CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211109Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 104839

MEETING MINUTES

Tetraphase Pharmaceuticals, Inc.
Attention: Maria S. Gawryl, Ph.D.
Vice President, Regulatory Affairs and Quality
480 Arsenal Way, Suite 110
Watertown, MA 02472

Dear Dr. Gawryl:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Eravacycline (TP-434) for injection.

We also refer to the meeting between representatives of your firm and the FDA on October 13, 2017. The purpose of the meeting was to discuss the planned NDA submission for Eravacycline (TP-434) for injection.

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 Mr. Gregory DiBernardo, Regulatory Project Manager, at (301) 796-4063.

Sincerely,

{See appended electronic signature page}

Sumathi Nambiar, M.D., M.P.H.
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 and Time: October 13, 2017, at 10:00 AM

Meeting Location: White Oak Campus, Building 22, Room 1311

Application Number: IND 104839

Product Name: Eravacycline (TP-434) for injection

Indication: Treatment of complicated Intra-Abdominal Infections

Sponsor Name: Tetraphase Pharmaceuticals, Inc.

Meeting Chair: Sumathi Nambiar, M.D., M.P.H.

Meeting Recorder: Gregory DiBernardo

FDA ATTENDEES

Division of Anti-Infective Products

Sumathi Nambiar, M.D., M.P.H.	Director
Dmitri Iarikov, M.D., Ph.D.	Acting Deputy Director
Joseph Toerner, M.D., M.P.H.	Deputy Director for Safety
Yuliya Yasinskaya, M.D.	Clinical Team Leader
Edward A. Weinstein, M.D., Ph.D.	Clinical Reviewer
Avery Goodwin, Ph.D.	Acting Clinical Microbiology Team Leader
Kerian K. Grande Roche, Ph.D.	Clinical Microbiology Reviewer
Terry Miller, Ph.D.	Pharmacology/Toxicology Team Leader
Amy C. Nostrandt, D.V.M., Ph.D.	Pharmacology/Toxicology Reviewer
Abimbola O. Adebowale, Ph.D.	Associate Director for Labeling
*Maureen Dillon-Parker	Chief, Project Management Staff
Gregory F. DiBernardo	Regulatory Project Manager
Christopher Smith, Pharm.D., M.P.H.	Regulatory Project Manager

Division of Clinical Pharmacology IV

Zhixia (Grace) Yan, Ph.D.	Clinical Pharmacology Team Leader

Kunyi Wu, Pharm.D.	Clinical Pharmacology Reviewer
*Jason Moore, Ph.D.	Clinical Pharmacology Reviewer

Division of Biometrics IV

Christopher E. Kadoorie, Ph.D.	Biostatistics Reviewer

Office of Pharmaceutical Quality

Milton J. Sloan, Ph.D.	Product Quality Reviewer
Jonathan Swoboda	Facility Reviewer
Arwa El Hagrasy, Ph.D.	Process Reviewer
*Jason God, Ph.D.	Sterile Product Quality Reviewer
*Christina Capacci-Daniel, Ph.D.	Facility Reviewer

Office of Surveillance and Epidemiology

Ingrid N. Chapman	Risk Management Analyst/DRISK
*Sevan Kolejian, Pharm.D.	Safety Evaluator/DMEPA

***** via phone

SPONSOR ATTENDEES

Tetraphase Pharmaceuticals, Inc.

Maria Gawryl, Ph.D.	Vice President, Regulatory Affairs and Quality
Anne Fornicola, Ph.D.	Director, Project Management, Chemistry, Manufacturing, and Controls
Anile Mico	Senior Director Regulatory Affairs
Patrick Horn, M.D.	Chief Medical Officer
Larry Tsai, M.D.	Vice President, Clinical Development
Sebastian Torres	Associate Director, Sterile Manufacturing

Biomedical Advanced Research and Development Authority (BARDA)

Melissa Willens, M.S.	Regulatory Affairs Specialist
Mark Albrecht, Ph.D.	Project Officer
Robert J. Stahl, Ph.D.	Subject Matter Expert
(b) (4)	Regulatory Affairs Consultant

