

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**213388Orig1s000**

**ADMINISTRATIVE and CORRESPONDENCE**  
**DOCUMENTS**



IND 115528

**MEETING MINUTES**

AbbVie Inc  
Attention: Lakshmi Rebbapragada, M.S.  
Associate Director, Regulatory Affairs  
1 N. Waukegan Road  
Dept. PA77/Bldg. AP30  
North Chicago, IL 60064

Dear Ms. Rebbapragada:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for elagolix plus estradiol/norethindrone acetate.

We also refer to the telecon between representatives of your firm and the FDA on June 13, 2019. The purpose of the meeting was to discuss the proposed content and format of the planned NDA for uterine fibroids.

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

If you have any questions, call Maria Wasilik, Regulatory Project Manager at 301-796-0567.

Sincerely,

*{See appended electronic signature page}*

Christina Chang, M.D., M.P.H.  
Clinical Team Leader  
Division of Bone, Reproductive, and Urologic  
Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes



## MEMORANDUM OF MEETING MINUTES

**Meeting Type:** Type B  
**Meeting Category:** Pre-NDA

**Meeting Date and Time:** June 13, 2019, @ 9:50 A.M.  
**Meeting Location:** teleconference

**Application Number:** IND 115528  
**Product Name:** elagolix plus estradiol/norethindrone acetate.

**Indication:** management of heavy menstrual bleeding associated with uterine fibroids

**Sponsor Name:** AbbVie

**Meeting Chair:** Christina Chang  
**Meeting Recorder:** Maria Wasilik

### FDA ATTENDEES

#### Division of Bone, Reproductive, and Urologic Products

Christine Nguyen, M.D., Deputy Director for Safety  
Christina Chang, M.D., M.P.H., Clinical Team Leader  
Marcea Whitaker, M.D., Clinical Reviewer  
Margaret Kober, R.Ph., M.P.A., Chief, Project Management Staff  
Maria Wasilik, R.Ph., Regulatory Health Project Manager  
Mukesh Summan, Ph.D., D.A.B.T., Pharmacology/Toxicology Supervisor  
Leslie McKinney, Ph.D. Pharmacology/Toxicology Reviewer

#### Office of Pharmaceutical Quality, Office of New Drug Products, Division of New Drug Products II

Mark Seggel, Ph.D., Acting Chemistry, Manufacturing, and Controls (CMC) Lead

#### Office of New Drugs, Immediate Office Policy Staff

Richard (Wes) Ishihara, M.E.M., Regulatory Policy Advisor

### SPONSOR ATTENDEES

Robert Scott, M.D., Vice President, Development and Chief Medical Officer  
Janet Hammond, M.D., Ph.D., Vice President, Infectious Diseases and General Medicine  
Andrew Campbell, M.D., Executive Medical Director, Infectious Disease and General Medicine

Charlotte Owens, M.D., Medical Director, Clinical Development, General Medicine  
James Thomas, M.S., Director, Statistics  
Ran Lui, Ph.D., Senior Manager, Statistics  
Deepa Chand, M.D., M.H.S.A., Associate Medical Director, Pharmacovigilance and Patient Safety  
Brian Enright, M.S., Ph.D., D.A.B.T., Senior Principal Research Scientist, Preclinical Safety  
Neal Mostafa, Ph.D., Senior Director, Clinical Pharmacology and Pharmacometrics  
Leslie Carter, PharmD., Vice President, Global Therapeutic Area Head, Global Regulatory Strategy  
David Perkins, J.D., Director, Global Regulatory Lead, Global Regulatory Strategy  
Sharon Graham, Associate Director, Regulatory Affairs, CMC  
Andrew Cagnassola, Pharm.D., Pharmacist Development Program, Global Regulatory Strategy

## 1.0 BACKGROUND

Elagolix is a gonadotropin-releasing hormone receptor antagonist. The Sponsor is developing elagolix 300 mg twice daily with E2/NETA 1 mg/0.5 mg daily add-back therapy for the management of heavy menstrual bleeding associated with uterine fibroids. The dosing regimen is as follows:

- Morning dose: elagolix/E2/NETA 300/1/0.5 mg capsule, a fixed-dose combination of one elagolix 300 mg tablet and one (b) (4) tablet encapsulated in a hard gelatin capsule;
- Evening dose: elagolix 300 mg capsule, consists of one elagolix 300 mg tablet in a hard gelatin capsule.

The purpose of the meeting is to reach agreement with the Agency regarding the proposed content and format of the planned NDA for uterine fibroids. This includes specific Chemistry, Manufacturing, and Controls (CMC), Nonclinical, Clinical, Regulatory, Pharmacovigilance, and data presentation-related topics.

Single-active ingredient elagolix sodium is approved as Orilissa (elagolix 150 mg and 200 mg oral tablets) for the management of moderate to severe pain associated with endometriosis under NDA 210450. E2/NETA (Activella, NDA 020907) used as add-back therapy in this regimen is approved for the treatment of moderate to severe vasomotor symptoms due to menopause and the prevention of postmenopausal osteoporosis. The Sponsor has obtained a right of reference letter to the Activella NDA for cross-referencing Activella's CMC information.

The FDA's preliminary responses (in *italics*) were sent to the Sponsor on May 24, 2019. On June 4, 2019, the Sponsor sent in a slide set containing discussion points, accompanied by follow-up questions regarding FDA's responses to Questions 1, 2b, 3b, 4a, 7e, 7f, and 9. The Sponsor acknowledged FDA's responses to Questions 2a, 3a, 4b, 5, 6, 7a-7d, and 8 and sought no further discussion for these responses. At the outset of

the teleconference, FDA stated that the additional information provided by the Sponsor to Questions 3b, 7e, 7f were adequate to address the preliminary responses. Discussions that occurred during the teleconference on Questions 1, 2b, 4a, and 9 are reflected under "Discussion at the Meeting." Additional discussions on review timelines and the combination drug rule are captured at the end of these minutes.

## 2. DISCUSSION

### **Question 1:**

Does the Agency agree with the master and executed batch record proposal?

### **FDA Response to Question 1:**

*Your proposal to include the executed batch records for one batch of the elagolix/estradiol/norethindrone acetate 300/1/0.5 mg capsule and one batch of the elagolix 300 mg capsule from the primary stability batches as well as the master production record for each capsule is, in principle, reasonable. In case the registration/stability executed batch records are different (including manufacturing site, scale, unit operations and process controls) from the batches used for clinical study, submit the clinical batch records as well. Also, refer to ICH M4Q (R1).*

### **Discussion at the Meeting:**

The proposal outlined on page 3 of the pre-NDA Meeting Discussion Points is acceptable. FDA noted, however, that records for other batches should be available upon request.

### **Question 2a:**

Does the Agency agree that the completed elagolix nonclinical studies previously submitted under the endometriosis NDA 210450 are adequate to support the uterine fibroids NDA and that no additional nonclinical studies are needed?

### **FDA Response to Question 2a:**

Yes.

### **Question 2b:**

AbbVie proposes to include the nonclinical overview Module 2.4 to support the uterine fibroids indication and will cross-refer to Modules 2.6 and 4 in the Orilissa 210450 NDA. Does the Agency agree?

### **FDA Response to Question 2b:**

Yes. Within the NDA submission, provide a tabular listing of the amount of each impurity and total impurities that will be administered in the proposed dose of elagolix of 300 mg twice daily.

### **Discussion at the Meeting:**

The Sponsor provided a table of impurities in their response document. The Agency agreed that the information in the table was adequate.

**Question 3a:**

Does the Agency agree with the planned content for the integrated efficacy analysis set?

