in males and females, and accumulation of cellular debris in the epididymis and testis and hypospermia in the epididymis were found at all dose levels. These lesions were generally of minimal to moderate severity. In view of the fact that the microscopic lesions observed at 1.0 mg/kg/day were relatively minor and did not correlate with other signs of toxicity, 1.0 mg/kg/day (0.5 mg/kg/dose bid) in both males and females may be considered to have represented a "low adverse effect level" (LOAEL) under the conditions of this study that would be unlikely to result in serious irreversible toxicity, and to have only minimally exceeded a NOAEL dosage. This dose level was associated with a mean AUC_{0-24} of 545 ng·hr/mL in males and 629 ng·hr/mL in females.

Tirbanibulin is genotoxic. Tirbanibulin was negative in a bacterial reverse mutation (Ames) assay, but positive in an in vitro assay for chromosome aberrations in CHO cells with and without metabolic activation, positive in an in vitro mutation assay with mammalian cells

(mouse lymphoma assay with L5178Y cells) with and without metabolic activation, and positive (clastogenic) in an in vivo rodent micronucleus assay.

Tirbanibulin was evaluated in a battery of reproductive toxicology studies involving oral dosing of rats and rabbits, as summarized below.

Assay for effects on fertility, reproductive function, or early embryonic development:
Tirbanibulin was evaluated for effects on fertility or reproductive performance in a study that involved administration by oral gavage to rats at dose levels of 0, 1, 2, and 4 mg/kg/day in males and 0, 0.25, 0.5, and 1 mg/kg/day in females. The males were treated for nine weeks and the females for two weeks prior to pairing, at which time the animals were paired 1:1 with an animal from the same group (control, LD, MD, or HD) for a maximum of 7 days. Treatment continued throughout mating and up to necropsy of the males, and until day 7 of gestation (inclusive) for the females. The males were sacrificed after approximately 90 days of treatment and subjected to necropsy. The testes and epididymides were weighed and subjected to histopathological examination, and sperm analysis was performed. The inseminated females were subjected to C-section on day 15 of gestation. There were no tirbanibulin related mortalities, clinical signs, effects on mean body weight gain, food consumption, mating performance, fertility, observations during gross necropsy, or embryo survival. In males at 4 mg/kg/day, sperm count was reduced, sperm motility was reduced, observations of morphologically abnormal sperm were increased, mean testis weight was reduced circa 12%, and microscopic lesions of the testes and epididymides were observed (including degeneration of the seminiferous epithelium, cellular debris in the lumen of the epididymides, and reduced numbers of sperm in the epididymides). There were no tirbanibulin related effects on sperm, or observed effects on reproductive organs, at ≤2mg/kg/day. The NOAEL for gonadal function, mating behavior and reproductive performance in male rats was 2 mg/kg/day (AUC_{0-24h} of 236 ng·h/mL). The NOAEL for gonadal function, mating behavior, reproductive performance and early gestation in the female was 1 mg/kg/day (AUC_{0-24h} of 299 ng·h/mL).

Assay for effects on embryofetal development in a rodent species:
Tirbanibulin was administered via oral gavage to female rats on days 6-17 of gestation, at dosages of 0, 0.5, 1.25, and 2.5 mg/kg/day. There was no effect on maternal survival. There were no test-article-related differences in gross maternal parameters, C-section parameters, or fetal parameters among animals dosed at 0.5 mg/kg/day. Dosing at 2.5 mg/kg/day resulted in significantly reduced mean maternal body weight gain during the period of dosing, which was attributed to fetal effects. Embryofetal survival was reduced at ≥1.25 mg/kg/day due to increased post-implantation loss. Mean fetal BW and mean fetal crown-rump length were significantly reduced in live fetuses at ≥1.25 mg/kg/day. The incidence of external, visceral, and skeletal malformations and variations was increased among animals treated at ≥1.25 mg/kg/day. A dosage of 2.5 mg/kg/day (AUC_{0-24h} of 509 ng·h/mL) was an apparent NOAEL for maternal toxicity, while 0.5 mg/kg/day (AUC_{0-24h} of 90 ng·h/mL) was a NOAEL for fetal effects.

Assay for effects on embryofetal development in a nonrodent species:

Tirbanibulin was administered via oral gavage to female rabbits on days 6-18 of gestation, at dosages of 0, 0.3, 1, and 3 mg/kg/day. One dam dosed at 3 mg/kg/day was found dead on gestation day (GD) 20; this death is presumed to be treatment-related. There were no other effects on maternal survival. There were no effects of treatment on mean maternal body weight, mean body weight change, or mean gravid uterine weight. Mean fetal weight and mean crown-rump length were slightly reduced among animals treated at 3 mg/kg/day, in comparison to controls. There were no other treatment-related effects on C-section parameters at any dose, with the exception that the incidence of external, visceral, and skeletal malformations and/or variations was increased among animals treated at 3 mg/kg/day. A dosage of 1 mg/kg/day (AUC_{0-24h} of 266 ng·h/mL) was an apparent NOAEL for both maternal and fetal toxicity.

Assay for effects on prenatal and postnatal development:
Tirbanibulin was evaluated for effects on prenatal and postnatal development, including maternal function, in a study that involved administration by oral gavage to female rats from day 6 of gestation until day 20 of lactation, at dosages of 0, 0.5 and 1.25 mg/kg/day. A dose of 2.5 mg/kg/day was not tolerated, and dams at that dose were sacrificed prematurely. A dosage of 1.25 mg/kg/day (AUC_{0-24h} of 373 ng·h/mL) was an apparent NOAEL for maternal toxicity during pregnancy and lactation and for developmental, neurobehavioral, and reproductive performance of the F1 generation.

Tirbanibulin was evaluated in a battery of special toxicology studies. Tirbanibulin 1% ointment induced only slight irritation of the ocular tissues when instilled into the left eye of New Zealand white rabbits. Tirbanibulin ointment exhibited some evidence of potential to induce sensitization when topically applied to the skin of guinea pigs in a Buehler assay.

Excipients in the product are limited to “mono- and di-glycerides, USP-NF”, at a concentration of (b)(4)% w/w, and propylene glycol, USP, which constitutes (b)(4)% w/w of the product. These materials are commonly used ingredients in topical pharmaceuticals and cosmetics. The available database, including nonclinical and clinical studies conducted with the clinical formulation, adequately qualifies the proposed use of these excipients.

Safety assessment:
Data from the pivotal maximum-use pharmacokinetic clinical trial conducted in association with NDA 213189 (trial KX01-AK-007) indicate that systemic exposure to tirbanibulin resulting from topical use of the product is low. In trial KX01-AK-007 it was found that application of the to-be-marketed formulation of 1% tirbanibulin ointment to the face resulted in a mean AUC_{0-24h} value of 5.0 ng•h/mL, while application to the scalp resulted in a mean AUC_{0-24h} value of 3.18 ng•h/mL. The nonclinical database, as summarized above, provides a substantial margin of safety in relation to a maximum clinical systemic exposure (AUC) of 5.0 ng•h/mL. Systemic exposure data associated with the pivotal nonclinical safety studies are summarized and compared to the projected maximum clinical value below:

Table 3: Safety Margins Provided by Selected Nonclinical Safety Studies

Study Type	Dose of Interest	Estimated AUC_{0-24h} (ng·hr/mL)	Safety Margin Provided*
5-Day Topical Minipig RDT	NOAEL (2 mL/kg/day of 1.0% tirbanibulin ointment) Males Females	100 46	20 9
28-Day Oral Rat RDT	NOAEL for males: 2.5 mg/kg/day NOAEL for females: 2.5 mg/kg/day	295 620	59 124
28-Day Oral Dog RDT	LOAEL for males: 1 mg/kg/day LOAEL for females: 1 mg/kg/day	545 629	109 126
Fertility	NOAEL for males: 2 mg/kg/day NOAEL for females: 1 mg/kg/day	236 299	47 60
EFD (Female Rats)	NOAEL for maternal toxicity: 2.5 mg/kg/day NOAEL for fetal effects: 0.5 mg/kg/day	509 90	102 18
EFD (Female Rabbits)	NOAEL for both maternal and fetal effects: 1 mg/kg/day	266	53
Perinatal Development (Dams plus pups)	NOAEL for both maternal and pup effects: 1.25 mg/kg/day	373	74

*Safety margin refers to the ratio of the AUC at the dose of interest in the nonclinical study to the maximum AUC value observed in patients that used the product per the label in trials (5.0 ng·hr/mL for both sexes), i.e., $AUC_{nonclinical}/AUC_{clinical}$. The NOAEL in both sexes in the 5-day topical repeat-dose toxicity (RDT) study with minipigs was also the highest dose tested in that study, so the relatively small safety margins provided by that study should not be misconstrued to suggest that toxicity was observed at higher dosages. The "LOAEL" reported for a dose of 1 mg/kg/day in the 28-day oral RDT study with dogs was considered unlikely to result in serious irreversible toxicity, and to have only minimally exceeded a NOAEL dosage.

Conclusions:
The available nonclinical database acceptably addresses all nonclinical issues associated with NDA 213189. These data adequately document the safety of the proposed clinical use of the product, within the context of nonclinical concerns. Although tirbanibulin is a genetic toxicant, this matter may be appropriately addressed through labeling. The product is intended for short-term use only, which partially assuages concerns about genotoxicity. Also, it should be considered that a currently marketed product that is labeled for topical treatment of actinic keratoses, Efudex (a clinical alternative) contains fluorouracil, which is a genetic toxicant.

No nonclinical post-marketing requirements are necessary. I recommend approval of NDA 213189 with respect to nonclinical concerns. Recommended labeling is presented in Appendix 19.3.1 of this review.

5.2. Referenced NDAs, BLAs, DMFs

IND 122464

5.3. Pharmacology

Primary pharmacology
Actinic keratosis is a manifestation of abnormal keratinocyte proliferation. Tirbanibulin inhibits the growth of human keratinocytes through inhibition of tubulin polymerization and disruption

of Src tyrosine kinase signaling. In vitro, the concentration of tirbanibulin at which proliferation of cultured keratinocytes is reduced by 50% is 40 nM.

In vitro studies indicate tirbanibulin binds to tubulin, resulting in inhibition of tubulin polymerization. Tirbanibulin disrupts the microtubule network, resulting in cell cycle arrest and apoptosis of keratinocytes. The established pharmacologic class for tirbanibulin is "microtubule inhibitor".

Safety Pharmacology

Safety pharmacology studies conducted with tirbanibulin included an Irwin test (functional battery for neural/behavioral effects), a hERG assay (in vitro assay for effects on cardiac potassium channels), and an in vivo assay for cardiovascular and respiratory effects in dogs. The Irwin and hERG assay were negative. Although some cardiovascular effects were observed in dogs following IV dosing at 7.5 mg/kg or higher, it is unlikely that those data would be relevant to the clinical use proposed under NDA 213189 (topical application involving much lower systemic exposures). No effects on the ECG were observed in dogs dosed orally with tirbanibulin for 4 weeks.

5.4. ADME/PK

Type of Study	Major Findings
Absorption	
Determination of the Pharmacokinetics of KX2-391 Following Single Intravenous and Oral Doses to Rats, study No. (b) (4) 7709-107.	Pharmacokinetic parameters of tirbanibulin were calculated in male Sprague Dawley rats following single oral and intravenous doses. Groups of three fasted animals received either 1 mg/kg IV bolus via the tail vein or 12.5, 25, or 50 mg/kg via oral gavage. T_{max} was approximately 0.5 hours following oral dosing, with a half-life of approximately 2.25 hours. Bioavailability was estimated at 55.5%, 54.1%, and 102.1% in the three dose groups, respectively. $AUC_{0-\infty}$ values of 2231, 4383, and 16434 ng•h/mL were calculated. These data are not relevant to the proposed clinical use of tirbanibulin which involves topical application to the skin but help to validate the relevance of nonclinical assays that involved oral dosing.
Distribution	

Type of Study	Major Findings
Mass Balance, Pharmacokinetics, Metabolism and Tissue Distribution of [^{3}H]KX2-391 in Male and Female Sprague-Dawley Rats after a Single Oral Administration of [^{3}H]KX2-391 at 5 mg/kg of Body Weight, study No. XBLC11639N.	[^{3}H]-Labeled tirbanibulin was administered as a single oral dose to male and female Sprague Dawley rats at a dose of 5 mg free base (200 µCi) per kg body weight. Urine, feces, and blood samples were obtained from intact animals at time points up to 168 hours post-dosing. Bile-duct-cannulated animals were sampled at time points up to 72 hours post-dosing. PK parameters were similar between sexes. The following sex-combined values were calculated from data concerning total activity in plasma: Half-life ($t_{1/2}$): 19.8 hrs; T_{max}: 1 hr; C_{max}: 3813 ng-Eq/g; $AUC_{0\text{-}inf}$: 18234 hr•ng-Eq/g. Activity achieved highest levels in plasma, liver, stomach, intestines, adrenals, kidneys, and thyroid. In intact animals, approximately 90% of the administered radioactivity was recovered in urine, feces and cage rinse during 0-168 hr post-dose period, including approximately 66% in feces, 20% in urine, and 5% in cage wash. In animals in which the bile duct had been cannulated, within 72 hours, approximately 62% of activity was excreted in bile, 9% in feces, 19% in urine, and 1% in cage wash.
Metabolism	
In Vitro Metabolism of KX2-391 in Rat, Dog, and Human Primary Hepatocytes, study No. 7709-114.	The metabolism of tirbanibulin was examined in vitro, using isolated hepatocytes from rat, dog, and humans. In addition, rat and dog plasma samples and dog urine samples retained from previous animal studies were analyzed to compare and contrast in vitro and in vivo metabolic profiles. Tirbanibulin was extensively metabolized by hepatocytes from each species. Fourteen metabolites were characterized. Four of the metabolites were observed in rat plasma, all of which were also produced by rat hepatocytes. Dog hepatocytes produced six metabolites, all of which and more were observed in dog plasma, dog urine, or both. Human hepatocytes produced five metabolites, all of which were observed in either rat or dog hepatocytes and in either dog plasma or urine. The primary human metabolites (designated KX2-5036 and KX2-5163) are also major metabolites in both dogs and rats. Clinical exposures to metabolites of tirbanibulin that may result from use of the product are qualified by the submitted toxicology data. No metabolites were found to be unique to humans.
Excretion	

Type of Study	Major Findings
Mass Balance, Pharmacokinetics, Metabolism and Tissue Distribution of [^{3}H]KX2-391 in Male and Female Sprague-Dawley Rats after a Single Oral Administration of [^{3}H]KX2-391 at 5 mg/kg of Body Weight, study No. XBLC11639N.	See above.
TK data from general toxicology studies KX2-391 OINTMENT: 5 DAY DERMAL APPLICATION TOXICITY AND TOXICOKINETICS STUDY IN THE MINIPIG WITH A 21-DAY RECOVERY, study No. 392-0054-TX.	<u>Minipig, topical administration for 5 days, @ NOAEL.</u> The following values were observed on day 5 of dosing in animals that received 2 mL/kg/day 1.0% tirbanibulin ointment: Tirbanibulin: Mean AUC_{0-24h} values on day 5 of 100 ng•h/mL in males and 46 ng•h/mL in females.
4-Week Oral Gavage Toxicity and Toxicokinetic Study with KX2-391 in Rats with a 2-Week Recovery Sprague-Dawley rats, study No. 7709-102.	<u>Rat, oral administration for 28 days, @ NOAEL</u> The following values were observed on day 27 of dosing in animals that received 2.5 mg/kg/day tirbanibulin via oral gavage: Tirbanibulin: Mean AUC_{0-24h} values of 295 ng•h/mL in males and 620 ng•h/mL in females.
Study title: 4-Week Oral Gavage Toxicity and Toxicokinetic Study with KX2-391 in Dogs with a 2-Week Recovery, study No. 7709-103.	<u>Dog, oral administration for 29 days, @ LOAEL</u> The following values were observed on day 29 of dosing in animals that received 1 mg/kg/day tirbanibulin via oral gavage: Tirbanibulin: Mean AUC_{0-24h} values of 545 ng•h/mL in males and 629 ng•h/mL in females.

Type of Study	Major Findings
TK data from reproductive toxicology studies	
Fertility: Study Title: KX2-391: Oral Study on Fertility and Early Embryonic Development to Implantation in Rats, study No. 321-0034-TX.	Rat @ NOAEL (Males: 2 mg/kg/day; females: 1 mg/kg/day) AUC_{0-24h}: 236 ng·h/mL and 299 ng·h/mL in males and females, respectively.
Embryo/Fetal Development: Study title: KX2-391: Oral Study on Embryo-Fetal Development Toxicity and Toxicokinetics in Rats, study No. 321-0047-TX.	Rat @ NOAEL A dosage of 2.5 mg/kg/day was an apparent NOAEL for maternal toxicity (AUC_{0-24h} of 509 ng·h/mL), while 0.5 mg/kg/day was a NOAEL for fetal effects (AUC_{0-24h} of 90 ng·h/mL).
Study title: KX2-391: Oral Study on Embryo-Fetal Development Toxicity and Toxicokinetics in Rabbits, study No. 321-0049-TX.	Rabbit @ NOAEL A dosage of 1 mg/kg/day was an apparent NOAEL for both maternal and fetal toxicity (AUC_{0-24h} of 266 ng·h/mL).
Prenatal and Postnatal Development: Study title: Oral Gavage Study for Effects on Pre- and Post-Natal Development, Including Maternal Function, with KX2-391 in Rats, study No. 8379929.	Rat @ NOAEL A dosage of 1.25 mg/kg/day was an apparent NOAEL for both maternal toxicity and developmental, neurobehavioral, and reproductive performance in the F1 generation (AUC_{0-24h} of 373 ng·h/mL).

5.5. Toxicology

5.5.1. General Toxicology

Study title/ number: KX2-391 OINTMENT: 5 DAY DERMAL APPLICATION TOXICITY AND TOXICOKINETICS STUDY IN THE MINIPIG WITH A 21-DAY RECOVERY, study No. 392-0054-TX

- Once daily topical administration of materials containing tirbanibulin ointment at concentrations of 0.1%, 0.5%, or 1.0% to minipigs on 5 consecutive days was well tolerated; treatment-related effects were limited to slight irritation of skin at the application site.

- The NOAEL for systemic effects was the highest dose tested, 2 mL/kg/day of 1.0% tirbanibulin ointment, which resulted in a mean AUC_{0-24h} value on day 5 of 100 ng•h/mL in males and 46 ng•h/mL in females. The NOAEL for local effects was the low-dose, 2 mL/kg/day of 0.1% tirbanibulin ointment.

Note: This study was selected as the pivotal repeat-dose toxicity study under NDA 213189 because it involves exposure to the drug product and API under conditions that

are directly relevant to the proposed clinical conditions of use. This study involves exposure to the to-be-marketed formulation once daily for five days via the clinical route of exposure, utilizing the best available nonclinical model for topical application to skin. The proposed clinical use of the product involves topical application to the skin on five consecutive days. A 28-day topical repeat-dose toxicity study with minipigs was conducted and submitted, but that study was not selected for capture within this review because toxicity was observed that was considered to be not relevant to the proposed clinical use of the product.

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Methods

Dose and frequency of dosing:	Formulations containing 0% (vehicle), 0.1%, 0.5%, and 1.0% tirbanibulin, applied once daily at a rate of 2 mL/kg/day on 5 consecutive days. This resulted in nominal exposures to tirbanibulin of 0, 2, 10, and 20 mg/kg/day, although it is unclear what portion of each applied dose was subsequently removed when the site was cleansed following each 8-hour treatment period.
Route of administration:	Topical to skin (10% of BSA)
Formulation/Vehicle:	Each formulation utilized the vehicle of the commercial product.
Species/Strain:	Minipig/Bama miniature pigs
Number/Sex/Group:	4
Age:	Approx. 3-4 months
Satellite groups/ unique design:	Yes; 2/sex in control and high-dose groups allowed to “recover” 3 weeks following treatment.
Deviation from study protocol affecting interpretation of results:	No

Observations and Results: changes from control

Parameters	Major findings
Mortality	No treatment-related deaths.
Clinical Signs	No systemic clinical signs which were related to treatment. Very slight to slight erythema and very slight edema were observed during the treatment period at the application site in animals that received ≥0.5% tirbanibulin ointment. During the recovery phase, desquamation (skin scaling) was noted in both sexes that had received 1.0% tirbanibulin.
Body Weights	No treatment-related effects.
Ophthalmoscopy	No treatment-related effects.
ECG	No treatment-related effects.
Hematology	No treatment-related effects.
Clinical Chemistry	No treatment-related effects.
Urinalysis	No treatment-related effects.
Gross Pathology	Treatment-related macroscopic effects were limited to skin at the application site and presented as multifocal red discoloration observed in animals that received ≥0.5% tirbanibulin ointment.
Organ Weights	No treatment-related effects.
Histopathology Adequate battery: Yes	Treatment-related microscopic findings were limited to skin at the application site. In animals that received 0.1% tirbanibulin ointment, only minimal single cell necrosis of epidermal cells occurred. In animals that received ≥0.5% tirbanibulin ointment, test article-related findings of skin at the application site included mild single cell necrosis and minimal to moderate intracellular edema of epidermal cells, minimal or mild mixed cell infiltration, minimal or mild epidermal hyperplasia, and mild or moderate vesicle/pustule in the epidermis and/or dermis. Mild epidermal ulceration occurred in one female administered 0.5% tirbanibulin ointment. No treatment-related microscopic findings were noted in animals killed at the end of the recovery period, indicating that the changes mentioned above were reversible.

General toxicology; additional studies

4-Week Oral Rat Study:
Study title: 4-Week Oral Gavage Toxicity and Toxicokinetic Study with KX2-391 in Rats with a 2-Week Recovery Sprague-Dawley rats, study No. 7709-102.

- In a general toxicology study conducted with rats, the animals were orally dosed with tirbanibulin for at least 28 days at 0, 2.5, 5, and 10 mg/kg/day in males and 0, 1.25, 2.5, and 4 mg/kg/day in females (administered in two equal daily doses).

- Toxicity in this study was largely limited to high-dose animals, and included mortality, minimally to mildly lower RBC count, hemoglobin, and hematocrit in both sexes, and, in males, reduced reticulocyte count and WBC count, and minimally elevated aspartate

aminotransferase. Reduced mean absolute weight of the thymus was observed in mid-dose and high-dose males, and reduced mean absolute weight of the testes was observed in high-dose males only.

- Treatment-related microscopic lesions in animals that survived to scheduled sacrifice were limited to males at ≥5 mg/kg/day and females at ≥2.5 mg/kg/day, and included findings in the thymus (lymphocyte deletion), testes (germ cell degeneration and depletion, sperm granuloma), epididymis (cellular debris, oligospermia), and bone marrow (hypocellularity). These effects tended to reverse during the recovery period.

- The NOAEL for oral administration of tirbanibulin in rats for 28 days is considered to have approximated 2.5 mg/kg/day in both males and females. This dosage was associated with a Day 27 AUC_{0-24} for tirbanibulin of 295 ng•hr/mL in males and 620 ng•hr/mL in females.

4-Week Oral Dog Study:

Study title: 4-Week Oral Gavage Toxicity and Toxicokinetic Study with KX2-391 in Dogs with a 2-Week Recovery, study No. 7709-103.

- In a general toxicology study conducted with dogs, the animals were orally dosed with tirbanibulin for at least 28 days at 0, 0.5, 1.0, and 2.0/1.5 mg/kg/day in both sexes (administered in two equal daily doses). High-dose animals were dosed twice daily at 1.0 mg/kg/dose for the first 5 days, only dosed once on day 6, were not dosed on days 7-14, and were dosed twice daily at 0.75 mg/kg/dose on days 15-28.

- Toxicity in this study was largely limited to high-dose animals, and included mortality in one high-dose male. Treatment-related adverse effects observed in the high-dose group included red, mucoid and liquid feces, vomiting, reduced mean body weight, and reduced food consumption.

- Microscopic lesions, including hypocellularity of the bone marrow, epithelial degeneration, hyperplasia, and mucosal edema in the small and large intestines, and epithelial degeneration in the gallbladder were found in males and females, and accumulation of cellular debris in the epididymis and testis and hypospermia in the epididymis were found at all dose levels. These lesions were generally of minimal to moderate severity.

- 1.0 mg/kg/day may be considered a “low adverse effect level” (LOAEL) that only minimally exceeded a NOAEL in both sexes under the conditions of this study. This dose level was associated with an AUC_{0-24} for tirbanibulin of 545 ng·hr/mL in males and 629 ng·hr/mL in females.

5.5.2. Genetic Toxicology

In Vitro Reverse Mutation Assay in Bacterial Cells (Ames)
Study title/ number: *Salmonella-Escherichia coli*/Mammalian-Microsome Reverse Mutation Assay with a Confirmatory Assay, study No. 7709-112
Key Study Findings:

- Tirbanibulin was negative in an Ames assay, either with or without metabolic activation.

