APPLICATION NUMBER:

210450Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS
IND 064802

MEETING PRELIMINARY COMMENTS

AbbVie, Inc.
Attention: Glen W. Spears, Ph.D.
Director, Regulatory Affairs
1 N. Waukegan Road
Dept. PA77, Bldg. AP30-1
North Chicago, IL 60064

Dear Dr. Spears:

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 your October 18, 2016, correspondence, requesting a meeting to discuss the proposed content and format of the NDA submission regarding specific Chemistry, Manufacturing, and Controls (CMC), Nonclinical, Clinical, Regulatory, Pharmacovigilance, and data presentation questions and to update the Agency on the status of available results from the phase 3 clinical trials.

Our preliminary responses to your meeting questions are enclosed.

You should provide a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

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

If you have any questions, call me at (301) 796-0567.

Sincerely,

Maria Wasilik, R.Ph.
Regulatory Health Project Manager
Division of Bone, Reproductive, and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURE:
Preliminary Meeting Comments
PRELIMINARY MEETING COMMENTS

Meeting Type: Type B
Meeting Category: Pre-NDA

Meeting Date and Time: December 9, 2016 @ 11:00 A.M.-12:00 Noon
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 21, Conference Room: 1539
Silver Spring, Maryland 20903

Application Number: IND 064802
Product Name: Elagolix

Proposed Indication: Management of endometriosis-associated pain
Sponsor: AbbVie, Inc.

Introduction:
This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for December 9, 2016 at 11:00 A.M., White Oak Building 21, Silver Spring, Maryland 20903, between AbbVie, Inc., and the Division of Bone, Reproductive, and Urologic Products. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). Contact me if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

1.0 BACKGROUND

The purpose of this Pre-NDA meeting is to reach agreement with the Agency regarding the proposed content and format of the planned NDA. This includes specific Chemistry, Manufacturing, and Controls (CMC), Nonclinical, Clinical, Regulatory, Pharmacovigilance, and data presentation-related topics that are critical to the NDA submission. The Sponsor will also summarize the efficacy and safety results from the Phase 3 clinical trials that will be submitted in the initial NDA to support the proposed indication.
2.0 DISCUSSION

Question 1:
Does the Agency agree with the proposal to include a document in 3.2.R Regional Information with hyperlinking to the relevant Module 3 sections in order to meet the requirements for the Method Validation Package?

FDA Response to Question 1:
Yes, the proposal is acceptable.

Question 2:
Does the Agency agree with the executed batch record proposal?

FDA Response to Question 2:
No. The application should include at least one executed batch record for each tablet strength. In addition, the application should include the proposed master production records for each tablet strength.

Question 3a:
Based on the data and rationale presented in Appendix D does the Agency agree that the available data are adequate to provide sufficient characterization and review for abuse liability potential (in accordance with the FDA's Draft Guidance for Industry: Assessment of Abuse Potential, January 2010), and therefore, no further nonclinical or clinical studies are required to assess abuse potential of elagolix?

FDA Response to Question 3a:
The abuse liability assessment package appears sufficient; however, a complete review of the package will occur following NDA submission and filing.

Question 3b:
Does the Agency agree that the format of the document is acceptable for submission and review in the NDA?

FDA Response to Question 3b:
Yes, the format of the document is acceptable for submission. Ensure that the submission includes all study reports, and appropriate linkage to those reports throughout the abuse potential assessment sections.

Question 4:
AbbVie will provide exposure data for over 3,480 subjects who received elagolix at a total daily dose of $\geq 150$ mg/day, including 6-month and 12-month exposure data for approximately 1,520 subjects and approximately 420 subjects, respectively. A summary of the exposure data is provided in Table 3. Does the Agency concur that the elagolix clinical program has provided sufficient exposure data in the application?

FDA Response to Question 4:
Yes, provided no unexpected safety signals are identified during the review.
Question 5:
AbbVie proposes to present the Phase 2 endometriosis clinical data within the Summary of Clinical Efficacy (CSE) (Module 2, Section 2.7.3). Due to differences in study endpoints and pain assessment scales, AbbVie does not intend to present pooled Phase 2 endometriosis clinical data in the ISE. Does the Agency agree with this proposal?

FDA Response to Question 5:
Yes.

Question 6:
In the integrated efficacy analyses of the Phase 3 studies (in the ISE and CSE), AbbVie proposes to retain an individual subject's response status as it was determined in the individual study to which the subject belongs. Does the Agency agree with this proposal?

FDA Response to Question 6:
Yes.

Question 7:
As a follow-up to the FDA requests from the Type C Preliminary Written Comments provided to AbbVie on August 18, 2016, the proposed pooling strategy and a summary of the integrated safety data sets to be included in the endometriosis NDA is described in Section 11.3.2. Does the Agency agree with AbbVie's proposed content and presentation of the elagolix safety data?

FDA Response to Question 7:
Yes.

