CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213189Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 122464

MEETING PRELIMINARY COMMENTS

Athenex, Inc. dba Kinex Pharmaceuticals, Inc.
Attention: Paola Teegarden, MS
Associate Director of Regulatory Affairs
Coventus Building
1001 Main St., Suite 600
Buffalo, NY 14203

Dear Ms. Teegarden:

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for tirbanibulin ointment, 1%.

We also refer to your correspondence dated and received August 2, 2019, requesting a meeting to discuss the content and format of the NDA submission for tirbanibulin ointment, 1%.

Our preliminary responses to your meeting questions are enclosed.

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

In accordance with 21 CFR 10.65(e) and FDA policy, you may not electronically record the discussion at this meeting. The official record of this meeting will be the FDA-generated minutes.

If you have any questions, call me at 240-402-4880.

Sincerely,

{See appended electronic signature page}

Jennifer Harmon, PharmD
Regulatory Project Manager
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURE:

- Preliminary Meeting Comments

U.S. Food and Drug Administration
Silver Spring, MD 20993
www.fda.gov

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PRELIMINARY MEETING COMMENTS

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: October 2, 2019 at 9:00 a.m. ET
Meeting Location: Teleconference

Application Number: IND 122464
Product Name: tirbanibulin ointment, 1%

Indication: For topical treatment of actinic keratosis (AK) of the face or scalp
Sponsor: Kinex Pharmaceuticals, Inc.

Introduction:
This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for October 2, 2019, from 9:00am-10:00am ET, via teleconference between Kinex Pharmaceuticals, Inc. and the Division of Dermatology and Dental Products. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). Contact the Regulatory Project Manager (RPM) if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

1.0 BACKGROUND

The purpose of this meeting is to discuss the content and format of the NDA submission for tirbanibulin ointment, 1%.

Regulatory History:

We have had the following meetings/teleconferences with you:

- End-of-Phase-2 Meeting: December 12, 2016

We have sent the following correspondences:

- Type C Meeting-Preliminary Comments: May 14, 2018
- Pediatric Study Plan- Initial Agreement: September 15, 2017
- Pediatric Study Plan- Written Response: June 23, 2017
- Study May Proceed: July 31, 2014

2.0 DISCUSSION

2.1. Regulatory

Question 1:
Does the Agency agree that the proposed content and format of the NDA as outlined in the documents provided, with clinical data limited to tirbanibulin ointment 1% in actinic keratosis, support filing and review of the NDA?

FDA Response to Question 1:
Marketing or licensing applications submitted to the FDA include a description and analysis of all available information and data relevant to an evaluation of the safety and effectiveness of the drug product, in accordance with the regulations for NDA submissions [21 CFR 314.50(d)(5)(iv)].

See additional responses below which address your specific inquiries regarding the ISS and ISE.

2.2. Chemistry, Manufacturing and Controls (CMC)

Question 2:
Does the Agency agree that the proposed content of the Quality modules for the planned commercialization of tirbanibulin ointment 1% is adequate to support the NDA filing and review?

FDA Response to Question 2:
From the API standpoint, we note your plan to cross-reference a DMF that will be submitted (b) (4) in the 4th quarter of 2019. We also note that (b) (4) (b) (4) has supplied active pharmaceutical ingredient (API) for the clinical program. Cross-reference to a DMF with an appropriate Letter of Authorization is acceptable. However, for ease of review, in addition to the drug substance batch analysis and stability data, provide the following information in the NDA for ease of review: General information, physico-chemical properties, and Specifications.

We also note your plan to submit a second API manufacturer in the NDA after submission of the NDA. If this is planned for the initial review cycle, as opposed to a

Post-Approval Supplement, this is not acceptable. The NDA should be complete upon submission. In order to qualify a second supplier of API, you would need to provide complete CMC information on the new supplier and provide side-by-side comparison that the API from both manufacturers is equivalent. In addition, stability data will need to be provided on API from the new supplier. All manufacturing sites for the new supplier would need to be ready for inspection at the time of NDA submission. Refer to the September 2018 draft guidance for industry, *Postapproval Changes to Drug Substances* (https://www.fda.gov/media/115733/download) for the scientific thinking on the scope of information that may need to be provided to support addition of a new API supplier.

The drug product information you intend to provide in your NDA submission seems reasonable. However, the adequacy of the information provided will be determined during the review of your application. We remind you that the drug product container closure should be qualified through leachable/extractable studies.

Acceptability of the drug product manufactured using APIs from the new manufacturer will depend on the comparability of the APIs manufactured at the original and new manufacturing sites as well as the comparability of the supporting drug product stability data.

2.3. Nonclinical

Question 3:
Does the Agency agree that the Sponsor has addressed the Agency's recommendations previously provided for the Nonclinical Program?

FDA Response to Question 3:
Judging by the summary provided in the briefing document, it appears the data described may adequately address the issues we previously raised. However, the adequacy of the data will be determined during review.

Question 4:
Does the Agency agree that the organizational structure and content described in the proposed Module 2.4 (Nonclinical Overview) and Module 2.6 (Nonclinical Written and Tabulated Summaries) tables of contents support the filing and review of the NDA?

FDA Response to Question 4:
The adequacy of the submission will be determined during review of the NDA.

2.4. Clinical Pharmacology

Question 5:
Does the Agency agree that the current clinical pharmacology package is sufficient to support the filing and review of the NDA?

FDA Response to Question 5:
Your overall clinical pharmacology program appears reasonable to support filing of your NDA and the adequacy of data will be reviewed in detail at the time of your NDA submission.

In your NDA you should submit PK data in Statistical Analysis System (SAS) transport format and you should submit bioanalytical method validation and bioanalysis reports for review.

2.5. Biostatistics/Clinical

Question 6:
Does the Agency agree that the content and presentation of efficacy results, with the written integration strategies within Module 2.7.3, are acceptable for filing and review of the NDA, and that a Module 5 ISE is not required?

FDA Response to Question 6:
We consider the ISE and ISS critical components of the clinical efficacy and safety portions of a marketing or licensing application. Therefore, the ISE and ISS are required in applications submitted to the FDA in accordance with the regulations for NDA submissions (21 CFR 314.50(d)(5)(v) and 21 CFR 314.50(d)(5)(vi)(a), respectively). Refer to the guidance for industry documents, *Integrated Summary of Effectiveness,* and *Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document.*
Note that the purpose of the ISE is to describe the available information regarding effectiveness, delineate strengths and weaknesses, and highlight important missing information per the guidance for industry, *Integrated Summary of Effectiveness.*

Question 7:
Does the Agency agree that the content and presentation of safety results, with the written integration strategies within the Module 2.7.4, are acceptable for filing and review of the NDA, and that a Module 5 ISS is not required?

FDA Response to Question 7:
See response to Question 6.

3.0 ADMINISTRATIVE COMMENTS

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our August 20, 2019 communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to “the Program” under PDUFA VI. Therefore, at this meeting be prepared to discuss and reach agreement with

FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions and, where applicable, the development of a Formal Communication Plan. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

Discussions and agreements will be summarized at the conclusion of the meeting and reflected in FDA's meeting minutes. If you decide to cancel this meeting and do not have agreement with FDA on the content of a complete application or late submission of any minor application components, your application is expected to be complete at the time of original submission.

In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities.

