CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210303Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 102563

MEETING MINUTES

Achaogen, Inc.
Attention: Anne Keane
Senior Director and Head, Regulatory Affairs
1 Tower Place, Suite 300
South San Francisco, CA 94080

Dear Ms. Keane:

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

We also refer to the meeting between representatives of your firm and the FDA on April 14, 2017. The purpose of the meeting was to discuss the data and elements to be submitted in a New Drug Application (NDA).

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 Carmen DeBellas, Chief Project Manager at (301) 796-1203.

Sincerely,

{See appended electronic signature page}

Sumathi Nambiar, MD, MPH
Director
Division of Anti-Infective Products
Office of Antimicrobial Products
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: Pre-NDA

Meeting Date: April 14, 2017

Application Number: IND 102563
Product Name: Plazomicin sulfate injection
Indication: Complicated Urinary Tract Infections (cUTI)
Sponsor/Applicant Name: Achaogen, Inc.

FDA ATTENDEES

Office of Antimicrobial Products

Edward Cox, MD, MPH	Director
John Farley, MD, MPH	Deputy Director

Division of Anti-Infective Products

Carmen DeBellas, PharmD	Chief Project Manager
Seong Jang, PhD	Clinical Pharmacology Team Leader
Shrimant Mishra, MD, MPH	Clinical Team Reviewer
Sumati Nambiar, MD, MPH	Director
Joseph Toerner, MD, MPH	Deputy Director for Safety
Kunyi Wu, PharmD	Clinical Pharmacology Reviewer
Daniel Rubin, PhD	Statistical Reviewer
Amy Ellis, PhD	Pharmacology/Toxicology Reviewer
Owen McMaster, PhD	Pharmacology/Toxicology Team Leader (Acting)
Simone Shurland, PhD	Clinical Microbiology Reviewer
Jeffry Florian, PhD	Pharmacometrics Team Leader
Fang Li, PhD	Pharmacometrics Reviewer
Seong Jang, PhD	Clinical Pharmacology Team Leader
John Lazor, PharmD	Director, Division of Clinical Pharmacology IV

Center for Devices and Radiologic Health
Office of In Vitro Diagnostics and Radiologic Health
Division of Chemistry and Toxicology Devices

Marianela Perez-Torres, MT, PhD	Lead Reviewer
Courtney Lias, PhD	Director

Eastern Research Group Attendees

Azada Hafiz	Independent Assessor

SPONSOR ATTENDEES - Achaogen, Inc.

Ian Friedland, MD	Chief Medical Officer
Lynn Connolly, MD, PhD	Vice President, Late Development
Dan Cloutier, PharmD	Medical Director
Richard Pushkin, MD	Medical Director
Kevin Krause, MBA	Director of Microbiology
Tao Wang, MD, PhD DABT	Director, Toxicology
Julie Seroogy	Director, DMPK/Bioanalytical
Aryun (Eileen) Kim, PharmD	Associate Director, Clinical Pharmacology
Alex Smith, MS	Director of Biostatistics
Kristie Kooken, MS	Director, Statistical Programming
Anne Keane, PA-C, JD	Senior Director, Regulatory Affairs
Scott Moore	Director, Regulatory Operations and Medical Writing
Raissa Trend, PhD	Director, CMC Regulatory Affairs
Caroline Stork, PhD	Senior Associate, Regulatory Affairs

Biomedical Advanced Research and Development Authority (BARDA)

Brian TSe, PhD	Health Scientist, Project Officer, Anti-Infective Program
Shar'Ron deDreu, MS	Subject Matter Expert, Division of Clinical Studies
Sandra Bihary-Waltz, DBA(c), MSN	Subject Matter Expert, Division of Regulatory and Quality Affairs

Via Phone

Kenneth Hillian, MD,ChB	Chief Executive Officer, Achaogen
Chris Houchens, PhD	Branch Chief, Antibacterials Program, Division of CBRN Countermeasures
Louise Latriano, PhD, BADT,	Toxicology/Pharmacokinetic Subject Matter Expert Division of CBRN Countermeasures
Kazimierz Chrzan, PhD	Subject Matter Expert, Division of Manufacturing and Facilities and Engineering
Nina Badry	Regulatory Specialist, BARDA Regulatory and Quality Affairs

BACKGROUND

The purpose of this meeting was to discuss and obtain agreement that the proposed content of the NDA is acceptable to the Division. The Sponsor (Achaogen) asked to reach agreement on the timing of the submission of the study report for the mass balance study and reach consensus that the data package adequately demonstrated the absence of circulating metabolites. FDA sent Preliminary Comments to Achaogen, Inc. on April 11, 2017 included in the discussion below as FDA Responses. Achaogen provided written responses, included in the discussion below as Achaogen Responses. During the meeting, Achaogen requested discussion for responses to questions 1, 2, 3, and 4 included below as Meeting Discussion.

