

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

211801Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**



IND 108732

MEETING MINUTES

Ardelyx, Inc.
Attn: Robert C. Blanks
Senior Director, Regulatory Affairs and Quality Assurance
34175 Ardenwood Blvd.
Suite 100
Fremont, CA 94555

Dear Mr. Blanks:

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

We also refer to the meeting between representatives of your firm and the FDA on May 1, 2018. The purpose of the meeting was to obtain the Agency's concurrence on submission plans of an NDA for marketing authorization of tenapanor, 50 mg BID for treatment of irritable bowel syndrome with constipation (IBS-C).

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 me at (301) 796-4075.

Sincerely,

{See appended electronic signature page}

Evangelina Covert, BS
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors
Products
Office of Drug Evaluation III
Office of New Drugs
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: Pre-NDA

Meeting Date and Time: May 1, 2018; 10:00AM-11:00AM (Eastern Standard Time)
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1313
Silver Spring, Maryland 20903

Application Number: 108732
Product Name: tenapanor
Indication: Constipation related diseases

Sponsor/Applicant Name: Ardelyx, Inc.

Meeting Chair: Dr. Juli Tomaino
Meeting Recorder: Evangela Covert

FDA ATTENDEES

Jessica Lee, M.D., Associate Director, Division of Gastroenterology and Inborn Errors Products (DGIEP)
Juli Tomaino, M.D., Clinical Team Leader, DGIEP
Michael Riel, D.O., Medical Officer, DGIEP
Sushanta Chakder, Ph.D., Supervisory Pharmacologist, DGIEP
Dinesh Gautam, Ph.D., Pharmacology Reviewer, DGIEP
Insook Kim, Ph.D., Team Leader, Division of Clinical Pharmacology III (DCPIII)
Sojeong Yi, Ph.D., Clinical Pharmacology Reviewer, DCPIII
George Kordzakhia, Ph.D., Acting Statistical Team Leader, Division of Biometrics III (DBIII)
Paul Imbriano, Ph.D., Statistical Reviewer, DBIII
Hitesh Shroff, Ph.D., Chemistry Team Leader, Office of Product Quality
Debasis Ghosh, Ph.D., Chemistry Reviewer, Division of New Drug API, ONDP, OPQ
Tien-Mien Chen, Ph.D., Acting Biopharm. Lead, Division of Biopharmaceutics, ONDP, OPQ

SPONSOR ATTENDEES

David Rosenbaum, Ph.D. Ardelyx, Inc., Chief Development Officer

Robert Blanks, M.S., RAC Ardelyx, Inc., Senior Vice President Regulatory Affairs and Quality Assurance

Jeff Jacobs, Ph.D. Ardelyx, Inc., Senior Vice President, Technical Operations

Kenji Kozuka, M.S. Ardelyx, Senior Manager, DMPK

(b) (4), Principal Consultant

James Vaughan, M.S. PAREXEL, Principal Biostatistician

Teri Roy, M.S. PAREXEL, Tenapanor Regulatory Manager

Amy Schutte PAREXEL, Project Leader

1.0 BACKGROUND

The purpose of the meeting is to discuss the submission plans for an NDA for marketing authorization of tenapanor 50 mg BID for treatment of irritable bowel syndrome with constipation (IBS-C).

FDA sent Preliminary Comments to Ardelyx, Inc. on April 24, 2018. Ardelyx, Inc. submitted responses on April 27, 2018.

2. DISCUSSION

Questions from Ardelyx, Inc. are in plain text. Responses from the FDA are in **bold text**. Comments from Ardelyx, Inc. are attached. Meeting Discussion is in *bold italics*.

2.1. Clinical/Clinical Pharmacology

Question 1: Does the Agency agree with the overall data strategy for the ISE and ISS?

FDA Response to Question 1: The proposed integration strategy for the Integrated Summary of Efficacy (ISE) that includes data from two Phase 3 trials (TEN-03-301 and TEN-301-01-302) and a supportive phase 2b trial (D5612C00001) appears reasonable, since these trials were generally similar in duration, patient population, and efficacy endpoints evaluated. We also agree with your proposal to present separately the phase 2a trial data (RDX5791-201) since the treatment duration and doses evaluated differ from the phase 2b and phase 3 trials. Since the open-label long-term safety trial (TEN-01-303) was not designed to assess efficacy, it is reasonable not to include data from that trial in the pooled analyses for the ISE. Your proposal to include a “Comparison of Results of Individual Studies” section with important data elements that are common and/or important to all trials, presented parameter by parameter, and within each parameter, for study TEN-01-301, TEN-01-302 and the supportive study D5612C00001, where the same parameter was also measured seems reasonable. Similarly, your proposal to include a “Comparison of Results in Subpopulations” section that will be limited to results of subpopulation analyses using the pooled data from studies TEN-01-301, TEN-01-302, and D5612C00001 seems reasonable. We remind you, as communicated in the November 18, 2015 Advice Letter, that results of subgroup analyses conducted in the context of the ISE cannot be used to support a labeling claim.

The proposed integration strategy for the Integrated Summary of Safety (ISS) to summarize the safety and tolerability of tenapanor across the 19 completed trials and analyzed as four separate analysis sets (listed below) appears reasonable; however, our primary safety assessment will rely upon the safety data (clinical study reports and datasets) provided for the phase 3 trials conducted in patients with IBS-C.

- 1. Core Safety Analysis Set (phase 2 and 3 trials in patients with IBS-C: D5612C00001, RDX5791-201, TEN-01-301, TEN-01-302, and TEN-01-303): Subject disposition, demographics and baseline characteristics, concomitant medications, exposure, AEs, clinical laboratory parameters, vital sign measurements, and ECG values.**
- 2. ESRD Supportive Safety Analysis Set**
- 3. CKD Supportive Safety Analysis Set**
- 4. Healthy Volunteers Supportive Safety Analysis Set**

Question 2: Does the Agency agree the Statistical Analysis Plan for the ISS is acceptable?