**FDA Response to Question 3a:**

*Yes. We agree with your proposal to split the integrated efficacy analysis between Module 2 and Module 5, with Module 2 containing text summary, making reference to the tables and data sets in Module 5.*

**Question 3b:**

Does the Agency agree with the proposed Integrated Summary of Efficacy (ISE) Statistical Analysis Plan (SAP) and the presentation of the efficacy data?

**FDA Response to Question 3b:**

*Yes. We agree with your proposed SAP for the ISE. The ISE should also compare and contrast the individual studies. See sample table below.*

*Additionally, include a summary of efficacy data from the Phase 2 dose-finding program.*

Visit	Study 1		Study 2		Integrated Studies	
	PBO/ Comparator (N=XXX)	Study Drug (N=XXX)	PBO/ Comparator (N=XXX)	Study Drug (N=XXX)	PBO/ Comparator (N=XXX)	Study Drug (N=XXX)
Baseline						
n	X	X	X	X	X	X
Mean (SD)	X	X	X	X	X	X
Median	X	X	X	X	X	X
Min, max	X	X	X	X	X	X
End of Study						
n	X	X	X	X	X	X
Mean (SD)	X	X	X	X	X	X
Median	X	X	X	X	X	X
Min, max	X	X	X	X	X	X
Change from Baseline						
n	X	X	X	X	X	X
Mean (SD)	X	X	X	X	X	X
Median	X	X	X	X	X	X
Min, max	X	X	X	X	X	X
Median Difference (Study drug -PBO)	X	X	X	X	X	X
p-value	X	X	X	X	X	X

**Question 4a:**

Does the Agency agree with the planned content for the integrated safety analysis sets?

**FDA Response to Question 4a:**

*We agree that the Phase 2 studies used different doses and different durations of treatment and should not be pooled with Phase 3 safety data. However, the 3- and 6-month, Phase 2 data (M12-663 and M12-813) need to be included in your safety assessment and should be presented separately in the ISS. Therefore, there should be a Phase 3 alone analysis and a combined Phase 2/3 analysis in your ISS. Also, your ISS should contain a presentation of safety data by treatment group/duration. Include both raw and analysis safety datasets for these studies.*

*Regarding Phase 2 data, particular interest will be given to the 65 subjects in M12-813 who received the to-be-marketed dosing, Elagolix 300 mg twice daily +E2/NETA, 0.5 mg/0.1 mg daily for 6 months.*

*Provide a tabular listing of the numbers of subjects/patients exposed to elagolix (total dose  $\geq$  600 mg/day) with and without E2/NETA for at least 6 months duration.*

**Discussion at the Meeting:**

The Sponsor clarified that Phase 3 raw and analysis datasets will be provided in SDTM format, along with a define file and SDTM reviewer's guide.

For Phase 2 studies M12-663 and M12-813, the Sponsor will submit the raw data in a legacy case report tabulation (CRT) format with annotated case report forms and define.pdf files. FDA agreed with the proposed approach.

The Sponsor also agreed to recode the adverse events in these Phase 2 studies using the same MedDRA version as that used in the Phase 3 studies.

**Question 4b:**

Does the Agency agree with the proposed Integrated Summary of Safety (ISS) SAP and the presentation of the safety data?

**FDA Response to Question 4b:**

*See Response to 4a above.*

**Question 5:**

Does the Agency agree with the proposed content and format of the clinical datasets and SAS programs to be provided?

**FDA Response to Question 5:**

*From the technical standpoint, the proposed format of the clinical datasets and SAS programs to be provided are acceptable.*

*We recommend that you submit datasets of drug plasma concentrations and pharmacokinetic parameters for the seven Phase 1 studies in SAS Institute Transport File format (xpt). See also response to Question 4a above.*

**Question 6:**

Does the Agency agree with the proposed plan for the 4- month safety update for the uterine fibroids studies?

**FDA Response to Question 6:**

Yes.

**Question 7:**

Does the agency agree with the cross-referencing strategy for the NDA as described in Appendix A? Specifically:

**Question 7a:**

Cross reference drug product and drug substance CMC information in Activella NDA 020907 for E2/NETA add-back therapy?

**FDA Response to Question 7a:**

Yes.

**Question 7b:**

Cross reference elagolix CMC drug substance information in the Orilissa NDA 210450?

**FDA Response to Question 7b:**

Yes.

**Question 7c:**

Cross reference nonclinical studies in the Orilissa NDA 210450?

**FDA Response to Question 7c:**

*Yes. Also, refer to our response to Question 9 for the information required to support the nonclinical section in Activella NDA 020907.*

**Question 7d:**

Cross reference abuse liability report in the Orilissa NDA 210450?

**FDA Response to Question 7d:**

Yes.

**Question 7e:**

*Cross reference environmental assessment in the Orilissa NDA 210450 and the categorical exclusion in the Activella NDA 020907?*

**FDA Response to Question 7e:**

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Yes. Also provide an assessment addressing the increase in use of elagolix related to the proposed action (including whether the increase is significant in terms of environmental impact) and justification for no increased use of E2/NETA.

**Question 7f:**

Cross reference clinical pharmacology studies in the Orilissa NDA 210450?

**FDA Response to Question 7f:**

Your plan of cross-referencing clinical pharmacology studies in the Orilissa NDA 210450 appears reasonable. However, we note that in your NDA 210450 submission, drug interaction with digoxin was assessed using a single dose of elagolix 200 mg and twice daily (BID) doses of elagolix 200 mg in Study M12-652. The study results are inadequate to support the proposed dosing regimen of 300 mg BID elagolix for your planned NDA for the fibroids program.

Furthermore, your clinical drug interaction study results showed that elagolix is an inducer of CYP3A. Considering the similarities in the mechanism of induction for CYP3A and P-gp, conduct a study to assess P-gp inhibition and induction using elagolix 300 mg BID dose.

**Question 8:**

Does the Agency agree with the proposal to provide financial disclosure information for the pivotal Phase 3 studies (M12-815 and M12-817) including the extension study and the BE/FE studies (Study M16-856 and Study M19-648)?

**FDA Response to Question 8:**

Yes. Also include financial disclosure information for the bioavailability study, M15-872.

**Question 9:**

Does the Agency agree that the proposed content and format of the planned NDA for elagolix, as described within this briefing package and outlined in the Table of Contents (Appendix B), is acceptable and constitutes a complete, fileable NDA to support a review for the proposed indication of management of HMB associated with uterine fibroids? (b) (4)

**FDA Response to Question 9:**

It is premature to comment on whether your application is fileable.

In general, if you own or have a right of reference to all of the data/information that you are relying upon for approval (b) (4)

However, we note on page 85 of your background package that you only intend to cross-reference NDA 210450 for Orilissa to address the nonclinical section of your NDA (i.e., to address the elagolix component of your proposed product). Clarify how you will address the nonclinical section of your proposed NDA for the estradiol and norethindrone acetate components of your proposed product. If you propose to cross-

*reference NDA 020907 for Activella tablets to address the nonclinical sections of your proposed NDA, you should clarify which specific information/data you intend to cross-reference.*

#### **Discussion at the Meeting:**

FDA clarified that Amneal's NDA 020907 for Activella is a 505(b)(2) NDA. If the Sponsor has a right of reference to all the data/information that they are relying upon for approval [REDACTED] (b) (4) However, the information Amneal's NDA relied upon that was necessary for its approval may impact the regulatory pathway for the planned NDA cross-referencing Amneal's NDA (through a Letter of Authorization). For example, if Amneal's NDA relied upon published literature necessary for its approval (and the Sponsor did not provide data that would otherwise fulfill the nonclinical requirement), the planned NDA may be presumed to be relying, in part, on the same published literature (that the Sponsor does not own or have right of reference to). This would constitute "505(b)(2) reliance." If, however, the Sponsor can demonstrate that they are only referencing portions of the Activella 505(b)(2) application that do not involve reliance on information that caused the Activella NDA to be a 505(b)(2) NDA [REDACTED] (b) (4)

#### **Additional Discussion on Review Timelines:**

FDA confirmed that the planned NDA will be a Type 4 NDA subject to a review cycle of 10 months. Because the NDA will not be in the Program, mid- and late-cycle review meetings are not applicable.

