

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

216578Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**



IND 130277

MEETING MINUTES

Astellas Pharma Global Development, Inc.
Attention: Jennifer Giese-Pagac
Director, Regulatory Affairs
1 Astellas Way
Northbrook, IL 60062

Dear Ms. Giese-Pagac:

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

We also refer to the teleconference between representatives of your firm and the FDA on January 28, 2022. The purpose of the meeting was to discuss your studies and other general information for the submission of a new drug application for fezolinetant tablet.

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

If you have any questions, call Samantha Bell, Regulatory Project Manager at (301) 796-9687.

Sincerely,

{See appended electronic signature page}

Shelley R. Slaughter, M.D., Ph.D.
Medical Officer Team Leader
Division of Urology, Obstetrics, and Gynecology
Office of Rare Diseases, Pediatrics, Urologic, and
Reproductive Medicine
Center for Drug Evaluation and Research

Enclosure: Meeting Minutes



MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: January 28, 2022, 10:45 a.m. – 12:00 p.m. EST
Meeting Location: Teleconference

Application Number: IND 130277
Product Name: Fezolinetant

Indication: Treatment of moderate to severe vasomotor symptoms (VMS) associated with menopause

Sponsor Name: Astellas Pharma Global Development, Inc.
Regulatory Pathway: 505(b)(1) of the Federal Food, Drug, and Cosmetic Act

Meeting Chair: Shelley R. Slaughter, M.D., Ph.D.
Meeting Recorder: Samantha Bell

FDA ATTENDEES

Division of Urology, Obstetrics, and Gynecology (DUOG)

Catherine Sewell, M.D., M.P.H., Deputy Director (Acting)
Shelley R Slaughter, M.D., Ph.D., Clinical Team Leader
Theresa Van Der Vlugt, M.D., M.P.H. Clinical Reviewer
Leah Berhane, M.D., M.H.A., Clinical Reviewer

Division of Regulatory Operations for Rare Diseases, Pediatrics, Urologic, and Reproductive Medicine

Margaret Kober, R.Ph., M.P.A., Chief, Project Management Staff
Samantha Bell, Regulatory Health Project Manager

Division of Pharmacology/Toxicology for Rare Diseases, Pediatrics, Urologic, and Reproductive Medicine

Kimberly Hatfield, Ph.D., Pharmacology and Toxicology Supervisor
Miyun Tsai-Turton, Ph.D., Pharmacology and Toxicology Reviewer

Office of Clinical Pharmacology

Yanhui Lu, Ph.D., Clinical Pharmacology Team Leader
Xiaomeng Xu, Ph.D. Clinical Pharmacology Reviewer

Office of Biostatistics

Daphne Lin, Ph.D., Deputy Division Director

Weiya Zhang, Ph.D., Statistical Team Leader

Yu Cao, Ph.D., Statistical Reviewer

SPONSOR ATTENDEES

Astellas

Andrew Krivoschik, M.D., Ph.D., Senior Vice President, Head Development and Therapeutic Areas

Nancy Martin, M.D., PharmD, FCP, Vice President, Global Medical Head- Medical Specialties

Faith Ottery, M.D., Ph.D., FACN, Executive Medical Director, Medical Specialties

Xuegong Wang, M.D., Ph.D. Senior Medical Director, Medical Specialties

Marci English, M.P.H., Senior Director, Global Development Project Leader

Misun Lee, Ph.D., Director, Biostatistics

Jun Zhao, Ph.D., Director, Biostatistics

Tong Zhu, Ph.D., FCP, Executive Director, Medical Specialties Science & Operations, Clinical Pharmacology & Exploratory Development

Jiayin Huang, Ph.D., Director, Clinical Pharmacology Exploratory Development

Jace Nielsen, PharmD, Director, Modeling & Simulation, Clinical Pharmacology and Exploratory Development

Cathy Franklin, Associate Director, Clinical Program Management, Global Clinical Sciences

Tanja Braakman, M.D., Senior Director, Medical Safety, Pharmacovigilance

Pien de Jong, M.D., Director, Medical Safety, Pharmacovigilance

Seiji Kaku, Ph.D., Director, Applied Research & Operations

Judy Kannenberg, M.B.A., Vice President, Regulatory Affairs Therapeutic Area Head Medical Specialties

Joe Gaugas, BSc (hons), DPharmDev, Executive Director, Team Lead-Medical Specialties, Regulatory Affairs

Rianne Crielaard-Weltak, M.Sc., Director, Regulatory Affairs

Jennifer Giese-Pagac, Director, Regulatory Affairs

1.0 BACKGROUND

Astellas is developing fezolinetant, a nonhormonal, selective NK3 receptor antagonist, for the treatment of moderate to severe VMS associated with menopause. Astellas has requested a pre-NDA meeting to discuss the studies they intend to rely on, to acquaint FDA reviewers with the general information to be submitted in the NDA, and to discuss the best approach to the presentation of data in the NDA.

FDA sent Preliminary Comments to Astellas on January 25, 2022.

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Introductory Discussion:

Astellas is targeting to submit the NDA in summer 2022 with the earliest time of submission as June 2022. Astellas is still considering the use of a priority review voucher and, if used, will notify the FDA of their intention to use at least 90 days in advance of submission of the NDA application.

2.0 DISCUSSION**2.1. Nonclinical**

Question 1: Does the Agency agree the completed nonclinical studies are sufficient to support an NDA filing and review?

FDA Response:

The completed nonclinical studies appear adequate to submit the NDA. It is premature to definitively agree that nonclinical studies are sufficient to support an NDA filing. That determination will be made upon submission of your NDA application and subsequent review.

Discussion:

There was no further discussion at the meeting.

2.2. Clinical Pharmacology

Question 2: Does the Agency agree the clinical pharmacology study package is sufficient to support an NDA filing and review?

FDA Response:

It is premature to definitively agree that the clinical pharmacology study package is adequate to support an NDA filing. That determination will be made upon submission of your NDA application and subsequent review.

Overall, the array of clinical pharmacology trials, completed or planned, appears to be reasonable. However, the human absorption, metabolism, and excretion Study ESN364_CPK_103 showed that the renal clearance of ES259564, i.e., the major metabolite of fezolinetant, had a mean renal clearance of 11.3 L/h, which is beyond the normal glomerular filtration rate and may be indicative of renal secretion. It appears that you have not assessed the drug interaction potential for ES259564 as a substrate of transporters. Conduct studies to test whether ES259564 is a substrate of transporters, including BCRP, OCT2, OAT1, OAT3, MATE1, MATE2, OATP1B1, OATP1B3, and P-glycoprotein, prior to your NDA submission.

Discussion:

Astellas explained they have profiled the metabolite ES259564, which has been shown to be pharmacologically and toxicologically inactive and referenced selected results from the meeting package (pages 23-24, Section 6.1. pages 40-45). Astellas had the following comments:

1. From a pharmacology perspective, the metabolite has approximately 20-fold lower potency on the target NK3 receptor compared to the parent fezolinetant, contributing to approximately 5% of the overall pharmacologic activity, which is substantially less than 50%.
2. From a toxicology perspective, the metabolite has shown no off-target activities. The 39-week toxicology study in female primates (cynomolgus monkey) provided a 26-fold higher AUC of the metabolite compared to the AUC in human at a dose of 45 mg. These data indicate the metabolite does not adversely impact the safety profile of fezolinetant. These data will be provided in a future NDA.
3. Therefore, the drug-drug interaction (DDI) of the metabolite due to transporters is unlikely to result in clinically meaningful alteration of efficacy or safety in vivo, which is consistent with the most recent regulatory guidance.

Astellas wanted to further understand the FDA's feedback to conduct additional in vitro transporter experiments. FDA noted in study 103 the exposure for the metabolite was 2-fold higher than the parent and the Agency is concerned the accumulation of the metabolite may have a clinical impact. FDA explained the DDI risk in humans still needs to be characterized because it is too early to rule out the potential of a DDI.

Astellas intends to include data from a dedicated renal impairment study in the NDA and asked the FDA if this would address the Agency's concerns. FDA continued to recommend that Astellas conduct the additional studies (as noted in the original response). FDA indicated that whether the inclusion of any additional information (as now proposed by Astellas in their discussion) will adequately address the Agency's concerns will be a review issue. Astellas asked if the additional DDI studies could be submitted in the NDA at the time of the 120-day safety update. FDA stated that the NDA should be complete upon submission.

Question 3: Does the Agency agree the nonclinical data support the mechanism of action statement?

FDA Response:

The nonclinical data appear to be supportive of the mechanism of action. A formal description of the mechanism of action for labeling will be determined following submission and successful filing and review of the submitted studies.

Discussion:

There was no further discussion at the meeting.

2.3. Clinical Safety

Question 4: Does the Agency agree that the extent of the fezolinetant exposure is sufficient to support an NDA filing and review?

FDA Response:

It is premature to definitively agree that the extent of the fezolinetant exposure is sufficient to support an NDA filing and subsequent review. Adequacy of the extent of fezolinetant exposure for filing and review will be determined upon submission of your NDA application.

That said, the projected exposures in completed/ongoing clinical trials conducted during your development program, as represented in your meeting briefing document [1100 and 1140 participants with overall exposure to 45 mg and 30 mg, respectively of fezolinetant once daily, 920 and 900 participants exposed to 45 mg and 30 mg, respectively of fezolinetant once daily for 24 weeks (6 months) and approximately 570 and 560 participants exposed to 45 mg and 30 mg, respectively of fezolinetant once daily for 52 weeks (12 months)], appear to meet the ICH E1 criteria regarding participant exposure to assess clinical safety for drugs intended for chronic use in the treatment of non-life-threatening conditions. The ICH E1 guidelines recommend exposure in 1500 participants overall, 300-600 participants for six months, and 100 participants for 1 year. These exposures should occur at the dose or dose range believed to be efficacious in the intended population of postmenopausal women.

Discussion:

There was no further discussion at the meeting.

Question 5a: *Does the Agency agree that the approach to the assessment of endometrial safety, including presentations and displays, is adequate to support an NDA filing and review?*

FDA Response:

It is premature to definitively agree that your approach to assess endometrial safety is adequate for filing and subsequent review of your NDA application. This determination will be made upon submission of your NDA application.

As outlined in Subsection 9.1 Endometrial Safety Assessments in your pre-meeting briefing document, participants in the primary endometrial health set for Trials 2693-CL-0301 (henceforth referred to as Trial 0301), 2693-CL-0302 (henceforth referred to as Trial 0302), and 2693-CL-0304 (henceforth referred to as Trial 0304) are defined as:

- 1) Randomized
- 2) Received at least one dose of trial medication
- 3) Have a postbaseline endometrial biopsy done within 30-days of the last dose of trial medication with:
 - a) Acceptable baseline biopsy with evaluable tissue and no evidence of endometrial hyperplasia, endometrial cancer, or disordered proliferative endometrium, and an
 - b) Acceptable postbaseline endometrial biopsy on Day 326 or after, or a
 - c) Diagnosis of endometrial hyperplasia, endometrial cancer, or disordered proliferative endometrium prior to Day 326.