FDA Response to Question 2: The statistical analysis plan for the ISS appears reasonable based on the information provided in the meeting background package. Also, see response to Question 1.

Question 3: Does the Agency agree the Statistical Analysis Plan for the ISE is acceptable?

FDA Response to Question 3: Based on the information provided in the meeting background package, the statistical analysis plan for the ISE appears acceptable. Please refer to the FDA Integrated Summary of Effectiveness Guidance for industry located at <https://www.fda.gov/downloads/drugs/guidances/ucm079803.pdf> for further information on the recommended content to include in the ISE.

We remind you that our primary efficacy assessment will be determined from the results of individual trials.

Question 4: Does that Agency agree that the exposure numbers presented above are acceptable for evaluation of the long-term safety of Tenapanor?

FDA Response to Question 4: The background package states that 130 patients with IBS-C have been treated with tenapanor for 1 year, and the data for these 130 patients were obtained from the following trials:

- **Study TEN-01-301**
 - o **31 patients treated with tenapanor for the 3-month treatment period, 1-month randomized withdrawal period, and 9-months during the open-label extension study, TEN-01-303 (13 months total).**
 - o **39 patients treated with tenapanor for the 3-month treatment period, received placebo during the 1-month randomized withdrawal period, and tenapanor for 9-months during the open-label extension study, TEN-01-303 (12 months total).**

- Study TEN-01-302
 - o 60 patients treated with tenapanor for the 6-month treatment period and 6-months during the open-label extension study, TEN-01-303 (12 months total).

For products intended for long-term treatment of non-life-threatening conditions, we generally recommend that the safety database include at least 100 patients exposed to dosage levels intended for clinical use for a minimum of one year; therefore, 130 patients exposed to tenapanor for 12 months appears reasonable. However, we note that the long-term safety data (9 months and 6 months of treatment following study TEN-01-301 and -302, respectively) were obtained from an open-label long-term safety study (TEN-01-303). In the absence of a concurrent control group, it may be difficult to assess the causality relationship between adverse reactions and the drug. The adequacy of the long-term safety data, including whether and how the data can be described in labeling, will be determined during the review of the NDA.

Meeting Discussion:

FDA provided clarification that the 130 patients followed for 1 year appear reasonable from a safety perspective to file an NDA.

Question 5: Does the Agency agree with the inclusion of the pre-specified key secondary endpoints and the presentation of clinical efficacy data as shown in the target product profile (TPP) within the clinical studies portion?

FDA Response to Question 5: The approach to the pre-specified secondary endpoints that includes a sequential testing procedure to control experiment-wise Type I error rate appears reasonable and the endpoints are generally aligned with the recommendations in the Guidance for Industry, Irritable Bowel Syndrome- Clinical Evaluation of Drugs for Treatment (May 2012). However, the adequacy of the proposed analyses to support labeling claims will be determined upon review of the NDA submission and will depend on the strength of evidence provided, as well as the interpretability and clinical meaningfulness of the data.

Meeting Discussion:

FDA recommends that in the NDA the sponsor provide 1) rationale to support the clinical meaningfulness of the 9/12 week secondary endpoint and 2) sensitivity analyses to support the failed 6/12 CSBM endpoint in Study TEN-01-301. FDA does not recommend using pooled analyses as part of the rationale to support efficacy claims.

Question 6: Does the Agency agree

(b) (4)

FDA Response to Question 6: No, we do not agree.

(b) (4)

(b) (4)

Analysis, and Impact on Dosing and Labeling.

<https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm072123.pdf>)

Meeting Discussion:

(b) (4)

Question 7: Does the Agency agree that the completed DDI studies are adequate as for submission of the NDA for tenapanor as described in the TPP?

FDA Response to Question 7: Yes, we agree that the completed DDI studies can support the submission of the NDA. In addition, we recommend that you conduct an additional DDI study with a concomitant strong CYP3A4/5 inhibitor to address the potential effects of CYP3A4/5 inhibitor on the PK of tenapanor and M1, as tenapanor and M1 are substrates of CYP3A4/5 based on an in vitro study. The adequacy of the studies and the results from the completed DDI studies will be reviewed during the NDA review.

Meeting Discussion:

The sponsor agrees to conduct the study with a CYP3A4 inhibitor but asked if the study results can be submitted during NDA review or post-marketing. FDA commented that the study does not need to be completed in order to file the NDA, but the FDA recommends that the study be completed as early as possible and ideally submitted with the NDA to properly inform the labeling regarding concomitant administration with CYP3A4 inhibitors.

Question 8: Does the Agency agree with the e-Data submission plan?

FDA Response to Question 8: Overall, the e-Data submission plan appears reasonable since the data from the phase 2 and 3 trials conducted in the patient population of interest (IBS-C) will be submitted in SDTM and ADaM format. In addition, your plan to provide SAS programs used to create all analysis datasets appears reasonable. During the review of the NDA, we may request, if necessary, datasets in SDTM and ADaM format for other trial data that you plan to provide in legacy format. In general, the data should be converted to clinical data interchange standards consortium (CDISC) format for data that will be submitted to the NDA.

Meeting Discussion:

FDA clarified that the data submission plan seems reasonable and clarified that upon review of the NDA, additional specific study data may be requested.

Question 9: Does FDA agree that the proposed clinical data to be included in Module 5 will support the filing of the NDA?