#### **Additional Discussion on Addressing the Combination Drug Rule**

FDA stressed that E2/NETA is not a single product; rather, it is a fixed dose combination product with two active ingredients. The Sponsor must justify the role of each active ingredient (E2 and NETA), be it safety or efficacy, in the combination of elagolix+E2/NETA. The Sponsor agreed to address this requirement in the NDA submission.

#### **ADDITIONAL COMMENTS:**

##### **Clinical Outcome Assessment:**

1. If any clinical outcome assessment information is provided electronically [e.g., a Patient-Reported Outcomes (PRO) evidence dossier], place it in section 5.3.5.3 of the electronic common technical document per the FDA Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims.<sup>1</sup>

<sup>1</sup> <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/patient-reported-outcome-measures-use-medical-product-development-support-labeling-claims>

**CMC:**

2. To ensure that the forthcoming NDA is complete, provide the following prior to the June 7, 2019 meeting, if feasible.
  - a. An overview of the stability program including the registration batch stability protocol. Indicate the planned duration of the stability studies at the time of submission.
  - b. A tabulation of all drug product formulations and batches used to support the NDA including batch number, formulation, date of manufacture, site of manufacture, site of packaging, use of batch (including clinical study number). Include information for elagolix tablets, estradiol/norethindrone acetate tablets, and combinations of the two including over-encapsulated products.
  - c. Indicate how the clinical trial materials will be bridged to product manufactured at the commercial site.

**Discussion at the Meeting:** The Agency acknowledged receipt of the May 31, 2019, submission with the stability program summary and the tabulation of drug product batches that will be used to support the NDA. The Agency had no further comments on the information provided.

### 3.0 ADDITIONAL INFORMATION

#### **DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION**

As stated in our April 2, 2019, communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to “the Program” under PDUFA VI. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions and, where applicable, the development of a Formal Communication Plan. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

Discussions and agreements will be summarized at the conclusion of the meeting and reflected in FDA’s meeting minutes. If you decide to cancel this meeting and do not

have agreement with FDA on the content of a complete application or late submission of any minor application components, your application is expected to be complete at the time of original submission.

In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities.

Information on the Program is available at

<https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm>.

## **PRESCRIBING INFORMATION**

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

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

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*

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(<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.

### **ABUSE POTENTIAL ASSESSMENT**

Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential and a proposal for scheduling will be required at the time of the NDA submission [21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of your NDA submission, see the Guidance for Industry, *Assessment of Abuse Potential of Drugs*, available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf>.

### **505(b)(2) REGULATORY PATHWAY**

The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the draft guidance for industry, *Applications Covered by Section 505(b)(2)* (October 1999), available at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at: <http://www.regulations.gov>).

If you intend to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

If you intend to rely on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature or on the other studies is scientifically appropriate. You should include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature (e.g. by trade name(s)).

If you intend to rely on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA's finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the "listed drug for which FDA has made a finding of safety and effectiveness," and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

If FDA has approved one or more pharmaceutically equivalent products in one or more NDA(s) before the date of submission of the original 505(b)(2) application, you must identify one such pharmaceutically equivalent product as a listed drug (or an additional listed drug) relied upon (see 21 CFR 314.50(i)(1)(i)(C), 314.54, and 314.125(b)(19); see also 21 CFR 314.101(d)(9)). If you identify a listed drug solely to comply with this regulatory requirement, you must provide an appropriate patent certification or statement for any patents that are listed in the Orange Book for the pharmaceutically equivalent product, but you are not required to establish a "bridge" to justify the scientific appropriateness of reliance on the pharmaceutically equivalent product if it is scientifically unnecessary to support approval.

If you propose to rely on FDA's finding of safety and/or effectiveness for a listed drug that has been discontinued from marketing, the acceptability of this approach will be contingent on FDA's consideration of whether the drug was discontinued for reasons of safety or effectiveness.

We encourage you to identify each section of your proposed 505(b)(2) application that is supported by reliance on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature (see table below). In your 505(b)(2) application, we encourage you to clearly identify (for each section of the application, including the labeling): (1) the information for the proposed drug product that is provided by reliance on FDA's finding of safety and/or effectiveness for the listed drug or by reliance on published literature; (2) the "bridge" that supports the scientific appropriateness of such reliance; and (3) the specific name (e.g., proprietary name) of each listed drug named in any published literature on which your marketing application relies for approval. If you are proposing to rely on published literature, include copies of the article(s) in your submission.

In addition to identifying the source of supporting information in your annotated labeling, we encourage you to include in your marketing application a summary of the information that supports the application in a table similar to the one below.

<b>List the information essential to the approval of the proposed drug that is provided by reliance on the FDA’s previous finding of safety and effectiveness for a listed drug or by reliance on published literature</b>	
<b>Source of information (e.g., published literature, name of listed drug)</b>	<b>Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)</b>
<i>1. Example: Published literature</i>	<i>Nonclinical toxicology</i>
<i>2. Example: NDA XXXXXX “TRADENAME”</i>	<i>Previous finding of effectiveness for indication A</i>
<i>3. Example: NDA YYYYYY “TRADENAME”</i>	<i>Previous finding of safety for Carcinogenicity, labeling section B</i>
<i>4.</i>	

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a “duplicate” of a listed drug and eligible for approval under section 505(j) of the FD&C Act, then it is FDA’s policy to refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an Abbreviated New Drug Application (ANDA) that cites the duplicate product as the reference listed drug.

### **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

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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>.

#### **4.0 ATTACHMENTS AND HANDOUTS**

The Sponsor provided a response document.

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/s/

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MARIA R WASILIK  
07/09/2019 04:02:47 PM

CHRISTINA Y CHANG  
07/09/2019 04:04:00 PM



PIND 115528

**MEETING MINUTES**

AbbVie Inc.  
Attention: Kelly Kaleck-Schlinsog, M.S.  
Associate Director, Regulatory Affairs  
1 N. Waukegan Road  
Dept. PA77/Bldg AP30  
North Chicago, IL 60064

Dear Ms. Kaleck-Schlinsog:

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

We also refer to the meeting between representatives of your firm and the FDA on May 27, 2015. The purpose of the meeting was to discuss your phase 3 clinical development plan for heavy menstrual bleeding associated with uterine fibroids.

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 Maria Wasilik, Regulatory Project Manager at (301) 796-0567.

Sincerely,

*{See appended electronic signature page}*

Lisa Soule, M.D.  
Clinical Team Leader  
Division of Bone, Reproductive, and Urologic 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**

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**MEMORANDUM OF MEETING MINUTES**

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

**Meeting Date and Time:** May 27, 2015 at 11:00 A.M.-12:30 P.M.  
**Meeting Location:** 10903 New Hampshire Avenue  
White Oak Building 22, Conference Room: 1415  
Silver Spring, Maryland 20903

**Application Number:** 115528  
**Product Name:** elagolix

**Indication:** Management of heavy menstrual bleeding associated with uterine fibroids  
**Sponsor/Applicant Name:** AbbVie Inc.

