CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209279Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 58317

MEETING MINUTES

Actelion Clinical Research, Inc.
Attention:
Frances Duffy-Warren, PhD
Vice President, US Drug Regulatory Affairs
1820 Chapel Avenue West | Suite 300
Cherry Hill, NJ 08002

Dear Dr. Duffy-Warren:

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

We also refer to the meeting between representatives of your firm and the FDA on July 22, 2015. The purpose of the meeting was to obtain FDA's input on the acceptability of the proposed data package to support a sNDA for the inclusion of information on pediatric use of Tracleer with an appropriate pediatric formulation.

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 Wayne Amchin, RAC, Regulatory Project Manager at (301) 796-0421.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
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-sNDA meeting
Meeting Date and Time:	July 22, 2015, 1-2pm
Meeting Location:	FDA White Oak Campus, Building 22
Application Number:	IND 58317/NDA 21290
Product Name:	Tracleer (bosentan)
Indication:	Treatment of Pulmonary Arterial Hypertension
Sponsor/Applicant Name:	Actelion Pharmaceuticals Ltd.
Meeting Chair:	Norman Stockbridge, M.D., Ph.D.
Meeting Recorder:	Wayne Amchin, R.A.C.

FDA ATTENDEES

Office of Commissioner Participants:

Office of Pediatric Therapeutics:

Robert "Skip" Nelson, M.D., Ph.D.	Deputy Director and Senior Pediatric Ethicist

CDER Participants:

Division of Cardiovascular and Renal Products:

Norman Stockbridge, M.D., Ph.D.	Director
Shari Targum, M.D.	Clinical Team Leader
Maryann Gordon, M.D.	Clinical Reviewer
John Koerner. Ph.D.	Nonclinical Reviewer
Wayne Amchin	Regulatory Project Manager

Office of Clinical Pharmacology, Division of Clinical Pharmacology I:

Raj Madabushi, Ph.D.	Clinical Pharmacology Team Leader

Office of Biostatistics, Division of Biometrics I:

Jim Hung, Ph.D.	Director
John Lawrence, Ph.D.	Biometrics Reviewer

SPONSOR ATTENDEES

Frances Duffy-Warren, Ph.D.	VP Head of US Regulatory Affairs, Global DRA
Diogo Espanhol Viera	Global DRA Project Leader
Catherine Lesage, M.D.	Sr. Director, Clinical Science Pediatrics Head

Andjela Kusic- Pajic, M.D.	Senior Clinical Project Physician
Franck-Olivier Le Brun, Ph.D.	Senior Statistician
Martine Gehin-Beurne, Ph.D.	Project Clinical Pharmacologist

1.0 BACKGROUND

Actelion requested this pre-supplemental New Drug Application (sNDA) meeting to obtain FDA's input on the acceptability of the proposed data package to support a sNDA for the inclusion of information on pediatric use of Tracleer with an appropriate pediatric formulation.

Tracleer has Orphan designation, so it is exempt from the PREA requirements.

Tracleer is an endothelin receptor antagonist (ERA) indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise ability and to decrease clinical worsening. Studies establishing effectiveness included predominantly patients with (b) (4) Functional Class II-IV symptoms and etiologies of idiopathic or heritable PAH (60%), PAH associated with connective tissue diseases (21%), and PAH associated with congenital heart disease with left-to-right shunts (18%).

NDA 21290 Tracleer (bosentan) was approved for the treatment of pulmonary arterial hypertension on November 20, 2001, under the regulations for accelerated approval, 21 CFR 314 subpart H (314.500-560), with a Risk Minimization Plan (RiskMAP) due to the risks of teratogenicity and hepatotoxicity. Tracleer was deemed to have an approved REMS because the RiskMAP included elements to assure safe use. Tracleer was also approved with two postmarketing study commitments (PMCs). One PMC was to investigate potential metabolic interactions between Tracleer and hormonal contraceptives (e.g., oral and implantable contraceptives). This PMC was released on July 12, 2004. The second PMC was to investigate the potential testicular toxicity of Tracleer in humans. This PMC was fulfilled on December 22, 2008.