FDA Response to Question 9: Based on the information provided in the background package, the proposed content for Module 5 that includes key clinical pharmacology, clinical, and statistical data appears reasonable. From a technical standpoint (not content-related), the proposed format for Module 5 is acceptable; however, please see additional comments below:

- Providing a table of contents in module 5.1 is not necessary in the eCTD structure. Instead, you can provide a Study Data Reviewers Guide (SDRG) that can be placed with the define file.
- Do not include placeholders stating “Not Applicable” for sections without documents (e.g., Module 5.3.1.1, 5.3.1.2, etc.). Provide the eCTD sections that contain documents.

2.2. Chemistry, Manufacturing and Controls

Question 10: Does FDA agree that the drug substance specified related substances/impurities in the proposed specifications are adequately qualified and controlled for approval?

FDA Response to Question 10: The qualification of the impurities in the drug substance specifications appear to be adequate. However, the adequacy of control strategy will be determined at the time of NDA review.

While an acceptance criterion of related substances/impurities in drug substance specification is part of the impurity control strategy, using a holistic approach provide in-process controls and discussion of origin, fate and control of each impurity in the NDA. We also remind you that the adequacy of the acceptance criteria for all drug substance tests is an NDA review issue, and the final determination will be made at that time.

Meeting Discussion:

FDA clarified that the proper control strategy for impurities should be provided in the NDA to demonstrate robustness of the drug substance manufacturing process.

Question 11: Does FDA agree that the drug product specified impurities/degradants in the proposed specifications are adequately qualified and controlled for approval?

FDA Response to Question 11: The qualification and control of the impurities/degradant levels in the drug product specification appear acceptable for your NDA submission. However, the final determination of the drug product specification will be based on the thorough review of the data provided in your NDA.

Question 12: Does the Agency agree that the dissolution method is adequate for the control of tenapanor drug product and the proposed acceptance criteria is reasonable?

FDA Response to Question 12: Although the proposed dissolution method appears reasonable, the acceptability of your proposed dissolution criterion for your product will be made upon thorough review of the NDA based on the totality of the dissolution data provided. Include the detailed dissolution method development report and complete dissolution data (individuals, mean, SD, and mean profiles), as well as the detailed information on the batch employed (e.g., batch number, and data, site, and size of the batch manufactured) in the future NDA submission.

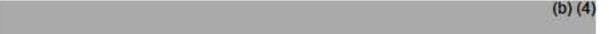
Question 13: Does the Agency have any additional comments on the CMC packages to be submitted in the NDA for tenapanor for the treatment of IBS-C?

FDA Response to Question 13: In preparation for the CMC sections in your NDA, we refer you to relevant CDER Pharmaceutical quality/CMC Guidances and ICH Quality Guidelines located at the following websites:

- <https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064979.htm>
- <http://www.ich.org/products/guidelines/quality/article/quality-guidelines.html>

We also have the following comments:

1.  (b) (4)

The drug substance is manufactured as  (b) (4)


Meeting Discussion:
The sponsor will provide justification  (b) (4)


3.0 CONTENT OF A COMPLETE APPLICATION

- 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.

- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. You stated you intend to submit a complete application and therefore, there are no agreements for late submission of application components.

4.0 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 Pedsdrugs@fda.hhs.gov. For further guidance on pediatric product development, please refer to: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>.

5.0 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.

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* (<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.

6.0 OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft Guidance for Industry Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions

(February 2018) and the associated Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft Guidance for Industry Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions (February 2018) and the associated Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications:

<https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332466.pdf>

<https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf>.

7.0 ISSUES REQUIRING FURTHER DISCUSSION

None.

8.0 ACTION ITEMS

None.

9.0 ATTACHMENTS AND HANDOUTS

Ardelyx, Inc. submitted responses to the preliminary comments on April 27, 2018 that are attached.

18 Pages have been Withheld in Full as b4 (CCI/TS)
immediately following this page

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

/s/

EVANGELA M COVERT
05/10/2018



IND 108732

MEETING MINUTES

Ardelyx, Inc.
ATTN: Robert C. Blanks
Vice President, Regulatory Affairs and Quality Assurance
34175 Ardenwood Blvd., Suite 100
Fremont, CA 94555

Dear Mr. Blanks:

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

We also refer to the meeting between representatives of your firm and the FDA on June 9, 2015. The purpose of the meeting was to discuss the phase 3 development plans for tenapanor tablets.

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 me at (301) 796-5016.

Sincerely,

{See appended electronic signature page}

Anissa Davis-Williams, RN, B.S.N., M.P.H.,
C.P.H.M.
CDR/USPHS
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

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

Meeting Date and Time: June 9, 2015; 10:00 a.m. – 11:00 a.m. (EST)
Meeting Location: FDA White Oak Bldg. 22, Room # 1309

Application Number: IND 108732
Product Name: tenapanor
Indication: treatment for irritable bowel syndrome-constipation (IBS-C)
Sponsor/Applicant Name: Ardelyx, Inc.

Meeting Chair: Dr. Laurie Muldowney
Meeting Recorder: CDR Anissa Davis-Williams

FDA ATTENDEES (tentative)

Donna Griebel, M.D., Director, Division of Gastroenterology and Inborn Errors Products (DGIEP)
Andrew E. Mulberg, M.D., F.A.A.P., C.P.I., Deputy Director, DGIEP
Laurie Muldowney, M.D., Medical Reviewer, DGIEP
Preeti Venkataraman, M.D., F.A.A.P., Medical Officer, DGIEP
Sushanta Chakder, Ph.D., Supervisory Pharmacologist, DGIEP
Dinesh Gautam, Ph.D., Pharmacology Reviewer, DGIEP
Yeh-Fong Chen, Ph.D., Statistical Reviewer, Division of Biometrics III (DBIII)
Wen-Jen Chen, Ph.D., Statistical Reviewer, DB III
Insook Kim, Ph.D., Clinical Pharmacology Reviewer, Division of Clinical Pharmacology 3

SPONSOR ATTENDEES

David Rosenbaum, Ph.D., Sr. VP of Development
Robert Blanks, M.S., VP of Regulatory Affairs and Quality Assurance
Andy Spencer, Ph.D., VP of Program Alliance
(b) (4) Consultant Statistician
Lars Weidolf, Ph.D., Biotransformation (AstraZeneca)
Susanne Johansson, Ph.D., Clinical Pharmacology (AstraZeneca)

1.0 BACKGROUND

Tenapanor is a locally acting, small molecule sodium (Na⁺)/hydrogen (H⁺) exchanger 3 (NHE3) inhibitor that exhibits minimal systemic exposure. This product is being developed to treat constipation-related disorders as well hyperphosphatemia in end-stage renal disease (ERSD) patients.

