CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214460Orig1s000
214461Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 067681

MEETING PRELIMINARY COMMENTS

Chimerix, Inc
Attention: A. Heather Knight-Trent, PharmD
Vice President, Regulatory Affairs
2505 Meridian Parkway, Suite 100
Durham, NC 27713

Dear Dr. Knight-Trent:[1]

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for brincidofovir (BCV).

We also refer to your January 21, 2020, correspondence, received January 21, 2020, requesting a meeting to discuss the contents of the planned BCV NDAs for the treatment of smallpox.

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) 402-5708 or the main line at (301) 796-1500.

Sincerely,

{See appended electronic signature page}

Andrew Gentles, PharmD, BCPS AQ-ID
Senior Regulatory Project Manager
Antivirals Group
Division of Regulatory Operations for Infectious Diseases
Office of Regulatory Operations
Center for Drug Evaluation and Research

[1] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

ENCLOSURE:
- Preliminary Meeting Comments

PRELIMINARY MEETING COMMENTS

Meeting Type:	Type B
Meeting Category:	Pre-NDA
Meeting Date and Time:	April 3, 2020 1:00 PM – 2:30 PM
Meeting Location:	Teleconference (Dial-in information to be provided by sponsor)
Application Number:	067681
Product Name:	brincidofovir (BCV)
Indication:	Treatment of Smallpox
Sponsor/Applicant Name:	Chimerix, Inc

FDA ATTENDEES (tentative)
John Farley, MD, MPH, Office Director (Acting), Office of Infectious Diseases (OID)
Barbara Styrt, MD, MPH, Associate Director for Medical Countermeasures, OID
Debra Birnkrant, MD, Director, Division of Antivirals (DAV)
Jeff Murray, MD, MPH, Deputy Director, DAV
Poonam Mishra, MD, MPH, Deputy Director for Safety, DAV
Karen Winestock, Chief, Project Management Staff
Andrew Gentles, PharmD, BCPS AQ-ID, Senior Regulatory Project Manager
Adam Sherwat, MD, Clinical Team Leader
Kirk Chan-Tack, MD, Clinical Reviewer
Hanan Ghantous, PhD, DABT, Nonclinical Supervisor, DAV
Laine Peyton Myers, PhD, Nonclinical Reviewer, DAV
David McMillan, PhD, Nonclinical Reviewer, DAV
Jules O'Rear, PhD, Clinical Virology Team Leader, DAV
Patrick Harrington, PhD, Clinical Virology Reviewer, DAV
Su-Young Choi, PhD, Clinical Pharmacology Team Lead, Office of Translational Sciences (OTS), Office of Clinical Pharmacology (OCP), Division of Infectious Disease Clinical Pharmacology (DIDP)
Hazem Hassan, PhD, MS, RPh, Clinical Pharmacology Reviewer, OTS, OCP, DIDP

Thamban Valappil, PhD, Statistics Team Lead, OTS, Office of Biometrics (OB), Division of Biometrics IV (DBIV)
Yu Cao, PhD, Statistics Reviewer, OTS, OB, DBIV
Erika Englund, PhD, Application Technical Lead, Office of Pharmaceutical Quality (OPQ)
George Lunn, PhD, Chemistry, Manufacturing Controls (CMC) Reviewer, OPQ
Sevan Kolejian, PharmD, MBA, Team Lead, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (DMEPA)
Valerie Vaughan, PharmD, Safety Evaluator, DMEPA
Rosemary Roberts, MD, Director, Counter-Terrorism and Emergency Coordination Staff (CTECS)
Carlos GonzalezMercado, PharmD, Regulatory Project Manager/Emergency Coordinator, CTECS

SPONSOR ATTENDEES
Chimerix
Mike Sherman, Chief Executive Officer, President
Garrett Nichols, MD, Chief Medical Officer
Randall Lanier, PhD, Chief Science Officer
Marion Morrison, MD, Executive Medical Director
Tom Brundage, MS, Executive Director, Biostatistics
Odin Naderer, PharmD, Vice President, Clinical Pharmacology and Translational Medicine
Heather Knight, PharmD, Vice President, Regulatory Affairs and Quality Assurance
Andrew Grigston, RAC, Director, Clinical Research and Regulatory Strategy
Tim Tippin, PhD, Senior Director, DMPK
I.M. (Gina) Grossi, PhD, Director, Toxicology
Scott Foster, PhD, Director, Virology
Heidi Colton, MS, Senior Director, Toxicology and Translational Medicine
Rebecca Heath, PMP, Sr. Project Manager