With the approval of supplements S-006 and S-007 on November 29, 2005, two more PMCs were added, one for a letter to Tracleer prescribers and one for a planned survey of physician practice. The PMC for the letter to prescribers was fulfilled on March 19, 2007, and the PMC for the survey was released on February 10, 2009.

The Risk Evaluation and Mitigation Strategy (REMS) for Tracleer (bosentan) was approved on August 7, 2009, and superseded the previous RiskMAP program. REMS modifications were approved on February 19, 2010, October 2, 2012, and July 1, 2013. The REMS consists of a Medication Guide, elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS. There is a REMS modification currently under review.

No ERA is approved for use in the pediatric population in the United States. That is not the case in the European Union. Actelion notes that the studies conducted to support pediatric approval in the EU were not designed in a manner normally expected to support a Written Request in the United States, but they believe these studies provide a solid basis for characterizing the use of Tracleer in the pediatric population using an appropriate pediatric formulation.

Actelion therefore is proposing that the information generated to support the pediatric use in the EU along with bridging to previously submitted adult data and the long-term postmarketing use information in pediatric patients be added to the US pediatric labeling.

2. DISCUSSION

Actelion stated that bosentan is coming off patent at the end of 2015. They were negotiating with FDA about a (b) (4) around 2012, but concerns over right heart catheritization (RHC) in pediatrics to measure a "research only" endpoint led to the end of those discussions. Actelion further noted that discussions are underway for a shared REMS for bosentan products.

Actelion stated there is no option for a new trial for use of bosentan in pediatrics, and they are not seeking a written request. They plan to submit a supplement based on the BREATH-3 data, submitted for the pediatric indication to the EMA. BREATH-3 was done at two Centers of Excellence in RHC. Actelion thinks they have an appropriate pediatric formulation for an unmet medical need in pediatric patients, and key opinion leaders in the US are asking what they can do for pediatric patients.

FDA stated that the ethical issues around repeat RHC is a review issue that would not preclude filing the sNDA when it is received. FDA further noted that where there are gaps in the data submitted in support of the sNDA, we may issue information requests to fill in the gaps.

2.1. Clinical

Question 1: Bridging of effectiveness observed in adults to the pediatric population: The clinical and hemodynamic characteristics of PAH and the therapeutic response to PAH-specific treatments are similar in adults and children. Studies conducted to support effectiveness of bosentan using hemodynamic variables in adult (AC-052-351, AC-052-364, AC-052-355 and AC-052-405) and pediatric (AC-052-356) PAH patients show similar improvement in both populations after administration of the film-coated tablet formulation.

Given the similarities in disease characteristics and treatment response, as well as the observed overlapping plasma exposure to bosentan following administration of the film-coated and the dispersible tablet formulations, does the Agency agree that there is adequate data to support the extrapolation of effectiveness observed in adults to the pediatric population?

FDA Response to Question 1: Theoretically, we would allow the use of hemodynamic variables as measures of effectiveness to support a pediatric indication as long as there is a demonstration of symptomatic effectiveness in the adult population. However, we currently are reviewing the appropriateness of using data (in this case, hemodynamic data) that were obtained by methods (in this case, right heart catheterization in children) we no longer consider ethical (as the follow-up right heart catheterization offers no therapeutic benefit and

presents significant risk). This issue will need to be resolved before we will accept the filing of your supplemental NDA.

Discussion: Actelion asked what will determine the FDA's acceptance of the NDA, realizing that they conducted only uncontrolled pediatric studies with small sample sizes. Actelion is planning to bridge adult and pediatric hemodynamic data. FDA responded that PK/PD bridging to determine ranges of exposures that are predicted to have the desired efficacy for pediatric PAH patients is an acceptable approach. If we were comfortable about efficacy, then an additional consideration is concern about the safety profile. Actelion noted that Tracleer has been used in studies with over 100 pediatric patients with a mean duration of 72 weeks of exposure to bosentan. They referenced Table 25 and 35 of the meeting package.