1.0 BACKGROUND

On July 28, 2017, Tetraphase Pharmaceuticals, Inc. (Tetraphase) submitted a type B, Pre-NDA meeting request for Eravacycline (TP-434) for injection. The Division of Anti-Infective Products (DAIP) granted the meeting for October 13, 2017. DAIP issued Preliminary Meeting Comments (attached) to the meeting package questions on October 6, 2017, via email. In a follow up email communication on October 11, 2017, Tetraphase indicated that the FDA Additional Comments 1, 2, 4, 5, and 9 and question 1a (CMC) would require further discussion at the meeting. Tetraphase noted that the other FDA responses were acceptable. Tetraphase included meeting slides in the email communication (attached).

2.0 DISCUSSION

A summary of the discussions and agreements reached during the meeting are provided below.

Additional Comments 1, 2, 4, 5, and 9:

Clinical:

To minimize information requests during the review process, we kindly request the following information be included in the NDA:

1. All newsletters and all other communications to investigational sites and national coordinators from the group(s) responsible for the conduct of your trials. Please bookmark the newsletters by date.

Meeting Discussion:
Tetraphase stated that for the Phase 3 cIAI studies they propose to include all newsletters, enrollment newsflashes, and study wide communication regarding clarification of the protocol or instruction regarding execution of the studies, from the CRO to investigational sites and national coordinators in Module 5 of the NDA under the specific study leaf node, Section 16.1.4.

2. Tables and figures featured in the clinical efficacy and safety sections (Modules 2.5 and 2.7) of the NDA should contain the following:

    a. a page number hyperlink to the location of the table or figure in the study report

Meeting Discussion:
Tetraphase will include hyperlinks to the tables and figures in the study reports for tables and figures in Modules 2.5 and 2.7.

    b. a name hyperlink to the SAS code (and/or macros) used to create the table or figure

Meeting Discussion:
Tetraphase proposed the following for the Phase 3 cIAI studies:

- To include the filename for each program used to create the table or figure at the bottom of the table or figure in the study report
- To include a SAS program level TOC detailing the CSR tables and figures and related datasets and programs with hyperlinks to the programs and macros only, in the appropriate header at the study level in Module 5 of the NDA.

    c. names of the datasets used to create the table or figure (hyperlinks are useful but not necessary).

Meeting Discussion:
For the Phase 3 cIAI studies and integrated summaries Tetraphase proposed to include the names of the datasets used to create the table or figure in the SAS program TOC in the program files of the analysis datasets for the individual study in Module 5 of the NDA.

d. For derived (analysis) datasets used to conduct your analyses, you should indicate the CRF pages and tabulation datasets from which the information was derived.

Meeting Discussion:
Tetraphase proposed the following for the Phase 3 cIAI studies:

- To include fully CDISC compliant ADaM and SDTM datasets along with their corresponding define.xml files; reviewer guides; and annotated eCRFs at the study level in Module 5 of the NDA.
- Tetraphase noted this set of standards compliant documents would allow full traceability of the data in the tables including derivation conditions back to the data originating CRFs.

Tetraphase provided examples of this plan in their slide presentation (see slides 8-12).

Tetraphase confirmed that the table of contents for the SAS program would be located at the individual study level.

4. Narratives for all patients who underwent any surgical intervention (with the type of surgery), died, experienced SAEs, discontinued study medication, or withdrew from the study.

Meeting Discussion:
For the Phase 3 cIAI studies Tetraphase plans to include narratives for all patients who underwent surgical intervention after the initial surgery, died, experienced SAEs, discontinued study medication due to an AE, or withdrew from the study due to an AE in the Integrated Summary of Safety in Module 5 of the NDA.

5. Tables with line listings of individual patients with outcomes of death, discontinuation (D/C) of drug, discontinuation from the study, and withdrawal from the study with study ID, patient ID, demographics, study arm, study day of D/C of drug or from study, or withdrawal, reason for this disposition, AE (if present), AE severity.