Question 8:
As a follow-up to the FDA requests from the Type C Preliminary Written Comments provided to AbbVie on August 18, 2016, AbbVie will provide additional supportive analysis sets for each of the completed Phase 2 studies in uterine fibroids; however, the data from these 2 uterine fibroid studies will not be pooled with each other (nor with any other endometriosis studies). AbbVie does not intend to include safety data from the currently ongoing blinded elagolix Phase 3 studies in women with uterine fibroids, nor any newly initiated blinded studies ongoing at the time of submission. Does the Agency agree with this proposal?

FDA Response to Question 8:
The Division agrees that blinded data from ongoing studies do not need to be included in the submission or the safety update; however, include blinded line listings of any additional deaths or serious adverse events. In addition, if, at the time of the safety update, any data from the fibroids trials or other ongoing trials has been unblinded, or if any new safety signals have been identified, or safety issues have arisen that have led to alterations in trial conduct, this information should be provided in the safety update.

Question 9:
AbbVie intends to provide case report forms (CRFs) and subject narratives for all subjects in the Phase 1, 2, and 3 studies included in the NDA who meet any of the following criteria prior to data cutoff for the submission described below.

- death
• treatment-emergent serious adverse event (SAE) (for elagolix subjects only)
• discontinuations during the treatment period due to AEs (for elagolix subjects only)
• treatment-emergent pregnancies for all subjects
In addition, AbbVie intends to provide CRFs and subject narratives for subjects in Phase 2 and Phase 3 studies included in the NDA for specific treatment-emergent adverse events of special interest (AESIs) as described in Section 11.2.4.1 (for elagolix subjects only). Does the Agency agree with this proposal?

FDA Response to Question 9:
Yes.

Question 10:
Does the Agency agree that the 2 pivotal studies (Studies M12-665 and M12-671), together with the two long-term extension studies (Studies M12-667 and M12-821) and other safety data, are adequate to establish elagolix safety and effectiveness for the management of endometriosis-associated pain?

FDA Response to Question 10:
The adequacy of the phase 3 trials and extensions to establish the safety and efficacy of elagolix for the proposed indication will be determined during the NDA review.

Question 11:
Does the Agency agree that our approach on the Draft Pharmacovigilance (PV) Plan (Appendix E) is appropriate for the postmarketing setting based on the clinical data provided to the Agency on the program to date?

FDA Response to Question 11:
No. It is premature to agree to the Draft Pharmacovigilance (PV) Plan provided in Appendix E. This will be a review issue during the course of the NDA review. While FDA agrees that PV activities are important for continued monitoring of potential risks, the brief outline does not provide sufficient details for FDA to agree to the plan fully. The Sponsor should provide a detailed description of the planned PV activities for Agency review with the original NDA submission.

Question 12:
At the time of the NDA submission (August 31, 2017), all endometriosis studies included in the submission will be complete, and the ongoing uterine fibroids and additional Phase 3b
endometriosis studies will be blinded. AbbVie does not propose to include any new data in the 4-Month Safety Update apart from any pregnancy outcomes or infant follow-up observed in the Phase 3 Studies M12-671 and M12-821, as well as any deaths or SAEs from any ongoing studies.

Does the Agency agree with the proposed plan for the 4-Month Safety Update?

**FDA Response to Question 12:**  
See the response to Question 8.

**Question 13:**  
As described in Section 11.2.4.2.1, it is anticipated that external bone specialist referral outcome data from the long-term extension Study M12-667, as well as a portion of the data from Study M12-821 will be available at the time of the initial NDA submission. Although the referral rate has been low, there may be a limited number of cases from the long-term extension Study M12-821 that will be reported in the 4-Month Safety Update due to the additional time required for coordination with external bone specialists.

Does the Agency agree with the proposed plan for the external bone specialist referral outcome data for the 4-Month Safety Update?

**FDA Response to Question 13:**  
In general, all evaluable data, including data from the long-term extension studies should be available for review at the time of the NDA submission. Under the Prescription Drug User Fee Act (PDUFA) V Program, the NDA should contain all data necessary for review of the application at the time of initial submission. Certain minor components may be acceptable for late submission within 30 days. For this application, it is not acceptable to submit additional clinical efficacy or safety data during the review unless requested by the Division.

The Sponsor should provide an estimate of the number of subjects in Study M12-821 that might be expected to have referral outcome data that would not be submitted until the 4-Month Safety Update. The Division’s response will depend on the magnitude of the data submission, as this is information of potential significance to the review.

**Question 14:**  
Does the Agency agree that the proposed format and content of the planned NDA for elagolix, as outlined in the Table of Contents (Appendix F), is acceptable and could constitute a complete NDA to support the proposed indication (Section 3.0)?