DISCUSSION

Clinical

Question 1

Does the Division agree that the proposed clinical data package and analysis for pivotal studies ACHN-490-009 and ACHN-490-007 will be adequate to support the Division's review of the NDA for the following proposed indications?

Plazomicin is indicated as a single agent in patients 18 years or older for the treatment of complicated urinary tract infections including pyelonephritis caused by the following susceptible microorganism(s): *Escherichia coli* (including cases with concurrent bacteremia), *Klebsiella pneumoniae, Proteus* species (including *Proteus mirabilis* and *Proteus vulgaris), Enterobacter cloacae,* and *Morganella morganii.* Plazomicin has been approved for use in patient with cUTI where limited or no alternative therapies are available. The safety and effectiveness of plazomicin have not been established beyond this patient population.

Plazomicin in combination with meropenem or tigecycline, is indicated in patients 18 years or older for the treatment of bloodstream infections (BSI), and hospital-acquired and ventilator-associated bacterial pneumonia (HABP/VABP) caused by the following susceptible microorganism(s): *Klebsiella pneumoniae* and *Enterobacter aerogenes.* (b) (4)

FDA Response:
We agree that the proposed clinical data package and analysis of the clinical studies will be adequate to support an NDA review. The data to support each of the proposed indications for cUTI, HABP/VABP, and BSI caused by the designated microorganisms will be evaluated during the NDA review.

The review of Study ACHN-490-007 may be assisted by a summary of evidence regarding the efficacy of colistin for the treatment of HABP/VABP and BSI due to carbapenem-resistant Enterobacteriaceae (CRE).

Achaogen Response:
Achaogen thanks the Division for their feedback. Because the number of patients enrolled in Study ACHN-490-007 with HABP/VABP is very small, we would like to discuss our current thinking with regard to pursuing a BSI indication alone on the basis of this study as well as FDA's thinking regarding small datasets in light of the new LPAD legislation. We would then like to discuss the purpose and scope of the summary of evidence regarding the efficacy of colistin that was requested by the Division.

Meeting Discussion: *The Sponsor began the discussion by stating that there were small numbers of patients in Study 007 with HABP/VABP, and enquired if the Division would consider them*

pursuing an indication only for BSI. The Division asked for clarification about the source of bacteremia in these patients. The Sponsor noted that in most cases the source was unknown. On further discussion, Achaogen noted that many patients had intravascular catheters. The Division asked how a patient's blood was sampled for the diagnosis of BSI and if it was obtained after the catheter was pulled. The Sponsor replied that cultures were taken from the newly placed catheter and peripheral blood draws. The Sponsor asked when information on the efficacy of colistin should be submitted. The Division replied that this information should be submitted at the time of the NDA submission and not during the review.

General
Question 2

Does the Division agree that the proposed overall NDA contents, including the outlined clinical pharmacology, nonclinical microbiology and pharmacokinetic (PK)/pharmacodynamics (PD), and toxicology packages will be considered adequate to support the Division's review of the plazomicin NDA for the above stated indications for plazomicin?

FDA Response:
The proposed Clinical Pharmacology information and data to be included in the NDA appear to be appropriate to support the review of the NDA.

