CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

217686Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 122772

MEETING PRELIMINARY COMMENTS

Idorsia Pharmaceuticals, Ltd.
Attention: Bradford Kirk Perry, PharmD, RPh
Director, US Drug Regulatory Affairs
1820 Chapel Avenue, West
Suite 150
Cherry Hill, NJ 08002

Dear Dr. Perry:

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for aprocitentan (ACT-132577).

We also refer to your September 30, 2022, correspondence requesting a meeting to gain alignment on the analyses of specific safety topics proposed for inclusion in your planned aprocitentan NDA.

Our preliminary responses to your meeting questions are enclosed. You should provide, to the Regulatory Project Manager, an electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

In accordance with FDA policy, you should not make audio or visual recordings of the discussion at this meeting. Consistent with 21 CFR 10.65(e), the official record of this meeting will be the FDA-generated minutes.

If you have any questions, please call me at (240) 402-6187.

Sincerely,

{See appended electronic signature page}

Sabry Soukehal, RAC
Senior Regulatory Health Project Manager
Cardiology and Nephrology
Division of Regulatory Operations for Cardiology, Hematology, Endocrinology, and Nephrology
Office of Regulatory Operations
Center for Drug Evaluation and Research

ENCLOSURE: Preliminary Meeting Comments

U.S. FOOD & DRUG ADMINISTRATION

PRELIMINARY MEETING COMMENTS

Meeting Type:	B
Meeting Category:	Pre-NDA
Meeting Date and Time:	November 28, 2022; 03:00 PM – 04:00 PM (Eastern Time)
Meeting Location:	Teleconference
Application Number:	122772
Product Name:	Aprocitentan (ACT-132577)
Indication:	Treatment of hypertension
Sponsor Name:	Idorsia Pharmaceuticals, Ltd.
Regulatory Pathway:	505(b)(1) of the Federal Food, Drug, and Cosmetic Act

Introduction:

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for November 28, 2022, from 03:00 PM to 04:00 PM, via teleconference between Idorsia Pharmaceuticals, Ltd. and the Division of Cardiology and Nephrology. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact the regulatory project manager (RPM)). If you choose to cancel the meeting, this document will represent the official record of the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda. It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the pre-meeting communications are considered sufficient to answer the questions. Contact the RPM if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

1.0 BACKGROUND

Aprocitentan (ACT-132577), an active metabolite of macitentan, is an orally active dual endothelin ET_A/ET_B receptor antagonist. It is being developed by Idorsia Pharmaceuticals Ltd. (Idorsia, the Sponsor) for the treatment of adults with difficult-to-control hypertension, defined as "failure to lower blood pressure (BP) to defined target levels with optimal doses of an appropriate regimen of three antihypertensive drugs from different classes, including a diuretic." Idorsia is not developing aprocitentan as a first-line monotherapy, but rather on a background of other antihypertensive therapies.

Previous regulatory interactions with the Division of Cardiology and Nephrology (DCN) include a topline results meeting on September 22, 2022, a meeting on June 2, 2022 to discuss Idorsia's proposed (b) (4) (REMS) for aprocitentan, a pre-NDA meeting planned for March 14, 2022 that was cancelled by Idorsia on March 11, 2022 after receiving DCN's meeting preliminary comments on March 9, 2022, an End-of-Phase 2 meeting on September 15, 2017, an initial IND submission on October 17, 2014, and a pre-IND meeting on July 28, 2014.

During the topline results meeting, DCN stated, "*The main issue however relates to the safety database. Specifically, DCN noted that novel antihypertensive agents have generally had safety databases of thousands of patients at the time of initial approval and the existing safety database for aprocitentan is much smaller. DCN was specifically concerned about risks of peripheral edema/fluid retention, heart failure, hepatotoxicity, and teratogenicity—some of which are clear from the existing, modest safety database.*"

This meeting was requested by Idorsia to discuss the safety issues raised by DCN during the topline results meeting and align with the Division on the appropriate safety analyses to be included in the aprocitentan NDA.

2.0 DISCUSSION

Question 1: Acceptability of safety analyses for the NDA
Does the Division agree that the proposed presentation of analyses for the specific safety topics support the review of the aprocitentan NDA for the treatment of hypertension?

FDA Response: We agree that your proposed safety analyses seem reasonable and that the safety evaluation should focus on the data from the pivotal phase 3 study, which evaluated aprocitentan as add-on therapy in patients with difficult-to-control hypertension. At the time of NDA submission, please also submit the following:

- The details of the methodology underlying your systematic literature review and real-world evidence study, along with the results of these studies.
- All code and datasets used to create analyses found in the main sections of the phase 3 trial clinical study report.