FDA commented that the lack of a control group makes the interpretation of the safety challenging and asked if there were any exposure-related side effects.

Actelion indicated that they observed no exposure-related relationships for either safety or efficacy. Tracleer has been in use in pediatrics in Europe for 6-7 years with around 6,500 pediatric patients in Europe and about 2,000 in the US, and there have been no safety signals that changed the labeling.

FDA noted that without good long-term data and not much information on hemodynamics, there does not appear to be a very good case for approval.

Question 2: Pediatric dose selection: Does the Agency agree that there is sufficient data to support the pediatric dosing recommendation of (b) (4) bosentan b.i.d.?

FDA Response to Question 2: No, we do not think there are adequate data to support a dose of (b) (4) b.i.d. in pediatric PAH patients. Based on PK and hemodynamic data generated in study AC-052-356 (Table 17 of briefing booklet), we see that in higher weight cohorts where exposures are closer (75%) to that of adult target exposures, there is no significant change from baseline in PVR (as well as for percent change from baseline). However, in lower weight cohorts whose exposures are about 50% lower to that of target adult exposures, there is a statistically significant change from baseline in PVR. We note that there are some differences in baseline PVR across the different weight cohorts. However, these changes by themselves do not seem to explain the exposure-effect.

Discussion: FDA inquired about the strength of the new dispersible tablets developed for pediatric patients. Actelion responded that they are 32 mg tablets breakable into (b) (4) mg. They do not match the adult strength. The pediatric formulation was only tested below 12 years of age.

Actelion provided clarification on BREATH 3. Across subgroups analyzed for efficacy, patients with highest body weight had on average less effect, but the analysis was not pre-specified and the study was underpowered to detect effects in subgroups. Actelion acknowledged that difference in baseline PVR across the body weight cohorts did not explain

this finding. Actelion believes that an outlier in the highest body weight cohort is likely responsible for this finding. The outlier had a PVR increase rather than decrease.

Actelion noted that there was long-term follow-up on 100 subjects out to one year, and postmarketing experience in 6,500 patients in Europe.

FDA further commented that at the present time people were grinding up the tablets so approval of a dispersible formulation could be desirable.

Question 3: Effectiveness endpoint: In a Cardiovascular and Renal Drugs Advisory Committee Meeting (29 July 2010), the question was discussed of whether a treatment effect PVRI could be used to demonstrate effectiveness and to derive dosing information in the pediatric PAH population for a product with an approved indication in adults with PAH. An interpretation of the outcome of the Advisory Committee Meeting was provided in the 28 March 2012 Medical Review for NDA 203109 (Revatio®) suggesting that for a product with an approved indication in adults with PAH, a treatment effect on PVRI can be used to demonstrate effectiveness and to derive dosing information in the pediatric PAH population. Especially, the use of PVRI as a basis for approval in some subgroups for which the 6 minute walking distance test is not appropriate, was recognized as theoretically possible [Lawrence 2012].

PVRI can be derived from PVR via the following equation: PVRI = PVR × body surface area. Given the variability in baseline PVR in the different studies of relevance, the percent of baseline is considered more appropriate than the absolute change from baseline.

Actelion therefore proposes to use PVR collected by right heart catheterization (RHC) and expressed as percent of baseline as the primary endpoint for the analysis of effectiveness of TRACLEER

Does the Agency agree with the use of PVR as an endpoint for establishing effectiveness of bosentan in the pediatric PAH population?

FDA Response to Question 3: See the response to question 1.

Discussion: See the questions 1 and 2.