Meeting Discussion:
For the Phase 3 cIAI studies Tetraphase plans to submit a line-listing of individual patients with outcomes of death, discontinuation of drug (regardless of reason), discontinuation/withdrawal from the study (regardless of reason) with study ID, patient ID, demographics, study arm, study day of D/C, reason for disposition, AE (if present), AE severity with the Integrated Summary of Safety in Module 5 of the NDA.

Clinical Microbiology:

9. Please submit a list of clinical microbiology studies including the titles, report numbers, and the location within the submission.

Meeting Discussion:
Tetraphase proposed to include the list of clinical microbiology studies including the titles, report numbers, and the location within the submission in Module 5.2. The list would include all studies described in the clinical microbiology section of 2.7.2.4.

FDA stated that the Sponsor's proposals noted above to address Additional Comments 1, 2, 4, 5, and 9 are acceptable.

Chemistry, Manufacturing, and Controls (CMC):

Q1a: (b) (4)

FDA Response:

(b) (4)

(b) (4)

Additional Meeting Discussion Points:

- FDA stated that the Initial Pediatric Study Plan (iPSP) is under review and will be sent to the Pediatric Review Committee (PeRC) in late October 2017.
    - **Post meeting note:** FDA sent written responses to Tetraphase on November 2, 2017.
- FDA requested that Tetraphase submit the following information in the NDA:
    - The PK and PK/PD analysis/parameter datasets in .xpt format for Phase 1 - 3 studies (data point and/or subjects that have been excluded from the analysis should be flagged and maintained in the datasets; the flag for exclusion should be clearly explained in the define.pdf file);
    - The NONMEM control streams of the base and final models for the population PK analysis;
    - The codes (R, SAS, etc.) for PK/PD analyses;
    - The output files for the final population PK and PK/PD models if applicable; the standard model diagnostic plots, tables with parameter estimates, and a description of the clinical application of modeling results;
    - Include a USUBJID (unique subject ID) column to all the population PK and PK/PD datasets so that these datasets could be linked to the corresponding clinical analysis datasets.
- (b) (4)
- FDA inquired why there were only a few U.S. sites in the cIAI trials.
    - Tetraphase stated they had a fair number of U.S. sites at the beginning of the trial, but enrollment was very slow.
    - The need for an experimental therapy is not pressing as patients in the U.S. expect very good standard of care.
- FDA inquired about the similarities and differences between the two cIAI trials.
    - Tetraphase stated the second trial used many of the same clinical sites, so the study populations were relatively similar, but did note a small difference in the proportion of patients with appendicitis. The sponsor will comment on the differences between the trials in the NDA submission.
- Tetraphase stated that their planned NDA submission date was December 31, 2017.

- FDA reminded Tetraphase that an iPSP would need to be agreed to prior to submission of the NDA.

3.0 OTHER IMPORTANT MEETING INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed. FDA emphasized that Tetraphase should follow published FDA guidance for additional details on requirements for content and format of a complete NDA submission.
- All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.
- A preliminary discussion was not held on the need for a REMS, other risk management actions and, where applicable, the development of a Formal Communication Plan and it was concluded that this will be determined upon NDA review.
- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. FDA reminded Tetraphase of the intention to submit a complete application. No agreements for late submission of application components were made.

In addition, if a chemistry pre-submission meeting is planned then a summary of agreements reached at that meeting will be documented in the respective meeting minutes.

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. As of **May 5, 2017,** the following submission types: **NDA, ANDA,** and **BLA** must be submitted in eCTD format. **Commercial IND** and **Master File** 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 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.