At a high-level, your definition of the primary endometrial health set appears reasonable.

You indicate, however, that participants initially randomized to placebo in the first 12 weeks of Trial 0301 and Trial 0302, who were re-randomized to fezolinetant 30 mg or 45 mg in the 40-week (9 month) extension period, will not be included in the primary endometrial health set. You indicate that this 40-week difference in duration of fezolinetant exposure creates “challenges in defining the endometrial health set for the integrated analysis.” Therefore, you propose “to conduct additional supportive analyses which include these re-randomized participants.”

Clarify the additional supportive analyses that will be performed. These initial placebo-assigned participants in Trials 0301 and 0302 had a baseline endometrial biopsy performed prior to start of placebo oral administration. Per the protocols for

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Trials 0301 and 0302, no endometrial biopsy was performed prior to re-randomization to fezolinetant (30 mg or 45 mg) in the 40-week extension period. Clarify how this will be addressed in your proposed supportive analyses.

At a high level, your proposed approach to the presentation/display of endometrial biopsy results appears reasonable. We remind you of your agreement to provide a line listing of endometrial biopsy diagnosis determined by pathologists 1, 2, and 3, and the final consensus diagnosis, for each participant with a uterus in phase 3 clinical trials. Include the trial day and date for each endometrial biopsy diagnosis per pathologists.

Discussion:

Astellas provided the following information, which are pre-specified in the ISS SAP version 2.0, to address FDA's requested clarification of additional supportive analyses:

1. Additional supportive analyses will be conducted for those participants who were initially randomized to placebo and were re-randomized to fezolinetant at week 12 ("placebo-switchers").
2. For "placebo-switchers", Astellas intends to use their screening biopsies as representative of a pre-fezolinetant treatment baseline biopsy.
3. Astellas will tabulate the data from the "placebo-switchers" separately from the primary endometrial health (EH) set.
4. Astellas will integrate "placebo-switchers" data from Trials 0301 and 0302 and report the results by 2 treatment groups: placebo/fezolinetant 30 mg and placebo/fezolinetant 45 mg.
5. Astellas will apply a similar approach consistent with the primary analysis by including hyperplasia, disordered proliferative pattern, or malignancy occurring any time during fezolinetant exposure.
6. Astellas does not intend to evaluate the supportive summary data using an upper limit of the one-sided 95% confidence interval (CI). This is in contrast to the analysis that will be performed for the primary EH set analysis.
7. Specifics are described in the table shell provided in Appendix 1 on page 148 of the briefing document.

Astellas expressed concern that the endometrial health data would be uninterpretable for the "placebo-switchers" because of the small number of "placebo switchers" (approximately 50 per arm) and shorter duration of exposure (40 weeks of exposure).

FDA stressed the importance of the availability of all endometrial safety data, including the retention of endometrial safety data for “placebo-switchers”. FDA recommended that the analysis of “placebo-switchers” should be performed in the same way as the analysis for the primary endometrial health set. FDA concluded the NDA should include 3 analysis groups: (1) all participants including “placebo-switchers,” (2) participants excluding “placebo-switchers,” and (3) “placebo-switchers” alone. The data from each of these 3 groups should be analyzed using an upper limit of the one-sided 95% CI.

Astellas confirmed that all 3 pathologists’ diagnoses will be included, along with the final diagnosis. Additionally, the biopsy sample collection date and the date the pathologist rendered the diagnosis will be included in the listing.

Question 5b: Does the Agency agree with Astellas’ definition of the evaluable endometrial health set for the primary analysis and the plan for the supportive analysis?

FDA Response:

See our response to Question 5a.

Discussion:

See discussion under Question 5a.

Question 6: Does the Agency agree that the approach to the assessment of hepatic safety, including presentations and displays, is adequate to support an NDA filing and review?

FDA Response:

It is premature to definitively agree that your approach to the assessment of hepatic safety, including presentations and displays, is adequate to support filing and subsequent review of your NDA application. This determination will be made upon submission of your NDA application.

At a high level your proposed approach including the assessment of hepatic safety and the presentations/displays appears reasonable.

Discussion:

There was no further discussion at the meeting.

Question 7a: Does the Agency agree with the general approach of safety data presentation and evaluation for the NDA?

FDA Response:

In general, we agree with your proposed approach for safety data presentation and evaluation for your future NDA application. We will advise you of any additional information requests after your NDA application is submitted.

Discussion:

There was no further discussion at the meeting.

Question 7b: Does the Agency agree with the areas of medical focus selected for these summative safety assessments for fezolinetant within Module 2.7.4 SCS?

FDA Response:

In general, we agree with your proposed areas of medical focus, identified on page 27 of your briefing document. Your proposed areas of medical focus include, but are not limited to:

1. Endometrial safety
2. Hepatic safety and risk for hepatotoxicity
3. Bone safety
4. CNS safety
5. Selected hematologic safety: thrombocytopenia

Address in your NDA application, as additional areas of medical focus:

1. glucose impairment and
2. creatinine phosphokinase (CPK) increase observed in completed Trials 0301 and 0302. We acknowledge that the preliminary safety data in your briefing document does not include treatment-emergent adverse event (TEAEs) for ongoing Trial 0304.

We will advise you of any additional requests for information after your NDA application is submitted.

Discussion:

There was no further discussion at the meeting.

Question 7c: *Are there any additional recommendations from the Agency to help ensure that the safety evaluation meets the FDA's expectations when the NDA is filed?*

FDA Response:

Not at this time. We will advise you of any additional requests for safety information after your NDA application is submitted.

Discussion:

There was no further discussion at the meeting.

2.4. Dose Selection

Question 8: *Does the Agency agree with the considerations for benefit-risk in the general approach to the proposed dose selection for fezolinetant in the future NDA filing?*

FDA Response:

No, we do not completely agree with the benefit:risk considerations for your 30 mg and 45 mg dosage strengths in the general approach of your dose selection for fezolinetant. The preliminary data presented in your briefing document appears to support your conclusion that the 45 mg fezolinetant dosage strength demonstrates statistically significant improvement (reduction) from baseline in moderate to severe hot flash frequency and severity at Week 4 and Week 12 in your confirmatory 12-week, placebo-controlled clinical Trial 0301 and Trial 0302. Additionally, a clinically meaningful threshold reduction in the frequency of moderate to severe hot flashes, defined as a frequency reduction of 2 moderate to severe hot flashes above placebo per day, appears to be demonstrated at Week 4 which is maintained through Week 12 in confirmatory Trials 0301 and 0302 for your 45 mg fezolinetant dosage strength.

Your 30 mg fezolinetant dosage strength also appears to demonstrate statistically significant improvement (reduction) in moderate to severe hot flashes at Week 4 and Week 12 in both confirmatory phase 3 clinical trials. However, your 30 mg fezolinetant dosage strength does not demonstrate the same consistent clinically meaningful threshold reduction in the frequency of hot flashes in both confirmatory phase 3 clinical trials at Week 4 maintained through Week 12. This will be a review issue for the 30 mg fezolinetant dose should your NDA application be filed.

(b) (4)

Discussion:

Astellas noted the FDA's comment regarding the lack of complete agreement with the benefit:risk considerations for the 30 mg and 45 mg dosage strengths as they relate to dose selection for fezolinetant. Astellas asked for additional feedback from FDA on the Agency's perspective. FDA explained that based on the meeting package it was unclear if Astellas plans to seek approval of the 30 mg fezolinetant dosage strength for the same indication as the 45 mg dosage strength for the treatment of moderate to severe vasomotor symptoms in a healthy postmenopausal population. FDA further stated the data for the 30 mg dosage strength does not demonstrate the same consistent clinically meaningful threshold reduction in hot flash frequency at week 4 maintained through week 12 as the 45 mg dosage strength. (b) (4)

. Astellas explained that they intend to submit data for each dosage strength to the NDA. The target dosage strength that they will seek for the indication of treatment of moderate to severe vasomotor symptoms due to menopause in healthy women is 45 mg fezolinetant. (b) (4)

2.5. Regulatory

Question 9: Does the Agency recommend an electronic pre-submission meeting with Astellas 30 to 60 days prior to the filing of a future NDA application for fezolinetant?

FDA Response:

It is premature to discuss filing of an NDA for fezolinetant. However, it does not appear that there are any technical aspects that still need to be discussed prior to the NDA submission in an electronic pre-submission meeting. We have the following comments regarding the submitted data to be included in your NDA.

The submitted study data should contain the following information:

1. Define.xml should be compatible to the current version of Internet Explorer (Version 11.0 or later).
2. In your analysis data reviewer's guide and study data reviewer's guide, clearly list which versions of CDISC ADaM (and ADaMIG), and SDTM (and SDTMIG), and define.xml are used for the study data.

For the study data submission, refer to the FDA Study Data Standards Resources website: <https://www.fda.gov/industry/fda-resources-data-standards/study-data-standards-resources>.

In addition, submit the software programs used to create all ADaM datasets and the software programs used to generate tables and figures associated with primary and secondary efficacy analyses. Refer to the FDA Study Data Technical Conformance Guide Section 4.1.2.10.

Discussion:

There was no further discussion at the meeting.

ADDITIONAL COMMENTS:

We acknowledge that you made some changes in the to-be-marketed compared to the clinical phase 3 formulations and provided comparative dissolution data in multiple dissolution media pH across the physiological pH range. However, you did not provide detailed information regarding the changes made in the to-be-marketed compared to the clinical phase 3 formulations. Therefore, to bridge the to-be-marketed and clinical phase 3 formulations, clearly explain in a side-by-side tabular format the differences between the formulations and your assessment of the level of the differences as per the principle of FDA guidance immediate release solid oral dosage forms scale-up and post-approval changes: chemistry, manufacture, and controls, in vitro dissolution testing, and in vivo bioequivalence documentation (<https://www.fda.gov/regulatory-information/search-fda-guidance-documents/supac-ir-immediate-release-solid-oral-dosage-forms-scale-and-post-approval-changes-chemistry>).

Once we receive and evaluate the information, we will be able to provide necessary comments on any bridging issues.

Discussion:

Astellas informed the FDA that this information was previously provided and referenced the October 2019 Written Responses for a CMC meeting. Astellas intends to also provide the requested information in the NDA.

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.