**FDA Response to Question 14:**  
Yes.

**Question 15:**  
Does the Agency have any additional comments about the content or structure of the NDA submission?

**FDA Response to Question 15:**  
No.
**Question 16:**
At this point in time, does the Agency anticipate convening an advisory committee meeting during the NDA review? If so, can the Agency provide estimated timelines for an advisory meeting, under a standard review, based on an August 2017 NDA submission?

**FDA Response to Question 16:**
Given that elagolix is a new molecular entity, it is possible that an Advisory Committee will be convened. If this is done, it would likely be held in Month 9 of the 12-month review clock. A final decision on whether an Advisory Committee meeting is needed will be made after NDA submission.

**Additional Clinical Pharmacology Comments:**
The Sponsor is proposing two different dosing regimens, but some of the drug-drug interaction studies (e.g., Studies M12-651 and M12-765) do not represent the worst case scenario. The Sponsor should address in the NDA how it proposes to interpret and label these study results.

There are ongoing exposure-response and population pharmacokinetic analyses that the Sponsor plans to include as part of the NDA submission. Refer to the following pharmacometric data and models submission guidelines for the submission:
http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm180482.htm

**3.0 ADDITIONAL INFORMATION**

**DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION**
As stated in our October 28, 2016 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 V. 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. 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.

Finally, in accordance with the PDUFA V agreement, FDA has contracted with an independent contractor, Eastern Research Group, Inc. (ERG), to conduct an assessment of the Program. ERG will be in attendance at this meeting as silent observers to evaluate the meeting and will not participate in the discussion. Please note that ERG has signed a non-disclosure agreement.
Information on PDUFA V and the Program is available at http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm.

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.

We received your Initial Pediatric Study Plan (iPSP) for elagolix on August 19, 2016. We issued you a Written Response dated November 14, 2016, containing our comments on the iPSP and in which we acknowledged your plan to request that FDA waive the requirement for pediatric assessments in all pediatric age groups. We encourage you to submit an Agreed iPSP no later than 90 calendar days from the date of our Written Response. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

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

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

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances.
- FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.
The application should include a review and summary of the available published literature regarding drug use in pregnant and lactating women, a review and summary of reports from your pharmacovigilance database, and an interim or final report of an ongoing or closed pregnancy registry (if applicable), which should be located in Module 1. Refer to the draft guidance for industry – Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf).

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

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

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.

**MANUFACTURING FACILITIES**

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

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

<table>
<thead>
<tr>
<th>Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, “Product name, NDA/BLA 012345, Establishment Information for Form 356h.”Site Name</th>
<th>Site Address</th>
<th>Federal Establishment Indicator (FEI) or Registration Number (CFN)</th>
<th>Drug Master File Number (if applicable)</th>
<th>Manufacturing Step(s) or Type of Testing [Establishment function]</th>
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<td>2.</td>
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</tbody>
</table>
Corresponding names and titles of onsite contact:

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<tr>
<th>Site Name</th>
<th>Site Address</th>
<th>Onsite Contact (Person, Title)</th>
<th>Phone and Fax number</th>
<th>Email address</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td></td>
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<td>2.</td>
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</tbody>
</table>
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.”

<table>
<thead>
<tr>
<th>DSI Pre-NDA Request Item(^1)</th>
<th>STF File Tag</th>
<th>Used For</th>
<th>Allowable File Formats</th>
</tr>
</thead>
<tbody>
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<td>I</td>
<td>data-listing-dataset</td>
<td>Data listings, by study</td>
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<td>I</td>
<td>annotated-crf</td>
<td>Sample annotated case report form, by study</td>
<td>.pdf</td>
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<tr>
<td>II</td>
<td>data-listing-dataset</td>
<td>Data listings, by study (Line listings, by site)</td>
<td>.pdf</td>
</tr>
<tr>
<td>III</td>
<td>data-listing-dataset</td>
<td>Site-level datasets, across studies</td>
<td>.xpt</td>
</tr>
</tbody>
</table>

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:

```
  [m5]
  datasets
    bimo
      site-level
```

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

FDA eCTD web page
(http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm)

For general help with eCTD submissions: ESUB@fda.hhs.gov
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARIA R WASILIK
12/05/2016
IND 064802

Abbott Laboratories
Attention: Christopher Leintz, M.A., M.P.H.
200 Abbott Park Road
PA72 AP34-3
Abbott Park, IL 60064-6188

Dear Mr. Leintz:

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

We also refer to the meeting between representatives of your firm and the FDA on March 28, 2011. The purpose of the meeting was to discuss the results of your phase 2 studies and plans for further clinical development to support a New Drug Application (NDA) for the indication of treatment of endometriosis.

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

If you have any questions, call Karl Stiller, Regulatory Project Manager at (301) 796-1993.

Sincerely,

{See appended electronic signature page}

Lisa Soule, M.D.
Clinical Team Leader
Division of 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: End of Phase 2
Meeting Date and Time: March 28, 2011, 1:00 PM – 2:30 PM
Meeting Location: CDER White Oak, Room 1419
Application Number: IND 064802
Product Name: elagolix sodium
Indication: Management of endometriosis-associated pain
Sponsor/Applicant Name: Abbott Laboratories
Meeting Chair: Lisa Soule, M.D.
Meeting Recorder: Karl Stiller, R.Ph.