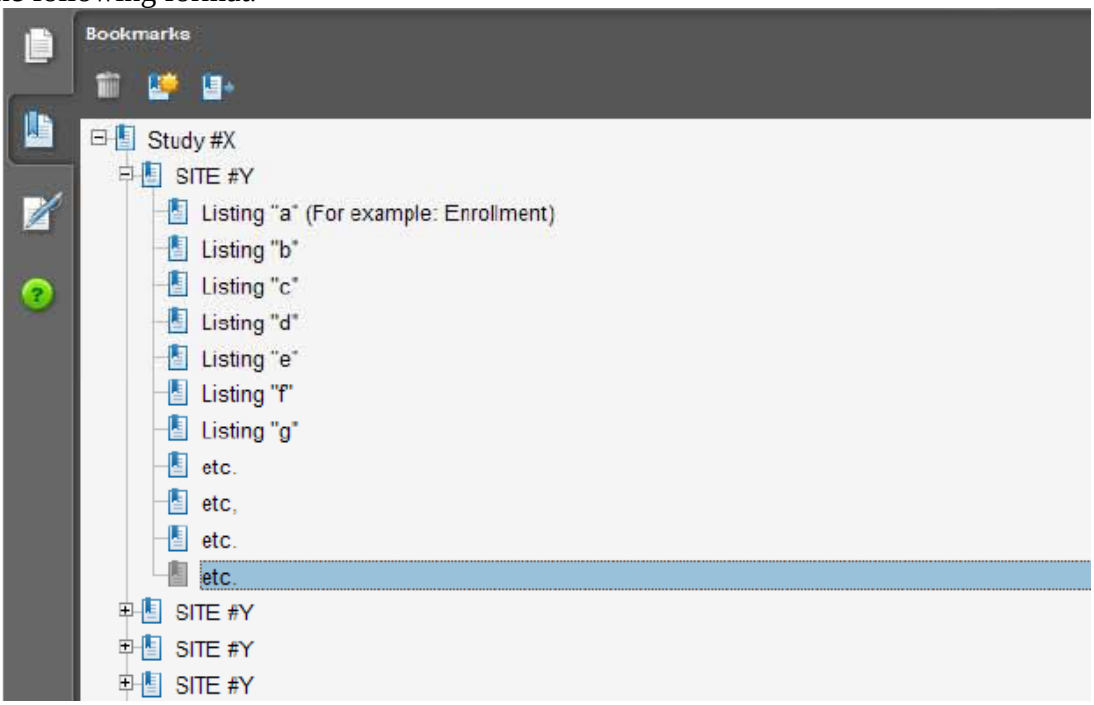
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere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

4.0 ISSUES REQUIRING FURTHER DISCUSSION

None.

5.0 ACTION ITEMS

Action Item/Description	Owner	Due Date
Issue Meeting Minutes	FDA	November 12, 2017
Submit meeting slides officially to IND	Sponsor	Within 1 month of the meeting

6.0 ATTACHMENTS

- October 11, 2017, Tetraphase email communication with slide presentation
- FDA October 6, 2017, Preliminary Meeting Responses

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

/s/

SUMATHI NAMBIAR
11/07/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 104839

MEETING MINUTES

Tetraphase Pharmaceuticals, Inc.
c/o [redacted] (b) (4)
Attention: [redacted] (b) (4)
Regulatory Affairs Consultant
14 Edinburgh Drive
Randolph, NJ 07869

Dear Dr. McCormack:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Eravacycline (TP-434).

We also refer to the teleconference between representatives of your firm and the FDA on January 25, 2013. The purpose of the meeting was to discuss the Phase 3 program for eravacycline for the treatment of complicated intra-abdominal infections [redacted] (b) (4)

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

If you have any questions, call Mr. Gregory DiBernardo, Regulatory Project Manager at (301) 796-4063.

Sincerely,

{See appended electronic signature page}

John J. Farley, M.D., M.P.H.
Acting 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: B

Meeting Category: End-of-Phase 2

Meeting Date and Time: January 25, 2013 at 11:00 A.M.

Meeting Location: Teleconference

Application Number: 104839

Product Name: Eravacycline (TP-434).

Indication: Treatment of complicated intra-abdominal infections (b) (4)

Sponsor Name: Tetraphase Pharmaceuticals, Inc.

Meeting Chair: John J. Farley, M.D., M.P.H.