**Meeting Chair:** Lisa Soule, M.D.  
**Meeting Recorder:** Maria Wasilik, R.Ph.

**FDA ATTENDEES**

Division of Bone, Reproductive, and Urologic Products (DBRUP)

Audrey Gassman, M.D., Deputy Director  
Lisa Soule, M.D., Clinical Team Leader  
Gerald Willett, M.D., Medical Officer  
Krishan Raheja, D.V.M., Ph.D., Pharmacology/Toxicology Reviewer  
Maria Wasilik, Regulatory Project Manager  
Margaret Kober, R.Ph., M.P.A., Chief, Project Management Staff  
Nikia Morris, M.S.H.A., M.B.A., Regulatory Project Manager

Office of Pharmaceutical Quality (OPQ), Office of New Drug Quality Assessment (ONDQA)

Vidula Kolhatkar, Ph.D., Biopharmaceutics Reviewer

Office of Translational Sciences (OTS), Office of Clinical Pharmacology (OCP), Division of Clinical Pharmacology III (DCPIII)

Chongwoo Yu, Ph.D., Clinical Pharmacology Reviewer

Office of Biostatistics (OB), Division of Biometrics III (DBIII)

Mahboob Sobhan, Ph.D., Team Leader  
Jia Guo, Ph.D., Mathematical Statistician

## **SPONSOR ATTENDEES**

Rita Jain, M.D., Vice President, Global Pharmaceutical Research and Development  
Laura Williams, M.D., M.P.H., Group Project Director, Global Pharmaceutical Research and Development  
Kristof Chwalisz, M.D., Ph.D., Senior Medical Director, Global Pharmaceutical Research and Development  
Charlotte Owens, M.D., Medical Director, Global Pharmaceutical Research and Development  
Khaudeja Bano, M.D., Senior Medical Director, Medical Safety Evaluation  
Bo Yang, Director, Statistics, Data and Statistical Sciences  
James Thomas, M.S., Principal Research Statistician, Data and Statistical Sciences  
Jingjing Gao, Ph.D., Manager, Statistics, Data and Statistical Sciences  
Juki Wing-Keung Ng, Pharm.D., Ph.D., Director, Clinical Pharmacokinetics and Pharmacodynamics  
Ramesh Garg, B.V.Sc., Ph.D., D.A.B.T., Director, Preclinical Safety  
Kelly Kaleck-Schlinsog, M.S., Associate Director, Regulatory Affairs, US & Canada Regulatory Affairs  
William Gray, M.S., Therapeutic Area Head, US & Canada Regulatory Affairs  
Brian A. Green, M.S., Director, Global Regulatory Lead

## **1.0 BACKGROUND**

Elagolix is a gonadotropin-releasing hormone (GnRH) antagonist. (b) (4)

On July 30, 2012, the Sponsor met with the Division for a pre-IND meeting to discuss the phase 2b study design and clinical development plan for a chronic indication for the management of heavy menstrual bleeding (HMB) associated with uterine fibroids. The current IND was opened on November 30, 2012, with the protocol for a phase 2b study (Protocol M12-813).

The purpose of the current meeting is to discuss the elagolix phase 3 clinical development plan for the fibroids indication. AbbVie is seeking to gain Agency agreement on the following:

1. The adequacy of the nonclinical and clinical pharmacology data to support the planned uterine fibroids New Drug Application (NDA) submission
2. The proposed phase 3 clinical development program to support the NDA and the target labeling claim
3. The safety database to support the NDA

## **2. DISCUSSION**

### **Question 1:**

*Does the Agency agree that the completed nonclinical studies will support an elagolix Phase 3 clinical development program and an NDA for an indication of the management of heavy menstrual bleeding associated with uterine fibroids?*

### **FDA Response to Question 1:**

Yes, pending review of the submitted toxicology information, the Division agrees that the completed nonclinical studies will support the phase 3 program and submission of an NDA.

**Question 2:**

*Does the Agency agree that the completed clinical pharmacology studies sufficiently support an elagolix NDA for an indication of the management of heavy menstrual bleeding associated with uterine fibroids?*

**FDA Response to Question 2:**

No, FDA notes that the dosing regimen for phase 3 studies has not yet been determined. FDA has the following comments:

- Food decreases the elagolix AUC and  $C_{max}$  of the immediate-release tablet by 33% and 53%, respectively, following administration of 150 mg elagolix, which is much lower than the proposed phase 3 and to-be-marketed (TBM) total daily dose of 600 mg. FDA strongly recommends that the Sponsor investigate and address the implications of this observed food effect at the proposed TBM dose. In addition, it is unclear what the food intake instructions were in the phase 2 clinical studies and whether the food effect was considered in the selection of the proposed phase 3 and TBM total daily dose. The phase 3 studies should be carefully designed and conducted reflecting the food intake instructions that will be recommended for the drug in product labeling.
- All intrinsic and extrinsic factors need to be addressed adequately during drug development if the TBM dosing regimen is different from what was studied. For instance, a number of drug-drug interaction (DDI) studies in which elagolix is the perpetrator, as well as renal and hepatic impairment studies, were conducted with doses lower than what is being proposed for the phase 3 and TBM dose.
- FDA notes that because the thorough QT (TQT) study was conducted at doses of 300 mg and 1200 mg, this study might not adequately support the current development program in which a total daily dose of 600 mg is being proposed. FDA recommends that the Sponsor submit its justifications in a QT package to the Division, who will consult FDA's QT-Interdisciplinary Review Team (QT-IRT) for review and advice.

In summary, FDA reminds the Sponsor that the clinical pharmacology data and information including food effect, intrinsic and extrinsic factors submitted at the time of NDA submission must be relevant to the proposed TBM dosing regimen; it is at the Sponsor's risk if the clinical pharmacology data are primarily based on doses lower than that to be marketed for this indication.

**Sponsor's Response to Division's Comments:**

**Food Effect:**

AbbVie acknowledges FDA comments regarding the labeled food intake instructions when designing the Phase 3 studies. During the UF [uterine fibroids] Phase 2 development, the protocols instructed the subjects to administer elagolix under fasted conditions, i.e., one hour before a meal or two hours after a meal.

Based on the bioequivalence Study M14-731, following the administration of elagolix 200 mg dose (i.e., the highest dose tested for endometriosis Phase 3), the reduction of exposure (AUC) with a high-fat meal was 32%. Of note, efficacy appears to be closely related to the exposure AUC, such that  $C_{max}$  is less critical in this setting. As elagolix exposure (both  $C_{max}$  and AUC) is proportional from 100-400 mg doses, AbbVie believes that the food effect observed at the 200 mg dose should be consistent with the 300 mg dose; as such, the food effect study was initially

not conducted for the 300 mg dose.

However, fully noting the Agency's comments, AbbVie plans to conduct an additional study to evaluate the food effect of the 300 mg dose. We will also evaluate the impact of different types of meals on elagolix exposure, since the high fat meal is considered to be the worst-case scenario for impacting the exposure of elagolix (32%). Based on these additional evaluations, AbbVie will propose appropriate language regarding the food intake instructions for proposed labeling.