- Kaplan-Meier time to event analysis datasets and code to evaluate adverse events of special interest (AESIs) up to 36 weeks ("collating double-blind Part 1 and single-blind Part 2" as you propose in your briefing document). Please include information on your criteria for censoring subjects in the analyses and ensure that the submitted datasets would support analyses of participants as randomized in Part 1 and as treated in Part 1.
- Dataset that contains a list of all subjects for whom you submitted a case report form (CRF), narrative, or adjudication packages. The dataset should contain four variables with an indicator for whether each item was submitted.
- A table set up similarly to the dataset requested in above, but with a hyperlink to the respective document. The table could be further organized by reason for narrative submission (subjects with cardiovascular events of interest, subjects with hepatic laboratory anomalies of interest, etc.).

We note the potential challenges associated with interpreting the safety data from the single-blind period of your phase 3 trial and acknowledge your proposal to use external data including a systematic literature review and a real-world evidence study to enable an indirect comparison with the incidence rate observed with aprocitentan for heart failure hospitalization and major adverse cardiac event(s) (MACE) in your phase 3 trial. While the proposed approach may provide insight into the background rate of the events of interest in the target patient population, it is unlikely that such comparisons will aid in a meaningful way to the characterization of aprocitentan's risks in the target population.

3.0 OTHER IMPORTANT MEETING INFORMATION

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[1] and Pregnancy and Lactation Labeling Final Rule[2] 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

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

- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

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

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

MANUFACTURING FACILITIES

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

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

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

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

Corresponding names and titles of onsite contact:

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

To facilitate our facility assessment and inspectional process for your marketing application, we refer you to the instructional supplement for filling out Form FDA 356h[3] and the guidance for industry, *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers*[4]. Submit all related manufacturing and testing facilities in eCTD Module 3, including those proposed for commercial production and those used for product and manufacturing process development.

Office of Scientific Investigations (OSI) Requests

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

[3] https://www.fda.gov/media/84223/download
[4] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/identification-manufacturing-establishments-applications-submitted-cber-and-cder-questions-and

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*.[5]

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

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

/s/

SABRY SOUKEHAL
11/23/2022 02:09:15 PM

IND 122772

MEETING PRELIMINARY COMMENTS

Idorsia Pharmaceuticals, Ltd.
Attention: Bradford Kirk Perry, PharmD, RPh
Director, US Regulatory Affairs
1820 Chapel Avenue, West
Suite 150
Cherry Hill, NJ 08002

Dear Dr. Perry:

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for aprocitentan (ACT-132577).

We also refer to your January 19, 2022, correspondence, received January 19, 2022, requesting a meeting to obtain FDA's input on the acceptability and sufficiency of the nonclinical, CMC, and clinical data package ahead of your NDA submission for aprocitentan for the treatment of hypertension.

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

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

If you have any questions, please call me at (240) 402-6187.

Sincerely,

{See appended electronic signature page}

Sabry Soukehal, RAC
Senior Regulatory Health Project Manager
Cardiology and Nephrology
Division of Regulatory Operations for Cardiology, Hematology, Endocrinology, and Nephrology
Office of Regulatory Operations
Center for Drug Evaluation and Research

ENCLOSURE: Preliminary Meeting Comments

PRELIMINARY MEETING COMMENTS

Meeting Type:	B
Meeting Category:	Pre-NDA
Meeting Date and Time:	March 14, 2022; 12:00 PM – 1:00 PM (Eastern Time)
Meeting Location:	Teleconference
Application Number:	122772
Product Name:	Aprocitentan (ACT-132577)
Indication:	Treatment of hypertension
Sponsor Name:	Idorsia Pharmaceuticals, Ltd.
Regulatory Pathway:	505(b)(1) of the Federal Food, Drug, and Cosmetic Act

Introduction:

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for March 14, 2022, from 12:00 PM to 1:00 PM via teleconference between Idorsia Pharmaceuticals, Ltd. and the Division of Cardiology and Nephrology. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact the regulatory project manager (RPM)). If you choose to cancel the meeting, this document will represent the official record of the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the pre-meeting communications are considered sufficient to answer the questions. Contact the RPM if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

1.0 BACKGROUND

Aprocitentan (ACT-132577), an active metabolite of macitentan, is an orally active dual endothelin ET_A/ET_B receptor antagonist. It is being developed by Idorsia Pharmaceuticals Ltd. (Idorsia, the Sponsor) for the treatment of adult patients with difficult-to-control hypertension, defined as "failure to lower blood pressure (BP) to defined target levels with optimal doses of an appropriate regimen of three antihypertensive drugs from different classes, including a diuretic." Idorsia is not developing aprocitentan as a first-line monotherapy, but rather on a background of other antihypertensive therapies.

Notable regulatory interactions with the Division of Cardiology and Nephrology (DCN) include a pre-IND meeting on July 28, 2014, an initial IND submission on October 17, 2014, and an End-of-Phase 2 meeting on September 15, 2017. DCN provided feedback on several aspects of product development via advice letters dated August 05, 2017, January 12, 2018, November 23, 2018, April 29, 2019, July 17, 2019, November 13, 2019, June 15, 2020, November 4, 2020, and December 02, 2021. IND ownership changed from Actelion Pharmaceuticals to Idorsia on June 19, 2017.

