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RESEARCH**

APPLICATION NUMBER:

216578Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	January 27, 2022
From	Shelley R Slaughter
Subject	Cross-Discipline Team Leader Review
NDA/BLA # and Supplement#	216578
Applicant	Astellas Pharma Global Development, Inc.
Date of Submission	June 22, 2022
PDUFA Goal Date	February 22, 2022
Proposed Proprietary Name	Veozah
Established or Proper Name	Fezolinetant
Dosage Form(s)	Tablet
Applicant Proposed Indication(s)/Population(s)	Treatment of moderate to severe vasomotor symptoms due to menopause.
Applicant Proposed Dosing Regimen(s)	45 mg tablet once daily with or without food
Recommendation on Regulatory Action	Approval , pending successful labeling negotiations with the applicant
Recommended Indication(s)/Population(s) (if applicable)	Postmenopausal Women
Recommended Dosing Regimen(s) (if applicable)	45 mg tablet once daily with or without food

1. Benefit-Risk Assessment

Benefit-Risk Assessment Framework

Benefit-Risk Integrated Assessment

Menopause (cessation of menstrual periods) is a natural and inevitable physiological process resulting from the progressive decline with age and eventual exhaustion of primordial follicles capable of developing into mature dominant follicles with oocytes capable of ovulating. Menopause, typically occurring between the age of 40 years of age to the mid-50s (mean age in the U.S. is 51 years of age), represents the end of a woman's ability to have biological children naturally. Though menopause is a natural condition and intrinsically is not life threatening, the physical symptoms such as vasomotor symptoms (hot flashes) and the emotional symptoms of menopause may be disruptive of the woman's sleep, energy level, or emotional health and, thus, negatively impact the woman's ability to carry out her day-to-day normal personal and/or employment-related activities. An individual woman's experience of hot flashes varies based on genetic background, psychological factors and other health conditions or treatments¹. The duration of vasomotor symptoms from the time of onset is typically 7.4 years² and symptoms commonly may persist for approximately a decade³.

Hormone therapy (consisting of estrogens therapy given alone in a woman without a uterus and estrogens plus progestogens therapy in a woman with a uterus) historically has been the predominant treatment for moderate to severe hot flashes. Hormone therapy carries a Boxed Warning of the risk of endometrial cancer with unopposed estrogen therapy and Warnings and Precautions for the risks of breast cancer (estrogen plus progestogen therapy), venous thromboembolism (estrogen-alone therapy and estrogen plus progestogen therapy), and stroke (estrogen-alone therapy and estrogen plus progestogen therapy).

Veozah (fezolinetant) is a neurokinin 3 (NK3) receptor antagonist which mimics estrogens inhibitory effect on KNDy neurons in the thermoregulatory center in the hypothalamus, and thus balances out the stimulatory actions of NKB (hypertrophy of the KNDy neuron and increased activity of the thermoregulatory center) on KNDY neurons. The current NDA presents clinical trial data on the evaluation of efficacy of Veozah in the first 12 weeks of two phase 3, 52-week trials (Trial 2693-CL-0301 and Trial 2693-CL-0302) in postmenopausal women with moderate to severe vasomotor symptoms. The efficacy criteria [statistically significant improvement (reduction) when comparing the drug product to placebo, in the frequency and severity of vasomotor symptoms at Week 4 and Week 12, and satisfying a clinically meaningful threshold for the improvement in frequency] for an indication of the treatment of moderate to severe vasomotor symptoms are well established available for reference in a draft Guidance for Industry, and were discussed with and agreed to by the applicant prior to the conduct of the phase 3 trials for efficacy. Our review of this NDA application has determined that the data were collected in a manner consistent with the provided regulatory guidance and provide independent and confirmatory (both Trial 2693-CL-0301 and Trial 2693-CL-0302 met primary efficacy criteria) substantial evidence of efficacy for the 45 mg dosage strength of Veozah.

The safety determination for Veozah was based on data collected in phase 3, 52-week Trial 2693-CL-0301 and Trial 2693-CL-0302) and 52-

¹ Management of Menopausal Symptoms Practice Bulletin: PB Number 141, January 2014

² Avis NE, et. al. Duration of menopausal vasomotor symptoms over the menopause transition. JAMA Intern Med. 2015; 175: 531-539.

³ Hunter MS, et. al. Prevalence, frequency and problem rating of hot flushes persist in older postmenopausal women: impact of age, body mass index, hysterectomy, hormone therapy use, lifestyle and mood in a cross-sectional cohort study of 10,418 British women aged 54-65. BJOG. 2012; 119:40-50.

week phase 3 Trial 2593-CL-0304, which was specifically designed to provide chronic exposure and long-term safety data, including endometrial health. Our clinical review has determined that overall, the safety of Veozah is acceptable and no issues preclude approval.

However, our clinical review in consult with Division of Hepatology and Nutrition (DHN) also determined that there is a modest signal for the risk of drug induced liver injury (DILI) with this product. As assessed in 2,859 unique participants from the three phase 3 trials, elevations in serum transaminase [alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST)] levels greater than three times the upper limit of normal (ULN) occurred in 2.3% [exposure adjusted incidence rate (EAIR) of 2.7 per 100 person-years] of women receiving VEOZAH and 0.9% (EAIR of 1.5 per 100 person-years) of women receiving placebo in three clinical trials. Seven cases were assessed as possible/probable DILI. No Hy's Law cases were seen. While our clinical review considered this finding not to be acutely worrisome, there is concern that should the product be used in a substantial proportion (even 1%) of the available population of approximately 10 million postmenopausal women seeking treatment for moderate to severe vasomotor symptoms in the postmarketing setting, a higher proportion of more severe liver injury may become evident. To aid in evaluation of this potential concern, we propose that labeling specify monitoring of hepatic function/injury before women begin Veozah and while on Veozah for a minimum of up to 9 months follow initiation of use (justified by latency of onset of elevations up to 250 days start of the product). Additionally, we are also recommending an enhanced pharmacovigilance program [as advised by the Office of Surveillance and Epidemiology (OSE)] involving active participation of the applicant in obtaining additional information from a reporter of adverse hepatic events to: **1)** evaluate and present evidence of any case of hepatic injury based on FDA recommended criteria [ALT/AST > 8x ULN confirmed on repeat testing or ALT/AST > 3x ULN and total bilirubin > 2x ULN (new onset biochemical abnormalities consistent with possible Hy's law cases) or ALT/AST > 3x ULN associated with symptoms suggestive of hepatic disease such as: anorexia, dark urine, fatigue, fever, jaundice, nausea, vomiting, rash, right upper quadrant pain, etc., or any liver adverse event leading to discontinuation or any hepatic event preferred term (PT) denoting the diagnosis of jaundice, liver injury, or non- infectious hepatitis] in 15-Day Safety Reports to the FDA; **2)** provide a summary analysis of these events in the periodic safety reports, submitted quarterly for the first 3 years after approval, as per 21 CFR 314.80(c)(1); and **3)** provide in the periodic safety report, medical literature reviews for case reports/case series of hepatic adverse events including liver injury reported with Veozah.

Ongoing at this time is assessment of applicant-reported imbalance in malignancy. This imbalance appears to vanish, once preexisting malignancies are taken into consideration. To confirm our conclusion, we have asked the OSE/Division of Pharmacovigilance to assess independently whether there is a signal for increased risk for malignancy with Veozah. This reassessment is ongoing.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	- Menopause is a natural condition of aging in a woman that represents the time when her menstrual periods permanently cease, and she is no longer capable of reproduction (i.e., she is no longer fertile). Operationally menopause is defined by the absence of menstrual periods for 12 consecutive months without any other biological or physiological cause. - Menopause results from diminished ovarian primordial follicles, failure of monthly development of an ovarian dominant follicle and ovulation, and eventual exhaustion of primordial follicles. This process is accompanied by greatly diminished ovarian production of the sex hormone estrogen (as well as progesterone) resulting in both very low serum concentrations of estrogens and cessation of menstruation. - Menopause symptoms include, but are not limited, to the following: - Vasomotor symptoms (or hot flashes) - feeling of warmth and excessive sweating (throughout the day), thought to result from the effects of estrogen withdrawal on hypothalamic thermoregulating system. Night sweats may interfere with the woman's ability to sleep at night. - Vulvar and vaginal atrophy symptoms - vaginal dryness, dyspareunia (pain with intercourse) and vaginal irritation resulting from withdrawal of estrogen stimulation to the lower genital tract (vulva and vagina) - While not life-threatening moderate to severe menopausal symptoms can be debilitating, affecting the woman's ability to carry out her day-to-day normal personal and/or employment-related activities. - In the US, nearly 63 million women are past the average age of natural menopause of 51 years of age (as of July 1, 2021).⁴ - VMS are experienced by up to 80% of individuals during	- Vasomotor symptoms associated with menopause can persist for long periods in some individuals - Menopause symptoms, though not life-threatening, may negatively impact the woman's ability to carry out her day-to-day normal personal and/or employment-related activities. - Given the size of the postmenopausal population in the U.S., menopausal symptoms, and their impact on affected individuals, constitute a significant public health concern.

⁴ <https://www.census.gov>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	menopause⁵. • The prevalence of moderate to severe VMS associated with menopause was 34% in the US, 40% in Europe and 16% in Japan.⁶ • Approximately 20 to 30% of women with vasomotor symptoms (hot flashes) seek medical attention for treatment⁷ • An individual woman's experience of hot flashes varies based on genetic background, psychological factors and other health conditions or treatments.² The duration of vasomotor symptoms from the time of onset is typically 7.4 years and symptoms commonly may persist for approximately a decade.³	
Current Treatment Options	• Current approved treatment options for an indication for the treatment of moderate to severe vasomotor symptoms include multiple oral, transdermal systems, topical gels/emulsion/spray, vaginal system products with estrogen-alone for use in a woman without a uterus or in combination with a progestogen for use in a woman with a uterus. One non-hormonal product is approved. These approved products offer a range of dosage strengths allowing titration of dose to relieve vasomotor symptoms based on treatment goals and risk for the individual woman.	• Although a wide range of hormone therapy product forms and formulations and at least one non-hormonal product exists for the treatment of moderate to severe vasomotor symptoms, options for individuals who cannot or choose not to use these products would increase the armamentarium available for treatment.

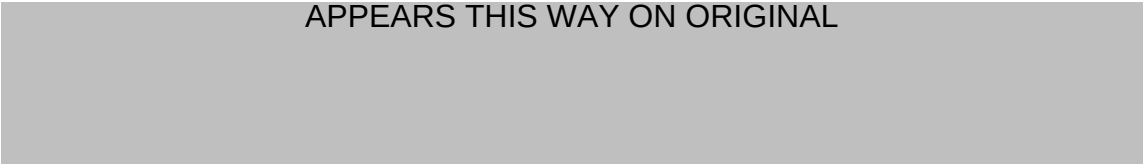
⁵ Gold EB, et. al. Longitudinal analysis of the association between vasomotor symptoms and race/ethnicity across the menopausal transition: study of women's health across the nation. Am J Public Health. 2006; 96:1226-1235.

⁶ Nappi RE, et. al. Global cross-sectional survey of women with vasomotor symptoms associated with menopause: prevalence and quality of life burden. Menopause. 2021; 28:875-882.

⁷ <https://www.uptodate.com/contents/menopausal-hot-flashes#:~:text=Many%20to%20most%20women%20describe,and%20do%20not%20require%20treatment.>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• Veozah 45 mg achieved statistical significance versus placebo consistently across the four co-primary vasomotor symptom endpoints (mean change in VMS frequency and severity at Weeks 4 and 12) in two confirmatory, 12-week, placebo-controlled clinical trials. • Veozah 45 mg achieved a clinically meaningful threshold reduction of hot flash frequency (defined as a reduction in hot flash frequency that exceeds placebo by at least 2 per day or 14 per week) at Week 4 maintained through Week 12. • Veozah 45 mg tablets can be used by non-hysterectomized and hysterectomized postmenopausal women.	• The data from the phase 3 clinical trials presented in NDA 216578 provide substantial evidence of effectiveness for Veozah in the treatment of moderate to severe vasomotor symptoms. • Both non-hysterectomized and hysterectomized women using Veozah can expect a reduction in the frequency and severity of moderate to severe vasomotor symptoms.
Risk and Risk Management	• The most common exposure adjusted adverse reactions (incidence $\geq 1\%$) with Veozah 45 mg fezolinetant are elevated hepatic transaminases, abdominal pain, and insomnia. • Hepatic transaminase elevations $> 3 \times \text{ULN}$ were observed that were approximately 2-fold greater in Veozah 45 mg compared with placebo. These hepatic transaminase elevations occurred at various timepoints in the 12-month phase 3 clinical trials, were generally transient, and resolved while on 45 mg fezolinetant or shortly after discontinuation. There were 8 cases assessed as probable/possible DILI (4 participants with probable DILI and three to four others with at least possible DILI). No cases of Hy's law were observed. The cases of DILI were predominantly hepatocellular with a median latency from drug start of 56 days, but the latency range was wide at 14 to 250 days. Many of the participants considered to have possible DILI improved even with continued Veozah use. • Though the demonstrated risk of DILI in the phase 3 clinical trials was modest and adaptation may concur with continued exposure, it not known what magnitude and severity of hepatic injury will be observed once Veozah 45 is available for use in the postmarketing setting. If even a minimum of 1% of the potential numbers of women seeking treatment for moderate to severe vasomotor symptoms are prescribed Veozah, potentially 100,000 or more women may be	Veozah may cause some DILI, but it appears modest, and adaption may occur with continued exposure. Labeling and enhance pharmacovigilance will be used to identify risk in the postmarketing setting. Depending upon the outcomes demonstrated with these measures, we will consider whether formal postmarketing trials should be required.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	exposed (1% of 20% of 63 million postmenopausal women in the U.S). In such a potentially large exposure population, more severe cases of DILI could be evident. In order to identify the potential for more serious DILI cases, we propose that labeling specify monitoring of hepatic function/injury before women begin Veozah and while on Veozah for a minimum of up to 9 months follow initiation of use (justified by latency of onset of elevations up to 250 days). Additionally, we are also recommending an enhanced pharmacovigilance program [as advised by the Office of Surveillance and Epidemiology (OSE)] involving active participation of the applicant in obtaining information as needed (by sending to the reporter of adverse hepatic events, a request for additional information in the form of an FDA-agreed upon hepatic adverse event follow-up questionnaire) to: 1) classify the evidence of any case of hepatic injury (ALT/AST > 8x ULN confirmed on repeat testing or ALT/AST > 3x ULN and total bilirubin > 2x ULN (new onset biochemical abnormalities consistent with possible Hy's law cases) or ALT/AST > 3x ULN associated with symptoms suggestive of hepatic disease such as: anorexia, dark urine, fatigue, fever, jaundice, nausea, vomiting, rash, right upper quadrant pain, etc., or any liver adverse event leading to discontinuation or any hepatic event preferred term (PT) denoting the diagnosis of jaundice, liver injury, or non- infectious hepatitis in a 15-Day Safety Reports to the FDA; 2) provide a summary analysis of these events in the periodic safety reports, submitted quarterly for the first 3 years after approval, as per 21 CFR 314.80(c)(1); and 3) provide in the periodic safety report, medical literature reviews for case reports/case series of hepatic adverse events including liver injury reported with Veozah. There was an imbalance in the three clinical trials for the serious adverse reactions of non-benign neoplasms (high level group term); the (EAIR) for Veozah 45 mg was 1.2 per 100 person years versus 0.2 for placebo group. Half of the non-benign neoplasms in the Veozah 45 mg group were noted to be pre-existing. There is no evidence in the nonclinical data submitted in NDA216578 nor in the published literature of a biological mechanism supporting an increased risk of malignancy with Veozah or NK3 antagonism.	APPEARS THIS WAY ON ORIGINAL The apparent imbalance in malignancies in the Veozah 45 mg group compared to placebo appears to disappear when likely preexisting cancers are taken into consideration. At the



2. Background

The following is a high-level discussion of presubmission and submission regulatory activity up to the NDA submission. It is not meant to be a comprehensive review. The reader is referred to the Drs. van der Vlugt's and Zopf's Clinical Review archived, November 26, 2022, for a more detailed discussion of presubmission regulatory activity.

- **March 22, 2016:** Submission by Ogeda S.A., Belgium, of IND 130277 for ESN364 (fezolinetant), an NK3 receptor antagonist, for the treatment of moderate to severe vasomotor symptoms associated with menopause.
- **March 22, 2017:** The Agency held a Type C meeting with Ogeda S.A. to discuss nonclinical and clinical development plans for the treatment of moderate to severe hot flashes in postmenopausal women. The discussion included, but was not limited to, the following discussion points:

 - There appears to be sufficient nonclinical information to proceed with phase 2b clinical Trial ESN 364_HF_205
 - There is sufficient data for assessing metabolite ES259564 safety.
 - There is sufficient data for assessing metabolite ES259564 safety.
 - Provide to the IND, a table of safety margins, based on animal exposure data (i.e., AUC and Cmax) to the IND.
 - Results of the proposed primary efficacy trial analyses should show a clinically and a statistically significant reduction, within 4 weeks of initiation of treatment and maintained throughout 12 weeks of treatment, in both the frequency and severity of hot flashes in the treated groups compared with the control groups. A clinically significant reduction in frequency is identified as a reduction of at least two moderate to severe hot flashes above placebo per day at Week 4 and Week 12.
 - Ogeda's proposal to [REDACTED] (b) (4)

[REDACTED]

Calculate severity as follows:

 - [(number of mild hot flashes/day × 1) + (number of moderate hot flashes/day × 2) + (number of severe hot flashes/day × 3)]/total number of daily (or weekly) mild/moderate/severe hot flashes- The assessment of endometrial histology is recommended both for phase 3 clinical trial efficacy and safety evaluation and long-term (minimum 12-months) general and endometrial safety, and drug exposure trials.

- *FDA considers ESN364 to be a new molecular entity. Two confirmatory 12-week phase 3 efficacy and safety clinical trials, and a long-term (minimum 12-months) general and endometrial safety trial should be conducted in support of this product.*
 - *The proposed phase 2b dose finding trial should enroll only the population of women intended to be evaluated at phase 3, which are identified as postmenopausal women experiencing hot flashes due to menopause.*
 - *The Division generally follows 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 at the dose or dose range believed to be efficacious.*
- **October 24, 2017:** Ogeda S.A. submitted two Special Protocol Assessment (SPA) protocols to FDA to obtain agreement on the 2-year rat carcinogenicity study ((b) (4) Study 8375967) and the 26-week mouse carcinogenicity study ((b) (4) Study 8375970). On December 6, 2017, the Executive Carcinogenicity Assessment Committee (ECAC) meeting minutes were sent to Ogeda S.A. Ogeda S.A. submitted the final FDA agreed-upon protocols on March 1, 2018.
- **May 1, 2018:** The Agency received a General Correspondence letter: Noting the transfer of IND from Ogeda S.A. to Astellas, “Effective May 1, 2018, the Ogeda IND 130277 has transferred to Astellas Pharma Global Development, Inc. (Astellas), which has accepted all sponsor responsibilities and obligations pertaining to Ogeda IND 130277 with the exception of the ongoing ‘Phase 2B Study ESN_HF_205’. Ogeda will remain the study sponsor of ‘Phase 2B Study ESN364_HF_205’.”
- **June 7, 2018:** FDA provided Astellas with a Type C Written Responses Only related to findings of *transient elevation of liver enzymes in the phase 2b Trial ESN364_HF_205*. The Agency’s response included, but was not limited to, the following discussion points:
 - Discontinue (pause) enrollment in Trial ESN364_HF_205 if one additional woman is withdrawn because she meets the previously agreed-to patient withdrawal criteria.
 - Women currently enrolled in Trial ESN364_HF_205 may continue with implementation of close observation, including more frequent serum liver biochemistry evaluation for women who develop transaminase abnormalities that do not meet the trial or individual participant stopping criteria, if enrollment is paused.
 - Participating women should also have serial serum alkaline phosphatase and prothrombin (PT)/international normalized ratio (INR) evaluated in addition to transaminase and total bilirubin. Obtain these tests every week when a woman has been found to have any abnormal liver function test.

- Obtain a baseline fractionation of the serum bilirubin (direct and indirect fractions) when abnormal transaminases are reported as defined above, as some women will have Gilbert's syndrome. Repeat bilirubin measurements simultaneously with all liver biochemistry tests until all elevations have returned below the ULN.
 - Investigate promptly with biochemical and physical evaluation and interrupt trial drug administration for any woman with symptoms of abdominal pain, worsening or new fatigue, anorexia, nausea, rash, vomiting or diarrhea. Discontinue investigational drug immediately if prompt evaluation is not possible.
 - Conduct a thorough evaluation of each woman who develops asymptomatic ALT and/or AST abnormalities $>3 \times$ ULN (or $2 \times$ baseline, but not more than $5 \times$ ULN in trial participants that are enrolled with elevations at baseline) in the absence of hyperbilirubinemia and/or elevated INR.
 - Provide the curriculum vitae of each member of the Liver Safety Monitoring Panel (LSMP) that you establish for Trial ESN364_HF_205, for our review.
 - Masked and unblinded safety data for ongoing and future clinical trials should be reviewed at three-month intervals by the Data Safety Monitoring Board (DSMB).
 - Provide datasets of all women enrolled in all ESN364 trials to date, including clinical studies/trials conducted outside the United States, using eDISH data plotting attached, to better assist you in your ESN364 development program."
- **July 3, 2018:** FDA provided Astellas an Advice/Information Request (A/IR) letter 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 Responses Only communication.
 - **October 16, 2018:** Astellas requested a Special Protocol Assessment (SPA) for a mouse Carcinogenicity Study. FDA responded on November 29, 2018. On January 16, 2019, Astellas submitted the SPA final protocol.
 - **October 24, 2018:** FDA provided a Type C Written Responses Only letter related to endometrial health assessment, bone safety assessment, and breast cancer treatment-related VMS development strategy. The FDA Written Responses Only letter included, but was not limited to, the following discussion points:
 - All non-hysterectomized women enrolled in planned phase 3 clinical trials should undergo a baseline endometrial biopsy before beginning trial medication. Non-hysterectomized woman with an endometrial diagnosis of endometrial hyperplasia and/or endometrial cancer should not be enrolled. A transvaginal ultrasound (TVU) examination should also be performed.

- Repeat the endometrial biopsy at completion of all 12-week trials and all 52-week trials or for vaginal bleeding at any time during the course of drug therapy.
 - Endometrial tissue obtained by endometrial biopsy prior to trial enrollment, during the conduct of the clinical trial, and at the End-of-Trial (EOT) should be processed in the same manner by a central laboratory.
 - We recommend concurrent reading by three independent expert pathologists from institutions with independent fiduciary and organizational reporting for the evaluation of the endometrium in a woman with a uterus. Each pathologist should be blinded to the treatment group and to the readings of the other pathologists. The concurrence of two of the three pathologists is accepted as the final diagnosis. If there is no agreement among the three pathologists, the most severe pathologic diagnosis should be used as the final diagnosis.
 - The same standardized criteria for the diagnosis of endometrial hyperplasia or endometrial cancer should be used by the three independent pathologists, and endometrial polyps should be fully characterized as to glandular proliferation and atypia.
 - Emerging research suggests that tachykinins may have a role in bone homeostasis. Therefore, a direct effect of ESN364 on bone turnover in postmenopausal women cannot be ruled out. The data from phase 2a Trial ESN364_HF_204 are insufficient to evaluate ESN364's effect on bone. Include BMD endpoints in your phase 3 development.
 - All BMD measurements should be interpreted at a central read facility and analyses should include areas where there are standardized DEXA placement procedures and normative data available for assessment (i.e., lumbar spine, femoral neck, and total hip). Analyses should be based on scans with standard (supine) patient positioning. Adequate quality control measures should be established for any multicenter trial that include bone density endpoints (Faulkner et al., 1995).
- **April 17, 2019:** The Agency held a Type B "End-of-Phase 2 (EOP2)" meeting with Astellas to discuss their nonclinical, clinical pharmacology, and clinical development plans for phase 3 development of fezolinetant. The discussion from FDA included, but was not limited to, the following discussion points:
 - Submit all nonclinical final study reports to IND 130277, with a summary table of safety margins based on animal exposure data for both fezolinetant and ES259564 as discussed at the March 2017 Type C meeting. Based on the proposed duration of the phase 3 clinical trial, the 39-week toxicology study report must be submitted and reviewed by FDA prior to the initiation of the phase 3 clinical trials.

- 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.
- The proposal to allow concomitant administration of weak CYP1A2 inhibitors (e.g., caffeine) with 30 mg fezolinetant daily in the phase 3 trials appears to be acceptable.
- The Agency does not agree that a thorough QT/QTc (TQT) study could be waived and requests that Astellas 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. Use the expected increase in C_{max} of fezolinetant with concomitant administration of a strong CYP1A2 inhibitor at steady-state for representing the worst-case scenario.
 - The study report for the drug interaction Trial 2693-CL-0006.
 - 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.
- 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. The sponsor was advised, “you may be at risk of not identifying an effective dose of fezolinetant for a VMS indication in your proposed phase 3 development program.
- The proposal to conduct a long-term, 52-weeks clinical trial including an initial 12-weeks placebo-controlled assessment of efficacy followed by a 40-week open-label extension (representing a total of 52-weeks of trial medication exposure), is acceptable.
- 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 (and similar Trial 2693-CL-0302) who declines participation in the proposed open-label 40-weeks trial extension. A diagnosis of disordered proliferative endometrium, endometrial hyperplasia, or endometrial cancer must be appropriately followed-up by Astellas until resolution.

- We do not distinguish between moderate to severe hot flashes experienced during nighttime 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.
- 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 Trial 2693-CL-0301 and similar Trial 2693-CL-0302, (b) (4)
- *Reported results of the proposed secondary and exploratory objectives/endpoints in clinical Trial 2693-CL-0301 and similar Trial 2693-CL-0302* (b) (4)
- Repeat the screening endometrial biopsy reported as insufficient tissue for evaluation to rule out the presence of disordered proliferative endometrium, endometrial hyperplasia, or endometrial cancer.
- Do not enroll a postmenopausal woman with a uterus and a screening endometrial biopsy reported as: disordered proliferative endometrium, endometrial hyperplasia, or endometrial cancer in proposed Trial 2693-CL-0301 and similar Trial 2693-CL-0302.
- The proposed sample sizes for Trials 2693-CL-0301 and similar Trial 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.
- Your proposed schedule of laboratory and clinical assessments appears reasonable to monitor the potential for liver injury with incorporation of the following:
 - 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.
 - Postmenopausal women with mild elevations in serum transaminases $<1.5 \times$ the upper limit of normal (ULN) may be

included, however, such participants must have a normal total bilirubin (TB) and direct bilirubin (DB) at enrollment.