GLP compliance: Yes
Test system: Salmonella typhimurium strains TA98, TA100, TA1535, TA1537, and E. coli strain WP2*uvr*A, in both the presence and absence of S9 mix.
Study is valid: Yes

In Vitro Assays in Mammalian Cells
Study title/ number: KX2-391 Freebase: Mouse Lymphoma TK Gene Mutation Assay, study No. 321-0045-GT
Key Study Findings:

- Tirbanibulin was weakly positive (genotoxic) under conditions that induced cytotoxicity in an in vitro mutation assay with mammalian cells (mouse lymphoma assay with L5178Y cells), with and without metabolic activation.
- These data suggest tirbanibulin is mutagenic.

GLP compliance: Yes
Test system: L5178Y $TK^{+/-}$ mouse lymphoma cells, in both the presence and absence of S9 mix.
Study is valid: Yes

Study title/ number: Chromosomal Aberrations in Chinese Hamster Ovary (CHO) Cells, study No. 7709-113
Key Study Findings:

- A significant increase in cells with chromosomal aberrations was observed under selected circumstances with and without metabolic activation.
- These data suggest tirbanibulin is clastogenic.

GLP compliance: Yes
Test system: Cultured Chinese hamster ovary cells, in both the presence and absence of S9 mix, with incubations of 3 and 20 hours.
Study is valid: Yes

In Vivo Clastogenicity Assay in Rodent (Micronucleus Assay)
Study title/ number: KX2-391 Freebase: Bone Marrow Micronucleus Assay by Oral Gavage in the Rat, study No. 321-0044-GT
Key Study Findings:

- Tirbanibulin was clastogenic in an in vivo rodent (micronucleus) assay, as indicated by increased incidence of MPE.
- These data suggest tirbanibulin is clastogenic.

GLP compliance: Yes

Test system: Sprague Dawley rats orally dosed once at 0, 7.5, 15, and 30 mg/kg for males, 0, 3.75, 7.5, and 15 mg/kg for females. High dosages used were selected based on observed bone marrow toxicity in males dosed at 40 and 50 mg/kg, and in females dosed at 10, 20 and 25 mg/kg. The incidence of polychromatic erythrocytes with micronuclei (micronucleated polychromatic erythrocytes, MPE) was elevated in a dose-dependent manner in all groups that received tirbanibulin (statistically significant in males and females at ≥15 mg/kg).
Study is valid: Yes

5.5.3. Carcinogenicity

Not applicable, as the proposed use does not involve chronic exposure.

5.5.4. Reproductive and Developmental Toxicology

Fertility and Early Embryonic Development
Study title/ number: KX2-391: Oral Study on Fertility and Early Embryonic Development to Implantation in Rats, study No. 321-0034-TX

Key Study Findings

- Tirbanibulin was evaluated for effects on fertility or reproductive performance in a study that involved administration by oral gavage to rats at dose levels of 0, 1, 2, and 4 mg/kg/day in males and 0, 0.25, 0.5, and 1 mg/kg/day in females.

- There were no treatment-related mortalities, clinical signs, effects on mean body weight gain, food consumption, mating performance, fertility, observations during gross necropsy, or embryo survival.

- In males at 4 mg/kg/day, sperm count was reduced, sperm motility was reduced, observations of morphologically abnormal sperm were increased, mean testis weight was reduced circa 12%, and microscopic lesions of the testes and epididymides were observed (including degeneration of the seminiferous epithelium, cellular debris in the lumen of the epididymides, and reduced numbers of sperm in the epididymides). There were no treatment-related effects on sperm, or observed effects on reproductive organs, at ≤2mg/kg/day.

- The NOAEL for gonadal function, mating behavior and reproductive performance in male rats was 2 mg/kg/day ($AUC_{0\text{-}24h}$ of 236 ng·h/mL). The NOAEL for gonadal function, mating behavior, reproductive performance and early gestation in the female was 1 mg/kg/day ($AUC_{0\text{-}24h}$ of 299 ng·h/mL).

Conducting laboratory and location: (b) (4)

	(b) (4)
GLP compliance:	Yes

Note: As noted in the ICH S5A guidance, *Detection of Toxicity to Reproduction for Medicinal Products*, some minimal toxicity is generally expected to be observed in high-dose animals in nonclinical reproductive toxicity studies. The dosages evaluated in females in study No. 321-0034-TX failed to achieve such toxicity. However, in a repeated-dose toxicity study in which rats were orally dosed for 28 days (study No. 7709-102), mortality was observed in a female at a dose 4-fold higher than the highest dose used in study No. 321-0034-TX. In my opinion, data from study 321-0034-TX involved adequately high dosages to yield acceptable data.

Methods

Dose and frequency of dosing:	Males: 0, 1, 2, and 4 mg/kg/day. Females: 0, 0.25, 0.5, and 1 mg/kg/day. All animals dosed once daily.
Route of administration:	Oral (gavage; 2.5 mL/kg for females, initially 10 mL/kg for males, reduced to 5 mL/kg for males starting day 25 due to toxicity ascribed to "GI irritation" caused by the acidic vehicle)
Formulation/Vehicle:	Solution/3% Acetic acid in water (pH 2 to 3)
Species/Strain:	Rat/Sprague Dawley (males approx. 8 weeks old at start of treatment, females approx. 15 weeks)
Number/Sex/Group:	24
Satellite groups:	None
Study design:	Males were treated for 9 weeks prior to mating, throughout mating, and until the day before necropsy. Females were treated 14 days before mating, throughout mating and until day 7 of gestation (inclusive). Animals were paired on the basis of one male and one female from the same group (control, LD, MD, or HD) for a maximum of 7 days. The day of mating, confirmed by vaginal smear or presence of a plug, was taken as day 0 of gestation (G0). Males were sacrificed after approximately 90 days of treatment; the testes and epididymides were weighed and sperm analysis (motility, morphology, and count) was performed on a sample from the left cauda epididymis. Testes and epididymides were processed and examined microscopically from control, MD, and HD males. F0 females were

	subjected to C-section on day 15 of gestation, and ovary, uterine, and litter parameters were recorded.
Deviation from study protocol affecting interpretation of results:	No

Observations and Results

Parameters	Major findings
Mortality	A total of 17 animals (2/24, 3/24, 5/24 and 4/24 male rats, and 2/24, 0/24, 1/24 and 0/24 female rats from control, low-dose, mid-dose and high-dose group, respectively) were terminated early due to moribund condition, or were found dead. The study report ascribed these mortalities to irritation of the larynx, trachea or lung resulting from acetic acid in the vehicle and did not consider them to be test article-related. Since the early deaths were observed approximately as frequently among animals in the control groups as in the treatment groups, and in consideration of data from a previously conducted 4-week oral study with rats (study No. 7709-102), this seems a plausible conclusion.
Clinical Signs	No treatment-related effects.
Body Weights	No treatment-related effects.
Necropsy findings *[Mating/Fertility Index, Corpora Lutea, Preimplantation Loss, etc.]*	There was no adverse effect of treatment on mating performance or fertility in any group, including estrus cycle duration, time-to-mating, and fertility indices. No treatment-related effects on C-section parameters, including number of corpora lutea, implantations, live embryos, nonviable embryos, pre-implantation loss, and post-implantation loss were observed in this study.
Sperm analysis	There were no treatment-related effects on sperm motility, count, or morphology at ≤2mg/kg/day. In high-dose group (4 mg/kg/day) males, sperm count was reduced, sperm motility was reduced, and observations of morphologically abnormal sperm were increased, relative to control.

<u>Embryo-Fetal Development</u>

Study title/ number: KX2-391: Oral Study on Embryo-Fetal Development Toxicity and Toxicokinetics in Rats, study No. 321-0047-TX

Key Study Findings

- Tirbanibulin was administered via oral gavage to female rats on days 6-17 of gestation, at dosages of 0, 0.5, 1.25, and 2.5 mg/kg/day.

- Dosing at 2.5 mg/kg/day resulted in significantly reduced mean maternal body weight gain during the period of dosing, which was attributed to fetal effects.

- Embryofetal survival was reduced at ≥1.25 mg/kg/day due to increased post-implantation loss. Mean fetal BW and mean fetal crown-rump length were significantly reduced in live fetuses at ≥1.25 mg/kg/day. The incidence of external, visceral, and skeletal malformations and variations was increased among animals treated at ≥1.25 mg/kg/day.

- A dosage of 2.5 mg/kg/day (AUC_{0-24h} of 509 ng·h/mL) was an apparent NOAEL for maternal toxicity, while 0.5 mg/kg/day (AUC_{0-24h} of 90 ng·h/mL) was a NOAEL for fetal effects.

Conducting laboratory and location:	(b) (4)
GLP compliance:	Yes

Methods

Dose and frequency of dosing:	0, 0.5, 1.25, and 2.5 mg/kg/day. Dams dosed once daily on days 6-17 of gestation.
Route of administration:	Oral (gavage; 5 mL/kg)
Formulation/Vehicle:	Solution/3% Acetic acid in water (pH 2 to 3)
Species/Strain:	Rat/Sprague Dawley, pregnant females, 9-10 weeks old.
Number/Sex/Group:	25 (females only)
Satellite groups:	Yes, 8 females per group used for TK analysis
Study design:	Gestation day 0 was considered to be the day of confirmed mating. F0 females were dosed on days 6 through 17, inclusive, of gestation. F0 females were euthanized on day 21 post-mating.
Deviation from study protocol affecting interpretation of results:	No

Observations and Results

Parameters	Major findings
Mortality	No unscheduled deaths of F0 animals occurred.
Clinical Signs	No treatment-related effects.
Body Weights	Among animals confirmed pregnant, mean body weight gain was significantly reduced over the intervals of GD 12-15, 15-18, and 18-21 in animals dosed at 2.5 mg/kg/day. Mean body weight of pregnant dams treated at 2.5 mg/kg/day was significantly reduced on days 18 and 21, compared to control values. No significant differences were observed at ≤ 1.25 mg/kg/day.

Necropsy findings Cesarean Section Data	Pregnancy was confirmed in 23/25 control, 19/25 LD, 23/25 MD, and 21/25 HD animals. Reduced embryo survival was observed at ≥1.25 mg/kg/day. The post-implantation loss was 11.0% and 71.1% in dams treated at 1.25 and 2.5 mg/kg/day, respectively, in comparison to 2.6% in controls. Mean fetal BW was significantly reduced in live fetuses at ≥1.25 mg/kg/day. In addition, the mean fetal crown-rump length was reduced at ≥1.25 mg/kg/day.
Necropsy findings Offspring	External fetal observations: No external malformations or variations were observed at 0.5 mg/kg/day. The incidence of fetuses and litters with external malformations was significantly increased at ≥1.25 mg/kg/day. Specifically, 3.3% of fetuses and 21.7% of litters exhibited external malformations at 1.25 mg/kg/day, 11.9% of fetuses and 44.4% of litters exhibited external malformations at 2.5 mg/kg/day, compared to 0.29% of fetuses and 4.35% of litters in the control group. External malformations observed at ≥1.25 mg/kg/day included absent pinna, malpositioned pinna, small pinna, absent eye bulge, small lower jaw, cleft upper jaw, cleft palate, digit misshapen (forepaw), cranial meningocele, exencephaly, meningo-encephalocele, hyperextension hindlimb, malrotated hindlimb, localized and generalized subcutaneous edema, bent, hooked, misshapen and thread-like tail, absent anus and omphalocele. Visceral observations: No test article-related visceral malformations or variations were observed at 0.5 mg/kg/day. The percentage of fetuses and litters that exhibited malformations of the brain (dilated lateral ventricle) or eye (eye absent and/or absent lens) was elevated at ≥1.25 mg/kg/day. Specifically, 3.52% of fetuses and 18.18% of litters exhibited external malformations at 1.25 mg/kg/day, and 11.11% of fetuses and 28.57% of litters exhibited external malformations at 2.5 mg/kg/day, compared to 0% of fetuses and litters in the control group. Skeletal observations: No test article-related skeletal malformations or variations were observed at 0.5 mg/kg/day. The percentage of fetuses and litters that exhibited skeletal malformations and variations was elevated at ≥1.25 mg/kg/day. Specifically, 10.60% of fetuses and 27.27% of litters exhibited skeletal malformations at 1.25 mg/kg/day, and 10.81% of fetuses and 42.86% of litters exhibited skeletal malformations at 2.5 mg/kg/day, compared to 0% of fetuses and litters in the control group. Skeletal malformations observed at 1.25 and/or 2.5 mg/kg/day included split basisphenoid, absent, branched, misshapen and fused cervical arch, absent cervical vertebra, fused exocipital and frontal, fused and misshapen lumbar arch, absent lumbar vertebra, supernumerary lumbar vertebra, absent rib, fused rib, misshapen scapula, absent sternebra, fused sternebra, absent, misshapen and fused thoracic arch. Skeletal variations, including incomplete or absent ossification of the cervical arch, frontal, lumbar centrum, parietal bone, ribs, sternebra, and thoracic centrum, were observed in 25.17% of fetuses and 63.64% of litters 1.25 mg/kg/day, and 48.65% of fetuses and 100% of litters at 2.5 mg/kg/day, compared to 6.94% of fetuses and 21.74% of litters in the control group.

LD: low dose; MD: mid dose; HD: high dose

Study title/ number: KX2-391: Oral Study on Embryo-Fetal Development Toxicity and Toxicokinetics in Rabbits, study No. 321-0049-TX

Key Study Findings

- Tirbanibulin was administered via oral gavage to female rabbits on days 6-18 of gestation, at dosages of 0, 0.3, 1, and 3 mg/kg/day.
- One dam dosed at 3 mg/kg/day was found dead on gestation day (GD) 20; this death is presumed to be treatment-related. There were no other effects on maternal survival.
- Mean fetal weight and mean crown-rump length were slightly reduced among animals treated at 3 mg/kg/day, in comparison to controls. There were no other treatment-related effects on C-section parameters at any dose.
- The incidence of external, visceral, and skeletal malformations and/or variations was increased among animals treated at 3 mg/kg/day.
- A dosage of 1 mg/kg/day (AUC_{0-24h} of 266 ng·h/mL) was an apparent NOAEL for both maternal and fetal toxicity.

Conducting laboratory and location:	(b) (4)
GLP compliance:	Yes

Methods

Dose and frequency of dosing:	0, 0.3, 1, and 3 mg/kg/day. Dams dosed once daily on days 6-18 of gestation.
Route of administration:	Oral (gavage; 2.5 mL/kg)
Formulation/Vehicle:	Solution/3% Acetic acid in water (pH 2 to 3)
Species/Strain:	Rabbit/New Zealand White, pregnant females, 5 to 6 months old.
Number/Sex/Group:	25 (females only)
Satellite groups:	Yes, 4 females per group used for TK analysis
Study design:	Presumed-to-be pregnant females arrived on approx. gestation day 3; day 0 was day of confirmed mating. F0 females were dosed on days 6 through 18, inclusive, of gestation. F0 females euthanized on day 29 of pregnancy.

Deviation from study protocol affecting interpretation of results: No

Observations and Results

Parameters	Major findings
Mortality	One HD (3 mg/kg/day) dam was found dead on gestation day (GD) 20. This animal was previously noted to exhibit inappetence, decreased defecation, thin appearance, soft stool, and red materials in pan. The cause of death was not determined but may have been related to effects of tirbanibulin on the GI epithelium. One main-study LD group animal was found dead (an apparent gavage error), and one satellite group control animal was sacrificed due to paralysis; these deaths were considered to be incidental.
Clinical Signs	Inappetence and decreased defecation were noted in treated animals more frequently than in controls and were likely related to treatment. No other treatment-related clinical signs were observed.
Body Weights	There were no treatment-related effects on mean body weight, mean body weight change, or mean gravid uterine weight.
Necropsy findings Cesarean Section Data	Pregnancy was confirmed in 21/25 control, 21/25 LD, 22/25 MD, and 21/25 HD animals. Mean fetal weight and mean crown-rump length were reduced 10.6% and 3.8%, respectively, in the HD group, in comparison to controls. There were no other treatment-related effects on pregnancy parameters at any dose, including no statistically significant differences in the numbers of live or dead fetuses, and no effects on pre- or post-implantation loss.
Necropsy findings Offspring	External fetal observations: No external malformations or variations were observed at ≤1 mg/kg/day. The incidence of the external malformation "first digit absent in forepaw" was significantly increased at 3 mg/kg/day; no other treatment-related external malformations were observed. Visceral observations: No test article-related visceral malformations or variations were observed at ≤1 mg/kg/day. At 3 mg/kg/day, the incidence of total visceral abnormalities was significantly increased compared to control, although the incidence of any given anomaly was low. Observations at 3 mg/kg/day included one of 161 fetuses with right testis absent, two of 161 fetuses with lung lobe absent, one of 161 fetuses with both gallbladders absent, one of 161 fetuses with right kidney and right ureter absent, one of 161 fetuses with dilated aorta, aortic arch, ductus arteriosus, and 5 of 161 fetuses with fused lung lobe. These malformations affected multiple litters. Skeletal observations: No test article-related skeletal malformations or variations were observed at ≤1 mg/kg/day. The incidence of skeletal anomalies was slightly increased at 3 mg/kg/day, and included observations of fused sternebrae, thoracic vertebra hemivertebra, branched ribs, fused ribs, unossified or incompletely ossified forepaw phalanx, and unossified metacarpal.

LD: low dose; MD: mid dose; HD: high dose

Prenatal and Postnatal Development

Study title/ number: Oral Gavage Study for Effects on Pre- and Post-Natal Development, Including Maternal Function, with KX2-391 in Rats, study No. 8379929

Key Study Findings

- Tirbanibulin was administered via oral gavage to female rats from day 6 of gestation until day 20 postpartum, at dosages of 0, 0.5 and 1.25 mg/kg/day. A dose of 2.5 mg/kg/day was not tolerated.

- A dosage of 1.25 mg/kg/day (AUC_{0-24h} of 373 ng·h/mL) was an apparent NOAEL for maternal toxicity of F0 dams and for developmental, neurobehavioral, and reproductive performance in the F1 generation.

Conducting laboratory and location:	(b) (4)
GLP compliance:	Yes

Methods

Dose and frequency of dosing:	0, 0.5 and 1.25 mg/kg/day, once daily, from day 6 of gestation until day 20 postpartum. The study initially involved an additional group that received 2.5 mg/kg/day, but this group was terminated and discarded prematurely due to excessive toxicity.
Route of administration:	Oral (gavage; 2.5 mL/kg)
Formulation/Vehicle:	Solution/3% Acetic acid in water (pH 2 to 3)
Species/Strain:	Rat/Sprague Dawley, pregnant females, 11-12 weeks old at initiation of dosing.
Number/Sex/Group:	24 (F0 animals female only)
Satellite groups:	Yes, 3 females per group used for TK analysis
Study design:	F0 females were presumed pregnant when received. F0 females dosed once daily from day 6 of gestation through day 20 postpartum. The test material was not administered to F0 males or to F1 animals. F0 females were sacrificed on day 21 postpartum. F1 animals (pups of F0 animals) of each sex were randomly selected for pairing with a non-sibling from the same treatment group for breeding of the F2 generation (cohabitated at approximately 11

	weeks of age). F1 breeder females were sacrificed on gestation day 13 and C-sectioned. F1 animals were also assessed for effects on developmental landmarks, sensory function, behavior, learning, and memory.
Deviation from study protocol affecting interpretation of results:	No

Observations and Results

Generation	Major Findings
F0 Dams	F0 dams administered 2.5 mg/kg/day were unable to maintain pregnancy or lactation and were terminated prematurely. Observations of audible and/or irregular respiration were noted for all groups during lactation, including control animals. This was ascribed to the acetic acid content of the vehicle. Mean body weight (BW) and BW-gain in animals administered 0.5 or 1.25 mg/kg/day were comparable with controls throughout gestation and lactation. Mean BW tended to be reduced in animals at 2.5 mg/kg/day, prior to termination. Delivery indices for dams administered 0.5 or 1.25 mg/kg/day were comparable with controls.
F1 Generation	No adverse effects of treatment were noted on clinical observations, body weight, food consumption, neurobehavioral assessment, reproductive performance, or macroscopic observations in pups from dams administered 0.5 or 1.25 mg/kg/day.
F2 Generation	No treatment-related effects.

5.5.5. Other Toxicology Studies

5.5.5.1. An Acute Ocular Irritation Study of KX01 Ointment in Male New Zealand White Rabbits, study No. 44103-13-830.

Methods. Tirbanibulin 1% ointment (apparently identical to the to-be-marketed formulation) was instilled into the left eye of each of three New Zealand white rabbits once at a volume of 0.1 g per eye. The eyes were examined at 1 hour, 24 hours, 48 hours, 72 hours, and 7 days post administration for signs of irritation.

Results. Slight erythema and edema of the conjunctiva were observed in all animals, indicating that the test article was slightly irritating to the eye. The irritation cleared within three days post-dose.

Conclusion. Under the conditions of this study, when topically administered into the "conjunctival sac" of the rabbit eye, the test item, tirbanibulin 1% ointment, induced slight

irritation of the ocular tissues.

5.5.5.2. A Buehler Test Study of KX01 via Epidermal Application in Guinea Pig, study No. 44103-13-837.

Methods. On Days 1, 7, and 14 (induction-treatment days), tirbanibulin 4% ointment, tirbanibulin 1% ointment, neomycin sulfate 0.5% (positive control article), or vehicle for the ointment, were applied on the shaved right flank of male guinea pigs (10/group) for 6 hours per treatment day, at a rate of 0.5 grams per animal. On Day 27 (challenge-treatment day), the same doses were applied to a site on the left flank of the same guinea pigs for 6 hours, with the exception of the vehicle site, which was instead dosed with tirbanibulin 4% ointment. Skin observations were performed prior to dosing on Day 1, at approximately 1 and 24 hours after each induction dose, and at approximately 24 and 48 hours after the challenge dose.

Results. The following clinical observations were noted:

Induction Doses:

Slight irritation, edema and/or erythema were noted in all guinea pigs in the neomycin sulfate and 1% and 4% tirbanibulin ointment dose groups after the 2nd and 3rd induction doses.

Challenge Dose:

Slight edema and/or erythema was noted in 2 animals treated with neomycin sulfate, 4 animals treated with 1% tirbanibulin ointment, and 5 animals treated with 4% tirbanibulin ointment at 48 hours following the challenge dose.

Conclusion. Under the conditions of this study, when applied topically to guinea pigs, tirbanibulin ointment exhibited some evidence of potential to induce sensitization when topically applied to the skin.

5.5.5.3. The sponsor has proposed a specification of NMT (b) (4)% (expressed as percentage of the API) in regard to a specified impurity, identified as (b) (4) for the drug product. (b) (4) The proposed specification (b) (4) in the drug product, NMT (b) (4)%, is acceptably qualified by submitted nonclinical data.

APPEARS THIS WAY ON ORIGINAL

6 Clinical Pharmacology

6.1. Executive Summary

Tirbanibulin (KLISYRI, also known as KX2-931) is a new molecular entity (NME), acting as a microtubule inhibitor.

Proposed indication:
For the topical treatment of [redacted] (b) (4) actinic keratosis (AK) of the face or scalp.

Proposed dosing regimen:
Apply sufficient KLISYRI ointment to evenly cover a 25 cm^2 treatment field on the face or scalp once daily for 5 consecutive days using 1 [redacted] (b) (4) packet [redacted] (b) (4) [redacted] (b) (4) per application.

Proposed dosage form:
Ointment 1%

Summary of clinical program:
The Applicant evaluated the safety and efficacy of tirbanibulin ointment 1% in two pivotal Phase 3 trials in which tirbanibulin ointment 1% was applied to evenly cover the 25 cm^2 treatment field on the face or scalp of the subjects with AK once daily for 5 consecutive days. The Applicant conducted a Phase 2 study to select an appropriate dose regimen for Phase 3 trials. The Applicant also submitted the results of six Phase 1 trials in healthy subjects or subjects with AK including a pivotal PK study under maximal use conditions in adult subjects with AK to support Clinical Pharmacology information of KLISYRI.

The key review findings with specific recommendations and comments are summarized in Table 4.

Table 4: Summary of Clinical Pharmacology Review

Review Issues	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	Efficacy is established in two pivotal Phase 3 trials (KX01-AK-003 and KX01-AK-004). See *Section 8.1* for efficacy studies and their results.
General dosing instructions	The efficacy data from Phase 3 trials support the proposed dosing regimen, i.e. apply sufficient tirbanibulin ointment 1% to evenly cover a 25 cm^2 treatment field on the face or scalp once daily for 5 consecutive days using 1 [redacted] (b) (4) packet per application.
Dosing in patient subgroups (intrinsic and extrinsic factors)	Therapeutic individualization based on intrinsic or extrinsic factors is not necessary due to low systemic tirbanibulin exposure and lack of drug-drug interaction concerns.