However, we have the following comments for your consideration:

- *We acknowledge the rationale provided for not conducting an in vivo DDI study to further investigate plazomicin as an MATE2-K transporter inhibitor. We need to discuss this further with our DDI-focused group and will provide a response at the meeting on April 14, 2017 or soon thereafter.*
- *We do not agree with your proposed timeline for the planned human mass balance study.*
- *Please refer to Questions 3 and 4 below for details.*
- (b) (4)

We agree with your plan to conduct population PK and PK/PD analyses. However, we do not have adequate information in this meeting package to comment on your planned analyses. In addition to your planned analyses, we recommend that you conduct an exposure-response (E-R) efficacy analysis using data from Study ACHN-490-009. For example, the E-R efficacy analysis

can be conducted with a logistic regression analysis that would characterize the relationship between exposure and primary and secondary efficacy endpoints as a function of patient factors. Exposure metrics (i.e., PK parameters such as AUC and C_{max}) for this analysis can be derived from the population PK analysis.

The following general recommendations regarding your population PK, exposure-response, and PK/PD datasets to be included in the NDA are listed below:

- *Submit NONMEM control streams of the base and final model for the population PK analysis.*
- *Submit the dataset and codes (NONMEM, R, SAS, etc.) used for simulation to support your dose rationale.*
- *Provide the output tables for final model runs for population PK and PK/PD models.*
- *Submit model codes or control streams and output listings for all major model building steps, e.g., base structural model, covariate model, final model, and validation model. These files should be submitted as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt).*
- *Submit a model development decision tree and/or tables which give an overview of modeling steps.*
- *Include a USUBJID (unique subject ID) column to all the population PK and PK/PD datasets so that we can relate these datasets to other clinical analysis datasets.*

Finally, it is not clear if you intend to submit electronic datasets for pharmacokinetic information (concentrations and parameters) for Study ACHN-490-001. We request that you submit electronic datasets because this information will assist in the review of this study.

Achaogen Response:
Achaogen thanks the Division for their feedback. With regard to the population PK, exposure-response, and PK/PD datasets, Achaogen plans to submit the data as requested as well as submit the electronic data format for Study ACHN-490-001 PK concentrations and parameters.

We would like to better understand the Division's request for exposure response efficacy analyses.

Additionally, we would like to receive clarification that, outside of the above comments, the proposed data packages for nonclinical microbiology, toxicology, and nonclinical PK/PD will be considered adequate to support the Division's review of the plazomicin NDA.

Meeting Discussion: *The Division replied that the proposed data packages for nonclinical microbiology, toxicology and nonclinical PK/PD appear adequate and it does not anticipate that additional studies other than what is planned by the Sponsor would be needed to support the NDA.*

The Sponsor confirmed that they would conduct exposure-response analyses for clinical safety endpoints. However, as only a single dose was evaluated in the Phase 3 studies and due to the overall high response rates, the Sponsor did not consider that exposure-response analyses would be particularly informative with regard to outcomes. The Division acknowledged the Sponsor's position, but pointed out that an analysis showing a lack of a relationship is informative and could be supportive information for the dosing regimen. No agreement was reached regarding the submission of exposure-response efficacy analyses for the submission. The Sponsor did agree to include data for plazomicin dose adjustment according to TDM in the NDA.

Question 3

Achaogen is currently planning to perform a human mass balance study to further support the excretion data package of plazomicin. The final study report is expected to be available for submission after the initial NDA submission. Will the Division accept submission of the human mass balance study report after the initial NDA is submitted?

FDA Response:

We prefer that you submit the mass balance study report together in the initial NDA submission. However, if the final study report is not available for submission at the time of the NDA submission, we recommend that you submit the final study report within 60 days of the NDA submission. Of note, if an unexpected metabolite is found in the mass balance study that is greater than 10 percent of the initial parent drug, it must be further evaluated for its pharmacological activity and toxicity. Please refer to the FDA Guidance for Industry: Safety Testing of Drug Metabolites (*http://www.fda.gov/OHRMS/DOCKETS/98fr/FDA-2008-D-0065-GDL.pdf*) *for details.*

Achaogen Response:

Achaogen thanks the Division for their feedback. We would like to come to an agreement regarding the timeline for submission of the final clinical study report for the mass balance study that will not result in a delay to the submission of the NDA.