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

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, 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*.¹ In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov. For further guidance on pediatric product development, please refer to FDA.gov.²

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 Information³ and Pregnancy and Lactation Labeling Final Rule⁴ 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.

¹ When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

² <https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development>

³ <https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information>

⁴ <https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule>

- 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*.

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

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

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

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

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There are no issues requiring further discussion.

5.0 ACTION ITEMS

Action Item/Description	Owner	Due Date
Meeting Minutes	FDA	February 27, 2022

6.0 ATTACHMENTS AND HANDOUTS

There were no attachments or handouts for the meeting summary.

⁵ <https://www.fda.gov/media/85061/download>

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

/s/

SHELLEY R SLAUGHTER
02/24/2022 05:54:07 PM



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 130277

MEETING MINUTES

Astellas Pharma Global Development, Inc.
Attention: Jennifer Giese-Pagac
Director, Regulatory Affairs
1 Astellas Way
Northbrook, IL 60062

Dear Ms. Giese-Pagac:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for ESN364 (fezolinetant).

We also refer to the meeting between representatives of your firm and the FDA on April 17, 2019. The purpose of the meeting was to discuss your nonclinical, clinical pharmacology, and clinical development program for fezolinetant.

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 Kim Shiley, R.N., B.S.N., Regulatory Project Manager at (301) 796-2117.

Sincerely,

{See appended electronic signature page}

Shelley R. Slaughter, M.D., Ph.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

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: End of Phase 2

Meeting Date and Time: April 17, 2019
11:30 a.m. – 12:45 p.m.

Meeting Location: 10903 New Hampshire Avenue
White Oak Building 21, Conference Room: 1537
Silver Spring, Maryland 20903

Application Number: 130277
Product Name: ESN364 (fezolinetant)
Proposed Indication: Treatment of moderate to severe vasomotor symptoms (VMS)
associated with menopause

Sponsor/Applicant Name: Astellas Pharma Global Development, Inc. (Astellas)

Meeting Chair: Shelley R. Slaughter, M.D., Ph.D.
Meeting Recorder: Kim Shiley, R.N., B.S.N., B.S.B.A.

FDA ATTENDEES

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

Hylton Joffe, M.D., M.M.Sc., Director
Shelley R. Slaughter, M.D., Ph.D., Clinical Team Leader
Theresa van der Vlugt, M.D., M.P.H., Clinical Reviewer
Regina Zopf, M.D., M.P.H., Clinical Reviewer
Kimberly Hatfield, Ph.D., Pharmacology and Toxicology Team Leader
Miyun Tsai-Turton, M.S., Ph.D., Pharmacologist
Margaret Kober, R.Ph., M.P.A., Chief, Project Management Staff
Kim Shiley, R.N., B.S.N., Regulatory Health Project Manager

Office of Clinical Pharmacology

Jihong Shon, M.D., Ph.D., Clinical Pharmacology Reviewer
Doanh Tran, Ph.D., Clinical Pharmacology Team Leader
Fang Li, Ph.D., Pharmacometrics Reviewer

Office of Pharmaceutical Quality, Office of New Drug Products

Division of New Drug Products II

Mark Seggel, Ph.D., CMC Lead

Office of Biostatistics

Mahboob Sobhan Ph.D., Biometrics Team Leader
Weiya Zhang, Ph.D., Statistical Reviewer

Clinical Outcome Assessment (COA)

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Astellas

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Consultants

(b) (4)

BACKGROUND

Astellas requested a meeting with the FDA to discuss their nonclinical, clinical pharmacology, and clinical plans for phase 3 development of fezolinetant. Fezolinetant is a small-molecule, nonhormonal, selective neurokinin (NK) 3 receptor antagonist currently being developed for the treatment of moderate to severe vasomotor symptoms associated with menopause.

Fezolinetant was initially discovered and developed by Ogeda S.A.; Ogeda completed 7 clinical studies: ESN364-CPK-101, ESN364-CPK-102, ESN364_CPK_103, ESN364-UF-02, ESN364-PCO-201, ESN364_HF_204 and ESN364_HF_205. In May 2018, Astellas acquired Ogeda and IND 130277 was transferred to Astellas. Astellas has also completed 3 phase 1 studies: 2693-CL-0020, 2693-CL-0006 and 2693-CL-0009.

Key regulatory interactions with the FDA:

- FDA Type C meeting held on March 22, 2017, with Ogeda to discuss the fezolinetant development plan, including nonclinical and clinical development.
- On October 24, 2017, Ogeda submitted a Final Protocol for Carcinogenicity and Toxicokinetic study with fezolinetant in rats as a special protocol assessment (SPA) request.
- On December 6, 2017, the Executive Carcinogenicity Assessment (ECAC) meeting minutes were provided to Ogeda; Ogeda responded to the ECAC on December 20, 2017.
- On January 26, 2018, FDA provided an Advice Information Request letter providing clarification of some ECAC recommendations. In response, Ogeda submitted the final FDA agreed-upon protocol on March 1, 2018.
- On June 7, 2018, FDA provided to Astellas, Type C Written Response Only Meeting Minutes related to findings of transient elevation of liver enzymes in the phase 2b Trial ESN364_HF_205.
- On July 3, 2018, FDA provided an Advice/Information regarding the sponsor's finding of two additional cases of transient elevation of liver enzymes and reiterated the advice provided in the June 7, 2018, Written Response Only Meeting Minutes. Astellas responded to the Agency's request letter and the request for information from the June 7, 2018, Type C meeting minutes.
- On October 16, 2018, Astellas requested a SPA for a mouse Carcinogenicity Study. FDA responded on November 29, 2018. On January 16, 2019, Astellas submitted the SPA final protocol.
- On October 24, 2018, FDA provided Type C Written Response Only Meeting Minutes related to endometrial health assessment, bone safety assessment, and breast cancer treatment-related VMS development strategy.

Per Astellas, they are pursuing a global development program for fezolinetant for the treatment of moderate to severe vasomotor symptoms associated with menopause, targeting simultaneous development and launch across multiple countries.

FDA sent Preliminary Comments to Astellas on April 12, 2019.

QUESTIONS/DISCUSSION

Quality (Chemistry, Manufacturing and Control)

No questions at this time. Chemistry, manufacturing and control will be discussed at a future meeting.

Nonclinical

Nonclinical Study Package

Astellas considers that the results of the nonclinical studies conducted to date [Section 6.1] and the ongoing and planned nonclinical studies outlined in [Sections 6.2 and 10.1] are adequate to support the proposed development plan and the NDA submission for fezolinetant.

Question 1: *Does the Agency agree that the completed, ongoing and planned nonclinical studies are adequate to support the proposed phase 3 development program and the NDA submission for fezolinetant?*

FDA Response:

No, we do not agree. The pharmacokinetic (PK)/pharmacodynamic (PD) profile of the major metabolite, ES259564, has not been adequately addressed, and the final study report for Study 8331280 (39-week monkey toxicity study), which should evaluate both the chronic toxicology profile of metabolite ES259564 and fezolinetant, has not been submitted for review. As discussed at the March 2017, Type C meeting, submit all final study reports to the IND, along with a summary table of safety margins based on animal exposure data for both fezolinetant and ES259564. Based on the proposed duration of the phase 3 clinical trial, the 39-week toxicology study report must be submitted and reviewed by us prior to the initiation of the phase 3 clinical trial. Any nonclinical deficiencies that must be addressed will be communicated following our review.

Submit electronically as eCTD files, all nonclinical study reports intended to support this IND. Many of your supportive studies are currently in non-eCTD format.

Meeting Discussion:

Astellas will re-submit, via eCTD, report(s) previously submitted by Ogeda as paper submission(s). Astellas will also provide a summary table of safety margins based on animal exposure data for both fezolinetant and its metabolite as a Response to Information Request.

Clinical Pharmacology

Planned Biopharmaceutics and Clinical Pharmacology Studies

The biopharmaceutics, pharmacokinetics and pharmacodynamics properties of fezolinetant have been investigated in a series of nonclinical and clinical studies [Sections 6 and 7]. An overview of the clinical pharmacology attributes of fezolinetant, including absorption, distribution, metabolism and elimination characteristics, drug-drug interactions and effects on QT

prolongation are provided in [Section 7.1.2, 7.1.3 and 7.1.4]. Information regarding exposure-response relationships are provided in [Section 7.1].

Astellas considers that the completed and planned biopharmaceutics and clinical pharmacology studies outlined in [Table 5] and further described in [Sections 7.1 and 10.2.1] are adequate to support the proposed development and the NDA submission for fezolinetant.

Question 2: *Does the Agency agree that the completed and planned biopharmaceutics and clinical pharmacology studies are adequate to support the proposed phase 3 development program and the NDA submission for fezolinetant?*

FDA Response:

The array of clinical pharmacology trials, completed or planned, appear to be reasonable. However, the adequacy of these trials to support the NDA submission will be a review issue and will depend on the quality of trial conduct and results.

Submit the protocol for any planned clinical pharmacology trial for our review and comment; allow sufficient lead time for our review prior to your planned trial initiation.

Meeting Discussion:

No discussion of the Preliminary Comments was requested.

CYP1A2 Inhibitors

In vitro data suggest that fezolinetant is primarily metabolized by the CYP1A2 enzyme [Section 7.1.3.1]. In clinical study 2693-CL-0006, fluvoxamine, a strong CYP1A2 inhibitor, increased the C_{max} and AUC of fezolinetant by 1.82-fold and 9.39-fold, respectively. Physiologically-based pharmacokinetic (PBPK) modeling [Section 9.2.4] was performed to predict the effect of CYP1A2 weak and moderate inhibitors on fezolinetant. The model predicted a C_{max} ratio of 1.20 (95% CI: 1.19, 1.22) and AUC ratio of 3.95 (95% CI: 3.81, 4.10) when fezolinetant is co-administered with 200 mg mexiletine, a moderate CYP1A2 inhibitor. This model showed that cimetidine, a weak CYP1A2 inhibitor, is predicted to increase the C_{max} and AUC of fezolinetant by 42% and 75%, respectively, suggesting that CYP1A2 weak inhibitors could be co-administered with fezolinetant in the phase 3 clinical studies at the 30 mg once daily dose selected. In addition, caffeine is a weak CYP1A2 inhibitor and the completed phase 2b study ESN364_HF_205 had no restriction on caffeine intake.

Taking into account these data as well as safety findings in Study ESN364_HF_205, Astellas proposes to prohibit moderate and strong CYP1A2 inhibitors as concomitant medications in the phase 3 studies to avoid potential increased exposure levels but to allow weak CYP1A2 inhibitors as concomitant medications.