*Does the Agency agree with the proposed strategy?*

**Intrinsic and Extrinsic Factors:**

AbbVie is planning to utilize the entire clinical pharmacology program conducted for the endometriosis indication to support the uterine fibroid program. AbbVie acknowledges the FDA's comments regarding the DDI studies with elagolix as a perpetrator. The DDI study conducted with rosuvastatin (Study M13-756), which evaluates the OATP and BCRP transporters, was conducted at the 300 mg elagolix BID dose. The other DDI studies with digoxin (P-gp substrate, elagolix 200 mg BID), midazolam (a sensitive CYP3A substrate, 150 mg QD), and oral contraceptives (ethinyl estradiol, norethindrone, norgestimate, 150 mg QD) were conducted at a lower elagolix dose. Currently, AbbVie does not intend to allow coadministration of elagolix and combination oral contraceptives in endometriosis nor uterine fibroids subjects. The doses for the DDI studies were selected based on the doses selected for the Phase 3 endometriosis studies (150 mg QD and 200 mg BID) and the planned Phase 3 Uterine Fibroid studies (300 mg BID).

AbbVie has evaluated the in vitro  $IC_{50}$  regarding CYP enzyme induction/inhibition in relation to concentrations achieved with the 150 mg dose versus the 300 mg dose. The average maximum plasma concentrations ( $C_{max}$ ) observed with daily dosing of 300 mg BID elagolix is 1,200 ng/mL (1.9  $\mu$ M) based on Study M12-790. At these observed plasma concentrations, elagolix is considered to be a weak inducer of CYP3A4 ( $EC_{50} = 6.1 \mu$ M) and a weak inhibitor of OATP1B1 ( $IC_{50} = 1.7 \mu$ M) and OATP1B3 ( $IC_{50} = 4.7 \mu$ M) hepatic uptake transporters (see Table 1).

The doses of elagolix used in the DDI studies ranged from 150 ( $C_{max} = 0.89 \mu$ M) to 300 mg ( $C_{max} = 1.9 \mu$ M). Elagolix exposure ( $C_{max}$  and AUC) are dose proportional from 100 to 400 mg BID. The ratio of the  $[I]/K_i$  or  $[I]/IC_{50}$  to assess a CYP or transporter mediated DDI is similar and small for elagolix doses between 150 to 300 mg, which is consistent with the relatively small change in concentrations observed in the DDI studies.

*AbbVie would like to confirm that the results from the DDI studies completed with doses between 150 to 300 mg are applicable to assess the potential risk of a DDI occurring with clinical doses of 300 mg BID for uterine fibroids.*

**Table 1: Summary of the *In Vitro* Characterization of the Metabolism and Transporter Parameters of Elagolix**

Interaction	K <sub>i</sub> (μM)	[I]/K <sub>i</sub> or [I]/IC <sub>50</sub> *	[I]/K <sub>i</sub> or [I]/IC <sub>50</sub> *
		150 mg QD M12-790	300 mg BID M12-790
<b>Metabolism</b>			
<b>Inhibition K<sub>i</sub></b>			
CYP3A4	74	0.012	0.026
CYP2C19	34	0.026	0.056
<b>Induction EC<sub>50</sub></b>			
CYP3A4	6.1	0.15	0.31
<b>Transporters</b>			
	<b>IC<sub>50</sub> (μM)</b>		
P-gp	37	0.024	0.051
BCRP	54	0.016	0.035
MRP2	280	0.0031	0.0068
OATP1B1	1.7	0.52	1.1
OATP1B3	4.7	0.19	0.40
OAT1	176	0.0051	0.011
OAT3	43	0.021	0.044
OCT2	>1000	-	-

Note: all *in vitro* metabolism and transporter values are referenced in the Elagolix Investigator Brochure edition 14.

\* = C<sub>max</sub> of 150 mg QD or 300 mg BID from the M12-790 study

**Special Populations:**

**Renal:** Elagolix is minimally excreted renally (~3%) and dose proportional in exposure in C<sub>max</sub> and AUC was observed between 100 and 400 mg doses. AbbVie believes that, with a dose proportional increase in C<sub>max</sub> and AUC, the increase in exposure in renal impairment subjects for the 300 mg dose should be consistent with the 150 mg dose.

**Hepatic:** The proposed Phase 3 studies will exclude subjects who have moderate to severe hepatic impairment, since these subjects are irrelevant for the treatment population of interest. In addition, based on the dose proportional increase in C<sub>max</sub> and AUC between 100 to 400 mg doses, the similar elagolix exposure observed in subjects with mild hepatic impairment versus normal subjects should be consistent for both the 150 mg dose and the 300 mg dose.

*AbbVie would like to confirm that the current hepatic impairment study (M12-662) and renal impairment study (M12-655) support the 300 mg BID dose.*

**Thorough QT:**

Based on the totality of data to-date, the 300 mg twice daily dose is the dose currently being considered for Phase 3 uterine fibroids.

Study M12-661 evaluated the potential of QTc prolongation by elagolix in 48 healthy adult premenopausal female subjects. Two doses of elagolix were tested: The 300 mg dose and the 1200 mg suprathereapeutic dose. Comparing the 300 mg dose and the 1200 mg dose, the ratio in C<sub>max</sub> is approximately 10-fold higher, and AUC 14-fold higher. Elagolix had no impact on cardiovascular QT parameters and thus a negative thorough tQT study was concluded. In the primary analyses, at both elagolix doses (300 mg and 1,200 mg), the 95% one-sided upper confidence interval (CI) for the difference of mean from placebo is within 10 msec for all time points. The maximum means (upper bound of the 95% one-sided CI) for differences in QTcF interval from placebo after baseline correction were 2.4 (4.4) msec for 300 mg elagolix and 6.0 (7.97) msec for 1,200 mg elagolix. Moxifloxacin met the predefined criteria for assay sensitivity.

*AbbVie would like the FDA to confirm that, the current QTc study (M12-661) support the 300 mg BID dose. The Clinical study report for M12-661 was submitted to IND 64,802 on 04 November 2014 (Sequence No. 273).*

**Discussion at the Meeting:**

The Division concurred with the Sponsor's plan to conduct a new food effect study with the 300 mg BID dose, but cautioned about trying to provide labeling that is too granular with respect to types of diet. The Sponsor clarified that the phase 2 studies were conducted under the fasting condition. The Division advised that while the Sponsor can also evaluate the impact of different types of meals on elagolix exposure as proposed, the impact of a high fat meal should definitely be evaluated, as it is considered to be the worst-case scenario for impacting elagolix exposure. It will be important to get data to inform the dosing instructions of the phase 3 trials; these instructions usually form the basis of labeling instructions regarding food intake.

The Sponsor was encouraged to use the to-be-marketed tablet formulation in the new food effect study. Reference is made to the Agency's *Guidance for Industry: Food-Effect Bioavailability and Fed Bioequivalence Studies* (<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064964.htm>). The Sponsor clarified that 300 mg tablets will be used for its planned food effect study and phase 3 studies.

The Division stated that is more challenging to extrapolate from a lower dose when doing DDI studies in which elagolix is the perpetrator drug. The Sponsor must provide justification of the relevance of the data it submits in the NDA and the adequacy of this justification will be a review issue.

The Sponsor was asked how it envisions labeling (e.g., in Dosage and Administration, Specific Populations) with respect to hepatic impairment, as they plan to exclude females with moderate or severe hepatic impairment in the planned phase 3 studies. The Division advised that contraindications are not typically labeled when a risk is merely hypothetical; if the only data available were based on a lower dose, the Sponsor would have to justify the relevance of those data to the to-be-marketed dose. It is also important to consider whether use by women with hepatic impairment would raise safety concerns and whether expected toxicities could be identified when elagolix is used at the planned clinical dose.

The QT team will be consulted to review the Sponsor's justification of the relevance of the TQT study. [**Post-meeting comment:** Comments from the QT team will be provided in a separate communication.]