Meeting Discussion: *The Division noted that the best possible scenario would be to have the final report from the mass balance study submitted with the NDA. Agreement was reached between the Division and the Sponsor that the final study report for the mass balance study would be submitted within 90 days after the NDA submission. The Sponsor stated that they would be taking a risk if an unexpected metabolite is found in the study. In addition, the Sponsor stated that the planned mass balance study is anticipated to be completed before the NDA submission and they would communicate with the FDA if any unexpected metabolites are identified.*

Question 4

(b) (4)

(b) (4)

FDA Response:

(b) (4)

Achaogen Response:

(b) (4)

The Division stated that the data provided in the meeting background package do not rule out plazomicin as a potential inhibitor of MATE 1 and MATE2-K transporters. The Division stated that they had confirmed with the Drug-Drug Interaction (DDI) working group in the Office of Clinical Pharmacology about the potential inhibition of MATE 1 and MATE2-K transporters by plazomicin. Therefore, the Division recommended that the Sponsor conduct an in vivo DDI study with a MATE1 and MATE2-K substrate such as metformin. In addition, to better interpret the metformin PK and PD results after co-administration with plazomicin, the Division suggested that the Sponsor investigate whether plazomicin is an inhibitor of OCT1 since OCT1 is responsible for metformin uptake in the liver. The Division also suggested that since plazomicin is primarily eliminated by the kidneys, it should be evaluated as a substrate of major renal transporters including OAT1/3 and OCT-2.

The Sponsor acknowledged the Division's recommendation regarding the in vivo DDI study for MATE1 and MATE2-K transporters and stated that they will consider conducting the in vivo DDI study. The Sponsor also stated that they will evaluate the data from the clinical trial as quite a few patients were on metformin. (b) (4)

(b) (4) *The Division noted that as metformin is a commonly used drug, especially in the patient population of interest, evaluating the DDI is optimal. The Sponsor stated that if they plan to conduct the study, they will provide a timeline to the Division. The Division stated that they could not agree to a timeline for the submission, unless they had more specific information. The Sponsor also stated that they did not plan to evaluate plazomicin as an inhibitor of OCT1 or plazomicin as a substrate of OAT1/3 and OCT2. The Division pointed out that the DDI would be potential review issues and would be reflected in the labeling.*

Biometrics
Question 5
Does the Division agree with the proposed study data submission plan supporting the plazomicin NDA?

FDA Response: *The proposal is acceptable, and we agree that it is not necessary to provide nonclinical study datasets in the NDA.*

Achaogen Response: Achaogen thanks the Division for their feedback.

Meeting Discussion: None.

Question 6
Does the Division agree with the proposal for inclusion of Case Report Forms (CRFs) supporting the plazomicin NDA?

FDA Response: *The proposal is acceptable*.

Achaogen Response: Achaogen thanks the Division for their feedback.

Meeting Discussion: None.

Question 7
Achaogen plans to submit key programs to support primary efficacy and safety analyses for our Phase 3 studies and formal integrated summaries. Does the Division agree that this subset of programs is sufficient?

FDA Response: *The proposal is acceptable.*

Achaogen Response: Achaogen thanks the Division for their feedback.

Meeting Discussion: None.

Regulatory
Question 8
Does the Division anticipate holding an advisory committee meeting for this application?

FDA Response: *We cannot comment at this time on the need for an advisory committee meeting as that will be determined once the NDA has been submitted.*

Achaogen Response: Achaogen thanks the Division for their feedback.

Meeting Discussion: ***None.***

Question 9
Does the Division agree with our proposed plan for provision of financial disclosure information in the NDA?

FDA Response: *You should report financial disclosure information for all covered studies at the time that the NDA is submitted. You are responsible for keeping updated financial information from investigators in your files, but it does not need to be submitted as an amendment to your NDA. We also refer you to the following link* https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-afdagen/documents/document/ucm341008.pdf

Achaogen Response: Achaogen thanks the Division for their feedback.

Meeting Discussion: ***None.***

Question 10
Plazomicin has been designated as a QIDP and qualifies for priority review and fast track. Achaogen would like to understand whether it would be helpful to the Division for Achaogen to submit portions (completed or partial Modules) of the NDA application before the complete application is ready for submission?

FDA Response: *Your proposal for the rolling submission is acceptable. We understand that you are planning to meet with the Office of Pharmaceutical Quality and agreements regarding the Chemistry, Manufacturing and Controls data will need to be made during that meeting.*

Achaogen Response: Achaogen thanks the Division for their feedback. Following input from the Office of Pharmaceutical Quality, we will propose a more detailed plan for rolling submission of the NDA to the Division.