Drug interactions	The results of *in vitro* studies suggest that under the conditions of clinical use, neither tirbanibulin nor its metabolite KX2-5036 is an inducer or inhibitor of cytochrome P450 (CYP) enzymes examined, and a substrate or inhibitor of uptake and efflux transporters studied (see *Section 19.4.3 Clinical Pharmacology Appendices* for details).
Pediatric subjects	A full waiver of pediatric studies for the proposed indication of AK of the face or scalp has been granted in the Agreed Initial Pediatric Study Plan.
Bridge between the to-be-marketed and clinical trial formulations	Any kind of bridging is not needed because the to-be-marketed formulation was used in the Phase 3 and in the maximal use PK trials.

6.1.1. Recommendations

From a Clinical Pharmacology standpoint, this NDA is acceptable to support the approval of KLISYRI (tirbanibulin ointment 1%) for the topical treatment of (b) (4) actinic keratosis of the face or scalp.

6.1.2. Post-Marketing Requirements and Commitment (PMR/PMC)

None.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

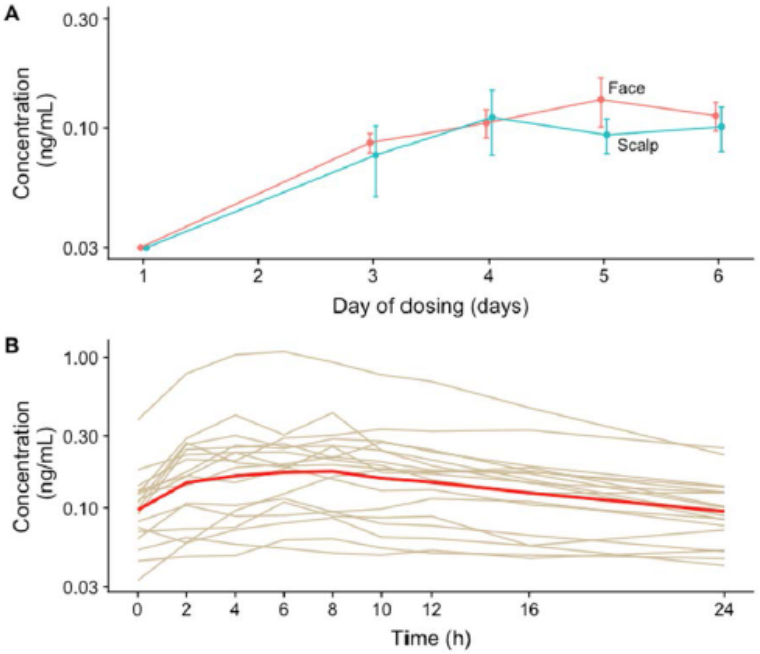
6.2.1.1 Mechanisms of action and pharmacodynamics

Tirbanibulin is a microtubule inhibitor. The mechanism of action of KLISYRI ointment for the topical treatment of AK is unknown.

6.2.2.2 Pharmacokinetics

Following topical application of a mean daily dose of 138 mg (range: 54 to 295 mg) of tirbanibulin ointment 1% once daily for 5 consecutive days to the 25 cm^2 contiguous area of the face or balding scalp that contained at least 6 AK lesions, steady-state systemic concentrations of tirbanibulin was achieved by 72 hours (Day 4) (Figure 1A). The PK results are summarized inTable 5. Overall, the mean systemic tirbanibulin exposure expressed as C_{trough}, C_{max}, or AUC_{24h} in the face treatment group were slightly higher than those in the scalp treatment group (Figure 1B and Table 5). The inter-individual variability (%CV) on Day 5 for the tirbanibulin C_{max} and AUC_{24h} were 90% and 77%, respectively, in the face and scalp combined group (n=18), with the highest C_{max} value of 1.1 ng/mL (2.5 nM) observed in one subject who had 6 AK lesions on the face and received the highest mean daily dose of 250 mg for 5 consecutive days (Figure 1B).

Figure 1A and 1B: Mean Trough Concentrations of Tirbanibulin in the Face or Scalp Group (A) and Individual Plasma Concentrations of Tirbanibulin on Day 5 in the Face and Scalp Combined Group (n=18) (B)



(Source of data: Clinical Study Report KX01-AK-007, Figure 1)

Table 5: Pharmacokinetics of Tirbanibulin in Subjects with AK on the Face and Scalp

Treatment Group	Mean (SD)							
	C_{trough} (ng/mL)					C_{max} (ng/mL)	T_{max}* (hr)	AUC_{24h} (h*ng/mL)
	Day 1	Day 3	Day 4	Day 5	Day 6	Day 5		
Face (n=9)	0	0.09 (0.03)	0.11 (0.04)	0.13 (0.10)	0.11 (0.05)	0.34 (0.30)	6.0 (2.0 - 9.8)	5.0 (3.9)
Scalp (n=9)	0	0.08 (0.08)	0.11 (0.11)	0.09 (0.05)	0.10 (0.07)	0.18 (0.10)	7.8 (2.0 - 10.0)	3.18 (1.92)
Combined (n=18)	0	0.08 (0.06)	0.11 (0.08)	0.11 (0.08)	0.11 (0.06)	0.26 (0.23)	6.9 (2.0 - 10.0)	4.09 (3.15)

*Median (minimum-maximum)
AUC_{24h}=area under the plasma concentration from time 0 to 24 hours, C_{max}=maximum plasma concentration, T_{max}=time C_{max} was reached
(Source of data: Reviewer's summary based on Clinical Study Report KX01-AK-007, Table 8)

6.2.1.3 Drug-drug interactions

In vitro, tirbanibulin and its metabolite KX2-5036 directly or time-dependently inhibited CYP 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, or CYP3A4 with an IC50 >17 µM. Tirbanibulin up to 1 µM (432 ng/mL) and the metabolite KX2-5036 up to 3 µM (1024 ng/mL) did not induce CYP 1A2, 2B6, or

3A4. In addition, tirbanibulin was mainly metabolized by CYP3A4 and, to a lesser extent, CYP2C8.

In vitro, neither tirbanibulin nor the metabolite KX2-5036 is a substrate of drug transporters tested (MDR1, BCRP, BSEP, MRP2, MATE1, MATE2-K, OAT1, OAT3, OATP1B1, OATP1B3, OCT1, and OCT2). Tirbanibulin and/or KX2-5036 inhibited MATE1, MATE2-K, OATP1B1, OATP1B3, OCT1, and/or OCT2 with the estimated IC50 values ranging from 1.4 (604 ng/mL) to 66.4 µM (28,654 ng/mL).

These findings suggest that tirbanibulin ointment 1% has no clinically meaningful effect on the PK of drugs metabolized by CYPs, and mediated by drug transporters. See Section 19.4 Clinical Pharmacology Appendices of this reviewer for details. Due to this, clinical studies evaluating the drug-drug interaction potential of tirbanibulin ointment 1% are considered unnecessary.

6.2.2. General Dosing and Therapeutic Individualization

6.2.2.1. General Dosing

The Applicant's proposed dosing regimen is to apply tirbanibulin ointment 1% (KLISYRI) evenly to a 25cm2 treatment field on the face or scalp once daily for 5 consecutive days using 1 (b) (4) (b) (4) packet (b) (4) per application. This dosing regimen is supported by systemic safety data from the maximal use trial (KX01-AK-007) and the two phase 3 pivotal trials (KX01-AK-003/004). See Section 8 for efficacy and safety findings from Phase 3 trials.

6.2.2.2. Therapeutic Individualization

Therapeutic individualization was not evaluated in this NDA.

6.2.3. Outstanding Issues

There are no outstanding issues that would preclude the approval of tirbanibulin ointment 1% for the topical treatment of AK of the face or scalp from a Clinical Pharmacology's perspective.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

General clinical pharmacology, pharmacokinetic (PK), and pharmacodynamic (PD) characteristics of tirbanibulin are summarized in

Table 6.

APPEARS THIS WAY ON ORIGINAL

Table 6: Summary of Clinical Pharmacology, Pharmacokinetics and Pharmacodynamics of Tirbanibulin

Pharmacology	
Mechanism of Action	Tirbanibulin is a microtubule inhibitor. The mechanism of action of KLISYRI ointment for the topical treatment of AK is not known but may be related to apoptosis.
Pharmacodynamics	TQT assessment 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 the phase 2 and 3 clinical studies. A thorough QT study is not usually necessary for topical drugs with low systemic bioavailability (See *IRT Memorandum by Dr. Girish K Bende dated 05/07/2020 in DARRTS* for details)
General Information	
Bioanalysis*	Plasma concentrations of tirbanibulin and its metabolites (KX2-5036 and KX2-5163) in humans were quantified using high-performance liquid chromatography with tandem mass spectrometry (LC/MS/MS) assays with the sensitivity of 0.01 ng/mL and 0.05 ng/mL, respectively.
PK model	The applicant has not conducted any PK modeling and simulation analysis.
Healthy vs. Patients	For topical dermatological indications, the healthy subject PK data is considered exploratory and maximal use PK data in patients with the disease is considered pivotal. Due to differences in drug application in terms of % BSA, disease state and dose, cross trial comparison of systemic exposure between healthy subjects and patients is not considered a viable approach.
Drug Exposure at Steady State	Following topical application of a mean dose of 138 mg (range: 54 to 295 mg) of tirbanibulin ointment 1% to the 25 cm^2 treatment field on the face or balding scalp once daily for 5 consecutive days, the steady-state concentrations of tirbanibulin were achieved by 72 hours (Day 4) with a mean ± SD C_{trough} of 0.11 ± 0.08 ng/mL (n=18).
Dose Proportionality	The systemic tirbanibulin exposure increased with dose, but the dose-exposure relationship was nonlinear (i.e. exponential increase) in subjects with AK.

ADME	
Absorption	Following topical treatment with a mean daily dose of 138 mg (range: 54 to 295 mg) of KLISYRI ointment to the 25 cm^2 treatment field on the face or scalp once daily for 5 consecutive days, the steady-state concentration of tirbanibulin was achieved by 72 hours (Day 4). On Day 5, systemic exposure to tirbanibulin was generally low with a mean ± SD C_{max} of 0.34 ± 0.30 ng/mL and 0.18 ± 0.10 ng/mL, and a mean ± SD AUC_{24h} of 5.0 ± 3.9 h*ng/mL and 3.2 ± 1.9 h*ng/mL, in subjects who received the face and scalp topical treatment, respectively. The median time to reach C_{max} (T_{max}) was ~7 hours.
Distribution	Plasma protein binding of tirbanibulin and KX2-5036 (metabolite) is 88% and 57%, respectively, and is independent of concentrations in the range of 0.01 to 10 µg/mL, *in vitro*.
Elimination	
• Metabolism	• Following topical treatment with KLISYRI ointment to adult subjects with AK, the plasma concentrations of two pharmacologically inactive metabolites, KX2-5036 and KX2-5163, were detectable with the highest plasma concentrations of 0.09 ng/mL and 0.12 ng/mL, respectively. None of them were found to be unique to humans • *In vitro,* incubation of tirbanibulin (1 and 10 µM) with human hepatocytes generated the metabolites KX2-5036 and KX2-5163 and other unidentified metabolites. • *In vitro*, tirbanibulin was mainly metabolized by CYP3A4 and, to a lesser extent, CYP2C8.
• Excretion	Excretion of tirbanibulin has not been fully characterized in humans.
Drug-Drug Interaction	*In Vitro* studies suggest that tirbanibulin ointment 1% has no clinically meaningful effect on the PK of drugs metabolized by CYP 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, or 3A4; and mediated by drug transporters MDR1, BCRP, BSEP, MRP2, MATE1, MATE2-K, OAT1, OAT3, OATP1B1, OATP1B3, OCT1 or OCT2.

ADME=Absorption, Distribution, Metabolism and Excretion.
*Bioanalytical methods were applied in the maximal use PK trial (KX01-AK-007)

6.3.2. Clinical Pharmacology Questions

6.3.2.1. Does the clinical pharmacology program provide supportive evidence of effectiveness?

The purpose of the pivotal clinical pharmacology trial was to assess systemic safety and to evaluate the PK of tirbanibulin and its metabolites under maximal use conditions. The maximal use PK trial did not directly provide any efficacy data. See *Clinical review under Section 8* for details on efficacy.

6.3.2.2. Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Based on the systemic safety under maximal use conditions and the efficacy and safety results from Phase 3 trials, the proposed dosing regimen is appropriate for adult subjects with AK. Of note, the dose and dosing regimen as well as the study subjects in the maximal use trial were similar to those in the Phase 3 trials.

6.3.2.3. Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

The effect of some intrinsic factors, such as age, gender, and lesion counts, was explored by the Applicant in this NDA, however, the sample size (n=18) is too small to make any concreate conclusions. As low systemic tirbanibulin exposure observed in the maximal use PK trial and lack of drug-drug interaction concerns based on the in vitro studies, together with efficacy and safety data from the Phase 3 trials, any dose adjustment will not be needed.

6.3.2.4. Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

- *Cytochrome P450s:*
  As a perpetrator, tirbanibulin and its metabolite KX2-5036 directly or time-dependently inhibited CYP 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, or CYP3A4 with an IC_{50} >17 µM. Tirbanibulin up to 1 µM (432 ng/mL) and its metabolite KX2-5036 up to 3 µM (1024 ng/mL) did not induce CYP 1A2, 2B6, or 3A4. With the observed highest C_{max} values of 1.1 ng/mL and 0.1 ng/mL respectively for tirbanibulin and its metabolite KX2-5036 in the maximal use PK trial, the topical application of tirbanibulin ointment 1% is not expected to produce any clinically meaningful effect on the PK of drugs metabolized by the CYPs examined. Hence further drug interaction assessment in clinical studies is not needed. As a victim, tirbanibulin was mainly metabolized by CYP3A4, to a lesser extent CYP2C8, *in vitro*.

- *Drug transporters:*

As a perpetrator, tirbanibulin and KX2-5036 inhibited MATE1, MATE2-K, OATP1B1, OATP1B3, OCT1, and OCT2 with the estimated IC_{50} values ranging from 1.4 (604 ng/mL) to 66.4 µM (28,654 ng/mL). With the highest C_{max} values of tirbanibulin and KX2-5036 observed in the maximal use PK trial, the topical application of tirbanibulin ointment 1% is not expected to produce any clinically meaningful effect on the PK of drugs mediated by the transporters examined. Hence further drug interaction assessment in clinical studies is not needed. As a victim, neither tirbanibulin nor the metabolite KX2-5036 was a substrate of MDR1, BCRP, BSEP, MRP2, MATE1, MATE2-K, OAT1, OAT3, OATP1B1, OATP1B3, OCT1 or OCT2.

- *Food-drug interaction*:
  Food-drug interaction study is not needed for topical products

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

The applicant conducted two identical pivotal trials to support efficacy and safety for tirbanibulin.To support safety, dermal safety studies were conducted to evaluate tirbanibulin local tolerability including irritancy, photosensitivity, and photoallergy. Phase 1 and 2a studies for clinical pharmacology supported the dose and duration for tirbanibulin use. (Table 8)

Table 7: Clinical Trials Relevant to the Tirbanibulin 1% NDA

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Period Duration/ Follow Up	No. of patients enrolled	Study Population	No. of US Centers
		Controlled Studies to Support Efficacy and Safety						
KX01-AK-003	NCT03285477	R, DB, VC	Apply IP to 25 cm^2 face or scalp daily x 5 days topically	100% Clear (0) at Day 57	Tx: 5 days F-up: 57 Days Recurrence: 12 mo	351	Adults; 4 to 8 AKs face or scalp	31 sites
KX01-AK-004	NCT03285490	R, DB, VC	Apply IP 25 cm^2 area face or scalp daily x 5 days topically	100% Clear (0) at Day 57	Tx: 5 days F-up: 57 Days Recurrence: 12 mo	351	Adults; 4 to 8 AKs face or scalp	31 sites
		Studies to Support Safety						
KX01-AK-006		R, C, EB Repeat Insult Patch Test Design	Apply IP 3 x a week for 3 weeks	No efficacy assessment	Challenge and rechallenge (prn) assessments 3 weeks	261	Healthy	1 site
KX01-AK-008		R, DB, PC within-subject comparison study	Single dose plus/minus UV irradiation	Phototoxicity	IP applied (4 sites) once for 24 hours +/- UV; evaluated through Day 4	31	Healthy	1 site
KX01-AK-009		R, DB, PC within- subject comparison study	IP under open patch conditions 2 times a week with irradiation for induction; plus 1 challenge with irradiation	Photoallergic reaction	Induction: 3 weeks. After 10 to 17-day rest, Challenge x 24 hrs, then UV. Evaluate at 24, 48, 72 hours post UV.	64	Healthy	1 site

					Rechallenge prn			
KX01-AK-010		R, DB, PC within-subject comparison study	IP under occlusive, semi-occlusive, and open patch conditions	Local Tolerability	3 times a week for 3 weeks. Final eval at 4 weeks.	36	Healthy	1 site
		Other studies pertinent to the review of efficacy or safety (e.g., clinical pharmacological studies)						
KX01-AK-002	NCT02838628	Phase 2a, Nonrandom Uncontrolled Open-label	3 Day vs. 5 Day regimen/applied daily	100% Clear (0) at Day 57	Tx: 3 or 5 Days F-up: to Day 57 Recurrence: CR to 12 months	168	4-8 AKs, face or scalp	16 sites
KX01-001-US	NCT02337205	Phase 1, Nonrandom Uncontrolled Open-label	4 cohorts; applied study drug to area for 3 or 5 days, topically	safety and tolerability assessment as determined by laboratory, AE and SAE information	Tx: 5 days Duration: 45 days	30	AK on dorsal forearm: 4 to 8 AKs in 25 cm^2 area; 8 to 16 AK lesions in 100 cm^2 area	I site
KX01-AK-007	NCT03575780	Phase 1, Nonrandom Uncontrolled Open-label Maximum use	Tx to 25 cm^2 area	PK under maximal use conditions	once daily for 5 days	18	At least 5 clinically typical, visible, and discrete AKs on 25 cm^2 of the face or balding scalp	2 sites

R=randomized; DB=double-blind; EB=evaluator blinded; PC=placebo-controlled; VC=vehicle controlled; IP=investigational product; Tx=treatment
UV=ultraviolet light; CR=clinical recurrence
Source: Clinical Reviewer

7.2. Review Strategy

The data sources used for the evaluation of the efficacy and safety of tirbanibulin ointment, 1%, included the Applicant's clinical study reports, datasets, clinical summaries, and proposed labeling. The submission was submitted in the Electronic Common Technical Document format and was entirely electronic. Both Study Data Tabulation Model datasets and Analysis Data Model (ADaM) datasets were submitted. The analysis datasets used in this review are archived at Application 213189–Sequence 0001–Analysis Data.

8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. 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

The sponsor conducted identical phase 3 pivotal trials, KX01-AK-003 (003) and KX01-AK-004 (004), to support efficacy for the indication of actinic keratosis of the face or scalp. The common features of the trials will be discussed in this section.

Study Design

KX02-AK-003 and KX02-AK-004 trials were randomized, double-blind, vehicle-controlled, parallel-group design conducted at multiple centers. Subjects were enrolled for treatment on the face or scalp at approximately 2:1 ratio, respectively. Eligible subjects were randomized to KX2-391 ointment 1% or vehicle ointment in a 1:1 ratio. Each subject was given a study kit containing five daily single-dose packets and instructions regarding self-administration of study drug/vehicle. The first dose was applied by the subject to a predetermined, 25 cm^2 marked area under study site personnel supervision. At home, subjects self-administered study drug/vehicle using single-dose packets once-daily for four consecutive days. Dermatologist investigators assessed subjects at Screening (Days -28 to 0), Treatment (Day 1), and Response Assessment Visits (Days 5, 8, 15, 29, and 57). Subjects with 100% clearance at Day 57 entered the Recurrence Follow-up Period, with assessments occurring 3, 6, 9, and 12 months after Day 57.

Study Endpoints

The primary endpoint was complete (100%) clearance rate of AK lesions, defined as the proportion of subjects at Day 57 with no clinically visible AK lesions in the treatment area.

The applicant defined the key seconday endpoint as partial (≥75%) clearance rate of AK lesions, i.e., the proportion of subjects at Day 57 with a ≥75% reduction in the number of AK lesions identified at Baseline (Day 1 predose) in the treatment area.

The applicant specified that an additional endpoint was recurrence rate of AK lesions in subjects who achieved complete (100%) clearance at Day 57. Recurrence was defined as appearance of any AK lesions in the treatment area, including those recurred (i.e., reappearance of previously cleared lesions) or newly identified.

Statistical Analysis Plan

As stated before, randomization to treatment (active or vehicle) was stratified by treatment location (face or scalp) and study site. For each site, a separate randomization schedule for each treatment location was generated, with 24 codes for the face and 12 codes for the scalp.

Analysis Populations

The analysis of the primary endpoint is to be conducted on the Intent-To-Treat (ITT) Population, defined as all randomized subjects. A supportive analysis is to be conducted on the Per-protocol (PP)/Evaluable Population, defined as all randomized subjects who have received at least 4 of the 5 doses, did not receive concomitant medications that can affect efficacy, and returned for the final visit on Day 57.

The recurrence Follow-up Population is defined as all subjects in the ITT Population who achieved complete clearance at the Day 57 visit.

Efficacy Analyses:

The Protocol/SAP specifies that analysis of the complete clearance is to be conducted using the Cochran-Mantel-Haenszel (CMH) model controlling for treatment location and treatment group. The Breslow-Day test, with a significance level of 10%, is to be used to explore heterogeneity of the odds ratios across treatment location subgroups.

In addition, analysis of the Key Secondary Efficacy Endpoint (Partial clearance rate) is to be carried using the same approach for analysis of the primary endpoint (i.e., CMH test). A gatekeeping testing strategy is applied to control the Type I error rate; that is, this endpoint is tested only if the null hypothesis for the primary endpoint is rejected.

Estimate of recurrence rate is based on a Kaplan-Meier method at each post-Day 57 visit. Subjects with missing AK assessments in the Recurrence Follow-up Period were considered as censored at their last AK assessment.

Subgroup Analyses for the primary and the key secondary efficacy endpoints will be carried out by treatment location (face or scalp), gender, age (<65 or ≥65 years), baseline AK lesion count (4, 5, 6, or 7, 8), skin type (Fitzpatrick I/II or III/IV/V/VI). Outliers will be clinically explained in the clinical study report. Subgroup analysis results will be presented graphically along with the Clopper-Pearson Exact 95% CI.

Protocol Amendments

According to the Applicant, the SAPs for both studies were based on the studies protocol Amendment 01 (v2.0) dated February 18, 2018 and finalized on June 4, 2019.

8.1.2. Study Results

Compliance with Good Clinical Practices

The applicant attested to conducting clinical trials 003 and 004 in compliance with good clinical practices (GCPs), including study design, monitoring, conduct, and ethical principles.

Financial Disclosure

For Studies 003 and 004, the applicant completed forms 3454 to document any financial conflicts of interest or arrangements with clinical investigators. According to the applicant, no investigator was the recipient of significant payments as defined in 21 CFR 54.2(f), and therefore no Form 3455 were submitted.

Patient Disposition and Protocol Violations/Deviations

Study KX01-AK-003 and Study KX01-AK-004 each enrolled 351 subjects for 702 subjects in total. For Study 003, one subject died and one withdrew. All subjects completed the randomized double-blind efficacy period for Study 004. Tables 9 and 10 report the subject disposition in Study 003 and Study 004.

Table 8: Subject Disposition in Study 003

	Study 003		
	KX2-391 Ointment 1%	Vehicle	Total
Randomized	175	176	351
ITT Population	175	176	351
PP Population	166	165	331
Reason for Exclusion from PP Population			
AK lesions not counted at Day 1 and Day 57 by the same evaluator	1	0	1
Discontinued prior to Day57	0	2	2
Missed >1 Dose of Study Drug	1	0	1
Out of Day 57 Visit Window	3	0	3
Prohibited Medication Taken	4	9	13
Discontinuation before Day 57			
Death	0	1	1
Withdrawl by subject	0	1	1

Source: Reviewer's analysis (same as Applicant's analysis)

Table 9: Subject Disposition in Study 004

	Study 004		
	KX2-391 Ointment 1%	Vehicle	Total
Randomized	178	173	351
ITT Population	178	173	351
PP Population	170	166	336
Reason for Exclusion from PP Population			
AK lesions not counted at Day 1 and Day 57 by the same evaluator	1	1	2
Discontinued prior to Day57	0	0	0
Missed >1 Dose of Study Drug	0	0	0
Out of Day 57 Visit Window	1	2	3
Prohibited Medication Taken	6	4	10

Source: Reviewer's analysis (same as Applicant's analysis)

Table of Demographic Characteristics

A summary of demographic characteristics for the ITT population is presented in Table 11 and Table 12 for Study 003 and Study 004, respectively. The demographics across study drug and vehicle ointment arms within Trials 003 and 004 were comparable. Additionally, the demographics were comparable for Trials 003 and 004. In both studies, subjects were predominantly male and white (>99% in each study) with median age 70 years.