Question 4: Presentation of efficacy data: The basis for demonstration of pediatric effectiveness involves the bridging from adult hemodynamic data from studies AC-052-351 (original NDA 11 September 2001), AC-052-355 (submitted in S-01, 4 December 2002), AC-052-364 (study in WHO FC II submitted in S-12, 3 August 2007) and AC-052-405 (study in Eisenmenger's syndrome submitted in S-09, 14 April 2006) to those obtained in the pediatric AC-052-356 study (submitted in S-01), a hemodynamic sub-study of AC-052-373 and a Japanese study AC-052-377. The pivotal study of bosentan in adults with PAH, (AC-052-352), is not included as no hemodynamic data were collected.

The main bosentan PAH pediatric study generating hemodynamic data was AC-052-356. It included pediatric patients aged 3 to 15 years, with either WHO class II or III PAH, and who were treatment naïve or were on stable epoprostenol treatment at enrolment and throughout the study. In addition, hemodynamic data from a subgroup of the AC-052-373 study and from a study in Japanese WHO Class II pediatric PAH below 15 years of age are available [Table 3].

Actelion proposes to compare the AC-052-356 pediatric data with those obtained in the four adult PAH studies, which also included a spectrum of disease severity (WHO Class II-IV), and patients with and without background treatment. Given the differences in study design, patient population, and treatment duration between the studies (both pediatric and adult), the clinical effectiveness data will be described separately for each study, i.e., no integration will be performed.

It is proposed that the comparison of adult and pediatric hemodynamic data will be summarized in 2.7.3 Summary of Clinical Efficacy (SCE). However, it is not planned that there will be any pooled effectiveness data presented in the SCE. Does the Agency agree with this approach?

FDA Response to Question 4: Your lack of controlled data is of concern to the Division.

Discussion: See the discussion under questions 1 and 2.

Question 5: Clinical Summary of Safety: A total of 4 pediatric PAH studies have been performed with bosentan: the three global studies AC-052-356, AC-052-365 and AC-052-373 (with the extensions of the latter two), and one Japanese study, AC-052-377. It is proposed to perform a pooled analysis of the safety data of the AC-052-365 and AC-052-373 studies and their respective extensions. These two studies have largely comparable populations and overall design. The dosing regimen of bosentan was approximately 2 mg/kg b.i.d. although AC-052-365 and AC-052-373 also investigated a dose of 4 mg/kg b.i.d. and a dose of 2 mg/kg t.i.d.,respectively. The dosing regimens resulted in similar daily exposures.

Due to differences in treatment exposure and size of population, it is proposed to describe the AC-052-356 and AC-052-377 studies separately.

An additional study was conducted in PPHN (AC-052-391). This study is not included in the safety evaluation due to the short term study drug administration and in a population of patients (neonates) affected by a transient form of PAH. It is of note that this entity carries more differences than similarities with other PAH subgroups, and is therefore withdrawn from PAH Group 1 in the most recent PAH Classification [Simonneau 2013].

Therefore, safety data will be presented as integrated pooled safety analysis for 100 pediatric PAH patients, aged 3 months to 11.7 years.

Additional sources of safety data for bosentan in the pediatric population, which will be described separately, will consist of:

• a review of serious adverse event (SAE) reports from ongoing trials reported to the Actelion Drug Safety department;

• a review of post-marketing data from various sources, spontaneous reports and solicited reports (including observational programs, regulatory authorities and literature), covering 13 years of marketed use of bosentan with an estimated cumulative exposure of 6,563 pediatric patients and 140,623 adult/elderly patients.

Case report forms (CRFs) and narratives will be provided from all completed studies identified in Table 4 (with the exception of AC-052-377) for all deaths, SAEs, adverse events (AEs) leading to discontinuation, and for patients who experienced a markedly abnormal laboratory finding associated with liver enzyme elevation (alanine aminotransferase [ALT] or aspartate aminotransferase [AST] > 3 × upper limit of normal [ULN]). CRFs and narratives may also be provided for AEs of special interest identified from the safety analysis of the PAH studies. Study AC-052-377 is considered as a secondary source of data and was not submitted to the Tracleer IND 058317 for PAH, therefore it is not planned to submit CRFs from this Japanese study.