Meeting Recorder: Gregory F. DiBernardo

FDA ATTENDEES

Division of Anti-Infective Products (DAIP)

John J. Farley, M.D., M.P.H.	Acting Director
Katherine A. Laessig, M.D.	Deputy Director
John J. Alexander, M.D., M.P.H.	Clinical Team Leader
Dmitri Iarikov, M.D., Ph.D.	Medical Officer
Lynette Berkeley, Ph.D.	Acting Clinical Microbiology Team Leader
Kerian K. Grande Roche, Ph.D.	Clinical Microbiology Reviewer
Wendelyn Schmidt, Ph.D.	Pharmacology/Toxicology Team Leader
Amy C. Nostrandt, D.V.M., Ph.D.	Pharmacology/Toxicology Reviewer
Maureen P. Dillon-Parker	Chief, Project Management Staff
Gregory F. DiBernardo	Regulatory Project Manager

Division of Clinical Pharmacology IV (DCP IV)

Kimberly L. Bergman, PharmD.	Clinical Pharmacology Team Leader
Ryan Owen, Ph.D.	Clinical Pharmacology Reviewer
Yang He, Ph.D.	Clinical Pharmacology Reviewer

Division of Biometrics IV (DBIV)

Thamban Valappil, Ph.D.	Biostatistics Team Leader
Scott S. Komo, Dr.PH.	Biostatistics Reviewer

Office of New Drug Quality Assessment (ONDQA)

Dorota M. Matecka, Ph.D.	Chemistry, Manufacturing, and Controls (CMC) Lead
Lin Qi, Ph.D.	CMC Product Quality Reviewer

SPONSOR ATTENDEES

Tetraphase Pharmaceuticals, Inc.

Guy Macdonald, BSc.	President and Chief Executive Officer
Patrick Horn, M.D., Ph.D.	Chief Medical Officer
Joyce Sutcliffe, Ph.D.	Senior Vice President Biology
Magnus Ronn, Ph.D.	Vice President CMC
Melissa Shamgochain	Project Manager
(b) (4)	Regulatory Affairs Consultant
(b) (4)	Director, Biological and Medical Services

HHS/ASPR/BARDA

Debra Yeskey, Pharm.D.	Director, Regulatory and Quality Affairs Division
Joseph Larsen, Ph.D.	Branch Chief
Melissa Stundick, Ph.D.	Project Officer
(b) (4)	(b) (4)

1.0 BACKGROUND

On October 23, 2012, Tetraphase Pharmaceuticals, Inc., c/o Creative Regulatory Solutions, LLC (Tetraphase) submitted an a type B meeting End-of-Phase 2 meeting request to discuss the Phase 3 program for eravacycline for the treatment of complicated intra-abdominal infections (b) (4) . In response to the submission, a meeting was granted for January 25, 2013. Tetraphase submitted a meeting package on December 26, 2012. FDA Preliminary Meeting Comments were issued to Tetraphase on January 22, 2013. A January 23, 2013, Tetraphase email communication informed FDA that following their review of the FDA Preliminary Meeting Comments they requested a change from a face-to-face meeting to a teleconference. Tetraphase provided a set of slides for the teleconference via a January 24, 2013, email communication (slides attached to minutes). The minutes below include Tetraphase's original questions in **bold** font, FDA's Preliminary Meeting Comments responses in normal font, and meeting discussion and additional recommendations in *italic* font.

2. DISCUSSION

Following introductions from representatives of Tetraphase and FDA the meeting began with a discussion of the questions listed below.

Microbiology and Nonclinical

1. **Does the Division agree that the microbiology studies, including the animal models of infection that have been completed and planned, support the Phase 3 development program and New Drug Application for eravacycline**?

FDA Response:
The completed and planned animal models are appropriate to support the Phase 3 program and NDA for eravacycline.

No Further discussion, Tetraphase agrees (slide #2).