On April 8, 2015, Ardelyx, Inc. (Ardelyx) requested an End of Phase 2 meeting to discuss the development plans for tenapanor tablets.

The meeting was granted to be held as a face-to-face at the FDA White Oak campus in Maryland.

FDA sent Preliminary Comments to Ardelyx on June 5, 2015.

2.0 DISCUSSION

Questions from Ardelyx are in plain text. Responses from the FDA are in **bold text**. Comments from Ardelyx on June 8, 2015 are in *italics*. Meeting Discussion held on June 9, 2015 is in ***bold italics***.

2.1. Nonclinical -Safety Testing of Drug Metabolites to Support the Start of Phase 3

Question 1a: Does the Agency agree that the assessment of the exposures of the metabolites of tenapanor has been addressed adequately?

FDA Response to Question 1a:

No, we do not agree. In human plasma, metabolite profiling of tenapanor has identified six metabolites. Metabolite M1 was detected at a level of 16% of total drug related material. As per the FDA Guidance -Safety testing of drug metabolites, human metabolites formed at >10% of the parent drug systemic exposure raise safety concerns. Your assessment of the exposure of metabolite M1 does not appear to be adequate. In order to address the safety concerns of metabolite M1, you need to address the following:

- 1. Repeated dose toxicity study in one species.**

You have compared the group mean plasma concentration of M1 in dogs at 1000 mg/kg/day with the human plasma concentration at the 15 mg BID dose. However, you did not compare the plasma exposures (AUC) between dogs and humans. In addition, you do not have data with a direct comparison of the exposures in dogs with that in humans at the anticipated clinical doses. The comparison for the higher human doses was based on the assumption of a linear relationship between tenapanor dose and exposure to metabolite M1. If a direct comparison of the exposures between dogs and humans at the higher doses does not provide the required safety margins, you will need to conduct a repeated dose chronic toxicity study with M1 in one species.

Ardelyx email response dated June 8, 2015:

The Sponsor agrees with the Agency on the need to further characterize the safety of metabolite M1 and work is ongoing in this regard. In addition, while the MIST guidance is designed primarily for systemically delivered drugs, there are elements of the guidance that we can apply for this special case of an essentially unabsorbed parent molecule. To this end, and after submission of the EOP2 briefing document, we have recently analyzed the dog plasma samples, using a qualified bioanalytical method at the NOAEL of 1000 mg/kg and have found that for

*M1 the AUC_{met} (0-24) is 340 ng*h/mL as compared to the human AUC_{met}(0-24) of 158 ng*h/mL at 15 mg bid. The AUC_{met}, dog/AUC_{met}, human ratio is 2.2. By this measure and the ICH MIST guidance [ICH M3(R2) Q&A(R2)Rev.1 (February 2013), the M1 metabolite is covered in the dog up to 66 mg bid in humans provided that M1 metabolite is dose proportional.*

As the Agency recommends, the Sponsor plans to quantify M1 in samples of plasma collected at steady-state from patients treated with 50 mg bid from the Phase 2a IBS-C study (D5612C00001, which is equivalent to the dose planned in the Phase 3 trials, as well as subjects treated with 90 mg bid in the JSMA study (D5611C00005).

From these data, we will calculate exposure multiples (e.g. AUC) in the dog to M1 divided by human exposure to M1 at the anticipated commercial dose (50 mg bid). If this exposure multiple provides a margin of ≥ 0.5 for M1, we propose that the safety of M1 will have been adequately characterized in the context of the completed and planned toxicity studies of tenapanor. If the exposure multiple does not provide a margin of ≥ 0.5 for M1, we will conduct 3 month toxicology study of M1 in one species (e.g. mouse, rat or dog) at dose levels that provide target exposure multiples of 0.5, 1.5, and 5 fold greater than human exposure of M1. The sponsor has proposed 0.5, 1.5 and 5 fold greater than human exposure of M1 to satisfy the ICH guidance with the minimum exposure multiple (0.5) and provide a range 1 log higher.

Meeting Discussion:

The FDA stated that Ardelyx's approach appears reasonable for the 50 mg BID dose level.

2. Embryo-fetal development study in one species.

You stated that metabolite M1 was tested in Zebrafish developmental toxicity study and found to be non-teratogenic. However, the Zebrafish developmental toxicity study is not a validated study, included in the standard battery of reproductive toxicity studies. In the reproductive toxicity studies conducted with tenapanor, the exposures of M1 to the animals were not adequate. Thus, you need to conduct an embryofetal development study in one species with the M1 metabolite.