Does the Agency agree that the content and presentation of the safety data as described in the Statistical Analysis Plan (SAP, presented in Appendix 1) for the Summary of Clinical Safety (SCS) are adequate to support the use of the dispersible tablet formulation at (b) (4) b.i.d. in the pediatric PAH population?

FDA Response to Question 5: We are concerned about lack of long term safety data. We understand that the longest trial in children was 24 weeks and included only 4 subjects.

Discussion: See the discussion under questions 1 and 2.

Question 6: 120-Day Safety Update: Actelion proposes in accordance with CFR 314.50 (d)(5)(vi)(b) to provide an update to the application with new safety information, 120 days after the sNDA submission. The safety update will include data available after the 1 March 2015 cut-off established for the application through the data cut-off of 19 November 2015 (which also coincides with the cut-off date for the Tracleer PBRER).

The 120 day safety update will include updated postmarketing safety data regarding pediatric use. It is also anticipated that updated information from the currently on-going Japanese study AC-052-378 (with up to 6 patients) will be included in the 120 day safety update. As study AC-052-378 is expected to still be on-going at the cut-off date for the 120 day safety update, clinical study safety data with narratives for any deaths, SAEs, and AEs leading to discontinuation will be provided. It is not anticipated that any new studies will be initiated and all completed studies will have been included in the sNDA.

Does the FDA agree with the proposal for the Day 120 safety update to the sNDA?

FDA Response to Question 6: Yes.

Discussion: This question was not discussed.

2.2. Regulatory

Question 7: Proposed Datasets: Actelion will submit datasets for the following studies: AC-052-116, AC-052-356, AC-052-365, AC-052-367, AC-052-373 and its extension AC-052-374.

Non-CDISC source datasets, and analysis datasets ("non-CDISC derived analysis datasets") were used by Actelion to produce tables, listings, and graphs for the efficacy and safety analyses included in the clinical study reports for the above mentioned studies.

For source data sets, SAS version 5 transport (.xpt) files will be provided. Each file will be described in the associated data definition document (define.pdf files). Annotated CRFs (the annotation will refer to the CRF data included in the non-CDISC source datasets) will be included with the submission. Examples of annotated CRF and definition file content for the source datasets can be found in Appendix 2.

Derived analysis datasets are based on non-CDISC source datasets and will be provided together with derived data definition documentation (metadata).

The structure and format of the above mentioned non-CDISC source and analysis datasets will be similar to the datasets provided for AC-055-302/ SERAPHIN (see NDA 204410 nda204410\0000\m5\datasets\ac-055-302\analysis\legacy\datasets).

A list of analysis datasets to be submitted for the AC-052-373 study is provided [Table 5]. A similar list of analysis datasets will be submitted for the other studies. If required analysis datasets for more domains will be included at the time of submission.

As noted in Section 9.1.5.1, study AC-052-377 is considered as a secondary source of data and therefore it is not planned to submit any datasets from this Japanese study. A waiver from patient profiles is requested.

Does the Agency agree with the proposed approach to the clinical datasets planned for submission in the application?

FDA Response to Question 7: Yes. The proposed submission of datasets seems adequate.

Discussion: This question was not discussed.

Question 8: Submission Content: Does the Agency agree with the overall eCTD content plan to support the sNDA filing for Tracleer in pediatric patients with PAH [as stated in Appendix 3]?

FDA Response to Question 8: Yes, the submission content appears to be adequate. Please ensure that you submit the required CRFs.

Discussion: This question was not discussed.

Question 9: Eligibility for Exclusivity: As a supplement to NDA 21-290, the application proposed will contain reports of new clinical investigations (other than bioavailability studies) conducted or sponsored by Actelion and considered essential to approval. Consistent with 21 CFR 314.108, the sponsor is of the opinion that the proposed application is eligible for 3 years of market exclusivity.