- Postmenopausal women with Gilbert's syndrome may be enrolled in clinical trials. These women may have elevated total bilirubin, but their direct bilirubin, reticulocyte count, and hemoglobin should be normal.
- Evaluate a postmenopausal woman with elevated alkaline phosphatase (ALP) at baseline, for cholestatic liver disease prior to trial enrollment.
- Immediately discontinue drug in trial participants 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)].
- FDA and Astellas agreed upon the criteria for drug-induced liver injury (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).
- FDA agreed 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. FDA also agreed with the role of the Data Safety Monitoring Board (DSMB) in interacting with the LSMP.
- FDA agreed that the nonclinical data and the adverse event (AE) data from 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.
- Submit separately an Initial Pediatric Study Plan (iPSP) within 60 days of an End-of-Phase-2 (EOP2) meeting.
- FDA agreed that the study data standardization plan (SDSP) for the nonclinical studies, clinical pharmacology trials, and clinical trials, appears reasonable. However, the reported results of the proposed secondary and exploratory objectives/endpoints in clinical Trials 2693-CL-0301 and similar Trial 2693-CL-0302, (b) (4)

Astellas may proceed with their analysis for

PROMIS® SD SF 8b for exploratory purposes at their own discretion.

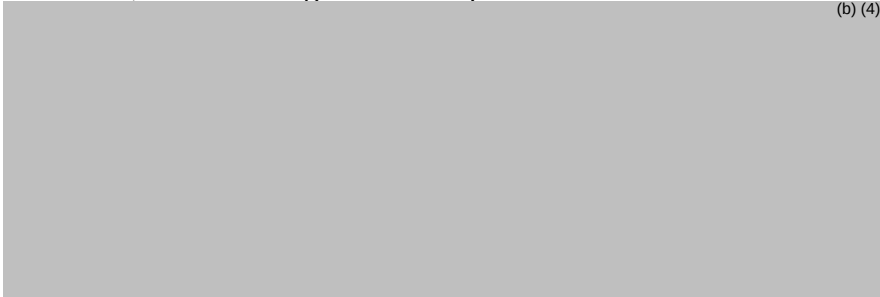
- For electronic data capture, perform usability testing of the selected devices with patient cognitive interviews to assess device functionality, questionnaire comprehension, and ease of use in the patient population. This would minimize the likelihood of having poor quality data due to patients' misunderstanding or incomplete understanding of how to use the device."
- **May 31, 2019:** Astellas submitted a TQT/QTc Study Waiver request. On December 20, 2019, FDA provided the following response via email/electronic communication to the IND, "From our QT Interdisciplinary Review Team: No significant QTc prolongation was detected in our QT assessment performed using data from the sponsor's single- / multiple- ascending dose study (Study # ESN364-CPK-102). A dedicated QT study is not needed. The submitted data was found to be adequate to support the substitution request of thorough QT study."
- **September 20, 2019:** The Agency's A/IR letter regarding phase 3, 12-month Trials 0301 and 0302 included, but was not limited to, the following discussion points:
 - Do not enroll a postmenopausal woman who has a screening endometrial biopsy reported as insufficient tissue for diagnosis and a screening transvaginal ultrasound (TVU) double wall thickness of greater than 4 mm in the proposed phase 3, 52-week efficacy and safety clinical trials without further evaluation.
 - Repeat any screening endometrial biopsy reported as insufficient tissue for diagnosis to rule out the presence of disordered proliferative endometrium, endometrial hyperplasia, or endometrial cancer in a postmenopausal woman with a uterus.
 - Do not enroll any postmenopausal woman with a uterus and a screening endometrial biopsy reported as disordered proliferative endometrium, endometrial hyperplasia, or endometrial cancer.
 - Have the histologic determination of the endometrial biopsy slides collected during the conduct of proposed Trials 2693-CL-0301 and 2693-CL-0302, made by three independent expert pathologists ((b) (4)), blinded to treatment and each other's readings.
 - We do not distinguish between moderate to severe hot flashes experienced during the nighttime hours (commonly referred to as night sweats) and those experienced during the daytime hours.
 - *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, EuroQOL5D-5L, and WPAI-VMS questionnaires), in your proposed phase 3 Trials 2693-CL-0301 and 2693-CL-0302, (b) (4)*

- (b) (4)
- *The reported results of the proposed secondary and exploratory objectives/endpoints in clinical Trials 2693-CL-0301 and 2693-CL-0302* (b) (4)
 - The primary efficacy analysis in phase 3 Trials 2693-CL-0301 and 2693-CL-0302 should demonstrate a statistically significant and clinically meaningful reduction in the frequency and statistically significant reduction in the severity of hot flashes in the treated group(s) compared with placebo. This reduction in frequency and severity should occur at 4 weeks from initiation of treatment and be maintained through 12 weeks of treatment.
 - We identify a clinically meaningful reduction in frequency as a reduction of at least two moderate to severe hot flashes above placebo at Week 4 and Week 12.
 - **October 4, 2019:** Astellas requested a Type C meeting to discuss and agree on the designation of the regulatory starting materials, the biopharmaceutics classification system (BCS) designation for fezolinetant and the CMC strategy for the development of fezolinetant immediate release tablets for commercial use based on ICH M9 draft guideline. The Agency provided Written Responses included, but were not limited to, the following discussion points: **APPEARS THIS WAY ON ORIGINAL**
 - **November 15, 2019:** The Agency's A/IR letter, regarding phase 3, 12-month Trial 0304 conveyed the following to Astellas:
 - Do not enroll any postmenopausal woman with a uterus who has a screening endometrial biopsy reported as insufficient tissue for diagnosis and a screening transvaginal ultrasound (TVU) double-wall thickness greater than 4 mm in your proposed phase 3, 52-week safety clinical trial without further evaluation (exclusion criterion # 7 in the proposed protocol for Trial 2693-CL-0304).
 - Repeat any screening endometrial biopsy that is reported as insufficient tissue for diagnosis to rule out the presence of disordered proliferative endometrium, endometrial hyperplasia, or endometrial cancer in a postmenopausal woman with a uterus.
 - Assess endometrial safety, i.e., rates of endometrial cancer and endometrial hyperplasia as a primary endpoint. Assess the rate of disordered proliferative endometrium in the same way as the primary endpoint.
 - Power proposed Trial 2693-CL-0304 based on the ability to demonstrate a rate of hyperplasia (as a surrogate for endometrial cancer) that is 1 percent with an upper bound of the one-sided 95 percent confidence interval for the rate, that does not exceed 4 percent.

- **January 7, 2020:** The Agency submitted a Written Responses Only to the Astellas submission, dated November 19, 2019, containing a meeting request to discuss and obtain Agency's agreement on the design of fish full lifecycle study for Environmental Assessment (EA). FDA agreed with the proposed study design of the fish study for the EA for fezolinetant.
- **March 2, 2020:** Astellas submitted IND 130277 protocol amendment, dated May 16, 2019, containing Astellas' Agreed Initial Pediatric Study Plan (Agreed iPSP) for the Treatment of Moderate to Severe Vasomotor Symptoms Associated with Menopause. The Agency responded with agreement to the Astellas' proposed Agreed iPSP and had no further comments at that time. The Agency noted that the attached copy of Astellas' Agreed iPSP serves as the official copy of this document and must be included in the appropriate section of an application for marketing approval for ESN364 (fezolinetant).
- **July 14, 2020:** The Agency submitted Written Responses Only to the Astellas submission, dated May 18, 2020, containing a Type C meeting request to obtain feedback and obtain Agency's agreement on the designation of a regulatory starting material (RSM) (b) (4) in the fezolinetant drug substance synthesis route. The Agency's Written Responses to Astellas included, but was not limited to the following discussion points:

 - (b) (4) complies with the definition of a "commercially available chemical" in ICH Q11.
 - The impurity spike and purge studies demonstrate that impurities of (b) (4) other than (b) (4) and (b) (4) do not contribute to the impurity profile of fezolinetant drug substance.
 - The revised specification proposed for (b) (4) appears to mitigate any risk of carryover of impurities through the manufacturing process of fezolinetant drug substance.
 - Based upon revised control strategy for (b) (4) and in accordance with ICH Q11 and Q11 Q&A guidances, the designation of (b) (4) as a regulatory starting material is reasonable. The final determination on the acceptability of the regulatory starting materials for the commercial manufacturing of fezolinetant drug substance will be made during the review of your proposed NDA.
- **September 18, 2020:** The Agency provided Written Responses Only to the Astellas submission, dated July 7, 2020, containing a Type C meeting request to obtain the Agency's feedback and agreement on (b) (4) in phase 3

Trials 0301 and 0302. The Agency's Written Responses Only conveyed, but not limited to, the following discussion points:

-  (b) (4)
 - You may propose as your primary analysis of clinical meaningfulness, meaningful within-patient change: change from the patients' perspective using your anchor-based measure in the ongoing phase 3 clinical trials, the patient reported outcome instrument Patient Global Impression of Change for Vasomotor Symptoms (PGIC-VMS) in lieu of the between-group determination that the reduction of the frequency of VMS in the fezolinetant treatment group exceeds that of placebo by the clinical meaningful threshold reduction of 2 moderate to severe hot flushes per day or 14 per week.
 - PGI-C VMS has limitations for this use including, though not necessarily limited to, the following:
 - The PGI-C VMS does not measure the concept of interest in the VMS diary (i.e., hot flash frequency). The anchor's concept should be the same as the specific concept being assessed by the clinical outcome assessment (COA) endpoint of interest.
 - The PGI-C VMS scale is susceptible to recall error; therefore, it is not a reliable measure for change from baseline data.
 - We do not object to a pooled analysis for the evaluation of clinically meaningful within-patient change from the phase 3 trials should you choose to proceed with assessment of the clinical meaningfulness of the frequency in the primary analyses based solely on within-patient change external anchors. We recommend that you blindly pool a subset (e.g., 100) of participating women in each trial to establish a meaningful change threshold(s), or a range of threshold(s), and then confirm using blinded, pooled data from remaining participating women in each study.
 - Submit the proposed meaningful change threshold(s) (e.g., a range of score changes) to the IND prior to data unblinding.
 - We recommend that you utilize a blinded, independent (external) statistician to conduct the analysis in order to maintain the integrity of the trial conduct prior to unblinding.
- **July 28, 2021:** Astellas submitted on May 14, 2021, a request for a Type C meeting to obtain guidance on efficacy, safety, and dataset strategies for

fezolinetant. The Agency's July 28, 2021, Written Responses Only included, but was not limited to, the following discussion points:

- Based on reported results in your pre-meeting package, from evaluation of efficacy of fezolinetant vs placebo in the first 12 weeks of treatment in 52-weeks Trials 2603-CL-0301 (henceforth referred to as Trial 0301) and 2693-CL-0302 (henceforth referred to as Trial 0302):
- The fezolinetant 30 mg dosage strength group and the fezolinetant 45 mg dosage strength group appear to demonstrate statistically significant improvement in the frequency and severity of moderate to severe vasomotor symptoms when compared to placebo groups at Weeks 4 and 12.
- The statistically significant decrease in frequency for the fezolinetant 45 mg dosage strength group exceeds the Agency's recommended clinical meaningful frequency threshold reduction of 2 per day above placebo at Weeks 4 and 12 in both Trials 0301 and 0302.
- *The statistically significant decrease in frequency for the fezolinetant 30 mg dosage strength group failed to meet the clinical meaningful frequency threshold reduction of 2 per day above placebo at Week 4 in either Trial 0301 or 0302 and at Week 12 in Trial 0302.*
- The statistically significant decrease in frequency for the fezolinetant 30 mg dosage strength group exceeds the clinical meaningful frequency threshold reduction of 2 per day above placebo at Week 12 in Trial 0301.
- We do not agree that (b) (4)
- The Patient Global Impression of Change for Vasomotor Symptoms (PGI-C VMS) has limitations for the determination of clinical meaningfulness including, though not necessarily limited to, the following:
 - The PGI-C VMS does not measure the concept of interest in the VMS diary (i.e., hot flush frequency). The anchor's concept should be the same as the specific concept being assessed by the clinical outcome assessment COA) endpoint of interest.
 - The PGI-C VMS scale is susceptible to recall error. Therefore, it is not a reliable measure for change from baseline data and interpretation of data.
- Using PGI-C VMS may be problematic. A patient global impression of severity (PGIS) scale is generally the preferred anchor scale over the patient global impression of change scale. That said, we acknowledge there is no perfect anchor scale.

- Clarify whether the PGI-C VMS was administered in all subjects in Trials 0301 and 0302 at both time points of primary endpoint collections (Weeks 4 and 12).
- Confirm the number of subjects who have completed the PGI-C VMS in Trials 0301 and 0302 at both primary time points (Weeks 4 and 12).
- Provide evidence to support that the "moderately better" response category represents a meaningful change in the PGI-C VMS.
- Submit a revised Psychometric Analysis Plan (PAP) for review as soon as possible prior to your planned NDA submission. The revised PAP should contain detailed information showing how you derived the meaningful change threshold(s), or a range of thresholds for each trial.
- For empirical cumulative distribution function (eCDF) and probability density function (PDF) curves (e.g., figures A-2 and A-3 in your psychometric analysis plan), include the curve for each anchor category at Week 4 and Week 12.
- *Your NDA application in support of an indication for the treatment of moderate to severe VMS due to menopause, if filed, will be based on the separate analyses of efficacy data for each of the two independent, phase 3, 12-week, placebo-controlled confirmatory clinical trials. Provide this data separately.* You may provide an Integrated Summary of Efficacy (ISE)/Summary of Clinical Efficacy (SCE) as supportive documentation.
- Provide efficacy data for each individual phase 3 trial (Trial 0301 and Trial 0302) for the agreed upon co-primary efficacy endpoints as follows:
 - Mean change in the frequency of moderate to severe vasomotor symptoms from baseline to Week 4.
 - Mean change in the frequency of moderate to severe vasomotor symptoms from baseline to Week 12.
 - Mean change in the severity of moderate to severe vasomotor symptoms from baseline to Week 4.
 - Mean change in the severity of moderate to severe vasomotor symptoms from baseline to Week 12.
- Provide the weekly (Week 1 through Week 12) assessment of the mean change from baseline in frequency and severity of moderate to severe vasomotor symptoms for the treatment and placebo groups for the two phase 3 trials. Include mean change difference between the treatment group and placebo and the statistical significance.
- Submit the pooled safety analysis for POP2 from the three 52-week phase 3 Trials 0301, 0302 and 2693-CL-0304 (henceforth referred to as 0304) in postmenopausal women with VMS associated with menopause conducted in North America and Europe.

- *We agree with the proposed approach to present the Integrated Summary of Safety (ISS) text portion in Module 2.7.4 and provide the associated ISS Tables, Listings, Figures (TLF) s in Module 5.3.5.3*
 - We agree with the proposed selection of medical events for which narratives will be provided.
 - Your proposed approach for the datasets and TLFs of clinical study reports 2693-CL-0301 and 2693-CL-0302 appears acceptable.
 - Your proposed approach for submission of datasets in a future NDA application as specified in the SDSP appears acceptable.
- **January 28, 2022:** A pre-NDA teleconference was conducted to discuss the fezolinetant completed nonclinical and clinical studies and other general information for the submission of an NDA for fezolinetant tablets with a submission target as early as June 2022. Final meeting minutes provided on February 24, 2022, included, but were not limited to, the following discussion points:
 - The completed nonclinical studies appear adequate to submit the NDA.
 - The nonclinical data appear to be supportive of the mechanism of action.
 - 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. In Study ESN364_CPK_103, the exposure for the metabolite was 2-fold higher than the parent and the Agency is concerned that the accumulation of the metabolite may have a clinical impact.
 - FDA requested that Astellas conduct studies to test whether metabolite ES259564 is a substrate of OATP1B3, and P-glycoprotein, prior to the NDA submission. Astellas explained that they have profiled the metabolite ES259564, which has been shown to be pharmacologically and toxicologically inactive, and referenced selected results from the meeting package:
 - 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%
 - 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. 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.

- When asked, FDA stated that any additional DDI studies should be submitted with submission of the completed NDA.
- Astellas stated their intent to include data from a dedicated renal impairment study in the NDA.
- The projected exposures in completed/ongoing clinical trials conducted during Astellas' development program [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)], appears 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.
- Astellas' approach including the assessment of hepatic safety and the presentations/displays appears reasonable at a high level.
- FDA agreed with Astellas' proposed areas of safety focus which include, but were not limited to:
 - Endometrial safety
 - Hepatic safety and risk for hepatotoxicity
 - Bone safety
 - CNS safety
 - Selected hematologic safety: thrombocytopenia
- Address in the NDA application, as additional areas of medical safety focus. 1) glucose impairment, and 2) creatinine phosphokinase (CPK) increase.
-  (b) (4)
- Provide the following information in the NDA application:
 - Define.xml should be compatible to the current version of Internet Explorer (Version 11.0 or later).
 - Clearly list which versions of CDISC ADaM (and ADaMIG), and SDTM (and SDTMIG), and define.xml are used for the study data in your analysis data reviewer's guide and study data reviewer's guide.
- Provide detailed information regarding the changes made in the to-be-marketed compared to the clinical phase 3 formulations. 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.

- March 22, 2022:** Astellas provided Notification of Intent to Submit an Application with a Rare Pediatric Disease Priority Review Voucher. Per this notification, "In accordance with section 529(b)(2) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), (b) (4) transferred the ownership of a rare pediatric disease priority review voucher (PRV) with tracking number (b) (4) to Astellas US, LLC (Astellas) on 20 April 2021." "In accordance with section 529(b)(4)(B)(i) of FD&C Act, Astellas hereby informs the Agency that we intend to redeem (b) (4) for fezolinetant NDA 216578, with the estimated NDA submission date of 22 June 2022."
- June 22, 2022:** Astellas submitted 505(b)(1) new drug application (NDA) 216578 with the request for approval of 45 mg fezolinetant for the treatment of moderate to severe vasomotor symptoms associated with menopause.

3. Product Quality

The individual members of the Office of Pharmaceutical Quality (OPQ) Review Team for NDA 216578, are identified in Table 1

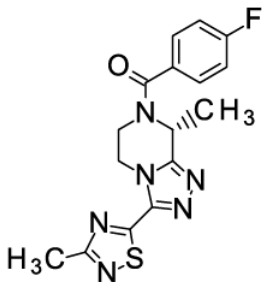
Table 1 OPQ Review Team by Subdiscipline

Subdiscipline	Primary Reviewer	Secondary Reviewer
Drug Substance	Friedrich Burnett, Ph.D.	Lawrence Perez, Ph.D.
Drug Product	Baoqing Ma, Ph.D.	Hamid Shafiei, Ph.D.
Manufacturing	Loqman Mohamed, Ph.D.	Vaikunth Prabhu, Ph.D.
Biopharmaceutics	Kalpna Paudel, Ph.D.	Tapas Ghosh, Ph.D.
Microbiology	Loqman Mohamed, Ph.D.	Vaikunth Prabhu, Ph.D.
Environmental Assessment	Xiaoqin Wu, Ph.D.	James P. Laurenson, Ph.D.
Labeling	Baoqing Ma, Ph.D.	Hamid Shafiei, Ph.D.
Regulatory Business Project Manager	Dahlia Walter, M.S., PMP	
Administrative Team Lead	Hamid Shafiei, Ph.D.	

Source: OPQ Administrative Team Lead Review (Hamid Shafiei, Ph.D.), Table page 2

Drug Information

CAS Registry Number: 1629229-37-3

Generic Name:	Fezolinetant
Code Name:	ESN364
Chemical Name:	(4-Fluorophenyl)[(8R)-8-methyl-3-(3-methyl-1,2,4-thiadiazol-5-yl)-5,6-dihydro[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl]methanone
Molecular Formula/Molecular Weight:	C ₁₆ H ₁₅ N ₆ O ₂ S, 658.39
Structure or Biochemical Description:	 The chemical structure of Fezolinetant is shown. It features a central 1,2,4-triazolo[4,3-a]pyrazine core. At the 7-position of the pyrazine ring, there is a 3-methyl-1,2,4-thiadiazol-5-yl group. At the 8-position, there is a (4-fluorophenyl)methyl ketone group. The stereochemistry at the 8-position is indicated as (8R).
Pharmacologic Class:	Neurokinin 3 (NK3) receptor antagonist

Drug Substance Assessment

As noted above, the primary and secondary reviews of the fezolinetant drug substance, were performed by Friedrich Burnett Ph.D. and Lawrence Perez Ph.D., respectively. No issues which would preclude approvability were identified in the review of the fezolinetant drug substance. The drug substance, (4-fluorophenyl) [(8R)-8-methyl-3-(3-methyl-1,2,4-thiadiazol-5-yl)-5,6-dihydro[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl]methanone, C₁₆H₁₅N₆O₂S (358.59 g/mol), is very slightly soluble in water (0.293 mg/mL) and sparingly soluble in ethanol (10.3 mg/mL). The drug substance is highly soluble in 0.1 N hydrochloric acid (0.44 mg/mL), pH 4.5 acetate buffer (0.40 mg/mL), and pH 6.8 phosphate buffer (0.37 mg/mL).

(b) (4)

(b) (4)

The proposed controls of materials and reagents are appropriate to adequately ensure the quality of the drug substance. The individual specifications for all the starting materials used in the manufacturing process were identified and deemed adequate. Additionally, the applicant has provided detailed information for the test methods (HPLC and GC), Batch Analyses, and Justification of the Specification for each of the Starting Materials, therefore the regulatory starting materials are appropriate and have been adequately justified.

The critical quality attributes (CQAs) that have an impact on the quality of fezolinetant and critical process parameters (CPPs) for the manufacturing process were identified by risk assessment. These CQAs include (b) (4), and the polymorph. During development, these drug substance **process impurities**, and the polymorph were monitored in three primary stability batches as listed in batch analyses and stability studies. All the test results confirmed that no increases of these process impurities were seen during (b) (4) and storage of fezolinetant tablets.

The characterization for fezolinetant is appropriate in support of the structure. All impurities (**process or degradants**) have been adequately described with respect to the origin, identification, and characterization of actual and potential impurities for the drug substance. Impurities in fezolinetant include drug substance process-related impurities, mutagenic impurities, degradants, residual solvents, and elemental impurities. All the impurities were controlled adequately in the drug substance per ICH guidances.

The applicant has provided a detailed description of the analytical methods employed and has provided a validation report for each of the analytical methods. Based on the validation data, the analytical methods have been demonstrated to be adequate for their intended purpose.

(b) (4)

Stability data for fezolinetant stored at (b) (4)

(b) (4) has demonstrated that the drug substance is stable with minimal to no changes for any of the measured attributes. The proposed (b) (4)-month retest period while stored at (b) (4) has been adequately satisfied as the results have shown no significant changes to any of the measured attributes and the stability trend of fezolinetant between (b) (4) and (b) (4) is equivalent.

For a more detailed description of the characterization and analytical methodology for the drug substance, the reader is referred to the archived review of Dr. Burnett. Dr. Burnett concludes, along with Dr. Perez's concurrence, that the 505(b)(1) new drug application has provided sufficient CMC information to provide assurance regarding the identity, strength, purity, and quality of the drug substance, fezolinetant.

Drug Product Assessment

As noted above the primary and secondary reviews of the Veozah drug product were performed by Baoqing Ma, Ph.D. and Hamid Shafiei, Ph.D., respectively. No issues which would preclude approvability, were identified in the review of the fezolinetant drug product. The NDA presented information on two dosage strengths of the drug product. The applicant did not request approval for marketing of the 30 mg dosage strength.

Fezolinetant tablets 30 mg are (b) (4) tablets containing 30 mg active ingredient (phase 3 tablet formulation). The tablets are (b) (4). Fezolinetant tablets 45 mg are round light red film-coated tablets containing 45 mg active ingredient (to-be-marketed tablet formulation). The tablets are debossed with the company logo and '645' on the same side. Fezolinetant Tablets are formulated as immediate release tablets dosage form. (b) (4)

(b) (4)

Fezolinetant Tablets, 45 mg strength are packaged in high density polyethylene (HDPE) child resistant cap (CRC) bottle with 30 and 90 counts and Aluminum-Aluminum blister packets. The blister package will be available for sample use only. The drug product storage condition is "Store at 20°C to 25°C (68°F to 77°F) with excursions permitted from 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature (CRT)]." The applicant provided 6 month accelerated data at 40°C/75% RH and 18-month CRT data at 25°C/60% relative humidity (RH). All the test results conform to the specification. A 30-months expiration period for this product is proposed.

The formulation compositions of the 30 and 45 mg tablets are presented in the Table 2 below.

Table 2: Composition of Fezolinetant Tablets 30 and 45 mg

Component	Function	Reference to Quality Standard	Quantity (mg/tablet)	
			30 mg	45 mg
Fezolinetant	Active ingredient	In-house	30.0	45.0
Mannitol	(b) (4)	USP	(b) (4)	
Hydroxypropyl Cellulose	(b) (4)	NF		
Low-Substituted Hydroxypropyl Cellulose		NF		
Microcrystalline Cellulose		NF		
Magnesium Stearate		NF		
		(b) (4)		
Total				

NF: National Formulary, USP: United States Pharmacopeia, N/A: Not applicable

(b) (4)

Source: OPQ Primary Drug Product Review (Baoqing Ma, Ph.D.), Table 1, page 3

The 505(b)(1) new drug application provides sufficient CMC information to assure the identity, strength, purity, and quality of the drug product, Veozah (fezolinetant) Tablets, 45mg.

All the excipients except for the film coating materials are USP/NF. Although the film coating materials (b) (4) are not compendial excipients, they are composed of compendial components. (b) (4) is used in the film coating for the tablets. The (b) (4) contents in the tablets are expected to be (b) (4) mg/day consumed by the patients per (b) (4). The daily maximum intake of the excipients is below the quantities listed in the IID. The applicant confirms that the fezolinetant tablets contain no sodium, potassium, or phosphorus as constituents of active and inactive drug ingredients.

Fezolinetant is classified as highly soluble because the highest single therapeutic dosage strength, 45 mg, is soluble in no more than 250 mL of aqueous media over the pH range of 1.2 – 6.8. Fezolinetant is classified as highly permeable as determined in permeability studies using Caco-2 cell monolayers and stability study in the gastrointestinal tract. Given this information, fezolinetant can be classified as a Biopharmaceutics Classification System (BCS) Class 1 drug, based on the guidance, “ICH Harmonised Guideline M9: Biopharmaceutics Classification System-Based Biowaivers”.

In the manufacturing process of Fezolinetant Tablets, (b) (4)

(b) (4). No incompatibility of fezolinetant with the excipients and no significant changes were observed in terms of description, assay, and related substances. Based on these results, the conclusion is that these excipients did not influence the product stability under the proposed formulation ratio.

Fezolinetant was initially developed as immediate-release hard gelatin capsules for oral administration of 3, 10, 15, 30, 60, 90, 120 and 180 mg strengths, which were evaluated in phase 1 and phase 2 trials. In the phase 3 trials, a tablet formulation was developed at 15, 30, and 120 mg dosage strengths. The composition of the phase 3 tablet is proportionally similar among 15, 30 and 120 mg dose strengths; the 15 mg and 30 mg tablets were used in the phase 3 trials to evaluate 30 mg and 45 mg dosage strengths, while the 120 mg dosage strength tablet was only used in the relative bioavailability. The to-be-marketed tablet formulations were developed at the dose strengths of 30 mg and 45 mg, which have different formulation from those in the phase 3 clinical trials. Compared to the phase 3 tablets the to-be marketed tablet contains the following changes: (b) (4)

. The applicant performed bioequivalence evaluation of to-be-marketed fezolinetant 45 mg tablet (test formulation) using phase 3 combination of one 15 mg fezolinetant tablet and one 30 mg fezolinetant tablet (reference formulation). The results demonstrated that the to-be-marketed tablet 45 mg strength was bioequivalent to the phase 3 tablets combination of 45 mg dosage strength. There was no impact of the particle size of fezolinetant on the dissolution property.