Ardelyx email response dated June 8, 2015:

*The approach described above for the general toxicity studies, will also be applied for the species used for the reproductive toxicity studies. As with the dog plasma samples, we have recently analyzed, using a qualified bioanalytical method, rabbit plasma samples given a dose of 45 mg/kg/day and found that for M1 the AUC_{met} (0-24) is 85ng*h/mL as compared to the human AUC_{met}(0-24) of 158 ng*h/mL at 15 mg bid, resulting in a AUC_{met}, rabbit/AUC_{met}, human ratio of 0.53. By this measure the M1 metabolite is covered in the rabbit up to a 16 mg bid dose level in humans, provided that M1 metabolite is dose proportional in humans. After further analysis, if at least one species provides a margin of 0.5, we propose that the reproductive safety of M1 has been adequately characterized in the context of the reproductive toxicity studies conducted with tenapanor. If neither species provides a margin of ≥ 0.5 , we will conduct an embryo-fetal development study in one species (e.g. mouse, rat or rabbit) and at dose levels that provide target exposure multiples of 0.5, 1.5, and 5 fold greater than human exposure of M1.*

Meeting Discussion:

The FDA stated that Ardelyx's approach appears reasonable to cover the exposures of M1 in reproductive toxicity studies.

3. A carcinogenicity study with M1 metabolite.

You have planned to conduct an in vitro bacterial reverse mutation assay with metabolite M1. However, in the in vivo micronucleus assay or the ongoing carcinogenicity study in rats, the animals were not adequately exposed to metabolite, M1. You need to address the carcinogenic potential of M1 by conducting a carcinogenicity study in one species with the metabolite.

Ardelyx email response dated June 8, 2015:

The Sponsor is currently evaluating the carcinogenic potential of M1 by conducting the following studies with M1:

- 1) In vitro bacterial reverse mutation assay*
- 2) In vitro mouse lymphoma micronucleus test*

The Sponsor has already performed an in vivo rat micronucleus test in which the parent drug was administered intravenously twice (24 hr apart) at doses up to 10 mg/kg. The mean maximum plasma concentration of parent was 3.53 µg/L and the test was negative. Since M1 concentrations were not determined in samples from this study, the Sponsor proposes to determine the concentration of M1 when 10 mg/kg of parent is administered intravenously to the same rat strain. If the concentration of M1 provides a margin of ≥ 0.5 of the human exposure at 50 mg BID clinical dose (or if the M1 concentration is not adequate then the Sponsor will perform an in vivo micronucleus assay using M1) and the other studies are negative, we propose that the results of these studies will adequately characterize the carcinogenic potential of M1. If positive or equivocal results are obtained in the above tests, we propose to include an additional dose group in the upcoming hRAS transgenic mouse study, in which M1 is added to tenapanor in one of the dose groups, at a level that targets a 1x multiple of M1 AUC compared to the human AUC associated with a 50 mg bid regimen of tenapanor.

Meeting Discussion:

The FDA stated that Ardelyx still needs to assess the carcinogenic potential of M1 even if the proposed genotoxicity studies are negative. The FDA stated that Ardelyx's approach to add an additional dose group in the transgenic mouse carcinogenicity study appears reasonable; however, the dose should be based on MTD or MFD; carcinogenicity study dose selection based on $\geq 25x$ -fold exposure margins is applicable to 2-year studies only, and not to transgenic mouse assay. If the sponsor decides to use a dose providing $\geq 25x$ exposure margins, they need to provide a justification.

Question 1b: Does the Agency agree that the available and planned data on the metabolite M1 (to include genotoxicity, secondary pharmacology, Zebrafish developmental toxicity assay,

exposures in the dog toxicology studies with the parent compound tenapanor) are adequate to assess the nonclinical toxicology of M1 to support the start of Phase 3 clinical trials?

FDA Response to Question 1b:

Please see our response to question 1a. The studies recommended above can be conducted in parallel to the proposed phase 3 clinical trial.

Ardelyx email response dated June 8, 2015:

The Sponsor requires no further discussion on this question except in the context of the discussion of Question 1a.

Meeting Discussion:

No further discussion needed.

Question 1c: Does the Agency agree that the overall nonclinical data set supports the start of Phase 3 clinical trials?

FDA Response to Question 1c:

Please see our response to questions 1a and 1b.

Ardelyx email response dated June 8, 2015:

The Sponsor requires no further discussion on this question except in the context of the discussion of Question 1a.

Meeting Discussion:

No further discussion needed.

2.2. Overall Nonclinical Development Plan to Support Registration

Question 2a: Based on the information provided does the Agency agree that the nonclinical evaluation of the M1 metabolite adequately supports the registration of tenapanor for the proposed indication?

FDA Response to Question 2a:

No, we do not agree. Please see our response to questions 1a and 1b.

Ardelyx email response dated June 8, 2015:

The Sponsor requires no further discussion on this question except in the context of the discussion of Question 1a.

Meeting Discussion:

No further discussion needed.

Question 2b: Based on the information provided does the Agency agree that the proposed nonclinical development plan adequately supports the registration of tenapanor for the proposed indication?

FDA Response to Question 2b:

No we do not agree. Please see our response to questions 1a and 1b.

Ardelyx email response dated June 8, 2015:

The Sponsor requires no further discussion on this question except in the context of the discussion of Question 1a. The Sponsor would like to understand that if we adequately address the Agency's concerns raised in Questions 1a and 1b that the proposed nonclinical development plan adequately supports the registration of tenapanor for the proposed indication.

Meeting Discussion:

The FDA agreed that if Questions 1a and 1b were addressed to the satisfaction of the Agency, the overall nonclinical development plan for the registration of tenapanor seemed reasonable.

2.3. Clinical Pharmacology- Clinical Pharmacology Package to Support Phase 3 and Registration

Question 3a: Does the Agency agree that the completed and planned evaluation of pharmacokinetics and pharmacodynamics of tenapanor, including the metabolite M1, is sufficient to support the registration of tenapanor for the proposed indication?

FDA Response to Question 3a:

No, we do not agree. We note that most of clinical pharmacology studies except for single and multiple dose ascending PK studies were conducted at 15 mg twice daily while the dose proposed for phase 3 trials is 50 mg twice daily and may be higher.