FDA ATTENDEES
Division of Reproductive and Urologic Products:
Scott Monroe, M.D., Director
Lisa Soule, M.D., Clinical Team Leader
Ronald Orleans, M.D., Medical Officer
Krishan Raheja, Ph.D., DVM, Toxicologist
Margaret Kober, R.Ph., M.P.A., Chief, Project Management Staff
Karl Stiller, R.Ph., Regulatory Health Project Manager

Office of Biometrics:
Mahboob Sobhan, Ph.D., Team Leader, Division of Biometrics III

Office of Clinical Pharmacology:
Chongwoo Yu, Ph.D., Clinical Pharmacology Reviewer, Division of Clinical Pharmacology III

SPONSOR ATTENDEES
Hubert H. Thole, M.D., Ph.D., Project Director, Global Pharmaceutical Research & Development
Steven Wojtanowski, R.Ph., MPH, Divisional Vice President, Regulatory Affairs, Global Product Strategy
Kristof Chwalisz, M.D., Ph.D., Senior Medical Director, Global Pharmaceutical Research & Development
Ramesh Garg, BVSc, Ph.D., DABT, Scientific Director, Global Preclinical Safety, Global Pharmaceutical Research and Development
Rita Jain, M.D., Divisional Vice President, Global Pharmaceutical Research & Development
Ping Jiang, MS, Director, Statistics, Global Statistics & Data Management

Reference ID: 2938472
BACKGROUND
On September 30, 2010, Neurocrine Biosciences, Inc. submitted a request for a meeting to discuss their preclinical and clinical development plan to support a New Drug Application (NDA) for NBI-56418 (elagolix). FDA was notified on October 20, 2010, of a change in sponsorship for the application to Abbott Laboratories. A background package containing the questions listed below was submitted on February 28, 2011. DRUP’s responses to the questions were conveyed to the sponsor on March 25, 2011, and are also included below. Additional meeting discussion is shown in bold font after each response.

CHEMISTRY, MANUFACTURING, AND CONTROLS

**Question 1:** The Sponsor will request a separate EOP2 meeting to discuss CMC topics including starting material designation, API, and DP formulation. Does the Agency agree that a separate CMC EOP2 meeting is acceptable?

**Division response:**
Yes.

**NONCLINICAL**

**Question 2:** As described in Section 11.0 and Appendix B, the Sponsor has completed a number of nonclinical studies, including the human metabolite characterization, chronic toxicity studies in two species and the reproductive toxicity study. Does the Division agree that the completed nonclinical data package is sufficient to support the initiation of the Phase 3 clinical program for elagolix?

**Division response:**
Yes.

**Question 3:** In addition to the completed nonclinical studies, Appendix B summarizes the ongoing and planned nonclinical studies designed to support the development of elagolix. Does the Agency agree that the planned, ongoing and completed nonclinical studies will support an elagolix NDA for the management of endometriosis associated pain?

**Division response:**
Yes.

**Question 4:** Based on lack of toxicity risk for API degradant (minimal binding to target receptor, evidence of being a metabolite of a metabolite, no genotoxicity hazard,
structural difference of minimal or no toxicity hazard), the Sponsor has presented a Scientific Rationale (Appendix C, Section B.1) for a ... limit for toxicological qualification of the degradant (b) (4). Does the Agency agree with the (b) (4) toxicological qualification limit for degradant (b) (4).

**Division response:**
Yes, the scientific rationale seems reasonable.

For additional information on the impurities, please provide the following:
- Calculation details for the toxicological qualification levels (%) given in Appendix C, Table 1
- The results of the Ames test for the impurity (b) (4)
- The levels of the (b) (4) in the drug product to be used in phase 3
- Levels of the described impurities and degradation product in the drug substance being administered in the ongoing rat and mouse carcinogenicity studies

**Additional Discussion at the Meeting:**
The Division indicated that the information sent (attached) in Table 1 sufficiently explained how the Toxicological Qualification Level presented in Table 1, Appendix C of the background package was calculated.

In response to the Division’s inquiry, the Sponsor stated that the genotoxic impurity, (b) (4), was not detected in the drug product.

**Question 5: The Sponsor has conducted**

**Division response:**
(b) (4) Fetal development risk will be determined during the NDA review.

**CLINICAL PHARMACOLOGY**

**Question 6: Does the Agency agree that the Proposed Phase 1 Drug Interaction, Special Population and Clinical Pharmacology studies are sufficient to support an elagolix NDA for the management of endometriosis associated pain (Table 11 and Section 12.3)?**

**Division response:**
Based on the limited information provided, the Sponsor’s approach appears to be reasonable. Refer to the Division’s responses to Questions 7-10 for recommendations on study designs.