Idorsia completed nine phase 1 studies including one evaluating the effect of aprocitentan on QT interval prolongation. A phase 2 study (Protocol AC-080A201) which investigated 4 doses of aprocitentan (5, 10, 25, and 50 mg) in 490 patients with essential hypertension was also completed.

Idorsia discussed with DCN the design of the pivotal phase 3 study described as a multi-center, blinded, randomized, parallel-group, phase 3 study with aprocitentan in subjects with resistant hypertension (PRECISION, study ID-080A301). One of the objectives of the study was to evaluate the safety and tolerability of aprocitentan in patients with difficult-to-control hypertension.

The objective of this pre-NDA meeting is to obtain the FDA's input and guidance on the acceptability and sufficiency of the nonclinical, CMC, and clinical data package ahead of a NDA submission for aprocitentan for the treatment of hypertension.

2.0 DISCUSSION

2.1. Nonclinical

Question 1: Idorsia proposes to submit datasets for the carcinogenicity studies performed with macitentan and available in legacy format and for study T-14.072, for which SEND datasets were already generated and submitted to FDA. Legacy format reports will be submitted for all applicable macitentan and aprocitentan nonclinical studies as all were initiated prior to 17 December 2016. Does the Division agree with the submission of legacy format reports?

FDA Response: You proposed to submit legacy format nonclinical study reports following current FDA Study Data Technical Conformance Guide. We have no objection to your proposal, assuming nonclinical sections are submitted per eCTD guidelines. In addition, we expect that functioning hypertext links will be provided in both summary sections and study listings, and full study reports will include study summaries, tables, graphs, etc., as appropriate.

In the meeting package Table 1 and Appendix 2, carcinogenicity studies and developmental and reproductive toxicology studies with macitentan submitted for NDA 204410 (Opsumit) are included in the list of nonclinical studies to support your NDA. Please clarify if you have the right of reference to the data of NDA 204410 and provide LOA (Letter of Authorization) accordingly. If you plan to submit the full study reports with macitentan in your NDA, please indicate that they are the same studies referenced to NDA 204410.

For pivotal nonclinical toxicology studies, including the referenced studies with macitentan, provide plasma exposures to aprocitentan (free and total), and include exposure multiples when compared to the clinical exposures at the maximum recommended human dose.

Question 2: Idorsia conducted a dedicated TQT study, study ID-080-108, to evaluate the effect of aprocitentan on cardiac repolarization. The design of this study was agreed to by the FDA IRT for QT studies. Digital ECG waveforms with annotations in electronic format (XML) following the HL7 aECG standard will be submitted through the FDA Electronic Submissions Gateway for this study only. Does the Division agree?

FDA Response: Yes, we agree. You can find information about submitting clinical trial datasets and annotated ECG waveforms for evaluation of QT/QTc interval prolongation in the Interdisciplinary Review Team for Cardiac Safety Studies (formerly QT-IRT) webpage at https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/interdisciplinary-review-team-cardiac-safety-studies-formerly-qt-irt.

2.2. Clinical

Question 3: Idorsia will provide CRFs and narratives for the phase 2 study AC-080A201 and the phase 3 study ID-080A301 for all subjects who died, experienced an SAE, had confirmed and unconfirmed MACE-plus (for ID-080A301 only), and prematurely discontinued treatment due to a TEAE. Does the Division agree with this approach?

FDA Response: Your proposal is acceptable to provide CRFs and narratives for the phase 2 AC-080A201 and phase 3 ID-080A301 studies for all subjects who died, experienced an SAE, had confirmed and unconfirmed MACE-plus events (for ID-080A301 only), and prematurely discontinued treatment due to a TEAE; however,

please note that adjudication packages for selected cases could be requested by the Agency as part of the review process.

Question 4: It is expected that approximately 1270 subjects will be exposed to aprocitentan across the entire development program, including approximately 627 subjects treated for 24 weeks and approximately 194 subjects treated for 48 weeks with aprocitentan 25 mg in study ID-080A301. Does the Division agree this safety database is adequate to support the filing of an NDA for aprocitentan for the treatment of hypertension?

FDA Response: The projected number of subjects that are expected to be exposed to aprocitentan (1270) and the duration of exposure across your development program is acceptable to support the filing of your NDA and adequate to perform a safety assessment of your drug product.

Question 5: Idorsia proposes no pooling of efficacy findings from the pivotal phase 3 study ID-080A301 and the phase 2 study AC-080A201 in the SCE. Does the Division agree?

FDA Response: Your proposal not to pool efficacy findings from the pivotal phase 3 study ID-080A301 and the phase 2 study AC-080A201 is acceptable.