The applicant performed the excipient compatibility study (b) (4). All excipients have no significant degradation increase observed (b) (4) stored for one month under 50°C/ambient humidity (closed) and 40°C/75% RH (open), demonstrating that Fezolinetant is compatible with these excipients.

The proposed container/closure system is common for the solid oral drug product and the applicant's assessment of compatibility was deemed adequate.

None of the excipients used in the Fezolinetant Tablets are novel excipients. All the excipients except for (b) (4) and (b) (4) are compendial and meet the corresponding USP/NF requirements. The applicant also stated that none of the excipients are of human or animal origin.

The latest specification being assessed (submitted in eCTD #1 dated 06/22/2022) are presented in Table 1, page 8 in Dr. Ma's review. Dr. Ma determined the assessment to be adequate.

There is no specific degradation impurity listed in the specification. The proposed limit of NMT (b) (4) % for individual impurity is in line with ICH Q3B and it is acceptable. The total impurity is set to NMT (b) (4) % excluding the process impurities. Although the proposed limit exceeds the total limit recommended in MAPP 5017.2, this is acceptable considering the value is low.

The applicant proposed In vitro release specifications at (b) (4) % (Q) in 30 minutes. The Biopharmaceutics review has determined that this is adequate in terms of dissolution method and acceptance criteria.

The residual solvent statements in Module 3.2.P.4.4. for all excipients, demonstrate the amount of residual solvents is within the USP <467> limit. The potential residual solvents in drug substance are well controlled and (b) (4)

(b) (4)

This is acceptable.

The applicant conducted the nitrosamine impurities risk assessment on drug product including drug substance, excipients, manufacturing process and facilities. The assessment shows no risk for the presence of nitrosamine and nitrosating agents in fezolinetant tablets.

The drug product meets USP <232> Elemental Impurities requirement based on ICH option 1. Certificates of analysis for the three primary registration batches of fezolinetant, 45 mg (Batch# 20024, 20025 and 20026) all meet the corresponding specification.

The methods of Assay and Related substances by HPLC and Dissolution by HPLC are all developed and validated at (b) (4). These methods are transferred to the drug product manufacturing site Astellas Pharma Inc., (b) (4). The applicant provided a method transfer report, which meets all the acceptance criteria.

The Assay, Identity and Related Substances methods were developed in house and validated for specificity, linearity, quantitation limit, detection limit, accuracy, precision (repeatability and intermediate precision), range, robustness, and stability of solutions. Forced degradation studies were performed on fezolinetant tablets by acid, base, oxidation, thermal, photolytic stresses and (b) (4). Results showed that the product was susceptible to acidic, basic, and oxidative conditions.

The dissolution was validated for specificity, linearity, range, accuracy, method precision, intermediate precision, robustness, and stability of solution. The method was found to be suitable for its intended use.

The firm has provided elemental impurities risk assessment on potential sources and levels for the product of Fezolinetant Tablets. All the elemental impurities potentially presented in Fezolinetant Tablets, 45 mg strength, have been found to be below the control threshold (30% PDE) as defined in ICH Q3D. The elemental impurities risk assessment meets the requirements of ICH Q3D Option 1 and USP <232>, and no further controls are required for the proposed drug products.

The applicant proposed that the commercial container for Fezolinetant Tablets 45 mg is same as that that used for the primary registration batches. The bottle container is made of 30 cc white wide-mouth pharmaceutical round HDPE bottle with 28 mm child resistant (b) (4) cap and 1 g silica (b) (4) canister. The HDPE CRC bottle will contain a 30 or 90 count.

The applicant provided the statement of child-resistant package feature.

The firm has also provided Manufacturer's certificate of conformance (COC) or certificate of authorization (COA) and Engineering drawings for all components. The proposed container/closure systems comply with USP <661> and USP <671> requirements. The DMF for (b) (4) are all found to be acceptable. Table 3 presents the Stability Study.

Table 3: Stability Study

Container Closure System	Counts	Storage Condition	Data Provided (in Months)
45 mg strength 30 cc HDPE bottle with desiccant with HIS	30	25°C ± 2°C and 60% RH ± 5% RH	0, 3, 6, 9,12,18
	90	40°C ± 2°C and 75% RH ± 5% RH	0, 1, 3, 6
45 mg strength Al-Al blister		25°C ± 2°C and 60% RH ± 5% RH	0, 3, 6, 9,12,18
		40°C ± 2°C and 75% RH ± 5% RH	0, 1, 3, 6

Source: OPQ Primary Drug Product Review (Baoqing Ma, Ph.D.), **Table 8-2, page 13**

The shelf-life specification is the same as the release specification except for the assay.
Item Release Shelf Life.

Three primary batches of fezolinetant tablets 45 mg (Batch# 20024, 20025 and 20026) manufactured using three batches of drug substance (Batch#RS19002, RS19003 and RS19004) and packaged in HDPE bottle and Al-Al blister were charged on stability at accelerated condition (40±2°C and 75±5% RH) and long-term condition (25±2°C and 60±5% RH). The applicant does not intend to market the blister package and it will be made available for sample use only. Though not debossed, per 21 CFR 314.70(d)(2)(viii) [changes considered as a minor change which are annually reportable for an immediate release tablet] the three primary registration stability batches can be used as the primary batches.

The firm has provided *6-months accelerated* stability data at 40±2°C/75±5% RH, and *18-months long-term* stability data at 25±2°C/60±5% for all batches in the exhibit batch package container closures. Stability data for Description, (b) (4), Dissolution, Related Substances, Assay and Microbial limits were provided. All test parameters are within the proposed specification limits.

The applicant has also performed photostability study on one batch of drug product through direct light irradiation and dark control under ICH Q1B condition. *The drug product is stable and meets all specifications.*

The bulk stability data demonstrate that the bulk tablets packaged in (b) (4) are stable under warehouse conditions for at least (b) (4) months after manufacture.

On the basis of the stability presented in this application, *a tentative 30-month expiration dating period is proposed*, which will be confirmed by real-time room temperature stability data.

The recommended storage condition for Fezolinetant Tablets is “Store at 20°C to 25°C (68°F to 77°F) with excursions permitted from 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].”

The applicant commits to perform the on-going stability studies for the three primary batches and commercial bulk batches following the protocol. The firm commits to carry out stability at long term condition (25°C ± 2°C/60% ± 5%RH) and accelerated condition (40°C ± 2°C/75% ± 5%RH) for the first three commercial production batches in the proposed packaging configurations.

For a more detailed description of the characterization and analytical methodology for the drug substance, the reader is referred to the archived review of Dr. MA. Dr. Ma concludes, along with Dr. Shafiei concurrence, that the 505(b)(1) new drug application has provided sufficient CMC information to provide assurance regarding the identity, strength, purity, and quality of the drug product, Veozah.

Environmental Assessment

As noted above, the primary and secondary reviews of the applicant’s environmental assessments, were performed by Xiaoqin Wu, Ph.D. and James P. Laurenson, Ph.D., respectively.

The National Environmental Policy Act of 1969 (NEPA) requires Federal agencies to assess the environmental impact of their actions. The Food and Drug Administration (FDA) is required under NEPA to consider the environmental impact of approving certain drug product applications as an integral part of its regulatory process. In support of its application, Astellas prepared an environmental assessment (EA) for fezolinetant. This EA evaluates the potential environmental impact from the use and disposal of this drug product. FDA’s Center for Drug Evaluation and Research (CDER) OPQ has reviewed the Astellas’ EA as well as other information and has carefully considered the potential environmental impacts due to approval of this application. Based on its review of the entirety of this information, FDA has determined that approval of the present application is not expected to have a significant impact on the environment. Therefore, FDA is issuing a finding of no significant impact (FONSI), and thus an environmental impact statement will not be prepared.

For a more detailed description of the EA for NDA 216578, the reader is referred to the archived review of Dr. Wu. Dr. Wu concludes, along with Dr. Laurenson’s concurrence, that the 505(b)(1)

new drug application has provided sufficient CMC information to provide assurance that no significant adverse environmental impacts are expected from the approval of this NDA. Therefore, FONSI is recommended for this application.

Biopharmaceutics

The Biopharmaceutics review of Dr. Paudel (secondarily reviewed by Dr. Ghosh was focused on the review evaluation and acceptability of dissolution method and dissolution acceptance criteria, as well as, ridging of the various clinical trial formulation used in phase 1 and 2, phase 3 and the to-be-marketed formulations.

The proposed criteria as presented in Table 4 are aligned with the 2018 FDA guide on dissolution testing of immediate-release solid oral dosage forms containing high solubility drug substances. The in vitro dissolution method and acceptance criteria for the release of the drug substance, fezolinetant, from the tablets are deemed adequate.

Table 4: InVitro Dissolution method and Acceptance Criteria

USP Apparatus	Speed (RPMs)	Medium/Temperature	Volume (mL)	Acceptance criterion
Apparatus 1	100	0.1N HCl/37°C ± 0.5°C	500	Q= ^(b) ₍₄₎ % in 30 minutes

Source: OPQ Primary Biopharmaceutics Review (Paudel, Ph.D.), **Table, page 1**

The 505(b)(1) new drug application presented the results of 1) Trial 2693-CL-0009 which assessed the relative bioavailability (BA) of the table formulation used in the phase 3 trials with the capsule formulation used in phase 1 and 2 trials and 2) bioequivalence (BE) Trial 2693-CL-0010 which evaluated bioequivalence between the phase 3 tablets and the to-be-marketed tablets. Results of the latter were previously discussed on page 28 of this review under Drug Product Assessment.

Assessment of all in vivo BA and BE studies are under the purview of Office of Clinical Pharmacology and these assessments are also be addressed in this review (beginning on page X) under Clinical Pharmacology. Two minor adjustments were made to the formulation development from the phase 3 to the to-be marketed tablet. Compared to the phase 3 tablets, ^(b)₍₄₎

respectively. The second adjustment involves the tablet color shade. Comparative dissolution data between tablet formulation used in the phase 3 clinical trials and the to-be-marketed tablets showed more than 85% dissolution at 15 min in all three evaluated pH media (see also page 28 of this review under Drug Product Assessment).

For a more detailed description of the Biopharmaceutics evaluation for NDA 216578, the reader is referred to the archived review of Dr. Paudel. From Biopharmaceutics perspective, Dr. Paudel,

with the concurrence of Dr. Ghosh, recommends NDA 216578 for Veozah 45 mg tablets for APPROVAL.

Microbiological Controls (for Solid Dosage Form) Assessment

As indicated, the primary microbiological controls review was performed by Loqman Mohamed, Ph.D. with secondary review by Vaikunth Prabhu, Ph.D. A summation of this review is presented in Table 5.

Table 5: Assessment of Microbiological Controls (for Solid Dosage Form)

(b) (4)	
Testing methods adhere to USP<61>/<62>	Yes
Acceptance criteria adhere to USP <1111>	Yes
(b) (4)	
The post-approval stability protocol is adequate	No
Raw material specifications are in line with USP<1111> or otherwise justified	Yes
(b) (4)	
Hold times and time limits are justified with microbial limits data	Yes
Stability results for the exhibit batches are available and adequate	Yes
Microbiology Assessment: Adequate	

Source: OPQ Primary Microbiological Controls Review (Loqman Mohamed, Ph.D.), unnumbered table, page 38.

For a more detailed description of the Microbiology Assessment for NDA 216578, the reader is referred to the archived review of Dr. Mohamed. As indicated in the above table, Drs. Mohamed and Prabhu have concluded that microbiology assessment to support this NDA is Adequate.

Manufacturers and Facilities Inspections

As indicated, the manufacturers and facilities inspections primary and secondary reviews of the manufacturers and testing facilities were performed by Loqman Mohamed, Ph.D. and Vaikunth Prabhu, Ph.D., respectively. A high summation of this review is presented as follows:

Manufacturing Summary:

Facility Assessment Recommendation: *Adequate*

Process Assessment Recommendation: *Adequate*

Assessment Summary: *Adequate* per amendment dated October 20, 2022

The manufacturing process of fezolinetant tablets 30 mg and 45 mg includes (b) (4)

(b) (4) The intended commercial batch sizes for fezolinetant tablets (b) (4) 45 mg are (b) (4) kg. The firm is intending to only market only the 45mg strength. No proposed scale-up. API is highly soluble (b) (4). DP to be packaged into blister, and 30 and 90 count HDPE bottles with silica (b) (4) desiccant.

Amendments dated October 11, 2022, and October 20, 2022. The firm adequately addressed Process Information Requests. There are no further outstanding issues. There are no proposed facility changes. All proposed facilities currently have *GMP compliant status* and are approvable at this review stage. The reviewer is referred to Dr. Mohamed archived review for a more detailed description of Facility and Process Assessment.

The final evaluation of the manufacturing and testing facilities are presented in the following Table 6.

Table 6: Facilities Table

Facility name and address	FEI	Responsibilities and profile code(s)	Status
Astellas Pharma Inc. (b) (4)	(b) (4)	Drug product manufacturing and release testing Drug substance stability testing 356h Status: Pending TCM Profile acceptable (FACTS, (b) (4)). The firm appears to have experience with the proposed manufacturing process ((b) (4)), which were covered in most recent 704a4 Records Review in lieu of PAI for	Approve - Based on Previous History

		NDA- ^{NON-RESPONSIVE} , recommended for approval on ^{NON-RESPONSIVE} .	
	(b) (4)	Drug substance manufacturing, release testing and stability testing 356h Status: Pending CSN acceptable profile code (FACTS, ^{(b) (4)}). Last inspections (PAI on ^{(b) (4)}, NAI, and GMP inspection on ^{(b) (4)}, NAI). Used for: Development, registration, and Clinical studies	Approve - Based on Previous History
		Drug substance manufacturing, release testing and stability testing 356h Status: Pending CSN acceptable profile code (FACTS, ^{(b) (4)}). Most recent GMP inspection was NAI ^{(b) (4)}. Used for: DS Stability studies and for the development studies without clinical trials or toxicological studies.	Approve - Based on Previous History
		Finished product primary and secondary Packaging and Labeling 356h Status: Pending TCM profile is acceptable on FACTS (^{(b) (4)}). This is a primary and secondary packaging site. TCM profile is acceptable on FACTS (^{(b) (4)}). Most recent GMP inspection covered testing function but updated other profiles including TCM (^{(b) (4)}) and was classified as NAI. The previous drug inspection, ^{(b) (4)}, covered the Quality and Packaging and Labeling System and was classified NAI. No noted	Approve - Based on Previous History

		issues for the packaging operations.	
Astellas Pharma Europe B.V. Hogemaat 2, Meppel, -, Netherlands, 7942 JG	3002808518	Drug product stability testing 356h Status: Pending LCP LMN firm has only CSN acceptable profile per FACTS, 6/27/2014 (GMP inspection). But the most recent inspection was 704a4 records review (03/08/2021), which covered LCP and LMN profile codes and recommended approval.	Approve - Based on Previous History
(b) (4)		Storage of bulk drug product 356h Status: Pending NEC	No Evaluation Necessary
		Storage of bulk drug product 356h Status: Pending NEC	No Evaluation Necessary
		Drug substance primary stability testing Drug product primary stability testing 356h Status: Pending LCP LMN profile code CTL is acceptable (FACTS, (b) (4)). Most recent inspection was 704a4 records review which was completed on (b) (4). The records review covered analytical and microbiology laboratory with no observations and no items for follow-up.	Approve - Based on Previous History

Source: OPQ Primary Manufacturers and Facilities Inspections Review (Loqman Mohamed, Ph.D.), unnumbered table, page 5-7.

The Office of Pharmaceutical Manufacturing Assessment has made the overall recommendation of adequate for the facilities involved in this NDA application.

For a more detailed description of the manufacturing and testing facilities for NDA 216578, the reader is referred to the archived review of Dr. Mohamed. As discussed, Drs. Mohamed and

Prabhu have concluded that the facility assessment and the process assessment for this NDA are adequate.

CMC Labeling

The Carton Labeling was found to be inadequate. It must include the desiccant warning, “Do not eat.”

OPQ overall has concluded:

1. Astellis has provided sufficient CMC information in this 505(b)(1) NDA to assure the identity, strength, purity, and quality of the drug substance, fezolinetant and the drug product, Veozah (fezolinetant) Tablets, 45mg.
2. The Office of Pharmaceutical Manufacturing Assessment has made the overall recommendation of adequate for the facilities involved in this application.
3. The CMC recommended changes to the labeling have been communicated to the Astellas and final labeling pending the successful labeling negotiations with the applicant.
4. Based on the review of the applicant’s environmental assessment report, the environmental assessment review team has concluded that no significant adverse environmental impacts are expected from the approval of this NDA. Therefore, FONSI is recommended for this application.
5. The NDA is recommended for approval from the OPQ perspective pending successful labeling negotiations. The drug product expiration dating period of 30 months is recommended.

4. Nonclinical Pharmacology/Toxicology

The primary and the secondary Nonclinical Pharmacology and Toxicology (P/T) reviews of NDA 216578 were conducted by Miyun Tsai-Turton, Ph.D., M.S. and Andrea Benedict, Ph.D., respectively. Their review findings are summarized below.

In vivo Pharmacology Nonclinical Studies

Preclinical data in this 505(b)(1) NDA submission demonstrated that fezolinetant attenuated hot flash-like symptoms in a nonclinical model of postmenopausal persons, ovariectomized (OVX) rats. These in vivo studies demonstrated that OVX rats exhibited several typical menopause symptoms: hyperphagia, increased body weight, significantly decreased plasma estradiol levels, increased LH and FSH levels, and significantly increased tail skin temperature. Increased neuronal activity in the MnPO (median preoptic nucleus) hypothalamic neurons was also observed in these OVX rats. Repeated oral administration of fezolinetant in OVX rats *reduced hyperphagia and weight gain; reduced plasma LH levels, without affecting estradiol or FSH levels; and attenuated hot flash-like symptoms*. Fezolinetant also inhibited the activation of MnPO neurons. Additionally, in intact female rats and monkeys, fezolinetant was found to *lower the circulating sex hormones LH, estradiol, and progesterone, but not FSH or testosterone, demonstrating that antagonism of the NK3 receptor inhibits LH secretion in female animals with functioning ovaries*. Therefore, ***fezolinetant antagonism of the NK3 receptor appears to affect***

the downstream signaling of KNDy neurons to gonadotropin releasing hormone (GnRH) neurons, modulating the GnRH pulse frequency and consequently the release of LH.

Pharmacokinetic (PK) Nonclinical Studies

Preclinical data in this 505(b)(1) NDA submission demonstrated that fezolinetant was rapidly absorbed and widely distributed to the tissues. The bioavailability of fezolinetant was 91.9 to 115% in rats and 74.6-103% in monkeys. The highest levels of fezolinetant in tissues were associated with the *kidney* cortex, clitoris, uveal tract/retina, *adrenal gland* (cortex and medulla) and *liver*. *CYP1A2* is the major CYP isozyme implicated in the metabolism of fezolinetant. One oxidated metabolite (ES00259564) was detected in cryopreserved hepatocytes from rats, monkeys, and humans, *suggesting that human-specific fezolinetant metabolites were not formed. Fezolinetant and its metabolite were excreted in urine and feces.* Additionally, fezolinetant-derived components can be transferred to the infant tissues via breast milk.

Repeated Dose Toxicity Studies

Repeat dose toxicity studies were conducted in rats up to 26 weeks and in monkeys up to 39 weeks as follows:

- In a 26-week rat study (Study No 8331724), fezolinetant was administered orally by daily gavage to sexually mature female rats at a dose of 0 (vehicle), 30, 100, or 200 mg/kg. ***No adverse effects on in-life parameters, clinical pathology, or microscopic changes were noted.*** Uterine atrophy and epithelial mucification of the vagina and cervix, attributed to exaggerated pharmacological effects of fezolinetant, did not affect the general health of the animals, and were not adverse. The NOAEL was the high-dose of 200 mg/kg/day, with AUC₂₄ = 569000 ng•h/mL (148X MRHD of 45 mg with AUC₂₄ = 3855 ng•h/mL obtained from clinical Study 2693-PD-0010). This study was originally reviewed under IND 130277 SN 14 (2-year rat carcinogenicity SPA). The PT review can be found in DARRTS dated 12/05/17 under IND 130277.
- In a 39-week monkey study (Study No 8331280), fezolinetant was administered orally by daily gavage to sexually mature female monkeys at a dose of 0, 10, 25, or 40 mg/kg. High doses of fezolinetant resulted in weight loss and microscopic findings (hyperplasia of lymphocytes in lymph nodes, spleen, and lung, as well as perivascular inflammation in the kidney). Decreased platelet counts (at 40 mg/kg/day in the 39-week study) due to decreased production in bone marrow resulted in hemorrhage and regenerative anemia. This was recoverable. The NOAEL was the mid-dose of 25 mg/kg/day, with AUC₂₄ = 166000 ng•h/mL (43X MRHD). The PT review can be found in DARRTS dated 07/01/19 under IND 130277.

The Nonclinical Pharmacology/Toxicology review team concludes that there are no risks identified in a full battery of safety pharmacology studies with fezolinetant, as represented above.

Central Nervous System and Drug Dependency

The applicant conducted additional studies to investigate the potential for effects on seizure threshold and drug dependency. *Fezolinetant was found to have no potential to induce seizures*

in a 13-week oral study in rats at doses up to 200 mg/kg/day (>100X MRHD) *and did not induce physical dependency* in a 4-week oral study in rats up to 100 mg/kg/day (108X MRHD).

Genotoxicity Studies

Genotoxicity studies were conducted in vitro (AMES assay, up to 5000 µg/plate and chromosomal aberration assay in cultured human lymphocytes, up to 358.4 µg/mL = 1 mmol/L), and in vivo (rats, up to 300 mg/kg/day). *Fezolinetant had no potential to induce gene mutation and chromosomal aberrations in vitro and in vivo.*

The Pharmacology/Toxicology review team concludes that fezolinetant is not mutagenic based on a standard battery of in vitro and in vivo genotoxicity studies.

Carcinogenicity Studies

Carcinogenicity studies were done in rats and transgenic mice. The final study reports were presented at the October 25, 2022, Executive Carcinogenicity Assessment (ECAC) meeting and *both studies were considered negative*. Both ECAC meeting minutes and final study review are in DARRTS dated October 27, 2022, and October 28, 2022, respectively.

- In the 2-year carcinogenicity study in female rats (0, 10, 30, and 100 mg/kg/day for 104 weeks), *fezolinetant had increased incidences of benign follicular cell adenomas in the thyroid* (common tumor, by trend analysis only, $p = 0.0094$). Additionally, the combination of ovarian epithelial tumors (benign rete ovarii adenoma, benign tubulostromal adenoma, benign cystadenoma, and malignant carcinoma) was noted in the mid-dose group when compared to the vehicle control (p -value = 0.0132 for common or rare tumors), *without corresponding statistically significant dose response relationship regardless of the tumor classification* (rare or common). *Therefore, no toxicologically significant, drug-related tumors were identified in female rats.* At the high dose of 100 mg/kg/day, AUC₂₄ = 718000 ng•h/mL at Week 26 (186X MRHD).
- In the 6-month carcinogenicity study in transgenic mice (0, 50, 150, and 450 mg/kg/day) in male and female transgenic mice, *fezolinetant did not induce neoplasms*. the high dose of 450 mg/kg/day, AUC₂₄ = 183000 ng•h/mL at Week 26 (47X MRHD).

In response to the inquiry as to the existence of any preclinical evidence that might support that findings of an imbalance in malignancy in the POP2 safety population [representing all three phase 3 clinical trials (see Section 8 Safety of this review)] may represent a true signal for the risk of malignancy, Dr Benedict's January 27, 2023, review addendum discusses her review of preclinical literature references related to NK3R antagonist risk of malignancy. She notes:

- “Antagonists of the NK3R have been suggested to decrease LH and testosterone in a dose-dependent manner², which may reduce proliferative effects in the sex-steroid sensitive tissues.
- In a mouse model of bone invasion by human oral squamous cell carcinoma, a selective NK3R antagonist reduced the osteoclastic bone destruction associated with invasion of oral squamous cell carcinoma³. These findings suggested that selective NK3R antagonism suppressed oral squamous cell carcinoma tumorigenesis in the osteolytic bone destruction associated with oral squamous

cell carcinoma invasion. No references could be located that outlined any specific drug class-related risk of malignancy from treatment with NK3R antagonists.

*The Pharmacology/Toxicology Review concludes that **fezolinetant was found not to be carcinogenic**. Non-neoplastic histopathological findings in the ovary and vagina in mice, and ovary, uterus, cervix, and mammary gland in female rats were related to the pharmacologic action of fezolinetant.*

Review of the nonclinical mutagenicity and carcinogenicity studies conducted with fezolinetant did not indicate a potential risk or mechanism for drug-related genetic toxicity or tumorigenesis. Information from the published literature did not indicate an increased risk or any theoretical mechanism for a risk of malignancy with NK3R antagonism.

Based on the nonclinical information provided by the Applicant and available in the published literature, no biological mechanism was identified that indicated an increased risk of malignancy with fezolinetant or NK3R antagonism.

Reproductive and Developmental Toxicity Studies

These studies were conducted in rats and rabbits as follows:

- In the fertility rat study in female rats, *fezolinetant did not affect fertility at doses up to 100 mg/kg/day*, though there was altered estrous cyclicity and reduced reproductive organ weight, which were exaggerated pharmacological effects of fezolinetant.
- In the embryo-fetal development toxicity rat study (0, 25, 50, and 100 mg/kg/day by oral gavage from GD 6-17), *embryo-lethality was seen at a dose of 100 mg/kg/day*, with maternal AUC₂₄ = 494600 ng•h/mL (128X MRHD). *Surviving fetuses at this dose showed no teratogenic findings (no developmental variations or abnormalities)*. Litter loss was regarded as an exaggerated pharmacological effect of fezolinetant (e.g., ↓ LH levels (inhibiting LH surge), ↓ estradiol levels during the follicular phase), ↓ progesterone levels during the luteal phase). The NOAEL was 100 mg/kg/day for dams. The NOAEL was 50 mg/kg/day for embryo-fetal development (with maternal AUC₂₄ = 238700 ng•h/mL, 62X MRHD). The PT review can be found in DARRTS dated May 13, 2016, under IND 130277.
- In the embryo-fetal developmental toxicity rabbit study (0, 45, 75, and 125 mg/kg/day by oral gavage from GD 7-19), the pregnant animals showed reduced body weight gain and food consumption at doses of fezolinetant ≥ 45 mg/kg/day. At 125 mg/kg/day, with maternal AUC₂₄ = 670200 ng•h/mL (174X MRHD), abortion or total litter loss were observed and an increase in mean percentage postimplantation loss, as well as early resorption and low gravid uterine weights, were noted. At doses of 75 or 125 mg/kg/day, fezolinetant was associated with reduced fetal weights and a dose-dependent increase in the percentage of late resorptions. *There were no fetal malformations at doses up to 125 mg/kg per day*. No maternal NOAEL was identified as decreased body weight gains and food consumption were noted in all doses. The fetal NOAEL for embryo-fetal development in rabbits was 45 mg/kg/day (with maternal AUC₂₄ = 60600 ng•h/mL, 16X MRHD). The PT review can be found in DARRTS, dated May 13, 2016, under IND 130277.