The Sponsor should characterize the single and multiple-dose pharmacokinetics (PK) of the to-be-marketed (TBM) formulation and dose strength. It is noted that the PK and food effect following a single dose of the 150 mg Elagolix was assessed using three tablets of 50 mg elagolix IR instead of the 150 mg elagolix IR tablet.

It is noted that the Sponsor is proposing a different formulation for the phase 3 study(ies). Provide the rationale for, and extent of, the formulation change.
Question 7: Does the Agency agree with the study designs, including the selection of oral contraceptives, selection of subjects and pharmacokinetic/pharmacodynamic measures, for the oral contraceptive pharmacokinetic/pharmacodynamic interaction studies (Table 11 and Section 12.3.2)?

Division response:
Based on the limited information provided, the Sponsor’s approach appears to be reasonable. PK characterization of the oral contraceptives to be used in these studies should be carefully considered in designing these studies (e.g., time to reach steady-state, half-life, food effect, etc.) and the study designed to appropriately control for these factors.

Question 8: Although the intended indication for elagolix is in women, does the Agency agree that the proposed DDI studies with ketoconazole and rifampin can be conducted in female subjects (Table 11 and Section 12.3.3)?

Division response:
Division recommends the Sponsor conduct these drug-drug interaction (DDI) studies in premenopausal females. Also, refer to the Division’s response to Question 9.

Question 9: Does the Agency agree that the 2 proposed DDI studies with ketoconazole and rifampin and the 2 pharmacokinetic/pharmacodynamic studies with oral contraceptives will appropriately characterize the drug interaction potential of elagolix to support an elagolix NDA for the management of endometriosis-associated pain (Section 12.3)?

Division response:
For the CYP DDI studies, strong inhibitors and inducers provide the most sensitive assessment and should generally be tested first. Because elagolix is metabolized by CYP3A, the proposed strong inhibitor and inducer appear to be adequate. If the study results are negative, then absence of a clinically important drug-drug interaction for the metabolic pathway is demonstrated. However, if the clinical study of the strong inhibitor (i.e., ketoconazole) or inducer (i.e., rifampin) is positive, the Sponsor would need to conduct in vivo studies of other less potent specific inhibitors or inducers, and develop advice on dosage adjustment. Reference is made to the Guidance for Industry: Drug Interaction Studies - Study Design, Data Analysis, and Implications for Dosing and Labeling.

The Sponsor is reminded that breast cancer resistance protein (BCRP), organic transporting polypeptides (OATP), organic anion transporters (OAT), and organic cation transporters (OCT) have been considered as important transporters in addition to P-glycoprotein (P-gp) and the potential for elagolix as a substrate, inhibitor, or inducer for these transporters should be evaluated during drug development. Reference is made to the Drug Transporter White Paper (Nat. Rev. Drug Discov., 2010; http://www.nature.com/nrd/journal/v9/n3/pdf/nrd3028.pdf).

Question 10: Does the Agency agree that the proposed special population studies (hepatic and renal) are adequate to support an elagolix NDA for the management of endometriosis-associated pain (Section 12.3.7)?
Division response:

Division recommends that the Sponsor conduct these studies in females.

In renal impairment studies, a reduced PK study that compares the PK parameters in subjects with end stage renal disease (ESRD) not yet on dialysis with PK in subjects with normal renal function may be conducted. If results from the initial study in ESRD patients show a substantial PK difference from normal subjects that would warrant dose adjustment in patients with renal impairment, a full PK study with subjects with varying degrees of renal impairment needs to be carried out. Reference is made to the Guidance for Industry: Pharmacokinetics in Patients with Impaired Renal Function - Study Design, Data Analysis, and Impact on Dosing and Labeling.

In hepatic impairment studies, patients across the entire spectrum of hepatic impairment (i.e., mild, moderate, and severe) should be evaluated so that specific dosing recommendations can be developed. Reference is made to the Guidance for Industry: Pharmacokinetics in Patients with Impaired Hepatic Function - Study Design, Data Analysis, and Impact on Dosing and Labeling.

Question 11: Based on the pharmacokinetic and pharmacodynamic, safety and efficacy data from the 18 completed Phase 1 and 2 studies, which evaluated doses of elagolix between 25 and 400 mg, the Sponsor proposes further evaluation in Phase 3 of a dose range of 100 mg to 200 mg (with a targeted dose of 150 mg QD) (Section 14.2). Does the Agency concur with the Sponsor's proposed dose range for Phase 3?

Division response:

Yes.

Additional Clinical Pharmacology Comment:

It was noted the elagolix AUC and C_max were decreased by 33% and 53%, respectively, and T_max was delayed by 2 hours under fed conditions. The phase 3 study(ies) should be carefully designed and conducted reflecting the food intake instructions that will be recommended for the drug in product labeling.