Meeting Discussion: ***None.***

The Sponsor noted that timing of the NDA submission was dependent on feedback from Office of Pharmaceutical Quality regarding flexibility in the timeline for submission of the Chemistry Manufacturing and Controls portions of the NDA (b) (4)

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: 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.

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 and Pregnancy and Lactation Labeling Final Rule 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.

The application should include a review and summary of the available published literature regarding drug use in pregnant and lactating women, a review and summary of reports from your pharmacovigilance database, and an interim or final report of an ongoing or closed pregnancy registry (if applicable), which 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 (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf).

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

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.

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.				

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 Sponsor 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 Sponsor 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.

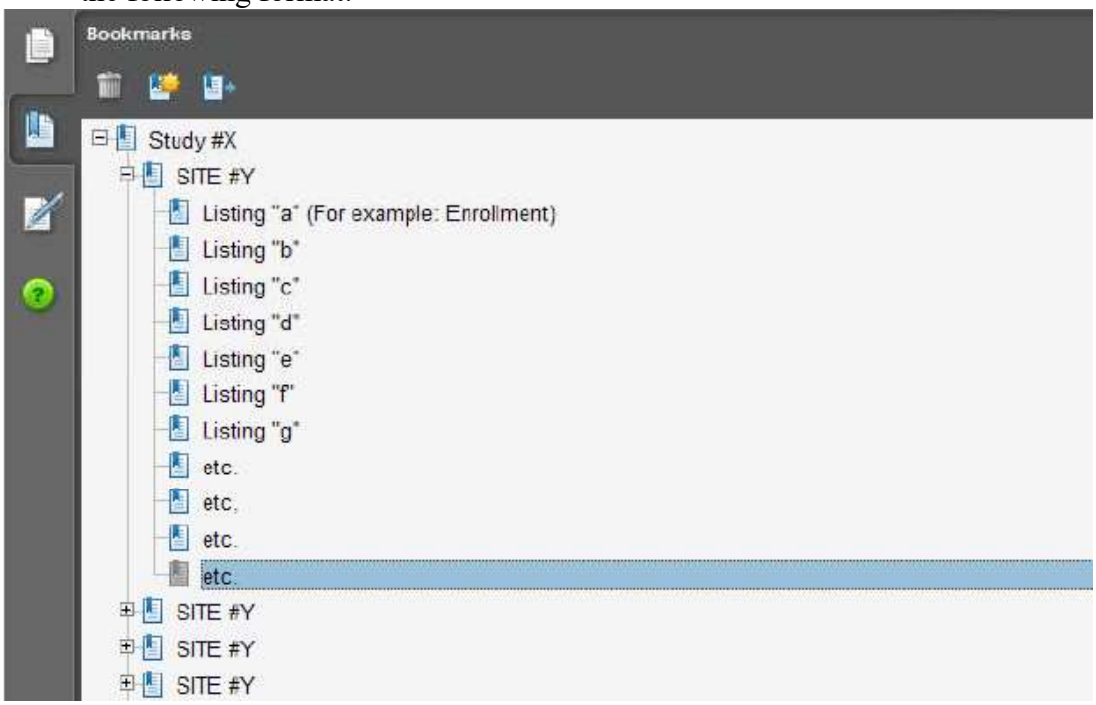
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere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

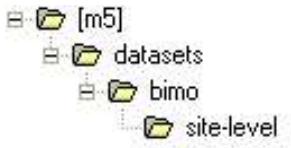
OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide 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 Item1	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/

SUMATHI NAMBIAR
05/12/2017

CDER Breakthrough Therapy Designation Determination Review Template

IND/NDA/BLA #	IND 102563
Request Receipt Date	3/29/2017
Product	Plazomicin
Indication	Treatment of bloodstream infections (BSI) caused by the following susceptible microorganism(s): *Klebsiella pneumoniae* and *Enterobacter aerogenes*. As only limited clinical safety and efficacy data for plazomicin are currently available, reserve plazomicin for use in patients who have limited or no alternative treatment options.
Drug Class/Mechanism of Action	Aminoglycoside
Sponsor	Achaogen
ODE/Division	DAIP
Breakthrough Therapy Request Goal Date (within 60 days of receipt)	5/28/2017

*Note: This document should be uploaded into CDER's electronic document archival system as a clinical review and will serve as the official Clinical Review for the Breakthrough Therapy Designation Request (BTDR)***.** *Note: Signatory Authority is the Division Director.*

Section I: Provide the following information to determine if the BTDR can be denied without Medical Policy Council (MPC) review.