Information on the Program is available at FDA.gov.[1]

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End-of-Phase-2 (EOP2) meeting. In the absence of an EOP2 meeting, refer to the draft guidance below. The iPSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry *Pediatric Study Plans:*

[1] https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm

Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans.[2] In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov. For further guidance on pediatric product development, please refer to FDA.gov.[3]

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information[4] and Pregnancy and Lactation Labeling Final Rule[5] websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant

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[2] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

[3] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development

[4] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information

[5] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format*.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

DISCUSSION OF SAFETY ANALYSIS STRATEGY FOR THE ISS

After initiation of all trials planned for the phase 3 program, you should consider requesting a Type C meeting to gain agreement on the safety analysis strategy for the Integrated Summary of Safety (ISS) and related data requirements. Topics of discussion at this meeting would include pooling strategy (i.e., specific studies to be pooled and analytic methodology intended to manage between-study design differences, if applicable), specific queries including use of specific standardized MedDRA queries (SMQs), and other important analyses intended to support safety. The meeting should be held after you have drafted an analytic plan for the ISS, and prior to programming work for pooled or other safety analyses planned for inclusion in the ISS. This meeting, if held, would precede the Pre-NDA meeting. Note that this meeting is optional; the issues can instead be addressed at the pre-NDA meeting.

To optimize the output of this meeting, submit the following documents for review as part of the briefing package:

- Description of all trials to be included in the ISS. Please provide a tabular listing of clinical trials including appropriate details.

- ISS statistical analysis plan, including proposed pooling strategy, rationale for inclusion or exclusion of trials from the pooled population(s), and planned analytic strategies to manage differences in trial designs (e.g., in length, randomization ratio imbalances, study populations, etc.).

- For a phase 3 program that includes trial(s) with multiple periods (e.g., double-blind randomized period, long-term extension period, etc.), submit planned criteria for analyses across the program for determination of start / end of trial period (i.e., method of assignment of study events to a specific study period).

- Prioritized list of previously observed and anticipated safety issues to be

evaluated, and planned analytic strategy including any SMQs, modifications to specific SMQs, or sponsor-created groupings of Preferred Terms. A rationale supporting any proposed modifications to an SMQ or sponsor-created groupings should be provided.

When requesting this meeting, clearly mark your submission "**DISCUSS SAFETY ANALYSIS STRATEGY FOR THE ISS**" in large font, bolded type at the beginning of the cover letter for the Type C meeting request.

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications* be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*.[6]

[6] https://www.fda.gov/media/85061/download

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/

KENDALL A MARCUS
09/26/2019 01:37:56 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 122464

MEETING MINUTES

Athenex, Inc.
d/b/a Kinex Pharmaceuticals, Inc.
Attention: Thomas J. Moutvic
Vice President of Regulatory Affairs
1001 Main Street, Suite 600
Buffalo, NY 14203

Dear Mr. Moutvic:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for KX2-391 ointment, 1%.

We also refer to the meeting between representatives of your firm and the FDA on December 12, 2016. The purpose of the meeting was to discuss the development program for KX2-391 ointment, 1%.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Cristina Attinello, Senior Regulatory Project Manager at (301) 796-3986.

Sincerely,

{See appended electronic signature page}

Kendall A. Marcus, MD
Director
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	End of Phase 2
Meeting Date and Time:	December 12, 2016, 8:30 am
Meeting Location:	WO22, Rm. 1311
Application Number:	IND 122464
Product Name:	KX2-391 ointment, 1%
Proposed Indication:	for the topical treatment (b) (4) actinic keratosis on the face and scalp
Sponsor Name:	Athenex, Inc.
Meeting Chair:	Kendall Marcus, MD
Meeting Recorder:	Cristina Attinello, MPH

FDA ATTENDEES
Kendall A. Marcus, MD, Director, DDDP
David Kettl, MD, Clinical Team Leader, DDDP
Roselyn E. Epps, MD, Clinical Reviewer, DDDP
Barbara Hill, PhD, Pharmacology Supervisor, DDDP
Norman See, PhD, Pharmacology Reviewer, DDDP
Chinmay Shukla, PhD, Acting Clinical Pharmacology Team Leader, DCP 3
Carin Kim, PhD, Biostatistics Reviewer, DB III
Mohamed Alosh, PhD, Biostatistics Team Leader, DB III
Cristina Attinello, MPH, Senior Regulatory Health Project Manager, DDDP

SPONSOR ATTENDEES
Tracey Burr, Head, CMC Regulatory Affairs, Kinex
James Clements, Project Manager, Kinex
David Cutler, VP, Clinical Development, Kinex
(b) (4) Pharmacology/Toxicology Consultant, Consultant to Kinex
(b) (4) Clinical Monitor/Consultant, Consultant to Kinex
Gerald Fetterly, VP, Clinical Pharmacology & Regulatory Affairs, Kinex
E. Douglas Kramer, VP, Regulatory Affairs & Pharmacovigilance, Kinex
Simon Pedder, VP, Corporate Strategy & Business Development, Kinex
Paola Teegarden, Manager, Regulatory Affairs, Kinex
Hui Wang, Biostatistician, Kinex

1.0 BACKGROUND

Purpose of Teleconference:
The primary purpose of this teleconference is to discuss the development program for KX2-391 ointment, 1%.

Regulatory Correspondence History:

We have sent the following correspondences:
- 7/31/2014 Study May Proceed Letter
- 7/7/2014 Information Request

2.0 DISCUSSION

2.1. Clinical

No Chemistry, Manufacturing and Controls questions were posed in the meeting package.

Question 1:
The Sponsor proposes to develop KX2-391 ointment 1% as a topical treatment (b) (4) actinic keratosis on the face and scalp.

Is this proposed indication acceptable? If not, what would be an acceptable indication?

FDA Response to Question 1:
The proposed indication is reasonable, but the precise labeling terminology will be determined during NDA review.

Question 2:
The proposed size of the safety database is approximately 600 subjects on active treatment, including subjects from studies KX01-AK-01-US and KX01-AK-002 and the proposed Phase 3 program.

Is the size of the safety database acceptable? If not, how many subjects would need to be included in the safety database?

FDA Response to Question 2:
The proposed number of subjects on active treatment may be acceptable, depending on the safety experience of your product.

Question 3:
We propose to conduct two Phase 3 efficacy studies. Subjects with complete response in both studies will be followed for recurrence in a common recurrence follow-up protocol. DRAFT synopses of the proposed Phase 3 studies are provided in **Error! Reference source not found.** and **Error! Reference source not found.**. APPEARS THIS WAY ON ORIGINAL

If successful, would the 2 proposed randomized, vehicle-controlled Phase 3 studies with a 12-month recurrence follow-up be adequate to support an NDA submission? If not, what additional information would be required?

FDA Response to Question 3:

Your proposed approach to conduct two safety and efficacy trials and assess long term safety appears to be reasonable, assuming successful outcomes of the trials. See Additional Comments under Question 9 regarding the Phase 3 trials.

Meeting Discussion:

The sponsor inquired as to whether the 12 month follow up period data could be submitted with the 120 day safety update. The Agency responded that the application should be complete, with this data, at the time of submission of the NDA application.

Question 4:

Safety evaluation in the Phase 3 clinical trials will include collection of AEs, assessment for LSRs, vital signs, physical examinations, ECGs, and clinical laboratory evaluations. As KX2-391 ointment 1% is expected to result in reversible LSRs, these will be captured as study outcomes. The Sponsor proposes to use a scale of 0-3 (0=absent; 1=mild, ie, slight, barely perceptible; 2=moderate, ie, distinct presence; 3=severe, ie, marked, intense) for the assessment and monitoring of LSRs including erythema, flaking/scaling, crusting, swelling, erosion/ulceration, vesiculation/pustulation, and pigmentation and scarring throughout the study. Investigators will be trained in the use of this LSR scale using representative photographs.

Will this safety assessment plan be acceptable to the Agency? If not, what additional assessment would be required?

FDA Response to Question 4:

Your proposed safety evaluation plan appears to be adequate.