Table 10: Demographic Characteristics in the ITT Population - Study 003

	Study 003		
	KX2-391 Ointment 1%	Vehicle	Total
Number of subjects in the ITT/Safety Population	175	176	351
Age (years)			
N	175	176	351
Mean (SD)	69.9 (8.51)	70.5 (9.40)	70.2 (8.96)
Median	70.0	70.0	70.0
Min, max	48, 87	45, 97	45, 97
Age group (years), n (%)			
<65	51 (29%)	42 (24%)	93 (26%)
≥65	124 (71%)	134 (76%)	258 (74%)
Sex, n (%)			
Female	28 (16%)	22 (13%)	50 (14%)

Male	147 (84%)	154 (87%)	301 (86%)
Race, n (%)			
American Indian or Alaska native	0(0%)	1 (<1%)	1 (<1%)
White	175 (100%)	175 (>99%)	350 (>99%)
Ethnicity, n (%)			
Hispanic or Latino	2 (1%)	5 (3%)	7 (2%)
Not Hispanic or Latino	173 (99%)	171 (97%)	344 (98%)
Fitzpatrick skin type, n (%)			
Type I	19 (11%)	21 (12%)	40 (11%)
Type II	104 (59%)	121 (69%)	225 (64%)
Type III	43 (25%)	31 (18%)	74 (21%)
Type IV	9 (5%)	3 (2%)	12 (3%)
Type V	0 (0%)	0 (0%)	0 (0%)
Type VI	0 (0%)	0 (0%)	0 (0%)

Source: Reviewer's analysis (same as Applicant's analysis)

Table 11: Demographic Characteristics of the ITT Population - Study 004

	Study 004		
	KX2-391 Ointment 1%	Vehicle	Total
Number of subjects in the ITT/Safety Population	178	173	351
Age (years)			
N	178	173	351
Mean (SD)	69.5 (8.70)	70.5 (8.87)	70.0 (8.79)
Median	69.5	71.0	70.0
Min, max	47, 91	47, 93	47, 93
Age group (years), n (%)			
<65	56 (31%)	39 (23%)	95 (27%)
≥65	122 (69%)	134 (77%)	256 (73%)
Sex, n (%)			
Female	20 (11%)	23 (13%)	43 (12%)
Male	158 (89%)	150 (87%)	308 (88%)
Race, n (%)			
American Indian or Alaska native	1 (<1%)	0 (0%)	1 (<1%)
White	177 (>99%)	173 (100%)	350 (>99%)
Ethnicity, n (%)			
Hispanic or Latino	11 (6%)	8 (5%)	19 (5%)
Not Hispanic or Latino	167 (94%)	165 (95%)	332 (95%)
Fitzpatrick skin type, n (%)			
Type I	30 (17%)	17 (10%)	47 (13%)

Type II	96 (54%)	103 (60%)	199 (57%)
Type III	45 (25%)	48 (28%)	93 (26%)
Type IV	6 (3%)	4 (2%)	10 (3%)
Type V	0 (0%)	1 (<1%)	1 (<1%)
Type VI	1 (<1)	0 (0%)	1 (<1%)

Source: Reviewer's analysis (same as Applicant's analysis)

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

A summary of baseline characteristics for the ITT population is presented in Table 13 and Table 14 for Study 003 and Study 004, respectively. The baseline characteristics across study drug and vehicle ointment arms within Trials 003 and 004 were comparable. In addition, baseline characteristics were comparable for Trials 003 and 004. The number of lesions at enrollment were similar for the two treatment groups in each study, with median number of lesions of 6 in each treatment arm. Few subjects (3% in Study 003 and <5% in Study 004) had Fitzpatrick Skin Types IV, V and VI, and Fitzpatrick skin type was balanced between the two treatment groups.

Table 12: Baseline Characteristics in the ITT Population – Study 003

	Study 003		
	KX2-391 Ointment 1%	Vehicle	Total
Location of treatment area, n (%)			
Face	119 (68%)	121 (69%)	240 (68%)
Scalp	56 (32%)	55 (31%)	111 (32%)
Number of Baseline AK Lesions, n (%)			
4	26 (15%)	31 (18%)	57 (16%)
5	58 (33%)	50 (28%)	108 (31%)
6	40 (23%)	40 (23%)	80 (23%)
7	25 (14%)	24 (14%)	49 (14%)
8	26 (15%)	31 (18%)	57 (16%)
Number of AK lesions at baseline			
N	175	176	351
Mean (SD)	5.8 (1.28)	5.9 (1.35)	5.8 (1.31)
Median	6.0	6.0	6.0
Min, max	4, 8	4, 8	4, 8
Baseline weight (kg)			
N	175	176	351
Mean (SD)	86.9 (15.1)	87.6 (16.2)	87.3 (15.7)
Median	86.4	84.5	85.5
Min, max	52, 140	51, 138	51, 140

Source: Reviewer's analysis

Table 13: Baseline Characteristics in the ITT Population – Study 004

	Study 004		
	KX2-391 Ointment 1%	Vehicle	Total
Location of treatment area, n (%)			
Face	119 (67%)	118 (68%)	237 (68%)
Scalp	59 (33%)	55 (32%)	114 (32%)
Number of Baseline AK Lesions, n (%)			
4	21 (12%)	21 (12%)	42 (12%)
5	50 (28%)	57 (33%)	107 (30%)
6	48 (27%)	42 (24%)	90 (26%)
7	28 (16%)	34 (20%)	62 (18%)
8	31 (17%)	19 (11%)	50 (14%)
Number of AK lesions at baseline			
N	178	173	351
Mean (SD)	6.0 (1.27)	5.8 (1.20)	5.9 (1.24)
Median	6.0	6.0	6.0
Min, max	4, 8	4, 8	4, 8
Baseline weight (kg)			
N	178	172	350
Mean (SD)	89.1 (18.1)	84.7(15.4) (15.39)	86.9 (16.9)
Median	86.6	83.1	84.8
Min, max	45,167	52,140	45, 167

Source: Reviewer's analysis

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

For Study 003, only one subject missed two of the planned 5 daily doses. Subject (b) (6) in the study drug arm, stopped treatment after Day 3 due to a traumatic wound in the treatment area. Study 004 reported that all doses were applied as directed.

Efficacy Results – Primary Endpoint

Table 15 and Table 16 present the reviewer's analysis results for the treatment effect for the primary endpoint, complete (100%) clearance data at Day 57, among the ITT population, overall and by treatment location (face and scalp) in Study 003 and Study 004. The Tirbanibulin Ointment 1% group had significantly higher ($p<0.0001$) complete clearance than the Vehicle group in the ITT population for both studies by the pre-specified Cochran-Mantel-Haenszel (CMH) test stratified by treatment site. The reviewer analysis results coincide with those of the applicant. In addition, the reviewer also reported the 95% CI for the overall treatment difference between Tirbanibulin ointment 1% and Vehicle using the Mantel-Haenszel confidence limit, to be consistent with the applicant's pre-specified CMH test stratified by treatment site. The 95% CI excludes 0 in each study. Similar results were also observed in the PP population, which is reported in the Appendix Table 50.

A similar trend was also observed in face and scalp (Table 15 and Table 16). The Tirbanibulin Ointment 1% group had a higher complete clearance rate than the Vehicle group at each treatment site in both studies. The reviewer's results confirmed those of the applicant. The sponsor reported p-values from the CMH test for the face and scalp, which was not pre-specified in the SAP, where the applicant noted "no statistical test will be performed between subgroups". In Table 15 and Table 16, the reviewer reported the 95% Clopper-Pearson Exact CI for the treatment difference in face and scalp, as the applicant pre-specified in the SAP for subgroup analysis. It should be noted that the reported 95% CI is intended as an exploratory analysis and not for confirmatory purpose. Given the duality between the hypothesis test and the confidence interval approach, we suggest not to report the 95% CI for the face and scalp in the label.

Table 14: Complete (100%) Clearance Rates at Day 57 in ITT Population Study 003

	Study 003			
Lesion Location	KX2-391 Ointment 1% N = 175 n/N (%)	Vehicle N = 176 n/N (%)	Treatment difference (KX2-391 Ointment 1% - Vehicle)	95% Confidence Interval for the Treatment difference
Overall	77/175 (44.0%)	8/176 (4.5%)	39.5%[a]	(31.6%, 47.5%)[a]
Face	60/119 (50.4%)	7/121 (5.8%)	44.6%	(32.8%, 55.4%)[b]
Scalp	17/56 (30.4%)	1/55 (1.8%)	28.5%	(10.4%, 45.7%)[b]

a. Based on Mantel-Haenszel risk limit stratified by treatment location. P- value from the CMH test is <.0001.

b. Based on Clopper-Pearson Exact 95% CI. Note that for subgroups face and scalp, the reported 95% CI is for exploratory rather than confirmatory purpose.

Source: Reviewer's analysis

Table 15: Complete (100%) Clearance Rates at Day 57 in ITT Population Study 004

	Study 004			
Lesion Location	KX2-391 Ointment 1% N = 178 n/N (%)	Vehicle N = 173 n/N (%)	Treatment difference (KX2-391 Ointment 1%-Vehicle)	95% Confidence Interval for the Treatment difference
Overall	97/178 (54.5%)	22/173 (12.7%)	41.9%[a]	(33.1%, 50.7%)[a]
Face	73/119 (61.3%)	16/118 (13.6%)	47.8%	(36.4%, 58.6%)[b]
Scalp	24/59 (40.7%)	6/55 (10.9%)	29.8%	(11.4%, 46.7%)[b]

a. Based on Mantel-Haenszel risk limit stratified by treatment location. P- value from the CMH test is <.0001.
b. Based on Clopper-Pearson Exact 95% CI. Note that for subgroups face and scalp, the reported 95% CI is for exploratory rather than confirmatory purpose.
Source: Reviewer's analysis

Data Quality and Integrity

Overall, the quality of the data submitted is adequate to characterize the safety and efficacy of tirbanibulin ointment. We discovered no significant deficiencies that would impede a thorough analysis of the data presented by the applicant.

Efficacy Results – Key Secondary Endpoint

Similarly, results for the secondary efficacy endpoint- Partial (≥75%) clearance rates at Day 57 for studies 003, and 004 are summarized in Table 17 and Table 18 respectively. Given that the primary endpoint was significant at the 0.05 level, then following the pre-specified step-down gatekeeping strategy, partial clearance rate can be tested at the same significance level. Tables 17 and 18 shows that the Tirbanibulin Ointment 1% group had significantly higher ($p<0.0001$) partial (≥75%) clearance than the Vehicle group for the ITT population in both studies. The reviewer's results coincide with those of the applicant. A similar trend was observed in face and scalp.

The reviewer also repeated the same analysis in the PP population and results were consistent across the study populations (reported in the Appendix Table 51).

Table 16: Partial (≥75%) Clearance Rates at Day 57 in ITT Population for Studies 003

	Study 003			
Lesion Location	KX2-391 Ointment 1% N = 175 n/N (%)	Vehicle N = 176 n/N (%)	Treatment difference (KX2-391 Ointment 1%-Vehicle)	95% Confidence Interval for the Treatment difference
Overall	119/175 (68.0%)	29/176 (16.5%)	51.6%[a]	(42.9%, 60.4%)[a]
Face	90/119 (75.6%)	23/121 (19.0%)	56.6%	(45.2%,66.5%)[b]
Scalp	29/56 (51.8%)	6/55 (10.9%)	40.9%	(23.6%, 57.2%)[b]

a. Based on Mantel-Haenszel risk limit stratified by treatment location. P value from the CMH test <0.0001.
b. Based on Clopper-Pearson Exact 95% CI. Note that for subgroup face and scalp, the reported 95% CI is for exploratory rather than confirmatory purpose.

Source: Reviewer's analysis

Table 17: Partial (≥75%) Clearance Rates at Day 57 in ITT Population for Studies 004

	Study 004			
Lesion Location	KX2-391 Ointment 1% N = 178 n/N (%)	Vehicle N = 173 n/N (%)	Treatment difference (KX2-391 Ointment 1%-Vehicle)	95% Confidence Interval for the Treatment difference
Overall	136/178 (76.4%)	34/173 (19.7%)	56.9%[a]	(48.3%, 65.4%)[a]
Face	95/119 (79.8%)	26/118 (22.0%)	57.8%	(46.4%, 67.7%)[b]
Scalp	41/59 (69.5%)	8/55 (14.6%)	55.0%	(38.4%, 69.1%)[b]

a. Based on Mantel-Haenszel risk limit stratified by treatment location. P value from the CMH test <0.0001.
b. Based on Clopper-Pearson Exact 95% CI. Note that for subgroup face and scalp, the reported 95% CI is for exploratory rather than confirmatory purpose.

Source: Reviewer's analysis

Efficacy Results – Other Secondary Endpoint

In the two pivotal trials, a total of 85 subjects (77 Tirbanibulin Ointment 1%, 8 Vehicle) in Study 003 and 119 subjects (97 Tirbanibulin Ointment 1%, 22 Vehicle) in Study 004 had complete (100%) clearance at Day 57 of the Treatment/Response Assessment Period and were eligible to enter the Recurrence Follow-up Period. The subject disposition for the recurrence follow-up period in Study 003 and Study 004 are reported in Table 19 and Table 20 respectively.

Table 18: Subject Disposition for the Rucurrence Follow-up Period – Study 003

	Study 003		
	KX2-391 Ointment 1%	Vehicle	Total
Subjects achieved 100% AK clearance at Day 57	77	8	85
Subjects Entered the Recurrence Follow-up Period	77	7	84

Source: Reviewer's analysis (same as Applicant's analysis)

Table 19: Subject Disposition for the Rucurrence Follow-up Period – Study 004

	Study 004		
	KX2-391 Ointment 1%	Vehicle	Total
Subjects achieved 100% AK clearance at Day 57	97	22	119
Subjects Entered the Recurrence Follow-up Period	96	22	118

Source: Reviewer's analysis (same as Applicant's analysis)

Subjects who achieved 100% clearance of AK lesions in the treatment area at Day 57 continued to be followed for up to 12 months following Day 57 to determine the recurrence rate. Tables 21-24 report the reviewer's analysis results, which coincide with the applicant's results. Table 21 and Table 22 report the recurrence and censoring status during follow-up among the subjects who achieved 100% clearance at Day 57 after treatment with Ointment 1% in Studies 003 and 004 respectively. Table 23 and Table 24 reports the Kaplan-Meier estimates for the recurrence rates at 3, 6, 9, and 12 months post-Day 57 in the two studies respectively.

Table 20: Summary of Recurrence Status and Rate by 12 Months post-Day 57 Among Tirbanibulin Ointment Subjects with Complete Clearance of Lesions at Day 57 In Study 003

	Study 003			
	Entered Follow-up	With Recurrence	Censored	KM Estimate Recurrence Rate
All subjects	77	55	22	0.74
Face	60	40	20	0.70
Scalp	17	15	2	0.88

KM = Kaplan-Meier
Source: Reviewer's analysis (Same as the applicant's analysis)

Table 21: Summary of Recurrence Status and Rate by 12 Months post-Day 57 Among Tirbanibulin Ointment Subjects with Complete Clearance of Lesions at Day 57 In Study 004

	Study 004			
	Entered Follow-up	With Recurrence	Censored	KM Estimate Recurrence Rate
All subjects	97	69	28	0.72
Face	73	49	24	0.68
Scalp	24	20	4	0.83

KM = Kaplan-Meier
Source: Reviewer's analysis (Same as the applicant's analysis)

Table 22: Recurrence Rates (Kaplan-Meier Estimates) at 3, 6, 9, and 12 Months Post-Day 57 Among Recurrence Follow-up Population in Study 003

Follow-Up Time	KX2-391 Ointment 1%
	Rate (95% CI)
	(N = 77)
3 months	0.33 (0.24 , 0.45)
6 months	0.53 (0.42 , 0.65)
9 months	0.69 (0.58 , 0.79)
12 months	0.74 (0.64 , 0.84)

CI = confidence interval; CSR = clinical study report;
N = number of subjects in the Recurrence Follow-up Set/Population.
Recurrence Follow-up Set was defined as all subjects who achieved complete (100%) clearance at Day 57.
Source: Reviewer's analysis(Same as the applicant's analysis)

Table 23: Recurrence Rates (Kaplan-Meier Estimates) at 3, 6, 9, and 12 Months Post-Day 57 Among Recurrence Follow-up Population in Study 004

Follow-Up Time	KX2-391 Ointment 1%
	Rate (95% CI)
	(N = 97)
3 months	0.27 (0.19 , 0.37)
6 months	0.50 (0.41 , 0.60)
9 months	0.64 (0.54 , 0.73)
12 months	0.72 (0.63 , 0.80)

CI = confidence interval; CSR = clinical study report;
N = number of subjects in the Recurrence Follow-up Set/Population.
Recurrence Follow-up Set was defined as all subjects who achieved complete (100%) clearance at Day 57.
Source: Reviewer's analysis(Same as the applicant's analysis)

8.1.3. Assessment of Efficacy Across Trials

The efficacy analysis result is consistent across the two pivotal trials.

Primary Endpoints

Given the evidence from the two Phase 3 studies 003 and 004, Tirbanibulin Ointment 1% showed superiority to Vehicle for the primary endpoint of complete (100%) clearance rate at Day 57 in the treatment of adults with AK on the face or scalp.

Secondary and Other Endpoints

Given the evidence from the two Phase 3 studies 003 and 004, Tirbanibulin Ointment 1% showed superiority to Vehicle for the key secondary endpoint of partial (75%) clearance rate at Day 57 in the treatment of adults with AK on the face or scalp.

Findings in Special/Subgroup Populations

Sex, Age, Baseline Lesion Count, and Fitzpatrick Skin Type

The complete clearance rates at Day 57 for subgroups of subjects based on sex, age, baseline lesion count, and Fitzpatrick skin type in Studies 003, and 004 are summarized in Table 25 and Table 26. Similar to the analysis results for the primary endpoint for treatment site in Table 15 and Table 16, we present the corresponding efficacy results for the subgroups along with the 95% Clopper-Pearson Exact CI, that are given for exploratory purpose.

Consistent with the observed greater complete clearance rate in Ointment 1% vs. Vehicle in the total study population (Table 15 and Table 16), this difference was seen across the subgroups for the primary endpoint complete clearance rate. Race and ethnicity are not presented in the subgroup analysis because no meaningful conclusion can be drawn based on the few number of subjects with other races than white and Hispanic/Latino ethnicity.

Table 24: Complete (100%) Clearance Rates at Day 57 in for Subgroups Based on Gender, Age, Baseline Lesion Count, and Fitzpatrick Skin Type for Study 003

	Study 003		
	KX2-391 Ointment 1% (N=175)	Vehicle (N=176)	Difference and 95% CI for Difference[1]
Sex			
Female, n/N (%)	17/28 (60.7%)	3/22 (13.6%)	47.1% (20.1%,68.9%)
Male, n/N (%)	60/147 (40.8%)	5/154 (3.3%)	37.6% (26.7%,47.8%)
Age			
<65 years, n/N (%)	23/51 (45.1%)	1/42 (2.4%)	42.7% (23.0%, 59.9%)
≥ 65 years, n/N (%)	54/124 (43.6%)	7/134 (5.2%)	38.3% (26.6%,49.2%)
Baseline Lesion Count			
4-6 AK lesion, n/N(%)	61/124 (49.2%)	7/121 (5.8%)	43.4% (31.5%,54.1%)
7-8 AK lesion, n/N (%)	16/51 (31.4%)	1/55 (1.8%)	29.6% (10.4%,46.7%)
Fitzpatrick Skin Type			
Type I or II, n/N (%)	55/123 (44.7%)	7/142 (4.9%)	39.8% (28.3%,50.4%)
Type III-VI, n/N (%)	22/52 (42.3%)	1/34 (2.9%)	39.4% (18.3%,57.6%)

AK = actinic keratosis; ITT = Intent-to-Treat.
Note: Complete (100%) clearance rate was defined as the proportion of subjects with no clinically visible AK lesions in the treatment area at Day 57.
1. Based on Clopper-Pearson Exact 95% CI. Note that for subgroup face and scalp, the reported 95% CI is for exploratory rather than confirmatory purpose

Source: Reviewer's analysis

Table 25: Complete (100%) Clearance Rates at Day 57 in for Subgroups Based on Gender, Age, Baseline Lesion Count, and Fitzpatrick Skin Type for Study 004

	Study 004		
	KX2-391 Ointment 1% (N=178)	Vehicle (N=173)	Difference and 95% CI for Difference[1]
Sex			
Female, n/N (%)	17/20 (85.0%)	3/23 (13.0%)	72.0% (45.2%,88.9%)
Male, n/N (%)	80/158 (50.6%)	19/150 (12.7%)	38.0% (27.2%,48.0%)
Age			
<65 years, n/N (%)	35/56 (62.5%)	4/39 (10.3%)	52.2% (33.4%,68.1%)
≥ 65 years, n/N (%)	62/122 (50.8%)	18/134 (13.4%)	37.4% (25.6%,48.3%)
Baseline Lesion Count			
4-6 AK lesion, n/N(%)	72/119 (60.5%)	16/120 (13.3%)	47.2% (35.1%,57.5%)
7-8 AK lesion, n/N (%)	25/59 (42.4%)	6/53 (11.3%)	31.1% (12.8%,47.9%)
Fitzpatrick Skin Type			
Type I or II, n/N (%)	68/126 (54.0%)	15/120 (12.5%)	41.5% (29.5%,52.5%)
Type III-VI, n/N (%)	29/52 (55.8%)	7/53 (13.2%)	42.6% (23.6%,58.2%)

AK = actinic keratosis; ITT = Intent-to-Treat.
Note: Complete (100%) clearance rate was defined as the proportion of subjects with no clinically visible AK lesions in the treatment area at Day 57.
2. Based on Clopper-Pearson Exact 95% CI. Note that for subgroup face and scalp, the reported 95% CI is for exploratory rather than confirmatory purpose
Source: Reviewer's analysis

Investigational Site

Study 003 enrolled and randomized subjects from 28 investigational sites, and Study 004 enrolled and randomized subjects from 31 investigational sites in the United State. However, 4 sites in Study 003 and 3 sites in Study 004 enrolled less than 5 subjects, and 2 sites in Study 004 only enrolled 1 subject each. Table 27 reports the treatment effect of the primary efficacy endpoint at Day 57 by investigational site in the ITT population in both studies. The complete clearance rate with Tirbanibulin ointment 1% treatment was higher than that with Vehicle treatment at most sites except 9 sites. However, we note that due to the large number of sites enrolled in each trial and small sample size in these sites, such results in the opposite direction may arise due to chance. Consequently, it is difficult to draw meaningful conclusions for results by site.

Table 26: Complete clearance rate at Day 57 by Investigational Site - Studies 003 and 004

Investigational Site	Tirbanibulin Ointment 1% n/N (%)	Vehicle n/N (%)	Clearance Rate Difference (Tirbanibulin Ointment 1%-Vehicle)
301	2/3 (67%)	0/4 (0%)	67%
302	2/4 (50%)	1/5 (20%)	30%
303	1/5 (20%)	0/4 (0%)	20%
304	3/6 (50%)	0/7 (0%)	50%
305	2/11 (18%)	0/9 (0%)	18%
306	5/11 (45%)	0/9 (0%)	45%
307	4/11 (36%)	0/9 (0%)	36%
308	4/7 (57%)	0/9 (0%)	57%
309	4/10 (40%)	1/9 (11%)	29%
311	0/2 (0%)	1/1 (100%)	-100%
312	1/6 (17%)	0/8 (0%)	17%
313	1/6 (17%)	0/8 (0%)	17%
314	3/5 (60%)	0/6 (0%)	60%
315	3/6 (50%)	2/6 (33%)	17%
316	3/4 (75%)	1/4 (25%)	50%
317	4/6 (67%)	0/8 (0%)	67%
318	0/2 (0%)	0/1 (0%)	0%
319	0/1 (0%)	0/1 (0%)	0%
320	6/10 (60%)	0/10 (0%)	60%
321	5/8 (63%)	0/8 (0%)	63%
322	4/4 (100%)	0/4 (0%)	100%
323	6/10 (60%)	0/10 (0%)	60%
324	1/3 (33%)	1/5 (20%)	13%
325	3/10 (30%)	0/8 (0%)	30%
326	5/10 (50%)	1/10 (10%)	40%
327	2/5 (40%)	0/5 (0%)	40%
329	1/3 (33%)	0/1 (0%)	33%
330	2/6 (33%)	0/6 (0%)	33%
401	1/3 (33%)	0/1 (0%)	33%
402	5/6 (83%)	0/4 (0%)	83%
403	7/10 (70%)	2/8 (25%)	45%
404	1/4 (25%)	0/4 (0%)	25%
405	0/1 (0%)	--	--
406	2/10 (20%)	0/6 (0%)	20%
407	8/11 (73%)	0/9 (0%)	73%
409	2/4 (50%)	0/3 (0%)	50%
410	1/3 (33%)	0/2 (0%)	33%

411	8/9 (89%)	1/11 (9%)	80%
412	3/6 (50%)	1/6 (17%)	33%
413	0/2 (0%)	0/5 (0%)	0%
414	1/4 (25%)	1/3 (33%)	-8%
415	4/4 (100%)	1/2 (50%)	50%
416	7/10 (70%)	3/10 (30%)	40%
417	4/9 (44%)	0/11 (0%)	44%
418	2/5 (40%)	0/5 (0%)	40%
419	4/6 (67%)	1/6 (17%)	50%
420	0/3 (0%)	0/4 (0%)	0%
421	3/9 (33%)	0/7 (0%)	33%
422	5/10 (50%)	0/10 (0%)	50%
424	4/8 (50%)	1/10 (10%)	40%
425	3/6 (50%)	0/7 (0%)	50%
426	8/10 (80%)	2/9 (22%)	58%
427	5/8 (63%)	0/8 (0%)	63%
428	5/6 (83%)	5/8 (63%)	20%
429	2/5 (40%)	1/6 (17%)	23%
430	--	0/1 (0%)	--
431	2/6 (33%)	3/7 (43%)	-10%

8.1.4. Integrated Assessment of Effectiveness

Given the evidence from the two Phase 3 studies 003 and 004, Tirbanibulin Ointment 1% showed superiority to Vehicle for the primary endpoint of complete (100%) clearance rate at Day 57 and the key secondary endpoint of partial (75%) clearance rate at Day 57 in the treatment of adults with AK on the face or scalp. Efficacy was somewhat greater for the face than the scalp, consistent with greater drug exposures achieved in the face relative to the scalp (Table 5).