Question 3: *Does the Agency agree that the proposal to prohibit moderate and strong CYP1A2 inhibitors but allow weak CYP1A2 inhibitors as concomitant medications is appropriate for the phase 3 clinical studies?*

FDA Response:

Your proposal to allow concomitant administration of weak CYP1A2 inhibitors (e.g. caffeine) with 30 mg fezolinetant daily in your phase 3 trials appears acceptable.

Meeting Discussion:

No discussion of the Preliminary Comments was requested.

Request to Waive Thorough QT/QTc Study

Following the ICH E14 Q&A (R3) guidance and Scientific White Paper on Concentration-QTc Modeling [Garnett et al, 2018], Astellas performed an analysis of the concentration-QTc relationship using data from single- and multiple-ascending dose study ESN364-CPK-102 to evaluate the QT prolongation potential of fezolinetant [Section 7.1.4]. Details of the electrocardiogram (ECG) data source and quality, pharmacokinetic exposure achieved, the methods and results of the concentration-QTc analysis are available in [Attachment 1]. The potential for QTc prolongation with fezolinetant was assessed in models evaluating fezolinetant as well as fezolinetant and its metabolite. Both models showed that the upper bound of the 90% CI was < 10 msec for the therapeutic and supratherapeutic concentration. The model predicted placebo-corrected QTc prolongation (Fredericia-corrected QT interval [QTcF]) had a 90% confidence interval (CI) with an upper limit of 3.2665 and 3.0945 msec on day 1 and day 7, respectively, at the therapeutic concentration for both parent and metabolite (fezolinetant: 0.250 µg/mL; ES00259564: 0.250 µg/mL). The model predicted placebo-corrected QTcF prolongation at the supratherapeutic concentration (fezolinetant: 1.5 µg/mL; ES00259564: 1.5 µg/mL), which is > 6 x the therapeutic concentration, had a 90% CI with an upper limit of 4.4130 and 3.9233 msec for day 1 and day 7, respectively. The analysis results showed no clinically relevant prolongation of QT by fezolinetant at the therapeutic or supratherapeutic concentrations.

Astellas considers that the quality of the ECG data, the pharmacokinetic exposures achieved in the clinical study ESN364-CPK-102 and the predefined concentration-QTcF analysis and results fulfill the requirements to assess the potential of QT prolongation and support a TQT study waiver. The detailed package to support the TQT waiver is available in [Attachment 1].

Question 4: Does the Agency agree to waive the requirement to conduct a stand-alone thorough QT/QTc (TQT) study based on the concentration-QTc analysis?

FDA Response:

No, we cannot agree at this time that a thorough QT/QTc (TQT) study can be waived. We cannot make this determination until we have reviewed the existing data to support your TQT study substitution request. We request that you submit the following data for our integrated nonclinical and clinical assessment:

- The proposed approach for justifying the supra-therapeutic exposures by combining the effects of strong CYP1A2 inhibition (~2-fold), the lowest body weight (1.44-fold), the to-be-marketed tablet formulation (1.225-fold), and an Asian patient population (1.25-fold) appears reasonable. For representing the worst-case scenario, use the expected increase in Cmax of fezolinetant with concomitant administration of a strong CYP1A2 inhibitor at

steady-state. Moreover, the empirical factor of ~2-fold (1.82-fold; pending clinical pharmacology studies) increase to represent the steady-state exposures at worst-case scenario (renal impairment, hepatic impairment etc.) is a review issue.

- Submit the following items for our further review:
 - The study report for the drug interaction (2693-CL-0006) study
 - The safety data from ongoing clinical trials
 - Trial report(s) for any other clinical trial that you have conducted, that evaluates the effect of product administration on the QT interval. Include:
 - Trial report
 - Statistical analysis plan
 - Clinical trial protocol
 - Investigator's Brochure
 - A completed Highlights of Clinical Pharmacology and Cardiac Safety Table
 - Annotated case report form (CRF)
 - A data definition file which describes the contents of the electronic data sets
 - Electronic data sets as SAS.xpt transport files (in CDISC SDTM and ADAM format – if possible) and all the SAS codes used for the primary statistical and exposure-response analyses. Include in the electrocardiogram (ECG) raw data set the following:
 - Subject ID
 - Treatment, period
 - ECG date
 - ECG time (down to second)
 - Nominal day
 - Nominal time
 - Replicate number
 - Heart rate
 - Intervals QT, RR, PR, QRS and QTc (including any corrected QT, e.g., QTcB, QTcF, QTcN, QTcI, along with the correction factors for QTcN and QTcI)
 - Lead and ECG ID (link to waveform files, if applicable)
 - Data set with QT/QTc values that are the average of the above replicates at each nominal time point
 - Adverse event analysis using the MedDRA SMQ “Torsade de pointes/QT Prolongation” and include the preferred term “Seizure” by treatment and dose level.
 - Narrative summaries and case report forms for any:
 - Deaths
 - Serious adverse events
 - Episodes of ventricular tachycardia or fibrillation
 - Episodes of syncope
 - Episodes of seizure
 - Adverse events resulting in the subject discontinuing from the study

- Submit all related ECG waveforms to the ECG warehouse (www.ecgwarehouse.com)

Meeting Discussion:

No discussion of the Preliminary Comments was requested.

Clinical

Phase 3 Dose Selection

Astellas proposes a fezolinetant dose of 30 mg once daily to be tested in the phase 3 program. This proposal is based on the efficacy results of phase 2b study ESN364_HF_205 [Sections 7.2.1.1 and 9.1], the multiple comparison procedure – modeling (MCP-Mod) results [Section 9.2.1], the population pharmacokinetic model results [Section 9.2.2], the population exposure-response model results [Section 9.2.3], safety considerations and the recommendations of an external independent liver safety monitoring panel [Section 9.3]. These considerations demonstrated that 30 mg once daily was the lowest effective dose. The rationale and considerations for dose selection for the phase 3 studies are described in [Section 9].

Question 5: *Does the Agency agree with the fezolinetant dose of 30 mg once daily selected for the phase 3 program?*

FDA Response:

No, we do not agree. In completed Trial ESN364_HF_205, the daily administered 30 mg dose of fezolinetant does not appear to demonstrate both a clinically meaningful **and** statistically significant reduction in the frequency and statistically significant reduction in the severity of moderate to severe vasomotor symptoms (hot flashes/hot flushes) at Week 4 and Week 12.

For products intended to treat moderate to severe vasomotor symptoms, the primary efficacy analysis should show both a clinically meaningful **and** statistically significant reduction in the frequency **and** statistically significant reduction in the severity of hot flashes in the treated group(s) compared with placebo. This reduction should occur within 4 weeks of initiation of treatment and be maintained through 12 weeks of treatment. A clinically meaningful reduction in frequency is identified as a reduction of at least two moderate to severe hot flashes above that demonstrated with placebo at Week 4 and maintained through Week 12. To fully demonstrate a reduction in severity of hot flashes at Week 4 maintained through Week 12, we recommend that mild, moderate, and severe hot flashes be captured at these time points. Primary efficacy endpoints are assessed at Week 4 and Week 12.

Reported results for completed phase 2b Trial ESN364_HF_205 show that the daily 30 mg fezolinetant dose demonstrated a clinically meaningful and statistically significant reduction in the frequency of hot flashes at Week 4 and Week 12 and demonstrated a statistically significant reduction in the severity of hot flashes at Week 4. However, a statistically significant reduction in the severity of hot flashes at Week 12 was not demonstrated for the daily 30 mg fezolinetant dose. Based on the reported results in 12-week, phase 2b Trial ESN364_HF-205, you may be at risk of not identifying an effective dose of fezolinetant for a VMS indication in your proposed phase 3 development program. We also acknowledge the safety concerns with transient

elevation of transaminases with fezolinetant doses 60 mg and greater. Therefore, we urge you to factor in the potential for successful efficacy demonstration and safety issues to determine the dose of fezolinetant to evaluate in phase 3.

We also refer you to the Agency's Advice/Information Request (A/IR) letter, dated June 16, 2016, the Agency's Meeting Minutes, dated April 17, 2017, for information provided to Ogeda S.A., and to the Agency's 2003 draft Guidance for Industry, entitled "Estrogen and Estrogen/Progestin Drug Products to Treat Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms — Recommendations for Clinical Evaluation", (henceforth referred to in this document as the Agency's Hormone Therapy Clinical Evaluation Guidance). While fezolinetant is not an estrogen/progestin drug product, this draft guidance includes recommendations that are also relevant for other products seeking a VMS indication.

Meeting Discussion:

Astellas acknowledged the Agency's advice regarding 1) the potential for failure to demonstrate efficacy for the 30 mg fezolinetant dose at phase 3, based on the findings in phase 2b Trial ESN364_HF_205 (i.e. failure to demonstrate statistical significance vs. placebo in the mean change from baseline in severity at week 12), and 2) safety signals (transient elevation of transaminases) for fezolinetant doses 60 mg and greater. Astellas

(b) (4)
[REDACTED] also inquired if FDA had any advice regarding a dose greater than 30 mg to evaluate in a dose ranging phase 3 trial. FDA inquired whether Astellas had done any modeling for a 45 mg fezolinetant dose. Astellas indicated that they had, stating that, using a mean baseline of 11.5 hot flashes, the 45 mg fezolinetant dose may produce a clinical meaningful reduction of 2.35 hot flashes per day above placebo, and a 0.41 reduction in severity at weeks 4 and 12. However, Astellas acknowledged that they have no safety data for the 45 mg fezolinetant dose.

Astellas indicated that they will conduct additional modeling to determine an additional dose to evaluate in phase 3 development. The protocols for the phase 3 trials including a 30 mg dose and to-be-identified second dose, will be provided to the FDA for the Agency's review and comments.

Astellas confirmed that their plan is to conduct the two-confirmatory efficacy and safety phase 3 clinical trials simultaneously. FDA recommended that the sponsor stagger the conduct of the two-confirmatory efficacy and safety trials so that they might have results from the first trial to better plan the second trial.

FDA inquired whether the sponsor had further plans to evaluate the effects of smoking status on the efficacy of fezolinetant. Astellas indicated that a prior phase 1 trial and the phase 2b trial had included current smokers and future phase 3 trials will also enroll women who are current smokers to address this issue.

Design of Pivotal Efficacy Studies 2693-CL-0301 and 2693-CL-0302

Two pivotal efficacy phase 3 studies are planned for the US/Europe in women with moderate to severe VMS associated with menopause: studies 2693-CL-0301 and 2693-CL-0302. These studies are described in [Section 10.2.2.1]. The clinical study protocol for Study 2693-CL-0301 is available in [Attachment 2]. The clinical study protocol for Study 2693-CL-0302 is the same as that of Study 2693-CL-0301 and is thus not provided with this briefing document.