Question 5:

The phototoxicity study of KX2-391 ointment 1% in rabbits was negative. The Sponsor proposes to conduct *in vitro* analysis of the KX2-391 planned TBM formulation to assess the absorbance properties (within (b) (4) nm) and if necessary, the potential (b) (4) (b) (4)

If negative, does the Agency agree that phototoxicity studies in healthy volunteers are not needed? If the Agency believes these studies are required, can they be conducted in parallel with the Phase 3 clinical trials?

FDA Response to Question 5:

You should address the potential of your topical drug product to induce phototoxicity if any of the components of the product absorb light in the range of approximately (b) (4) nm. This study should utilize the clinical to-be-marketed formulation of the product. Refer to the ICH S10 guidance for industry, *Photosafety Evaluation of Pharmaceuticals*.

Additionally, provocative studies to evaluate photoallergy will be needed prior to marketing if your product absorbs light in the range of approximately (b) (4) nm. This trial should be conducted with the final to-be-marketed formulation with an adequate number of subjects (e.g., 45 subjects). To enhance study yield, topical safety studies should be conducted under exaggerated (occlusive) conditions, which allows screening for cutaneous safety signals to be accomplished with fewer subjects than would be needed under normal (non-occlusive) conditions.

It is not necessary to evaluate photoallergenicity in a nonclinical model because it has been demonstrated that animal photoallergenicity studies do not predict clinical photoallergenicity.

If dermal safety studies are necessary, the trials can be conducted in parallel with Phase 3 clinical trials.

Question 6:

The Buehler test of KX2-391ointment 1% and 4% demonstrated potential for contact hypersensitivity in guinea pigs and the murine lymph node assay of KX2-391 ointment 1% suggested the potential for contact sensitization.

The Sponsor proposes to conduct a clinical trial on contact hypersensitivity in healthy volunteers in parallel with the proposed Phase 3 program. Is this acceptable?

FDA Response to Question 6:

Provocative dermal safety studies can be conducted in parallel with the Phase 3 program, as they should be conducted with the final, to-be-marketed formulation.

Question 7:

Preclinical and clinical experience indicates that KX2-391 ointment results in local skin reactions. Because some degree of skin irritation is expected in clinical studies and will be evaluated in those studies, the Sponsor believes that a cumulative irritation study in healthy volunteers is not needed.

Does the Agency agree that a cumulative irritation study does not need to be conducted?

FDA Response to Question 7:

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 will be identified as such in proposed labeling.

Question 8:

In safety pharmacology evaluation of KX2-391, the hERG IC_{50} was found to be 44 uM (approx. 20 ug/mL, ie, over 500-fold higher than the highest human plasma concentration observed following topical administration). In addition, no electrocardiographic effects occurred in a nonclinical cardiovascular safety study of KX2-391 up to 15 mg/kg IV in telemetrized dogs. Moreover, the majority of the plasma concentrations from the two clinical trials (KX01-AK-01-US, KX01-AK-002) are below 2 ng/mL or below the lower limit of quantification (LLOQ, < 0.1

ng/mL). Therefore, KX2-391 appears to have a low risk of QT prolongation. Single, non-standardized ECG readings are being obtained prior to treatment and on the day after the final dosing from both clinical trials (KX01-AK-01-US, KX01-AK-002) and will be analyzed for cardiac intervals, rhythms, and ECG waveforms. If this analysis does not reveal findings of concern, the Sponsor will conduct only routine (pre- and post-dose) ECGs in the Phase 3 studies.

Does the Agency consider this plan sufficient to evaluate cardiac risk? If not, what additional information will be necessary?

FDA Response to Question 8:

As noted below, the PK parameters of your dosing regimen have not yet been completely characterized, so you should propose adequate cardiovascular screening and monitoring during future trials of your product to insure safety of subjects. We recommend that ECG evaluations include baseline, at T_{max}, at steady state, and periodically during the treatment.

You should address the ICH guidance for industry E14: *Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non- Antiarrhythmic Drugs* as your development plan proceeds. The need for a thorough QT study will be impacted by the results of your maximal use PK trial.

Question 9:

The Sponsor intends to submit a full pediatric waiver request in accordance with guidance. Only a single published case report of AK in an adolescent with primary immune deficiency has been identified.

Given the low incidence of AK in the pediatric population, what information does the Agency feel would be helpful to submit in support of the waiver request?

FDA Response to Question 9:

A waiver for pediatric subjects is reasonable. You should support your proposal in your initial PSP with incidence and prevalence data for actinic keratoses, or lack thereof, in pediatric populations.

2.2. Clinical/Clinical Pharmacology

Introductory Comments

You provided what you called “preliminary” results of your ongoing open-label Phase 2a study as well as your open-label, Phase 1 pharmacokinetic (PK) study. Based on your “cross-study tabulation of complete clearance rates” for KX2-391 ointment and Picato gel, you stated that the KX2-391 ointment 1% is the appropriate strength to take into Phase 3 trials (page 26). We have the following comments concerning your study results:

- Both Phase 1 and the Phase 2a studies were open-label and did not include a vehicle arm, which would make it difficult to estimate the treatment effect of KX2-391 ointment 1% for powering future trials.

- Your cross-study tabulation of complete clearance rates for the KX2-391 3-day regimen was based on 4 subjects with AK on the forearm with no data for scalp or face as your Phase 2a study is currently ongoing (i.e., Cohort 2).
- Your results for the KX2-391 ointment, 1% 5-day regimen were based on "evaluable set" of 67 subjects while the results for the Picato gels were based on the ITT analysis set.
- Note that the method of handling missing data would impact the results.

Your Phase 2 program does not appear to be sufficient to identify a dose/dosing regimen which is optimized for Phase 3 development. Prior to conducting Phase 3 trials, we recommend that you conduct 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 your product, you run the risk of having underpowered trials.

As you submitted a Phase 3 protocol synopsis, the following are general comments.

- You stated that you plan to conduct two randomized, vehicle-controlled Phase 3 studies with a 12-month recurrence follow-up study. It is not clear whether your two Phase 3 studies will be identical in design and analysis.
- Assessment of site-to-site variability is an important component of clinical trial evaluation for the interpretation of study findings (e.g., assessing consistency or identifying outliers). As such, we recommend the randomization be stratified by site to ensure balance across the treatment arms within each site, and consequently the analysis should account for such stratification. For interpretation of study findings, the protocols should include a plan to investigate the treatment-by-site interaction and propose a sensitivity analysis to address site outliers if present.
- The analysis population for efficacy analyses should be based on the ITT should be defined as all randomized subjects whether or not they have had any post-baseline assessments.
- Your protocols should include a scientifically sound method of handling missing data.
- As you only conducted uncontrolled studies to date, it is not clear how you obtained the estimates for powering your Phase 3 trials. Without reasonable estimates for your product, you run the risk of having an underpowered trial.

Question 10:

The clinical studies have evaluated sequential cohorts of subjects who have topically administered 50 or 200 mg of 1% ointment over 25 or 100 cm^2 for a duration of 3 or 5 consecutive days. Preliminary analysis of accumulating data from the KX01-AK-002 study indicates that a 5-day application of KX2-391 Ointment 1% is active and associated with mild to moderate LSRs. A second cohort of a 3-day application is being evaluated. Based on the findings of the activity and safety of both cohorts in study KX01-AK-002, a dosing regimen will be selected for the Phase 3 studies.

Is this process of selecting a dosing regimen for Phase 3 studies acceptable?

FDA Response to Question 10:
See Introductory Comments above.

Question 11:
Study KX01-AK-01-US administered weighed amounts of KX2-391 ointment 1% to contiguous areas on the dorsal forearm for 3 or 5 days. Subjects received 50 mg over a 25 cm^2 area or 200 mg over a 100 cm^2 area. All treatments were administered by clinic staff. In study KX01-AK-002, subjects received 50 mg of KX2-391 ointment 1% applied to a 25cm^2 contiguous area of the face or scalp. As in the previous study, all treatments were administered at the clinic by clinic staff.