- In the pre- and post-natal developmental toxicity rat study (0, 10, 30, and 100 mg/kg/day by oral gavage from GD6 to LD21), *delayed parturition and embryo-lethality were observed at 100 mg/kg/day* (with maternal AUC₂₄ = 788000 ng•h/mL, 204X MRHD). In addition, F1 males at 100 mg/kg per day showed decreases in mating and fertility associated with incomplete balanopreputial separation. However, F1 females did not show effects on either mating or fertility at any doses. The NOAEL for *maternal toxicity and embryotoxicity* was 30 mg/kg/day (AUC₂₄ = 140,000 ng•h/mL on LD 21, 36X MRHD), based on *delayed parturition and in utero embryo-lethality for 4 HD females*. The NOAEL for F1 generation development was 100 mg/kg/day (F1 females, AUC₂₄ = 788000 ng•h/mL on LD 21, 204X MRHD) and 10 mg/kg/day (F1 males, AUC₂₄ = 42500 ng•h/mL on LD 21, 11X MRHD), based on the changes in fertility mainly due to incomplete balanopreputial separation in MD and HD males.

The Pharmacology/Toxicology review team concludes that based on the above studies, it could be presumed that incorrect administration to a pregnant female could carry the risks of early pregnancy loss or delayed maturation of a male fetus. (b) (4)

However, given that the intended clinical population for fezolinetant is comprised of menopausal women, the risks to pregnancy and fetal development for this drug product are low.

For a more detailed presentation of the nonclinical findings, the reader is referred to Dr. Tsai-Turton's primary review archived in DARRTS on November 22, 2022, and Dr. Benedict's review archived in DARRTS on November 22, 2022. Overall, Drs. Tsai-Turton and Benedict conclude that the nonclinical data in the NDA application support the clinical safety of fezolinetant. There are no anticipated concerns for use of fezolinetant when used clinically in the intended patient population of women of non-childbearing potential for the proposed indication. From a Pharmacology/Toxicology perspective approval of fezolinetant is recommended for the treatment of moderate to severe vasomotor symptoms due to menopause.

5. Clinical Pharmacology

The reviewing team for the Office of Clinical Pharmacology (OCP) included Lin Zhou, Ph.D., Yaning Sun, Ph.D., Junshan Qiu, Ph.D., Jingyu (Jerry) Yu, Ph.D. Manuela Grimstein, Ph.D., Yuching Yang, Ph.D., and Yanhui Lu, Ph.D. Their review findings are summarized below.

General Clinical Pharmacology Considerations

Fezolinetant is a NK3 receptor antagonist that blocks neurokinin B (NKB) binding on the kisspeptin/neurokinin B/dynorphin (KNDy) neuron to modulate neuronal activity in the thermoregulatory center.

In healthy women, fezolinetant C_{max} and AUC increased proportionally over a dosage range from 20 and 60 mg once daily (0.44 to 1.33 times the approved recommended dosage). Steady-state plasma concentrations of fezolinetant were reached after two once-daily doses, with minimal fezolinetant accumulation.

Absorption

The median (range) time to reach fezolinetant C_{max} is 1.5 (1 to 4) hours in healthy women.

No clinically meaningful differences in fezolinetant pharmacokinetics were observed following administration with a high-calorie, high-fat meal.

Distribution

The mean apparent volume of distribution (V_z/F) of fezolinetant is 189 L. The plasma protein binding of fezolinetant is 51%. The blood-to-plasma ratio is 0.9.

Elimination

The apparent clearance at steady state of fezolinetant is 10.8 L/h. The mean terminal elimination half-life ($t_{1/2}$) of fezolinetant is 13.1 hours in healthy women. The effective half-life for a typical subject (70 kg, white, non-smoking female) is 9.6 hours.

Metabolism

Fezolinetant is primarily metabolized by CYP1A2 in humans to oxidized major metabolite ES259564. ES259564 is approximately 20-fold less potent against human NK3 receptor. The metabolite-to-parent ratio ranges from 0.7 to 1.8.

Excretion

Following oral administration, fezolinetant is mainly eliminated in urine (76.9%) and to a lesser extent in feces (14.7%). In urine, a mean of 1.1% of the administered fezolinetant dose was excreted unchanged and 61.7% of the administered dose was excreted as ES259564. In feces, about 0.1% of the administered fezolinetant dose was excreted unchanged and 14.6% of the administered dose was excreted as ES259564.

Food effect

Food effect study 2693-CL-0012 assessed the impact of a high-fat breakfast on fezolinetant pharmacokinetics following ingestion of a single 45 mg dose of fezolinetant (to-be-marketed formulation) in healthy female participants. The high-fat, high-calorie meal did not affect fezolinetant AUC_{inf} and AUC_{last} compared to AUC_{inf} and AUC_{last} obtained under fasted conditions. The high-fat, high-calorie meal decreased C_{max} by ~23% of fezolinetant and delayed the time to reach C_{max} by ~30 minutes. The decrease in exposure is not considered clinically relevant. The OCP review recommends that fezolinetant can be administered with or without food.

Intrinsic Factors Considerations

Renal impairment

Dedicated renal impairment Trial 2693-CL-0008 was a phase 1 open-label study, conducted in women x to x years of age, to investigate the effect of renal impairment on the pharmacokinetics, safety, and tolerability of fezolinetant. A total of 27 participating women, inclusive of 6 with mild renal impairment, 6 with moderate renal impairment, 5 with severe renal impairment, and 10 with normal renal function, were enrolled and received a single oral dose of 30 mg fezolinetant under fasted conditions. The following definitions were used for renal function status:

- Mild renal impairment – eGFR* 60 to < 90 mL/min per 1.73 m²
- Moderate renal impairment – eGFR 30 to < 60 mL/min per 1.73 m²

- Severe renal impairment – eGFR < 30 mL/min per 1.73 m² and not on hemodialysis (the protocol designated that at least 50% of participants should have had an eGFR of $\leq$ 20 mL/min per 1.73 m²)
- Normal renal function – eGFR $\leq$ 90 mL/min per 1.73 m²

*eGFR -

One participant with normal renal function withdrew on Day 3 during the investigational period, but agreed to participate in the end of study visit [ESV]; the participants data was excluded from the pharmacokinetic analysis but included in the safety analysis. This participant was replaced by a new participant with normal renal function.

Results of the statistical assessment of the effect of renal impairment on the PK of fezolinetant are provided in Table 35. These analyses used PK analysis set, which included all enrolled participants who received at least 1 dose of investigational product for which concentration data were available to facilitate derivation of at least 1 primary pharmacokinetic parameter. Note: Normal participants may have been enrolled to match more than 1 impaired participant in different impairment groups; these participants were not re-treated.

Table 7: Statistical Assessment of the Effect of Renal Impairment on Plasma Pharmacokinetics of Fezolinetant

Parameter	Comparison (Test/Reference)	Reference		Test		Geometric LS Mean Ratio (%)†	90% CI of Ratio (%)†
		n	Geometric LS Mean	n	Geometric LS Mean		
AUC _{inf} (h•ng/mL)	Mild/Normal to Match Mild	6	1980	5	1240	62.74	(34.48, 114.15)
	Moderate/Normal to Match Moderate	6	2240	5	1080	48.02	(31.95, 72.18)
	Severe/Normal to Match Severe	5	2150	3	2540	117.93	(60.13, 231.28)
AUC _{last} (h•ng/mL)	Mild/Normal to Match Mild	6	1830	6	1480	80.76	(43.05, 151.51)
	Moderate/Normal to Match Moderate	6	2000	6	1380	68.84	(40.12, 118.11)
	Severe/Normal to Match Severe	5	2240	5	2030	90.44	(55.14, 148.35)
C _{max} (ng/mL)	Mild/Normal to Match Mild	6	265	6	264	99.48	(75.35, 131.33)
	Moderate/Normal to Match Moderate	6	251	6	262	104.28	(78.28, 138.92)
	Severe/Normal to Match Severe	5	284	5	301	105.94	(81.86, 137.12)

Source: OCP Review Table 35, page 72 and NDA 216578 Trial Report 2693-CL-0008, Table 13

The OCP review concludes:

- Compared to respective normal renal function groups, severe renal impairment had marginal effects on fezolinetant's PK exposure (GMR: 118% for AUC_{inf}; 90% for AUC_{last}; and 106% for C_{max}; with all 90% CI including 100%).
- Compared to respective normal renal function groups, mild and moderate impairment groups had similar C_{max} but lower AUC_{last} (GMR: 81% for Mild; 69% for Moderate; with all 90% CI including 100%).

A total of 201 participants with normal renal function, 267 participants with mild renal function, and 7 participants with moderate renal impairment were enrolled in the phase 3 Trials 2693-CL-0301 and 2693-CL-0302. The steady-state AUCs of fezolinetant in participants with normal, mild, and moderate renal impairment from these two phase 3 studies were predicted based on a population PK analysis. The total exposure of fezolinetant in subjects with mild or moderate renal impairment was similar to the exposures in subjects with normal renal function. The mean (CV%) of population PK model-predicted steady-state AUCs (ng.hr/mL) were 4159 (45.4%), 4097 (41.8%), and 4061 (36.6%) for subjects with normal, mildly impaired, and moderately impaired renal functions after once daily dosing. In addition, creatine clearance was not identified as a statistically significant covariate for the clearance of fezolinetant.

Based on the totality of the renal impairment data from the dedicated renal impairment study and the population PK data, OCP reviewers recommend that *no dose adjustment of fezolinetant for mild or moderate renal impairment, but use of fezolinetant should be avoided in patients with severe renal impairment or end-stage renal disease.*

Hepatic impairment

Dedicated hepatic impairment Trial 2693-CL-0007, conducted in the U.S., was as an open-label, single oral dose study, in women 18 to 75 (inclusive) years of age, intended to investigate the effect of mild and moderate hepatic impairment on the pharmacokinetics, safety and tolerability of fezolinetant. A total of 26 participants, inclusive of 8 women with mild hepatic impairment, 8 women with moderate hepatic impairment and 10 women with normal hepatic function were enrolled and received a single oral dose of 30 mg fezolinetant under fasting conditions. Healthy participants with normal hepatic function were matched (1:1) to the participants with mild and/or moderate hepatic impairment by age (± 10 years), BMI ($\pm 20\%$), race and sex. Women with severe hepatic impairment were not evaluated.

The following definitions were used for hepatic function status:

- Mild hepatic impairment - Child-Pugh* classification Class A, score 5 or 6
- Moderate hepatic impairment - Child-Pugh classification Class B, score 7 to 9
- Normal hepatic function

*Child-Pugh

Eligible participants were admitted to the clinical unit on day -1 and were residential for a single period of 6 days/5 nights. The study was conducted at 4 study sites in the US. Eligible participants were admitted to the clinical unit on day -1 and were residential for a single period of 6 days/5 nights. Participants were to remain semi-recumbent for 4 hours post their fezolinetant

dose. Standard safety and tolerability assessments were made. The following 96-hour in-house blood and urine sampling for pharmacokinetic evaluation were collected postdose.

- Blood samples for fezolinetant pharmacokinetics and ES259564 (fezolinetant metabolite) concentrations were collected predose on day 1 and at the following postdose time points on day 1: 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, 48, 72 and 96 hour(s).
- Urine samples for fezolinetant pharmacokinetics and ES259564 (fezolinetant metabolite) concentrations were collected predose on day 1 and at the following postdose intervals on day 1: 0 to 4, 4 to 8, 8 to 12, 12 to 24, 24 to 36, 36 to 48, 48 to 72 and 72 to 96 hours.

All participants completed the treatment, the investigational period, and the follow-up as per the protocol. One participant in the normal hepatic function group (who was matched to both a participant with mild hepatic impairment and a participant with moderate hepatic impairment) completed the study, was excluded from the pharmacokinetic analysis due to excluded concomitant medication use and was replaced by a new participant in the normal hepatic function group. A summary of the PK parameters of fezolinetant by hepatic function group are presented in Table 8 and results of the statistical assessment of the effect of hepatic impairment on the PK of fezolinetant are provided in Table 9.

Table 8. Plasma Pharmacokinetic Parameters of Fezolinetant by Hepatic Function Group

Parameter Category/Statistics	Hepatic Function Group			
	Mild	Normal to Match Mild	Moderate	Normal to Match Moderate
AUC_{inf} (h•ng/mL)				
n	8	8	8	8
Mean (SD)	3570 (1140)	2300 (793)	4810 (2080)	2340 (797)
%CV	31.9	34.4	43.3	34.1
Median	3740	2230	4390	2370
Min, Max	1870, 4960	1260, 3360	2110, 7290	1260, 3360
AUC_{last} (h•ng/mL)				
n	8	8	8	8
Mean (SD)	3530 (1130)	2280 (785)	4680 (1980)	2320 (789)
%CV	31.9	34.4	42.3	34.1
Median	3710	2210	4340	2350
Min, Max	1840, 4900	1250, 3330	2040, 7010	1250, 3330
C_{max} (ng/mL)				
n	8	8	8	8
Mean (SD)	408 (121)	358 (65.7)	323 (55.8)	384 (81.7)
%CV	29.5	18.3	17.3	21.3
Median	413	356	309	401
Min, Max	276, 623	272, 435	270, 436	272, 515
CL/F (L/h)				
n	8	8	8	8
Mean (SD)	9.48 (3.97)	14.7 (5.73)	7.56 (3.70)	14.5 (5.81)
%CV	41.9	39.0	48.9	40.1
Median	8.02	13.5	6.94	12.7
Min, Max	6.05, 16.0	8.94, 23.8	4.12, 14.2	8.94, 23.8
V_z/F (L)				
n	8	8	8	8
Mean (SD)	158 (31.5)	211 (70.0)	226 (188)	231 (84.6)
%CV	19.9	33.1	83.0	36.6
Median	154	216	147	243
Min, Max	113, 204	104, 299	103, 651	104, 351
t_g (h)				
n	8	8	8	8
Mean (SD)	12.7 (3.84)	10.8 (5.01)	19.3 (6.13)	12.2 (6.06)
%CV	30.1	46.2	31.8	49.8
Median	14.3	9.31	17.6	9.90
Min, Max	6.77, 17.6	6.82, 21.5	13.5, 31.7	6.82, 21.5

Source: OCP review **Table 31, page 65** and NDA 216578, Trial 2693-CL-0007 Report, **Table 11**.

Table 9: Statistical Assessment of the Effect of Hepatic Impairment on the Plasma Pharmacokinetics of Fezolinetant

Parameter	Comparison (Test/Reference)	Reference		Test		Geometric LS Mean Ratio (%) [†]	90% CI of Ratio (%) [†]
		n	Geometric LS Mean	n	Geometric LS Mean		
AUC_{inf} (h•ng/mL)	Mild/Normal to Match Mild	8	2170	8	3380	155.89	(108.04, 224.92)
	Moderate/Normal to Match Moderate	8	1960	8	3850	196.11	(131.64, 292.15)
AUC_{last} (h•ng/mL)	Mild/Normal to Match Mild	8	2150	8	3350	155.82	(108.01, 224.80)
	Moderate/Normal to Match Moderate	8	1940	8	3750	193.63	(130.53, 287.23)
C_{max} (ng/mL)	Mild/Normal to Match Mild	8	336	8	413	122.72	(100.40, 149.99)
	Moderate/Normal to Match Moderate	8	429	8	366	85.14	(73.94, 98.05)

Source: **Table 32, page 66** and NDA 216578, Trial 2693-CL-0007 Report, Table 12.

After a single oral dose of 30 mg fezolinetant in the dedicated hepatic impairment study, when compared to their respective normal hepatic function groups the mild hepatic impairment group had an approximate 56% increase in AUCs and 23% increase in C_{max} of fezolinetant. Dosing patients with mild hepatic impairment with 45 mg daily of fezolinetant may lead to a ~50% higher exposure than that evaluated in phase 3 studies.

After a single oral dose of 30 mg fezolinetant in the dedicated hepatic impairment study, when compared to their respective normal hepatic function groups the moderate hepatic impairment group had ~95% increase in AUCs and 15% decrease in C_{max} of fezolinetant.

Each of the three phase 3 trials (2693-CL-0301, 2693-CL-0302 and 2693-CL-0304) did include enrollment criteria based on Child-Pugh categorization for screening. In response to an Agency Information Request, the applicant stated that “While not captured as Child-Pugh score, review of the components of the score does not support presence of chronic hepatic impairment as defined by Child-Pugh categories, and participants with chronic hepatic impairment were excluded from the study.” Therefore, there are no clinical data to support a safe clinical use of fezolinetant in patients with severe, moderate, or mild hepatic impairment.

Based on the overall assessment from the dedicated hepatic impairment trial and lack of data to support safe use in the phase 3 trials, the OCP review recommends that women with mild, moderate, and severe hepatic impairment avoid the use of 45 mg fezolinetant. Labeling will specify that use of fezolinetant is contraindicated in women with cirrhosis.

Drug-Drug Interactions

In a dedicated DDI study, concomitant use of fluvoxamine (a strong CYP1A2 inhibitor) resulted in a 9.4-fold increase in fezolinetant AUC_{inf} and 1.8-fold increase in C_{max}. The applicant did not conduct a dedicated DDI study to evaluate the impact of weak or moderate CYP1A2 inhibitors. Instead, they used a physiological-based pharmacokinetic (PBPK) approach to predict the magnitude of change in fezolinetant exposure with concomitant use of weak or moderate CYP1A2 inhibitors. The predicted results are shown in Table 10.

Table 10: Physiological-Based Pharmacokinetic (PBPK) Predicted C_{max} and AUC Geometric Mean Ratios (GMR) for Fezolinetant in the Presence of CYP1A2 Inhibitors.

Co-administration treatment		PBPK predicted fezolinetant GMR	
		C _{max}	AUC _{inf}
Weak CYP1A2 inhibitor	Cimetidine 300 mg every 6 hours	1.3	2.0
	Cimetidine 400 mg BID	1.4	1.6
Moderate CYP1A2 inhibitor	Mexiletine 400 mg every 8 hours	1.4	4.6

Source: OCP Review **Table 1, page 16** and NDA 216578, Table 3 in Appendix 4.4 **PBPK** review.

Using a PBPK approach, weak CYP1A2 inhibitors are predicted to increase fezolinetant exposure by *1.6- to 2-fold*. In the phase 3 studies, 22 subjects received 45 mg fezolinetant had concomitant use of weak CYP1A2 inhibitors. Although treatment emergent adverse events (TEAEs) in these subjects were generally mild and resolved, the number of subjects with concomitant use of weak CYP1A2 inhibitors is relatively small.

The OCP reviews concludes that given the predicted *60% to 100%* increase in exposure with concomitant use of weak CYP1A2 inhibitors and limited safety data from phase 3 studies, that patients *avoid* the concomitant use of 45 mg once daily fezolinetant with weak CYP1A2 inhibitors. Moderate and strong CYP1A2 inhibitor were predicted to lead to 4.6- (based on PBPK model) and 9.4 -fold (based on a dedicated DDI study) increase in fezolinetant AUC. There are no clinical data to support such a high exposure in postmenopausal women. Therefore, patients should *avoid* the concomitant use of moderate and strong inhibitors of CYP1A2 with fezolinetant.

Demographics

Race

African American/Black race was identified as a predictive covariate on central volume of distribution, but not a statistically significant covariate of clearance. Women who self-identified as African American were also predicted to have a small increase in central volume of distribution resulting in a small (6.6%) reduction in C_{max} compared to women who did not self-identify as African American. The OCP review does not recommend dose adjustment based on race.

Age

Studies designed to assess the effect of age on fezolinetant PK have not been conducted to date. A population PK model including female participants ranging from 19 to 65 years of age showed no trends between age and PK parameters. The OCP review did not recommend any dose-adjustments based on age within this age range. No pediatric participants have been studied with fezolinetant. Therefore, we recommend no dose adjustment based on age.

Weight

In a population PK analysis (Report 2693-PK-0010), body weight was identified as a predictive covariate on central volume of distribution, but not a statistically significant covariate of clearance. Participants weighing 100 kg were predicted to have a 17.2% lower fezolinetant C_{max} than participants with a typical 75 kg weight. Participants weighing 55 kg were predicted to have a 25.6% higher fezolinetant C_{max} than participants with a typical 75 kg weight. The OCP review did not recommend any dose-adjustments based on body weight.

Bridging of Clinical Trial Formulations and the To-Be-Marketed Formulation

Fezolinetant was initially developed as immediate-release, hard gelatin capsules for oral administration in 3, 10, 15, 30, 60, 90, 120 and 180 mg strengths. This formulation was used in phase 1 and phase 2 trials. For the phase 3 clinical development (including some phase 1 trials which were conducted in parallel), the applicant developed an immediate-release tablet formulation (15, 30 and 120 mg dose strengths) for oral administration. The composition of the phase 3 tablet is proportionally similar among the dose strengths; the 15 mg and 30 mg strength tablets were used in the phase 3 trials. The phase 3 tablet formulation was used in special population and drug-drug interaction studies to provide support for labeling claims.

The applicant conducted Trial 2693-CL-0009 to assess the relative bioavailability of a single dose of 120 mg fezolinetant tablet (test formulation) compared to a single dose of 120 mg fezolinetant capsule (reference formulation) under fasting conditions in healthy postmenopausal female participants. Trial 2693-CL-0009 was a randomized, open-label, 2-period, 2-sequence, single dose crossover study conducted in 16 healthy postmenopausal female subjects. Each subject participated in 2 treatment periods separated by a washout of 4 days between study drug administrations in each period. Subjects were randomized to 1 of 2 sequences [Sequence 1 (8 participants completed Sequence A {120 mg tablet (new formulation)}) and after the 4-day washout period crossed over and completed Sequence B {120 mg capsule (reference formulation)}; Sequence 2 (8 participants completed Sequence B and after the 4-day washout period crossed over and completed Sequence A)]. Pharmacokinetic samples were collected predose on day 1 of each period and at multiple time points postdose (i.e., 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36 and 48 hours).

All 16 of the randomized healthy postmenopausal female subjects completed the trial. Findings from this relative bioavailability trial are presented in Tables 11 (pharmacokinetic parameters) and 12 (bioequivalence assessment).

Table 11: Trial 2693-CL-0009 - Presentation of Plasma Pharmacokinetic Parameters of Fezolinetant by Formulation

Parameter Category/Statistics	Fezolinetant 120 mg	
	Tablet n = 16	Capsule n = 16
AUCinf (ng·h/mL)		
Mean (SD)	7600 (2010)	7070 (1950)
%CV	26.5	27.6
Median	7450	6660
Min - Max	4260 – 13,300	3790 – 12,100
AUClast (ng·h/mL)		
Mean (SD)	7530 (1910)	6950 (1830)
%CV	25.4	26.3
Median	7400	6580
Min - Max	4240 – 12,700	3750 – 11,500
Cmax (ng/mL)		
Mean (SD)	1190 (190)	983 (231)
%CV	16.0	23.5
Median	1200	929
Min - Max	843 - 1650	632 - 1390
tmax (h)		
Median	1.03	1.50
Min - Max	0.500 - 3.00	0.500 - 3.00
CL/F (L/h)		
Range	9.05 - 28.2	9.91 - 31.7
VZ/F (L)		
Range	119 - 502	151 - 605

Abbreviations: CV = coefficient of variation; Max = maximum; Min = minimum; SD = standard deviation.
Source: OCP primary review **Table 5, page 24** and NDA 216578, Trial Report 2693-CL-0009, **End-of-Text Table 12.4.2**

Table 12: Trial 2693-CL-0009 - Statistical Assessment¹ of Relative Bioavailability of Fezolinetant

Parameter	Fezolinetant 120 mg				Geometric LS Mean Ratio (%)†	90% CI of Ratio†
	Capsule		Tablet			
	n	Geometric LS Mean	n	Geometric LS Mean		
AUCinf (ng·h/mL)	16	6840	16	7370	107.80	(100.88, 115.21)
AUClast (ng·h/mL)	16	6730	16	7320	108.74	(101.86, 116.09)
Cmax (ng/mL)	16	957	16	1170	122.51	(110.43, 135.92)

¹ Included all randomized participants who took at least 1 dose of study drug for which concentration data were available to facilitate derivation of at least 1 primary pharmacokinetic parameter. Assessment based on an analysis of variance performed on natural logarithmic-transformed parameters with formulation and period as fixed effects and participant as a random effect.

† Ratios and confidence limits were back-transformed to raw scale and values are expressed as percentages.

Abbreviations: CI = confidence interval; LS = least squares

Source: OCP primary review **Table 5, page 24** and NDA 216578, Trial Report 2693-CL-0009, **End-of-Text Table 12.4.3.**

The OCP review concluded that that following a single dose administration, the results demonstrate that geometric LS means of AUCinf, AUClast and Cmax of tablet formulation increased approximately 8%, 9% and 23% respectively, relative to capsule formulation. While the 90% CI of Cmax (101-136%) exceeds the BE criteria of 80-125% criteria, the 90% CI of AUCinf and AUClast are contained within the criteria of 80-125% for bioequivalence.

The applicant conducted Trial 2693-CL-0010 to assess the bioequivalence of a single dose of the to-be-marketed drug product formulation of fezolinetant (Test Formulation) compared to a single dose of the phase 3 formulation of fezolinetant (Reference Formulation). Trial 2693-CL-0010 was a randomized, open-label, 2-period, 2-sequence, single dose crossover trial conducted in healthy female subjects. Each subject participated in 2 treatment periods separated by a washout of at least 5 days between investigational product (IP) administrations in each period. Participants received a single oral dose of 45 mg fezolinetant to-be-marketed formulation (test formulation) or one 30 mg and one 15 mg fezolinetant phase 3 formulation (reference formulation) under fasting conditions on day 1 of each period. Subjects were randomized to 1 of 2 sequences. Each subject participated in 2 treatment periods separated by a washout of 5 days between study drug administrations in each period. Subjects were randomized to 1 of 2 sequences [Sequence 1 (11 participants completed Sequence A {one 45 mg fezolinetant to-be-marketed tablet (test formulation)} and after the 5-day washout period crossed over and completed Sequence B {45 mg fezolinetant comprising one 30 mg and one 15 mg fezolinetant phase 3 tablet (reference formulation)}); Sequence 2 (11 participants completed Sequence B and after the 5-day washout period crossed over and completed Sequence A)]. Pharmacokinetic samples were collected predose on day 1 of each period and at multiple time points postdose (i.e., 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16, 24, 36, 48 and 72 hours).

In the current BE study (2693-CL-0010), no significant protocol deviations were identified. The risk of compromised data integrity is low

All 22 of the randomized healthy postmenopausal female subjects completed the trial and their data were included in the analyses of safety and PK. A request of routine inspection for the clinical site of the BE study (PAREXEL Early Phase Clinical, Baltimore, MD) was sent to Office of Study Integrity and Surveillance (OSIS). Inspection of the site was not done because of insufficient time for inspection to be completed for the given goal date. OSIS reported that the site was inspected in October 2018 under another NDA. After review of the inspection findings, OSIS concluded that data from the reviewed study were reliable. No significant protocol deviations were identified. The risk of compromised data integrity is low.