Question 6: *Does the Agency agree with the pivotal efficacy studies 2693-CL-0301 and 2693-CL-0302, regarding:*

6a: *Study design?*

FDA Response:

We do not agree that your overall trial designs for Trial 2693-CL-0301 and Trial 2693-CL-0302 are acceptable.

Include the following in your proposed designs for both Trial 2693-CL-0301 and Trial 2693-CL-0302:

- Perform an endometrial biopsy in any participating woman with a uterus who completes the 12-week, placebo-controlled period in proposed Trial 2693-CL-0301 or Trial 2693-CL-0302 and declines participation in the proposed open-label 40-week trial extension. A diagnosis of disordered proliferative endometrium, endometrial hyperplasia, or endometrial cancer must be appropriately followed-up by Astellas until resolution.
- Perform a mammogram at the completion of your proposed 52-week Trial 2693-CL-0301 and Trial 2693-CL-0302 for all participating postmenopausal women; this is consistent with the recommendation that women greater than 40 years of age have an annual screening mammogram performed.

We do not agree with your proposal included in submodule 5.4.7 Endometrial Biopsy in the protocol submitted for 52-week Trial 2693-CL-0301, found in Attachment 2 of your meeting briefing package. Specifically, we do not agree with the statement: (b) (4)

Any woman with an abnormal endometrial biopsy at Week 52 reported as disordered proliferative endometrium, endometrial hyperplasia, or endometrial cancer must be appropriately followed-up by Astellas until resolution.

Your proposal to conduct a long-term 52-week clinical trial of which the first 12-weeks will be placebo-controlled and followed by a 40-week open-label extension (representing a total of 52-weeks of trial medication exposure), is acceptable. We also agree with your proposal to 1) enroll approximately 300 healthy postmenopausal women, 40 to 65 years of age, experiencing 7 to 8 moderate to severe hot flashes or 50 to 60 moderate to severe hot flashes per week at Baseline and 2) randomize participants in a 1:1 ratio to daily fezolinetant tablets or daily oral placebo tablets during the first 12-weeks, then daily fezolinetant-alone tablets for the 40-week extension period. See our comments under Question 5 regarding the dose of fezolinetant.

Meeting Discussion:

Astellas requested clarification regarding the need to conduct a mammogram at completion of a 52-week trial. FDA responded that an annual screening mammogram is recommended for the age group population in the proposed clinical trials. FDA indicated that Astellas should ensure that any participating woman 40 years of age or older receives her annual mammogram at the completion of the 52-week trial.

6b: *Coprimary and key secondary efficacy endpoints?*

FDA Response:

The four co-primary efficacy endpoints proposed in Trial 2693-CL-0301 and Trial 2693-CL-0302 are acceptable. Postmenopausal women experiencing 7 to 8 moderate to severe hot flashes per day (over a 24-hour period) at Baseline or 50 to 60 moderate to severe hot flashes per week (over a 7-day period), who meet other trial specific inclusion/exclusion criteria will be eligible for randomization.

We do not distinguish between moderate to severe hot flashes experienced during night time hours (commonly referred to as night sweats) and those experienced during the daytime hours. Count hot flashes experienced at night the same as those experienced during daytime hours. We refer you to the Agency's Advice/Information Request letter, dated June 16, 2016, provided to Ogeda S.A.

Reported results for proposed secondary and exploratory objectives/endpoints (for example, the PROMIS® SD SF 8b, PROMIS® SRI SF 8a, PGI-C, PGI-SSD, PGI-CSD, MENQOL, EuroQOL 5D-5L, and WPAI-VMS questionnaires), in your proposed phase 3 Trials 2693-CL-0301 and 2693-CL-0302, (b) (4)

. See also our comments on efficacy included in our response to Question 5.

(b) (4)
, the reported results of the proposed secondary and exploratory objectives/endpoints (stated above) in clinical Trials 2693-CL-0301 and 2693-CL-0302 (b) (4)
. We refer you to the Agency's Advice/Information Request letter, dated October 19, 2017, provided to Ogeda S.A.

Meeting Discussion:

No discussion of the Preliminary Comments was requested.

6c: *Inclusion/ exclusion criteria?*

FDA Response:

The proposed inclusion criteria for Trial 2693-CL-0301 and Trial 2693-CL-0302 are acceptable. The proposed exclusion criteria for Trial 2693-CL-0301 and Trial 2693-CL-0302 are appropriate with the following exceptions:

- Define hypertension as systolic blood pressure ≥ 130 mmHg or diastolic blood pressure as ≥ 80 mmHg (not uncontrolled hypertension, as proposed), based on average of two to three readings on at least two different occasions. Medically clear any postmenopausal woman with a medical history of hypertension to participate in Trial 2693-CL-0301 and Trial 2693-CL-0302.

A woman with a uterus with a screening endometrial biopsy reported as insufficient tissue for diagnosis and screening transvaginal ultrasound (TVU) double-wall thickness of 4 mm should not be enrolled in the proposed phase 3, 52-week efficacy and safety clinical trials without further evaluation. A screening endometrial biopsy reported as insufficient tissue for evaluation should be repeated to rule out the presence of disordered proliferative endometrium, endometrial hyperplasia, or endometrial cancer. A postmenopausal woman with a uterus and a screening endometrial biopsy reported as:

- disordered proliferative endometrium, endometrial hyperplasia, or endometrial cancer should not be enrolled in proposed Trial 2693-CL-0301 or Trial 2693-CL-0302.
- You propose to exclude women with moderate or severe renal impairment from Trial 2693-CL-0301 and Trial 2693-CL-0302. Given the contribution of renal elimination of the major metabolite, ES259564, the currently proposed exclusion criterion with respect to renal function appears to be reasonable. However, we note that you have not assessed the PK of the parent and metabolite in women with varying degrees of renal impairment. Consider conducting your planned renal impairment study (Study 2693-CL-0008) prior to conducting the proposed phase 3 trials. Based on the results of the renal impairment study, when they become available, and scientific rationale (e.g. exposure-safety relationship), revise the exclusion criterion for moderate or severe renal impairment in the phase 3 trials, if appropriate.

Meeting Discussion:

Astellas asked for clarification from the Agency regarding the statement: “Medically clear any postmenopausal woman with a medical history of hypertension...” FDA responded that a woman with hypertension on treatment should be stable and compliant with her prescribed medication prior to enrollment.

6d: Sample size?

FDA Response:

You propose that each phase 3 efficacy and safety trial will randomize approximately 300 healthy postmenopausal women, 40 to 65 years of age, to active drug or placebo (approximately 150 per treatment group) in the first 12-week, placebo-controlled, period of these two 52-week trials (additional 40 weeks are open-label active treatment only).

Your estimated participant drop-out rate of 32%, appears to be high. We recommend that you specify strategies to minimize missing data in the protocol. During the trial conduct, every effort should be made to keep the participants in the trial and finish protocol specified visits and

procedures. The proposed sample sizes for Trials 2693-CL-0301 and 2693-CL-0302 appear to be reasonable to detect treatment differences between active drug and placebo.

We generally follow the ICH E1 guidelines for patient exposure for drug products intended for chronic use. These guidelines recommend exposure in 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures should occur at the dose or dose range anticipated to be efficacious. Note that larger exposures may be needed if there are safety concerns that emerge during drug development that need further characterization prior to approval.

Meeting Discussion:

No discussion of the Preliminary Comments was requested.

6e: *Analysis of the coprimary endpoint after all patients complete the 12-week treatment period (12-week analysis)?*

FDA Response:

See our response to Question 5. Analyze efficacy endpoints at Week 4 and Week 12 in Trial 2693-CL-0301 and Trial 2693-CL-0302. It is acceptable to conduct analysis of the co-primary endpoints after all women complete the 12-week treatment period. Submit the data analysis for Trial 2693-CL-0301 separately from that obtained for Trial 2693-CL-0302. Submit the data from two confirmatory 12-week, double-blind, placebo-controlled efficacy and safety clinical trials to support an indication for the treatment of moderate to severe vasomotor symptoms, due to menopause.

Meeting Discussion:

No discussion of the Preliminary Comments was requested.

6f: *Primary analysis method using mixed models repeated measures (MMRM) and multiplicity adjustment?*

FDA Response:

The mixed model repeated measures (MMRM) analysis is used under the assumption of missing at random (MAR). Provide justifications that the study data is under this assumption. In addition, conduct sensitivity analyses that deviate from this underlying modeling assumption to evaluate the robustness of your inference.

See also our response to Question 6b.

(b) (4)

All the four co-primary efficacy endpoints should be tested at a significance level of 0.05.

Meeting Discussion:

No discussion of the Preliminary Comments was requested.

6g: Calculation method for the coprimary endpoint of VMS severity ([REDACTED] (b) (4) weighted average)?

FDA Response:

[REDACTED] (b) (4)
Calculate the mean change in hot flash severity at Week 4 and Week 12 as follows:

- $$\frac{[(\text{number of mild hot flashes/day} \times 1) + (\text{number of moderate hot flashes/day} \times 2) + (\text{number of severe hot flashes/day} \times 3)]}{\text{total number of daily (or weekly) mild/moderate/severe hot flashes}}$$

We refer you to the Agency's communications with Ogeda S.A., dated June 16, 2016, and April 17, 2017.

Meeting Discussion:

Astellas requested clarification that the weighted average hot flash severity efficacy calculations at Week 4 and Week 12 included mild, moderate, and severe hot flashes. FDA confirmed that hot flash severity efficacy calculations at Week 4 and Week 12 include mild, moderate, and severe hot flashes to capture all hot flashes on treatment with an expectation that less severe hot flashes will be reported at week 4 and week 12. FDA reiterated that at baseline for purposes of enrollment, only moderate and severe hot flashes are to be counted. FDA requested that Astellas submit weekly hot flash severity (and frequency) efficacy evaluations for Week 1 through Week 12.

Liver Safety Monitoring

Astellas proposes a fezolinetant dose of 30 mg once daily to be tested in the phase 3 program [Section 5.4.1]. In the phase 2b study ESN364_HF_205, no liver safety findings were observed for the phase 3 selected dose of 30 mg once daily. However, based on the asymptomatic transient liver function test elevations observed in the higher dose groups in the phase 2b study [Section 7.2.1.3.2], Astellas considers that liver injury should be categorized as an important potential risk for the phase 3 fezolinetant program [Section 11.3.1.1]. Therefore, Astellas proposes to continue to monitor the potential for liver injury in phase 3 clinical studies; the approach for this assessment is presented in [Section 11.3]. Astellas also proposes to establish an independent liver safety monitoring panel to review the emerging liver safety data for the phase 3 clinical program for fezolinetant [Section 11.2].