1. **Briefly describe the indication for which the product is intended (Describe clearly and concisely since the wording will be used in the designation decision letter):**

The product is intended for the following indication: treatment of bloodstream infections caused by the following susceptible microorganism(s): Klebsiella pneumoniae and Enterobacter aerogenes. As only limited clinical safety and efficacy data for plazomicin are currently available, reserve plazomicin for use in patients who have limited or no alternative treatment options.

2. **Are the data supporting the BTDR from trials/IND(s) which are on Clinical Hold?** ☐YES ☒NO

If 2 above is checked "Yes," the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked "No", proceed with below:

3. **Consideration of Breakthrough Therapy Criteria:**

   a. Is the condition serious/life-threatening[1])? ☒YES ☐NO

If 3a is checked "No," the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked "Yes", proceed with below:

[1] For a definition of serious and life threatening see Guidance for Industry: "Expedited Programs for Serious Conditions—Drugs and Biologics" http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf

b. Are the clinical data used to support preliminary clinical evidence that the drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints adequate and sufficiently complete to permit a substantive review?

☒ YES the BTDR is adequate and sufficiently complete to permit a substantive review
☐ Undetermined
☐ NO, the BTDR is inadequate and not sufficiently complete to permit a substantive review; therefore the request must be denied because (check one or more below):

i. Only animal/nonclinical data submitted as evidence ☐
ii. Insufficient clinical data provided to evaluate the BTDR (e.g. only high-level summary of data provided, insufficient information about the protocol[s]) ☐
iii. Uncontrolled clinical trial not interpretable because endpoints are not well-defined and the natural history of the disease is not relentlessly progressive (e.g. multiple sclerosis, depression) ☐
iv. Endpoint does not assess or is not plausibly related to a serious aspect of the disease (e.g., alopecia in cancer patients, erythema chronicum migrans in Lyme disease) ☐
v. No or minimal clinically meaningful improvement as compared to available therapy[2]/ historical experience (e.g., <5% improvement in FEV1 in cystic fibrosis, best available therapy changed by recent approval) ☐

4. Provide below a brief description of the deficiencies for each box checked above in Section 3b:

If 3b is checked "No", BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off (Note: The Division always has the option of taking the request to the MPC for review if the MPC's input is desired. If this is the case, proceed with BTDR review and complete Section II). If MPC review is not required, email Miranda Raggio and Sandy Benton as soon as this determination is made so that the BTDR can be removed from the MPC calendar.

If 3b is checked "Yes" or "Undetermined", proceed with BTDR review and complete Section II, as MPC review is required.

5. Clearance and Sign-Off (no MPC review)

Deny Breakthrough Therapy Designation ☐

Reviewer Signature: {See appended electronic signature page}
Team Leader Signature: {See appended electronic signature page}
Division Director Signature: {See appended electronic signature page}

Section II: If the BTDR cannot be denied without MPC review in accordance with numbers 1-3 above, or if the Division is recommending that the BTDR be granted, provide the following additional information needed by the MPC to evaluate the BTDR.

6. A brief description of the drug, the drug's mechanism of action (if known), the drug's relation to existing therapy(ies), and any relevant regulatory history. Consider the following in your response.

Plazomicin is an aminoglycoside, an antibacterial drug which kills susceptible pathogens via inhibition of protein synthesis. Similar to other aminoglycosides such as gentamicin and amikacin, it is primarily active against Gram negative pathogens. Plazomicin has been shown to be active against carbapenem resistant Enterobacteriaciae (CREs) in

[2] For a definition of available therapy refer to Guidance for Industry: "Expedited Programs for Serious Conditions—Drugs and Biologics" http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf

vitro. These difficult to treat Gram negative organisms often are resistant to multiple classes of antibacterial drugs beyond beta-lactams, including aminoglycosides. Plazomicin appears to retain activity against some of the typical mechanisms of resistance to aminoglycosides thus making it a potentially valuable treatment for CREs.