Question 12: The Sponsor and independent experts evaluated the three cases of congenital malformations observed in the development program (two cases with exposure to elagolix and one post-exposure). It was concluded that all cases of congenital malformation were unlikely related to elagolix exposure (Sections 15.4, 15.5, 15.6, and 15.7). Does the Agency agree with the assessments by the Sponsor and independent experts that the congenital malformations observed in the development program are unlikely to be related to treatment with elagolix?

Division response:

At this time, the Division cannot concur that the congenital malformations observed in the development program are unlikely to be related to treatment with elagolix. Further review of the submitted reports of the case histories and the consultant reports will be necessary. In addition, the Sponsor should provide the Case Report Forms (CRFs) for these subjects.

However, the Division does not consider these reports a safety signal that would prevent initiation of phase 3 studies. The Division concurs with the Sponsor’s plans for additional pregnancy testing and increased emphasis on use of adequate contraception.
Additional Discussion at the Meeting:
The Sponsor will submit the CRFs; the Division indicated that it would review these during the course of the NDA review.

CLINICAL

Question 13: Based on the proposed Phase 3 program, Abbott plans on pursuing the following proposed indication to be supported by an elagolix NDA for the management of endometriosis-associated pain:

TRADE NAME (elagolix) is indicated for management of endometriosis associated pain. Efficacy has been established in clinical studies in which premenopausal women (18–49 years of age) with endometriosis participated for up to 1 year as well as in clinical studies with a 6 month treatment period.  

(b)(4)

Does the Agency agree that the proposed elagolix development program for the management of endometriosis-associated pain would support this indication?

Division response:
Based on the general overview presented in the meeting package, the development program appears appropriate to support the proposed indication and treatment durations sought. It is premature, however, to discuss specific wording for the indication and other aspects of labeling.

Question 14: The sponsor plans to conduct two 6-month, placebo-controlled, pivotal efficacy studies in women aged 18–49 with laparoscopically confirmed (within (b)(4) years) endometriosis, and moderate to severe endometriosis related pain (Sections 16.2, 16.2.1, and 16.2.2). Does the Agency agree with the proposed study designs and selected study population for the Pivotal Phase 3 efficacy studies?

Division response:
Yes. The Division is in general agreement with the study designs and the selected study population for the primary phase 3 trials. The Division has the following preliminary comments; further comments will be provided when the full protocols are submitted for review:

• The Division recommends that the eligibility criteria contain no restriction on BMI.
• Consider requiring that sexual partners with recent vasectomies be at least 6 months post-surgery, or perform semen analysis to ensure sterility if subjects whose partners had more recent vasectomies are allowed entry.

(b)(4)

Question 15 a and b: Extensive discussions between the Sponsor and the Agency on appropriate scales for endometriosis-associated pain have led to modified, daily scales for the assessment of dysmenorrhea and nonmenstrual pelvic pain (NMPP) as described in Appendix F. Additional supportive work including cognitive debriefing studies was completed at the request of the Agency (Appendix G).
a) Does the Agency agree that the modified daily scales for assessment of Dysmenorrhea and Nonmenstrual Pelvic Pain are acceptable for use as the co-primary endpoints in the pivotal efficacy studies (Appendix F and Section 16.2.3)?

b) Does the Agency agree that the supportive validation work is sufficient (Appendix G)?

**Division response:**
The co-primary endpoints of dysmenorrhea and nonmenstrual pelvic pain are acceptable. The modified daily scales to be used for pain evaluation are appropriate. The Division finds the cognitive debriefing information useful in supporting the proposed scales.

**Additional Discussion at the Meeting:**
The Sponsor does not plan further cognitive debriefing or validation in the US. The studies will likely be multinational, so validation of translations and possibly country-specific cognitive debriefing will be conducted abroad. The Division agreed that this was appropriate.

**Question 16:** The Sponsor proposes the co-primary endpoints will be the proportion of responders in pain scores assessed by the daily modified pain scale for dysmenorrhea and NMPP. Elagolix will need to demonstrate a statistically significantly (2-sided alpha of 0.05) greater proportion of responders for both dysmenorrhea and NMPP in order for a study to be considered successful. Does the Agency agree that the proposed responder analysis for the co-primary endpoints in the Pivotal efficacy studies is acceptable?

**Division response:**
While use of a responder analysis may be acceptable, the Division does not concur. The definition should be based upon the magnitude of reduction in pain that is clinically meaningful to women treated. This should be determined during the study, e.g., through the use of an appropriate anchoring question regarding the benefit derived from treatment and receiver operator characteristics (ROC) methodology.

The Division also does not concur. The Sponsor should propose criteria for determining that the responder rate difference is both clinically meaningful and statistically significant in order for the study to be declared successful.