Question 7: Does the Agency agree with the following aspects of the liver safety assessment for fezolinetant:

7a: Frequency of monitoring schedule?

FDA Response:

Your proposed schedule of laboratory and clinical assessments appears reasonable with incorporation of the following.

- Initially evaluate liver biochemistry at 2 weeks and then every 4 weeks for the entire duration of the trial and approximately 2 to 4 weeks after the trial drug is discontinued for both Trials 2693-CL-0301 and 2693-CL-0302. If a woman rolls over from placebo to treatment at any time, evaluate liver biochemistry initially at 2 weeks and then every 4 weeks.
- Women who develop a signal for liver injury should be monitored every 2 to 4 weeks if the investigated product is discontinued.
 - If participating women with signals of liver injury are maintained on drug, they should enter “close monitoring” as per your protocol.

See also our Additional Clinical Comments below.

Meeting Discussion:

No discussion of the Preliminary Comments was requested.

7b: Overall approach for ‘detailed testing for liver enzymes and follow-up procedures’ for patients with confirmed abnormalities as described per protocol?

FDA Response:

Your approach appears reasonable with the following recommended revisions:

- You may include women with mild elevations in serum transaminases $<1.5 \times$ the upper limit of normal (ULN), however, such participants must have a normal total bilirubin (TB) and direct bilirubin (DB) at enrollment. Elevations in TB, DB, or international normalized ratio (INR) are indicative of significant underlying liver disease and probable cirrhosis.
- Women with Gilbert’s syndrome may be enrolled in clinical trials. While these women may have elevated total bilirubin, their direct bilirubin, reticulocyte count, and hemoglobin should be normal.
- If a woman has elevated alkaline phosphatase (ALP) at baseline, she should be evaluated for cholestatic liver disease prior to trial enrollment. However, if no cause for elevated ALP is diagnosed other than fatty liver disease, women with elevations $<1.5 \times$ ULN may be enrolled.
- (b) (4)
(b) (4) We recommend that you remove (b) (4) from liver injury/function screening tests.

Meeting Discussion:

Astellas confirmed that phase 2 data demonstrated transient transaminase elevations above the upper limit of normal (ULN) with resolution after discontinuation, but did not demonstrate evidence of bilirubin elevations above ULN, symptomatic signs, or other serious liver events. FDA agreed that the trial(s) may proceed with adequate liver safety monitoring, as proposed. FDA requested copies of both the Liver Safety Monitoring Panel (LSMP) charter and the Data Monitoring Committee (DMC) charter.

Astellas summarized their liver safety plan, which will include all of FDA's recommendations on appropriate monitoring, management, and follow up.

7c: *Patient discontinuation criteria related to liver function in the phase 3 clinical studies?*

FDA Response:

No, we do not agree. While it is acceptable to monitor patients with mild liver injury (transaminase elevations alone without elevations in TB or INR), you should immediately discontinue drug in patients with persistent elevations in AST/ALT >3 X ULN accompanied by sign or symptoms consistent with drug-induced liver injury (DILI) for example, fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (> 5% above pretreatment levels).

Refer immediately any participating woman who meets the criteria listed below, for a consultation with a hepatologist, who is experienced in the management of DILI. Have one or more such hepatologists "on call" to assist in patient management and decisions related to discontinuation of the investigational drug.

Criteria for DILI:

- ALT or AST >8 X ULN
- ALT or AST >5 X ULN for more than 2 weeks
- ALT or AST >3 X ULN and (TB >2 X ULN or INR >1.5 X ULN)
- ALT or AST >3 X ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (> 5% above pretreatment levels).

Meeting Discussion:

No discussion of the Preliminary Comments was requested.

7d: *Establishment of the independent liver safety monitoring panel?*

FDA Response:

We agree with the establishment of a Liver Safety Monitoring Panel (LSMP), the general plan for the blinded and unblinded assessments, and the composition of the panel. Provide the curriculum vitae for each of the panel members and a copy of the charter for the panel once it has been developed.

We also agree with the role of the Data Monitoring Committee (DMC) in interacting with the LSMP. Provide the identity and curriculum vitae for each DMC member once you have identified these individuals and provide a copy of the DMC charter once it is developed.

Meeting Discussion:

Astellas clarified that they will be responsible for any decision regarding trial stopping. They further clarified that input from both the LSMP and the sponsor's expert consultants on hepatic diseases and drug-induced liver injury (DILI) would be taken into

consideration in the sponsor's decision whether to stop the phase 3 trial(s). Astellas agreed to notify the FDA if any of the members of the LSMP recommended that the trial be stopped. Astellas summarized that the LSMP and DMC would have separate charters; however, the chairs of both committees can communicate freely to each other. FDA questioned whether the DMC could influence the LSMP. Astellas clarified that each committee is independent with different charters and did not think this would be an issue.

See Meeting Discussion under Question 5. Astellas will be considering including in phase 3 a second dose that is greater than the originally proposed 30 mg dose. The sponsor also acknowledges that the hepatotoxicity observed to date is dose-related. FDA indicated that adequate numbers of women would have to be exposed to any proposed higher dose(s) to appropriately assess safety of that dose(s); the safety profile of lower doses cannot be used to support the safety of higher doses.

7e: (b) (4) related to marked serum aminotransferase elevation or evidence of functional impairment?

FDA Response:

Establish trial stopping rules related to liver injury; consider FDA's previous advice provided in Advice/Information Request letters provided on October 19, 2017, and June 7, 2018.

Notify FDA if one or more members of the liver safety monitoring panel recommends that the study be terminated.

Additional Clinical Comments:

1. Participating women, caregivers and all investigational staff should be educated about the known risk for liver injury and the signs and symptoms of potential liver injury. To date only mild/moderate liver injury has been documented with use of ESN364 (fezolinetant). Instruct participants and caregivers who note signs or symptoms of potential liver injury, to call the site for urgent evaluation, which should occur within 1-3 days.
2. Report all significant elevations in liver biochemistry consistent with a signal of liver injury as adverse events (AEs) of special interest. Report all participants meeting the criteria below as serious adverse events (SAEs):
 - ALT or AST >3X ULN and total bilirubin is >2X ULN
 - ALT or AST >8X ULN
 - ALT or AST >5X ULN for more than 2 weeks
 - ALT or AST >3X ULN and TB >2X ULN or INR >1.5X ULN
 - ALT or AST >3X ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (> 5% above pretreatment levels).
3. Obtain samples for PK analysis on any participant with a signal of elevated transaminases when she returns for a repeat blood draw. This sample can be held for potential analysis based on the woman's clinical outcome.

4. Because of the dose-related signal of liver injury demonstrated with use of fezolinetant, conduct and provide the results of a Hepatic Impairment Study prior to marketing.
5. The terminology “liver function tests” used in your meeting briefing package and in the protocol synopses, is incorrect. Liver functional capacity is evaluated by TB, DB, INR and albumin levels. In general, elevations in transaminases (ALT and AST) indicate injury to hepatocytes and elevations in ALP and GGT indicate potential for bile duct injury. Use the correct terminology in your final protocol and related documents.

Meeting Discussion:

Refer to the Meeting Discussion under Question 7d. The FDA stated that the LSMP should review unblinded data (with the appropriate firewalls to maintain the integrity of the trial) to adequately protect patient safety and provide summary reports and recommendations to Astellas and the Agency.

Design of Long-term Safety Study 2693-CL-0304

A double-blinded, placebo-controlled, 52-week safety study 2693-CL-0304 is planned in women with VMS associated with menopause. The proposed approach for this phase 3 clinical study is presented in [Section 10.2.2.2]. The clinical study protocol synopsis is available in [Attachment 3].

Question 8: *Does the Agency agree with the long-term safety study 2693-CL-0304 regarding:*

8a: *Study design?*

FDA Response:

We cannot agree at this time. You provided only limited information in your synopsis of your proposed phase 3, 52-week, placebo-controlled Trial 2693-CL-0304. In general, it appears that your proposed Trial 2693-CL-0304 is of appropriate duration (12-months) and general design. However, we cannot provide definitive concurrence with the adequacy of proposed long-term safety Trial 2693-CL-0304 until we receive your final protocol.

Provide a final protocol for Trial 2693-CL-0304 to IND 130277 for our review and comments.

Meeting Discussion:

No discussion of the Preliminary Comments was requested.

8b: *Study duration?*

FDA Response:

The proposed 52-week trial duration appears to be of appropriate duration. However, we cannot provide definitive concurrence with the adequacy of your proposed long-term safety Trial 2693-CL-0304 until we receive your final protocol. See our response to Question 8a.

Meeting Discussion:

No discussion of the Preliminary Comments was requested.

8c: *Inclusion/exclusion criteria, including that there is no specific entry criteria for frequency or severity of VMS?*

FDA Response:

The enrollment criteria proposed for Trial 2693-CL-0304, intended to assess general and endometrial safety and chronic drug use exposure, appear appropriate with the following modifications:

- Define hypertension as systolic blood pressure ≥ 130 mm Hg or diastolic blood pressure as ≥ 80 mmHg (not as uncontrolled hypertension, as proposed), based on average of two to three readings on at least two different occasions. Medically clear any postmenopausal woman with a medical history of hypertension to participate in Trial 2693-CL-0304.
- A woman with a uterus with a screening endometrial biopsy reported as insufficient tissue for diagnosis and a screening transvaginal ultrasound (TVU) double-wall thickness of 4 mm should not be enrolled in the proposed phase 3, 52-week safety clinical trial. A screening endometrial biopsy reported as insufficient tissue for evaluation should be repeated to rule out the presence of disordered proliferative endometrium, endometrial hyperplasia, or endometrial cancer. A postmenopausal woman with a uterus with a screening endometrial biopsy reported as disordered proliferative endometrium, endometrial hyperplasia, or endometrial cancer should not be enrolled in proposed Trial 2693-CL-0304.

Meeting Discussion:

No discussion of the Preliminary Comments was requested.

8d: *Safety assessments and proposed analyses of safety?*

FDA Response:

No, we do not agree. Only limited information is provided to assess the adequacy of the proposed safety assessment and analyses of safety in the synopsis of your proposed phase 3, 52-week, placebo-controlled Trial 2693-CL-0304. We cannot be fully definitive with our recommendations for safety monitoring until we have had a chance to review your full clinical protocol for Trial 2693-CL-304.

Meeting Discussion:

No discussion of the Preliminary Comments was requested.

8e: *Sample size?*

FDA Response:

The synopsis presented for proposed phase 3, 52-week, placebo-controlled Trial 2693-CL-0304, in the meeting briefing package, indicates that a total of 1150 healthy postmenopausal women,

40 to 65 years of age, will be enrolled and randomized to daily administered oral 30 mg fezolinetant tablets (approximate number = 766) or daily administered oral placebo tablets (approximate number = 384).