Findings from this relative bioavailability trial are presented in Tables 13 (pharmacokinetic parameters) and 14 (bioequivalence assessment).

Table 13 Fezolinetant pharmacokinetic parameters of 45 mg to-be-marketed tablet (test formulation) and Phase 3 tablets [30 mg + 15 mg] (reference formulation)

Fezolinetant Parameter Category/Statistics	Fezolinetant 45 mg (to-be-marketed tablet)	Fezolinetant 45 mg (30 mg + 15 mg phase 3 tablets)
AUCinf (ng·h/mL)	n=14 [§]	n=14 [§]
Mean	3840	3960
%CV	25.0	24.4
Median	3430	4160
Min - Max	2670 – 5230	2080 – 5050
AUClast (ng·h/mL)	n=22	n=21
Mean	3220	3230
%CV	35.7	39.8
Median	2980	3140
Min - Max	1310– 5200	1220 – 5000
Cmax (ng/mL)	n=22	n=21
Mean	506	527
%CV	31.0	46.0
Median	488	438
Min - Max	222 - 900	246 - 1200
t _{1/2} (h)	n=14 [§]	n=14 [§]
Mean	13.1	13.4
%CV	34.8	29.4
Median	12.2	12.4
Min - Max	6.92-24	7.88-22.4
t _{max} (h)	n=22	n=21
Median	1.50	1.50
Min - Max	0.483- 4.02	0.483- 4.02
CL/F (L/h)	n=14 [§]	n=14 [§]
Range	8.60- 16.8	8.91- 21.6
VZ/F (L)	n=14 [§]	n=14 [§]
Range	137 - 544	131 - 408

§ AUCinf, CL/F and t_{1/2} values from 7 participants were not reported and thus not included in the statistical assessment due to undefined elimination phase.

Source: OCP primary review **Table 8, page 26** and NDA 216578, Trial Report 2693-CL-0010, **End-of-Text Table 9.4.2.1.**

Table 14 Statistical Assessment of Bioequivalence for Fezolinetant

Parameter	Treatment B		Treatment A		Geometric LS Mean Ratio [†] (%)	90% CI of Ratio [†]	Geometric Intra-subject %CV
	n	Geometric LS Mean	n	Geometric LS Mean			
AUClast (h·ng/mL)	21 [‡]	2950	22	3010	102.17	(96.53, 108.15)	10.7
AUCinf (h·ng/mL)	14 [§]	3720	14 [‡]	3680	99.00	(92.45, 106.01)	9.3
Cmax (ng/mL)	21 [‡]	488	22	483	99.12	(85.54, 114.87)	28.3

Treatment A: one 45 mg fezolinetant to-be-marketed tablet (test formulation); Treatment B: 45 mg fezolinetant dose consisting of one 30 mg and one 15 mg fezolinetant phase 3 tablets (reference)

formulation); CI: confidence interval; CV: coefficient of variation; IP: investigational product; LS: least squares.

Assessment based on an analysis of variance performed on natural logarithmic-transformed parameters with period and treatment as fixed effects and participants as a random effect.

The pharmacokinetic analysis set comprised all randomized participants who received at least 1 dose of IP for which concentration data were available to facilitate derivation of at least 1 primary pharmacokinetic parameter.

† Ratios and confidence limits were transformed back to raw scale and values are expressed as percentages.

‡ One participant (treatment sequence AB) who received treatment B had concentrations that were below the level of quantification on all sample timepoints pre- and postdose for both fezolinetant and ES259564. This participant was excluded from the summary and parameter calculations.

§ AUCinf values from 7 participants were not reported and thus not included in the statistical assessment due to undefined elimination phase. AUClast including all evaluable participants, as well as AUCinf excluding these 7 participants, provided consistent bioequivalence results.

Source: OCP primary review **Table 10, page 28** and NDA 216578, Trial Report 2693-CL-0010, **End-of-Text Table 9.4.3.1**

The Office of Clinical Pharmacology concluded that the test formulation (45 mg fezolinetant to-be-marketed tablet) is bioequivalent to the reference formulation (45 mg fezolinetant comprising one 30 mg and one 15 mg fezolinetant phase 3 tablets).

For more detailed coverage of all of the above noted OCP review considerations as well as any additional discussion clinical pharmacology concerns, the reader is encouraged to refer to the OCP Review, archived in DARRTS on November 23, 2022.

Overall, The Office of Clinical Pharmacology, Division of Cardiometabolic and Endocrine Pharmacology, has reviewed the information contained in NDA 216578 and recommends approval of this NDA pending successful labeling negotiation.

6. Clinical Microbiology

Not applicable to the review of this NDA submission

7. Clinical/Statistical- Efficacy

Review of the data included in the 505(b)(1) NDA application intended to provide substantial evidence for the effectiveness of Veozah were reviewed by Theresa H van der Vlugt, M.D., M.P.H (clinical reviewer) and Juan Vivar, Ph.D. (statistical reviewer). The review that follows is meant to be a summary of the major efficacy information from the clinical efficacy and statistical reviews and to present my own conclusions about the evidence submitted in support of effectiveness under the proposed conditions of use. This review is not meant to replicate the clinical and statistical reviews. For a more detailed discussion of the efficacy findings, the reader is referred to Dr. Van der Vlugt's (clinical) review, archived November 28, 2022, and Dr. Vivar (statistical) review, archived November 21, 2022.

Design and Conduct of the Phase 3 Efficacy Trials

Two independent, confirmatory, phase 3 efficacy and safety trials, Trial 2693-CL-0301 and Trial 2693-CL-0302, provide the data for consideration regarding the efficacy of fezolinetant oral tablets, 45 mg, for the treatment of moderate to severe vasomotor symptoms (VMS), due to menopause.

The original protocols for Trials 2693-CL-0301 and 2693-CL-0302 were submitted May 30, 2019 (Version 1.0, dated January 28, 2019). Overall, three (3) protocol amendments were submitted for each trial:

1. Amendment 1 (Version 2, dated May 17, 2019)
2. Amendment 1 (Version 2.1, dated December 5, 2019)
3. Amendment 2 (Version 3.0, dated July 1, 2020).

The Clinical Trial Reports for Trial 2693-CL-0301 and Trial 2693-CL-0302, included in the NDA application, are dated February 24, 2022, and February 23, 2022, respectively.

Per the NDA application, the impact of the COVID-19 pandemic was minimal and there was no impact on participant safety. In addition, there does not appear to have been any impact on the integrity and interpretation of results due to the COVID-19 pandemic. The mechanism of missing data due to COVID-19 was assumed to be missing at random (MAR).

Trial 2693-CL-0301 and Trial 2693-CL-0302 were identical in design. They had the same trial objectives, efficacy endpoints, safety endpoints, enrollment criteria, trial procedures and evaluations, and statistical analysis plan. Each trial evaluated a 30-mg dosage strength and a 45 mg dosage strength. The applicant is seeking marketing approval for only the 45 mg dosage strength. Each of these two primary phase 3 trials were 52-weeks in total duration and included an initial 12-week placebo-controlled period, in which efficacy data was collected, followed by a 40-week extension period of fezolinetant only treatment to assess chronic exposure and long-term safety.

Participants initially randomized to placebo in the first 12-weeks, who agreed to continued participation in the 40-week extension period, were re-randomized to fezolinetant for an additional 40-weeks. Participants initially randomized to 30 mg or 45 mg fezolinetant in the first 12-weeks, remained on their assigned treatments if they agreed to continue participation in the 40-weeks extension period. Both Trial 2693-CL-0301 and Trial 2693-CL-0302 were conducted in the U.S., Canada, and Europe.

The primary efficacy objectives of both Trial 2693-CL-0301 and Trial 2693-CL-0302 were to evaluate the efficacy of 30 mg or 45 mg fezolinetant versus placebo on the frequency and severity of moderate to severe vasomotor symptoms during the first 12-weeks of treatment. The 40-week uncontrolled fezolinetant treatment extension period intended to assess the chronic use and long-term safety of fezolinetant. Trials 2693-CL-0301 and 2693-CL-0302 were designed as randomized, double-blind, placebo-controlled, and parallel group (placebo, 30 mg fezolinetant, and 45 mg fezolinetant) trials for the first 12-weeks of the trial.

The protocol defined primary efficacy objectives of both trials were to be met by evaluation of

four co-primary endpoints:

- Mean change in the frequency of moderate to severe vasomotor symptoms from baseline to Week 4.
- Mean change in the frequency of moderate to severe vasomotor symptoms from baseline to Week 12.
- Mean change in the severity of moderate to severe vasomotor symptoms from baseline to Week 4.
- Mean change in the severity of moderate to severe vasomotor symptoms from baseline to Week 12.

The protocol for each trial defined numerous secondary endpoints including:

- Mean change in the frequency of moderate to severe vasomotor symptoms from baseline to each week up to Week 12.
- Mean percent reduction in the frequency of moderate to severe vasomotor symptoms from baseline to each week up to Week 12.
- Mean change in the frequency of mild, moderate to severe vasomotor symptoms from baseline to each week up to Week 12.
- Percent reduction $\geq 50\%$ and at 100% in the frequency of moderate to severe vasomotor symptoms from baseline to each week up to Week 12.
- Mean and mean change from baseline in the daily frequency of moderate to severe vasomotor symptoms for the first week
- Mean percent reduction in the frequency of mild, moderate to severe vasomotor symptoms from baseline to each week up to Week 12.
- Percent reduction $\geq 75\%$ and $\geq 90\%$ in the frequency of moderate to severe vasomotor symptoms from baseline to each week up to Week 12 (VMS responder).
- Percent reduction $\geq 50\%$, $\geq 75\%$, $\geq 90\%$ and at 100% in the frequency of mild, moderate to severe vasomotor symptoms from baseline to each week up to Week 12 (VMS responder).
- Mean change in the severity of moderate to severe vasomotor symptoms from baseline to each week up to Week 12.
- Mean change in the severity of moderate to severe vasomotor symptoms from baseline to each week up to Week 12 (excluding mild events postbaseline).
- Mean change in the severity of mild, moderate to severe vasomotor symptoms from baseline to each week up to Week 12.
- Score on the Patient Global Impression of Change in Vasomotor Symptoms (PGI-C vasomotor symptoms) at each visit.
- Mean change in the frequency of moderate to severe vasomotor symptoms from baseline to Week 24.*
- Mean change in the severity of moderate to severe vasomotor symptoms from baseline to Week 24.*
- Mean change in the frequency and severity of moderate to severe vasomotor symptoms from baseline to each visit in the active treatment extension period and the follow-up visit.*

- Mean change in the Patient-reported Outcomes Measurement Information System Sleep Disturbance – Short Form 8b (PROMIS SD SF 8b) total score from baseline to Week 12.
- Mean change on the PROMIS SD SF 8b total score from baseline to each visit.
- Mean change on the Patient-reported Outcomes Measurement Information System Sleep Related Impairment – Short Form 8a (PROMIS SRI SF 8a) total score from baseline to each visit.
- Score on Patient Global Impression of Severity in Sleep Disturbance Patient Global Impression of Severity in Sleep Disturbance (PGI-S SD) at each visit.
- Score on Patient Global Impression of Change in Sleep Disturbance (PGI-C SD) at each visit.
- Mean change on the Menopause-Specific Quality of Life (MENQOL) total score from baseline to each visit.
- Mean change on the MENQOL domain scores from baseline to each visit.
- Mean change on the Euro-Qol 5D-5L (EQ-5D-5L) total score and Visual Analog Scale (VAS) from baseline to each visit.
- Mean change on the Work Productivity and Activity Impairment questionnaire specific to vasomotor symptoms (WPAI-VMS) domain scores from baseline to each visit.
- Change in serum concentrations of sex hormones and sex hormone binding globulin (SHBG) from baseline to each visit.
- Mean change in serum concentrations of bone-specific alkaline phosphatase (BSAP), procollagen type 1 amino-terminal propeptide (P1NP) and carboxy-terminal telopeptide of type I collagen (CTX) from baseline to each visit.
- Plasma concentrations of fezolinetant and metabolite ES259564 at prespecified time points.

*Per the NDA application, assessments after the 12-week placebo-controlled period were descriptive only because there was no placebo control.

The applicant was advised on numerous occasions during clinical development (see Section 2 Background of this review) that results of the proposed secondary and exploratory objectives/endpoints in clinical Trials 2693-CL-0301 and 2693-CL-0302 (b) (4)

The trial population consisted of hysterectomized and non-hysterectomized postmenopausal women who met the major trial enrollment criteria, including though not limited to:

1. Can provide written informed consent and is able and willing to complete the study procedures
2. ≥ 40 years of age and ≤ 65 years of age at the screening visit
3. Body mass index (BMI) ≥ 18 kg/m² and ≤ 38 kg/m²
4. Confirmed as menopausal per one of the following criteria at the screening visit:
 - Spontaneous amenorrhea for ≥ 12 consecutive months
 - Spontaneous amenorrhea for ≥ 6 months with FSH > 40 IU/L or
 - Had a bilateral oophorectomy ≥ 6 weeks prior to the screening visit.

5. Seeking treatment for relief for moderate to severe vasomotor symptoms, due to menopause and exhibiting a minimum average of *7 to 8 moderate to severe hot flashes per day*, or *50 to 60 per week* within 10 days prior to randomization
6. Acceptable findings from a TVU assessment at screening (i.e., visualization of the full length of endometrial cavity and no clinically significant findings)
7. No disordered proliferative endometrium, endometrial hyperplasia, endometrial cancer, or other clinically significant findings on endometrial biopsy
 - No history within the last 6 months of undiagnosed uterine bleeding.
8. Healthy woman, assigned female at birth, with normal clinical pelvic and breast examinations
 - No history of severe allergy, hypersensitivity, or intolerance to drugs in general, including the trial drug and any of its excipients
 - No history of seizures or other convulsive disorders
 - No previous or current history of a malignant tumor, *except for basal cell carcinoma*
 - No medical condition or chronic disease [including history of neurological (including cognitive), hepatic, renal, cardiovascular, gastrointestinal, pulmonary (e.g., moderate asthma), endocrine or gynecological disease] or malignancy that could confound interpretation of the trial outcome in the opinion of the investigator.
 - Systolic blood pressure is < 130 mmHg or diastolic blood pressure is < 80 mmHg based on the average of 2 to 3 readings, on at least 2 different occasions within the screening period.
 - Participants who do not meet these criteria may, at the discretion of the investigator, be re-assessed after initiation or review of antihypertensive measures
 - Participants with a medical history of hypertension can be enrolled at the discretion of the investigator once they are medically clear (stable and compliant)
 - No active liver disease, jaundice, elevated liver aminotransferases (ALT or AST), elevated total or direct bilirubin, elevated INR, or elevated alkaline phosphatase (ALP).
 - Participants with *mildly elevated ALT or AST up to 1.5 times the upper limit of normal (ULN) can be enrolled if total and direct bilirubin are normal*. Participants with *mildly elevated ALP (up to 1.5 x ULN) can be enrolled if cholestatic liver disease is excluded and no cause other than fatty liver is diagnosed*. Participants with Gilbert's syndrome with elevated total bilirubin may be enrolled as long as direct bilirubin, hemoglobin, and reticulocytes are normal.
 - Creatinine < 1.5 x ULN; or estimated glomerular filtration rate (eGFR) using the Modification of Diet in Renal Disease formula > 59 mL/min per 1.73 m² at screening.
 - No known substance abuse or alcohol addiction within 6 months of screening, as assessed by the investigator.
 - No history of suicide attempt or suicidal behavior within the last 12 months or has suicidal ideation within the last 12 months [a response of "yes" to question 4 or 5

on the suicidal ideation portion of the Columbia Suicide Severity Rating Scale (C-SSRS)], or who is at significant risk to commit suicide, as assessed by the investigator at screening and at Visit 2 (randomization).

9. No previous enrollment in a clinical trial with fezolinetant
10. Not in another interventional study or participated in an interventional study within 28 days prior to screening or received any investigational drug within 28 days or within 5 half-lives prior to screening, whichever is longer.

The enrollment criteria were appropriate for clinical trials intended to support the efficacy and safety of a product for the indication of treatment of moderate to severe vasomotor symptoms.

Consistent with discussions with FDA during clinical development, the trial design, population, and primary endpoint assessment were all consistent with the FDA 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 in this review referred to as *2003 draft HT Clinical Trial Guidance*) and additional FDA guidance provided throughout the clinical development of fezolinetant.

Clinical evaluations for both trials were scheduled as: Visit 1 (Screening): Day -35 to Day -1, Visit 2 (Randomization): Day 1; Visit 3 (Interim): Day 29 (Week 4); Visit 4 (Interim): Day 57 (Week 8); Visit 5 (Interim): Day 85 (Week 12); Visits 6 - 15 (*Interim*): Day 113 - 365 (Week 16 - 53); and Visit 16 (Follow-up): Day 386 (Week 55).

Even though Trial 2693-CL-0301 and 2693-CL-0302 were designed identically, FDA advised the applicant to provide confirmatory (both trials would need to be positive) substantial evidence of effectiveness from each of two phase 3 trials, Trial 2693-CL-0301 and Trial 2693-CL-0302. Therefore, effectiveness was not determined on the basis of an Integrated Summary of Efficacy but rather on the independent assessments and conclusions on effectiveness from each of the two trials.

Figure 1 presents the planned trial scheme for both trials.

Figure 1: Study Schema

Screening	Randomization (1:1:1)	Fezolinetant 30 mg once daily (N _{planned} = 150)	Fezolinetant 30 mg once daily	Follow-up		
		Fezolinetant 45 mg once daily (N _{planned} = 150)	Fezolinetant 45 mg once daily			
		Placebo once daily (N _{planned} = 150)	Fezolinetant 30 mg once daily OR Fezolinetant 45 mg once daily			
V1† (Day -35 to -1)	V2‡ (Day 1)	V3 (Day 29)	V4 (Day 57)	V5‡ (Day 85)	V6-V15 (Day 113-365)	V16 (Day 386)
		Week 4	Week 8	Week 12	Weeks 16-52	Week 55

Definitions: N = number; V = visit.

Screening was performed up to 35 days prior to randomization, with a minimum of 10 days to allow for baseline collection of VMS frequency and severity.

Source: Clinical Review **Figure 1, page 85** and NDA 216578, Trials 2693-CL-0301 Synopsis **Figure 1, page 18** and 2693-CL-0302 Synopsis, **Figure 1, page 18**.

Major protocol deviations in each of the two trials were defined as those protocol deviations which may potentially impact the completeness, accuracy or reliability of data contributing to the primary endpoint or affect the rights, safety, or well-being of a participant criteria. Major protocol deviations were summarized at the end of each phase 3 trial according to the following categories:

- PD1: Entered into the trial even though the participant did not satisfy entry criteria
- PD2: Developed withdrawal criteria during the trial and was not withdrawn
- PD3: Received wrong treatment or incorrect dose
- PD4: Received excluded concomitant treatment/medication

The efficacy assessment conducted for Trial T2693-CL-0301 and 2693-CL-0302 are based upon the following agreed-to four co-primary endpoints:

- Mean change in the frequency of moderate to severe vasomotor symptoms from baseline to Week 4.
- Mean change in the frequency of moderate to severe vasomotor symptoms from baseline to Week 12.
- Mean change in the severity of moderate to severe vasomotor symptoms from baseline to Week 4.
- Mean change in the severity of moderate to severe vasomotor symptoms from baseline to Week 12.

The baseline frequency was calculated based on the number of moderate and severe hot flashes in at least 7 of the 10 days *immediately* prior to randomization in order to meet the eligibility criterion, and the average was based on all the *non-missing* days. Participants recorded daily the number (frequency) and severity of each vasomotor symptom via an electronic diary.

The severity of an individual vasomotor symptom was defined as follows:

- Mild: sensation of heat without sweating
- Moderate: sensation of heat with sweating, able to continue activity
- Severe: sensation of heat with sweating, causing cessation of activity

The severity score for mild, moderate, and severe VMS is coded as 1, 2, and 3, respectively.

The calculation for severity at baseline is calculated as follows and is based on the same days as the baseline frequency.

$$([\# \text{Moderate/day} \times 2] + [\# \text{Severe/day} \times 3]) / (\# (\text{Moderate} + \text{Severe}) / \text{day})$$

The severity for the *post-baseline co-primary severity endpoints* is calculated using a weighted average over non-missing days over 7 days period defined as follows:

$$\frac{[\#Mild/day \times 1] + [\#Moderate/day \times 2] + [\#Severe/day \times 3]}{\#(Mild + Moderate + Severe)/day}$$

Per the 2003 draft HT Clinical Trial Guidance, successful demonstration of efficacy is shown with a statistically significant improvement (reduction), at Week 4 and Week 12, in both the frequency and severity of hot flushes in the treated groups compared with placebo. Additionally, the statistically significant reduction in frequency should also meet a clinical threshold determination of two hot flashes per day or 14 hot flashes per week superiority of the evaluated drug product over placebo. The recommendation to add clinically meaningful threshold in addition to statistically significant superiority to the efficacy assessment, is not included in the 2003 draft HT Clinical Trial Guidance, but was added to FDA recommendations in order to address that a statistically significant change alone may not reflect a clinically meaningful finding. FDA has consistently provided this recommendation to provide to sponsors (including Astellas) of products intended to treat moderate to severe vasomotor symptoms.

Analyses sets were defined as follows:

- All Randomized Set: Consisted of all participants who were randomized regardless of whether they received on dose of study drug.
- Full Analysis Set (FAS): Consisted of all participants who were randomized and received at least one dose of study drug. This was the primary set for efficacy analyses. All efficacy analyses were conducted by treatment group according to the FAS.
- Safety Analysis Set (SAF): Consisted of all participants who were randomized who took at least one dose of study drug. The SAF was used for the safety analyses and the summaries of demographic and baseline characteristics.
- Per Protocol Set (PPS): Consisted of the subset of participants in the FAS who did not meet the following criteria:
 - No measurement of the primary efficacy endpoint available at week 4 (week 12).
 - <85% interactive diary compliance during the 4- (12-) week treatment period.
 - Treatment compliance less than or equal to 85% between randomization and week 4 (week 12).

For the efficacy assessment for Trial 2693-CL-0301 and 2693-CL-0302, for each of the four co-primary efficacy endpoints, a mixed model repeated measures analysis of covariance (MMRM) was used with treatment group, week (week 1 through week 12) and smoking status (current vs former/never) as factors, with baseline weight and baseline vasomotor symptoms as covariates, as well as an interaction of treatment by week and an interaction of baseline measurement by week. An unstructured covariance structure shared across treatment groups was used to model the within-patient errors (and then Toeplitz if model did not converge). The Kenward-Roger approximation was used to estimate denominator degrees of freedom and adjust standard errors.

This analysis used a restricted maximum likelihood-based repeated-measures approach.

Descriptive statistics were reported for each endpoint. Least Square (LS) estimates of mean differences from placebo for each dose and week with the associated 2-tailed 95% confidence interval (CI) were derived. The LS means were estimated using weights proportional to the percentage of women who were randomized as current smokers.

The applicant proposed

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. As communicated by FDA in previous meetings with the applicant, all the four co-primary efficacy endpoints should be tested at a significance level of 0.05.

In the primary analysis, missing data were implicitly imputed assuming a missing at random (MAR) missing data mechanism. To assess the robustness of the primary analysis results to departures from the underlying MAR assumption, the applicant performed a discontinuation-reason based multiple imputation (MI) where data for subjects who discontinue early follow a pattern which is missing not at random. Specifically, subjects who discontinued early from the two active dose groups were multiply imputed using the placebo group. The applicant also performed additional sensitivity analyses for the co-primary efficacy endpoints based on the per-protocol population. The data was analyzed using the same MMRM model as the primary analyses.

The key and other secondary endpoints in both studies were analyzed similarly to the analysis strategy of the co-primary efficacy endpoints.

Efficacy Assessment for Trial 2693-CL-0301 and Trial 2693-CL-0302

Trial 2693-CL-0301

Of the 527 participants randomized in this trial, 522 took at least 1 dose of trial medication and were included in the safety analysis set (SAF) and full analysis set (FAS). Five (5) participants did not take any trial medication; two randomized to 30 mg fezolinetant and 3 randomized to 45 mg fezolinetant. One participant who was randomized into the 45 mg fezolinetant treatment group was given an incorrect treatment with 30 mg fezolinetant, which occurred during the first 4-weeks of treatment. This participant was considered as part of the 30 mg fezolinetant group in the safety analyses.

Of the 522 participants who took the trial medication, 87 participants were excluded from the per protocol set (PPS) at Week 4 and 158 at Week 12. The main reasons for exclusion from the PPS included:

- No measurement of primary efficacy endpoint available (highest exclusion for 30 mg fezolinetant at Weeks 4 and 12).
- < 85% interactive diary compliance (highest exclusion for 30 mg fezolinetant at Week 4 and 45 mg fezolinetant at Week 12).

A total of 96 of 527 randomized participants (FAS) had a major protocol deviation during the 12-week double-blind period of Trial 2593-CL-0301 See Table 15.

Table 15: Major Protocol Deviations (All Randomized Participants); 12-week Double-blind Period; Trial 2693-CL-0301

Category	Placebo (n = 175)	Fezolinetant 30 mg (n = 176)	Fezolinetant 45 mg (n = 176)	
Overall protocol deviations	29 (16.6%)	33 (18.8%)	34 (19.3%)	9
Entered into the study even though they did not satisfy entry criteria (PD1)	28 (16.0%)	26 (14.8%)	31 (17.6%)	8
Developed withdrawal criteria during the study and was not withdrawn (PD2)	0	0	0	
Received wrong treatment or incorrect dose (PD3)	1 (0.6%)	5 (2.8%)	4 (2.3%)	
Received excluded concomitant treatment (PD4)	0	3 (1.7%)	0	

PD = Protocol deviation.

Source: Clinical Review **Table 12, page 96** and NDA 216578, Trial 2593-CL-0301 Final Study Report, **Table 4, page 33**.

Major protocol deviations occurred in 17% of placebo participants. 19% of participants receiving 30 mg fezolinetant and 19% of participant receiving 45 mg fezolinetant. Of these major protocol violations, the most common in all treatment groups was for participants who did not satisfy enrollment criteria, but were allowed to enter the trial. The 3 most common enrollment criteria deviations were failure to meet criteria for definition of menopause; enrollment despite having systolic blood pressure is ≥ 130 mmHg or diastolic blood pressure is ≥ 80 mmHg based on 2 to 3 readings on at least 2 different occasions, which was an exclusion criterion; and endometrial biopsy confirming presence of disordered proliferative endometrium, endometrial hyperplasia, endometrial cancer or other clinically significant findings at screening, which was an exclusion criterion.

Table 16 shows the summary of participant disposition and the primary reasons for study discontinuation during the 12-week double-blinded treatment period in Trial 2693-CL-0301.