For the planned Phase 3 studies, drug or vehicle will be provided as daily unit dose packs with a maximum fill weight of (b) (4) mg, which will be administered by the subject at home for (b) (4) 5 days (one package per day). The maximum deliverable amount is estimated to be not more than 250 mg. Subjects will be instructed to wash their hands and the treatment area, then dry the treatment area before application of ointment. A small amount of ointment is to be applied to the fingertip and rubbed gently over the 25 cm^2 treatment area. Finger cots are not planned to be used, so as to mimic anticipated clinical usage. Subjects will be instructed to wash their hands after applying the ointment and avoid washing the treatment area for at least 8 hours. In addition, subjects will be instructed to avoid getting the ointment in the eyes. If ointment gets into the eyes, the subjects are to flush their eyes and contact the investigator for referral to an ophthalmologist.

Are the proposed dosing instructions and the proposed unit dose packaging acceptable?

FDA Response to Question 11:
Subjects should be instructed to wash their hands ***immediately*** after applying the ointment to the treatment area. Otherwise, your proposed dosing instructions and proposed unit dose packaging are acceptable.

Question 12:
Does the agency agree that the pharmacokinetics of KX2-391 ointment 1% have been adequately characterized and reflect minimal absorption into systemic circulation? If not, does the Agency recommend that the Sponsor should conduct a maximal use protocol to further assess the pharmacokinetics?

FDA Response to Question 12:
You are developing KX2-391 ointment, 1% for the topical treatment of actinic keratosis on the face or scalp in adults. Your projected dosing regimen will be (b) (4) treatment on a 25 cm^2 area of the face or scalp. Your ongoing Phase 2a study (KX01-AK-002) evaluated the pharmacokinetics (PK) of KX2-391 following topical applications of 50 mg dose on a 25 cm^2 area for 5 days in the treatment of AK of the face and scalp. Additionally, you have conducted one Phase 1 study (KX01-AK-01-US) that evaluated the PK of KX2-391 following topical applications of doses 50 mg on a 25cm^2 area or 200 mg on a 100 cm^2 area for 3 or 5 days in the treatment of AK on the dorsal forearm.

The available PK data to-date from studies KX01-AK-002 and KX01-AK-01-US indicate a low systemic exposure of KX2-391 in majority of subjects. However, we do not agree at this time that the PK of KX2-391 ointment, 1% have been adequately characterized in these two studies for at least the following reasons: (1) there were limited number of subjects in each cohort of study KX01-AK-01-US; (2) you may not have captured full PK profiles of KX2-391 in study KX01-AK-002 because you have collected PK samples only up to 4 hours post-dose; and (3) it is not clear whether the PK data from these two studies represent maximal use conditions for the proposed indication.

Therefore, we recommend that you conduct a maximal use PK trial during development. Provided below is some information you should consider when designing a maximal use PK trial for your product.

A maximal use PK trial is conducted by obtaining adequate number of PK samples following administration of your to-be-marketed formulation. This trial should be conducted in a suitable number of subjects with the disease of interest at the upper range of severity as anticipated in both your clinical trials and proposed labeling. Such a trial would attempt to maximize the potential for drug absorption to occur by incorporation of the following design elements:

- Frequency of dosing
- Duration of dosing
- Use of highest proposed strength
- Total involved surface area to be treated at one time
- Amount applied per square centimeter
- Method of application/site preparation
- Sensitive and validated analytical method

The maximal use PK trial could be a stand-alone trial in Phase 2 or could be a sub-group of subjects in a larger Phase 3 trial. Either approach is acceptable. Should a stand-alone trial approach be used, you should take steps to assure that the target patient population (age, gender, race etc.) is properly represented in your maximal use PK trial.

You plan to treat actinic keratosis on the face and scalp concurrently. We recommend you to conduct the maximal use PK trial by applying the drug to the face and scalp in the same subject.

Meeting Discussion:

The sponsor proposed to conduct a maximal use PK trial and proposed to use one sachet of the product per day [dose less than 200 mg] applied to 100 cm^2 treatment area. The sponsor inquired if this design would be reasonable. The Agency responded that this was new information, not submitted to the meeting package, and no agreements can be made at this time. The Agency reiterated the maximal use PK trial design and encouraged the sponsor to capture the worst case scenario.

The Agency also recommended that the sponsor address drug interaction potential during development.

Corrigendum:
The Agency recommends that the sponsor record the amount of formulation used per subject in the maximal use PK trial.

Question 13:
Preliminary pharmacokinetic results obtained from the two clinical studies with KX2-391 ointment 1% showed that following up to 5 days of treatment, low systemic exposure (<1 ng/mL), and limited drug accumulation was observed in the majority of subjects. Based on the exposures observed, the Sponsor believes that a radiolabeled ADME study in subjects would be infeasible and would not provide useful information.

The Sponsor will rely on in vitro metabolism and protein binding data to characterize the metabolism and distribution of KX2-391 following topical administration. Is this plan acceptable to the agency?

FDA Response to Question 13:
KX2-391 is a new molecular entity and we recommend that you make every effort to completely characterize its disposition in humans. We agree that a radiolabeled ADME study in human may not be needed based on the currently available PK information.

You should conduct in vitro studies to characterize metabolism and protein binding properties of KX2-391. You should also conduct in vitro studies to evaluate the drug-drug interaction potentials for KX2-391 and its major metabolites. Based on your in vitro study findings, it may be necessary that you further assess the PK of the major metabolites of KX2-391 in clinical trials using validated bioanalytical assays.

To address the potential for drug interactions, you are referred to draft guidance for industry *Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations*.

2.3. Nonclinical

Question [14]:
APPEARS THIS WAY ON ORIGINAL

The nonclinical studies completed to support oral dosing of KX2-391 are summarized in **Error! Reference source not found.**. The panel of studies conducted to evaluate toxicity and toxicokinetics of KX2-391 following dermal administration are described in **Error! Reference source not found.**. The ongoing studies to further advance the clinical development of KX2-391 ointment 1% are described in **Error! Reference source not found.**. Summaries of completed nonclinical studies supporting oral and dermal administration of KX2-391 are presented in **Error! Reference source not found.**.

Does the Agency concur that the completed and ongoing nonclinical studies will fully satisfy the requirements to support Phase 3 testing and marketing registration of KX2-391 ointment 1%?

FDA Response to Question [14]:

This matter is unclear, particularly in regard to the utility or acceptability of the ongoing nonclinical studies that were summarized in the briefing package, but have yet to be submitted for review. According to the summary provided, substantial adverse actions were apparently observed in 28-day topical repeated-dose toxicity studies with rats and minipigs, apparently at least in part due to the methodology that was used. In general, it is not recommended that topical repeated-dose toxicity studies involve wrapping or occlusion of the treatment site, particularly for studies conducted with rodents. It is suggested that the methodology and dosages to be used in definitive studies be evaluated in preliminary dose-range finding studies, to help ensure that the procedures used (e.g., the application procedure, concentrations of API in the test articles, volume per dose, etc.) will be optimal. We may request that nonclinical studies be repeated if we are not satisfied with the levels of exposure and/or stress that were achieved in those studies, or the methodology used. We outlined the nonclinical issues that we anticipated may need to be acceptably addressed in regard to IND 122464 in a letter dated July 31, 2014. Consult that letter for further guidance.

Question [15]:

Does the Agency concur that KX2-391 ointment 1%, if approved for the proposed indication and treatment regimens, will not be considered as chronic therapy, and, therefore, chronic toxicity, carcinogenicity, and peri/post- natal nonclinical studies will not be needed to support the marketing registration?

FDA Response to Question [15]:

We agree that data from repeated-dose toxicity studies of greater than 28-days duration, or from carcinogenesis assays conducted with KX2-391, are not necessary to support development or marketing of this product for this indication. However, acceptable data which concern 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. It is 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.