8.2. Review of Safety

8.2.1. Safety Review Approach

Two Phase 3 randomized, controlled clinical trials, 003 and 004, reported safety findings including assessments for local skin reactions, adverse events, and laboratory assessments. The safety database for each trial was evaluated separately and compared.

Subjects who were 100% clear at Day 57 entered the 12-month follow-up period; severe adverse events as well as Treatment Area skin reactions, actinic keratoses, and skin cancers were reported. This data was reviewed for AK recurrence, local reactions, and adverse events of special interest (AESI).

8.2.2. Review of the Safety Databases

Overall Exposure

Overall, 1331 subjects were exposed to the proposed tirbanibulin product, with an additional population of 341 subjects who were treated with vehicle ointment. The primary analysis dataset for the review of safety for tirbanibulin ointment included data from two pivotal phase 3 trials 003 and 004. Data from the other trials were not integrated because of dissimilar study designs and different dosing regimens.

The Phase 3 safety population includes all subjects who were randomized and dispensed the study drug at Baseline (Day 0), excluding subjects who returned all the trial medication unused. The ITT and safety populations were identical (N=702). The safety population included 353 subjects treated with tirbanibulin ointment and 349 subjects treated with vehicle.

For the Phase 3 trials, all enrolled and successfully screened subjects were exposed to one packet (2.5 mg tirbanibulin drug substance or vehicle) each day for five consecutive days.

Relevant Characteristics of the Safety Population
In the safety populations for the Study 003, the majority of subjects were white (>99%), male (86%), and ≥ 65 years of age (74%). The safety populations for Study 004 were comparable; the majority of subjects were white (>99%), male (88%), and ≥ 65 years of age (73%). The demographic characteristics of the two treatment groups were comparable. Most subjects in Study 003 and Study 004 were non-Hispanic or Latino (98% and 95%, respectively). Refer to Section 8.1.2 for the demographic characteristics of the subjects in the safety population.

Table 27: Safety Population, Size and Denominators

Safety Database for the Study Drug[1] Individuals exposed to the study drug in this development program for the indication under review N=1680 (N is the sum of all available numbers from the columns below)		
Clinical Trial Groups	New Drug (n=1331)	Vehicle (n=349)
Controlled trials conducted for this indication[2]	353	349
All other than controlled trials conducted for this indication[3]	978	0
Controlled trials conducted for other indications[4]	0	0

[1] *study drug* means the drug being considered for approval.

[2] to be used in product's labeling
[3] if placebo arm patients switch to study drug in open label extension, the n should include their number; do not count twice patients who go into extension from randomized study drug arm
[4] include n in this column only if patients exposed to the study drug for indication(s) other than that in the marketing application have been included in the safety database under review. Consider n=0 in this column if no patients treated for other indication(s) were included in this safety database.

Adequacy of the safety database:

The total subject exposure to tirbanibulin ointment 1% applied once daily for five days provides adequate data for the evaluation of safety. The demographics of the study population are sufficiently representative of the target population. Therefore, the safety database submitted by the Applicant is sufficient to characterize the safety profile of tirbanibulin ointment 1% for the topical treatment of actinic keratosis.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The applicant submitted integrated summaries and data sets so that the application could be filed by the Agency and reviewed.

Deficiencies of note regarding the safety information data:

- When reporting adverse events during the trial, the treatment emergent flag was missing for 100% of the AEs for Study 003 (N=248 AEs) and Study 004 (N=268 AEs).
- Screen failures did not have information regarding the Inclusion/Exclusion criteria not met
    - Study 003: 14% (8 of 57 screen failures)
    - Study 004: 33.9% (20 of 59 screen failures)
- SAEs were missing seriousness criteria in 83.3% (5 of 6) for Study 003, and 100% (7 of 7) for Study 004.
- One subject was missing laboratory test or baseline value in Study 004.

Reviewer comment: The SAEs reported were small in number during the double-blind period, and the CRFs were reviewed for details.

Since the treatment emergent flag was missing, the AEs reported were considered treatment emergent.

Categorization of Adverse Events

The criteria for identifying adverse events (AEs) in this study were:

- any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an IP, whether or not considered related to the IP
- any new disease or exacerbation of an existing disease
- any deterioration in non-protocol-required measurements of a laboratory value or other clinical test (e.g., ECG or x-ray) that resulted in symptoms, a change in treatment, or discontinuation of study drug, and
- recurrence of an intermittent medical condition (egg, headache) not present pretreatment (Baseline)

The applicant graded the adverse events on a 3-point scale of mild, moderate, or severe and reported in the detail indicated on the eCRF. The definitions of grade follow:

- Mild = Discomfort noticed, but no disruption of normal daily activity
- Moderate = Discomfort sufficient to reduce or affect normal daily activity
- Severe = Incapacitating with inability to work or to perform normal daily activity

The applicant assessed the relationship of an AE to the study treatment considering the following:

- temporal relationship of the onset of the event to the initiation of the study treatment
- course of the event, especially the effect of discontinuation of study treatment or reintroduction of study treatment, as applicable
- whether the event was known to be associated with the study treatment or with other similar treatments
- presence of risk factors in the study subject known to increase the occurrence of the event
- presence of non-treatment-related factors that were known to be associated with the occurrence of the event.

The relationship of each AE to the study drug was to be recorded on the eCRF using the following criteria:

- Definitely Related: A clinical event, including laboratory test abnormality, occurring in a plausible time relationship to drug administration, and which could not be explained by concurrent or underlying disease or other drugs or conditions
- Probably Related: A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent or underlying disease or other drugs or conditions
- Possibly Related: A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, but which could also be explained by concurrent or underlying disease or other drugs or conditions
- Not Related: The AE was clearly not related to IP and was clearly related to underlying disease, environmental or toxic factor(s), or other drug therapy

An SAE is any untoward medical occurrence that at any dose:

- resulted in death
- was life threatening (i.e., the subject was at immediate risk of death from the AE as it occurred; this did not include an event that, had it occurred in a more severe form or was allowed to continue, might have caused death)
- required inpatient hospitalization or prolongation of existing hospitalization
- resulted in persistent or significant disability/incapacity
- was a congenital anomaly/birth defect (in the child of a subject who was exposed to the study drug)

Adverse events of special interest (AESI) reported during the Treatment and Response Assessment Periods (Day 1 to Day 57) were:

- skin cancers (including BCC, SCC, and melanoma) and their location and treatment were reported
- ocular exposures to study medication
- overdose of study medication
- pregnancy

The reported adverse events' grade, severity, and relationship to study drug application were evaluated during this review.

Routine Clinical Tests

The two identical pivotal trials scheduled routine clinical tests. The clinical tests with the scheduled study visit were as follows:

Height and weight	Screening and end of study
Vital signs	Screening, Baseline, Days 5 and 57
Clinical chemistry, hematology, urinalysis	Screening, Days 8, 15
Serum pregnancy test (PWCBP)	Screening
Urine pregnancy test (PWCBP)	Baseline, Day 57
Electrocardiogram	Screening, Baseline, Days 5, 15

8.2.4. Safety Results

Deaths

One death was reported during Study 003. Study 004 reported no deaths.

Subject (b) (6) was an 89-year old white male in the vehicle group who reported completed suicide at Day 38. The investigator reported that the subject was diagnosed with a BCC of the ear, outside of the application field. After MOHS surgery on Day 37 which could not complete the treatment, the subject reportedly "became depressed". On Day 38, he committed suicide.

> ***Reviewer comment:*** *The investigator reported the completed suicide after depression due to unsuccessful skin cancer surgery. The subject was enrolled in the vehicle arm. This reviewer considers the suicide unrelated to study drug and no labeling is recommended.*

Serious Adverse Events

Study KX01-AK-003 Serious Adverse Events

Subject (b) (6) was an 83-year-old white male with history of AKs, BCC (lt. forehead, (b) (6); rt. wrist, (b) (6)), SCC (rt. forearm, (b) (6); rt. abdomen, (b) (6); rt. hand, (b) (6); Lt. forearm, (b) (6); lt. shin, (b) (6); rt. shin, (b) (6)), prostate cancer treated in (b) (6), s/p inguinal hernia, s/p rt. cataract surgery, dizziness. The subject was enrolled and received study drug through Day 5; he completed Day 57 with 100% AK clearance per the investigators. On Recurrence Follow Up (RFU) Period Day 126, the subject reported an ANC of 0.2 x 10^9/L, Hb 5.7 g/dL, and Ht 17.8%. On RFU Day 129 the subject was diagnosed with hairy cell leukemia, and hospitalized for one day with anemia for a 3-unit blood transfusion. Allopurinol and cladribine treatment were initiated. The hairy cell leukemia was considered severe and unrelated to study drug by the investigator. The low hemoglobin level was considered severe and related to the leukemia.

On RFU Day 159, the subject was diagnosed and hospitalized with pancytopenia, neutropenia, and fever. He received transfusions of platelets (1 unit) and packed RBCs (2 units). On ECG, significant findings were sinus rhythm with premature ventricular contractions (PVC), marked ST abnormality, and possible subendocardial injury. He was treated with meropenem 0.9% suspension IV, vancomycin IV, and micafungin prn IV. On RFU Day 170, he was discharged and finished oral treatment with Bactrim, carvedilol, ciprofloxacin, valacyclovir. On RFU Day 177 the Subject withdrew consent due to hairy cell leukemia.

> ***Reviewer comment:*** *The hairy cell leukemia, anemia, and sepsis event were severe AEs reported during the Recurrence Follow Up Period. The sponsor did not list the second hospitalization or the reported pancytopenia requiring platelet and PRBC transfusions as SAEs; they were not AESI nor concern the treatment area.*

The drug application period and exposure were limited, and onset of hairy cell leukemia was 120 days later. This reviewer has insufficient information to consider whether or not the hairy cell leukemia is related to study drug. However, in the absence of similar reports of non-skin cancer related events for malignancies, labeling is not recommended for this event. The anemia and pancytopenia were severe and secondary to hairy cell leukemia and treatments.

Two subjects in the 003 vehicle group reported SAEs.

- Subject (b) (6) was an 89-year old white male in the vehicle group who reported completed suicide at Day 38. See Death Section.
- Subject (b) (6) was an 87-year-old white male in the vehicle group who reported an increased heart rate, myocardial infarction (MI), and aortic valve replacement.

Study KX01-AK-004 Serious Adverse Events

Subject (b) (6) was a 65-year-old white male with past treatments of cryosurgery, and participated in clinical trials for topical ingenol disoxate gel (b) (6) and topical diclofenac (b) (6) enrolled in the study drug group, scalp application. On Study Day 33, the subject reported chest pain. He was hospitalized with a diagnosis of pulmonary embolism of the bilateral lower lobes, supported by CT scan and mild elevation of antithrombin III. Negative or normal evaluations included chest x-ray, ECG, d-dimer blood test, cardiac stress test, cardiac echocardiogram, venous Doppler ultrasound of the legs. He was treated with paracetamol for pain, and acetylsalicylic acid orally (one dose), enoxaparin injections, and rivaroxaban orally for pulmonary emboli. The investigator considered the chest pain mild and the pulmonary emboli severe, and both SAEs unlikely related to study drug.

Reviewer comment: The study drug was applied Days 1 to 5, and the onset of symptoms occurred 28 days later. Therefore, this reviewer considers the reported pulmonary emboli and chest pain unlikely related to study drug.

Four subjects in the 004 vehicle group reported SAEs.

- Subject (b) (6) reported hospitalization for severe arthralgia and lumbar degenerative disc disease.
- Subject (b) (6) reported complete heart block and received a pacemaker.
- Subject (b) (6) reported Group B streptococcus agalactiae sepsis.
- Subject (b) (6) reported chest pain at rest, coronary artery stenosis and underwent cardiac catheterization and stent placement during the Screening Period.

Dropouts and/or Discontinuations Due to Adverse Effects

For Study 003, two male subjects in the vehicle group discontinued from the trial prior to Day 57. Subject (b) (6) withdrew consent on Day 30. Subject (b) (6) discontinued on Day 38 due to completed suicide (see narrative, Section 8.2.4).

Table 28: Study kx01-ak-003 - Demographics by Disposition - Age

	KX2-391 Ointment 1%		Vehicle Ointment		Total	
	<65 (N=51)	>=65 (N=124)	<65 (N=42)	>=65 (N=134)	<65 (N=93)	>=65 (N=258)
TOTAL COMPLETION N (%)	51 (100)	124 (100)	42 (100)	132 (98.5)	93 (100)	256 (99.2)
DEATH	0	0	0	1 (0.7)	0	1 (0.4)
WITHDRAWAL BY SUBJECT	0	0	0	1 (0.7)	0	1 (0.4)

Source: OCS Analysis Studio, Custom Table Tool. Table modified by Clinical Reviewer.
Columns - Dataset: Demographics; Filter: RANDFL = 'Y'.
Primary reason for discontinuation prior to Day 57 Visit - Dataset: Disposition; Filter: DSCAT = 'DISPOSITION EVENT', DSSCAT = 'PRIOR TO DAY 57 STATUS'.

For Study 004, all subjects completed the trial, with no dropouts or discontinuations due to adverse events.

Treatment Emergent Adverse Events and Adverse Reactions

Comparable numbers of subjects reported treatment-emergent adverse events (TEAE) in the pivotal trials. The tirbanibulin and vehicle arm data were comparable for Study 003 and Study 004, with approximately 33% and 38% of subjects reporting at least one TEAE, respectively.

Four subjects reported cellulitis. The location was documented in two of three who applied study drug. In Study 003, subject (b) (6) repoted cellulitis on the bilateral lower extremities. In Study 004, cellulitis was reported on subject (b) (6)'s left dorsal wrist (study drug) and on the subject (b) (6)'s bilateral lower legs (vehicle). Subject (b) (6) (study drug) reported cellulitis in an undocumented location on Day 40; this TEAE was unlikely related to study drug.

Table 29: Treatment Emergent Adverse Events for Tirbanibulin Pivotal Trials

	003 Tirbanibulin N=175 n (%)	003 Vehicle N=176 n(%)	004 Tirbanibulin N=178 n(%)	004 Vehicle N=173 n(%)
At least (1)TEAE	59 (33.7)	57 (32.4)	68 (38.2)	67 (38.7)
URI (incl viral)	10 (5.7)	12 (6.8)	15 (8.4)	14 (8.0)
Oral herpes/simplex	2 (1.1)	0	0	1 (<1)
Headache	3 (1.7)	2 (1.1)	1 (<1)	2 (1.1)
Glucosuria	2 (1.1)	0	0	0
Cellulitis	1 (<1)	0	2 (1.1)	1 (<1)
Back pain	0	1 (<1)	2 (1.1)	1 (<1)
Hemochromatosis	0	0	2 (1.1)	0

Source: Clinical Reviewer table.

Reviewer comment: In general, the majority of TEAEs were low in number and did not show a consistent pattern across studies.

While no cases of hemochromatosis were identified in the vehicle groups, the background prevalence of hemochromatosis in the US is approximately 1 in 300 individuals. Labeling for this event is not recommended.

The cases of cellulitis were unrelated or unlikely related to study drug application, so that labeling for this adverse event is not recommended.

Adverse reactions reported were related to local skin reactions due to tirbanibulin use. All reactions were higher in the study drug arm compared to the vehicle arm. The adverse reactions application site pain, pruritus and paresthesia occurred greater than 1%, and are listed in the Table below.

Table 30: Application site reactions: Skin Reactions > 1%

	003 Tirbanibulin N=175 n (%)	003 Vehicle N=176 n (%)	004 Tirbanibulin N=178 n (%)	004 Vehicle N=173 n (%)
At least one skin TEAE n (%)	23 (13.1)	18 (10.2)	36 (20.2)	20 (11.6)
Application site pain	11 (6.3)	6 (3.4)	24 (13.5)	5 (2.9)
Application site pruritus	13 (7.4)	8 (4.5)	19 (10.7)	13 (7.5)
Application site paresthesia	2 (1.1)	1 (0.6)	NR	NR

NR= not reported
Source: Clinical reviewer table.

Reviewer comment: In both studies, application site pain and pruritus were adverse reactions occurring more frequently in the study drug population compared to vehicle.

Laboratory Findings

Safety assessments included laboratory test monitoring for tirbanibulin ointment 1%, an NME. Chemistry, complete blood count, and urinalysis were scheduled at Screening, Day 8 and Day 15 of the Treatment Period.

- Hematology Red blood cells (RBC), hemoglobin, hematocrit, platelets, and white blood cells (WBC) with differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils)
- Electrolytes: Chloride, potassium, sodium, bicarbonate (HCO3)
- Liver function tests: Alanine aminotransferase (ALT), alkaline phosphatase (ALP), aspartate aminotransferase (AST), direct bilirubin, total bilirubin
- Renal function tests: Blood urea/blood urea nitrogen, creatinine
- Other: Albumin, calcium, cholesterol, glucose, lactate dehydrogenase (LDH), phosphorus, total protein, triglycerides, uric acid
- Urinalysis (dipstick): Hydrogen ion concentration (pH), specific gravity, protein, glucose, ketones, leukocyte esterase, nitrite, bilirubin, urobilinogen, blood
- Pregnancy Testing: Serum pregnancy test or urine pregnancy test

Chemistry Tests

For both studies, few abnormal chemistry tests were reported. Sodium and potassium values reported no pattern for changes up to two subjects in tirbanibulin and vehicle arms (< 2%), and no trend was identified.

Hypophosphatemia was observed in Studies 003 and 004. A change in phosphate levels from Grade 0 to Grade 2 (<.8 to .6 mmol/L) was noted in both studies: for Study 003, 5.7% (10 of 175) of tirbanibulin subjects and 6.3% (11 of 176) of vehicle subjects; for Study 004, 5.2% (9 of 178) of tirbanibulin subjects and 3.5% (6 of 173) of vehicle subjects. No trend was identified.

Kidney Function

There was no evidence for acute kidney injury due to study drug, as changes in creatinine were more frequent in vehicle subjects. Urinalysis was assessed by urine dipstick.

Liver Function Tests

In Study 003, peak elevated AST and ALT values were reported for two vehicle subjects; all values were 2 x ULN < 2.5 x ULN and were consistent with cholestasis. No study drug or vehicle subjects met Hy's Law criteria or mapped to Temple's Corollary graphically.
In Study 004, three vehicle subjects reported elevated ALT values, which were 2 x ULN < 2.5 x ULN. No study drug or vehicle subjects met Hy's Law criteria graphically.

Reviewer comment: No signal or sentinel events were identified. Labeling regarding laboratory evaluations is not recommended.

Vital Signs

Of the Vital Signs recorded and reported, blood pressure (BP) is an important clinical sign which can adversely impact the population affected by AKs. The Baseline BP values by grade were comparable across study drug and vehicle arms. The majority of subjects reported mild, Grade 1 hypertension value(s). In Study 003, one subject in the vehicle group did not report baseline BP values.

Table 31 : Study 003 Baseline Blood Pressure Values

Baseline Adult Hypertension	KX2-391 n (%)	Vehicle n (%)
Grade 0: SYSBP 100-120 mm Hg or DIABP 60-79 mm Hg	32 (18.3%)	27 (15.3%)
Grade 1: SYSBP 120-139 mm Hg or DIABP 80-89 mm Hg	100 (57.1%)	96 (54.5%)
Grade 2: SYSBP 140-159 mm Hg or DIABP 90-99 mm Hg	35 (20.0%)	47 (26.7%)
Grade 3: SYSBP>=160 mm Hg or DIABP>=100 mm Hg	8 (4.6%)	5 (2.8%)
Total Subjects	175 (100.0%)	175 (99.4%)

SYSBP=systolic blood pressure; DIABP=diastolic blood pressure
Source: Clinical Reviewer's Table.

Table 32: Study 004 Baseline Blood Pressure Values

Baseline Adult Hypertension	KX2-391 n (%)	Vehicle n (%)
Low: SYSBP <100 mm Hg or DIABP <60 mm Hg	0 (0.0%)	1 (0.6%)
Grade 0: SYSBP 100-120 mm Hg or DIABP 60-79 mm Hg	17 (9.6%)	26 (15.0%)
Grade 1: SYSBP 120-139 mm Hg or DIABP 80-89 mm Hg	95 (53.4%)	90 (52.0%)
Grade 2: SYSBP 140-159 mm Hg or DIABP 90-99 mm Hg	60 (33.7%)	48 (27.7%)
Grade 3: SYSBP>=160 mm Hg or DIABP>=100 mm Hg	6 (3.4%)	8 (4.6%)
Total Subjects	178 (100.0%)	173 (100.0%)

SYSBP=systolic blood pressure; DIABP=diastolic blood pressure
Source: Clinical Reviewer's Table

.

For Study 003 and 004, the majority of subjects did not report a change in their blood pressure during the trial period. Of those subjects documenting worsening change in blood pressure, the changes were comparable across the arms and within each study.

Table 33: Maximum Worse Change in Blood Pressure Grade, Study 003

Baseline: Adult Hypertension	Change in Grade of Hypertension	KX2-391 Ointment 1% N=175	Vehicle Ointment N=176
	Total number of subjects reporting change	67 (38.3%)	62 (35.2%)
Grade 0: SYSBP 100-120 mm Hg or DIABP 60-79 mm Hg	Grade 1: SYSBP 120-139 mm Hg or DIABP 80-89 mm Hg	22 (12.6%)	19 (10.8%)
	Grade 2: SYSBP 140-159 mm Hg or DIABP 90-99 mm Hg	2 (1.1%)	2 (1.1%)
Grade 1: SYSBP 120-139 mm Hg or DIABP 80-89 mm Hg		32 (18.3%)	27 (15.3%)
	Grade 3: SYSBP>=160 mm Hg or DIABP>=100 mm Hg	2 (1.1%)	5 (2.8%)
Grade 2: SYSBP 140-159 mm Hg or DIABP 90-99 mm Hg		9 (5.1%)	9 (5.1%)

SYSBP=systolic blood pressure; DIABP=diastolic blood pressure
Source: Clinical Reviewer's Table

Table 34: Maximum Worse Change in Blood Pressure Grade, Study 004

Baseline Hypertension Grade	Change in Grade of Hypertension	KX2-391 Ointment 1% N=178	Vehicle Ointment N=173
	Total number of subjects reporting change	50 (28.1%)	51 (29.5%)
Low: SYSBP <100 mm Hg or DIABP <60 mm Hg	Grade 0: SYSBP 100-120 mm Hg or DIABP 60-79 mm Hg	0 (0.0%)	1 (0.6%)
Grade 0: SYSBP 100-120 mm Hg or DIABP 60-79 mm Hg	Grade 1: SYSBP 120-139 mm Hg or DIABP 80-89 mm Hg	8 (4.5%)	13 (7.5%)
	Grade 2: SYSBP 140-159 mm Hg or DIABP 90-99 mm Hg	1 (0.6%)	6 (3.5%)
Grade 1: SYSBP 120-139 mm Hg or DIABP 80-89 mm Hg		35 (19.7%)	23 (13.3%)
Grade 2: SYSBP 140-159 mm Hg or DIABP 90-99 mm Hg	Grade 3: SYSBP>=160 mm Hg or DIABP>=100 mm Hg	6 (3.4%)	8 (4.6%)

SYSBP=systolic blood pressure; DIABP=diastolic blood pressure
Source: Clinical Reviewer's Table

.