2. **Does the Division agree that the completed ADME, safety pharmacology, and toxicology studies, plus the studies to be submitted to the IND prior to the initiation of the Phase 3 trials (*i.e.*, embryo-fetal development toxicity studies in the rat and rabbit) are adequate to support the Phase 3 program with eravacycline?**

FDA Response:
Definitive comments cannot be made regarding the adequacy of studies that have not been submitted. Final study reports for completed studies should be submitted for Agency review. Based on the summary data provided, there are a few considerations that should be taken into account:

- First, interspecies dose comparisons should be made based on body surface area-normalized doses or on steady state AUC (if available), not on nominal doses. Conversion factors can be found in the FDA Guidance for Industry: Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers. The appropriate comparator for the highest proposed clinical dose would be the human equivalent dose (HED) for the NOAELs in the nonclinical studies. This applies to the (b) (4) metabolite doses as well; comparisons should be made between exposure or HED at NOAEL doses.
- Secondly, a full set of developmental and reproductive toxicology studies should be performed (i.e., fertility and embryonic development and peri-/post-natal development, in addition to the proposed embryo-fetal toxicity studies). As long as pregnant women are adequately excluded in Phase 3 clinical trials, it may be possible to defer the peri-/post-natal development study until the NDA submission.

Discussion (slides #3 to #6):
FDA requested that animal range finding and animal ADME study reports be submitted to the IND. Tetraphase agreed to submit the reports to the IND. Tetraphase also stated that the requested safety margins for each toxicology species would be provided in the NDA.

Tetraphase stated that it plans to submit the results of the GLP-compliant embryo-fetal development studies in both rat and rabbit species prior to the start of the Phase 3 trials. Tetraphase stated that FDA had been provided the study design for the GLP-compliant rat embryo-fetal development study that includes the qualification of TP-6208 (metabolite) by exogenous addition in combination with eravacycline. Once feedback is received from FDA regarding the design of the rat study, Tetraphase plans to execute the embryo-fetal reproductive toxicology studies and submit the results prior to initiating the Phase 3 studies.

Tetraphase stated that they proposed in the meeting package to conduct the male fertility study concurrently with Phase 3 (b) (4).

(b) (4)

(b) (4)

FDA stated that a female fertility study would be required and that the male and female fertility studies could be conducted concurrently with the Phase 3 studies.

Post Meeting note: On January 28, 2013, FDA sent Tetraphase a correspondence that stated in accordance with FDA Guidance M3 (R2), the male fertility study in the rat should be conducted prior to Phase 3 studies.

(b) (4)

FDA stated that the specific effects of eravacycline should be evaluated. A peri-/post-natal study in the rat would need to be conducted and the results need to be submitted to the NDA. Tetraphase agreed to submit the results of the study to the NDA.

3. Does the Division agree that the ADME and toxicology studies planned to be submitted in the NDA are adequate to support the filing of a marketing application for eravacycline?

FDA Response:
No. The standard support for a marketing application for an antibacterial drug would be 3-month toxicology studies in 2 species. As discussed above, a full set of developmental and reproductive toxicology studies should be submitted.

Discussion (slide #7):
Tetraphase agreed to conduct 13-week toxicology studies by the intravenous (IV) route of administration in the rat and cynomologous monkey prior to submission of the NDA.

4. (b) (4)

FDA Response:
(b) (4)

No further discussion, Tetraphase agrees (slide #8).

Clinical

5. Does the Division agree that the Phase 1 clinical pharmacology program, the planned Thorough QTc study, and the results from the Phase 2 study in cIAI support proceeding to Phase 3 studies in cIAI (b) (4)?

FDA Response:
The Phase 1 and Phase 2 data support the initiation of the Phase 3 trials. However, we urge you to consider completion of the renal and hepatic impairment trials prior to Phase 3 so that any possible dose adjustments can be implemented and evaluated.

Discussion (slide # 9):
Tetraphase stated that studies in patients with renal impairment and hepatic impairment are planned to be conducted in parallel with the Phase 3 studies. Until studies in these special populations are complete, patients with renal and hepatic impairment would be excluded from the Phase 3 studies. Once the studies in these special populations are complete, the inclusion criteria for the Phase 3 studies would be amended to allow enrollment of patients with renal and hepatic impairment.

FDA stated that it was acceptable to conduct the renal and hepatic impairment studies concurrently with Phase 3; however, FDA also suggested that some patients with renal and hepatic impairment should be enrolled in the Phase 3 studies once the renal and hepatic impairment studies were completed.