Meeting Discussion:

The sponsor asked if the Agency would require a peri/postnatal study of KX2-391 if final evaluation of the embryo-fetal development study results confirm KX2-391 is fetotoxic and, as a consequence, the label for KX2-391 ointment contains precautions for use in women of child-bearing potential. The Agency mentioned that ICH documents indicate that peri/postnatal development data are typically considered to be appropriate in support of an NDA. However, the Agency indicated that it would be willing to consider a request for a waiver of the need for such data, at such time as final embryofetal development data were submitted with a scientific rationale to support the waiver request. The Agency also suggested that the waiver request include an example of the proposed labeling.

3.0 ADMINISTRATIVE COMMENTS

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase (EOP2) meeting. In the absence of an End-of-Phase 2 meeting, refer to the draft guidance below. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format. Failure to include an agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

DATA STANDARDS FOR STUDIES

Under section 745A(a) of the FD&C Act, electronic submissions "shall be submitted in such electronic format as specified by [FDA]." FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog (Catalog) (See http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm).

On December 17, 2014, FDA issued final guidance, *Providing Electronic Submissions in Electronic Format--- Standardized Study Data* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf). This guidance describes the submission types, the standardized study data requirements, and when standardized study data will be required. Further, it describes the

availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide (Conformance Guide) (See http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf), as well as email access to the eData Team (cder-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data will be required in marketing application submissions for clinical and nonclinical studies that start on or after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that start on or after December 17, 2017. CDER has produced a *Study Data Standards Resources* web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that start before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

Additional information can be found at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm.

For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, CDER encourages sponsors to use Standards for the Exchange of Nonclinical Data (SEND) and submit sample or test data sets before implementation becomes required. CDER will provide feedback to sponsors on the suitability of these test data sets. Information about submitting a test submission can be found here: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled, Study Data Standards Resources and the

CDER/CBER Position on Use of SI Units for Lab Tests website found at http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/ucm372553.htm.

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. Beginning May 5, 2017, the following submission types: NDA, ANDA, BLA and Master Files must be submitted in eCTD format. Commercial IND submissions must be submitted in eCTD format beginning May 5, 2018. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: http://www.fda.gov/ectd.

Office of Scientific Investigations (OSI) Requests

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
   a. Site number
   b. Principal investigator
   c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
   d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.

2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
   a. Number of subjects screened at each site
   b. Number of subjects randomized at each site
   c. Number of subjects treated who prematurely discontinued for each site by site

3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
   a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
   b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
   c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.

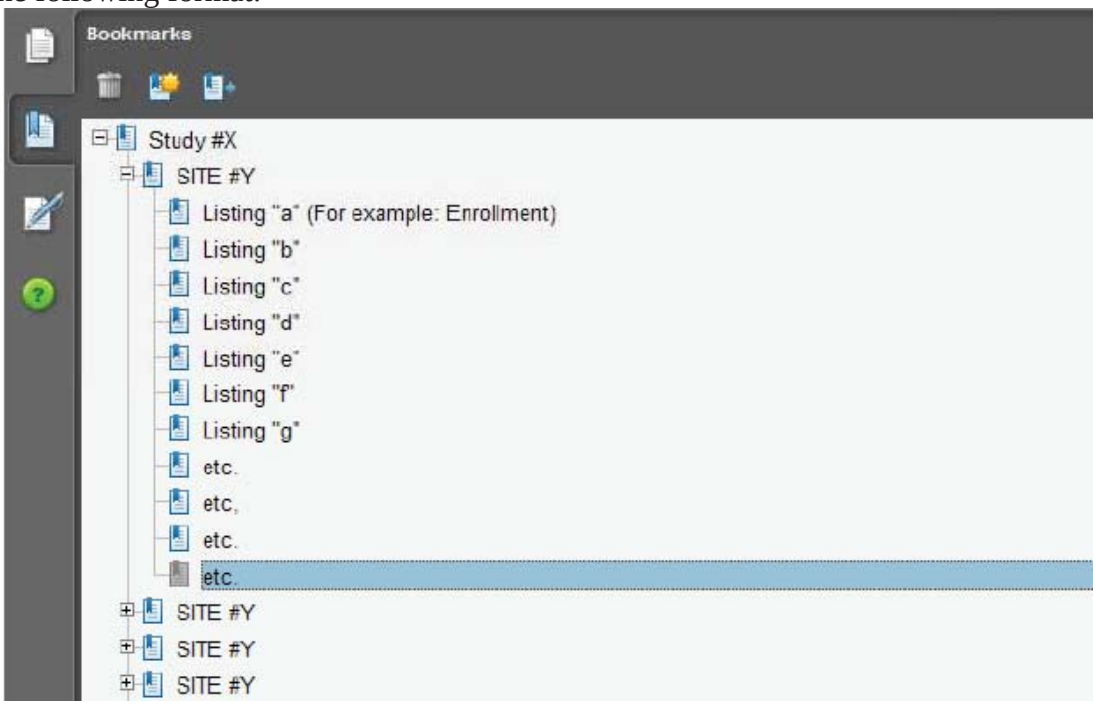
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as "line listings"). For each site, provide line listings for:
   a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
   b. Subject listing for treatment assignment (randomization)
   c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
   d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
   e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
   f. By subject listing, of AEs, SAEs, deaths and dates
   g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation

h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring

2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER's Inspection Planning" (available at the following link http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf) for the structure and format of this data set.

Attachment 1

Technical Instructions:
Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named "BIMO [list study ID, followed by brief description of file being submitted]." In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be "bimo." Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be "clinsite.xpt."

DSI Pre-NDA Request Item[1]	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:

C. It is recommended, but not required, that a Reviewer's Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be "BIMO Reviewer Guide." The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

[1] Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1
(http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf)

FDA eCTD web page
(http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm)

For general help with eCTD submissions: ESUB@fda.hhs.gov

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KENDALL A MARCUS
12/16/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 122464

MEETING PRELIMINARY COMMENTS

Athenex, Inc.
d/b/a Kinex Pharmaceuticals, Inc.
Attention: Thomas J. Moutvic
Vice President of Regulatory Affairs
Conventus Building
1001 Main Street, Suite 600
Buffalo, NY 14203

Dear Mr. Moutvic:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for KX2-391 ointment, 1%.

We also refer to your October 13, 2016, correspondence, received October 14, 2016, requesting a meeting to discuss the development program for KX2-391 ointment, 1%.

Our preliminary responses to your meeting questions are enclosed.

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

In accordance with 21 CFR 10.65(e) and FDA policy, you may not electronically record the discussion at this meeting. The official record of this meeting will be the FDA-generated minutes.

If you have any questions, call me, at (301) 796-3986.

Sincerely,

{See appended electronic signature page}

Cristina Attinello, MPH
Senior Regulatory Project Manager
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURE:
Preliminary Meeting Comments

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PRELIMINARY MEETING COMMENTS

Meeting Type:	Type B
Meeting Category:	End of Phase 2
Meeting Date and Time:	December 12, 2016, 8:30 am
Meeting Location:	WO22, Rm. 1311
Application Number:	IND 122464
Product Name:	KX2-391 ointment, 1%
Proposed Indication:	for the topical treatment (b) (4) actinic keratosis on the face and scalp
Sponsor Name:	Athenex, Inc.

Introduction:

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for December 12, 2016 at 8:30 am in WO22 Rm. 1311 between Athenex, Inc. and the Division of Dermatology and Dental Products. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact the regulatory project manager (RPM)). If you choose to cancel the meeting, this document will represent the official record of the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the pre-meeting communications are considered sufficient to answer the questions. Contact the RPM if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

1.0 BACKGROUND

Purpose of Teleconference:

The primary purpose of this teleconference is to discuss the development program for KX2-391 ointment, 1%.