Question 6: The efficacy data to support the use of aprocitentan in the treatment of hypertension will be presented and discussed in the Module 2 SCE in sufficient detail to serve as the narrative portion of the ISE. The datasets, tables, and figures to support the SCE will come from the individual study reports because no pooling across studies is proposed and, therefore, no ISE is planned for the NDA submission. Does the Division agree that a detailed SCE is sufficient?

FDA Response: Your plan for the SCE (Module 2) in your NDA submission to serve as the ISE and include datasets, tables, and figures from individual study reports describing your efficacy data supporting the use of aprocitentan for the treatment of hypertension is reasonable.

Question 7: Idorsia considers the safety generated from the single pivotal phase 3 study ID-080A301 to provide the main evidence for the safety profile of aprocitentan in the treatment of patients with hypertension. Idorsia proposes no pooling of safety data across studies in the SCS and ISS. Does the Division agree?

FDA Response: Please see our response to Question 4. However, we recognize the heterogeneity between your phase 2 and phase 3 population and therefore agree with your approach to the safety evaluation of aprocitentan focusing on your phase 3 data as the main source of evidence for the safety profile, because the phase 3 subject population characterizes the target patient population for whom aprocitentan will be prescribed.

2.3. Regulatory

Question 8: Does the Division agree that the proposed content and eCTD format of the NDA, as outlined in the eCTD Content Outline and discussed in the pre-NDA briefing document, are acceptable?

FDA Response: The proposed content and eCTD format of your NDA outlined in the pre-NDA briefing document (page 15) is acceptable.

Question 9: Idorsia, as the Sponsor and IND application holder, is conducting the phase 3 development of aprocitentan and will submit the NDA for the treatment of patients with hypertension. Per the agreement between Idorsia and Janssen Biotech, Inc. ("Janssen"), Janssen will have the sole worldwide commercialization rights to aprocitentan. Upon a positive action taken on the NDA, (b) (4) . Does the Division agree?

FDA Response: No, we do not agree. The labeling, if approved, will need to reflect the information in the NDA at the time of approval.

2.4. Additional comments:

At this time, the Office of New Drugs and the Office of Surveillance and Epidemiology have insufficient information to determine whether a risk evaluation and mitigation strategy (REMS) will be necessary to ensure that the benefits of the drug outweigh the risks, and if it is necessary, what the required elements will be. Of note, other products within the same drug-class have a REMS to mitigate the risk of embryo-fetal toxicity. We encourage you to submit a proposed REMS with your application or submit rationale for why you believe a REMS is not needed. We will determine the need for a REMS during the review of your application.

3.0 OTHER IMPORTANT MEETING INFORMATION

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.

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.

We acknowledge receipt of your amendment dated February 21, 2018, containing your Agreed Initial Pediatric Study Plan (iPSP).

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[1] and Pregnancy and Lactation Labeling Final Rule[2] websites, which include:

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

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to

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

the draft guidance for industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format*.

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

DISCUSSION OF SAFETY ANALYSIS STRATEGY FOR THE ISS

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

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

- Description of all trials to be included in the ISS. Please provide a tabular listing of clinical trials including appropriate details.
- ISS statistical analysis plan, including proposed pooling strategy, rationale for inclusion or exclusion of trials from the pooled population(s), and planned analytic strategies to manage differences in trial designs (e.g., in length, randomization ratio imbalances, study populations, etc.).
- For a phase 3 program that includes trial(s) with multiple periods (e.g., double-blind randomized period, long-term extension period, etc.), submit planned criteria for analyses across the program for determination of start / end of trial period (i.e., method of assignment of study events to a specific study period).
- Prioritized list of previously observed and anticipated safety issues to be evaluated, and planned analytic strategy including any SMQs, modifications to specific SMQs, or sponsor-created groupings of Preferred Terms. A rationale supporting any proposed modifications to an SMQ or sponsor-created groupings should be provided.

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

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)				

To facilitate our facility assessment and inspectional process for your marketing application, we refer you to the instructional supplement for filling out Form FDA 356h[3] and the guidance for industry, *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers*[4]. Submit all related manufacturing and testing facilities in eCTD Module 3, including those proposed for commercial production and those used for product and manufacturing process development.

[3] https://www.fda.gov/media/84223/download

[4] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/identification-manufacturing-establishments-applications-submitted-cber-and-cder-questions-and

Office of Scientific Investigations (OSI) Requests

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

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*.[5]

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

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

/s/

SABRY SOUKEHAL
03/09/2022 08:49:31 AM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug
Administration Silver
Spring MD 20993

IND 122772

MEETING MINUTES

Idorsia Pharmaceuticals Ltd.
Attention: Alaine Zumpino, MS
Associate Director, US Regulatory Affairs
1820 Chapel Avenue West, Suite 150
Cherry Hill, NJ 08002

Dear Ms. Zumpino:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for ACT-132577 (aprocitentan).