Reviewer comment: The majority of subjects did not report a change in blood pressure, and over 95% did not report a Grade 3 measurement. The blood pressure changes were unlikely related to study drug. Tirbanibulin does not pose a significant blood pressure risk for patients treated for actinic keratosis and does not require labeling for this event.

Electrocardiograms (ECGs)

The sponsor submitted a report detailing the pooled results of the cardio dynamic evaluation of studies KX01-AK-003 and KX01-AK-004. As scheduled, ECGs were recorded on Day 1 pre-dose (baseline), Day 5 post dose, and Day 15 in both studies.

The Interdisciplinary Review Team (IRT) for Cardiac Safety Studies reviewed the applicant's Cardiac Safety Report, and concluded that ECG data from Study 003 and 004 do not indicate a clinically relevant effect of tirbanibulin on the QTc interval at the proposed therapeutic dose.

QT

The Clinical team consulted the Interdisciplinary Review Team (IRT), which reviewed the data and concluded:

> *Submitted data by the Sponsor do not indicate a clinically relevant effect of tirbanibulin on the QTc interval at the proposed therapeutic dose.*

As noted above in the clinical Pharmacology section of this review:

"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 the phase 2 and 3 clinical studies. A thorough QT study is not usually necessary for topical drugs with low systemic bioavailability (See IRT Memorandum by Dr. Girish K Bende dated 05/07/2020 in DARRTS for details)".

Therefore, a thorough QT study was not considered necessary for this product and such an assessment was not conducted. The IRT proposed to not include QT-related language in section 12.2 of the labeling.

Immunogenicity

Immunogenicity was not necessary and was not assessed during the trials.

8.2.5. Analysis of Submission-Specific Safety Issues

Adverse events of special interest during the Treatment and Response Assessment Periods included the following: skin cancers; ocular exposures to study medication; overdose of study medication; pregnancy. No ocular exposures, study medication overdose, or pregnancy were reported.

8.2.5.1. Skin Cancers Diagnosed During the Studies

In Study 003, nine skin cancers were reported in seven treatment group subjects, and four skin cancers in four vehicle group subjects. One treatment group subject, (b) (6) reported an SCC in the right superior scalp within the treatment area on Study Day 74.

All subjects reporting skin cancers were white, male, and had a history of skin cancer. All subjects in the study drug group reported SCCs or SCC in situ, as well as one MM in situ and BCC, each.

Table 35: Skin Cancers Reported, Study KX02-AK-003

Subject	Demo	Product	Tx Area	Skin Cancer Type	Skin Cancer Location	DX Study Day	History Skin Ca	100 % Clear D57	RFU D/C Day, Reason
(b) (6)	59,W, M	Tx	Face	SCC in situ; MM in situ	Lt cheek/ jaw; chest	55	BBC SCC MM	Yes	Day 94 AK rec
	61,W, M	Tx	Face	SCC rec	Rt cheek[1]	1	SCC	Yes	Day 92 AK rec
	79,W, M	Tx	Face	SCC in situ	Lt cheek; Rt helix; Lt forearm	55	BCC SCC	No	DNE
	71,W, M	Tx	Face	SCC in situ	Lt neck	-7	BCC SCC in situ	No	DNE
	84,W, M	Tx	Face	SCC;BCC	Rt nose; Rt ear	7	SCC	No	DNE
	68,W, M	Tx	Scalp	SCC	Rt sup scalp	74	BCC	No	DNE
	80,W, M	Tx	Scalp	SCC	Lt hand	15	BCC SCC MM	Yes	Day 170 AK rec
	77,W, M	V	Face	SCC	Rt temple	43	BCC SCC	No	DNE
	62,W, M	V	Scalp	BCC	Lt forehead	-7	BCC SCC	No	DNE
	89,W, M	V	Face	SCC[2]	Rt ear	8	BCC SCC	-	-
	68,W, M	V	Scalp	BCC	Lt postau-ricular	29	BCC	No	DNE

W= white; M=male; Tx=treatment; V=vehicle; RFU = Recurrence Follow Up Period; sup=superior; rec=recurrence; DNE=did not enter RFU

1 Skin cancer location was not in Treatment area.

2 Subject 313-107 reported an SCC on Day 37 and death by suicide on Day 38, prior to Day 57 assessment.

Source: Clinical reviewer's table.

Reviewer comment: While the SCC of the scalp treatment area in subject 317-504 was diagnosed on Day 74, the skin cancer may have evolved before study drug application

over five days. AKs are known to progress to SCC; however, it is not possible to determine causality of tirbanibulin application which occurred 69 days prior to SCC diagnosis. Serial biopsies of suspect lesions were not obtained in the trials.

In Study 004, five skin cancers were reported in five treatment group subjects, compared to six skin cancers reported in four vehicle group subjects. No skin cancer occurred in an area treated with investigational product.

Table 36: Skin Cancers Reported, Study KX02-AK-004

Subject	Demo	Product	Tx Area	Skin Cancer Type	Skin Cancer Location	DX Study Day	History Skin Ca	100% Clear D57	RFU D/C Day, Reason
(b) (6)	78,W,M	Tx	Face	BCC	Lt Neck	8	NMSC, MM	Yes	182 AK rec
	62,W,F	Tx	Face	BCC	Lt temple	42	BCC,SCC	Yes	175 AK rec
	78,W,M	Tx	Scalp	MM in situ	Rt upper back	43	BCC,SCC	Yes	175 AK rec
	69,W,M	Tx	Face	SCC	Lt forearm	7	BCC,SCC	Yes	84 AK rec
	55,W,M	Tx	Face	SCC	Rt Med Forehead[1]	57	No	No	DNE
	78,W,M	V	Scalp	SCC	Lt frontal scalp; Rt Thigh	-7	SCC	No	DNE
	70,W,F	V	Face	BCC	Rt sup nasal side wall	15	BCC,SCC	No	DNE
	61,W,F	V	Face	SCC	Post neck	9	BCC	No	DNE
	65,W,M	V	Face	SCC	Rt clavicle; Lt shoulder	-28; 43	BCC	No	DNE

1 Skin cancer was not located in Treatment Area.
W= white; F=female; M=male; Tx=treatment; V=vehicle; RFU = Recurrence Follow Up Period; rec=recurrence; DNE=did not enter
Source: Clinical reviewer's table.

Reviewer comment: It is possible that the skin cancers reported were already present subclinically in subjects with known history of actinic keratoses and skin cancer. In this 004 trial, none of the skin cancers were reported in the Treatment Area. No signal for subject skin cancer development, nor association of skin cancer diagnosis and study drug application could be identified.

8.2.5.2. Local Skin Reactions

The sponsor collected and reported local skin reactions (LSR) at each visit in Studies 003 and 004. Subjects were monitored for erythema, flaking and scaling, crusting, swelling, and vesicles and pustules, erosions and ulcers. The most reported LSRs were erythema and flaking/scaling, which were also significant at baseline. Over 50% of subjects who received study drug reported mild to moderate erythema, with the peak at Days 8 and 15, while mild erythema was predominant in the vehicle group. Mild flaking and scaling occurred in significant numbers for tirbanibulin and vehicle groups, consistently throughout the study period for both arms. More study drug subjects reported flaking/scaling of moderate severity than in the vehicle group.

The study drug and vehicle subjects reported lower LSR numbers in the crusting, swelling, vesiculation/pustulation, and erosion/ulceration categories; no vehicle subjects reported moderate or severe vesiculation/pustulation, and erosion/ulceration. Overall, the peak study drug subgroup LSR reports for these clinical signs were higher compared to the vehicle group.

The highlighted LSRs reported after Baseline occurred at a rate of 20% and greater.

Table 37: Local Skin Reactions (LSR) by Reaction, Severity, Day, and Treatment Group in Study 003, Safety Population

Skin Reaction	KX2-391 N=175 n(%)			Vehicle N=176[a] n(%)		
	Mild	Moderate	Severe	Mild	Moderate	Severe
Erythema						
Baseline	32 (18)	2 (1)	0	34 (19)	5 (3)	0
Day 5	63 (38)	84 (48)	4 (2)	69 (40)	6 (3)	0
Day 8	60 (35)	100 (58)	2 (1)	59 (34)	1 (<1)	0
Day 15	113 (65)	20 (11)	0	45 (26)	6 (3)	0
Day 29	46 (26)	4 (2)	0	35 (20)	1 (<1)	0
Day 57	26 (15)	0	0	21 (12)	0	0
Flaking/Scaling						
Baseline	52 (30)	1 (<1)	0	56 (32)	2 (1)	0
Day 5	97 (56)	21 (12)	0	69 (40)	3 (2)	0

Day 8	65 (38)	72 (42)	10 (6)	54 (31)	7 (4)	0
Day 15	84 (48)	21 (12)	2 (1)	56 (32)	7 (4)	0
Day 29	38 (22)	1 (<1)	0	54 (31)	0	0
Day 57	27 (15)	0	0	39 (22)	0	0
Crusting						
Baseline	14 (8)	3 (2)	0	15 (9)	2 (1)	0
Day 5	40 (23)	5 (3)	0	17 (10)	1 (<1)	0
Day 8	58 (34)	17 (10)	2 (1)	20 (11)	1 (<1)	0
Day 15	27 (16)	4 (2)	0	18 (10)	0	0
Day 29	8 (5)	0	0	13 (8)	1 (<1)	0
Day 57	5 (3)	0	0	13 (7)	1 (<1)	0
Swelling						
Baseline	1 (<1)	0	0	1 (<1)	0	0
Day 5	41 (24)	7 (4)	1 (<1)	6 (3)	1 (<1)	0
Day 8	44 (25)	9 (5)	0	2 (1)	0	0
Day 15	16 (9)	2 (1)	0	6 (3)	0	0
Day 29	2 (1)	0	0	0	0	0
Day 57	1 (<1)	0	0	1 (<1)	0	0
Vesiculation/Pustulation						
Baseline	1 (<1)	0	0	0	0	0
Day 5	9 (5)	1 (<1)	0	0	0	0
Day 8	8 (5)	0	0	0	0	0
Day 15	1 (<1)	1 (<1)	0	1 (<1)	0	0
Day 29	1 (<1)	0	1 (<1)	1 (<1)	0	0
Day 57[a]	0	0	0	0	0	0
Erosion/Ulceration						
Baseline	4 (2)	0	0	1 (<1)	0	0
Day 5	5 (3)	1 (<1)	0	2 (1)	0	0
Day 8	8 (5)	3 (2)	0	5 (3)	0	0
Day 15	6 (3)	3 (2)	0	3 (2)	0	0
Day 29	0	0	0	2 (1)	0	0
Day 57	0	0	0	1 (<1)	0	0

a : N=174 at Day 57, due to one death and one withdrawal.
Source: Clinical reviewer's table, adapted from Applicant's Clinical Study Report Table.

Table 38: Local Skin Reactions (LSR) by Reaction, Severity, Day, and Treatment Group in Study 004, Safety Population

Skin Reaction	KX2-391 N=175 n(%)			Vehicle N=173 n(%)		
	Mild	Moderate	Severe	Mild	Moderate	Severe
Erythema						
Baseline	50 (28)	6 (3)	0	50 (29)	3 (2)	0
Day 5	65 (38)	89 (52)	6 (3)	69 (40)	7 (4)	0
Day 8	56 (31)	99 (56)	12 (7)	58 (34)	4 (2)	0
Day 15	113 (63)	37 (21)	0	50 (29)	4 (2)	0
Day 29	60 (34)	3 (2)	0	37 (22)	1 (<1)	0
Day 57	32 (18)	3 (2)	0	33 (19)	2 (1)	0
Flaking/Scaling						
Baseline	44 (25)	3 (2)	0	44 (25)	6 (3)	0
Day 5	93 (54)	18 (10)	2 (1)	51 (30)	8 (5)	0
Day 8	57 (32)	80 (45)	17 (10)	50 (29)	9 (5)	0
Day 15	87 (49)	31 (17)	3 (2)	51 (29)	4 (2)	1 (<1)
Day 29	33 (19)	0	0	35 (20)	3 (2)	0
Day 57	26 (15)	1 (<1)	0	32 (18)	3 (2)	0
Crusting						
Baseline	10 (6)	0	0	14 (8)	2 (1)	0
Day 5	31 (18)	7 (4)	0	9 (5)	2 (1)	0
Day 8	40 (22)	26 (15)	5 (3)	9 (5)	0	0
Day 15	32 (18)	4 (2)	0	8 (4)	1 (<1)	0
Day 29	1 (<1)	0	0	3 (2)	1 (<1)	0
Day 57	2 (1)	1 (<1)	0	7 (4)	2 (1)	0
Swelling						
Baseline	0	0	0	1 (<1)	0	0
Day 5	35 (20)	11 (6)	0	1 (<1)	0	0
Day 8	37 (21)	13 (7)	1 (<1)	3 (2)	0	0
Day 15	18 (10)	1 (<1)	0	1 (<1)	0	0
Day 29	3 (2)	0	0	0	0	0
Day 57	0	1 (<1)	0	0	0	0

Vesiculation/Pustulation						
Baseline	0	0	0	0	0	0
Day 5	4 (2)	0	0	0	0	0
Day 8	8 (4)	0	1 (<1)	1 (<1)	0	0
Day 15	1 (<1)	0	0	1 (<1)	0	0
Day 29	1 (<1)	0	0	0	0	0
Day 57	0	0	0	0	0	0
Erosion/Ulceration						
Baseline	0	0	0	1 (<1)	0	0
Day 5	5 (3)	2 (1)	0	1 (<1)	0	0
Day 8	11 (6)	2 (1)	0	1 (<1)	0	0
Day 15	5 (3)	0	0	0	0	0
Day 29	0	0	0	0	0	0
Day 57	0	0	0	0	0	0

Source: Clinical reviewer's table, adapted from Applicant's Clinical Study Report Table.

Reviewer comments: Vehicle group LSR occurrences and severity was less compared to study drug group; only one vehicle subject in both trials reported a severe LSR (flaking/scaling), and moderate LSRs were infrequent (less than 10) for all study visits.

While mild to moderate reactions were common for both study drug arms, the LSR frequency returned to or near baseline at Day 57. The LSR safety profile did not identify a sentinel event or major safety risk for AK patients. The action of the proposed product makes it likely that these events would be observed and are typical of other products in the class of treatments for actinic keratoses.

8.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

No clinical outcome assessment tool was utilized during the pivotal trials.

8.2.7. Safety Analyses by Demographic Subgroups

The safety population was over 99% white, and of non-hispanic ethnicity (95% and 99%). Therefore, no analysis could be conducted based on race and ethnicity due to low numbers for comparison.

When considering the sex subgroup, the safety population for the pivotal trials was predominantly male. For Studies 003 and 004, the safety populations were 84% and 89% male, respectively. While the trial populations were comparable, no meaningful subgroup comparisons could be made between male and female subjects.

8.2.8. Specific Safety Studies/Clinical Trials

Dermal safety studies were conducted to assess irritancy, contact sensitivity, photosensitivity, and phototoxicity. These studies were typical of dermal safety studies for topical products and included sufficient subjects and adequate exposures to investigational products in patch applications to allow conclusions that may be useful in labeling.

KX01-AK-010: A Pilot Study to Assess the Tolerability of KX2-391 Ointment 1% under Occlusive, Semi-occlusive, and Open Patch Conditions
This study was used to determine safety and patch conditions for dermal study 006. The investigational products were study drug, vehicle, and 0.9% saline for topical administration as study control.

The product application portion of this study consisted of a series of 9 applications of the study material and subsequent evaluations of the application sites. The subjects returned to the facility for dose administration 3 times per week for 3 consecutive weeks.

The study population was 36 subjects, 9 males (25.0%) and 27 females (75.0%). Nine subjects (25.0%) were white and 27 subjects (75.0%) were black/African American. Thirty subjects (83.3%) completed the study.

The majority of subjects assigned KX2-391 occlusive and semi-occlusive patch applications discontinued early in the treatment period, whereas the majority of subjects assigned KX2-391 under open conditions tolerated treatment. KX2-391 under open conditions reported less irritation than KX2-391 applied under occlusive and semi-occlusive conditions. Therefore, the applicant determined that the Repeat Insult Patch Test (RIPT) study KX01-AK-006 would use an open patch test design.

Study outlines are provided in Table 6.

KX01-AK-006: A Randomized, Controlled Study to Evaluate the Sensitizing Potential of KX2-391 Ointment 1% in Healthy Subjects Using a Repeat Insult Patch Test Design
There were no signs suggestive of contact sensitization for all investigational products (KX2-391; vehicle; normal saline 0.9%).

KX01-AK-008: A 4-Day, Randomized Study to Evaluate the Potential of KX2-391 Ointment 1% to Induce a Phototoxicity Skin Reaction in Healthy Subjects, Using a Controlled Photopatch Test Design
There was no evidence of phototoxicity for KX2-391 Ointment 1% and vehicle ointment.

KX01-AK-009: A 6-Week, Randomized Study to Evaluate the Potential of KX2-391 Ointment 1% to Induce a Photoallergic Skin Reaction in Healthy Subjects, Using a Controlled Photopatch Test Design

There was no evidence of photosensitization for KX2-391 Ointment 1% and vehicle ointment.

In these dermal safety studies with patch applications of investigational products, no clinically relevant safety events were identified.

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

See section 8.2.5.1.

Ocular exposure
The sponsor did not report cases of ocular exposure to study medication for Study 003 and Study 004. Three ocular AEs were reported for both studies; two cases occurred in subjects randomized to the vehicle group.

Study 003
Subject (b) (6) was a 62 year-old white male assigned to KX2-391 group, who reported left eye blepharospasm on Day 5. The treatment area was on the left face. The blepharospasm resolved on Day 9 without treatment. Any IP exposure in or around the eye was denied. The subjects completed the study with 100% clearance at Day 57; he entered the Recurrence Follow-up Period and discontinued due to AK recurrence. The investigator considered the AE blepharospasm of mild severity, and unlikely related to study drug.

Reviewer comment: Blepharospasm occurred on the same (left) side as the KX2-391 treatment area on Day 5, which was after five consecutive days of treatment. It is possible that inadvertent IP migration or transfer occurred due to anatomical proximity. Therefore, this reviewer considers blepharospasm AE possibly related to study drug.

Subject (b) (6) was an 82 year-old white man was randomized to the vehicle group, underwent five days of application to the scalp. After left eye cataract surgery on Day 8, the subject reported left eye iritis on Day 31, which resolved by Day 32 without treatment. The investigator considered the TEAE mild and not related to study drug treatment.

Study 004
Subject (b) (6) was a 57 year-old white male in the vehicle group who reported right eye diplopia. The treatment area was on left side of face; the subject had right diplopia from Day 38 to 78. The investigator considered the TEAE mild and not related to study drug treatment.

Human Reproduction and Pregnancy

No pregnancy events were reported for Study 003 or Study 004.

Pediatrics and Assessment of Effects on Growth

No pediatric population was enrolled, as actinic keratosis is a condition seen in adults. Therefore, no assessment of the pediatric population was warranted or conducted.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

No overdose was reported during Study 003. For Study 004, one subject reported overdose of vehicle, two applications on Day 1. No drug abuse potential, withdrawal, or rebound effects were identified.

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Tirbanibulin is a new molecular entity, and not marketed in any country. There is no postmarketing experience.

Expectations on Safety in the Postmarket Setting

Safety in the postmarketing setting will consist of ongoing monitoring. No PMR or PMC studies are requested by the Agency at this time.

8.2.11. Integrated Assessment of Safety

Safety data from two identical pivotal phase 3 trials support this application for the treatment of actinic keratosis. Tirbanibulin is a small molecule NME which when applied topically as directed is not expected to result in systemic adverse reactions or events.

In general, tirbanibulin ointment treatment was well tolerated; no subjects discontinued the studies due to adverse events. All local skin reactions occurred more frequently in the tirbanibulin treated population than in the vehicle group; erythema, scaling and flaking, crusting, and swelling dominated the adverse event reports. The LSRs were mild to moderate in severity; all but one severe reaction was reported in the tirbanibulin group. The local skin reaction rates returned to baseline or less by Day 57. There were no deaths, and no serious adverse events considered associated with tirbanibulin ointment use. The adverse event of special interest skin cancer in the treatment area occurred in one patient over two studies. An association between tirbanibulin use and skin cancer development could not be established. During the one-year follow up period enrolling subjects 100% clear at Day 57, 73% of these subjects reported AK recurrence as defined by the applicant. Continued or recurrent actinic keratosis development is not unusual in a population with a history of multiple AK lesions and skin cancer.

The preponderance of data supports the overall safety of tirbanibulin ointment 1% for the treatment of actinic keratosis of the face or scalp.

8.3. Statistical Issues

There were no major statistical issues affecting the overall conclusions. The treatment effect was generally consistent across the two studies and analysis populations. There were no substantial differences in efficacy among subgroups.

Missing data were very few, only two subjects in the vehicle arms in Study 003 were discontinued prior to the Day 57 visit, and consequently, treating these two subjects as non-responders, as prespecified in the protocol, had a negligible impact on the reported efficacy results.

The Statistical analysis plan pre-specified that for subgroup analysis, "Clopper-Pearson Exact 95% CI will be provided for each estimation. But no statistical test will be performed between subgroups." Yet, the applicant reported p-values for the face and scalp treatment areas for the primary and secondary endpoints in the label. The reviewer suggested to remove the p-values for the treatment area as such analysis does not consider the issue related to un-prespecified analysis. Even for the Clopper-Pearson Exact 95% CI, due to the duality of the confidence interval approach and the hypothesis test, the 95% CI should be considered for exploratory purpose but not for confirmatory purpose. The reviewer noted this when reporting the 95% CI for all subgroup analyses (Tables 15, 16, 17, 18, 25 and 26).

The applicant also presented plots for lesion count over time by treatment group with p-values tested at each visit to show efficacy over time with the goal to be in the label. However, such results are based on post-hoc analysis and do not consider the multiplicity issues that arise, as the trials were not designed to establish efficacy over time by study visit. In addition, the applicant's proposed analysis did not take the missing data into account during the trials. Therefore, the reviewer suggested to remove the efficacy over time plot during the treatment period from the label.

8.4. Conclusions and Recommendations

This multidisciplinary review recommends approval for KLISYRI (tirbanibulin) ointment, 1%, for the indication of multiple actinic keratoses of the face or scalp in adults.

Athenex has provided sufficient evidence that tirbanibulin ointment treats actinic keratoses of the face or scalp superiorly to vehicle in adults. There are no safety findings that impact approvability of this application.

Labeling and postmarketing surveillance is adequate to inform prescribers and patients regarding this therapy for actinic keratoses.

9 Advisory Committee Meeting and Other External Consultations

No Advisory Committee meeting was held for this application as there were no complex or substantive review issues.

10 Pediatrics

Tirbanibulin was not evaluated in the pediatric population as this condition typically does not occur in pediatric patients. The applicant's request to waive pediatric studies was reviewed and granted by the Agency's Pediatric Review Committee according to PREA. Supporting information for the waiver specified that actinic keratosis is an indication overwhelmingly seen in adults, and studies in the pediatric population would be difficult or impossible to conduct and complete.

11 Labeling Recommendations

11.1. Prescription Drug Labeling

Prescribing Information
The Applicant submitted proposed prescribing information (PI) for Klisyri. The review team provided recommendations regarding PI which are provided throughout this review. The Office of Prescription Drug Promotion (OPDP) reviewed and provided comments regarding the PI, proposed patient information and the carton/container. These comments are reflected in final labeling. Refer to the Office of Medical Policy patient labeling review by Susan Redwood, MPH, BSN,RN, (DMPP) and Laurie Buonaccorsi, PharmD (OPDP) dated July 30, 2020.

Madhuri R. Patel, PharmD from the Division of Medication Error Prevention and Analysis provided comments regarding the proposed labeling and labels for areas that may lead to medication errors. The first review was dated May 26, 2020 from the NDA submission; latest review was dated September 10, 2020 regarding revised container labels and carton labeling received on September 1, 2020. Labeling negotiations are in progress.

The members of the team who provided recommendations regarding PI are tabulated below.

Table 39: Summary of Significant High-Level Labeling Changes

Section	Location of Reviewer Comments on Proposed Labeling
1 INDICATIONS AND USAGE	Clinical Team Section 1.1, 2
2 DOSAGE AND ADMINISTRATION	Product Quality Team Section 4.2
3 DOSAGE FORMS AND STRENGTHS	Product Quality Team Section 4.2
4 CONTRAINDICATIONS	Clinical Team Section 8.2
5 WARNINGS AND PRECAUTIONS	Clinical Team Section 8.2
6 ADVERSE REACTIONS	Clinical Team Section 8.2
7 DRUG INTERACTIONS	Clinical Pharmacology Team Section 6, Appendix 19.4
8 USE IN SPECIFIC POPULATIONS	Nonclinical Team Section 5, Clinical Pharmacology Team Section 6, Appendix 19.4, 19.5
11 DESCRIPTION	Product Quality Team Section 4.2
12 CLINICAL PHARMACOLOGY	Clinical Pharmacology Team Section 6, Appendix 19.4
13 NONCLINICAL TOXICOLOGY	Nonclinical Team Section 5, Appendix 19.3
14 CLINICAL STUDIES	Statistical Team Section 8, Appendix 19.5
16 HOW SUPPLIED	Product Quality Team Section 4.2
17 PATIENT COUNSELING INFORMATION	Reflects the data in other sections of labeling, Sections 4, 5, 6

Source: Reviewer's Table

Other Prescription Drug Labeling

The Applicant submitted proposed patient package insert for Klisyri (tirbanibulin) ointment, for topical use. The Division of Medical Policy Programs (DMPP) and OPDP reviewed and provided comments on the patient package insert. The final labeling will reflect their recommendations.