**Question 3:**

*Based on previous Agency meetings and the totality of data to date, AbbVie proposes to proceed to Phase 3 with the following regimens. Does the Agency agree?*

- a. *The elagolix 300 mg BID plus (b) (4) (estradiol 1.0 mg/norethindrone acetate 0.5 mg [E2/NETA]) regimen, to be evaluated in Phase 3 to support the objective of obtaining an indication "for the management of HMB associated with uterine fibroids."*

**FDA Response to Question 3a:**

The Division agrees with the selection of a 600 mg total daily dose for elagolix. Because the phase 2b study, which includes additional potential dosing regimens, is ongoing, the Division prefers to await the results of the full study before commenting on the dose regimen selected for phase 3. The current protocol synopsis for Study M12-815 states that "Dosing frequency will be based on additional data from Cohort 2 in the ongoing phase 2b study..."

- b. *The elagolix 300 mg BID alone regimen, which in addition to placebo, will serve as a control arm in the Phase 3 program.*

**FDA Response to Question 3b:**

The Sponsor needs to provide a detailed statistical analysis plan regarding how the elagolix-alone arm will be addressed as a "control arm" in the analysis. See also response to Question 10.

**Discussion at the Meeting:**

The Sponsor provided a high-level summary of data from the interim analysis of Cohort 2 from their phase 2b study: efficacy and safety appear similar for the 300 mg BID and 600 mg QD dose, but tolerability (especially regarding gastrointestinal side effects) was slightly better for the BID dose. It also appears that better exposure is achieved with BID dosing. For these reasons, the Sponsor plans to take the dose regimen of 300 mg BID plus standard add-back into phase 3. The Division noted that it did not have access to the interim data and therefore cannot concur with the dose selection, but does not object based on the Sponsor's report of results. The Division asked if compliance data with the two dosing regimens were available; the Sponsor noted that "compliance packaging" was used in the study, and that overall, compliance was about 70%. The Sponsor will look further into compliance with the two dose regimens and acknowledged that this should be considered in selecting a BID regimen.

The Sponsor clarified the role of the elagolix-alone arm, which is to serve as a "reference," not a "control" arm. The primary efficacy assessment will compare the treatment effect of elagolix plus add-back vs. placebo. The elagolix-alone arm will be used to provide a benchmark for efficacy and safety findings, particularly with respect to bone mineral density (BMD) and hot flashes, and will provide additional context to the 12-month data on BMD changes, which will not be placebo-controlled. The Sponsor does not plan formal hypothesis testing for this treatment arm. However, the Division noted that the Sponsor will need to address the benefit of add-back in addition to the elagolix regimen, and will need to provide a formal demonstration of the impact on safety parameters such as BMD. This should be described in the statistical analysis plan (SAP).

**Question 4:**

*Does the Agency agree, assuming the efficacy, safety, and BMD data are acceptable, that the proposed Phase 3 development program would support the use of elagolix in combination with standard-dose E2/NETA for the management of HMB associated with uterine fibroids and that labeling would not require limitations on duration of therapy?*

**FDA Response to Question 4:**

The proposed development plan to date appears appropriate in support of a chronic use product, but it is premature to discuss specific labeling regarding duration of therapy, as this will depend upon any temporal trends or signals identified in the efficacy and safety findings.

**Question 5:**

*The current plan is that elagolix 300 mg BID would be co-prescribed with estradiol 1.0 mg/norethindrone acetate 0.5 mg, such that each product would contain its own Package Insert.*

(b) (4)

**FDA Response to Question 5:**

This approach appears acceptable provided (b) (4).  
Further discussion of labeling will be reserved until the NDA review cycle.

**Discussion at the Meeting:**

(b) (4)

**Question 6:**

*Does the Agency agree with the proposed study designs for the two pivotal 6-month Phase 3 efficacy studies and the single 6-month extension study?*

**FDA Response to Question 6:**

The proposed study design for the two phase 3 studies and the extension study appears generally acceptable, pending review of the final study protocols. See additional comments below regarding specific aspects of the design.

**Question 7:**

*Does the Agency agree with the proposed inclusion/exclusion criteria for the Phase 3 studies?*

**FDA Response to Question 7:**

Most of the eligibility criteria appear acceptable; however, the Division does not agree with the fourth bulleted point of inclusion criterion #3 (b) (4), which lacks a description of fibroid size.

Elagolix exposure was increased by approximately 3- and 7-fold in premenopausal females with moderate and severe hepatic impairment, respectively, when studied with a lower dose than what is being proposed for the phase 3 studies and as the TBM total daily dose. It is unclear what the clinical implication of these observations is and whether the Sponsor plans to include/exclude this population in the proposed phase 3 studies. The Sponsor should address this at the time of the final protocol submission.

Additional comments may be made by the Division following review of the final protocol.

**Discussion at the Meeting:**

The Sponsor will revise the entry criterion relating to fibroid location and size to address the Division's comment.

The BMI restriction is included only because DXA machines are limited to patients weighing <300 lbs. The Division noted that it strives to ensure that trial populations are representative of the target population, particularly with respect to inclusion of high weight/BMI women. However, a justification such as this is reasonable. The Division recommended that the exclusion criterion be changed to focus on women weighing > 300 lbs., rather than using BMI as a surrogate. This would allow the entry of women without regard to BMI.

The Sponsor noted that the exclusion of well-controlled diabetics was an error, and will be removed.

The Sponsor plans to exclude women with moderate to severe hepatic impairment; this is acceptable. See additional comments on this issue in response to Question 2.

**Question 8:**

*Does the Agency agree with the proposed primary endpoint and responder analysis for the Phase 3 studies?*

**FDA Response to Question 8:**

The proposed primary endpoint appears acceptable. The statistical analysis plan (SAP) should describe what findings on the responder analysis would constitute a "win." The Division would not accept a finding solely of a statistically significant difference between treatment arms if the difference is small or the response rates in both arms are low. The Division acknowledges that such an outcome does not appear likely based on phase 2 data, but this still must be addressed in the SAP.

For the responder analysis, the Division recommends a model based approach (Multiple Imputation method) rather than last-observation-carried-forward (LOCF) to handle missing data. Other approaches should be proposed for sensitivity assessment of the impact of missing data.

The Division also recommends a modification to the missing data algorithm shown in Figure 14 (page 110). If the eDiary indication of bleeding is "no" because there are no data entered in the diary, the subject should not be assigned 0 for MBL. This value should be assigned only if there are affirmative statements in the diary that no bleeding occurred.

**Discussion at the Meeting:**

The protocol will provide a detailed discussion of the handling of missing data.

The Sponsor proposed that the primary efficacy analysis will use the modified intent-to-treat (mITT) population, which excludes subjects who have less than 28 days of exposure to study drug, because such subjects would not provide full efficacy data, which requires evaluation of the menstrual period associated with each 28-day treatment cycle. Based on historical experience, the Sponsor expects that about 3% of subjects will be excluded from the mITT. The Division found this analysis population acceptable.

The Sponsor plans to define as non-responders any women who discontinue prematurely due to adverse events, lack of efficacy, or surgical/interventional management of fibroids. For women who discontinue for other reasons, data imputation will be utilized, which will be detailed in the protocol.

Regarding what would constitute a “win,” the Sponsor noted that the planned sample size will permit detection of a 17% or greater difference in responder rate with 80% power; the Sponsor believes that such a treatment difference is clinically meaningful. The Division agreed that such a justification of the treatment benefit would be appropriate. The Division’s concern was avoiding sole reliance on a statistically significant p-value, particularly if the responder rates or treatment difference were low.