We also refer to the meeting between representatives of your firm and the FDA on September 15, 2017. The purpose of the meeting was to discuss the adequacy of your proposed Nonclinical, Clinical Pharmacology and Phase 3 Clinical programs.

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, please contact Sabry Soukehal, Regulatory Health Project Manager, at (240) 402 6187.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, MD, PhD
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation 1
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: September 15, 2017, 11:00 am to 12:00 pm
Meeting Location: White Oak Building 22, Conference Room: 1421
Application Number: IND 122772
Product Name: ACT-132577 (aprocitentan)
Indication: Treatment of resistant hypertension
Sponsor Name: Idorsia Pharmaceuticals Ltd.
Meeting Chair: Norman Stockbridge, MD, PhD
Meeting Recorder: Sabry Soukehal

FDA ATTENDEES

*Office of Drug Evaluation I

Robert Temple, MD	Deputy Director
Naomi Lowy, MD	Associate Director for Regulatory Science

*Division of Cardiovascular and Renal Products

Norman Stockbridge, MD, PhD	Director
Stephen Grant, MD	Deputy Director
Michael Monteleone, MS, RAC	Associate Director for Labeling
Shari Targum, MD	Clinical Team Leader
Maryann Gordon, MD	Clinical Reviewer
Aliza Thompson, MD	Clinical Team Leader
Albert Defelice, PhD	Non-Clinical Team Leader
John Koerner, PhD	Non-Clinical Reviewer
Sabry Soukehal	Regulatory Health Project Manager

*Office of Clinical Pharmacology

Sudharshan Hariharan, PhD	Clinical Pharmacology Team Leader
Venkateswaran ChithambaramPillai, PhD	Clinical Pharmacology Reviewer

*Office of Biostatistics, Division of Biometrics I

Steven Bai, PhD	Statistician

*Office of Pharmaceutical Quality

Mohan Sapru, PhD	CMC Team Leader

SPONSOR ATTENDEES

(b) (4)	Medical Expert
Elliott Barnathan, MD	Senior Director, Janssen Research and Development
Parisa Danaietash, PhD	Director, Senior Clinical Project Scientist
Bruno Flamion, MD, PhD	VP, Head of Strategic Development
Jacques-Alexis Funel, PhD	Associate Director, Senior Technical Project leader, Drug Substance Operations
James List, MD, PhD	Global Therapeutics Head, Cardiovascular and Metabolism, Janssen R&D
Frederic Naud, PhD	Director, Life Cycle Leader
Brian D. Schlag, MA, MS	VP, Head of US Regulatory Affairs
Patricia Sidharta, PharmD, PhD	Senior Director, Senior Clinical Pharmacologist
Pierre Verweij, PhD	Associate Director, Expert Statistician
Alaine Zumpino, MS	Associate Director, Global Regulatory Affairs

1.0 BACKGROUND

ACT-132577, an active metabolite of macitentan, is an orally active dual endothelin ET_A/ET_B receptor antagonist (ERA) being developed by Idorsia Pharmaceuticals Ltd. ('Idorsia') for the treatment of "resistant hypertension" (RHT), defined as blood pressure inadequately controlled by administration of maximal doses of three antihypertensive drugs of different pharmacological classes, including a diuretic. Because of its distinct mechanism of action, Idorsia believes that its antihypertensive effect is additive to those of RAS blockers, diuretics, calcium channel blockers, and beta blockers.

The IND was opened on 17 October 2014 with a Phase 1 SAD and MAD study. Idorsia has completed a six-arm dose finding study in which 490 patients with grade 1 and 2 hypertension on no background antihypertensive drugs were randomized to 5, 10, 25, or 50 mg of ACT-132577, placebo, or 20 mg of Lisinopril for 8 weeks (protocol AC-080A201). The blood pressure effect of 5 mg was not clearly different from placebo. The blood pressure effects of 10, 25, and 50 mg were greater than placebo but not clearly different from each other. There did appear to be a dose-dependent increase in plasma volume.

Idorsia now proposes to conduct (b) (4) conducted in RHT patients. The objective of (b) (4) is to demonstrate superiority of ACT-132577 dosed at 12.5 or 25 mg over placebo on systolic blood pressure in RHT patients. (b) (4)

Additionally, Idorsia plans to study the efficacy and safety of ACT-132577 in patients with [redacted] hypertensive patients with moderate to severe chronic kidney disease.

Idorsia requested an End-of-Phase 2 meeting to gain the Division's agreement on their proposed nonclinical, clinical pharmacology, and Phase 3 clinical programs to support an NDA submission.

FDA sent Preliminary Comments to Idorsia on September 12, 2017.

2.0 DISCUSSION

2.1. CMC

Question 1 (Source of background therapy required per RHT definition): [redacted] Patients enrolled into study ID-080A301 will receive [redacted], a triple fixed-dose combination of amlodipine (a CCB), valsartan (an angiotensin receptor blocker [ARB]), and hydrochlorothiazide (a diuretic); [redacted]. These medications will be provided by the sponsor to all subjects enrolled in study ID-080A301 [redacted]. Idorsia is considering sourcing [redacted] ([redacted]®, [redacted]) from a single source in the EU for use in this global Phase 3 program. Does the FDA agree that using EU approved products for background therapy is acceptable?