Consultant
(b) (4) Clinical Pharmacology and PK/PD Modeling Consultant

BARDA
David Boucher, PhD, Branch Chief, Antiviral and Antitoxin Branch (AVAT)/CBRN
Danielle Turley, PhD, Project Officer, AVAT/CBRN
Michael Merchlinsky, PhD, Scientific Program Manager, CBRN
Paul Roney, PhD, DABT, Regulatory Specialist, RQA

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 April 3, 2020 1:00 PM – 2:30 PM, via teleconference between Chimerix, Inc and the Division of Antivirals. 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

Chimerix Inc is currently developing brincidofovir (BCV) for the treatment of smallpox in adult and pediatric patients under the Animal Rule pathway in accordance with 21 CFR 314 Subpart I (Approval of New Drugs When Human Efficacy Studies are Not Ethical or Feasible) with plans for 2 oral dosage forms (oral tablet and suspension formulation for adults and pediatric subjects unable to take solid medication). Brincidofovir is a novel, lipid-modified acyclic nucleotide providing unique intracellular delivery of a potent antiviral that has demonstrated in cell culture activity against multiple double-stranded DNA (dsDNA) viruses, including the orthopoxviruses, herpesviruses, and adenoviruses (AdV). BCV was granted fast track designation on July 8, 2005 for the treatment of smallpox and granted orphan drug designation on June 5, 2018. On January 21, 2020, a Type B Pre-NDA meeting request was submitted to discuss the contents for the 2 planned BCV NDAs for the treatment of smallpox. The FDA granted the request on January 24, 2020, with a meeting scheduled for April 3, 2020.

2.0 DISCUSSION

2.1. Nonclinical

Question 1: Chimerix believes that the efficacy of BCV in the rabbit and mouse models has been sufficiently established based on the pivotal VIR-106 and VIR-044 efficacy and supportive studies. Does the Agency concur that VIR-106 and VIR-044 with the supportive studies (including PK) are sufficient for the planned smallpox NDA?

FDA Response to Question 1: *We agree that the pivotal rabbit/RPXV (CMX001-VIR-106) and mouse/ECTV (CMX001-VIR-044) efficacy studies and supportive studies are sufficient to support the NDA review, pending independent confirmation of results and confirmation of the data quality and integrity.*

Question 2: Does the Agency agree that the nonclinical safety program, as described, supports the planned NDA submission for BCV for the treatment of smallpox?

FDA Response to Question 2: *Yes, we agree.*

Question 3: Does the Agency have comments to the draft Animal Model Defense document?

FDA Response to Question 3: *The draft Animal Model Defense document appears to cover the key issues with respect to smallpox animal models used to support the NDA. We have no comments at this time.*

Question 4: Does the Agency agree on the approach to scale from the animal data to the proposed human dose?

FDA Response to Question 4:
The proposed scaling approach from the animal data to the proposed human dose is acceptable.

2.2. Clinical Pharmacology

Question 5: Does the Agency agree that the clinical pharmacology program, as described, will support the planned NDA submissions of brincidofovir for the treatment of smallpox?

FDA Response to Question 5:

The clinical pharmacology program, as described, is acceptable to support the planned NDA submission. Please include a comprehensive list of results from in vitro metabolism/transporter studies in module 2.7.2. when the NDA is submitted.

2.3 Clinical

Question 6: Does the Agency agree that the BCV safety database and human PK studies are sufficient to support the assessment of the BCV benefit:risk profile for the 200 mg QW for 2 weeks dosing regimen in the treatment of smallpox?