Regulatory Correspondence History:

We have sent the following correspondences:

- 7/31/2014 Study May Proceed Letter
- 7/7/2014 Information Request

2.0 DISCUSSION

2.1. Clinical

No Chemistry, Manufacturing and Controls questions were posed in the meeting package.

Question 1:

The Sponsor proposes to develop KX2-391 ointment 1% as a topical treatment (b) (4) actinic keratosis on the face and scalp.

Is this proposed indication acceptable? If not, what would be an acceptable indication?

FDA Response to Question 1:

The proposed indication is reasonable, but the precise labeling terminology will be determined during NDA review.

Question 2:

The proposed size of the safety database is approximately 600 subjects on active treatment, including subjects from studies KX01-AK-01-US and KX01-AK-002 and the proposed Phase 3 program.

Is the size of the safety database acceptable? If not, how many subjects would need to be included in the safety database?

FDA Response to Question 2:

The proposed number of subjects on active treatment may be acceptable, depending on the safety experience of your product.

Question 3:

We propose to conduct two Phase 3 efficacy studies. Subjects with complete response in both studies will be followed for recurrence in a common recurrence follow-up protocol. DRAFT synopses of the proposed Phase 3 studies are provided in **Error! Reference source not found.** and **Error! Reference source not found.**. APPEARS THIS WAY ON ORIGINAL

If successful, would the 2 proposed randomized, vehicle-controlled Phase 3 studies with a 12-month recurrence follow-up be adequate to support an NDA submission? If not, what additional information would be required?

FDA Response to Question 3:

Your proposed approach to conduct two safety and efficacy trials and assess long term safety appears to be reasonable, assuming successful outcomes of the trials. See Additional Comments under Question 9 regarding the Phase 3 trials.

Question 4:

Safety evaluation in the Phase 3 clinical trials will include collection of AEs, assessment for LSRs, vital signs, physical examinations, ECGs, and clinical laboratory evaluations. As KX2-391 ointment 1% is expected to result in reversible LSRs, these will be captured as study outcomes. The Sponsor proposes to use a scale of 0-3 (0=absent; 1=mild, ie, slight, barely perceptible; 2=moderate, ie, distinct presence; 3=severe, ie, marked, intense) for the assessment and monitoring of LSRs including erythema, flaking/scaling, crusting, swelling, erosion/ulceration, vesiculation/pustulation, and pigmentation and scarring throughout the study. Investigators will be trained in the use of this LSR scale using representative photographs.

Will this safety assessment plan be acceptable to the Agency? If not, what additional assessment would be required?

FDA Response to Question 4:

Your proposed safety evaluation plan appears to be adequate.

Question 5:

The phototoxicity study of KX2-391 ointment 1% in rabbits was negative. The Sponsor proposes to conduct *in vitro* analysis of the KX2-391 planned TBM formulation to assess the absorbance properties (within (b) (4) nm) and if necessary, the potential (b) (4) (b) (4)

If negative, does the Agency agree that phototoxicity studies in healthy volunteers are not needed? If the Agency believes these studies are required, can they be conducted in parallel with the Phase 3 clinical trials?

FDA Response to Question 5:

You should address the potential of your topical drug product to induce phototoxicity if any of the components of the product absorb light in the range of approximately (b) (4) nm. This study should utilize the clinical to-be-marketed formulation of the product. Refer to the ICH S10 guidance for industry, *Photosafety Evaluation of Pharmaceuticals*.

Additionally, provocative studies to evaluate photoallergy will be needed prior to marketing if your product absorbs light in the range of approximately (b) (4) nm. This trial should be conducted with the final to-be-marketed formulation with an adequate number of subjects (e.g., 45 subjects). To enhance study yield, topical safety studies should be conducted under exaggerated (occlusive) conditions, which allows screening for cutaneous safety signals to be accomplished with fewer subjects than would be needed under normal (non-occlusive) conditions.

It is not necessary to evaluate photoallergenicity in a nonclinical model because it has been demonstrated that animal photoallergenicity studies do not predict clinical photoallergenicity.

If dermal safety studies are necessary, the trials can be conducted in parallel with Phase 3 clinical trials.

Question 6:

The Buehler test of KX2-391ointment 1% and 4% demonstrated potential for contact hypersensitivity in guinea pigs and the murine lymph node assay of KX2-391 ointment 1% suggested the potential for contact sensitization.

The Sponsor proposes to conduct a clinical trial on contact hypersensitivity in healthy volunteers in parallel with the proposed Phase 3 program. Is this acceptable?

FDA Response to Question 6:

Provocative dermal safety studies can be conducted in parallel with the Phase 3 program, as they should be conducted with the final, to-be-marketed formulation.

Question 7:

Preclinical and clinical experience indicates that KX2-391 ointment results in local skin reactions. Because some degree of skin irritation is expected in clinical studies and will be evaluated in those studies, the Sponsor believes that a cumulative irritation study in healthy volunteers is not needed.

Does the Agency agree that a cumulative irritation study does not need to be conducted?

FDA Response to Question 7:

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 will be identified as such in proposed labeling.

Question 8:

In safety pharmacology evaluation of KX2-391, the hERG IC_{50} was found to be 44 uM (approx. 20 ug/mL, ie, over 500-fold higher than the highest human plasma concentration observed following topical administration). In addition, no electrocardiographic effects occurred in a nonclinical cardiovascular safety study of KX2-391 up to 15 mg/kg IV in telemetrized dogs. Moreover, the majority of the plasma concentrations from the two clinical trials (KX01-AK-01-US, KX01-AK-002) are below 2 ng/mL or below the lower limit of quantification (LLOQ, < 0.1 ng/mL). Therefore, KX2-391 appears to have a low risk of QT prolongation. Single, non-standardized ECG readings are being obtained prior to treatment and on the day after the final dosing from both clinical trials (KX01-AK-01-US, KX01-AK-002) and will be analyzed for cardiac intervals, rhythms, and ECG waveforms. If this analysis does not reveal findings of concern, the Sponsor will conduct only routine (pre- and post-dose) ECGs in the Phase 3 studies.

Does the Agency consider this plan sufficient to evaluate cardiac risk? If not, what additional information will be necessary?

FDA Response to Question 8:

As noted below, the PK parameters of your dosing regimen have not yet been completely characterized, so you should propose adequate cardiovascular screening and monitoring during future trials of your product to insure safety of subjects. We recommend that ECG evaluations include baseline, at T_{max}, at steady state, and periodically during the treatment.

You should address the ICH guidance for industry E14: *Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non- Antiarrhythmic Drugs* as your development plan proceeds. The need for a thorough QT study will be impacted by the results of your maximal use PK trial.

Question 9:

The Sponsor intends to submit a full pediatric waiver request in accordance with guidance. Only a single published case report of AK in an adolescent with primary immune deficiency has been identified.

Given the low incidence of AK in the pediatric population, what information does the Agency feel would be helpful to submit in support of the waiver request?

FDA Response to Question 9:

A waiver for pediatric subjects is reasonable. You should support your proposal in your initial PSP with incidence and prevalence data for actinic keratoses, or lack thereof, in pediatric populations.

2.2. Clinical/Clinical Pharmacology

Introductory Comments

You provided what you called "preliminary" results of your ongoing open-label Phase 2a study as well as your open-label, Phase 1 pharmacokinetic (PK) study. Based on your "cross-study tabulation of complete clearance rates" for KX2-391 ointment and Picato gel, you stated that the KX2-391 ointment 1% is the appropriate strength to take into Phase 3 trials (page 26). We have the following comments concerning your study results:

- Both Phase 1 and the Phase 2a studies were open-label and did not include a vehicle arm, which would make it difficult to estimate the treatment effect of KX2-391 ointment 1% for powering future trials.
- Your cross-study tabulation of complete clearance rates for the KX2-391 3-day regimen was based on 4 subjects with AK on the forearm with no data for scalp or face as your Phase 2a study is currently ongoing (i.e., Cohort 2).
- Your results for the KX2-391 ointment, 1% 5-day regimen were based on "evaluable set" of 67 subjects while the results for the Picato gels were based on the ITT analysis set.