One Phase 2 and one Phase 3 trial have been completed evaluating plazomicin for the treatment of complicated urinary tract infections (cUTI). The sponsor will also seek a cUTI indication in an upcoming NDA based on successfully demonstrating noninferiority in the Phase 3 trial, (b) (4)

7. Information related to endpoints used in the available clinical data:

a. Describe the endpoints considered by the sponsor as supporting the BTDR and any other endpoints the sponsor plans to use in later trials. Specify if the endpoints are primary or secondary, and if they are surrogates.

All-cause mortality at Day 28 or significant disease related complications. (b) (4)

b. Describe the endpoint(s) that are accepted by the Division as clinically significant (outcome measures) for patients with the disease. Consider the following in your response:

(b) (4)

c. Describe any other biomarkers that the Division would consider likely to predict a clinical benefit for the proposed indication even if not yet a basis for accelerated approval.

Not applicable.

8. A brief description of available therapies, if any, including a table of the available Rx names, endpoint(s) used to establish efficacy, the magnitude of the treatment effects (including hazard ratio, if applicable), and the specific intended population. Consider the following in your response:

Ceftazidime-avibactam is approved for cUTI and cIAI and has activity against CRE in vitro and in animal models of infection. Also, several drugs are used off-label for treatment of CREs, including various combinations of colistin, a carbapenem, and tigecycline.

9. A brief description of any drugs being studied for the same indication, or very similar indication, that requested breakthrough therapy designation[3].

None.

10. Information related to the preliminary clinical evidence:

a. Table of clinical trials supporting the BTDR (only include trials which were relevant to the designation determination decision), including study ID, phase, trial design[4], trial endpoints, treatment group(s), number of subjects enrolled in support of specific breakthrough indication, hazard ratio (if applicable), and trial results.

Study ACHN-490-007 was a randomized, active controlled, open-label trial comparing plazomicin with colistin (in combination with either meropenem or tigecycline in both arms) for the treatment of subjects with bloodstream

[3] Biweekly reports of all BTDRs, including the sponsor, drug, and indication, are generated and sent to all CPMSs.
[4] Trial design information should include whether the trial is single arm or multi-arm, single dose or multi-dose, randomized or non-randomized, crossover, blinded or unblinded, active comparator or placebo, and single center or multicenter.

infection (BSI) or hospital- acquired or ventilator-assocated pneumonia (HABP/VABP) caused by CRE. (b) (4)

(b) (4)

(b) (4)

(b) (4)

b. Include any additional relevant information.

The data submitted to date should be considered preliminary as an NDA has not been submitted, and the data have not been throroughly reviewed. However, these results do appear to show an important clinical benefit over existing therapies in a serious and life-threatening indication. These efficacy results are supported by preliminary efficacy results showing that plazomicin was noninferior to an active comparator (intravenous meropenem followed by oral levofloxacin) in the treatment of complicated urinary tract infections. (b) (4)

11. Division's recommendation and rationale (pre-MPC review):

☒ GRANT :

Provide brief summary of rationale for granting:

Note, if the substantial improvement is not obvious, or is based on surrogate/pharmacodynamic endpoint data rather than clinical data, explain further.

☐DENY:

Provide brief summary of rationale for denial:

Note that not looking as promising as other IND drugs is not a reason for denial; the relevant comparison is with available (generally FDA-approved) therapy. If the Division does not accept the biomarker/endpoint used as a basis for traditional approval or accelerated approval or as a basis for providing early clinical evidence of a substantial improvement over available therapy, explain why:

12. Division's next steps and sponsor's plan for future development:

The Phase 3 study in cUTI has been completed and will be submitted as part of the NDA submission later this year. (b) (4)

13. List references, if any:

14. Is the Division requesting a virtual MPC meeting via email in lieu of a face-to-face meeting? YES ☒ NO ☐

15. Clearance and Sign-Off (after MPC review):

Grant Breakthrough Therapy Designation ☐
Deny Breakthrough Therapy Designation ☐

Reviewer Signature: {See appended electronic signature page}
Team Leader Signature: {See appended electronic signature page}
Division Director Signature: {See appended electronic signature page}

Revised 1/15/16/M. Raggio

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/s/

KAYLA J GARVIN
05/15/2017

SUMATHI NAMBIAR
05/15/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 102563

MEETING MINUTES

Achaogen, Inc.
Attention: Christine Welch
Senior Director, Regulatory Affairs
7000 Shoreline Court, Suite 371
South San Francisco, CA 94080

Dear Ms. Welch:

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

We also refer to the meeting between representatives of your firm and the FDA on December 17, 2012. The purpose of the meeting was to review End-of Phase 2 data and discuss Phase 3 development plans.