FDA Response to Question 6: *We agree that the BCV safety database and human PK studies are sufficient to support the assessment of the BCV benefit:risk profile. Our determination of the sufficiency of the safety and human PK data to support NDA approval is a review issue.*

Question 7: Does the Agency agree with the design of the outbreak study with respect to the following?
a. Subject population
b. Number of subjects / sample size
c. Data collection
d. Safety measures

FDA Response to Question 7:

a. *For the following inclusion criterion:*

"Prospective subjects are those presenting with a case of acute, generalized vesicular/pustular rash that are determined, per the clinical definition of smallpox, to meet the Center for Disease Control and Prevention (CDC) criteria for having confirmed, suspected, or probable smallpox."

Please clarify whether the referenced risk categories are based on the following CDC algorithm: https://www.cdc.gov/smallpox/clinicians/algorithm-protocol.html

If they are, please clearly define this in the protocol.

b. *Please specify how sample size is calculated, including relevant parameters used for the calculation. Please provide the corresponding confidence interval(s) of anticipated survival rate supporting the sample size determination.*

For example, the sample size calculation for the study should include more details for an informative study and consider the anticipated survival rate of variola infection with supportive care alone, your estimate of anticipated survival rate of variola infection with tecovirimat (as this would likely be considered as the current standard-of-care), and the anticipated treatment effect (benefit) of BCV when added to standard-of-care management as in an add-on superiority trial.

Please provide justification for your sample size calculation based on your estimate of the anticipated survival rate of variola infection with supportive care (based on a review of historical data), the anticipated treatment effect (benefit) of tecovirimat as the current standard-of-care (SOC) management, and the anticipated treatment effect (benefit) of BCV when added to SOC management.

For your sample size determination, we recommend using 99% CI instead of 95% CI. We acknowledge that this will increase the sample size slightly but, given the uncertainties around the anticipated survival rate of variola infection with tecovirimat (as this would likely be considered as the current SOC) and the anticipated treatment effect (benefit) of BCV, we prefer that 99% CI is used.

c. *Data collection*

I. *History of receipt of smallpox vaccine at any time in their lives should be recorded for all study subjects.*

II. *Your synopsis states that "most data in this observational field study is anticipated to be collected retrospectively."*

We do not agree with your assumption that prospective data collection would be unlikely or not feasible. We recommend that, wherever feasible, every effort should be made to collect data prospectively to avoid any potential biases. Prospectively collected data would be highly informative in helping with the evolving logistics that may occur during a mass smallpox event.

d. *All serious adverse events (SAEs), AEs, and clinically significant laboratory abnormalities should be followed until resolution or stabilization, to the extent possible.*

e. *All discontinuations due to toxicity should be followed until resolution or stabilization of said toxicity, to the extent possible.*

f. Regarding the prohibition of the concomitant use of cyclosporin, please refer to the Clinical Pharmacology comment under Question 8.

2.4 Draft Label

Question 8: Does the Agency have advice or comments on the draft labeling with particular attention to the following sections:
a. Warnings and Precautions (Section 5)
b. Adverse Reactions (Section 6)
c. Microbiology (Section 12.4)

FDA Response to Question 8: *We appreciate your sharing the draft labeling. We have the following preliminary comments and note that additional comments will be provided during the NDA review:*

a. The dose-limiting gastrointestinal toxicities that have been observed across your development programs should be described in the Warnings and Precautions.

b. For Section 6 (Table 1), your proposed cut-off (b) (4) *may not sufficiently describe the safety profile of BCV. You may use this cutoff in labeling as a starting point, but please also provide the following analyses in the clinical summary section of your NDA submission:*

Version 1: Adverse Reactions Reported in ***≥5%*** *of Subjects in the TEMBEXA Group with a Difference of 2% from the Placebo Group*

Version 2: Adverse Reactions Reported in ***≥2%*** *of Subjects in the TEMBEXA Group with a Difference of 2% from the Placebo Group*

This information will help inform additional discussions that will occur during the NDA review.

c. We have no comments on Section 12.4 Microbiology at this time.

Although data for BCV activity in immune deficient animals are limited, the study by Zaitseva et al., 2015, J Virol 89:3295–3307 showed that BCV was not sufficient to clear lethal vaccinia virus infection in mice lacking T cells. Therefore, based on these data we believe a limitation of use statement should be included in the BCV label (e.g., "efficacy

may be reduced in immunocompromised patients based on studies in immune deficient animals").