We generally follow the ICH E1 guidelines for patient exposure when a drug product is used on a chronic basis. These guidelines recommend exposure in 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures should occur at the dose or dose range believed to be efficacious. Note that larger exposures may be needed if there are safety concerns that emerge during drug development that need further characterization pre-approval. In addition, see our response to Question 5 regarding the dose of fezolinetant for phase 3 trials.

Provide a final protocol for Trial 2693-CL-0304 to IND 130277 for our review and comments.

Meeting Discussion:

No discussion of the Preliminary Comments was requested.

Total Safety Database

Astellas considers that the completed and planned clinical studies are aligned with the ICH E1 criteria regarding patient exposure to assess clinical safety for drugs intended for long-term treatment of non-life-threatening conditions at the time of first registration of fezolinetant [Section 10.3]. The proposed clinical development program targets exposure to fezolinetant in a total of approximately 2006 unique subjects/patients, including 1147 subjects/patients exposed for 24 weeks (6 months) and 725 subjects/patients exposed for 52 weeks (1 year).

Question 9: *Does the Agency agree with the size of the proposed safety database to support the NDA submission for fezolinetant?*

FDA Response:

It appears that your proposed safety database may meet our recommendations for exposure for the daily administered oral 30 mg fezolinetant dose, if that dose is found to be effective for the intended population of postmenopausal women.

Your meeting briefing package indicates that cumulative expected exposure of daily administered oral 30 mg fezolinetant in phase 2 and 3 could include:

- 43 postmenopausal women exposed to fezolinetant capsules in completed Trial ESN364_HF_205
- Approximately 300 postmenopausal women exposed to daily oral 30 mg fezolinetant tablets during the first 12-weeks of proposed Trials 2693-CL-0301 and 2693-CL-0302
- Approximately 600 postmenopausal women exposed to daily oral 30 mg fezolinetant tablets during the 40-week open-label extension of proposed Trials 2693-CL-0301 and 2693-CL-0302
- Approximately 766 postmenopausal women exposed to daily oral 30 mg fezolinetant tablets for 52-weeks in proposed Trial 2693-CL-0304

Meeting Discussion:

Astellas indicated that the proposed size of the safety data base would be revised with the addition of a second active-treatment group.

Multidisciplinary

Abuse Liability Assessment

Astellas has conducted assessments for fezolinetant according to the FDA Guidance for Industry on the Assessment of Abuse Potential of Drugs. The results of nonclinical studies [Section 8.1.1] showed that neither fezolinetant nor its metabolite ES259564 bind to neurotransmitter receptors, transporters or ion channels related to abuse potential. Despite crossing the blood brain barrier, fezolinetant does not contain chemical structures of central nervous system (CNS)-depressant drugs and is eliminated fairly rapid from brain tissues over time. While sedative effects and constricted pupils were observed in rats (but not in cynomolgus monkeys) treated with fezolinetant, they were observed at very high, nonclinically relevant concentrations and were not observed 24 hours after dosing. In the phase 1 and phase 2 clinical studies, there was a very low incidence of abuse-related treatment-emergent adverse events (TEAEs) following administration of fezolinetant to humans [Section 8.1.2]. Based on the very low incidence of TEAEs possibly indicative of abuse potential, there is currently no clinical evidence of abuse potential with fezolinetant. The safety results of the planned phase 3 studies will also be assessed for abuse related TEAEs.

Therefore, Astellas considers that the nonclinical and clinical data collected to date, with the assessment of phase 3 safety results will provide sufficient information for the NDA submission and that no further nonclinical or dedicated clinical studies to evaluate human abuse potential are necessary.

Question 10: *Does the Agency agree that no further nonclinical or clinical studies are necessary to assess the abuse liability of fezolinetant for the NDA submission?*

FDA Response:

We agree that the nonclinical data and the AE data from your clinical trials with fezolinetant do not provide a signal warranting further abuse-related studies with fezolinetant. However, if a signal of abuse potential arises in future clinical trials, additional abuse-related information or studies may be requested. We recommend the following:

1. As described in the FDA Guidance for Industry, Assessment of Abuse Potential of Drugs (2017), include in your NDA submission for the CNS-active drug, fezolinetant, your proposal for drug scheduling, i.e., that fezolinetant does not have abuse potential and does not warrant scheduling under the Controlled Substances Act. Provide support for your conclusions that fezolinetant does not have abuse potential. The Guidance for Industry, *Assessment of Abuse Potential of Drugs*, is available at:
<https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm198650.pdf>

2. Provide a discussion of all animal toxicology and general behavioral observations to support your assertions with respect to the abuse potential of fezolinetant.
3. Monitor and report all potentially abuse-related adverse events (AEs) from your clinical trials with fezolinetant and provide detailed narratives for these AEs as recommended in section V.B. of the 2017 Guidance mentioned above. Also, provide the list of terms that prompt these reports (including abuse-related AE terms such as euphoria, attention, mood, psychomotor effects, inappropriate affect, patient dropouts, overdoses, misuse, lost or unaccounted for medication, and unjustified dose increases). Where narratives are provided, they should include time of onset, and duration of the event, dose of drug taken, severity, and outcome. If available, pharmacokinetic values for each individual participant who experienced these AEs should be provided to understand if there is a temporal correlation between drug plasma levels and AEs.
4. If applicable, you should also report all possible cases of abuse (participants taking the drug for nontherapeutic purposes, e.g., for psychoactive effects such as high or euphoria) occurring in your clinical trials. In such cases, information collected by the investigator should include explanations from the participants when there are drug accountability discrepancies. Towards this end:
 - Provide data in tabular form for all reports of abuse, overuse, lost/stolen/missing or unaccounted product that occurred in clinical trials. These data should include study number, and type of trial, participant ID number, narratives, case description, and details.
 - Provide narratives for cases where the participants drop out from trials for reasons that might be coded as “protocol violation”, “lack of efficacy” (to capture aberrant behavior in participants who drop out of the trial supposedly due to lack of efficacy), “lost to follow up”, “non-compliance to study medication or procedures”, “over compliance”, or for “other”. Case reports should be provided separately.
 - Report any use of the investigational formulation by individuals other than the participants (family member, health care practitioner, etc.).

Meeting Discussion:

No discussion of the Preliminary Comments was requested.

Assessment of Drug Effects on Driving Ability

Neither fezolinetant nor its metabolite ES259564 bind to neurotransmitter receptors, transporters or ion channels related to abuse potential [Section 8.1.1]. Fezolinetant is eliminated fairly rapid from brain tissues over time. After a single oral administration of radiolabeled fezolinetant at a dose of 30 mg/kg to female albino rats, radioactivity elimination $t_{1/2}$ in brain tissues (6.26 hours) were mostly below those in blood and plasma [Section 8.2.1]. While sedative effects and constricted pupils were observed in rats, they were observed at very high, nonclinically relevant concentrations and were not observed 24 hours after dosing [Section 8.1.1.4]. Additionally, in female Wistar Han rats, convulsive-like episodes were observed in only the 13-week toxicity study but considered unlikely to be related to fezolinetant. Notably, no signs of convulsive or

convulsive-like activity were observed in 26-week dose rat study or in cynomolgus monkey studies. Furthermore, there was no indication that administration of fezolinetant was correlated with increased risk of seizure. In the phase 1 and phase 2 clinical studies, there was a very low incidence of CNS-related TEAEs following administration of fezolinetant to humans [Section 8.2.2]. There is no evidence of a dose relationship based on the data available to date.

Based on these results, Astellas concludes there is no evidence indicating that fezolinetant causes CNS impairment and that therefore, there is a low potential for impacting the ability to operate a motor vehicle. Astellas considers that no further clinical studies are necessary, including a dedicated fezolinetant driving impairment study or CNS-impairment tests. Furthermore, Astellas considers that no additional CNS impairment-related monitoring is required for future clinical studies beyond the standard adverse event (AE) safety monitoring.

Question 11a: Does the Agency agree that no further clinical studies, including a dedicated driving impairment study, are necessary for the NDA submission?

FDA Response:

No, we cannot agree at this time. We would have to review all reported results including those from proposed phase 3 clinical trials conducted during the fezolinetant development program to determine what, if any, additional clinical trials are needed.

Meeting Discussion:

No discussion of the Preliminary Comments was requested.

Question 11b: Does the Agency agree that the current safety monitoring plan for phase 3 clinical studies is sufficient for assessing potential CNS effects of fezolinetant?

FDA Response:

Your proposed safety monitoring plan for the phase 3 clinical trials appears to conform with the standard recommendations for defining, recording and reporting adverse events (AEs), serious adverse events (SAEs), and treatment-emergent adverse events (TEAEs) and may be adequate to record and report potential CNS effects of fezolinetant.

Meeting Discussion:

No discussion of the Preliminary Comments was requested.

Regulatory

Target Product Profile

Based on the fezolinetant data collected and the planned studies for fezolinetant [Sections 6, 7 and 10], Astellas proposes the labeling statements summarized in the TPP ([Attachment 4] and [Section 12]). Specific questions for feedback from the Agency have been included in the TPP.

Question 12: Does the Agency have any comments on the proposed labeling statements identified in the TPP considering the data summarized in the briefing document and the proposed development plan for fezolinetant?

FDA Response:

No. It is premature to discuss drug product labeling at this stage of fezolinetant product development. See our response to Questions 6b and 15 regarding the efficacy endpoints that would be labeled if your product could be approved.

Meeting Discussion:

No discussion of the Preliminary Comments was requested.

Pediatric Development

In women aged < 40 years, menopause is known as primary ovarian insufficiency. Primary ovarian insufficiency affects only approximately 0.01% of women aged < 20 years [Gordon et al, 2015]. The occurrence of VMS in these female pediatric subpopulation would thus be at a very low frequency. Treatment of VMS associated with menopause is not a condition that occurs in males.

Question 13: *Does the Agency agree that a waiver of the requirement to conduct clinical studies in pediatric patients is appropriate in this indication?*

FDA Response:

We cannot agree at this time. See PREA REQUIREMENTS below. You must separately submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End-of-Phase-2 (EOP2) meeting.

Meeting Discussion:

No discussion of the Preliminary Comments was requested.

Study Data Standardization Plan

As per the requirements for an electronic submission of standardized clinical and nonclinical study data under section 745A(a) of the Federal Food, Drug and Cosmetic Act, Astellas proposes the study data standardization plan (SDSP) available in [Attachment 5]. The SDSP establishes and documents a plan for describing the data standardization approach for the nonclinical and clinical studies of the fezolinetant development program. The SDSP includes historical, current and planned information about the use of study data standards for clinical and nonclinical studies. The SDSP will be maintained throughout the development of the compound.