6. Does Division agree that the dose selection and design of the Phase 3 clinical studies in cIAI (b) (4) are acceptable to support an NDA filing? We have proposed dosing eravacycline at 1.0 mg/kg q12h in the pivotal cIAI study (b) (4)

FDA Response:
The proposed dose for the cIAI trial is acceptable as it has been successfully evaluated in a Phase 2 clinical trial. (b) (4)

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No further discussion, Tetraphase agrees (slide #21).

9. Does the Division agree that the outline of the pediatric development plan, (b) (4)

FDA Response:
No, it is not acceptable. (b) (4)

Discussion (slide #22 to #23):
Tetraphase stated that a full pediatric plan including study outlines, timelines for protocol submission, and estimated size of the pediatric safety database would be developed and submitted to FDA for review prior to the initiation of Phase 3 studies. FDA stated this approach was acceptable.

CMC

10. Does the Division agree that completed and planned physicochemical characterization studies of the API is acceptable to support an NDA for an IV product?

FDA Response:
The planned physicochemical characterization studies of the API appear reasonable to support an NDA. The acceptability of the physicochemical characterization will be evaluated during the NDA review.

No further discussion, Tetraphase agrees (slide #24).

11. Does the Division agree that the release and stability tests for the drug substance and drug product are acceptable to support the Phase 3 studies and the NDA?

FDA Response:
The release and stability tests for the drug substance and drug product are acceptable to support the Phase 3 studies. However, there is insufficient information to evaluate if these tests are acceptable to support the NDA. Based on the available information, we have the following recommendations:

(b) (4)

No further discussion, Tetraphase agrees (slide #25).

12. (b) (4)

FDA Response:

(b) (4)

13. Does the Division agree that the proposed regulatory starting materials are acceptable for filing in an NDA?

FDA Response:
No, the Division does not agree with the proposed TP-034 starting material. (b) (4)

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Discussion (slide #32):

Additional FDA Requests:

Clinical Microbiology:

1. Do the major TP-434 metabolites have any antimicrobial activity?

Discussion (slide #33):
Tetraphase stated TP-6208 does not have pharmacologically useful antibacterial activity.

Clinical Pharmacology:

2. It was noted in the meeting package that TP-434 was metabolically stable when incubated with cryopreserved hepatocytes, and that a major metabolite (TP-6208) was later discovered in the human multiple ascending dose study. Please confirm that the metabolic stability observed with the cryopreserved hepatocytes was a result of actual stability and not an inability to detect the TP-6208 metabolite.

Discussion (slide #34):
Tetraphase stated that it confirms TP-6208 could have been detected in this assay if it were present.

3.0 OTHER IMPORTANT INFORMATION

PREA REQUIREMENTS

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit a Pediatric Study Plan (PSP) within 60 days of an End-of-Phase 2 (EOP2) meeting held on or after November 6, 2012. If an EOP2 meeting occurred prior to November 6, 2012 or an EOP2 meeting will not occur, then:

- if your marketing application is expected to be submitted prior to January 5, 2014, you may either submit a PSP 210 days prior to submitting your application or you may submit a pediatric plan with your application as was required under the Food and Drug Administration Amendments Act (FDAAA).
- if your marketing application is expected to be submitted on or after January 5, 2014, the PSP should be submitted as early as possible and at a time agreed upon by you and FDA. We strongly encourage you to submit a PSP prior to the initiation of Phase 3 studies. In any case, the PSP must be submitted no later than 210 days prior to the submission of your application.

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, including a PSP Template, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm . In addition, 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

ABUSE POTENTIAL ASSESSMENT

Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential

and a proposal for scheduling will be required at the time of the NDA submission [21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of your NDA submission, see the draft guidance for industry, "Guidance for Industry Assessment of Abuse Potential of Drugs", available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There are no issues that require further discussion at this time.

5.0 ACTION ITEMS

Action Item/Description	Owner	Due Date
Issue Meeting Minutes	FDA	February 24, 2013

6.0 ATTACHMENTS AND HANDOUTS

Tetraphase's slide set

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

/s/

JOHN J FARLEY
04/25/2013