Clinical Pharmacology

We note [redacted] (b) (4) *the concomitant use of cyclosporine. While this is a review issue,* [redacted] (b) (4) *There appears to be sufficient safety and PK data in transplant patients receiving concomitant cyclosporine and brincidofovir that may be able to support the use of low dose cyclosporine with brincidofovir for the proposed duration. We also suggest submitting a summary of your safety and PK data when brincidofovir is used with cyclosporine to support the use of cyclosporine with brincidofovir in your NDA submission.*

2.5 Advisory Committee Meeting

Question 9: Is an Advisory Committee Meeting anticipated for BCV treatment of smallpox?

FDA Response to Question 9: *The need for an Advisory Committee Meeting will be a review issue and determined after the submission of the NDA.*

2.6 Administrative

Question 10: In order to address the requirements for Bioresearch Monitoring Program (BIMO) for Clinical Data, Chimerix proposes to provide this information only for the clinical study CMX001-301. Does the Agency agree?

FDA Response to Question 10: *No, we do not agree. This information should be provided for clinical study CMX001-201 and clinical study CMX001-301. We note that clinical study CMX001-201 is the only study with a cohort that evaluated 200 mg once weekly.*

Question 11: Does the Agency agree to the proposal for cross-referencing of the suspension NDA to tablet NDA and plan for a tablet NDA rolling submission?

FDA Response to Question 11: *We agree with your proposal.*

2.7 Emergency Use Authorization (EUA)

Question 12: Does the Agency agree that BCV is ready for a formal EUA Request for widespread distribution in a smallpox emergency?

FDA Response to Question 12: *The Agency appreciates Chimerix's interest in using BCV under a potential Emergency Use Authorization (EUA); however, the Agency has significant concerns in this regard.*

At present, the Sponsor has only recently provided the final study report for your key rabbit/rabbitpox efficacy study (reference your March 5, 2020 submission) and the data integrity from this study has not yet been assessed.

The Sponsor has also not provided final study reports for key studies in the mouse/ectromelia models and consequently the data integrity from these studies has not yet been assessed.

Additionally, the demonstrated safety profile of BCV (including evidence of significant, dose-limiting gastrointestinal and hepatic toxicities) raises concerns about the appropriateness of an EUA mechanism.

We also note that, at this time, the Office of New Drugs and the Office of Surveillance and Epidemiology have insufficient information to conclusively determine whether a risk evaluation and mitigation strategy (REMS) will be necessary to ensure that the benefits of the drug outweigh the risks. We will make a final determination for the need for a REMS during the review of your NDA.

However, the Agency appreciates the Sponsor's interest in having a mechanism to provide BCV in the event of a smallpox outbreak. Therefore, in addition to continuing to submit the components of your NDA submission, we encourage you to submit a draft protocol for a clinical trial that can be conducted under IND in the event of an outbreak. This is consistent with recommendations in the FDA Guidance for Industry: Smallpox (Variola) Infection: Developing Drugs for Treatment or Prevention. At a minimum, your draft protocol should address the comments that the Agency has provided regarding your draft protocol synopsis (that was submitted as part of this pre-NDA package).

Given the above issues, the Agency recommends that the Sponsor design the clinical trial with the dual goals of providing access to the drug and generating interpretable clinical data that could inform the risk/benefit assessment of BCV for the treatment of smallpox. We would suggest the use of a randomized, controlled trial design (e.g., tecovirimat vs. tecovirimat + BCV) but would be open to considering other trial designs that also meet these goals. We would be happy to work with you toward the development of a clinical trial that addresses these issues. We also encourage you to collaborate with other stakeholders (e.g. CDC, etc.) so that your protocol is pre-positioned and can be implemented rapidly if the need arises.

Additional Comments

Biometrics: In your proposed outbreak (i.e. field) study, please specify how missing data will be handled, including discontinuation due to AEs. If there is no effect of treatment other than safety events, then it might be possible that subjects experiencing toxicity may be most likely to withdraw early from the study. This may potentially lead to biased estimates.

We also recommend that the protocol distinguish withdrawal from treatment and withdrawal from study assessments, and that subjects should be asked to complete assessments even if they no longer choose to take study medication.