FDA Response: It is not clear whether or not you propose to use only FDA-approved drug products as background therapy. If you plan to do so, please provide the NDC numbers for these drugs in your submission. However, if you propose to use drug products that are not FDA-approved, please provide the complete CMC information concerning the drug substance and drug product for each of the unapproved products in your IND submission. For details concerning the CMC requirements for Phase 1I/III studies, refer to *Guidance for Industry - INDs for Phase 2 and 3 Studies Chemistry, Manufacturing, and Controls Information (2003).*

Meeting discussion: The Division explained that the active metabolite of macitentan was not previously approved by the Agency and is considered a new chemical entity; hence a complete CMC package needs to be submitted. Regarding sourcing of background therapies from a single EU source, the Sponsor asked if, in agreement with the approved manufacturer [redacted], NDC numbers or letters of authorization can be provided. The Division indicated that providing NDC numbers for FDA approved drugs or letters of authorization from original NDA holders for FDA approved products will be acceptable.

2.2. NONCLINICAL

Question 2 (Nonclinical toxicology studies to support NDA): Core safety pharmacology studies (respiratory and central nervous system safety pharmacology studies in rats, and a cardiovascular safety pharmacology study in dogs), the 4-week repeated-dose toxicity studies in rats and dogs, and the *in vitro* genotoxicity assays (Ames-test and chromosomal aberration test)

were conducted with ACT-132577.

Recently, sub-chronic and chronic toxicity studies (26 weeks of treatment in rats and 13 and 39 weeks of treatment in dogs), segment I reproductive toxicity studies in male and female rats, and an *in vivo* genotoxicity assay (micronucleus test in rats) have also been performed with ACT-132577.

During the pre-IND meeting of 28 July 2014, the FDA agreed to waive the segment II reproductive toxicity studies and the carcinogenicity studies, based on existing knowledge with macitentan. In addition, Idorsia would like to ask for a waiver for the segment III reproductive toxicity study, for which macitentan data are also considered appropriate to be used for risk assessment.

Does the FDA agree with the proposed nonclinical program including waivers for the segment II and III reproductive toxicity studies and carcinogenicity studies, taking into account data of recently completed toxicity studies, in order to support the NDA of ACT-132577 (b) (4) ?

FDA Response: Yes

Meeting discussion: No further discussion occurred during the meeting.

2.3. CLINICAL PHARMACOLOGY

Question 3 (Clinical Pharmacology Studies for NDA): Idorsia considers the clinical pharmacology program adequate and sufficient to support the submission and review of an NDA for ACT-132577. Does the FDA agree?

FDA Response: The clinical pharmacology program you propose appears reasonable. Please provide details of the in vitro study results evaluating the status of aprocitentan as a substrate/inhibitor/inducer for drug metabolic enzymes and transporters.

Meeting discussion: The Sponsor shared their intent to provide the requested data and seek the Division's feedback.

Question 4 (TQT Study): (b) (4)

FDA Response: The exposure of active metabolite [maximum plasma concentration (Cmax) with 30 mg macitentan: 2.1 µg/ml] observed in the macitentan TQT study does not cover the expected exposure [Cmax at 25 mg aprocitentan: 3.6 µg/ml] of aprocitentan in your proposed Phase 3 trials. We recommend that you perform a TQT study using doses of aprocitentan that will achieve plasma exposures higher than that expected to be seen in your proposed Phase 3 trials.

Meeting discussion: The Sponsor was informed that the Division will provide a more detailed response after consultation with the QT-IRT team.

Post meeting note from the QT-IRT team:

(b) (4)

The Sponsor can either conduct a TQT study using C-QTc as the primary analysis, which requires fewer subjects than using the traditional by-time analysis, or pool the data from the MAD study with another study with robust ECGs at high doses (greater than 25 mg) to increase the precision of the slope estimate. When pooling data across studies, it is important that the control procedures (e.g., placebo, food control) be similar as well as the timing of ECG measurements. A better understanding of PK variability might also suffice.

2.4. CLINICAL

Question 5 (Dosage selection for Phase 3 clinical trials in RHT): Does the FDA agree that the doses selected from the Phase 2 dose-finding study (AC-080A201) with support from the Phase 1 study AC-080-102, are appropriate for the pivotal, confirmatory Phase 3 trials in RHT?

FDA Response: It appears that there was a minimal difference in effect on blood pressure between the 10 and 25 mg doses in study AC-080A201. Please provide a more detailed dose rationale, keeping in mind that the targeted population, i.e., patients who are not adequately controlled with other blood pressure medications, could differ in their response to treatment, and will likely be on background medications, such as diuretics, that may limit the amount of edema observed. In addition, the difference between the doses you selected (12.5 mg and 25 mg) is only two-fold, and given the results of your Phase 2 study, may not result in marked difference in blood pressure lowering effect in your proposed Phase 3 trials. You should consider studying a wider dose range.