We note that a study is on-going to identify metabolizing enzymes for tenapanor. Further studies may be needed to address a potential effect of concomitant inhibitor(s) of tenapanor metabolizing enzymes as the information becomes available.

the information on systemic exposure to the major metabolite and its potential contributions to drug interactions are not available at this point. Therefore, additional drug-drug interaction studies may be needed.

Ardelyx email response dated June 8, 2015:

The Sponsor would like to have further discussion with respect to Question 3a.

As previously noted, we have collected PK data from multiple studies including RDX5791-

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101, RD579-201 and D5611C00005 at doses up to 90 mg bid. With respect to tenapanor, less than 1% of all PK samples have had measurable tenapanor plasma concentrations ($BLQ=0.5$ ng/mL) and samples with measurable plasma concentrations have been scattered across the dose range. With respect to the M1 metabolite, the Sponsor plans to analyze plasma samples from subjects who received 50 mg bid in the Phase 2b IBS-C study (D5612C00001) and up to 90 mg bid in the D5611C00005 study to determine the dose proportionality of M1. Based on these existing PK and efficacy data and the PK data in the process of being collected, the Sponsor feels that the PK will have been adequately addressed at the proposed Phase 3 dose of tenapanor of 50 mg bid.

As noted by the Agency, the Sponsor is in the process of identifying metabolizing enzymes for tenapanor and M1. Preliminary data using an *in vitro* system shows that tenapanor is metabolized by several CYPs including CYP3A4. With these *in vitro* data, a risk assessment of concomitant administration of inhibitors of CYPs involved in tenapanor metabolism will be done according to draft FDA Guidance “Drug Interaction Studies-Study Design, Data Analysis, Implications for Dosing and Labeling Recommendations”, 2012.

Based on *in vitro* studies the only risk for inhibition of intestinal enzymes for tenapanor is CYP3A4. The risk that tenapanor will affect the pharmacokinetics of a Cyp3A4 metabolized drug has already been assessed in the midazolam *in vivo* study showing no effect (7% difference in exposure ratios) on midazolam PK when co-administered with tenapanor 15 mg bid. It is reasonable to assume that the potential inhibitory effect is dose-proportional (Honkalammi et al, 2011, Baldan et al 2006, references available upon request) and, therefore, a 21% increase in midazolam would be expected for 50 mg bid tenapanor dose. An effect of this magnitude is not likely to be clinically relevant for sensitive CYP3A substrate and the Sponsor proposes that no additional clinical study is needed.

The risk for inhibition of intestinal transporters is the indirect inhibition of proton-coupled transporters such as PepTI. Based on the lack of effect on the pharmacokinetics of cefadroxil (a known PepTI substrate, AUC ratio, 90% CI) of 93% (range 91% to 96%) it is likely that the proposed Phase 3 clinical dose of tenapanor would not lead to clinically relevant change in cefadroxil exposure and the Sponsor proposes no additional studies.

It is currently unknown if M1 is formed within the enterocytes and/or liver. We plan to determine the enzyme(s) and mechanism(s) involved in the metabolism and absorption of tenapanor and M1 and use those data to guide the need for additional drug-interaction trials.

(b) (4)

(b) (4)

The Sponsor proposes that we submit a final plan for potential additional clinical pharmacology studies to support NDA, once we have completed the studies of the mechanism of metabolism and absorption of tenapanor and M1 for Agency review.

Meeting Discussion:

As stated above, Ardelyx will provide additional data along with a plan for additional clinical pharmacology studies and submit to the FDA for review and comment.

Question 3b: Does the Agency agree that based on the minimal systemic availability of tenapanor and the drug-drug interactions studies completed to date, no further drug-drug interaction studies are needed?

FDA Response to Question 3b:

Please see our response to question 3a.

Ardelyx email response dated June 8, 2015:

The Sponsor requires no further discussion on this question except in the context of the discussion of Question 3a.

Meeting Discussion:

No further discussion needed.

Question 3c: Does the Agency agree that

(b) (4)

FDA Response to Question 3c:

No, we do not agree.

(b) (4)

(b) (4)

Meeting Discussion:
The FDA reiterated the response noted above.

Question 3d: Does the Agency agree, that based on the minimal systemic availability of tenapanor and the currently available nonclinical and clinical data showing no signal of QT-prolongation, Ardelyx does not need to perform a thorough QT/QTc study (per ICH E14 Guidance Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Arrhythmic Drugs)?

FDA Response to Question 3d:
Based on the information provided, a tQT study is not necessary for the proposed 50 mg twice daily dosing regimen. However if the clinical doses will be higher than 50 mg twice daily, the necessity of the tQT study should be assessed again.

Ardelyx email response dated June 8, 2015:
The Sponsor requires no further discussion on this question.

Meeting Discussion:
No further discussions needed at this time.

2.4. Clinical- Phase 3 Clinical Studies to Support Registration

Question 4a: Does the Agency agree that the proposed dose(s) and dose regimen in the Phase 3 studies are appropriate to support the registration for the proposed indication?

FDA Response to Question 4a:
Based on the data provided, the proposed dose appears reasonable.

Ardelyx email response dated June 8, 2015:

The Sponsor requires no further discussion on this question.

Meeting Discussion:

No further discussions needed.

Question 4b: Does the Agency agree with the proposed Phase 3 study designs with regard to monitoring and duration are appropriate for the registration of tenapanor for the proposed indication?

FDA Response to Question 4b:

The proposed phase 3 design appears reasonable.

Ardelyx email response dated June 8, 2015:

The Sponsor requires no further discussion on this question.

Meeting Discussion:

No further discussions needed.

Question 4c: Does the Agency agree that the primary endpoint in the Phase 3 studies is appropriate for the registration of tenapanor for the proposed indication?