12 Risk Evaluation and Mitigation Strategies (REMS)

After consultation with and review by the Division of Risk Management (DRM) in the Office of Surveillance and Epidemiology (OSE), no serious safety issue was been identified. Therefore, no Risk Evaluation and Mitigation Strategies program is recommended at this time. Labeling and postmarketing surveillance are adequate to inform prescribers of relevant risks of this product.

13 Postmarketing Requirements and Commitment

After clinical review, no known serious risk or signals of serious risk related to the use of the drug were identified. Additionally, there are no available data to indicate the potential for serious risk related to drug use. Therefore, the Agency is not requesting that the sponsor conduct Postmarketing Requirement or Postmarketing Commitment studies. There are no recommendations for PMR's from any review disciplines.

14 Division Director (Clinical) Comments

I concur with the review team's recommendation to approve tirbanibulin ointment, 1% for the topical treatment of actinic keratosis of the face or scalp in adults.

Actinic keratosis (AK) occurs on a background of UV-related skin damage. While the natural history of AK is variable, with the possibility of spontaneous resolution, AKs are considered to be "benign neoplasms of the epidermis and are considered precursor lesions to nonmelanoma skin cancers" (Soutor and Hordinsky). Currently available treatments, outlined in Section 2.2 of this review, include drug therapy, laser, cryotherapy and surgical removal.

Tirbanibulin is a small molecule, new molecular entity microtubule inhibitor. Tirbanibulin's effectiveness in treating AK was demonstrated In two randomized, double-blind, vehicle-controlled clinical trials, where tirbanibulin was superior to vehicle in complete clearance at Day 57. The main risks appear to be local skin reactions. Of the skin cancer cases across the two pivotal studies, one case of squamous cell carcinoma occurred in the treatment area. Based on the available data, the reviewers were unable to establish an association between tirbanibulin use and the occurrence of skin cancer and I concur with this conclusion, considering the increased background risk in this population. There are no safety issues that impact approvability.

In the pivotal trials, subjects achieving 100% clearance were followed to 12 months and the recurrence rate was 72%; it is not clear whether these recurrences represent new lesions appearing on previously damaged skin or recurrences of previously treated lesions. Because subjects with partial clearance were not followed after Day 57, the longer term outcome of these treated lesions was not recorded.

Tirbanibulin offers another nonsurgical therapeutic option to adult patients with actinic keratosis. Risks can be communicated via labeling and monitored via surveillance.

15 Office Director Comments

I concur with the recommendation of the Division of Dermatology and Dentistry to approve Klisyri (tirbanibulin) ointment, 1% for topical administration for the treatment of actinic keratosis of the face or scalp in adults. This new molecular entity is a microtubule inhibitor that is applied to lesions on the face or scalp for a total of 5 consecutive days. It represents another nonsurgical treatment option that can be administered by the patient at home.

The efficacy of tirbanibulin was demonstrated in two identically-designed, phase 3, randomized, double-blind, vehicle-controlled trials. In both trials, tirbanibulin ointment was superior to vehicle ointment in achieving complete (100%) or partial (75%) clearance of actinic keratosis lesions in the treatment area at Day 57. Actinic keratosis lesions occurred in 73% of subjects with complete clearance at Day 57 when assessed 12 months later, not an unexpected finding in individuals with a history of multiple actinic keratosis lesions.

In the phase 3 trials, treatment with tirbanibulin ointment was well tolerated; local skin reactions included mild to moderate erythema, scaling and flaking, crusting, and swelling. There was a single report of squamous cell carcinoma occurring in the treatment area of a tirbanibulin-treated subject. Labeling and postmarketing surveillance are adequate to inform prescribers of the risks of this product.

16 Appendices

16.1. References

Werner RN, Sammain A, Erdmann R, Hartmann V, Stockfleth E, Nast A: The natural history of actinic keratosis: a systematic review. Br J Dermatol 2013 Sep;169(3):502-18.

16.2. Financial Disclosure

For the tirbanibulin development program, the applicant attested that none of the clinical investigators reported financial disclosures, proprietary interest, or equity relationship with the sponsor. Each clinical investigator [as defined in 21 CFR 54.2(d)], as required in 21 CFR 54.4(a)(l), submitted a completed Form FDA 3454, attesting to the absence of financial interests and arrangements described in 21 CFR 54.4(a)(3).

Covered Clinical Study (Name and/or Number): The applicant submitted investigator forms for the following studies:

- KX01-AK-01: 3 investigators
- KX01-AK-002: 72 investigators
- KX01-AK-003: 126 investigators
- KX01-AK-004: 142 investigators
- KX01-AK-006: 2 investigators
- KX01-AK-007: 14 investigators
- KX01-AK-008: 3 investigators
- KX01-AK-009: 2 investigators
- KX01-AK-010: 2 investigators

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 366		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be		

influenced by the outcome of the study: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in S Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements: N/A	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided: N/A	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 366		
Is an attachment provided with the reason: N/A	Yes ☐	No ☐ (Request explanation from Applicant)

16.3. Nonclinical Pharmacology/Toxicology

19.3.1 Nonclinical Labeling

I recommend that the "INDICATIONS AND USAGE" section of the "HIGHLIGHTS OF PRESCRIBING INFORMATION" portion of the draft label be modified to indicate that the established pharmacologic class of tirbanibulin is "microtubule inhibitor", instead of (b) (4) (b) (4) I recommend that sections 8.1, 8.3, 11, 12.1, 13.1 and 13.2 of the label of the product be modified as indicated below. Other portions of the proposed label are acceptable with respect to nonclinical issues.

The "dose multiples" (nonclinical exposures expressed as a ratio of the maximum observed clinical exposure) stated in the label are based upon comparison of systemic exposure values ($AUC_{nonclinical}/AUC_{clinical}$). The clinical value used for this purpose was the mean $AUC_{0\text{-}24h}$ resulting from application of TRADENAME ointment to the face in a maximum-use clinical trial (trial KX01-AK-007; 5.0 ng•h/mL). This value was greater than the mean $AUC_{0\text{-}24h}$ resulting from application to the scalp (3.18 ng•h/mL), and therefore is considered to represent a "worst case" (maximum exposure) scenario. Tirbanibulin was evaluated for potential to affect fertility, embryofetal development, and perinatal development. Systemic exposure data associated with those studies and comparisons of those data to relevant clinical data are summarized below:

Table 40: Comparisons of Systemic Exposures (AUC_{0-24h}) Observed in Selected Nonclinical Safety Studies to Systemic Exposure Observed in Clinical Trials (Dose Multiples), as Presented in the Label

Study Type	Dose of Interest (NOAEL or dose that resulted in toxicity as described in label)	Estimated AUC_{0-24h} (ng·hr/mL)	Dose Multiple
Fertility	Males, adverse effects on spermatogenesis: 4 mg/kg/day Males, NOAEL: 2 mg/kg/day Females, NOAEL: 1 mg/kg/day	472 236 299	94 47 60
EFD (Female Rats)	NOAEL for fetal effects: 0.5 mg/kg/day Min. dose at which fetal effects were observed: 1.25 mg/kg/day	90 372	18 74
EFD (Female Rabbits)	NOAEL for fetal effects: 1 mg/kg/day Min. dose at which fetal effects were observed: 3 mg/kg/day	266 795	53 159
Perinatal Development (Dams plus pups)	NOAEL for maternal effects: 1.25 mg/kg/day NOAEL for F1 Generational effects: 1.25 mg/kg/day	373 373	74 74

I recommend that section (b) (4) of the sponsor's proposed label be omitted, (b) (4) For these reasons, section (b) (4) is unnecessary. I recommend that section (b) (4) of the sponsor's proposed label be omitted (b) (4) and therefore should not be presented in the label.

Recommended changes from the sponsor's proposed labeling in regard to the "INDICATIONS AND USAGE" section of the "HIGHLIGHTS OF PRESCRIBING INFORMATION" portion of the draft label, and sections 8.1, (b) (4), 11, 12.1, (b) (4) and 13.2 are indicated below through use of strikeout (deletions) and underline (additions) fonts.

HIGHLIGHTS OF PRESCRIBING INFORMATION
INDICATIONS AND USAGE
TRADENAME is a (b) (4) microtubule inhibitor indicated for the topical treatment of actinic keratosis of the face or scalp.

8.1 Pregnancy
Risk Summary

There are no available data with TRADENAME use in pregnant women to evaluate for a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. (b) (4)

(b) (4)

In animal reproduction studies, oral administration of tirbanibulin to pregnant rats during the period of organogenesis resulted in an increased incidence of fetal deaths and malformations at a systemic exposure that was at least 74 times the exposure associated with the maximum recommended human dose (MRHD). Oral administration of tirbanibulin to pregnant rabbits during the period of organogenesis resulted in reduced mean fetal weight and size at a systemic exposure that was 159 times the exposure associated with the MRHD (*see Data*).

The background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Data

Animal Data

(b) (4)

(b) (4)

Tirbanibulin induced fetal deaths and external, visceral, and skeletal malformations when administered orally to pregnant rats during the period of organogenesis at doses greater than or equal to 1.25 mg/kg/day, which resulted in systemic exposures at least 74 times the exposure associated with the MRHD on an Area Under the Curve (AUC) comparison basis. Tirbanibulin had no apparent effects on fetal development in rats at a dose of 0.5 mg/kg/day, which resulted in systemic exposures 18 times the exposure associated with the MRHD.

Tirbanibulin reduced mean fetal weight and size (crown-rump length) when administered orally to pregnant rabbits during the period of organogenesis at a dose of 3 mg/kg/day, which resulted in a systemic exposure 159 times the exposure associated with the MRHD on an AUC comparison basis. Tirbanibulin had no apparent effects on fetal development in rabbits at a dose of 1 mg/kg/day, which resulted in systemic exposures 53 times the exposure associated with the MRHD.

Tirbanibulin was assessed for effects on peri- and post-natal development of rats in a study that involved oral administration to pregnant rats during the period of organogenesis through lactation at dosages up to 1.25 mg/kg/day. These dosages resulted in systemic exposures up to 74 times the exposure associated with the MRHD on an AUC comparison basis. No adverse effects on maternal function or developmental, neurobehavioral, or reproductive performance of offspring were observed.

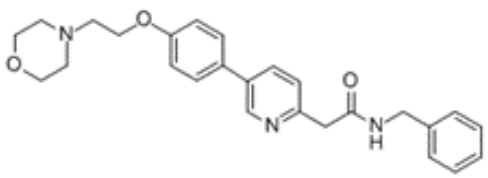
(b) (4)

(b) (4)

11 DESCRIPTION

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

The chemical name of tirbanibulin is *N*-benzyl-2-(5-(4-(2-morpholinoethoxy)phenyl)pyridin-2-yl)acetamide. The (b) (4) molecular weight is 431 (b) (4) (b) (4) and the molecular formula is $C_{26}H_{29}N_3O_3$. Tirbanibulin's structural formula is:



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

12.1 Mechanism of Action

(b) (4) Tirbanibulin is a microtubule inhibitor. The mechanism of action of TRADENAME ointment for the topical treatment of actinic keratosis is unknown.

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No studies have been performed to evaluate the potential of tirbanibulin (b) (4) to induce carcinogenesis.

Tirbanibulin was negative (b) (4) in an in vitro bacterial reverse mutation (b) (4) (Ames) assay, (b) (4) Tirbanibulin was positive in an in vitro chromosomal aberration assays (b) (4) with Chinese hamster ovary (CHO) cells, an in vitro mouse lymphoma (b) (4) -assay with L5178Y/TK$^{+/-}$ cells, and an in vivo (b) (4) -micronucleus assay in rats. (b) (4)

(b) (4)

Tirbanibulin was assessed for effects on fertility or reproductive function in rats. Reproductive performance of rats was unaffected by oral doses of tirbanibulin up to 4 mg/kg/day (94 times the MRHD on an AUC comparison basis) in males and 1 mg/kg/day (60 times the MRHD on an AUC comparison basis) in females. However, oral administration of 4 mg/kg/day of tirbanibulin to male rats adversely affected spermatogenesis, including reduced sperm count and motility, and increased observations of morphologically abnormal sperm. No effects on sperm were observed in males treated at 2mg/kg/day (47 times the MRHD on an AUC comparison basis).

(b) (4)

The revised portions of the draft label are presented as clean-copy text below:

HIGHLIGHTS OF PRESCRIBING INFORMATION
INDICATIONS AND USAGE
TRADENAME is a microtubule inhibitor indicated for the topical treatment of actinic keratosis of the face or scalp.

8.1 Pregnancy
Risk Summary
There are no available data with TRADENAME use in pregnant women to evaluate for a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes.

In animal reproduction studies, oral administration of tirbanibulin to pregnant rats during the period of organogenesis resulted in an increased incidence of fetal deaths and malformations at

a systemic exposure that was at least 74 times the exposure associated with the maximum recommended human dose (MRHD). Oral administration of tirbanibulin to pregnant rabbits during the period of organogenesis resulted in reduced mean fetal weight and size at a systemic exposure that was 159 times the exposure associated with the MRHD (*see Data*).

The background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Data

Animal Data

Tirbanibulin induced fetal deaths and external, visceral, and skeletal malformations when administered orally to pregnant rats during the period of organogenesis at doses greater than or equal to 1.25 mg/kg/day, which resulted in systemic exposures at least 74 times the exposure associated with the MRHD on an Area Under the Curve (AUC) comparison basis. Tirbanibulin had no apparent effects on fetal development in rats at a dose of 0.5 mg/kg/day, which resulted in systemic exposures 18 times the exposure associated with the MRHD.

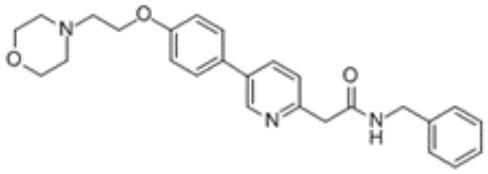
Tirbanibulin reduced mean fetal weight and size (crown-rump length) when administered orally to pregnant rabbits during the period of organogenesis at a dose of 3 mg/kg/day, which resulted in a systemic exposure 159 times the exposure associated with the MRHD on an AUC comparison basis. Tirbanibulin had no apparent effects on fetal development in rabbits at a dose of 1 mg/kg/day, which resulted in systemic exposures 53 times the exposure associated with the MRHD.

Tirbanibulin was assessed for effects on peri- and post-natal development of rats in a study that involved oral administration to pregnant rats during the period of organogenesis through lactation at dosages up to 1.25 mg/kg/day. These dosages resulted in systemic exposures up to 74 times the exposure associated with the MRHD on an AUC comparison basis. No adverse effects on maternal function or developmental, neurobehavioral, or reproductive performance of offspring were observed.

11 DESCRIPTION

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

The chemical name of tirbanibulin is *N*-benzyl-2-(5-(4-(2-morpholinoethoxy)phenyl)pyridin-2-yl)acetamide. The molecular weight is 431 and the molecular formula is $C_{26}H_{29}N_3O_3$. Tirbanibulin's structural formula is:



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

12.1 Mechanism of Action

Tirbanibulin is a microtubule inhibitor. The mechanism of action of TRADENAME ointment for the topical treatment of actinic keratosis is unknown.

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No studies have been performed to evaluate the potential of tirbanibulin to induce carcinogenesis.

Tirbanibulin was negative in an in vitro bacterial reverse mutation (Ames) assay. Tirbanibulin was positive in an in vitro chromosomal aberration assay with Chinese hamster ovary (CHO) cells, an in vitro mouse lymphoma assay with L5178Y/TK$^{+/-}$ cells, and an in vivo micronucleus assay in rats.

Tirbanibulin was assessed for effects on fertility or reproductive function in rats. Reproductive performance of rats was unaffected by oral doses of tirbanibulin up to 4 mg/kg/day (94 times the MRHD on an AUC comparison basis) in males and 1 mg/kg/day (60 times the MRHD on an AUC comparison basis) in females. However, oral administration of 4 mg/kg/day of tirbanibulin to male rats adversely affected spermatogenesis, including reduced sperm count and motility, and increased observations of morphologically abnormal sperm. No effects on sperm were observed in males treated at 2mg/kg/day (47 times the MRHD on an AUC comparison basis).

16.4. OCP Appendices (Technical documents supporting OCP recommendations)

The tirbanibulin actinic keratosis (AK) clinical development program included 9 clinical trials in support of the proposed indication.

- Six Phase 1 trials in healthy subjects or subjects with AK
    - Study KX01-AK-010: a local tolerability trial in healthy subjects
    - Study KX01-AK-006: a dermal sensitization potential trial in healthy subjects
    - Study KX01-AK-008: a phototoxic potential trial in healthy subjects
    - Study KX01-AK-009: a photoallergic potential trial in healthy subjects
    - Study KX01-AK-01-US: a safety, tolerability and PK trial in subjects with AK
    - Study KX01-AK-007: a maximal use PK trial in subjects with AK

- One Phase 2 trial in subjects with AK
    - Study KX01-AK-002: an efficacy and safety study to support Phase 3 trials
- Two Phase 3 efficacy and safety trials in subjects with AK
    - Study KX01-AK-003
    - Study KX01-AK-004

Of note, the PK study (Study KX01-AK-007) conducted under maximal use conditions is considered as a pivotal Clinical Pharmacology study for this NDA.

The Applicant has also characterized the absorption, distribution, metabolism, and excretion (ADME) property of tirbanibulin *in vitro* by using human biomaterials.

Biopharmaceutics program

Two formulations, Formulation I and the to-be-marketed, were developed. Formulation I was used in nonclinical, early Phase 1 and Phase 2 clinical trials. The to-be-marketed formulation was used in 5-day pivotal nonclinical toxicology studies; the clinical maximal use PK, Phase I dermal safety, and pivotal Phase 3 trials.

16.4.1. Summary of Bioanalytical Method Validation and Performance

Determination of concentrations of tirbanibulin and its metabolites in human plasma

Three LC/MS/MS assays for determination of plasma concentrations of tirbanibulin (KX2-391) and its metabolites KX2-5036 and KX2-5163 were developed. In brief, the methods utilized a liquid-liquid or a Supported-Liquid extraction (SLE) procedures to extract the analyte from 0.1 or 0.2 mL of K_2EDTA human plasma, a reverse phase HPLC column to elute tirbanibulin, its metabolites, and the internal standard, and an LC/MS/MS instrument with positive ESI MRM mode to quantify tirbanibulin, its metabolites, and the internal standard. The assays (18141-M01 and 19052-M01) applied in the maximal use PK study (KX01-AK-007) are applicable for quantitation of tirbanibulin within a nominal range of 0.01 to 5 ng/mL with lower limit of quantitation (LLOQ) of 0.01 ng/mL; and for quantitation of the metabolites of tirbanibulin (KX2-5036 and KX2-5163) within a nominal range of 0.05 to 25 ng/mL with LLOQ of 0.05 ng/mL. The validation parameters and performance of each assay are summarized in Table 40.

Table 41: Bioanalytic Methods and Validation Parameters of Tirbanibulin and Its Metabolites in Human Plasma

Method	Analyte	Sample Volume (µL)	Linear Range (ng/mL)	LLOQ (ng/mL)	Intra Batch	
					Accuracy (%RE)	Precision (%CV)
07047-M03/4	Tirbanibulin	100	0.1 - 50	0.1	-3.50 – 0.33	1.45 – 4.19
18141-M01*	Tirbanibulin	200	0.01 - 5	0.01	-3.00 – 6.75	0.62 – 7.15
19052-M01*	KX2-5036	100	0.05 - 25	0.05	-10.00 – 8.00	1.37 – 5.36
	KX2-5163	100	0.05 - 25	0.05	-1.33 – 12.00	0.98 – 10.26

*Bioanalytical methods were applied in the maximal use PK study (Study KX01-AK-007)
%CV=percent coefficient of variation, %RE=percent of relative error, LLOQ=lower limit of quantification
Long-term storage stability: tirbanibulin was stable in human plasma up to 91 days and 194 days when stored frozen at -20°C and -70°C, respectively. KX2-5036 and KX2-5163 were stable in human plasma up to 118 days when stored frozen at -20°C and -70°C.
(Source of data: Reviewer's summary based on Bioanalytical Validation Reports (XBL:07047-RPT01897 Amendment 1 and 18141-RPT04883) and Modul 2.7.1)

16.4.2. Clinical Pharmacology Studies

16.4.2.1. Study KX01-AK-01-US: a safety, tolerability, and PK study in subjects with AK

Study KX01-AK-01-US was a proof-of-concept, open-label, uncontrolled, nonrandomized, sequential group study of KX2-391 ointment 1% in adult subjects with AK on the dorsal forearm. The study design is summarized in Table 42.

Table 42 : Study Design of Study KX01-AK-01-US

Cohort (N)	Application Area	Amount of Study Medication per Application	Dose of Active KX2-391	Treatment Duration
1 (N=4)	25 cm^2	50 mg	0.5 mg	3 days
2 (N=10)	100 cm^2	200 mg	2 mg	3 days
3 (N=8)	25 cm^2	50 mg	0.5 mg	5 days
4 (N=8)	100 cm^2	200 mg	2 mg	5 days

Source: Clinical Study Report KX01-AK-01-US

Pharmacokinetic results:
PK parameters of KX2-391 (tirbanibulin) were not characterized due to the low number of detectable concentrations of KX2-391. Of the 30 subjects enrolled, plasma concentrations of KX2-391 were not detectable in 6 subjects (20%) at any timepoints. The other 24 (80%) subjects had at least 1 post-dose sample with measurable KX2-391, however, the plasma concentrations of KX2-391 were not detectable or below LLOQ of 0.1 ng/mL in the majority of the samples.

Reviewer's comments: Study KX01-AK-01-US is considered as an exploratory PK trial.

16.4.2.2. Study KX01-AK-007: a maximal use PK study in subjects with AK

Study KX01-AK-007 was a Phase 1, open-label, uncontrolled, non-randomized, maximal use PK trial to evaluate the systemic exposure and safety of KX2-391 ointment 1% when applied under maximal use conditions, defined as the application of a small amount (total dose up to 250 mg from a single-use packet) of KX2-391 ointment 1% to 25 cm^2 of the face or balding scalp that contained at least 6 AK lesions (severe conditions), once daily for 5 consecutive days. Medication was self-administered each day, using the single-use packet to mimic clinical usage. The packets were weighted after dose administration so that the dose of drug administered could be determined. A total of 18 subjects were enrolled, demographic information is summarized in

Table 43.

Table 43: Demographic Information for Study KX01-AK-007

		Face (N=9)	Scalp (N=9)	Combined (N=18)
Age (years)	Mean (SD)	71.1 (6.92)	61.8 (9.58)	66.4 (9.42)
	Median	71.0	64.0	67.0
	Min, Max	57, 83	43, 76	43, 83
Sex, n (%)	Male	6 (66.7)	9 (100)	15 (83.3)
	Female	3 (33.3)	0	3 (16.7)
Race, n (%)	White	9 (100)	9 (100)	18 (100)
Ethnicity, n (%)	Not Hispanic or Latino	9 (100)	7 (77.8)	16 (88.9)
	Hispanic or Latino	0	2 (22.2)	2 (11.1)
Fitzpatrick Skin Type, n (%)	Type III	5 (55.6)	4 (44.4)	9 (50.0)
	Type I	2 (22.2)	2 (22.2)	4 (22.2)
	Type II	2 (22.2)	2 (22.2)	4 (22.2)
	Type IV	0	1 (11.1)	1 (5.6)
Baseline AK Lesion Count, n (%)	6	2 (22.2)	3 (33.3)	5 (27.8)
	7	3 (33.3)	2 (22.2)	5 (27.8)
	8	0	2 (22.2)	2 (11.1)
	9	1 (11.1)	1 (11.1)	2 (11.1)
	10	1 (11.1)	0	1 (5.6)
	11	1 (11.1)	0	1 (5.6)
	13	1 (11.1)	0	1 (5.6)
	14	0	1 (11.1)	1 (5.6)
Baseline AK Lesion Count	Mean (SD)	8.4 (2.46)	7.9 (2.52)	8.2 (2.43)
	Median	7.0	7.0	7.0
	Min, Max	6, 13	6, 14	6, 14
BMI, n (%)	25-29.9 (overweight)	3 (33.3)	5 (55.6)	8 (44.4)
	18.5-24.9 (normal)	4 (44.4)	3 (33.3)	7 (38.9)
	30-34.9 (class I obese)	0	1 (11.1)	1 (5.6)
	35-39.9 (class II obese)	1 (11.1)	0	1 (5.6)
	>= 40 (class III obese)	1 (11.1)	0	1 (5.6)
BMI, (kg/m²)	Mean (SD)	28.5 (7.76)	26.3 (3.23)	27.4 (5.88)
	Median	27.0	26.1	26.4
	Min, Max	20.7, 43.8	21.4, 31.9	20.7, 43.8

(*Source of data*: *Clinical Study Report KX01-AK-007, Table 6)*

Actual Dose Used:

The mean daily actual dose used in Study KX01-AK-007 was 138 mg with the range of 54 mg to 295 mg. The individual mean ± SD daily dose and numbers of AK lesions treated are summarized in Table 44. Of note, the to-be-marketed formulation was used in this study.