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Table 16 Trial 2693-CL-0301 Participant Disposition and Reasons for Discontinuation

Category	Trial 2693-CL-0301		
	Placebo (N=175)	Fezolinetant	
		30 mg (N = 174)	45 mg (N = 173)
Randomized	175	176	176
Safety Analysis Set †	175	174	173
Full Analysis Set ††	175	173	174
12-week Double-blind Period (Safety Analysis Set)			
Completed	152 (86.9%)	143 (82.2%)	160 (92.5%)
Treatment discontinuation	23 (13.1%)	31 (17.8%)	13 (7.5%)
Primary reason for trial intervention discontinuation			
Adverse event	9 (5.1%)	8 (4.6%)	5 (2.9%)
Death	0	0	0
Lost to follow-up	3 (1.7%)	4 (2.3%)	0
Protocol deviation	0	2 (1.1%)	2 (1.2%)
Withdrawal by subject	9 (5.1%)	12 (6.9%)	4 (2.3%)
Other	2 (1.1%)	5 (2.9%)	2 (1.2%)

† Summary was based on the actual treatment subjects received. One participant (Subject (b) (6)) randomized into Fezolinetant 45 mg treatment group was given an incorrect treatment with Fezolinetant 30 mg. This participant was considered as part of the Fezolinetant 30 mg group in the safety analyses.

†† Summary was based on the number of subject randomized to the treatment groups

Source: Statistical Review **Table 5, pp 15** and NDA 216578, Trial 2693-CL-0301 Report, **Figure 2** and **Table 3**.

In Trial 2693-CL-0301, a total of 527 subjects were randomized. Of those, 522 took the study intervention. The trial had an 87% completion rate of the 12-week double-blinded treatment period. The most common reason for treatment discontinuation was “withdrawal by subject (5%, 6.9% and 2.3% in placebo, 30 mg dosage strength group and 45 mg dosage strength group, respectively). Eight [8 (1.6%)] participants in Trial 2693-CL-0301 discontinued treatment due to COVID-19.

The demographic information based on the full analysis set for Trial 2693-CL-0301 is presented in Table 17.

Table 17 Trial 2693-CL-0301 Demographic and Selected Baseline Characteristics (Full Analysis Set)

Demographic Parameters	Treatment Group		
	Control Group (N=175) n (%)	30 mg Fezolinetant Treatment Group (N= 174) n (%)	45 mg Fezolinetant Treatment Group (N=173) n (%)
Age (Years)			
Mean (SD)	54.7 (4.8)	54.1 (4.8)	54.2 (5.1)
Median	54	53	54
Range	41 - 65	42 - 65	40 - 65
Age Category			
< 55 years	91 (52%)	63 (53%)	97 (56%)
> 55 years	84 (48%)	81 (47%)	76 (44%)
Race			
White	142 (81.1%)	147 (85.5%)	142 (81.6%)
Black or African American	28 (16.0%)	21 (12.2%)	26 (14.9%)
American Indian or Alaska Native	2 (1.1%)	0	1 (0.6%)
Asian	3 (1.7%)	3 (1.7%)	3 (1.7%)
Native Hawaiian or Other Pacific Islander	0	0	1 (0.6%)
Other	0	1 (0.6%)	1 (0.6%)
Missing	0	1	0
Ethnicity			
Hispanic or Latino	46 (26.4%)	42 (24.3%)	48 (27.6%)
Not Hispanic or Latino	128 (73.6%)	131 (75.7%)	126 (72.4%)
Missing	1	0	0
Weight (kg) (n)			
Mean (SD)	74.4 (12.14)	75.0 (13.86)	75.7 (12.8)
Median	73.6	73.8	74.4
Range	47.7 - 111.0	42.0 - 121.2	50.6 - 110.6
BMI (kg/m ²) (n)			
Mean (SD)	28.2 (4.28)	28.1 (4.80)	28.3 (4.39)
Median	28.2	27.9	27.9
Range	18.8 - 37.7	18.0 - 37.8	18.4 - 37.9
BMI Category (kg/m ²)			
< 18.5	0	1 (0.6%)	1 (0.6%)
≥ 18.5 to < 25	44 (25.1%)	50 (28.9%)	40 (23.1%)
≥ 25 to < 30	71 (40.6%)	60 (34.7%)	79 (45.7%)
≥ 30	60 (34.3%)	62 (35.8%)	53 (30.6%)
Missing	0	0	1
Smoking Status			

	Treatment Group		
Stratification factor†			
Current	22 (12.6%)	21 (12.1%)	23 (13.2%)
Former/never	153 (87.4%)	152 (87.9%)	151 (86.8%)
Prior Hormone Therapy			
Yes	33 (19.4%)	31 (18.1%)	30 (17.8%)
No	137 (80.6%)	141 (82.0%)	138 (82.1%)
Missing	5	2	5
History of Hysterectomy - Yes	51 (29.1%)	60 (34.7%)	57 (32.8%)
History of Oophorectomy - Yes,	38. (21.7%)	36 (20.8%)	38 (21.8%)

† = Current vs former or never smoking status was a stratification factor for randomization

Source: Statistical Review **Table 6**, page **15** and NDA 216578, Trial 2693-CL-0301 Applicant's Summary of Clinical Efficacy **Tables 4** and **5**, **pages 24-26**

The mean age in Trial 2693-CL-0301 was 54.3. Self-identified racial makeup of participants was 82.7% White, 14.4% Black/African American and 1.7% Asian, and less than 1% other racial groups. Seventy-five kg was the mean weight, and the mean BMI was 28.2 kg/m². Most participants were former/never smokers (87.4%) and hormone therapy naive. The median months since onset of amenorrhea was 61.1 months for 511 total participants, with a mean (SD) of 86.1 (81.1) and a range of 2 months (min) to 443 months (max).

The applicant's primary efficacy analyses of Trial 2693-CL-0301 are present in Tables 18 (frequency) and Table 19 (severity).

Table 18 **Applicant's Primary Analysis of Co-primary Endpoints:
Change from Baseline in Mean Frequency of Moderate to Severe
Vasomotor Symptoms Over 24 Hours (Full Analysis Set); 12-week
Double-blind Period of Trial 2693-CL-0301**

Analysis Visit	Statistic	Placebo (n = 175)	Fezolinetant 30 mg (n = 173)	Fezolinetant 45 mg (n = 174)
Baseline	n	175	173	174
	Mean (SD)	10.51 (3.79)	10.65 (4.73)	10.44 (3.92)
	Median	9.40	9.60	9.28
	Min, Max	7.0, 31.2	3.4, 54.4	7.0, 37.0
Week 4	n	166	157	164
	Mean (SD)	7.25 (4.29)	5.36 (3.76)	5.20 (4.48)
	Median	7.50	5.00	4.27
	Min, Max	0, 27.2	0, 14.9	0, 31.6
	Change from Baseline†			
	n	166	157	164
	Mean (SD)	-3.27 (4.18)	-5.35 (5.57)	-5.20 (4.07)
	Median	-2.59	-5.10	-5.18
	Min, Max	-28.1, 5.4	-52.3, 4.2	-22.5, 8.7
	LS mean (SE)	-3.32 (0.29)	-5.19 (0.30)	-5.39 (0.30)
	95% CI (2-sided)	-3.89, -2.74	-5.78, -4.60	-5.97, -4.81
	Difference in LS Means‡: Fezolinetant vs Placebo			
	LS mean (SE)	NA	-1.87 (0.42)	-2.07 (0.42)
	95% CI (2-sided)		-2.69, -1.05	-2.89, -1.25
	P value (2-sided unadjusted) §		< 0.001	< 0.001
	P value (2-sided adjusted) ¶		0.012††	0.007††
Week 12	n	139	131	146
	Mean (SD)	6.85 (4.66)	4.46 (3.72)	4.06 (3.85)
	Median	6.43	3.80	3.29
	Min, Max	0.0, 29.3	0.0, 17.1	0.0, 23.7
	Change from Baseline†			
	n	139	131	146
	Mean (SD)	-3.67 (4.18)	-6.44 (6.15)	-6.38 (4.48)
	Median	-3.29	-5.83	-6.70
	Min, Max	-14.9, 8.6	-51.1, 5.0	-34.7, 5.6
	LS mean (SE)	-3.90 (0.31)	-6.28 (0.32)	-6.44 (0.31)
	95% CI (2-sided)	-4.50, -3.29	-6.90, -5.66	-7.04, -5.84
	Difference in LS Means‡: Fezolinetant vs Placebo			
	LS mean (SE)	NA	-2.39 (0.44)	-2.55 (0.43)
	95% CI (2-sided)		-3.25, -1.52	-3.40, -1.70
	P value (2-sided unadjusted) §		< 0.001	< 0.001
	P value (2-sided adjusted) ¶		0.012††	0.007††

Full Analysis Set = All participants who were randomized and received at least 1 dose of trial intervention. The LS means, SE, CI, and P values come from a MMRM analysis of covariance model with change from baseline as the dependent variable and treatment group, week, and smoking status (current vs former/never) as factors, with baseline measurement and baseline weight as covariates, as well as an interaction of treatment by week and an interaction of baseline measurement by week.

Source: Clinical Review **Table 15, page 101** and NDA 216578, Trial 2693-CL-0301, Final Trial Report, **Table 11, page 43**.

Table 19 **Applicant's Primary Analysis of Co-primary Endpoints: Change from Baseline in Mean Severity of Moderate to Severe Vasomotor Symptoms Over 24 Hours (Full Analysis Set); 12-week Double-blind Period; Trial 2693-CL-0301**

Analysis Visit	Statistic	Placebo (n = 175)	Fezolinetant 30 mg (n = 173)	Fezolinetant 45 mg (n = 174)
Baseline	n	175	173	174
	Mean (SD)	2.43 (0.35)	2.39 (0.34)	2.40 (0.35)
	Median	2.35	2.33	2.36
	Min, Max	1.8, 3.0	1.8, 3.0	1.8, 3.0
Week 4	n	166	157	164
	Mean (SD)	2.13 (0.58)	1.95 (0.60)	1.95 (0.64)
	Median	2.05	2.00	2.00
	Min, Max	0.0, 3.0	0.0, 3.0	0.0, 3.0
	Change from Baseline†			
	n	166	157	164
	Mean (SD)	-0.28 (0.50)	-0.43 (0.56)	-0.45 (0.61)
	Median	-0.11	-0.24	-0.25
	Min, Max	-2.4, 0.6	-2.4, 0.4	-3.0, 0.4
	LS mean (SE)	-0.27 (0.04)	-0.42 (0.04)	-0.46 (0.04)
	95% CI (2-sided)	-0.35, -0.19	-0.50, -0.34	-0.54, -0.37
	Difference in LS Means‡: Fezolinetant vs Placebo			
	LS mean (SE)	NA	-0.15 (0.06)	-0.19 (0.06)
	95% CI (2-sided)		-0.27, -0.03	-0.30, -0.07
	P value (2-sided unadjusted) §		0.012	0.002
	P value (2-sided adjusted) ¶		0.012††	0.007††
Week 12	n	139	131	146
	Mean (SD)	2.06 (0.59)	1.79 (0.69)	1.83 (0.75)
	Median	2.00	2.00	1.97
	Min, Max	0.0, 3.0	0.0, 3.0	0.0, 3.0
	Change from Baseline†			
	n	139	131	146
	Mean (SD)	-0.35 (0.58)	-0.57 (0.73)	-0.58 (0.75)
	Median	-0.18	-0.31	-0.33
	Min, Max	-3.0, 0.6	-3.0, 0.4	-2.9, 0.7
	LS mean (SE)	-0.37 (0.05)	-0.60 (0.05)	-0.57 (0.05)
	95% CI (2-sided)	-0.47, -0.26	-0.71, -0.50	-0.67, -0.47

Full Analysis Set = All participants who were randomized and received at least 1 dose of trial intervention

Source: Clinical Review **Table 16, page 103** and NDA 216578, Trial 2693-CL-0301 Trial Report, **Table 12, page 44**.

The Biometric review replicated and verified the applicant's results for the change from baseline in the mean frequency of moderate to severe vasomotor symptoms (see Table X below) and the mean severity of moderate to severe vasomotor symptoms (see Table Y below) in Trial 2693-CL-0301.

Table 20 Biometric Review of Primary Analysis of Mean Baseline and Change from Baseline in the Mean Frequency of Moderate to Severe Vasomotor Symptoms per 24 Hours at Week 4 and Week 12 for the Full Analysis Set¹ in Trial 2693-CL-0301

	Trial 2693-CL-0301		
	Placebo	Fezolinetant 30 mg	Fezolinetant 45 mg
Baseline (N)	175	173	174
Mean frequency (SD)	10.51 (3.79)	10.65 (4.73)	10.44 (3.92)
Week 4 (N)	166	157	164
Mean frequency (SD) change from baseline	-3.27 (4.18)	-5.35 (5.57)	-5.20 (4.07)
LS Mean (SE) difference vs. placebo		-1.87 (0.42)	-2.07 (0.42)
95% CI		(-2.69, -1.05)	(-2.89, -1.25)
p-value		< 0.001	< 0.001
Week 12 (N)	139	131	146
Mean frequency (SD) change from baseline	-3.67 (4.18)	-6.44 (6.15)	-6.38 (4.48)
LS Mean (SE) difference from placebo		-2.39 (0.44)	-2.55 (0.43)
95% CI (2-sided)		(-3.25, -1.52)	(-3.40, -1.70)
p-value		< 0.001	< 0.001

¹All participants who were randomized and received at least 1 dose of study intervention.

Abbreviations: LS Means – Least Square Means; SE: Standard Error, CI – Confidence Interval; SD – Standard Deviation.

Note: The LS means, SE, CI and p-values were obtained using mixed model for repeated measures analysis (MMRM) analysis with change from baseline as the dependent variable and treatment group, week, and smoking status (current vs former/never) as factors, with baseline measurement and baseline weight as covariates, as well as an interaction of treatment by week and an interaction of baseline measurement by week.

Source: Biometric Review, **Table 7, page 16** and NDA 216578, Trial 2693-CL-0301 **Table 11, pages 43**.

Table 21 Biometric Review of Primary Analysis of Mean Baseline and Change from Baseline in the Mean Severity of Moderate to Severe Vasomotor Symptoms per 24 Hours, at Week 4 and Week 12 for the Full Analysis Set¹ in Trial 2693-CL-0301

	Trial 2693-CL-0301		
	Placebo	Fezolinetant 30 mg	Fezolinetant 45 mg
Baseline (N)	175	173	174
Mean severity (SD)	2.43 (0.35)	2.39(0.34)	2.40 (0.35)
Week 4 (N)	166	157	164
Mean severity (SD) change from baseline	-0.28 (0.50)	-0.43 (0.56)	-0.45 (0.61)
LS Mean (SE) difference vs. placebo		-0.15 (0.06)	-0.19 (0.06)
95% CI		(-0.27, -0.03)	(-0.30, -0.07))
p-value		0.012	0.002
Week 12 (N)	139	131	146
Mean severity (SD) change from baseline	-0.35 (0.58)	-0.57 (0.73)	-0.58 (0.75)
LS Mean (SE) difference from placebo		-0.24 (0.08)	-0.20 (0.08)
95% CI (2-sided)		(-0.39, -0.09)	(-0.35, -0.06)
p-value		0.002	0.007

¹All participants who were randomized and received at least 1 dose of study intervention

Note: The LS means, SE, CI and p-values were obtained using MMRM analysis with change from baseline as the dependent variable and treatment group, week, and smoking status (current vs former/never) as factors, with baseline measurement and baseline weight as covariates, as well as an interaction of treatment by week and an interaction of baseline measurement by week.

Source: Biometric Review, Table 8, page 17, dated November 21, 2022, and NDA 216578, Trial 2693-CL-0301 Table 12, page 44.

Data presented in Tables 18 through 21 demonstrate that in Trial 2693-CL-0301 both the 30 mg and 45 mg fezolinetant dosage strength groups had a statistically significant reduction in the frequency and severity of hot flashes at Week 4 and Week 12 when compared to placebo. Only the 45 mg group met the clinical threshold of superiority in reduction of vasomotor symptoms by at least 2 per day or 14 per week when compared to placebo. *Astellas is requesting approval for only the 45 mg fezolinetant dose for the treatment of moderate to severe vasomotor symptoms due to menopause.*

Trial 2693-CL-0302

Of the 501 participants randomized in this trial, 500 took at least 1 dose of trial medication (1 placebo participant did not take any trial medication) and were included in the safety analysis set (SAF) and full analysis set (FAS).

Of the 500 participants who took the trial medication, a total of 458 completed the 12-week double-blind period; of these 457 entered the 40-weeks extension period. In total, 383 participants completed the full 52-weeks in Trial 2693-CL-0302. Eighty-seven (87) participants were excluded from the per protocol set (PPS) at Week 4 and 139 at Week 12. The main reasons for exclusion from the PPS included:

- No measurement of primary efficacy endpoint available (highest exclusion for placebo at Week 4 (9.5%) and 30 mg fezolinetant at Week 12 (19.9%).
- Less than 85% interactive diary compliance
- $\leq 85\%$ treatment compliance (highest exclusion for placebo and 45 mg fezolinetant at Week 4 (4.2% for both) and 30 mg fezolinetant at Week 12 (3.0%).

A total of 104 of 501 randomized participants (FAS) had a major protocol deviation during the 12-week double-blind period of Trial 2593-CL-0302 (see Table 22 below).

Table 22: Major Protocol Deviations (All Randomized Participants); 12-week Double-blind Period; Trial 2693-CL-0302

Category	Placebo (n = 168)	Fezolinetant 30 mg (n = 166)	Fezolinetant 45 mg (n = 167)	Total (n = 501)
Overall protocol deviations	33 (19.6%)	39 (23.5%)	32 (19.2%)	104 (20.8%)
Entered into the study even though they did not satisfy entry criteria (PD1)	31 (18.5%)	34 (20.5%)	29 (17.4%)	94 (18.8%)
Developed withdrawal criteria during the study and was not withdrawn (PD2)	0	1 (0.6%)	0	1 (0.2%)
Received wrong treatment or incorrect dose (PD3)	1 (0.6%)	6 (3.6%)	4 (2.4%)	11 (2.2%)
Received excluded concomitant treatment (PD4)	1 (0.6%)	0	2 (1.2%)	3 (0.6%)

Definitions: PD = Protocol deviation.

Source: Clinical Review **Table 27, page 127** and NDA 216578, Trial 2693-CL-0302 Final Trial Report, **Table 4, page 34**.

Major protocol deviations occurred in 20% of placebo participants. 24% of participants receiving 30 mg fezolinetant and 19% of participant receiving 45 mg fezolinetant. Of these major protocol violations, the most common in all treatment groups was for participants who did not satisfy enrollment criteria, but were allowed to enter the trial. The 3 most common enrollment criteria deviations were failure to meet criteria for definition of menopause; lack of a negative urine pregnancy test at screening; enrollment despite having systolic blood pressure is ≥ 130 mmHg or diastolic blood pressure is ≥ 80 mmHg based on 2 to 3 readings on at least 2 different occasions, which was an exclusion criterion

Table 23 shows the summary of participant disposition and the primary reasons for trial

discontinuation during the 12-week double-blinded treatment period in Trial 2693-CL-0302.

Table 23: Summary of Participant Disposition and Reasons for Trial Discontinuation in Trial 2693-CL-0302

Category	Trial 2693-CL-0302		
	Placebo (N=167)	Fezolinetant	
		30 mg (N = 166)	45 mg (N = 167)
Randomized	168	166	167
Safety Analysis Set †	167	166	167
Full Analysis Set ††	167	166	167
12-week Double-blind Period (Safety Analysis Set)			
Completed	151 (90.4%)	152 (91.6%)	155 (92.8%)
Treatment discontinuation	16 (9.6%)	14 (8.4%)	12 (7.2%)
Primary reason for study intervention discontinuation			
Adverse event	1 (0.6%)	1 (0.6%)	2 (1.2%)
Death	0	0	0
Lost to follow-up	2 (1.2%)	1 (0.6%)	2 (1.2%)
Protocol deviation	1 (0.6%)	5 (3.0%)	0
Withdrawal by subject	11 (6.6%)	6 (3.6%)	6 (3.6%)
Other	1 (0.6%)	1 (0.6%)	2 (1.2%)

Source: Statistical Review **Table 5, page 15** and NDA 216578, Trial 2693-CL-0302 Report, **Figure 2 and Table 3, pages 33 and 34, respectively**

In Trial 2693-CL-0302, a total of 501 subjects were randomized. Of those, 500 took the trial medication intervention. The trial had a 92% completion rate of the 12-week double-blinded treatment period. The most common reason for treatment discontinuation was “withdrawal by subject (5%, 4% and 4% in the placebo, 30 mg dosage strength group, and 45 mg dosage strength group, respectively). four [4 (0.8%)] participants in Trial 2693-CL-0301 discontinued treatment due to COVID-19.

The demographic information based on the safety analysis set for Trial 2693-CL-0302 is presented in Table 24.

Table 24 Trial 2693-CL-0302 Demographic and Selected Baseline Characteristics (Full Analysis Set)

Demographic Parameters	Control Group (N=167) n (%)	30 mg Fezolinetant Treatment Group (N= 166) n (%)	45 mg Fezolinetant Treatment Group (N=167) n (%)
Age (Years)			
Mean (SD)	54.7 (4.6)	53.9 (4.9)	54.3 (5.4)
Median	54	54	55.0
Range	44 - 65	42 - 65	40 - 65
Race			
White	134 (80.2%)	131 (78.9%)	132 (79.0%)
Black or African American	28 (18.6%)	35 (21.1%)	33 (19.8%)
American Indian or Alaska Native	0	0	1 (0.6%)
Asian	1 (0.6%)	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Other	1 (0.6)	0	1 (0.6)
Missing	0	0	0
Ethnicity			
Hispanic or Latino	32(19.3%)	34 (20.5%)	41 (24.6%)
Not Hispanic or Latino	134 (80.7%)	132 (79.5%)	126 (75.4%)
Missing	1	0	0
Weight (kg) (n)			
Mean (SD)	74.6 (14.68)	75.3 (14.09)	74.6 (12.45)
Median	71.7	74.1	73
Range	46.2 - 125.0	48.0 - 108.4	45.0 - 107.4
BMI (kg/m²) (n)			
Mean (SD)	28.2 (4.99)	27.9(4.69)	27.9 (4.35)
Median	27.8	27.8	27.3
Range	18.6 - 38.0	18.1 - 37.6	18.0 - 37.5
BMI Category (kg/m²)			
< 18.5	0	1 (0.6%)	1 (0.6%)
≥ 18.5 to < 25	53 (31.7%)	54 (32.5%)	45 (26.9%)
≥ 25 to < 30	62 (37.1%)	58 (34.9%)	73 (43.7%)
≥ 30	52 (31.1%)	53 (31.9%)	48 (28.7%)
Missing	0	0	1
Smoking Status Stratification factor†			
Current	35 (21.0%)	34 (20.5%)	34 (20.4%)
Former/never	132 (79.0%)	132 (79.5%)	133 (79.6%)

Prior Hormone Therapy			
Yes	31 (18.6%)	37 (22.6%)	38 (23.3%)
No	137 (80.6%)	141 (82.0%)	138 (82.1%)
Missing	5	2	5
History of Hysterectomy- Yes	37 (22.2%)	34 (20.5%)	38 (22.8%)
History of Oophorectomy- Yes,	51 (30.5%)	53 (31.9%)	56 (33.5%)

† = Current vs former or never smoking status was a stratification factor for randomization; NC = Not calculated. Clinical Review Table

Source: Statistical Review **Table 6, page 15** and NDA 216578, Trial 2693-CL-0301 Applicant's Summary of Clinical Efficacy **Tables 4 and 5, pages 24-26**.

The mean age in Trial 2693-CL-0302 was 54.3. Self-identified racial makeup of participants was 79% White, 20% Black/African American and less than 1% as other. Seventy-five kg was the mean weight, and the mean BMI was 27.6 kg/m². Most participants were former/never smokers (79.4%) and hormone therapy naive. The median time to onset of amenorrhea in 500 total participants in Trial 2693-CL-0302 was 58.6 months (range 3 to 491 months).

The applicant's primary efficacy analyses of Trial 2693-CL-0302 are present in Table 25 (frequency) and Table 26 (severity).

Table 25 Applicant's Primary Analysis of Co-primary Endpoints: Change from Baseline in Mean Frequency of Moderate to Severe Vasomotor Symptoms Over 24 Hours (Full Analysis Set); 12-week Double-blind Period; Trial 2693-CL-0302

Analysis Visit	Statistic	Placebo (n = 167)	Fezolinetant 30 mg (n = 166)	Fezolinetant 45 mg (n = 167)
Baseline	N	167	166	167
	Mean (SD)	11.59 (5.02)	11.23 (4.88)	11.79 (8.26)
	Median	10.10	10.15	9.90
	Min, Max	5.6, 40.7	2.5, 54.1	7.0, 91.1
Week 4	N	151	155	155
	Mean (SD)	8.08 (6.50)	5.79 (6.02)	5.67 (7.29)
	Median	7.29	4.17	4.14
	Min, Max	0.0, 48.7	0.0, 49.1	0.0, 68.7
	Change from Baseline†			
	N	151	155	155
	Mean (SD)	-3.64 (4.15)	-5.52 (4.23)	-6.24 (4.78)
	Median	-3.44	-5.89	-6.34
	Min, Max	-18.6, 12.2	-21.9, 5.7	-28.8, 7.4
	LS mean (SE)	-3.72 (0.33)	-5.53 (0.33)	-6.26 (0.33)
	95% CI (2-sided)	-4.36, -3.07	-6.17, -4.90	-6.90, -5.62
	Difference in LS Means‡: Fezolinetant vs Placebo			
	LS mean (SE)	NA	-1.82 (0.46)	-2.55 (0.46)
	95% CI (2-sided)		-2.73, -0.91	-3.45, -1.64
	P value (2-sided unadjusted) §		< 0.001	< 0.001
	P value (2-sided adjusted) ¶		0.049 ††	< 0.001 ††
Week 12	n	140	133	145
	Mean (SD)	6.73 (7.58)	4.80 (5.59)	4.49 (5.39)
	Median	5.00	3.29	2.83
	Min, Max	0.0, 64.0	0.0, 44.0	0.0, 33.3
	Change from Baseline†			
	n	140	133	145
	Mean (SD)	-4.57 (5.14)	-6.43 (4.77)	-7.43 (6.47)
	Median	-5.11	-6.53	-7.00
	Min, Max	-19.9, 25.9	-25.7, 6.4	-57.8, 8.4
	LS mean (SE)	-4.97 (0.39)	-6.83 (0.39)	-7.50 (0.39)
	95% CI (2-sided)	-5.73, -4.20	-7.59, -6.06	-8.25, -6.74
	Difference in LS Means‡: Fezolinetant vs Placebo			
	LS mean (SE)	NA	-1.86 (0.55)	-2.53 (0.55)
	95% CI (2-sided)		-2.94, -0.78	-3.60, -1.46
	P value (2-sided unadjusted) §		< 0.001	< 0.001
	P value (2-sided adjusted) ¶		0.049 ††	< 0.001 ††

Full Analysis Set = All participants who were randomized and received at least 1 dose of trial intervention.

The LS means, SE, CI, and P values come from a MMRM analysis of covariance model with change from baseline as the dependent variable and treatment group, week, and smoking status (current vs former/never) as factors, with baseline measurement and baseline weight as covariates, as well as an interaction of treatment by week and an interaction of baseline measurement by week.

† A negative change indicates an improvement(reduction) from baseline.

‡ Differences were calculated by subtracting the LS mean of placebo group from the LS mean of fezolinetant group.

Source: Clinical Review **Table 30, page 132** and NDA 216578, Trial 2693-CL-0302, Final Study Report, **Table 11, page 45**.