FDA Response to Question 4c:

We agree that the primary endpoint proposed (percent overall responder where a responder is defined based on simultaneous improvement in CSBM and abdominal pain for 50% of the weeks) is appropriate for your Phase 3 studies. Please note that the abdominal pain responder definition of a greater than or equal to 30 percent reduction in abdominal pain intensity compared with baseline is primarily based on published literature concerning other chronic pain conditions. Therefore, we recommend conducting additional responder sensitivity analyses that evaluate greater reductions in abdominal pain intensity with treatment (i.e., greater than or equal to 40 and/or 50 percent reduction in abdominal pain intensity compared with baseline). In addition, it would be useful to examine the cumulative distribution of several magnitudes of abdominal pain intensity reduction associated with treatment (e.g., 30 percent, 40 percent, 50 percent) as well as particular reductions (e.g., 100 percent pain intensity reduction) as secondary endpoints. However, the variations on primary endpoints (e.g., alternate responder definitions) are generally considered hypothesis generating and would not generally be included in labeling unless cited as key secondary endpoints.

Ardelyx email response dated June 8, 2015:

The Sponsor would like to get clarification on the FDA's characterization of "key secondary endpoints" discussed here and in 4e.

Meeting Discussion:

FDA reiterated the response to Question 4e, please see below.

Question 4d: Does the Agency agree that the statistical methods and proposed sample size for the Phase 3 studies are appropriate for the registration of tenapanor for the proposed indication?

FDA Response to Question 4d:

We have the following comments:

- **To determine whether the sample size assumptions are reasonable, please provide the literature or historical trial support for the same indication.**
- **For pooling of investigator sites as a stratification factor in CMH test, you need to pre-define a site-pooling rule. In addition, to avoid the analysis results are sensitive to the pooling method, further evaluation with different pooling rules may be necessary.**
- **If this study will be conducted in multi-regions or multiple countries, you should also propose method to assess the regional or country effect.**
- **For the primary analyses on the binary / responder endpoints, patients who take any rescue medication during the study should be treated as failures.**
- **You need to propose several sensitivity analyses to assess the impact of missing data on the efficacy comparisons. For your primary analyses on the binary / responder endpoints, patients with less than 4 diary days per week are treated as failures / non-responders for that week. In addition, for assessing the impact of the missing data on the primary analysis, instead of imputing patients who have missing data as failures / non-responders for that week, as sensitivity analyses, please impute them as success / responders.**
- **The final protocol and SAP should be submitted to the Agency for review prior to conducting the trial. Major changes to the statistical analysis plan, including the primary and key secondary endpoints, primary analysis methods as well as the multiple comparison procedure for controlling the overall type I error rate, after the start of a trial may compromise the interpretability of the results and/or present significant review concerns.**

Ardelyx email response dated June 8, 2015:

The Sponsor would like to get clarification of the pre-defined site-pooling rules; it is the sponsor's position that site-pooling rules would be specified in an addendum to the SAP, once randomization is closed and regional distribution can be identified and prior to database lock.

The Sponsor agrees to provide the literature and historical trial support for the same indication to support the sample size assumptions prior to the start of the Phase 3 trial.

Finally, the Sponsor agrees to submit the final protocol and SAP for Agency review prior to

conducting the Phase 3 trial. The Sponsor respectively requests further clarification on the timeframe required for the Agency to review the protocol and SAP and provide feedback to the Sponsor.

Meeting Discussion:

Ardelyx plans to submit the final protocol and SAP for FDA to review in advance and will summarize, in the cover letter, the proposed labeling claims and request Division feedback as a Written Response Only meeting request.

Question 4e: Does the Agency agree with

(b) (4)

FDA Response to Question 4e:

The proposed secondary endpoints appear reasonable; however, for any results of the secondary endpoints to be included in the label, you must pre-specify a multiplicity adjustment procedure to control the overall study-wise Type I error rate at the two-sided significance level of 5% for the analyses of the primary and key secondary endpoints. As the primary endpoint is a composite endpoint and it is important to assess the drug's effect based on individual components, we recommend you further test each component after winning on the primary endpoint. In terms of type I error control, please propose a method that will test the two components with equal weight or sequentially with a pre-specification.

Ardelyx email response dated June 8, 2015:

The Sponsor would like to discuss the FDA's recommendation for a multiplicity adjustment procedure to control overall study-wise Type I error rate for key secondary endpoints.

Meeting Discussion:

The FDA reiterated the response annotated above.

2.5. Clinical- Phase 3 Clinical Studies to Support Registration

Question 5a: Based on the information provided, does the Agency agree that the proposed clinical development plan and the proposed safety database are appropriate to adequately support the registration of tenapanor for IBS-C?

FDA Response to Question 5a:

The proposed safety database appears appropriate. We remind you that per the ICH E1 guidance, a minimum of 300 patients treated for 6 months at dosage levels intended for clinical use would be adequate to observe whether more frequently occurring events increase or decrease over time as well as to observe delayed events of reasonable frequency; at least 100 patients exposed for a minimum of one-year is considered to be acceptable to include as part of the safety data base. We refer you to the ICH E1 Guidance for further details:

http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E1/Step4/E1_Guideline.pdf

Ardelyx email response dated June 8, 2015:

The Sponsor requires no further discussion on this question.

Meeting Discussion:

No further discussion needed.

2.6. Additional Clinical Development and Labeling Considerations

Question 6a: Does the Agency agree that [REDACTED] (b) (4)

FDA Response to Question 6a:

No, we do not agree. [REDACTED] (b) (4)

Ardelyx email response dated June 8, 2015:

The Sponsor requires no further discussion on this question.

Meeting Discussion:

No further discussion needed.

Question 6b: Does the Agency agree [REDACTED] (b) (4)

FDA Response to Question 6b:

[REDACTED] (b) (4)

Ardelyx email response dated June 8, 2015:

The Sponsor requires no further discussion on this question and agrees with the Agency's recommendations.