Table 44: Mean ± SD Daily Dose Used and Numbers of AK Lesions Treated

Face (n=9)			Scalp (n=9)		
Subject# CSR/PK	Dose (mg) Mean ± SD	AK lesion count	Subject# CSR/PK	Dose (mg) Mean ± SD	AK lesion count
(b) (4)	250 ± 33	6	(b) (4)	205 ± 42	8
	167 ± 44	6		207 ± 46	7
	102 ± 18	10		149 ± 16	9
	133 ± 34	7		124 ± 36	8
	87 ± 11	7		150 ± 65	7
	148 ± 53	9		109 ± 39	6
	157 ± 9	7		96 ± 27	14
	97 ± 25	13		101 ± 33	6
	83 ± 16	11		116 ± 39	6

*n=4

(*Source of data*: *Reviewer's summary based on Clinical Study Report KX01-AK-007, Application Dosing Record)*

Reviewer's comments: *The dosing administration instructions applied in the maximal use PK (KX01-AK-007) and Phase 3 trials (KX01-AK-003 and KX01-AK-004) were the same: a small amount of a single-use packet was to be self-applied over a contiguous area of 25 cm^2 each day for 5 consecutive days by study subjects. The only difference between the maximal use PK study and Phase 3 trials is the severity of the disease. Subjects in Study KX01-AK-007 had higher numbers of AK lesions in the treatment area at Baseline than those in the Phase 3 trials. The median (min, max) of AK lesions for Study KX01-AK-007 was 7 (6-14). The median (min, max) of AK lesions for Phase 3 trial KX01-AK-003 and KX01-AK-004 was 6 (4,8).*

Pharmacokinetics:

- *Tirbanibulin (KX2-391)*

The PK results of KX2-391 are summarized in Table 45.

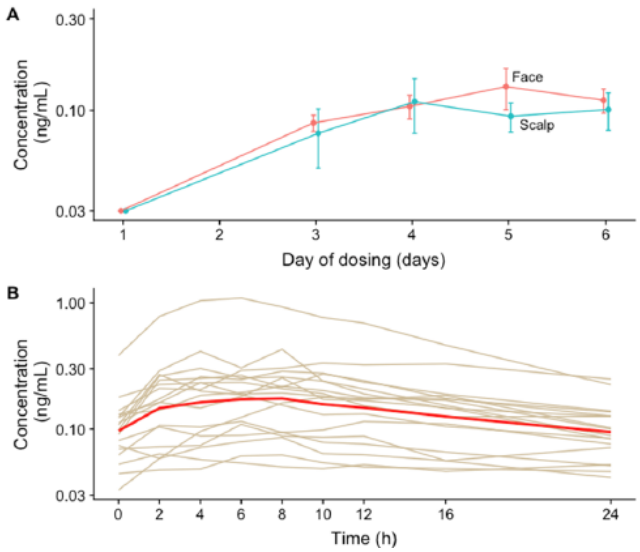
The C_{trough} data demonstrated that steady-state concentrations of KX2-391 in both face and scalp treatment groups were achieved by 72 hours (Day 4) (Figure 2A). The systemic exposure to KX2-391 expressed as C_{max} and AUC_{24h} in the face treatment group were slightly higher than those in the scalp treatment group (Table 45). On Day 5, the highest C_{max} value of 1.1 ng/mL (2.5 nM) was observed in Subject # (b) (4) who had 6 AK lesions on the face and received the highest mean daily dose of 250 ± 33 mg for 5 consecutive days (Figure 2B, Table 44). While, all other 17 subjects had the C_{max} values of <0.43 ng/mL. There was a linear correlation between the Day-5 C_{max} and Day-5 AUC_{24h} (Figure 3). The AUC_{24h} values for KX2-391 increased with dose, but the dose-exposure relationship was nonlinear (Figure 4).

Table 45: PK of KX2-391 in Subjects with AK Under Maximal Use Conditions

Treatment Group	Day:	1	3	4	5	6	5		
	Descriptive Statistics	KX2-391 Trough Concentration (ng/mL)					C_{max} (ng/mL)	t_{max} (h)	AUC_{24h} (h*ng/mL)
Face (N = 9)	Mean	0.00	0.0861	0.105	0.133	0.111	0.340	-	5.0
	SD		0.0250	0.0444	0.0969	0.0476	0.297	-	3.9
	CV%	-	29.0	42.4	72.9	43.1	87.4	-	78.7
	Median	0.00	0.0771	0.0918	0.108	0.0879	0.270	6.0	4.04
	Min	0.00	0.0588	0.0571	0.0625	0.0636	0.109	2.0	1.78
	Max	0.00	0.124	0.190	0.383	0.219	1.09	9.8	15.0
Scalp (N = 9)	Mean	0.00	0.0760	0.111	0.0932	0.099	0.176	-	3.18
	SD		0.0778	0.105	0.0487	0.0677	0.102	-	1.92
	CV%	-	102.3	94.7	52.2	68.1	57.8	-	60.4
	Median	0.00	0.0391	0.0760	0.0812	0.102	0.179	7.8	3.3
	Min	0.00	0.0232	0.0273	0.0329	0.0413	0.0623	2.0	1.2
	Max	0.00	0.271	0.368	0.179	0.254	0.333	10.0	6.7
Combined (N = 18)	Mean	0.00	0.0811	0.1078	0.1131	0.105	0.258	-	4.09
	SD	-	0.0563	0.0782	0.0772	0.0571	0.231	-	3.15
	CV%	-	69	73	68	54	90	-	77
	Median	0.00	0.0718	0.0806	0.1033	0.0949	0.234	6.91	3.86
	Min	0.00	0.0232	0.0273	0.0329	0.0413	0.0623	2.0	1.2
	Max	0.00	0.271	0.368	0.383	0.254	1.09	10.0	15.0

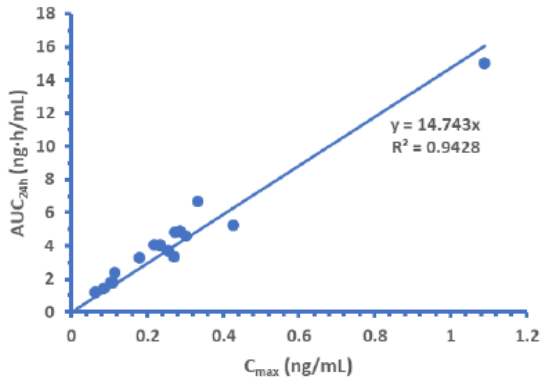
(*Source of data*: *Clinical Study Report KX01-AK-007, Table 8)*

Figure 2A and 2B: Mean Trough Plasma Concentrations of KX2-391 in the Face or Scalp Group (A) and Individuals Plasma Concentrations of KX2-391 on Day 5 in the Face and Scalp Combined Group (n= 18) (B)



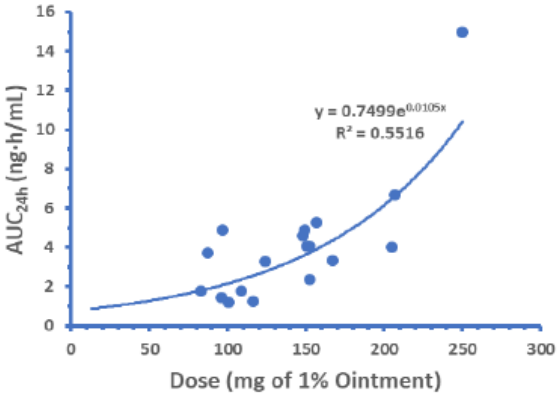
(*Source of data*: *Clinical Study Report KX01-AK-007, Figure 1)*

Figure 3: Correlation between Day-5 Cmax and Day-5 AUC24h of KX2-391



(*Source of data*: *Clinical Study Report KX01-AK-007, Figure 2)*

Figure 4: Correlation between Mean Daily Dose and Day-5 AUC24h of KX2-391



(*Source of data*: *Clinical Study Report KX01-AK-007, Figure 3)*

- *Metabolites of tirbanibulin (KX2-391)*

Among 18 subjects who received the topical treatment of KX2-391 ointment 1% daily for 5 days, the metabolites of KX2-5036 and KX2-5163 were detectable in 3 (17%) and 5 subjects (28%) on Day 5, respectively, at the level within 3-fold of LLOQ (0.05 ng/mL for both metabolites). The highest observed plasma concentrations of KX2-5036 and KX2-5163 were 0.09 ng/mL (0.27 nM) and 0.12 ng/mL (0.35 nM), respectively, under maximal use conditions. See *19.4.3* for the proposed metabolic pathways of KX2-391 in humans.

16.4.2.3. Study KX01-AK-002: a Phase 2a efficacy and safety study in subjects with AK

Study KX01-AK-002 was an uncontrolled, open-label, Phase 2a, sequential group study to evaluate the efficacy, safety and PK of KX2-391 ointment 1% in adult subjects with AK. A total of 168 subjects were enrolled with 84 per cohort. Subjects were primarily White (99%) and male

(88%), with a mean age of 68 years and a mean weight of 193 pounds. All subjects had 4 to 8 AK lesions in a 25 cm^2 area on the face or scalp. The study design is summarized in Table 46. Of note, Formulation I was used in this study and the plasma concentrations of KX2-391 were determined by a less sensitive LC/MS/MS assay with the LLOQ of 0.1 ng/mL.

Table 46: Study Design of Study KX01-AK-002

Cohort (N)	Application Area	Amount of Study Medication per Application	Dose of Active KX2-391	Treatment Duration
1 (N=84)	25 cm^2	50 mg	0.5 mg	5 days
2 (N=84)	25 cm^2	50 mg	0.5 mg	3 days

Source: Clinical Study Report KX01-AK-002

Pharmacokinetic results:

PK parameters of KX2-391 were not characterized due to the low number of detectable concentrations of KX2-391. In Cohort 1, at 4-hours after the last dose (Day 5), 41 of 83 subjects (49%) had measurable plasma concentrations of KX2-391 ranging from 0.11 to 0.58 ng/mL. In Cohort 2, at 4 hours after the last dose (Day 3), 45 of 83 subjects (54%) had measurable plasma concentrations of KX2-391 ranging from 0.10 to 1.42 ng/mL.

Reviewer's comments: The PK data in Study KX01-AK-002 is considered as exploratory information as to-be-marketed formulation was not used.

16.4.3. Studies Using Human Biomaterials

16.4.3.1. Plasma protein binding

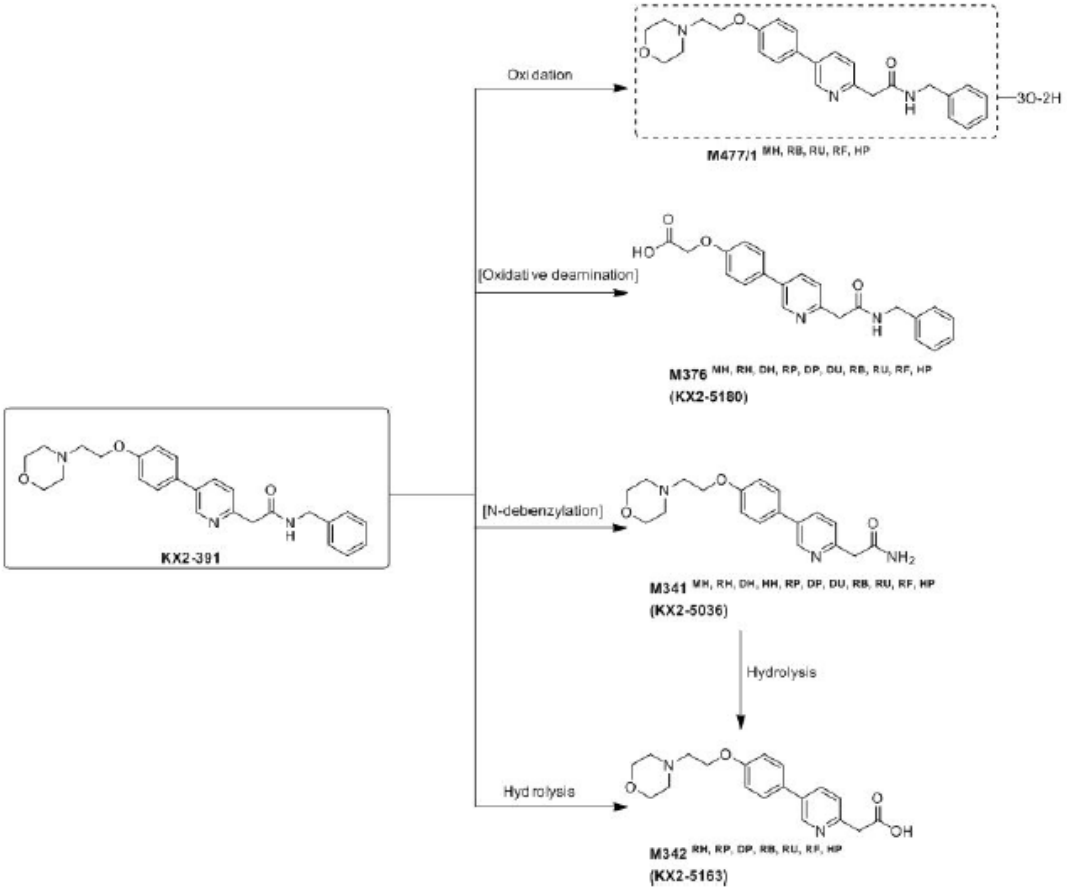
Plasma protein binding of KX2-391 and the metabolite KX2-5036 is approximately 88% and 57%, respectively, and is independent of concentrations in the range of 0.01 to 10 µg/mL, *in vitro* (XBL17622 and C18092).

16.4.3.2. Metabolism

- An *in vitro* CYP phenotyping study suggested that KX2-391 was mainly metabolized by CYP3A4 and, to a lesser extent, CYP2C8 (Study XBL08671).

- Incubation of KX2-391 (1 and 10 µM) with human hepatocytes generated serval metabolites including the metabolites KX2-5036 and KX-5163 (Figure 5). None of them were found to be unique to humans (Study 7709-114).

Figure 5: Proposed Metabolic Pathways of KX2-391 in Humans



The following footnotes represent the observation of human metabolites in clinical and non-clinical biological matrices: RH = Rat Hepatocyte, MH = Minipig Hepatocyte, HH = Human Hepatocyte, DH = Dog Hepatocyte, RP = Rat Plasma, DP = Dog Plasma, RB = Rat Bile, RU = Rat Urine, DU = Dog Urine, RF = Rat Feces, HP = Human Plasma

Source: KX01-AK-007, C19017, Section 5 of Module 2.6.4

16.4.3.3. Drug-drug interaction

Cytochrome P450s

- CYP induction studies (XBL17621 and C18089): *In vitro*, KX2-391 up to 1 µM (431.5 ng/mL) and the metabolite KX2-5036 up to 3 µM (1024 ng/mL) did not induce CYP1A2, 2B6, or 3A4.

- CYP inhibition studies (C18087,): *In vitro*, KX2-391 and KX2-5036 directly or time-dependently inhibited CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 3A with an IC_{50} value of >17 µM (Error! Reference source not found.Table 47 and Table 48).

Table 47: Direct and Time-Dependent CYP Inhibition by KX2-391

CYP	Marker Substrate (Conc.)[a]	Isoform-Catalyzed Reaction	Direct Inhibition IC_{50}[b] (µM)	Time-dependent Inhibition IC_{50}[b] (µM)	IC_{50} Shift Fold[c]
1A2	Phenacetin (50 µM)	*O*-Deethylation	> 90	> 90	N/A
2B6	Bupropion (50 µM)	Hydroxylation	> 90	> 90	N/A
2C8	Amodiaquine (2 µM)	*N*-Deethylation	> 90	> 90	N/A
2C9	Diclofenac (5 µM)	4'-Hydroxylation	73.5	47.3	1.6
2C19	*S*-mephenytoin (20 µM)	4'-Hydroxylation	40.8	21.5	1.9
2D6	Bufuralol (5 µM)	1'-Hydroxylation	> 90	> 90	N/A
3A4/5	Midazolam (2 µM)	1'-Hydroxylation	> 90 (~103)	67.8	1.5
3A4/5	Testosterone (50 µM)	6β-Hydroxylation	35.2	17.6	2.0

N/A – Not Applicable.

(*Source of data*: *2.6.4 Pharmacokinetics Written Summary, Table 26)*

Table 48: Direct and Time-Dependent CYP Inhibition by KX2-5036

CYP	Marker Substrate (Conc.)[a]	Isoform-Catalyzed Reaction	Direct Inhibition IC_{50}[b] (µM)	Time-dependent Inhibition IC_{50}[b] (µM)	IC_{50} Shift Fold
1A2	Phenacetin (50 µM)	*O*-Deethylation	> 100	> 100	N/A
2B6	Bupropion (50 µM)	Hydroxylation	> 100	> 100	N/A
2C8	Amodiaquine (2 µM)	*N*-Deethylation	> 100	> 100	N/A
2C9	Diclofenac (5 µM)	4'-Hydroxylation	> 100	> 100	N/A
2C19	*S*-mephenytoin (20 µM)	4'-Hydroxylation	> 100	> 100	N/A
2D6	Bufuralol (5 µM)	1'-Hydroxylation	> 100	> 100	N/A
3A4/5	Midazolam (2 µM)	1'-Hydroxylation	> 100	> 100	N/A
3A4/5	Testosterone (50 µM)	6β-Hydroxylation	> 100	> 100	N/A

N/A – Not Applicable.
Data are calculated from triplicate measurements.
a Incubation concentrations of marker substrates at or below their reported K_m.
b IC_{50} (inhibitor concentration that decreased the enzyme activity by 50%) was estimated by fitting the calculated % CYP activity data as a function of test article concentration to normalized sigmoidal inhibitory non-linear regression model using GraphPad Prism®.
> 100 – no inhibition greater than 50% within the concentration ranging 0.1 – 100 µM.

(*Source of data*: *2.6.4 Pharmacokinetics Written Summary, Table 29)*

Drug Transporters

- KX2-391 (Study XBL17619) is neither a substrate nor an inhibitor of MDR1, BCRP, BSEP, or MRP2. KX2-391 is not a substrate of MATE1, MATE2-K, OAT1, OAT3, OATP1B1, OATP1B3, OCT1 and OCT2, but inhibited MATE1, MATE2-K, OATP1B1, OATP1B3, OCT1 and OCT2 with the estimated IC_{50} values ranging from 1.4 to 66.4 µM (Table 49).

- The metabolite KX2-5036 (Study C18090) is not a substrate for MDR1, BCRP, BSEP, MRP2, MATE1, MATE2-K, OAT1, OAT3, OATP1B1, OATP1B3, OCT1 and OCT2. KX2-5036 inhibited MATE2-K and OCT2 with IC_{50} values of 63.1 and 9.1 µM, respectively (Table 49).

Table 49: IC50 Values of Tirbanibulin and KX2-5036

		MATE1	MATE 2K	OATP1B1	OATP1B3	OCT1	OCT2
Tirbanibulin IC_{50}	µM	2.6	7.3	66.4	27.4	3.5	1.4
	ng/mL	1122	3150	28654	11824	1510	604
KX2-5036 IC_{50}	µM	--	63.1	--	--	--	9.1
	ng/mL	--	21543	--	--	--	3107

-- = no measurable IC_{50}
Source: XBL-17619; C18090

16.5. Additional Clinical Outcome Assessment Analyses

Assessment of efficacy in the primary and key secondary endpoints were conducted in the PP population to verify the results from the primary efficacy analysis in the ITT population. Table 50 shows the reviewer's analysis result in the primary endpoint complete (100%) clearance rate at Day 57 in the PP population in Studies 003 and 004. Table 51 shows the reviewer's analysis result in the key secondary endpoint partial (75%) clearance rate at Day 57 in the PP population in Studies 003 and 004. The analysis results are consistent with the primary analysis results in the ITT population (Tables 15, 16, 17, 18).

Table 50: Reviewer's Analysis Result: Complete (100%) Clearance Rates at Day 57 in PP Population for Studies 003 and 004

	Study 003				Study 004			
Lesion Location	Tirbanibulin Ointment 1% N = 166 n/N (%)	Vehicle N = 165 n/N (%)	Treatment difference (Tirbanibulin Ointment 1%-Vehicle)	95% Confidence Interval for the Treatment difference	Tirbanibulin Ointment 1% N = 170 n/N (%)	Vehicle N = 166 n/N (%)	Treatment difference (Tirbanibulin Ointment 1%-Vehicle)	95% Confidence Interval for the Treatment difference
Overall	76/166 (45.8%)	8/165 (4.9%)	40.8%[a]	(32.6%,49.0%)[a]	94/170 (55.3%)	21/166 (12.7%)	42.9%[a]	(34.0%,51.9%)[a]
Face	60/114 (52.6%)	7/112 (6.3%)	46.4%	(34.4%, 57.4%)[b]	70/113 (61.9%)	16/114 (14.0%)	47.9%	(35.6%, 58.5%)[b]
Scalp	16/52 (30.8%)	1/53 (1.9%)	28.9%	(9.6%, 46.0%)[b]	24/57 (42.1%)	5/52 (9.6%)	32.5%	(14.0%, 49.4%)[b]

a. Based on Mantel-Haenszel risk limit stratified by treatment location.
b. Based on Clopper-Pearson Exact 95% CI. Note that for subgroups face and scalp, the reported 95% CI is for exploratory rather than confirmatory purpose.
Source: Reviewer's analysis

Table 51: Reviewer's Analysis Result: Partial **(≥75%)** Clearance Rates at Day 57 in PP Population for Studies 003, and 004

	Study 003				Study 004			
Lesion Location	Tirbanibulin Ointment 1% N = 166 n/N (%)	Vehicle N = 165 n/N (%)	Treatment difference (Tirbanibulin Ointment 1%-Vehicle)	95% Confidence Interval for the Treatment difference	Tirbanibulin Ointment 1% N = 170 n/N (%)	Vehicle N = 166 n/N (%)	Treatment difference (Tirbanibulin Ointment 1%-Vehicle)	95% Confidence Interval for the Treatment difference
Overall	114/166 (68.7%)	29/165 (17.6%)	51.0%	(41.9%,60.0%)[a]	130/170 (76.5%)	33/166 (19.9%)	56.8%	(48.1%,65.5%)[a]
Face	87/114 (76.3%)	23/112 (20.5%)	55.8%	(44.1%,66.1%)[b]	91/113 (80.5%)	26/114 (22.8%)	57.7%	(46.1%, 67.9%)
Scalp	27/52 (51.9%)	6/53 (11.3%)	40.6%	(21.5%, 56.3%)[b]	39/57 (68.4%)	7/52 (13.5%)	55.0%	(37.8%, 69.3%)

a. Based on Mantel-Haenszel risk limit stratified by treatment location.
b. Based on Clopper-Pearson Exact 95% CI. Note that for subgroup face and scalp, the reported 95% CI is for exploratory rather than confirmatory purpose.
Source: Reviewer's analysis

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/

BARBARA J GOULD
12/09/2020 09:36:17 AM

HAMID R SHAFIEI
12/09/2020 10:27:02 AM

NORMAN A SEE
12/09/2020 10:29:10 AM

BARBARA A HILL
12/09/2020 10:35:13 AM

ANDREW C GOODWIN
12/09/2020 10:36:15 AM

LIPING PAN
12/09/2020 01:18:18 PM

CHINMAY SHUKLA
12/09/2020 01:20:05 PM

CHANDRAHAS G SAHAJWALLA
12/09/2020 01:52:24 PM

GUOYING SUN
12/09/2020 03:10:01 PM

WANJIE SUN
12/09/2020 03:53:52 PM

KATHLEEN S FRITSCH
12/09/2020 04:02:23 PM

MOHAMED A ALOSH
12/09/2020 04:05:29 PM

LAURA L JOHNSON
12/09/2020 04:25:06 PM

ROSELYN E EPPS
12/09/2020 04:33:12 PM

DAVID L KETTL
12/09/2020 04:41:20 PM

SHARI L TARGUM
12/09/2020 04:43:28 PM

JULIE G BEITZ
12/09/2020 04:44:30 PM