Meeting discussion: The Sponsor stated that 12.5 mg and 25 mg significantly reduced blood pressure and doses above 25 mg did not result in a further reduction. Also, ACT-132577 causes a dose-dependent reduction in hemoglobin, so the Sponsor is reluctant to study a higher dose.

Question 6 (Patient population of the confirmatory Phase 3 studies in RHT): Does the FDA agree that the patient population to be enrolled in the proposed ID-080A301 (b) (4) is appropriate to support the NDA for the indication "treatment of resistant hypertension"?

FDA Response: No. Demonstration that ACT-132577 is superior to placebo in reducing blood

pressure in hypertensive patients on maximally tolerated doses of three or more antihypertensive medications will result in a claim that ACT-132577 is indicated for the treatment of hypertension, to lower blood pressure. The background medications taken during the study will be described in Section 14. The indication is likely to include a limitation of use that states ACT-132577 is not indicated for initial treatment because of teratogenicity.

[redacted] (b) (4)

Meeting discussion: The Division noted that most antihypertensive drugs are labeled for use "alone or in combination with other antihypertensive agents", indicating that adding an antihypertensive to another antihypertensive of a different class is expected to result in further reduction of blood pressure. The utility of giving a special claim to an antihypertensive drug based on demonstrating it decreases blood pressure compared to placebo is unclear, especially if it carries significant risks.

The Division believes that the term 'resistant hypertension' is problematic for several reasons:

1. The term resistant in a regulatory context is generally used to identify a product effective in a condition that cannot be treated adequately by other products.
2. The term 'resistant hypertension' is sometimes used to identify patients whose blood pressure is inadequately controlled on three or more antihypertensive drugs. It is not clear that this actually identifies a unique disease, as opposed to simply representing hypertension on the more severe part of a continuum.
3. The definition of 'resistant hypertension' is likely to evolve over time, depending on availability of new treatments and evolving treatment algorithms. It is very difficult to identify a target population based on a definition that will change over time.

[redacted] (b) (4)

Question 7 (Study design of the confirmatory Phase 3 studies in RHT): Does the FDA agree that the designs of the ID-080A301 and [redacted] (b) (4) studies are appropriate to support the NDA for the indication "treatment of resistant hypertension" in regards to [redacted] (b) (4), overall duration of treatment (including run-in period and DB period), monitoring of potential safety issues of special interest, efficacy endpoints, and statistical methodology?

FDA Response: No, we do not agree that these studies will support an NDA for the indication "treatment of resistant hypertension." Please see the response to Question 6.

As we suggested previously, you might consider shortening the duration of the double-blind period or evaluating the primary endpoint prior to 12 weeks; doing so will lessen the likelihood of missing data.

The secondary endpoints are all different variations of blood pressure measurement. We do not

believe any additional claims can be added if you perform formal statistical tests to these endpoints. You can simply compare between each dose of ACT-132577 and placebo using descriptive statistics.

Please provide detailed information on the control-based imputation.

Meeting discussion: The Sponsor stated they intend to develop ACT-132577 globally and they believe regulatory bodies in other regions will require (b) (4). The Division responded that the Sponsor may propose a US-specific analytic plan and if they do so, do not need to adjust alpha for multiplicity. The Division advised the Sponsor to choose the timepoint for ascertainment of the primary outcome based on the time course of antihypertensive effect.

Detailed information on the control-based imputation was not provided. The Sponsor will provide detailed algorithm and implementation of the imputation in an upcoming submission.

Question 8 (Long-term extension study): Does the FDA agree that (b) (4) is appropriate to support the NDA?

FDA Response: No, we do not agree. (b) (4)

We recommend that subjects remain on background therapy and receive at least 3 months open label treatment with ACT-132577, followed by a double-blind period in which subjects are randomized to remain on ACT-132577 or receive placebo (withdrawal) while maintaining stable doses of background therapy. Results of this trial would support that the blood pressure-lowering effect of ACT-132577 is durable.

Meeting discussion: The Division advised the Sponsor that success on the primary endpoint of the proposed study and in the withdrawal study would represent having two successful studies.

Question 9 ((b) (4)

FDA Response: (b) (4)

(b) (4)

Meeting discussion: No further discussion occurred during the meeting.

Question 10 (b) (4)

FDA Response: (b) (4)

Meeting discussion: (b) (4)

Question 11 (Safety database): Does the FDA agree that the proposed safety database will be adequate to support the NDA for the indication "treatment of resistant hypertension"?

FDA Response: Please see our response to Question 7.