**Question 9:**

*a. Does the Agency agree with the proposed key secondary endpoints for the Phase 3 studies?*

**FDA Response to Question 9a:**

Specify all key secondary (or other non-primary) endpoints that are intended to support labeling claims. Secondary endpoints may be included in labeling if they are agreed upon in advance by the Division, appropriately addressed in the statistical analysis, and evaluated using an appropriately validated instrument. Secondary endpoints that are designated for inclusion in labeling will likely be reported whether the outcome is successful or not.

*b. Does the Agency agree that, if the Phase 3 data demonstrate a > 1 g/dL increase in hemoglobin, these data could be included in the label?*

**FDA Response to Question 9b:**

See response to Question 9a. Further discussion would be needed regarding the clinical meaningfulness of a 1 g/dL increase in hemoglobin, particularly if the study population is not required to be anemic.

c. [REDACTED] (b) (4)

**FDA Response to Question 9c:**

No. The Division does not support labeling claims [REDACTED] (b) (4)

**Discussion at the Meeting:**

The Sponsor will provide a complete list of endpoints for which it might request labeling claims.

Some general examples were discussed as follows; for those outcomes that may be appropriate to support labeling claims, the assessment must be appropriately accounted for in the SAP:



**Question 10:**

*Does the Agency agree with the proposed sample size for the Phase 3 pivotal studies?*

**FDA Response to Question 10:**

The proposed sample size appears acceptable. However, if the elagolix 300 mg BID alone regimen is intended to serve as a control arm (in addition to placebo) in the phase 3 program, the sample size must provide adequate power to show the difference between the elagolix plus add-back regimen, and the elagolix-alone regimen.

**Discussion at the Meeting:**

Refer to discussion under Question 3.

**Question 11:**

*Does the Agency agree that the dual energy x-ray absorptiometry (DXA) methodology described and the management of subjects regarding their BMD loss at Month 6 of the Treatment Period in the pivotal studies (Studies M12-815 and M12-816), during 6-month extension study (Study M12-817), and during the Post-Treatment Follow-Up Period is appropriate?*

**FDA Response to Question 11:**

The Division notes that the plan for BMD evaluation and management is not identical to that agreed upon for the endometriosis program (IND 64,802); e.g., use of T-scores rather than Z-scores in the entry criteria, different thresholds for BMD changes that trigger various actions. For ease of review, the Sponsor is requested to provide a side-by-side comparison of the two plans, with justification of any changes from the methods agreed-upon in IND 64,802. The Division will provide further comments after review of this summary.

**Sponsor's Response to Division's Comments:**

AbbVie acknowledges the differences for the planned BMD evaluations across the two elagolix development indications. The changes reflected in the UF program were the result of discussions with key bone experts on "real world practices". However, having reviewed a side-by-side comparison across the two programs, as well as feedback from the Agency, AbbVie proposes to standardize the planned BMD algorithms and evaluation across both programs. Therefore, the UF program will mimic the endometriosis program from a BMD perspective, with the following exceptions:

*1. Use of T-score rather than Z-score*

The rationale for the use of a T-score instead of a Z-score in the UF development program is that the mean age of women in our first pivotal endometriosis study (M12-665) was 31.5 years, with 11.5% of women aged 40 years or older. In the Phase 2 uterine fibroid program, the mean age is 42.8 years, with 76.5% of women 40 years of age or older. For women greater than 40 years old, the use of the T-score is more suitable than Z-score, since Z-scores are generally higher than T-scores in this age group. For women less than 40 years old, T-scores and Z-scores are very similar.

*2. Follow-up DEXA scan in all subjects at Month 6 in the post-treatment follow-up period.*

Similar to a planned protocol amendment for the second pivotal endometriosis study (M12-671) and its extension study (M12-821), AbbVie will conduct follow-up DEXA scans for all subjects at Month 6 in the post-treatment follow-up period.

*Does the Agency agree with this proposal regarding BMD evaluation?*

**Discussion at the Meeting:**

The Division agreed that use of T-scores for the fibroids program is appropriate.

The Sponsor clarified that the previous plan was to conduct a DXA at 6 months post-treatment only for subjects who met prespecified criteria relating to BMD loss. The current plan, which will also apply to the second endometriosis study that is ongoing, will provide more post-treatment data. The Division agreed with the plan.

**Question 12:**

- a) *Can the Agency confirm that evaluating the placebo-adjusted mean percentage change from baseline in BMD after 6 months of exposure in the pivotal studies and the within-group mean percentage change from baseline in BMD after 12 months of exposure in the extension study are appropriate as the assessments for BMD loss?*

**FDA Response to Question 12a:**

See response to Question 11. The Division is concerned that evaluation of BMD after six months of treatment is unlikely to provide a sufficient assessment of any impact on BMD.

Therefore, the number of subjects on whom 12-month data are obtained will be an important consideration. In addition, the protocol should also provide additional details on how BMD measurement and evaluation will be standardized across the trials.

- b) *Can the Agency confirm that the lower bound of the 95% confidence interval of the placebo-adjusted mean percentage change from baseline in BMD at Month 6 not exceeding -2.2% and the lower bound of the 95% confidence interval of the within-group mean percentage change from baseline in BMD at Month 12 not exceeding -2.2% remain the preferred assessment method? And, if these criteria are not exceeded, would it support the use of elagolix in combination with standard-dose E2/NETA without restriction on the duration of use?*

**FDA Response to Question 12b:**

The Division agrees with the proposal regarding the change in BMD at Month 6, but remains concerned that interpretation of changes at one year of treatment may be difficult in the absence of a control arm, particularly since younger subjects, who have not attained peak bone mass, would be expected to have a positive change in BMD over time.

See response to Question 4 regarding duration of use.

- c. *Can the Agency confirm that using the pooled data on the BMD safety endpoint from the two pivotal studies (Studies M12-815 and M12-816) to evaluate BMD loss at Month 6 in the pivotal studies is acceptable?*

**FDA Response to Question 12c:**

See response to Question 11.

**Discussion at the Meeting:**

The Sponsor acknowledged the Division's concern about 12-month data. The Sponsor anticipates that about 200 subjects in total over the two phase 3 studies will complete 12 months of treatment. The Division asked the Sponsor to discuss the magnitude of change in BMD associated with use of elagolix (compared to that observed in placebo subjects) that could be ruled-out with this sample size. The standardization and methodology of DXA assessment will be detailed in the protocol and will be consistent with that in the endometriosis program.

The Sponsor believes that it is not feasible to include women on placebo for 12 months, but noted that use of the elagolix-alone arm as a reference group to evaluate the change in BMD after 12 months of treatment will provide additional useful information. Across the development programs for fibroids and endometriosis, there will be 6-month data on approximately 800 women, which should allow for subgroup analyses by age and other relevant covariates. The Division noted that the phase 2 data suggesting that the general age of fibroid subjects is in the 40s obviates some of the concern about accounting for the accrual of BMD that would be expected in placebo subjects at younger ages.

The Division asked about the extent of outliers who had more marked BMD decreases (e.g., > 3%, > 5%, > 8%). The Sponsor noted that one outside expert had suggested that changes in the hip BMD may take more than six months' exposure to develop. However, the cross-study and within phase 2b six-month data indicates that elagolix plus add-back has a lower proportion of outliers than the elagolix-alone arm.

The Division agreed that pooling of data on BMD from the two phase 3 studies would be acceptable provided that the demographics of the two study populations were similar and that the BMD data were generally consistent. The Sponsor will also provide BMD data for each trial, but the hypothesis testing will be based on the pooled data.