**Additional Discussion at the Meeting:**
The Sponsor asked if the Patient Global Impression of Change (PGIC) was acceptable as the standard question for establishing the clinical meaningfulness of the treatment response. The Division will need to review the specific wording of the PGIC, which the Sponsor will provide. The Sponsor plans to conduct the ROC analysis on data pooled from both studies, and will then calculate the response criterion individually for dysmenorrhea and for non-menstrual pelvic pain. This is acceptable to the Division.
The Sponsor should propose the cut point in the PGIC used to dichotomize subjects as satisfied or not; on a 7-point scale, the Division prefers that the cut be between those who are moderately or very improved vs. those minimally improved or worse.

The Sponsor asked what the Division’s emphasis would be in determining the criterion for a responder on each endpoint. ROC analysis can attempt to maximize sensitivity and specificity, weighting each equally, or can place more weight on one particular parameter. The Division would tend to place slightly greater weight on specificity, in order to minimize misclassification of nonresponders.

The Sponsor initially discussed the outcome on each primary endpoint; the Division has typically recommended using mean change from baseline.

The Sponsor plans to conduct the ROC analysis prior to breaking the study blind, and will then update the Statistical Analysis Plan to specify the criterion used to define a response on each endpoint. The Division would like to review the ROC methodology proposed prior to unblinding of the study; the Sponsor will therefore plan to administer the PGIC at an interim visit rather than waiting until the final study visit. The Division recommended that it be given as close to the end of the study as feasible.

The Sponsor asked whether the protocol should specify a difference in responder rate between elagolix and placebo arms that would be considered clinically significant. Alternatively, the Sponsor suggested they could consider reducing the sample size of the efficacy trials and conducting a safety study in parallel. The Division preferred the current plan to conduct two large safety and efficacy trials, and noted that the Sponsor should justify the difference in response rate in the context of the risk/benefit profile of the drug. If the drug has a very good safety profile, a smaller difference from placebo in response rate would likely be acceptable, while approval of a drug with safety concerns would have to be justified by a more notable difference in response rate as compared to placebo subjects.

**Question 17:** Based on prior discussions with the Agency, assessment of the potential impact of concomitant analgesic use on efficacy measures needs to be addressed. As such, the Sponsor proposes to conduct a sensitivity analysis for the co-primary endpoints as described in Sections 16.2.3 and 16.2.4. Does the Agency agree that the proposed sensitivity analysis is adequate to assess the potential impact of concomitant analgesic use?

**Division response:**
Yes, the sensitivity analysis that considers subjects with increased use of analgesics as nonresponders appears acceptable, provided that the parameters considered regarding analgesic use are prespecified in the protocol. It will be a significant review issue if the results of the primary analysis and those from the sensitivity analysis that take into account analgesic use differ substantially.

**Question 18:** The Sponsor will include secondary efficacy endpoints, as described in Section 16.2.5 in the proposed pivotal efficacy studies. Can the Agency provide comment on the potential inclusion of proposed secondary endpoints in the elagolix label?
Division response:
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.

The Division encourages the Sponsor to include a secondary endpoint relating to improvement in dyspareunia, as this is a key symptom of endometriosis. The Division is unlikely to support inclusion of secondary endpoints based on other instruments (such as the PGIC, EHP-5 or CPSS Total Score), as these are unlikely to be useful to prescribers.

Question 19 a and b: Bone safety will be assessed in the Phase 3 program by DEXA (Section 16.5.3). Historically, the lower bound of the 95% confidence interval for the mean percent change from baseline has been the statistical method employed to evaluate changes in BMD with the requirement being that the lower bound not exceed -2.2%.

a) Does the Agency agree that the DEXA methodology described and the proposed % mean change from baseline in BMD as the primary assessment are appropriate?

b) Can the Agency confirm that the lower bound of the 95% confidence interval not exceeding -2.2% remains the preferred method?

Division response:
The Division agrees with the proposed methodology and use of mean percent change to characterize change in BMD at the spine and femur. The criterion for change in lumbar spine BMD of -2.2% over a one year interval beyond that in the comparator group is likely to be acceptable, but the Sponsor should provide further justification for its use in this premenopausal population. The Sponsor will need to provide justification for the change in BMD at the hip believed to be acceptable for eligolix.

Clarify whether stopping rules in case of excessive BMD loss will be included in the protocol(s). Although mean percent change is acceptable for the primary analysis, individual cases of excessive bone loss will be a consideration in the overall assessment of bone safety.

Additional Discussion at the Meeting:
The Sponsor asked for clarification that the Division had agreed that a lower bound of the 95% confidence interval around mean change from baseline in BMD of no worse than -2.2% would be an acceptable criterion for BMD change at the lumbar spine. The Sponsor noted that the placebo arm will provide only six months of data, so one year comparative data will not be available. The Division stated 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.