Table 26 Applicant's Primary Analysis of Co-primary Endpoints: Change from Baseline in Mean Severity of Moderate to Severe Vasomotor Symptoms Over 24 Hours (Full Analysis Set); 12-week Double-blind Period; Trial 2693-CL-0302

Analysis Visit	Statistic	Placebo (n = 175)	Fezolinetant 30 mg (n = 173)	Fezolinetant 45 mg (n = 174)
Baseline	n	175	173	174
	Mean (SD)	2.43 (0.35)	2.39 (0.34)	2.40 (0.35)
	Median	2.35	2.33	2.36
	Min, Max	1.8, 3.0	1.8, 3.0	1.8, 3.0
Week 4	n	166	157	164
	Mean (SD)	2.13 (0.58)	1.95 (0.60)	1.95 (0.64)
	Median	2.05	2.00	2.00
	Min, Max	0.0, 3.0	0.0, 3.0	0.0, 3.0
	Change from Baseline†			
	n	166	157	164
	Mean (SD)	-0.28 (0.50)	-0.43 (0.56)	-0.45 (0.61)
	Median	-0.11	-0.24	-0.25
	Min, Max	-2.4, 0.6	-2.4, 0.4	-3.0, 0.4
	LS mean (SE)	-0.27 (0.04)	-0.42 (0.04)	-0.46 (0.04)
	95% CI (2-sided)	-0.35, -0.19	-0.50, -0.34	-0.54, -0.37
	Difference in LS Means‡: Fezolinetant vs Placebo			
	LS mean (SE)	NA	-0.15 (0.06)	-0.19 (0.06)
	95% CI (2-sided)		-0.27, -0.03	-0.30, -0.07
	P value (2-sided unadjusted) §		0.012	0.002
	P value (2-sided adjusted) ¶		0.012††	0.007††
Week 12	n	139	131	146
	Mean (SD)	2.06 (0.59)	1.79 (0.69)	1.83 (0.75)
	Median	2.00	2.00	1.97
	Min, Max	0.0, 3.0	0.0, 3.0	0.0, 3.0
	Change from Baseline†			
	n	139	131	146
	Mean (SD)	-0.35 (0.58)	-0.57 (0.73)	-0.58 (0.75)
	Median	-0.18	-0.31	-0.33
	Min, Max	-3.0, 0.6	-3.0, 0.4	-2.9, 0.7
	LS mean (SE)	-0.37 (0.05)	-0.60 (0.05)	-0.57 (0.05)
	95% CI (2-sided)	-0.47, -0.26	-0.71, -0.50	-0.67, -0.47

Baseline includes moderate to severe incidences. Postbaseline includes mild, moderate, and severe incidences.

Full Analysis Set = All participants who were randomized and received at least 1 dose of study intervention.

The LS means, SE, CI, and P values come from a MMRM analysis of covariance model with change from baseline as the dependent variable and treatment group, week, and smoking status (current vs former/never) as factors, with baseline measurement and baseline weight as covariates, as well as an interaction of treatment by week and an interaction of baseline measurement by week.

Definitions: CI = confidence interval; LS = least squares; Max = maximum; Min = minimum; MMRM = mixed model repeated measures; NA = not applicable.

† A negative change indicated a reduction/improvement from baseline.

‡ Differences were calculated by subtracting the LS mean of placebo group from the LS mean of fezolinetant group.

§ P value is for comparison of fezolinetant with placebo from the above described MMRM model. Largest p-value within each dose compared with placebo.

†† Statistically significant adjusting for multiplicity using the Hochberg procedure at the 5% significance level (statistical significance of the 4 co-primary endpoints).

Source: Clinical Review **Table 31, page 134** and NDA 216578, Trial 2693-CL-0302, Final Trial Report, **Table 12, page 46**.

The Biometric review replicated and verified the applicant's results for the change from baseline in the mean frequency of moderate to severe vasomotor symptoms (Table 27) and the mean severity of moderate to severe vasomotor symptoms (Table 28 b) in Trial 2693-CL-0302.

Table 27 **Biometric Review of Primary Analysis of Mean Baseline and Change from Baseline in the Mean Frequency of Moderate to Severe Vasomotor Symptoms per 24 Hours, at Week 4 and Week 12, for the Full Analysis Set¹ in Trial 2693-CL-0302**

	Trial 2693-CL-0302		
	Placebo	Fezolinetant 30 mg	Fezolinetant 45 mg
Baseline (N)	167	166	167
Mean (SD)	11.59 (5.02)	11.23 (4.88)	11.79 (8.26)
Week 4 (N)	151	155	155
Mean (SD) change from baseline	-3.64 (4.15)	-5.52 (4.23)	-6.24 (4.78)
LS Mean (SE) difference from placebo		-1.82 (0.46)	-2.55 (0.46)
95% CI		(-2.73, -0.91)	(-3.45, -1.64)
p-value		< 0.001	< 0.001
Week 12 (N)	140	133	145
Mean (SD) change from baseline	-4.57 (5.14)	-6.43 (4.77)	-7.43 (6.47)
LS Mean (SE) difference from placebo		-1.86 (0.55)	-2.53 (0.55)
95% CI (2-sided)		(-2.94, -0.78)	(-3.60, -1.46)
p-value		< 0.001	< 0.001

Abbreviations: LS Means – Least Square Means; SE: Standard Error, CI – Confidence Interval; SD – Standard Deviation.

Note: The LS means, SE, CI and p-values were obtained using MMRM analysis with change from baseline as the dependent variable and treatment group, week, and smoking status (current vs former/never) as factors, with baseline measurement and baseline weight as covariates, as well as an interaction of treatment by week and an interaction of baseline measurement by week.

Source: Biometrics Review **Table 7, page 16** and NDA 216578, Trial 2693-CL-0302, Final Trial Report, **Table 11, page 45**.

Table 28 **Biometric Review of Primary Analysis of Mean Baseline and Change from Baseline in the Mean Severity of Moderate to Severe Vasomotor Symptoms per 24 Hours, at Week 4 and Week 12, for the Full Analysis Set¹ in Trial 2693-CL-0302**

	Trial 2693-CL-0301		
	Placebo	Fezolinetant 30 mg	Fezolinetant 45 mg
Baseline (N)	167	166	167
Mean (SD)	2.41 (0.32)	2.44 (0.33)	2.41 (0.34)
Week 4 (N)	151	155	155
Mean (SD) change from baseline	-0.31 (0.48)	-0.47 (0.58)	-0.61 (0.63)
LS Mean (SE) difference from placebo		-0.15 (0.06)	-0.29 (0.06)
95% CI (2-sided)		(-0.27, -0.02)	(-0.41, -0.16)
p-value		0.021	< 0.001
Week 12 (N)	140	133	145
Mean (SD) change from baseline	-0.46 (0.65)	-0.60 (0.75)	-0.74 (0.71)
LS Mean (SE) difference from placebo		-0.16 (0.08)	-0.29 (0.08)
95% CI (2-sided)		(-0.33, 0.00)	(-0.45, -0.13)
p-value		0.049	< 0.001

The LS means, SE, CI and p-values were obtained using MMRM analysis with change from baseline as the dependent variable and treatment group, week, and smoking status (current vs former/never) as factors, with baseline measurement and baseline weight as covariates, as well as an interaction of treatment by week and an interaction of baseline measurement by week.

Source: Biometrics Review **Table 8, page 17** and NDA 216578, Trial 2693-CL-0302, Final Trial Report, **Table12, page 46**

Data presented in Tables 25 through 28 demonstrate that in Trial 2693-CL-0302 both the 30 mg and 45 mg fezolinetant dosage strength groups had statistically significant reduction in the frequency and severity vasomotor symptoms at Week 4 and Week 12 when compared to placebo. Only the 45 mg group met the clinical threshold of superiority in frequency reduction by at least 2 per day or 14 per week when compared to placebo at Weeks 4 and 12. *Astellas is requesting approval for only the 45 mg fezolinetant dose for the treatment of moderate to severe vasomotor symptoms due to menopause.*

Sensitivity, subgroup, key secondary, and secondary endpoint analyses

Sensitivity analyses were conducted for the four co-primary efficacy endpoints based on the Per Protocol Set [see per protocol analysis for Trial 2693-CL-0301 (Table 29)]

Table 29 Applicant's Per Protocol Set (PPS) Sensitivity Analyses of Co-primary Endpoints Over 24 Hours; 12-week Double-blind Period

Analysis Visit	Statistic	Placebo (n = 151)	Fezolinetant 30 mg (n = 141)	Fezolinetant 45 mg (n = 148)
Frequency of moderate to severe VMS				
Baseline for Week 4	n	151	141	148
	Mean (SD)	10.46 (3.42)	10.79 (5.06)	10.58 (4.09)
Baseline for Week 12	n	132	116	121
	Mean (SD)	10.48 (3.55)	10.79 (5.25)	10.72 (4.17)
Week 4	Mean (SD)	7.56 (3.83)	5.50 (3.72)	5.39 (4.45)
	Change from Baseline†			
	Mean (SD)	-2.90 (3.65)	-5.29 (5.70)	-5.18 (4.20)
	LS mean (SE)	-3.01 (0.30)	-5.18 (0.31)	-5.21 (0.31)
	Difference in LS Means‡: Fezolinetant vs Placebo			
	LS mean (SE)	NA	-2.18 (0.44)	-2.20 (0.43)
	95% CI (2-sided)		-3.03, -1.32	-3.05, -1.36
	P value (2-sided unadjusted) §		< 0.001	< 0.001
	Mean (SD)	7.03 (4.64)	4.75 (3.75)	4.40 (3.90)
	Change from Baseline†			
Week 12	Mean (SD)	-3.46 (4.11)	-6.03 (6.06)	-6.33 (4.77)
	LS mean (SE)	-3.58 (0.34)	-5.95 (0.37)	-6.28 (0.36)
	Difference in LS Means‡: Fezolinetant vs Placebo			
	LS mean (SE)	NA	-2.36 (0.50)	-2.70 (0.50)
	95% CI (2-sided)		-3.36, -1.37	-3.68, -1.72
	P value (2-sided unadjusted) §		< 0.001	< 0.001
Severity of moderate to severe VMS				
Baseline for Week 4	n	151	141	148
	Mean (SD)	2.41 (0.35)	2.38 (0.34)	2.41 (0.36)
Baseline for Week 12	n	132	116	121
	Mean (SD)	2.41 (0.36)	2.37 (0.34)	2.42 (0.37)
Week 4	Mean (SD)	2.18 (0.51)	1.98 (0.59)	1.98 (0.61)
	Change from Baseline†			
	Mean (SD)	-0.23 (0.41)	-0.40 (0.53)	-0.43 (0.57)
	LS mean (SE)	-0.23 (0.04)	-0.40 (0.04)	-0.42 (0.04)
	Difference in LS Means‡: Fezolinetant vs Placebo			
	LS mean (SE)	NA	-0.18 (0.06)	-0.20 (0.06)
	95% CI (2-sided)		-0.29, -0.06	-0.31, -0.08
	P value (2-sided unadjusted) §		0.003	< 0.001
	Mean (SD)	2.08 (0.57)	1.85 (0.66)	1.90 (0.69)
	Change from Baseline†			
Week 12	Mean (SD)	-0.33 (0.56)	-0.52 (0.66)	-0.51 (0.68)
	LS mean (SE)	-0.33 (0.05)	-0.54 (0.06)	-0.51 (0.06)
	Difference in LS Means‡: Fezolinetant vs Placebo			
	LS mean (SE)	NA	-0.21 (0.08)	-0.18 (0.08)
	95% CI (2-sided)		-0.36, -0.06	-0.33, -0.03
	P value (2-sided unadjusted) §		0.007	0.019

‡ Differences were calculated by subtracting the LS mean of placebo group from the LS mean of fezolinetant group.

§ P value is for comparison of fezolinetant with placebo from the above described MMRM model

All randomized participants from the Full Analysis Set who were treated according to the protocol without any major deviations at Week 4 and Week 12 endpoints (Per Protocol Set).

The LS means, SE, confidence interval, and p-values come from a MMRM analysis of covariance model with change from baseline as the dependent variable and treatment group, week, and smoking status (current vs former/never) as factors, with baseline measurement and baseline weight as covariates, as well as an interaction of treatment by week and an interaction of baseline measurement by week.

The number of participants (n) is different for baseline measurements by week 4 and week 12 due to a different proportion of participants being excluded from PPS. Excluded participants could have more than one reason of exclusion.

Definitions: CI = confidence interval; LS = least squares; MMRM = mixed model repeated measures; NA = not applicable; PPS = per protocol set; VMS = vasomotor symptoms.

Source: Clinical Review **Table 24, page 117** and NDA216578, Trial 2693-CL-0301, Final Trial Report, **Table 13, page 46**.

Reductions in the frequency and the severity of moderate to severe vasomotor symptoms from baseline to Week 4 and Week 12 compared to the placebo group were statistically significant for the 30mg and 45 mg fezolinetant dosage strength groups, similar to those noted in the primary efficacy results based on the FAS. The multiple imputation sensitivity analyses also supported the primary analysis conclusions.

The mean change in the Patient-Reported Outcomes Measurement Information System Sleep Disturbance – Short Form 8b (PROMIS SD SF 8b) total score from baseline to week 12 was defined in both Trial 2693-CL-0301 and Trial 2693-CL-0302 as the “Key Secondary Endpoint”. The results of analyses of this endpoint are presented in Table 30 below.

Table 30: Change from Baseline in PROMIS Sleep Disturbance – Short Form 8b; 12-week Double-blind Period (Full Analysis Set)

	Trial 2693-CL-0301			Trial 2693-CL-0302		
	Placebo	Fezolinetant 30 mg	Fezolinetant 45 mg	Placebo	Fezolinetant 30 mg	Fezolinetant 45 mg
Baseline	175	172	174	166	165	167
Mean (SD)	26.4 (6.6)	26.4 (6.6)	27.1 (7.0)	27.4 (7.0)	27.3 (6.6)	26.2 (6.6)
week 12 (N)	148	133	156	144	139	145
Mean (SD) change from baseline	-3.2 (7.3)	-3.7 (8.2)	-4.6 (7.3)	-3.6 (7.3)	-4.6 (8.1)	-4.8 (6.8)
LS Mean (SE) difference from placebo		-0.5 (0.8)	-1.1 (0.7)		-0.7 (0.7)	-2.0 (0.7)
95% CI (2-sided)		(-2.0, 1.0)	(-2.5, 0.4)		(-2.1, 0.8)	(-3.5, -0.6)
p-value		0.489	0.155		0.381	0.007

The LS means, SE, CI and p-values were obtained using MMRM analysis with change from baseline as the dependent variable and treatment group, week, and smoking status (current vs former/never) as factors, with baseline measurement and baseline weight as covariates, as well as an interaction of treatment by week and an interaction of baseline measurement by week.

Source: Biometric Review, **Table 9, page 18**, dated November 21, 2022, and NDA 216578, Trials 2693-CL-0301 and 2693-CL-0302 Report **Table 16, page 50**.

There was a reduction (improvement) in the PROMIS total scores for all the treatment arms in both studies but the only reduction that was statistically significant occurred in the fezolinetant 45 mg dosage strength group for Trial 2693-CL-0302.

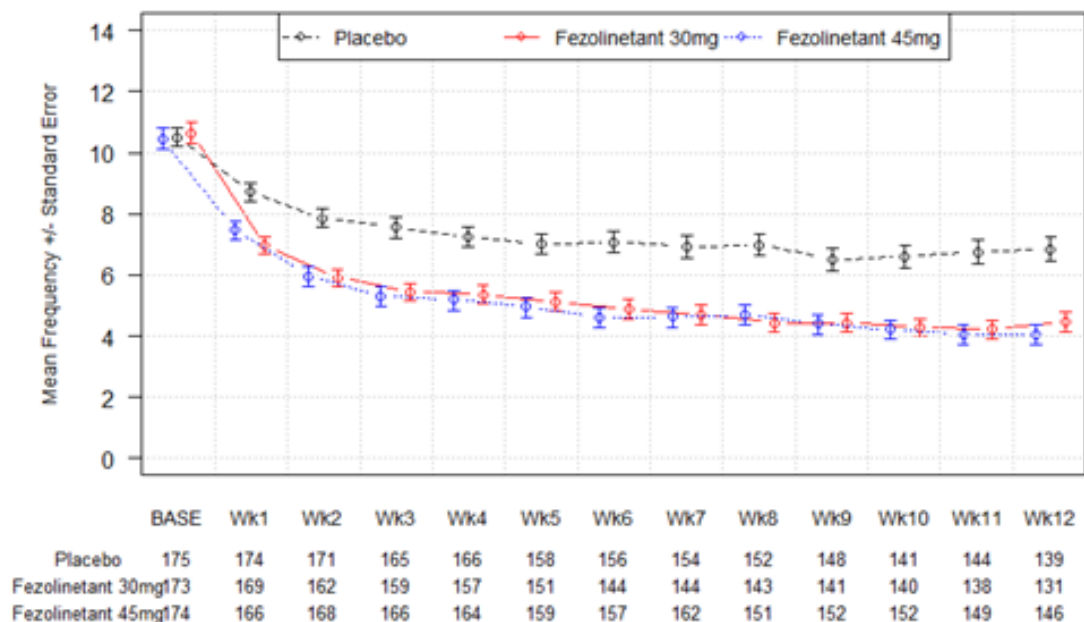
Table 31 presents the applicant's analyses of change in mean frequency of moderate to severe vasomotor symptoms from Weeks 4 through 12.

Table 31: Applicant's Analyses of Change in Mean Frequency of Moderate to Severe Vasomotor Symptoms over 24 Hours, at Week 4 Through Week 12, in Trial 2693-CL-0301, Full Analysis Set

Visit/Statistics	Trial 2693-CL-0301		
	Placebo (N = 175)	Fezolinetant 30 mg (N = 173)	Fezolinetant 45 mg (N = 174)
Baseline			
Mean Frequency (SD)	10.51 (3.79)	10.65 (4.73)	10.44 (3.92)
Week 4 (N)	166	157	164
Mean Frequency Change (SD)	-3.27 (4.18)	-5.35 (5.57)	-5.20 (4.07)
LS Mean Change (SE)	-3.32 (0.29)	-5.19 (0.30)	-5.39 (0.30)
LS Mean Difference from Placebo (SE)	--	-1.87 (0.42)	-2.07 (0.42)
Week 5 (N)	158	151	159
Mean Frequency Change (SD)	-3.42 (3.87)	-5.68 (5.76)	-5.52 (3.90)
LS Mean Change (SE)	-3.49 (0.28)	-5.56 (0.29)	-5.52 (0.29)
LS Mean Difference from Placebo (SE)	--	-2.07 (0.41)	-2.18 (0.40)
Week 6 (N)	156	144	157
Mean Frequency Change (SD)	-3.36 (3.97)	-5.85 (5.54)	-5.82 (4.04)
LS Mean Change (SE)	-3.58 (0.29)	-5.70 (0.30)	-5.97 (0.29)
LS Mean Difference from Placebo (SE)	--	-2.11 (0.41)	-2.39 (0.41)
Week 7 (N)	154	144	162
Mean Frequency Change (SD)	-3.54 (3.83)	-5.91 (5.52)	-5.81 (4.65)
LS Mean Change (SE)	-3.71 (0.30)	-5.80 (0.31)	-5.97 (0.30)
LS Mean Difference from Placebo (SE)	--	-2.10 (0.43)	-2.27 (0.43)
Week 8 (N)	152	143	151
Mean Frequency Change (SD)	-3.49 (3.61)	-6.25 (5.66)	-5.83 (4.89)
LS Mean Change (SE)	-3.71 (0.30)	-6.10 (0.31)	-6.10 (0.30)
LS Mean Difference from Placebo (SE)	--	-2.30 (0.43)	-2.39 (0.42)
Week 9 (N)	148	141	152
Mean Frequency Change (SD)	-3.99 (3.73)	-6.43 (5.93)	-6.10 (4.88)
LS Mean Change (SE)	-4.09 (0.30)	-6.16 (0.31)	-6.24 (0.30)
LS Mean Difference from Placebo (SE)	--	-2.08 (0.43)	-2.16 (0.43)
Week 10 (N)	141	140	152
Mean Frequency Change (SD)	-3.79 (3.61)	-6.54 (5.89)	-6.20 (4.60)
LS Mean Change (SE)	-4.09 (0.30)	-6.30 (0.31)	-6.25 (0.30)
LS Mean Difference from Placebo (SE)	--	-2.21 (0.43)	-2.16 (0.42)
Week 11 (N)	144	138	149
Mean Frequency Change (SD)	-3.27 (3.92)	-6.49 (5.55)	-6.34 (4.63)
LS Mean Change (SE)	-3.89 (0.31)	-6.37 (0.31)	-6.34 (0.30)
LS Mean Difference from Placebo (SE)	--	-2.48 (0.44)	-2.43 (0.43)
Week 12 (N)	139	131	146
Mean Frequency Change (SD)	-3.67 (4.18)	-6.44 (6.15)	-6.38 (4.48)
LS Mean Change (SE)	-3.90 (0.31)	-6.28 (0.32)	-6.44 (0.31)
LS Mean Difference from Placebo (SE)	--	-2.39 (0.44)	-2.55 (0.43)

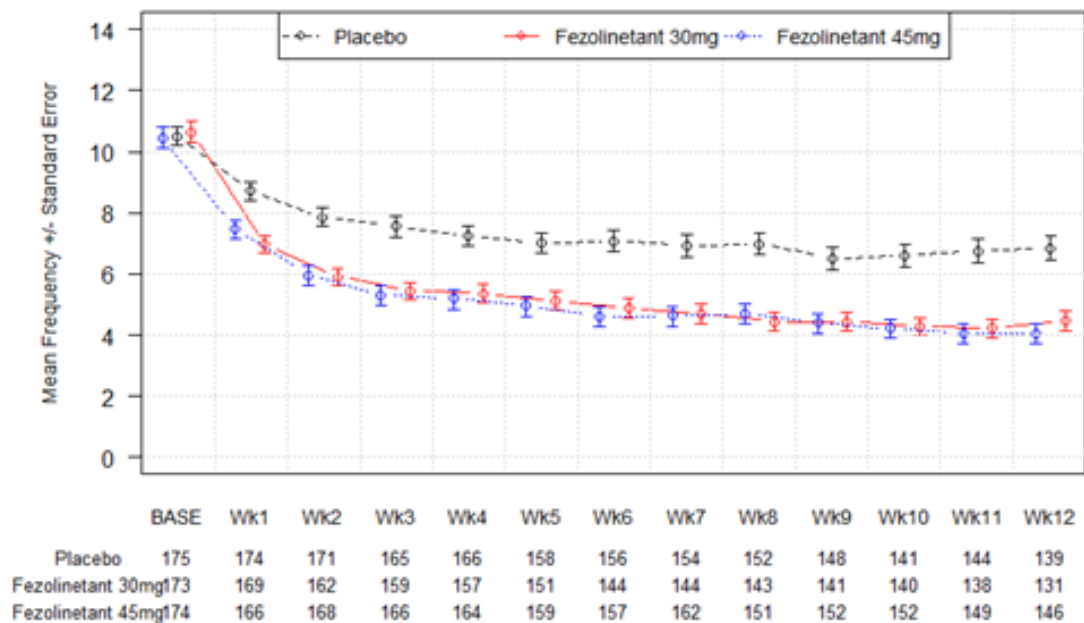
Figures 2 shows the mean frequency of vasomotor symptoms by week in Trial 2693-CL-0301 and Figure 3 shows the same for Trial 2693-CL-0302. Figure 4 and Figure 5 show the mean severity of vasomotor symptoms by week in Trial 2693-CL-0301 and Trial 2693-CL-0302, respectively.

Figure 2: Mean Frequency of Vasomotor Symptoms by week (Trial 2693-CL-0301)



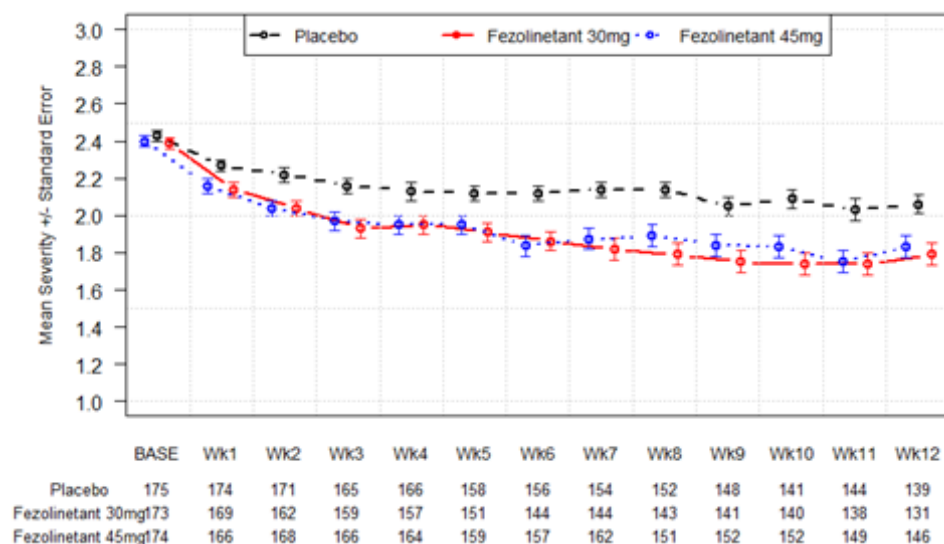
Source: Biometric Review **Figure 2, page 19**, dated November 21, 2022, and NDA 216578, Trial 2693-CL-0301 Report **Figure 3, page 52**.

Figure 3: Mean Frequency of Vasomotor Symptoms by week (Trial 2693-CL-0302)



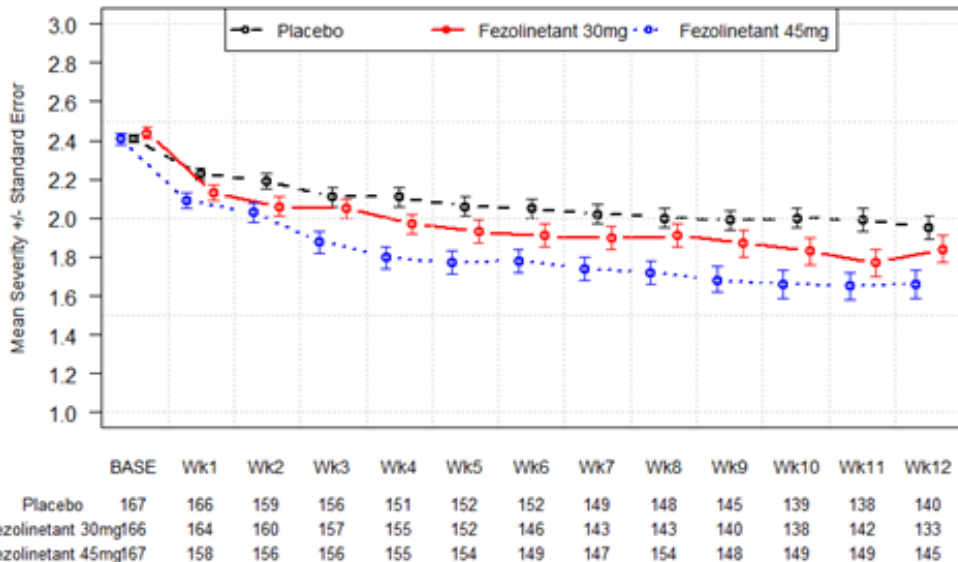
Source: Biometric Review **Figure 3, page 19**, dated November 21, 2022, and NDA 216578, Trial 2693-CL-0302 Report, **Figure 3, page 53**.