Virology
If not already planned for inclusion in the Virology summary document, please include a brief summary of assay methods and performance characteristics for the plaque assays and qPCR assays used in the pivotal RPXV and ECTV studies, and cite relevant assay validation study reports as applicable. Include a brief description of data analysis methods used for presentation of blood and tissue results from these studies.

3.0 DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our January 24, 2020 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.[2]

In addition, we note that a chemistry pre-submission meeting is planned for April 1, 2020. A summary of agreements reached at that meeting will be documented in the respective meeting minutes.

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

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.

Because this drug product for this indication has an orphan drug designation, you are exempt from these requirements. Please include a statement that confirms this finding, along with a reference to this communication, as part of the pediatric section (1.9 for eCTD submissions) of your application. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

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[3] and Pregnancy and Lactation Labeling Final Rule[4] 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

[3] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information
[4] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

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 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.

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
(1)				
(2)				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
(1)				
(2)				

FDA has made a preliminary determination that the application for this product would be reviewed as a new molecular entity (NME) and therefore subject to the Program, under PDUFA VI. Please note that this is a preliminary determination, based on information available to FDA at this time, and will be re-evaluated at the time your application is submitted. This determination is based on our understanding of the active moiety (21 CFR 314.108(a)) and whether another marketing application containing the same active moiety is approved or marketed. Please also note that the NME determination for an application is distinct from and independent of the new chemical entity (NCE) determination and any related exclusivity determinations, which are made after approval of an NDA.

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*.[5]

[5] 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/

ADAM I SHERWAT
03/26/2020 12:09:45 PM

IND 067681

MEETING PRELIMINARY COMMENTS

Chimerix, Inc.
Attention: Heather Knight, PharmD
Vice President, Regulatory Affairs
2505 Meridian Parkway
Suite 100
Durham, NC 27713

Dear Dr. Knight:

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for CMX001, Brincidofovir (BCV).

We also refer to your January 31, 2020 correspondence requesting a Type B Pre-NDA meeting to discuss the continued development of brincidofovir tablets and oral suspension in support of future NDAs. Our preliminary responses to your meeting questions are enclosed.

You should provide, to the Regulatory Business Process 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 Shamika P. Brooks, Regulatory Business Process Manager at 301-796-2888.

Sincerely,

{See appended electronic signature page}

Erika Englund, Ph.D. for
Balajee Shanmugam, Ph.D.
Branch Chief, Branch II
Office of New Drug Products
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

ENCLOSURE:

- Preliminary Meeting Comments

PRELIMINARY MEETING COMMENTS

Meeting Type:	Type B
Meeting Category:	Pre-NDA, CMC
Meeting Date and Time:	April 1, 2020
Meeting Location:	Dial in information to be provided by sponsor
Application Number:	067861
Product Name:	CMX001, Brincidofovir (BCV)
Indication:	Treatment of smallpox in adult and pediatric patients.
Sponsor/Applicant Name:	Chimerix, Inc.

FDA ATTENDEES (tentative)

Thomas Oliver, PhD	Division Director, OPQ/ONDP/DNDPI
Erika Englund, PhD	CMC Lead, OPQ/ONDP/DNDPI
Peter Guerrieri, PhD	Drug Product Reviewer, OPQ/DNDP I/ONDP
Mark Johnson, PhD	OPMA Reviewer, OPQ/OPF/DPAI/PAB2
Bo Jiang, PhD	OPMA Reviewer, OPQ/OPF/DIA/IAB1
Angelica Dorantes, PhD	Biopharmaceutics Branch Chief, OPQ/ONDP/DB
Elsbeth Chikhale, PhD	Biopharmaceutics Lead, OPQ/ONDP/DB
Sarah Ibrahim, PhD	Biopharmaceutics Reviewer, OPQ/ONDP/DB
Shamika Brooks, PharmD, MHA	Regulatory Business Process Manager, OPQ

SPONSOR ATTENDEES

TBD

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 April 1, 2020, 10:00AM, via Teleconference between Chimerix, Inc and the Office of Pharmaceutical Quality. 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 Business Process Manager (RBPM) 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

On January 31, 2020, Chimerix, Inc. submitted a Type B Pre-NDA meeting request to discuss Chemistry, Manufacturing, and Controls (CMC) for CMX001, Brincidofovir. The purpose of the meeting is to discuss the continued development of brincidofovir tablets and oral suspension to include the following topics the Dissolution Development Report for Brincidofovir Oral Suspension, extractables and leachables testing of the container closure system and particle size testing of Brincidofovir Oral Suspension, and proposal for submission of executed batch records for Brincidofovir Tablets and Oral Suspension.