The Division noted that it would be equally interested in results at each location, and that the evaluation of the hip should be done with equal precision. Hip BMD is of particular concern due to potential risk of hip fracture.
The Sponsor asked whether duration of treatment would be restricted if BMD change greater than -2.2% were observed, noting that the lower bound of the change at one year in femoral neck BMD described in the labeling for depo-subQ provera 104 is -2.5%. The Division did not specify an absolute cut-off for BMD change that would be unacceptable, but would evaluate the overall risk/benefit profile of the product.

As far as persistent decrements in BMD at the Month 12 post-treatment follow-up evaluation, the Division does not have a specific value that would trigger concern; rather, BMD loss that did not show resolution after a year off treatment would be of concern. The Sponsor should provide data on mean BMD and proportions of subjects with various levels of BMD loss (e.g., > 5%, >10%). It will be important to have reliable baseline data on subjects. The Sponsor agreed, and noted that Extension Study 2,

The Sponsor will address stopping criteria relative to bone loss in the full protocol. The Division requested that these not be overly strict, as the Division is interested in getting full data on BMD over the course of treatment and post-treatment recovery. If subjects are discontinued for excessive bone loss, they should remain under follow-up to evaluate BMD recovery.

**Question 20:** Endometrial safety will be assessed in the Phase 3 program with Transvaginal ultrasound and endometrial biopsies as outlined in Section 16.5.4. Does the Agency agree with the proposed assessments for endometrial safety as outlined in Section 16.5.4?

**Division response:**
Yes.

**Question 21 a and b:** The Sponsor has proposed a contraception program and procedures for assessment of pregnancies and outcomes (Section 16.6).

a) Is the proposed contraception plan for future clinical studies acceptable?

b) Does the Agency agree with the proposed procedures for assessment of pregnancies and pregnancy outcomes? Phase 3 Extension Studies No. 1 and No. 2

**Division response:**
a) Yes, the proposed contraception program using double barrier methods is acceptable. However, the pregnancy rate should be monitored closely and if pregnancies continue to occur in the phase 3 trials, further efforts to reduce the risk of pregnancy must be undertaken.

b) Yes, the proposed procedures appear adequate.

**Additional Discussion at the Meeting:**
The Sponsor noted that the annualized pregnancy rate was about 5-6%, similar to literature reports of 4-10% with use of non-hormonal contraception. However, the Division noted that the endometriosis population would be expected to be less fertile than the general population, so the number of pregnancies was surprising.
The Division does not plan to ask for stopping criteria based on pregnancy rate, but would encourage the Sponsor to consider additional measures, such as provision of emergency contraception, if the pregnancy rate is of concern in phase 3.

The Division’s major concern would be about the risk of pregnancy in clinical use; if fertility is maintained while women are using the product, additional data on safety and teratogenicity might be required. No additional reproductive toxicity studies appear to be needed. However, the Sponsor might be required to conduct postmarketing surveillance of pregnancy rates and outcomes and/or establish a pregnancy registry if women are likely to conceive while using elagolix, despite double barrier contraception.

**Question 22 a and b:** Two Phase 3 Extension Studies are proposed to evaluate the safety and efficacy of elagolix with exposure beyond the 6 months planned in the pivotal efficacy studies. The basic designs for these two studies are as follows (Section 16.3):

- **Phase 3 Extension Study 1** will evaluate elagolix treatment for 12 months of continuous treatment (6 months in the pivotal study and 6 months in the extension study) followed by 12 months of follow-up post discontinuation of treatment (Section 16.3.1.).

- **Phase 3 Extension Study 2**

  - a) 
  - b) 

**Division response:**
The study designs appear appropriate; further comments will be provided when the full protocols are submitted for review.

**Additional Discussion at the Meeting:**
**Question 23:** The Sponsor proposes that the initial NDA submission is planned with the following data (Section 16.3):

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**Division response:**

No. All studies supporting the NDA should be completed and the data included at the time of submission.

**Additional Discussion at the Meeting:**

If the Sponsor decides to defer Extension Study 1, and not submit this in the initial application, the complete data from Extension Study 2 should be provided at the time of NDA submission.

**Question 24:** It is anticipated that at the time of NDA submission the safety data base will include more than 2,000 subjects exposed to at least a single dose of elagolix, more than 1,000 subjects exposed to elagolix for at least 6 months and more than 150 subjects exposed to elagolix for 12 months (Section 17.1 and Section 17.2). Does the Agency agree that the proposed number of subjects in the elagolix safety data base at the time of NDA submission is adequate?
Division response:
Barring any unanticipated safety signals, it appears that the safety database will be adequate to support the NDA submission.

Additional Post-Meeting Comment:

Data Standards for Studies
CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for 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 studies. CDER has produced documents that provide specifications for sponsors regarding implementation and submission of study data in a standardized format. These documents will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. These documents may be found at the following webpage:
http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm

ISSUES REQUIRING FURTHER DISCUSSION
None

ACTION ITEMS

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<th>Action Item/Description</th>
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ATTACHMENTS AND HANDOUTS
Table 1 from the background package
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LISA M SOULE
04/26/2011