Meeting discussion: The Sponsor asked if 1200 patients studied for 6 to 12 months were

sufficient. The Division stated that it is likely acceptable provided the Sponsor does not seek a first-line claim.

Additional Comment: Because aprocitentan likely has the same teratogenicity risk as other endothelin receptor antagonists (ERAs), your proposed studies should include the same risk management approach as those required for other ERAs (as described in their Risk Evaluation and Minimization Strategy) including the use of highly effective forms of contraception (see the Medication Guide for Opsumit® for an example chart) and monthly pregnancy tests for females of childbearing potential during the double-blind and open label portion of the studies.

Meeting discussion: No further discussion occurred during the meeting.

3.0 OTHER IMPORTANT MEETING INFORMATION

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.

DATA STANDARDS FOR STUDIES

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

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

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

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

For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, CDER encourages sponsors to use Standards for the Exchange of Nonclinical Data (SEND) and submit sample or test data sets before implementation becomes required. CDER will provide

feedback to sponsors on the suitability of these test data sets. Information about submitting a test submission can be found here: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm

LABORATORY TEST UNITS FOR CLINICAL TRIALS

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

SECURE EMAIL COMMUNICATIONS

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

NEW PROTOCOLS AND CHANGES TO PROTOCOLS

To ensure that the Division is aware of your continued drug development plans and to facilitate successful interactions with the Division, including provision of advice and timely responses to your questions, we request that the cover letter for all new phase 2 or phase 3 protocol submissions to your IND or changes to these protocols include the following information:

1. Study phase
2. Statement of whether the study is intended to support marketing and/or labeling changes
3. Study objectives (e.g., dose finding)
4. Population
5. A brief description of the study design (e.g., placebo or active controlled)
6. Specific concerns for which you anticipate the Division will have comments
7. For changes to protocols only, also include the following information:
    - A brief summary of the substantive change(s) to the protocol (e.g., changes to endpoint measures, dose, and/or population)
    - Other significant changes
    - Proposed implementation date

We recommend you consider requesting a meeting to facilitate discussion of multiple and/or complex issues.

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:

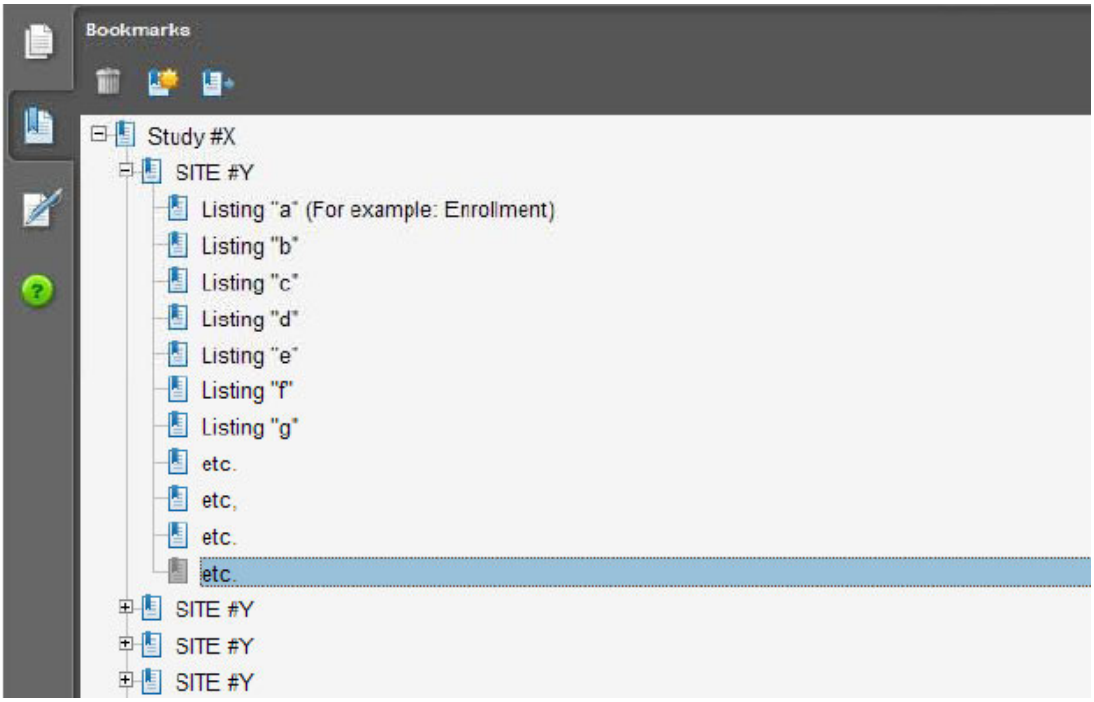
a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents 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

There were no issues requiring further discussion.

5.0 ACTION ITEMS

There were no action items

6.0 ATTACHMENTS AND HANDOUTS

There were no attachments or handouts for the meeting minutes.

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

/s/

NORMAN L STOCKBRIDGE
10/06/2017