Actelion is of the opinion that the proposed pediatric supplement to the NDA meets the criteria for 3 years of market exclusivity, if approval is granted. Does the Agency agree?

FDA Response to Question 9: FDA does not grant exclusivity prior to approval of a drug product. We do agree that a clinical study is needed for approval, which is supportive of exclusivity.

Discussion: FDA asked if we end up with no claim but language in the pediatrics section regarding dosing, would that be sufficient for Actelion to pursue the sNDA?

Actelion noted that a clinical study is necessary to get Hatch-Waxman exclusivity.

FDA responded that if the Division asserted that the clinical trial submitted in support of the sNDA was essential to the decision than Actelion may get Hatch-Waxman exclusivity.

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.
Because this drug product for this indication has an orphan drug designation, you are exempt from these requirements. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *PLLR Requirements for Prescribing Information* websites including:

- 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 in the PI for human drug and biological products
- 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 42 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.

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

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.

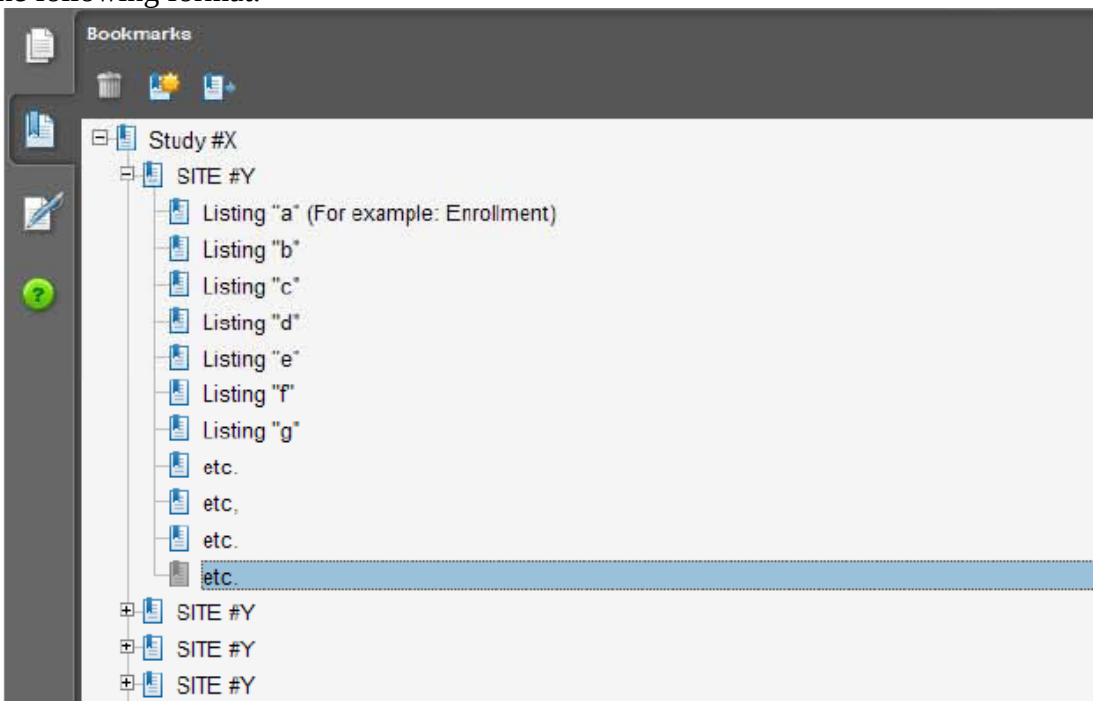
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere 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 are no action items.

6.0 ATTACHMENTS AND HANDOUTS
Actelion's meeting handout is attached.

2 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

NORMAN L STOCKBRIDGE
08/10/2015