The office of Pharmaceutical Quality granted Chimerix, Inc. a teleconference meeting on February 18, 2020.

2.0 DISCUSSION

Question 1:

Does the Agency agree the leachable and extractable data presented supports the requirements for qualifying the primary container-closure system, high density polyethylene bottle (b) (4) for Brincidofovir Oral Suspension, 10 mg/mL?

FDA Response to Question 1:

We acknowledge the extractables/leachables data provided. Your approach and results to-date appear reasonable to support qualification of the container closure system. However, final determination will be an NDA review issue. Please provide additional information in the NDA submission, including the detailed results of the E/L studies and stability batch testing. This should include any correlation between leachables observed in the batch testing and those observed in the E/L studies. Additional E/L data on the three drug product registration/stability batches, which you have indicated would undergo continued testing, to cover the proposed expiry should also be provided in the NDA submission. Include justification of any impurities above the applicable qualification threshold; refer to USP <1663>, <1664> for additional recommendations.

Question 2:

Does the Agency agree to the approach for demonstrating the discriminating properties of the dissolution method and the proposed conditions of the dissolution method for Brincidofovir Oral Suspension, 10 mg/mL?

FDA Response to Question 2:
The dissolution method development report for Brincidofovir Oral Suspension 10 mg/mL, submitted on 01/30/2020, will be reviewed and feedback will be provided by approximately the end of April.

Question 3:
Does the Agency agree that the justification presented supports discontinuing particle size testing at time of release and during stability for Brincidofovir Oral Suspension, 10 mg/mL?

FDA Response to Question 3:
As you have indicated, particle size is a critical quality attribute with potential impact on homogeneity, palatability and stability. We acknowledge the stability results provided for the registration/stability batches through 12 months (long-term) and 6 months (accelerated). However, at this time, we do not consider there to be sufficient batch history available to support the waiver of release and stability testing of particle size, which is considered a key quality characteristic. We recommend that you include release and stability testing for particle size in your drug product specifications.

Question 4:
Does the Agency agree to the selection of Brincidofovir Tablets, 100 mg and Brincidofovir Oral Suspension, 10 mg/mL executed batch records selected for submission in the NDAs?

FDA Response to Question 4:
The Agency agrees with the proposal for submission of executed batch records for Brincidofovir Tablets, 100 mg and Brincidofovir Oral Suspension, 10 mg/mL to be provided in Submission #1.

In accordance with "Instructions For Filling Out Form FDA 356h", complete establishment information of all manufacturing, packaging, testing, and storage facilities should be captured in Field 28 therein and be provided in Submission #1 as well.

Additional comments:

Conduct and submit a risk assessment for the presence of elemental impurities as described in the ICH guidance Q3D Elemental Impurities (https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM371025.pdf). The risk assessment should identify known and potential sources of elemental impurities that may be present in the drug product, and evaluate the presence of each particular elemental impurity likely to be present in the drug product by determining the observed or predicted level of the impurity and comparing it with the permitted daily exposure (PDE) established in ICH Q3D(R1). If the risk assessment or testing results fail to show that an elemental impurity level is consistently less than the control threshold (defined as being 30 percent of the established PDE in the drug product), you should propose additional controls (e.g., component, in-process, or drug product controls) to ensure that the elemental impurity level does not exceed the PDE in the drug product. For additional information, also see:
https://www.fda.gov/Drugs/DevelopmentApprovalProcess/Manufacturing/ucm590075.htm

3.0 SECURE EMAIL COMMUNICATIONS

Secure email is required for all email communications from FDA when confidential information (e.g., trade secrets, manufacturing, or patient information) is included in the message. To receive email communications from FDA that include confidential information (e.g., information requests, labeling revisions, courtesy copies of letters), you must establish secure email. To establish secure email with FDA, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

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

/s/

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