Question 14: *Does the Agency have any comments on the current SDSP for fezolinetant?*

FDA Response:

The study data standardization plan (SDSP) for the nonclinical studies, clinical pharmacology trials, and clinical trials, appears reasonable.

Meeting Discussion:

No discussion of the Preliminary Comments was requested.

Clinical Outcomes Assessment: PROMIS SD SF 8b

Content Validity of the PROMIS SD SF 8b

The PRO Measurement Information System Sleep Disturbance - Short Form 8b (PROMIS SD SF 8b) will be administered in the phase 3 fezolinetant program. This instrument derives from the PROMIS sleep disturbance item bank, which was developed using a rigorous and systematic process involving literature reviews, expert consensus, qualitative research methods, classic test theory methods, and item response theory analysis in general and clinical populations. The PROMIS SD SF 8b correlates with the PROMIS sleep disturbance item bank ($r = 0.96$), thus indicating that the PROMIS SD SF 8b captures the full range of the concept. The validity and reliability of the PROMIS SD SF 8b were confirmed using computerized adaptive testing simulations, item discrimination parameters, item means and clinical judgement from content experts. Importantly, Astellas completed a US qualitative interview study in women experiencing moderate to severe VMS [Study 2693-MA-3214]; results from this study support the content validity of the PROMIS SD SF 8b to measure sleep disturbance in this patient population. Detailed information on the development history and Astellas-sponsored research to establish the content validity of this instrument in the target population are provided in this briefing document [Buysse et al 2010] and [Yu et al 2011] and [Clinical Outcomes Assessment Dossier: PROMIS SD SF 8b].

Question 15: *Does the Agency agree that the content validity evidence of the PROMIS SD SF 8b demonstrates that it is fit for purpose as a measure of sleep disturbance within the context of treatment for moderate to severe VMS associated with menopause?*

FDA Response:

In general, we agree that the evidence provided demonstrates that sleep disturbance is a relevant concept to women with moderate to severe vasomotor symptoms due to menopause. However, while this is a relevant concept to patients, sleep disturbance can be influenced by factors other than treatment and, consequently, it is not sensitive to treatment effect. Thus, it is a difficult concept to measure. Despite this, we are open to review the data as it captures the participants experience.

Generally, PROMIS SD SF 8b appears to measure the concept of sleep disturbance in the context of this target population. However, based on your qualitative study, there are some components of sleep disturbance that may not be relevant for this target population (e.g., Item 4 -problems falling asleep). We note that none of the women with moderate to severe vasomotor due to menopause reported having problems falling asleep.

However, independent from our review and comments for the PROMIS SD SF 8b, the reported results of the proposed secondary and exploratory objectives/endpoints in clinical Trials 2693-CL-0301 and 2693-CL-0302, (b) (4)

. Refer to our response to Questions 5, and 6b.

Meeting Discussion:

No discussion of the Preliminary Comments was requested.

Planned Phase 3 Pivotal Trial Designs

Astellas will evaluate fezolinetant as a treatment for moderate to severe VMS associated with menopause in 2 pivotal phase 3 efficacy studies: 2693-CL-0301 and 2693-CL-0302. The coprimary endpoints, i.e., the frequency and severity of VMS at weeks 4 and 12, will be defined in accordance with regulatory guidance Draft Guidance for Industry “Estrogen and Estrogen/Progestin Drug Products to Treat Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms – Recommendation for Clinical Evaluation”, Jan 2003. The PROMIS SD SF 8b is included (b) (4) as the key secondary endpoint in both studies. Change from baseline to week 12 in the PROMIS SD SF 8b total score will form the basis of this assessment. The clinical study protocol for Study 2693-CL-0301 is available in [Attachment 2]. The clinical study protocol for Study 2693-CL-0302 is the same as that of Study 2693-CL-0301 and is thus not provided with this briefing document. (b) (4)

(b) (4) This instrument has been established as content valid in the target population and in accordance with regulatory guidance FDA Guidance for Industry “Patient-Reported Outcome Measure: Use in Medical Product Development to Support Labeling Claims”, Dec 2009. The Endpoint Model (b) (4) are provided in [Clinical Outcomes Assessment Dossier: PROMIS SD SF 8b].

Question 16: *Does the Agency agree that Studies 2693-CL-0301 and 2693-CL-0302, which pre-specify the PROMIS SD SF 8b as a key secondary endpoint (b) (4) at week 12, are designed to (b) (4) ?*

FDA Response:

No, we do not agree. See our response to Question 15. The reported results of the proposed secondary and exploratory objectives/endpoints in clinical Trials 2693-CL-0301 and 2693-CL-0302, (b) (4) . See also comments (b) (4) in our responses to Questions 5 and 6b.

Meeting Discussion:

No discussion of the Preliminary Comments was requested.

Meaningful Within-subject Change on the PROMIS SD SF 8b

Astellas will establish a responder threshold for meaningful within-subject change on the PROMIS SD SF 8b based on data from Studies 2693-CL-0301 and 2693-CL-0302 and in accordance with regulatory guidance FDA Guidance for Industry “Patient-Reported Outcome Measure: Use in Medical Product Development to Support Labeling Claims”. This threshold will be determined empirically to aid score interpretation. To determine what constitutes meaningful within-subject change on the PROMIS SD SF 8b, anchor-based methods, distribution-based methods and visual displays using raw scores will be used. These methods are in accordance

with regulatory guidance for determining the responder threshold. A subject will be defined as a responder if the improvement in the PROMIS SD SF 8b raw score from baseline to week 12 is greater than the estimate of meaningful within-subject change. A detailed psychometric analysis plan is presented as part of this briefing document [PROMIS SD SF 8b Psychometric Analysis Plan].

Question 17: *Does the Agency agree with the psychometric analysis plan for establishing a meaningful within-subject change on the PROMIS SD SF 8b?*

FDA Response:

In principle, your proposed psychometric plan appears reasonable. However, as stated in our response to Question 5 and 6b, the reported results of the proposed secondary and exploratory objectives/endpoints in clinical Trials 2693-CL-0301 and 2693-CL-0302, (b) (4) .

You may proceed with your analysis for PROMIS® SD SF 8b for exploratory purposes at your own discretion. As such, we provide the following comments for your consideration for the analysis of the PROMIS® SD SF 8b:

- Consider excluding item 4 from the instrument, or at the minimum excluding it in the calculation of the total score. Conduct a sensitivity analysis by excluding Item 4 in your psychometric analysis plan for PROMIS® SD SF
- We are more interested in meaningful change from the participant's perspective rather than minimum difference in the treatment change. Establish meaningful within-patient score change in the PROMIS® SD SF total score excluding Item 4. Refer to FDA response to Question 15.

Meeting Discussion:

No discussion of the Preliminary Comments was requested.

Additional Clinical Outcome Assessment Comments:

We recommend electronic data capture using a device with a reminder or alarm function, when appropriate and feasible, as this tends to facilitate operation, minimize the extent of missing data, and allows for the collection of other important information (e.g., timestamps for data input). You may refer to the FDA guidance for industry on electronic source data.¹

If you proceed with electronic data capture, perform usability testing of the selected devices with patient cognitive interviews to assess device functionality, questionnaire comprehension, and ease of use in the patient population. This would minimize the likelihood of having poor quality data due to patients' misunderstanding or incomplete understanding of how to use the device. Implement a back-up plan (e.g., web-based, phone-based [interactive voice response system]) prior to using the devices in your clinical trials, in case of any electronic device malfunctions.

¹ Guidance for Industry: Electronic Source Data in Clinical Investigations
(<http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm328691.pdf>)

PREA REQUIREMENTS

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

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

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

DATA STANDARDS FOR STUDIES

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

On December 17, 2014, FDA issued final guidance, *Providing Electronic Submissions in Electronic Format--- Standardized Study Data* (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf>). This guidance describes the submission types, the standardized study data requirements, and when standardized study data will be required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide (Conformance Guide) (See

<http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf>), as well as email access to the eData Team (cdeler-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data will be required in marketing application submissions for clinical and nonclinical studies that started after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that started after December 17, 2017. CDER has produced a [Study Data Standards Resources](#) web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

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

If you have not previously submitted an eCTD submission or standardized study data, we encourage you to send us samples for validation following the instructions at <https://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm>. The validation of sample submissions tests conformance to FDA supported electronic submission and data standards; there is no scientific review of content.

The Agency encourages submission of sample data for review before submission of the marketing application. These datasets will be reviewed only for conformance to standards, structure, and format. They will not be reviewed as a part of an application review. These datasets should represent datasets used for the phase 3 trials. The [FDA Study Data Technical Conformance Guide](#) (Section 7.2 eCTD Sample Submission pg. 30) includes the link to the instructions for submitting eCTD and sample data to the Agency. The Agency strongly encourages Sponsors to submit standardized sample data using the standards listed in the Data Standards Catalog referenced on the [FDA Study Data Standards Resources](#) web site. When submitting sample data sets, clearly identify them as such with **SAMPLE STANDARDIZED DATASETS** on the cover letter of your submission.

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

DISCUSSION OF SAFETY ANALYSIS STRATEGY FOR THE ISS

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

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

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

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

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled, [Study Data Standards Resources](https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM587505.pdf) and the CDER/CBER Position on Use of SI Units for Lab Tests website found at <https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM587505.pdf>.

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>.

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft Guidance for Industry Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions (February 2018) and the associated Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

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

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

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

NEW PROTOCOLS AND CHANGES TO PROTOCOLS

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

1. Study phase

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

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

UNITED STATES PATIENT POPULATION

FDA expects sponsors to enroll participants who are relevant to the planned use of the drug in the US population. Describe the steps you are taking to ensure that the clinical trial population will be relevant to the US patient population that will receive the drug. Include a discussion of participation of US vs. non-US sites and discuss whether the subjects likely to be enrolled will adequately represent the US patient population in terms of disease characteristics, sex, race/ethnicity, age, and standards of care. See 21 CFR 312.33(a)(2) and 21 CFR 314.50(d)(5)(v) and the Guidance for Industry, Collection of Race and Ethnicity Data in Clinical Trials (available at: <https://www.fda.gov/downloads/regulatoryinformation/guidances/ucm126396.pdf>) and for more information.

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

ISSUES REQUIRING FURTHER DISCUSSION

There are no issues requiring further discussion.

ACTION ITEMS

Action Item/Description	Owner	Due Date
Meeting Minutes	FDA	May 17, 2019

ATTACHMENTS AND HANDOUTS

There are no attachments or handouts for the meeting minutes.

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

/s/

SHELLEY R SLAUGHTER
05/16/2019 01:51:41 PM