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 Carmen DeBellas, Regulatory Project Manager at (301) 796-796-1203.

Sincerely,

{See appended electronic signature page}

John J. Farley, MD, MPH
Acting Director
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: End-of-Phase 2

Meeting Date: December 17, 2012

Application Number: IND 102563
Product Name: **P**lazomicin
Indication: Complicated Urinary Tract Infection/Acute Pyelonephritis and infection due to carbapenem-resistant Enterobacteriaceae
Sponsor/Applicant Name: Achaogen, Inc.

FDA ATTENDEES
Division of Anti-Infective Products

Dr. John Farley	Acting Division Director
Dr. Katherine Laessig	Deputy Director
Dr. Daniel Rubin	Statistical Reviewer
Dr. Lynette Berkeley	Clinical Microbiology Reviewer
Dr. Ryan Owen	Clinical Pharmacology Reviewer
Dr. Kimberly Bergman	Clinical Pharmacology Team Leader
Dr. Eileen Navarro Almario	Clinical Team Leader
Dr. Amy Ellis	Pharmacology/Toxicology Reviewer
Dr. Wendelyn Schmidt	Pharmacology/Toxicology Team Leader
Dr. Fugiang Liu	Chemistry Reviewer
Dr. Carmen DeBellas	Regulatory Project Manager

SPONSOR ATTENDEES
Achaogen, Inc.

Dr. Cory Kostrub	Director Development Science
Dr. Todd Clobes	Director, Clinical Operations
Dr. Kenneth Hillan	Chief Executive Officer and Chief Medical Officer
Mr. Scott Moore	Associate Director, Regulatory Affairs
Dr. Lynn Connolly	Medical Director
Ms. Christine Welch	Vice President, Regulatory Affairs

Consultants to Achaogen:

(b) (4)	Consultant Physician
	Biostatistics Consultant

(b) (4)

(b) (4) Consultant Microbiologist

Biomedical Advanced Research and Development Authority (BARDA):

Dr.Joseph Larsen	BARDA Program Chief
Dr. Matthew Metz	BARDA Project Officer
Dr. Christopher Davis	BARDA Clinical
Ms. Shar'Ron DeDreu	Subject Matter Expert, Division of Clinical Studies, BARDA

BACKGROUND

On October 3, 2012, Achaogen submitted a request for an End-of-Phase 2 meeting. A briefing package was submitted on November 19, 2012. The Agency provided responses to the questions outlined in the briefing package on December 14, 2012, via email. The meeting served to clarify those responses outlined in the discussion section below. The preliminary response are attached at the end of the minutes.

The objectives of the End of Phase 2 meeting are:

- To review the status of the plazomicin clinical program and results from completed Phase 1 and Phase 2 clinical studies
- To obtain agreement on the proposed Phase 3 study design in serious infections due to carbapenem-resistant Enterobacteriaceae (CRE)
- To provide an overview and obtain input on the microbiology, nonclinical, and clinical plans to support a new drug application for plazomicin

DISCUSSION

Phase 3 Clinical Study Design

Questions 3–11 address the design of the Phase 3 CRE clinical study. A summary of the study is provided in Section 7.3 and a detailed protocol is provided in Appendix A.3.

(b) (4)

Division Response:

(b) (4)

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(b) (4)

PREA PEDIATRIC STUDY PLAN

Please be advised that you must submit a Pediatric Study Plan within 60 days of your scheduled end-of-Phase 2 meeting. 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. For additional guidance on submission of the PSP you may contact the Pediatric and Maternal Health Staff at 301-796-2200 or email pdit@fda.hhs.gov

DATA STANDARDS FOR STUDIES

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for investigational new drugs and product registration. Such implementation 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. CDER has produced a 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. The web page may be found at:
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm

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/s/

JOHN J FARLEY
01/23/2013