- Note that the method of handling missing data would impact the results.

Your Phase 2 program does not appear to be sufficient to identify a dose/dosing regimen which is optimized for Phase 3 development. Prior to conducting Phase 3 trials, we recommend that you conduct 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 your product, you run the risk of having underpowered trials.

As you submitted a Phase 3 protocol synopsis, the following are general comments.

- You stated that you plan to conduct two randomized, vehicle-controlled Phase 3 studies with a 12-month recurrence follow-up study. It is not clear whether your two Phase 3 studies will be identical in design and analysis.
- Assessment of site-to-site variability is an important component of clinical trial evaluation for the interpretation of study findings (e.g., assessing consistency or identifying outliers). As such, we recommend the randomization be stratified by site to ensure balance across the treatment arms within each site, and consequently the analysis should account for such stratification. For interpretation of study findings, the protocols should include a plan to investigate the treatment-by-site interaction and propose a sensitivity analysis to address site outliers if present.
- The analysis population for efficacy analyses should be based on the ITT should be defined as all randomized subjects whether or not they have had any post-baseline assessments.
- Your protocols should include a scientifically sound method of handling missing data.
- As you only conducted uncontrolled studies to date, it is not clear how you obtained the estimates for powering your Phase 3 trials. Without reasonable estimates for your product, you run the risk of having an underpowered trial.

Question 10:

The clinical studies have evaluated sequential cohorts of subjects who have topically administered 50 or 200 mg of 1% ointment over 25 or 100 cm^2 for a duration of 3 or 5 consecutive days. Preliminary analysis of accumulating data from the KX01-AK-002 study indicates that a 5-day application of KX2-391 Ointment 1% is active and associated with mild to moderate LSRs. A second cohort of a 3-day application is being evaluated. Based on the findings of the activity and safety of both cohorts in study KX01-AK-002, a dosing regimen will be selected for the Phase 3 studies.

Is this process of selecting a dosing regimen for Phase 3 studies acceptable?

FDA Response to Question 10:

See Introductory Comments above.

Question 11:

Study KX01-AK-01-US administered weighed amounts of KX2-391 ointment 1% to contiguous areas on the dorsal forearm for 3 or 5 days. Subjects received 50 mg over a 25 cm^2 area or 200 mg over a 100 cm^2 area. All treatments were administered by clinic staff. In study KX01-AK-002, subjects received 50 mg of KX2-391 ointment 1% applied to a 25cm^2 contiguous area of the face or scalp. As in the previous study, all treatments were administered at the clinic by clinic staff.

For the planned Phase 3 studies, drug or vehicle will be provided as daily unit dose packs with a maximum fill weight of (b) (4) mg, which will be administered by the subject at home for (b) (4) 5 days (one package per day). The maximum deliverable amount is estimated to be not more than 250 mg. Subjects will be instructed to wash their hands and the treatment area, then dry the treatment area before application of ointment. A small amount of ointment is to be applied to the fingertip and rubbed gently over the 25 cm^2 treatment area. Finger cots are not planned to be used, so as to mimic anticipated clinical usage. Subjects will be instructed to wash their hands after applying the ointment and avoid washing the treatment area for at least 8 hours. In addition, subjects will be instructed to avoid getting the ointment in the eyes. If ointment gets into the eyes, the subjects are to flush their eyes and contact the investigator for referral to an ophthalmologist.

Are the proposed dosing instructions and the proposed unit dose packaging acceptable?

FDA Response to Question 11:

Subjects should be instructed to wash their hands ***immediately*** after applying the ointment to the treatment area. Otherwise, your proposed dosing instructions and proposed unit dose packaging are acceptable.

Question 12:

Does the agency agree that the pharmacokinetics of KX2-391 ointment 1% have been adequately characterized and reflect minimal absorption into systemic circulation? If not, does the Agency recommend that the Sponsor should conduct a maximal use protocol to further assess the pharmacokinetics?

FDA Response to Question 12:

You are developing KX2-391 ointment, 1% for the topical treatment of actinic keratosis on the face or scalp in adults. Your projected dosing regimen will be (b) (4) treatment on a 25 cm^2 area of the face or scalp. Your ongoing Phase 2a study (KX01-AK-002) evaluated the pharmacokinetics (PK) of KX2-391 following topical applications of 50 mg dose on a 25 cm^2 area for 5 days in the treatment of AK of the face and scalp. Additionally, you have conducted one Phase 1 study (KX01-AK-01-US) that evaluated the PK of KX2-391 following topical applications of doses 50 mg on a 25cm^2 area or 200 mg on a 100 cm^2 area for 3 or 5 days in the treatment of AK on the dorsal forearm.

The available PK data to-date from studies KX01-AK-002 and KX01-AK-01-US indicate a low systemic exposure of KX2-391 in majority of subjects. However, we do not agree at this time that the PK of KX2-391 ointment, 1% have been adequately characterized in these two studies for at least the following reasons: (1) there were limited number of subjects in each cohort of study KX01-AK-01-US; (2) you may not have captured full PK profiles of KX2-391 in study KX01-AK-002 because you have collected PK samples only up to 4 hours post-dose; and (3) it is not clear whether the PK data from these two studies represent maximal use conditions for the proposed indication.

Therefore, we recommend that you conduct a maximal use PK trial during development. Provided below is some information you should consider when designing a maximal use PK trial for your product.

A maximal use PK trial is conducted by obtaining adequate number of PK samples following administration of your to-be-marketed formulation. This trial should be conducted in a suitable number of subjects with the disease of interest at the upper range of severity as anticipated in both your clinical trials and proposed labeling. Such a trial would attempt to maximize the potential for drug absorption to occur by incorporation of the following design elements:

- Frequency of dosing
- Duration of dosing
- Use of highest proposed strength
- Total involved surface area to be treated at one time
- Amount applied per square centimeter
- Method of application/site preparation
- Sensitive and validated analytical method

The maximal use PK trial could be a stand-alone trial in Phase 2 or could be a sub-group of subjects in a larger Phase 3 trial. Either approach is acceptable. Should a stand-alone trial approach be used, you should take steps to assure that the target patient population (age, gender, race etc.) is properly represented in your maximal use PK trial.

You plan to treat actinic keratosis on the face and scalp concurrently. We recommend you to conduct the maximal use PK trial by applying the drug to the face and scalp in the same subject.

Question 13:

Preliminary pharmacokinetic results obtained from the two clinical studies with KX2-391 ointment 1% showed that following up to 5 days of treatment, low systemic exposure (<1 ng/mL), and limited drug accumulation was observed in the majority of subjects. Based on the exposures observed, the Sponsor believes that a radiolabeled ADME study in subjects would be infeasible and would not provide useful information.

The Sponsor will rely on in vitro metabolism and protein binding data to characterize the metabolism and distribution of KX2-391 following topical administration. Is this plan acceptable to the agency?

FDA Response to Question 13:

KX2-391 is a new molecular entity and we recommend that you make every effort to completely characterize its disposition in humans. We agree that a radiolabeled ADME study in human may not be needed based on the currently available PK information.

You should conduct in vitro studies to characterize metabolism and protein binding properties of KX2-391. You should also conduct in vitro studies to evaluate the drug-drug interaction potentials for KX2-391 and its major metabolites. Based on your in vitro study findings, it may be necessary that you further assess the PK of the major metabolites of KX2-391 in clinical trials using validated bioanalytical assays.