**Question 13:**

*If the data from the ongoing Phase 2b study support a 6-month post-treatment follow-up as sufficient to assess potential return to Baseline for BMD changes for elagolix 300 mg BID plus estradiol 1.0 mg/norethindrone acetate 0.5 mg, would the Agency agree to a similar 6 month post-treatment follow-up period in the Phase 3 clinical development program?*

**FDA Response to Question 13:**

The Division cannot answer this question until the final dose regimen selection is made following completion of the phase 2b study and until it sees the data from phase 2b regarding return to baseline for BMD.

**Question 14:**

*Does the Agency agree with the proposed assessment for endometrial safety?*

**FDA Response to Question 14:**

The proposed assessment appears acceptable, pending review of the final protocol.

**Question 15:**

*Does the Agency agree with the proposed lipid assessment?*

**FDA Response to Question 15:**

The proposed assessment appears acceptable, pending review of the final protocol

**Question 16:**

*Does the Agency have any comments or additional requirements to be considered for the Phase 3 studies?*

**FDA Response to Question 16:**

No; however, the Division will likely have additional comments after the final protocol(s) are submitted for review.

**Question 17:**

*Does the Agency agree that the proposed safety database is adequate to support the planned NDA?*

**FDA Response to Question 17:**

The Division's expectation is that the ICH E1 exposure requirements for a new molecular entity will be met with subjects exposed to doses at or higher than the TBM dose of elagolix for fibroids. The Sponsor should clarify the number of subjects it anticipates will receive at least a 600 mg total daily dose of elagolix overall, and for six and 12 months, without regard to the inclusion of add-back therapy. It is not clear that the overall requirement of 1,500 subjects exposed to the TBM total daily dose will be met.

**Sponsor's Response to Division's Comments:**

AbbVie estimates that a total of approximately 1175 women will be exposed to at least one dose



of elagolix at a total daily dose of 600 mg, with more than 700 women exposed to elagolix 300 mg BID for 6 months and approximately 200 women exposed to elagolix 300 mg BID for 12 months.

Although the overall safety database for the 600 mg total daily dose is < 1500 (~1175), additional data from the endometriosis program will be extensive (approximately 1035 women exposed to 200 mg BID, of which approximately 790 women will be exposed for 6 months and approximately 215 will be exposed for 12 months).

The overall safety profile of the 200 mg BID dose to date from the endometriosis program is generally similar to what has been observed with 300 mg BID dosing in the uterine fibroid Phase 2 program, albeit in a different study population and a known dose-dependent hypoestrogenic side effects.

Based upon the large number of exposures at 200 mg BID, AbbVie considers the 1175 subjects exposed to a total daily dose of 600 mg to be adequate for the UF program. *Does the Agency agree?*

**Discussion at the Meeting:**

The Division stated that, because elagolix is a US and global new molecular entity (NME), exposure data from the full 1500 subjects delineated in the ICH E1 document will be needed. While the additional data on the lower dose for the endometriosis indication will be of interest, it is speculative to assume that the safety profiles of the two dose regimens will be similar enough to rely upon the lower dose data to support the safety of the dose to-be-marketed for the fibroids indication. The Division noted that an additional study conducted to support a short-term indication (see response to Question 18) might close the exposure gap.

**Question 18:**

*The Phase 3 program includes elagolix 300 mg BID alone as a control arm. Given that the efficacy and safety of elagolix 300 mg BID will also be rigorously evaluated, and assuming the data are acceptable, based on the current program* (b) (4)

**FDA Response to Question 18:**

(b) (4)

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**Question 19:**

*Does the FDA have a preference regarding which version of SDTM is used? If not, then AbbVie is proposing to use SDTM v1.3 with SDTMIG v3.1.3 for the submission. AbbVie also proposes using the most current version of controlled terminology available at the time a study is run. Within the Study Data Standards Plan, AbbVie will outline the process regarding updates to extensible controlled terminology that may differ from sponsor-defined values used on previous studies. Can the FDA confirm if this is acceptable?*

**FDA Response to Question 19:**

Yes, the Sponsor can use Study Data Tabulation Model (SDTM) v1.3 and Study Data Tabulation Model Implementation Guide (SDTMIG) v3.1.3 for the submission. Refer to the data standards catalog and associated submission information at the link:

<http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm>

As for terminology, use of the most current at the time of the study is acceptable, as long as the Sponsor consistently uses the terminology through the study.

### **3.0 ADDITIONAL REGULATORY COMMENTS**

#### **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](mailto:pdit@fda.hhs.gov). For further guidance on pediatric product development, please refer to: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>.

### **DATA STANDARDS FOR STUDIES**

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>

### **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> ).

### **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.

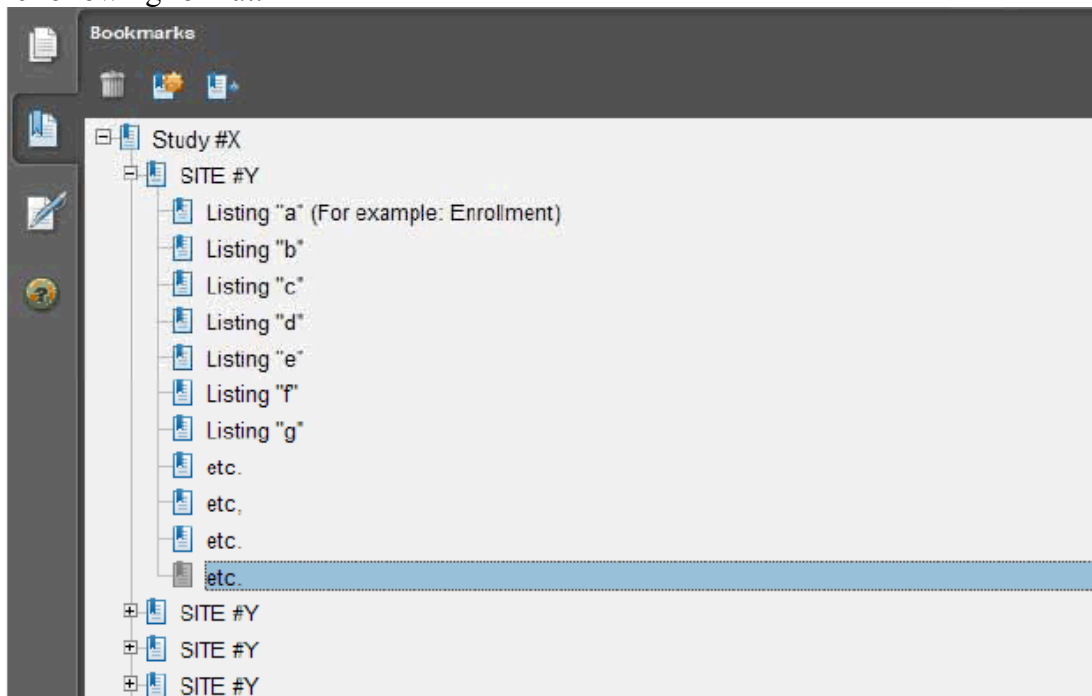
This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

- 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 <sup>1</sup>	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.

References:

<sup>1</sup> Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

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](mailto:ESUB@fda.hhs.gov)

#### **4.0 ACTION ITEMS**

FDA will provide comments from the QT team in a separate Advice Letter.

The Sponsor will submit:

- Justification of the relevance of data it submits to the NDA regarding DDI studies conducted at lower doses than that proposed for this indication
- A Target Product Profile if it wishes to include PRO outcomes in labeling
- A complete list of endpoints for which it might request labeling claims
- A clear flow chart detailing the revised plan for monitoring BMD, with identification of any differences between the plans for the fibroids and endometriosis programs



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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.**  
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/s/  
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LISA M SOULE  
06/19/2015