Meeting Discussion:

No further discussion needed at this time.

Question 6c: Does the Agency agree that

(b) (4)

FDA Response to Question 6c:

No, we do not agree.

(b) (4)

<http://www.fda.gov/downloads/Drugs/.../Guidances/ucm078749.pdf>

Ardelyx email response dated June 8, 2015:

The Sponsor requires no further discussion on this question.

Meeting Discussion:

No further discussion needed at this time.

2.7. Pediatric Study Plan

Question 7a: Does the Agency agree with the proposed outline of the pediatric development strategy of tenapanor for IBS-C including a deferral to conduct pediatric studies until the safety and efficacy has been established in adult IBS-C patients and a waiver for children age (b) (4) and younger?

FDA Response to Question 7a:

We have generally waived the pediatric study requirement for ages 0 months to less than 6 years for this indication because necessary studies are impossible or highly impracticable. This is because IBS is uncommon in this age group, and it may be difficult to diagnose younger children as they may not be able to report IBS-related symptoms accurately and consistently. However, we encourage you to include younger subjects as this data may be informative. We remind you that ultimately, decisions regarding waivers/deferrals will be evaluated upon submission of the iPSP with assessment by the Pediatric Review Committee. If possible, please provide your proposed PIP to the FDA for review.

Ardelyx email response dated June 8, 2015:

The Sponsor requires no further discussion on this question and plans to submit an iPSP to the FDA in accordance with the Food and Drug Administration Safety and Innovation Act (FDASIA)

and the Guidance for Industry, “Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans”.

Meeting Discussion:

No further discussion needed at this time.

2.8. Additional Comments from FDA:

Please provide further information on the mechanism of action of the product, specifically at what level does the product exert its effect (e.g., protein or transcription), and address the potential for tachyphylaxis.

Ardelyx email response dated June 8, 2015:



Meeting Discussion:

No further discussion took place during the meeting.

2.9. Additional Clinical Pharmacology Comments

Please include the summary and results of in-vitro studies using materials from humans in the clinical pharmacology section.

Ardelyx email response dated June 8, 2015:

In reference to the above comment, we interpret it as follows:

In all future communications and submissions, the Sponsor should include all summary and results of in vitro studies using human materials (human plasma, blood, etc) in the clinical

pharmacology section of these submissions (instead of in the nonclinical section as has been the practice in the past).

Based on this understanding, the Sponsor will follow the Agency's recommendation.

Meeting Discussion:

No further discussion took place during the meeting.

3.0 PREA REQUIREMENTS

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

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

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

4.0 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>

5.0 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 [CDER/CBER Position on Use of SI Units for Lab Tests](http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/ucm372553.htm) (<http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/ucm372553.htm>).

6.0 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).

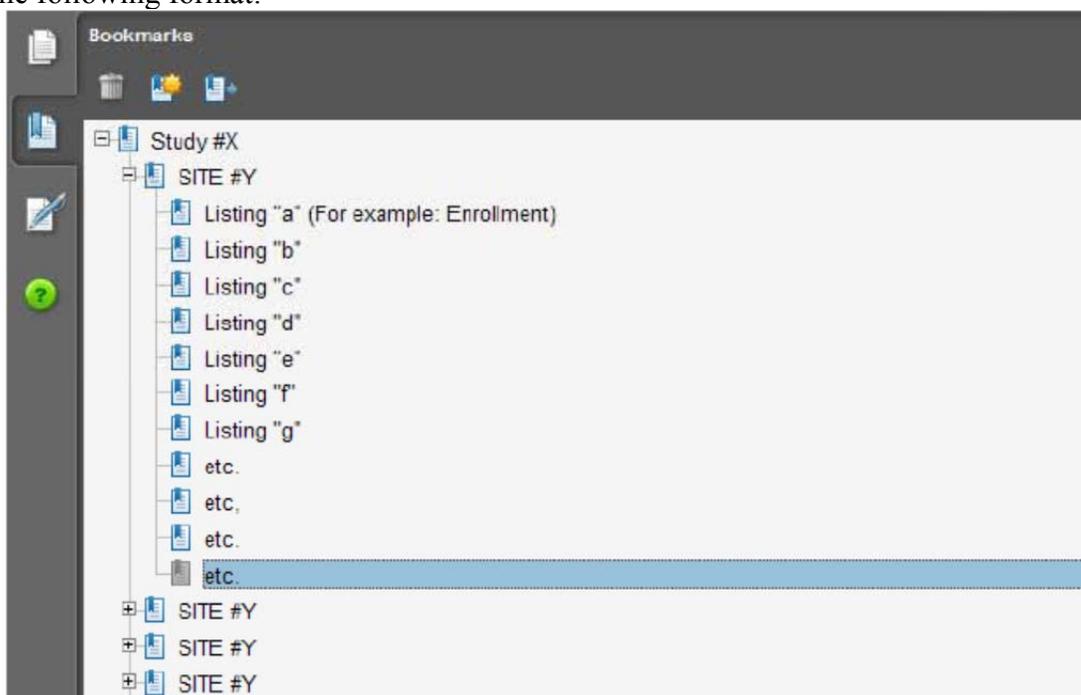
1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
 - a. Site number
 - b. Principal investigator
 - c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)

- 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.

7.0 ISSUES REQUIRING FURTHER DISCUSSION

Please see “Meeting Discussion” under 3a and 4d.

8.0 ACTION ITEMS

Action Item/Description	Owner	Due Date
Refer to “Meeting Discussion” under 3a and 4d.	Ardelyx	unknown

9.0 ATTACHMENTS AND HANDOUTS

Email responses from Ardelyx dated June 8, 2015.

15 Pages have been Withheld in Full as b4 (CCI/TS)
immediately following this page

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

/s/

ANISSA A DAVIS
06/12/2015