To address the potential for drug interactions, you are referred to draft guidance for industry *Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations*.

2.3. Nonclinical

Question [14]:

The nonclinical studies completed to support oral dosing of KX2-391 are summarized in **Error! Reference source not found.**. The panel of studies conducted to evaluate toxicity and toxicokinetics of KX2-391 following dermal administration are described in **Error! Reference source not found.**. The ongoing studies to further advance the clinical development of KX2-391 ointment 1% are described in **Error! Reference source not found.**. Summaries of completed nonclinical studies supporting oral and dermal administration of KX2-391 are presented in **Error! Reference source not found.**.

APPEARS THIS WAY ON ORIGINAL

Does the Agency concur that the completed and ongoing nonclinical studies will fully satisfy the requirements to support Phase 3 testing and marketing registration of KX2-391 ointment 1%?

FDA Response to Question [14]:

This matter is unclear, particularly in regard to the utility or acceptability of the ongoing nonclinical studies that were summarized in the briefing package, but have yet to be submitted for review. According to the summary provided, substantial adverse actions were apparently observed in 28-day topical repeated-dose toxicity studies with rats and minipigs, apparently at least in part due to the methodology that was used. In general, it is not recommended that topical repeated-dose toxicity studies involve wrapping or occlusion of the treatment site, particularly for studies conducted with rodents. It is suggested that the methodology and dosages to be used in definitive studies be evaluated in preliminary dose-range finding studies, to help ensure that the procedures used (e.g., the application procedure, concentrations of API in the test articles, volume per dose, etc.) will be optimal. We may request that nonclinical studies be repeated if we are not satisfied with the levels of exposure and/or stress that were achieved in those studies, or the methodology used. We outlined the nonclinical issues that we anticipated may need to be acceptably addressed in regard to IND 122464 in a letter dated July 31, 2014. Consult that letter for further guidance.

Question [15]:

Does the Agency concur that KX2-391 ointment 1%, if approved for the proposed indication and treatment regimens, will not be considered as chronic therapy, and, therefore, chronic toxicity, carcinogenicity, and peri/post- natal nonclinical studies will not be needed to support the marketing registration?

FDA Response to Question [15]:

We agree that data from repeated-dose toxicity studies of greater than 28-days duration, or from carcinogenesis assays conducted with KX2-391, are not necessary to support development or marketing of this product for this indication. However, acceptable data which concern 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. It is 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.

3.0 ADMINISTRATIVE COMMENTS

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase (EOP2) meeting. In the absence of an End-of-Phase 2 meeting, refer to the draft guidance below. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format. Failure to include an agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to:

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

DATA STANDARDS FOR STUDIES

Under section 745A(a) of the FD&C Act, electronic submissions "shall be submitted in such electronic format as specified by [FDA]." FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog (Catalog) (See http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm).

On December 17, 2014, FDA issued final guidance, *Providing Electronic Submissions in Electronic Format--- Standardized Study Data* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf). This guidance describes the submission types, the standardized study data requirements, and when standardized study data will be required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide (Conformance Guide) (See http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf), as well as email access to the eData Team (cder-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data will be required in marketing application submissions for clinical and nonclinical studies that start on or after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that start on or after December 17, 2017. CDER has produced a *Study Data Standards Resources* web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that start before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

Additional information can be found at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm.

For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, CDER encourages sponsors to use Standards for the Exchange of Nonclinical Data (SEND) and submit sample or test data sets before implementation becomes required. CDER will provide feedback to sponsors on the suitability of these test data sets. Information about submitting a test submission can be found here:
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled, Study Data Standards Resources and the CDER/CBER Position on Use of SI Units for Lab Tests website found at http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/ucm372553.htm.

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. Beginning May 5, 2017, the following submission types: NDA, ANDA, BLA and Master Files must be submitted in eCTD format. Commercial IND submissions must be submitted in eCTD format beginning May 5, 2018. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: http://www.fda.gov/ectd.

Office of Scientific Investigations (OSI) Requests

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
   a. Site number
   b. Principal investigator
   c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
   d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.

2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
   a. Number of subjects screened at each site
   b. Number of subjects randomized at each site
   c. Number of subjects treated who prematurely discontinued for each site by site

3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
   a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
   b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
   c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.

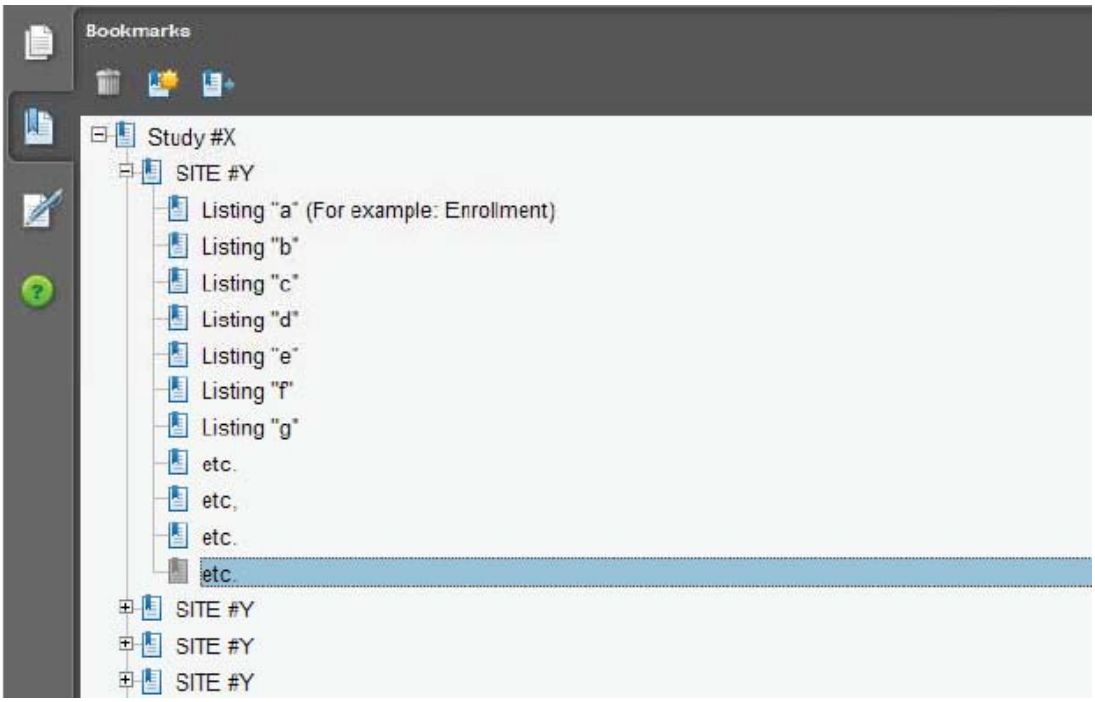
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).

5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as "line listings"). For each site, provide line listings for:
   a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
   b. Subject listing for treatment assignment (randomization)
   c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
   d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
   e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
   f. By subject listing, of AEs, SAEs, deaths and dates
   g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
   h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
   i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
   j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring

2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER's Inspection Planning" (available at the following link http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf) for the structure and format of this data set.

Attachment 1

Technical Instructions:
Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named "BIMO [list study ID, followed by brief description of file being submitted]." In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be "bimo." Files for items I, II and III below should be linked into

this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be "clinsite.xpt."

DSI Pre-NDA Request Item[1]	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:

C. It is recommended, but not required, that a Reviewer's Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be "BIMO Reviewer Guide." The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

[1] Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1
(http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf)

FDA eCTD web page
(http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm)

For general help with eCTD submissions: ESUB@fda.hhs.gov

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/s/

CRISTINA Petruccelli Attinello
12/08/2016