Figure 4. Mean Severity of moderate to severe VMS by week (Trial 2693-0301)



Source: Biometric Review **Figure 4, page 20**, dated November 21, 2022, and NDA 216578, Trial 2693-CL-0301 Report, **Figure 4, page 53**.

Figure 5 Mean Severity of moderate to severe VMS by week (Trial 2693-0302)



Source: Biometric Review **Figure 5, page 20**, dated November 21, 2022, and NDA 216578, Trial 2693-CL-0302 Report, **Figure 4, page 54**.

In both Trial 2693-CL-0301 and Trial 2693-CL-0302, participants in the fezolinetant arms (30 mg and 45 mg) had greater reductions from baseline in the mean frequency of moderate to severe vasomotor symptoms compared with the placebo arm through the 12-week double-blind period. The effect was seen as early as week 1. Similarly in both trials, participants in the fezolinetant arms (30 mg and 45 mg) had numerically greater reductions from baseline in mean severity of

moderate to severe vasomotor symptoms compared with the placebo arm through the 12-week double-blind period.

Supplemental prespecified secondary analyses on the clinically meaningful within-subject change thresholds in the frequency of moderate to severe VMS were conducted according to the prespecified Psychometric Analysis Plan (PAP, Version 3.0, dated October 7, 2021). The *anchor-based* method was the primary approach, and the PGI-C VMS was proposed as the primary anchor measure. The score on the PGI-C VMS at Weeks 4 and 12 was provided in the NDA application. The PGI-C VMS is a patient-reported global outcome, designed to provide the participant's assessment of change in VMS experience from the start of the trial. The PGI-C VMS asks the following: "Compared to the beginning of this study, how would you rate your hot flushes/night sweats now?" Participant ratings are as follows: much better, moderately better, a little better, no change, a little worse, moderately worse, and much worse.

The reported results for the 12-week double-blind period are shown in Table 32.

Table 32: Applicant's Analyses of Patient Global Impression of Change – Vasomotor Symptoms (PGI-C VMS)

12-week Double-blind Period (Full Analysis Set)				
Visit	Response	Placebo (n = 167)	Fezolinetant 30 mg (n = 166)	Fezolinetant 45 mg (n = 167)
Week 4	Much better	25/151 (16.6%)	61/155 (39.4%)	68/159 (42.8%)
	Moderately better	23/151 (15.2%)	21/155 (13.5%)	32/159 (20.1%)
	A little better	46/151 (30.5%)	42/155 (27.1%)	42/159 (26.4%)
	No change	43/151 (28.5%)	29/155 (18.7%)	16/159 (10.1%)
	A little worse	6/151 (4.0%)	2/155 (1.3%)	0
	Moderately worse	6/151 (4.0%)	0	0
	Much worse	2/151 (1.3%)	0	1/159 (0.6%)
	P value †	NA	< 0.001	< 0.001
Week 12	Much better	35/144 (24.3%)	68/140 (48.6%)	70/146 (47.9%)
	Moderately better	24/144 (16.7%)	25/140 (17.9%)	35/146 (24.0%)
	A little better	36/144 (25.0%)	26/140 (18.6%)	32/146 (21.9%)
	No change	39/144 (27.1%)	17/140 (12.1%)	8/146 (5.5%)
	A little worse	6/144 (4.2%)	1/140 (0.7%)	1/146 (0.7%)
	Moderately worse	2/144 (1.4%)	2/140 (1.4%)	0
	Much worse	2/144 (1.4%)	1/140 (0.7%)	0
	P value †	NA	< 0.001	< 0.001

All participants who were randomized and received at least 1 dose of fezolinetant during either the 12-week double-blind or the active treatment extension periods (Full Analysis Set, Fezolinetant).

† P-value was obtained using Cochran-Mantel-Haenszel test with modified ridit scores. The association between response and treatment group (fezolinetant 30 mg vs placebo and fezolinetant 45 mg vs placebo) at each analysis visit was tested.

Source: Clinical Review **Table 41, page 150** and NDA 216578, Trial 2693-CL-0301, Final Trial Report, **Table 21, page 60**.

A higher proportion of participants in the 30 mg and 45 mg fezolinetant groups compared with placebo reported a positive change in PGI-C VMS at Weeks 4 and 12. Overall, participants in both the 30 mg and 45 mg fezolinetant groups had a statistically significant difference relative to placebo.

On May 24, 2022, FDA provided an Information Request letter regarding the revised Psychometric Analysis Plan (PAP) and the PAP Summary Report submitted to IND 130277 on March 3, 2022, asking that Astellas provide in their NDA application, evidence to support that the “moderately better” response category in the PGI-C VMS would constitute a meaningful change in the anchor scale. In the subsequent NDA application, Astellas clarifies that PGI-C VMS reported results are considered exploratory and only intended as supplementary evidence of efficacy.

The applicant indicated, “Astellas understands that the primary assessment of clinically meaningful change will be in accordance with the Agency's prior communications that fezolinetant must demonstrate a mean reduction of 2 hot flashes per day compared to placebo in each pivotal study, at both 4 and 12 weeks. Astellas is not proposing that the PAP analyses are alternative criteria for demonstrating clinically meaningful change...Astellas is in agreement that to obtain an indication for the treatment of moderate to severe vasomotor symptoms (VMS) due to menopause, we would need to demonstrate a statistically significant decrease from baseline in the frequency and severity of moderate to severe VMS at Weeks 4 and 12 for fezolinetant compared to placebo and the magnitude of the reduction from baseline in frequency of moderate to severe VMS at Weeks 4 and 12 exceed that of placebo at these timepoints by at least 2 moderate to severe hot flushes per day. Astellas fully agrees and is aligned with the Agency's approach to use this criterium when assessing the clinical efficacy of fezolinetant during the NDA review”

The Division of Clinical Outcomes Assessment (DCOA) Biometric Consult Reviewer response, dated November 22, 2022, concluded “In the NDA submission, in addition to the “14/2 Concept” (Applicant’s primary assessment of clinically meaningful reduction in VMS frequency), the Applicant conducted additional exploratory analyses using clinically meaningful within-patient change thresholds derived from anchor-based analyses to interpret the change in the frequency of moderate to severe vasomotor symptoms. DCOA team has concluded that the selected primary anchor PGIC-VMS has limitations which make it difficult to interpret the results of the anchor-based analyses. Acknowledging the limitations of PGIC-VMS as the only available anchor included in the studies for the VMS frequency, we observed a clear and consistent separation between the treatment group eCDF curves (fezolinetant 30 mg vs. placebo and fezolinetant 45 mg vs. placebo) across the entire range of score change, including both FDA- and applicant-derived meaningful change thresholds as determined by PGIC-VMS at both Week 4 and Week 12 for both phase 3 trials.”

The reader is referred to the DCOA final consult response, dated November 22, 2022, for further information on the limitations of the PGI-C VMS anchor.

The reader is also referred to the reviews of Drs. van der Vlugt and Vivar for discussion of additional secondary analyses. As discussed with the applicant at several timepoints during the clinical development of fezolinetant, (b) (4)

CDTL Conclusions on the Substantial Evidence of Effectiveness:

This reviewer agrees with Drs. van der Vlugt and Vivar's conclusion that the data collected in Trial 2693-CL-0301 and Trial 2693-CL-0302 and subsequently submitted in NDA 216578 are consistent with recommendations provided in the *draft 2003 HT Clinical Trial Guidance* and additional advice provided to the applicant during clinical development, including the agreed-to coprimary endpoints. Data on effectiveness from Trial 2693-CL-0301 and Trial 2693-CL-0302 provide independent and confirmatory substantial evidence of efficacy for the 45 mg dosage strength of Veozah.

8. Safety

Review of the data included in the 505(b)(1) NDA application intended to provide substantial evidence for safety of Veozah were reviewed by Regina Zopf, MD and Theresa H van der Vlugt, M.D., M.P.H.

Veozah is a “first in class” neurokinin 3 (NK3) receptor antagonist. As such the Agency advised the applicant that the NDA be supported by two confirmatory phase 3 trials and long-term trial to assess chronic exposure and long-term safety. To satisfy these recommendations, safety data were submitted from treatment with fezolinetant in 40-week, non-controlled extension phases of 52-week Trials 2693-CL-0301 and 2693-CL-0302, and 52-week, placebo-controlled, long-term safety and chronic use exposure Trial 2693-CL-0304. These trials constitute the primary evidence for the safety assessment of Veozah.

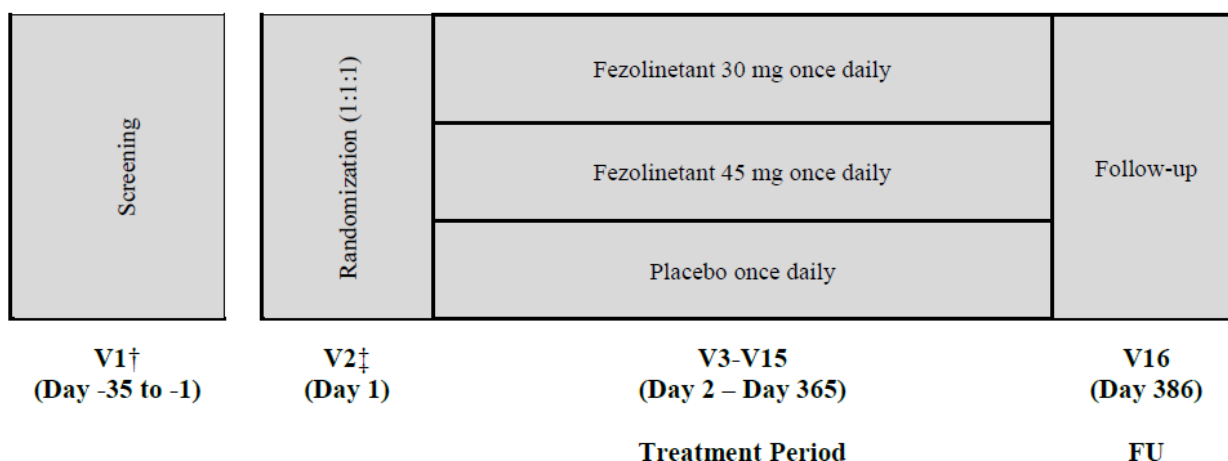
Trial Design and General Considerations of the Phase 3 Safety Assessments

The design of Trials 2693-CL-0301 and 2693-CL-0302 were previously discussed under Section 7 -Efficacy in this review.

Trial 2693-CL-0304 was conducted in support of the general and endometrial safety and long-term drug exposure safety for fezolinetant for use in a postmenopausal woman with a uterus and a postmenopausal woman without a uterus. Trials 2693-CL-0301 and 2693-CL-0302 employed a crossover study design in which all participants were transitioned from 12 weeks of double-blind, double-dummy designed evaluation of fezolinetant versus placebo to an open-label fezolinetant exposure arm without a placebo control group for 40 weeks at dosage levels of 30 and 45 mg oral tablets. Therefore, half of the participants in Trial 2693-CL-0301 and Trial 2693-CL-0301 had up to 52 weeks of fezolinetant exposure and the other half had up to 40 weeks of exposure. Trial 2693-CL-0304 was a double blind, placebo-controlled trial for its entire 52-week durations. Most of the participants in the safety database were enrolled in Trial 2693-CL-0304. The Safety Analysis Set for each population consisted of all randomized participants (people with VMS associated with menopause) who took at least 1 dose of study intervention.

The trial schema for Trial 2693-CL-0304 is presented in Figure 6.

Figure 6: Trial 2693-CL-0304 Schema



† Screening was to be performed up to 35 days prior to randomization.

‡ Visit 2b assessments

Definitions: FU = follow-up, V = visit

Source: NDA 216578 Synopsis of Trial 2693-CL-0304, **Figure 1, Page 2.**

Participants received baseline and a complete physical examination, vital signs, and clinical laboratory specimens at every visit. The following evaluations were completed at screening (Visit 1), and all except the pap test, serology and mammography were repeated at study completion or termination (Visit 15/EOT):

- Screening mammogram
- 12 lead electrocardiogram (ECG)
- Pap test
- Transvaginal ultrasound (TVUS)
- Endometrial biopsy
- DXA
- Serology

Any participant who experienced unscheduled bleeding underwent an additional endometrial biopsy. All endometrial biopsies were read concurrently by three independent expert pathologists from institutions with independent fiduciary and organizational reporting. Each pathologist was blinded to the treatment group and to the readings of the other pathologists. The concurrence of two of the three pathologists was accepted as the final diagnosis. If there was no agreement among the three pathologists, the most severe pathologic diagnosis would be used as the final diagnosis. Pathologists were instructed to use the standardized criteria for histologic evaluation as presented in the *2003 draft HT Clinical Trial Guidance*.

An Adverse Event (AE) was defined as any untoward medical occurrence in a participant administered a study drug, and which does not necessarily have to have a causal relationship with this treatment. AE collection (collected in open-ended, non-leading verbal questioning fashion) began after the signing of the informed consent and continued until 21 days after the last dose of study drug or if the participant was determined to be a screen failure. AE intensity was assessed as mild, moderate, or severe.

Adverse events (AEs) were coded to standard preferred term (PT) and summarized by system organ class (SOC) as defined in MedDRA, Version 23.0. Treatment Emergent Adverse Events (TEAEs) were defined as the AEs which occurred on or after the first dose of study intervention and up to 21 days after the last dose. All AEs occurring during or after the participant has discontinued the study were to be followed up until resolved or judged to be no longer clinically significant, or until they were deemed to be chronic by the investigator.

The applicant provided an overview and separate summaries by system organ class (SOC) and preferred term of the number and percentage of participants as well as the EAIR of TEAEs, drug-related TEAEs, TEAEs leading to withdrawal of treatment and TEAEs excluding SAEs and drug-related TEAEs leading to withdrawal of treatment were presented by treatment group. Also included in the overview are the number and percentage of subjects with serious TEAEs, drug-related serious TEAEs, TEAEs leading to death, and drug-related TEAEs leading to death.

The investigator used the following definitions to rate the severity of each AE

- Mild: No disruption of normal daily activities
- Moderate: Affect normal daily activities
- Severe: Inability to perform daily activities

AE causality was assessed by the site investigator as not related, possibly related, probably related, or definitely related. When making an assessment of causality, the following factors were considered when deciding if there was evidence and/or arguments to suggest there was a 'reasonable possibility' that an (S)AE may have been caused by the study drug (rather than a relationship cannot be ruled out) or if there was evidence to reasonably deny a causal relationship:

- Plausible temporal relationship between exposure to the study drug and (S)AE onset and/or resolution. Has the subject actually received the study drug? Did the (S)AE occur in a reasonable temporal relationship to the administration of the study drug?
- Plausibility, i.e., could the event have been caused by the study drug? Consider biologic and/or pharmacologic mechanism, half-life, literature evidence, drug class, preclinical and clinical study data, etc.
- Dechallenge/Dose reduction/Rechallenge:
- Did the (S)AE resolve or improve after stopping or reducing the dose of the suspect drug?
- Did the (S)AE reoccur if the suspected drug was reintroduced after having been stopped?
- Laboratory or other test results; a specific lab investigation supports the assessment of the relationship between the (S)AE and the study drug (e.g., based on values pre-, during and post-treatment)
- Available alternative explanations independent of study drug exposure, such as other concomitant drugs, past medical history, concurrent or underlying disease, risk factors including medical and family history, season, location, etc. and strength of the alternative explanation

AEs were presented in exposure adjusted incidence rate per 100-person year to adjust for variable exposure times on fezolinetant and/or placebo.

The following were defined a priori as Adverse Events of Special Interests (AESIs):

- Liver test elevations
- Uterine bleeding
- Endometrial hyperplasia or cancer or disordered proliferative endometrium
- Thrombocytopenia
- Bone fractures
- Potential abuse liability
- Depression
- Wakefulness
- Effect on memory

The clinical laboratories evaluated included:

- Urine Pregnancy Test:
 - β -HCG
- Hematology:
 - CBC: white blood cell count with differential (neutrophils, lymphocytes, eosinophils, monocytes, and basophils)
 - hemoglobin
 - hematocrit
 - red blood cell count platelets
- Biochemistry
 - Blood urea nitrogen Chloride
 - Creatinine
 - Inorganic phosphorus Sodium
 - Bicarbonate Calcium Creatine kinase
 - Estimated glomerular filtration rate
 - Glucose
 - Lactate dehydrogenase Potassium
 - Uric acid
- Liver Biochemistry:
 - Alanine aminotransferase
 - Alkaline phosphatase Aspartate aminotransferase Albumin
 - Gamma-glutamyltransferase
 - Total bilirubin
- Urinalysis:
 - Protein
 - Glucose
 - pH
 - Blood
- Coagulation Panel:
 - International normalized ratio
 - Activated partial thromboplastin time
 - Prothrombin time
- Serology:

- HBsAg
- HCV antibody
- HIV antibody
- Hormone Levels:
 - LH
 - FSH
 - Estradiol
 - SHBG
 - Testosterone
 - Total/Free Androstenedione
 - DHEA
 - Estrone

For quantitative laboratory measurements descriptive statistics were used to summarize results and change from baseline for participants by treatment group and time point. Shifts relative to normal ranges from baseline to each time point were evaluated and laboratory data is provided in the lab datasets.

The liver safety assessments are summarized by the categories below based on the measurements from ALP, ALT, TBL, AST and their combination. The parameters are based on measurements from a central laboratory. The subject's highest value during the treatment period is used.

- ALT > 3X ULN, > 5X ULN, > 10X ULN, > 20X ULN
- AST > 3X ULN, > 5X ULN, > 10X ULN, > 20X ULN
- ALT or AST > 3X ULN, > 5X ULN, > 10X ULN, > 20X ULN
- ALP > 1.5X ULN
- TBL > 2X ULN
- (ALT or AST > 3X ULN) and TBL > 2X ULN
- (ALT or AST > 3X ULN) and ALP < 2X ULN and TBL > 2X ULN

The last 2 criteria where two or more parameters are evaluated will be with the measurements on the same day or up to 1 day apart.

The applicant followed FDA recommendations related to clinical assessments for evaluating the general safety of fezolinetant in the treatment of moderate to severe VMS in healthy postmenopausal women.

The applicant employed several pooled populations for analyses of safety. which are summarized in below. Pooling strategies were presented in the statistical analysis plan submitted in the Pre-NDA phase and were reviewed and accepted by FDA. Table 33 presents the pooled populations considered by the applicant.

Table 33 Applicant's Pooled Populations for Consideration of Safety

Population	Studies	Treatment Groups Summarized	Rationale
POP1 Phase 3 Pivotal Placebo-controlled 12-week	2693-CL-0301 2693-CL-0302	- Placebo - Fezolinetant 30 mg - Fezolinetant 45 mg - Fezolinetant total	- Assess the short-term safety profile of fezolinetant 30 mg and 45 mg doses relative to placebo for 12 weeks - The same subject population as for the efficacy profile for 12 weeks of exposure - The tablet formulation was administered
POP2† Phase 3 52-week	2693-CL-0301 2693-CL-0302 2693-CL-0304	- Placebo - Fezolinetant 30 mg - Fezolinetant 45 mg - Placebo/fezolinetant 30 mg ‡ - Placebo/fezolinetant 45 mg ‡ - Fezolinetant 30 mg total - Fezolinetant 45 mg total - Fezolinetant total	- Assess the safety profile of fezolinetant 30 mg and 45 mg doses up to 52 weeks - Assess the 52-week endometrial health endpoints including TVU and endometrial biopsy findings - Varying exposure for fezolinetant and placebo, used for exposure-adjusted safety endpoints - The tablet formulation was administered
POP3 VMS Phase 2 and 3 12-week	ESN364_HF_204 ESN364_HF_205 2693-CL-0301 2693-CL-0302 2693-CL-0304	- Placebo - Fezolinetant 30 mg total § - Fezolinetant 45 mg total ¶ - Fezolinetant 15 mg bid †† - Fezolinetant ≥ 60 mg (including 30, 60, 90 mg bid, 60, 120, 180 mg qd) †† - Fezolinetant total	To accommodate difference in, formulations (capsule, tablet), dosing regimen (qd, bid) and doses within each set of dosing regimen, this population is used to assess the following: - The 12-week safety from all phase 2/3 studies in VMS subject population who were exposed to fezolinetant - The safety profile of fezolinetant doses that are lower than 30 mg and higher than 45 mg daily dose
POP4 Phase 3 Placebo-controlled 52-week	2693-CL-0304	- Placebo - Fezolinetant 30 mg - Fezolinetant 45 mg - Fezolinetant total	- Assess the long-term safety profile of fezolinetant 30 mg and 45 mg doses relative to placebo for 52 weeks - Perform additional analyses that may not have been planned in the study CSR
POP5 VMS Phase 2 12-week	ESN364_HF_204 ESN364_HF_205	- Placebo - Fezolinetant 30 mg qd - Fezolinetant 15 mg bid - Fezolinetant ≥ 60 mg (including 30, 60, 90 mg bid, 60, 120, 180 mg qd) §¶ - Fezolinetant total §¶	- The 12-week safety from the phase 2 studies in VMS subject population who were exposed to fezolinetant (subset of POP3) - The safety profile of fezolinetant doses that are lower than 30 mg and higher than 45 mg daily dose.

† In addition, POP2 was evaluated at 12 weeks (12-week POP2) to assess the placebo-controlled safety profile from the 3 phase 3 Trials 2693-CL-0301, 2693-CL-0302 and 2693-CL-0304, specifically for AEs and categorical increases in liver parameters.

‡ Placebo/fezolinetant 30/45 mg represents treatment for participants who received placebo initially and completed 12 weeks of treatment and were re-randomized to fezolinetant 30/45 mg for the remaining 40 weeks of treatment (i.e., active treatment extension period) in the two confirmatory phase 3 Trials 2693-CL-0301 and 2693-CL-0302. Thus, for the two treatment groups, the treatment duration was up to 40 weeks.

§ Includes fezolinetant 30 mg (tablet) and placebo/fezolinetant 30 mg (tablet) in Trials 2693-CL-0301 and 2693-CL-0302 fezolinetant 30 mg (tablet) in Trial 2693-CL-0304, and fezolinetant 30 mg daily (capsule) in ESN364_HF_205.

¶ Includes fezolinetant 45 mg (tablet) and placebo/fezolinetant 45 mg (tablet) in Trials 2693-CL-0301 and 2693-CL-0302 and fezolinetant 45 mg (tablet) in Trial 2693-CL-0304. Note that this treatment group is the same as POP2 fezolinetant 45 mg total group.

†† Includes doses from the 2 phase 2 Studies ESN364_HF_204 and ESN364_HF_205, which used the capsule formulation.

Definitions; AE: adverse event; TVU: transvaginal ultrasound; VMS: vasomotor symptoms.

Source: Clinical review table **pages 156 and 157** and Summary of Clinical Safety/Integrated Summary of Safety **Table 3, page 19.**

In their review, Drs. van der Vlugt and Zopf focussed primarily on the integrated safety data generated in the phase 3 trials, as reflected in the POP2 population. POP2 is the only pooled population that encompasses all pooled phase 3 data with up to 40 to 52 weeks of fezolinetant exposure and no phase 2 data.

The POP 2 52 -week pooled safety analysis for fezolinetant is comprised of the three phase 3

clinical trials. Trials 2693-CL-0301 and 2693-CL-0302 employed a crossover study design where all participants were transitioned from 12 weeks of double-blind, double-dummy designed evaluation of fezolinetant versus placebo to an open-label fezolinetant exposure arm without a placebo control group for 40 weeks at dosage levels of 30 and 45 mg oral tablets. Trials 2693-CL-301 and 2693-CL-302 contained 40 weeks of noncontrolled safety data. Therefore, half of the participants in studies 301 and 302 had up to 52 weeks of fezolinetant exposure and the other half had up to 40 weeks of exposure. By contrast, Trial 2693-CL-0304 was a double blind, placebo-controlled trial for the entire 52-weeks. Most of the participants in the safety database were in enrolled in Trial 2693-CL-0304. Because Trial 2693-CL-0304 is included in POP2 and it was the largest and only trial which followed a placebo control design for the entire 52-week duration, most of the data generated in POP2 was placebo-controlled.

Per the consultative advice from the Division of Biometric 7 (DB7), in order to evaluate pooled data that includes variable duration of exposures to placebo we used the exposure adjusted incidence rate (EAIR) of adverse events for statistical analysis of adverse events. When evaluating the results of Trial 2693-CL-304 alone, the rates of adverse event in placebo versus treatment can be compared along with the risk difference.

Table 34 present the analyses set classification for the POP2 52week population

Table 34: Analyses Set Classification - POP2: Phase 3 52-week – All Randomized Participants

Analyses Set	Placebo (N=954)	Fezolinetant 30 mg (N=953)	Fezolinetant 45 mg (N=952)	Placebo/ Fezolinetant 30 mg (N=152)	Placebo/ Fezolinetant 45 mg (N=151)	Total (3,162)
Randomized¹	954 (100%)	953 (100%)	952 (100%)	152 (100%)	151 (100%)	3,162 (100%)
Took Study Drug²	952 (99.8)	951 (99.84)	949 (99.74)	152 (100%)	151 (100%)	3155 (99.78)
Safety Analysis Set²	952 (99.8)	951 (99.84)	949 (99.74)	152 (100%)	151 (100%)	3155 (99.78)

¹Planned treatment at randomization

²In 2693-CL-0301, one subject who was randomized to fezolinetant 45 mg group received fezolinetant 30 mg in the first 12 weeks.

A total of 2859 unique participants were originally randomized in the totality for the first 12-week placebo-controlled phase of Trials 2693-CL-301 and Trials 2693-CL-301 and 52-week placebo-controlled Trials 2693-CL-304. The Safety Analysis Set (SAF) for POP2 includes those 2859 women originally randomized for the first 12-week placebo-controlled phase of Trials

2693-CL-301 and Trials 2693-CL-302, and 52-week placebo-controlled Trials 2693-CL-304 in addition to 303 women re-randomized from placebo to fezolinetant in the 40-week extension phase of Trial 2693-CL-301 and Trial 2693-CL-302. The SAF for POP2 includes 3,162 randomized participants who also took at least 1 dose of study intervention for a total of 3,155 participants, (952 participants in the placebo group, 951 participants in the fezolinetant 30 mg group, 949 participants in the fezolinetant 45 mg group, 152 participants in the placebo/fezolinetant 30 mg group and 151 participants in the placebo/fezolinetant 45 mg group). Around three-quarters of all participants in POP2 completed the full 52-week trials.

General Phase 3 Safety Findings

Protocol Deviations, Discontinuations, Demographics and Exposure

Tables 35, 36 and 36 presents the major protocol violations for the three phase 3 trials, Trial 2693-CL-301, Trial 2693-CL-302, and Trial 2693-CL-0304 included in the POP2 population.

Table 35 Major Protocol Deviations (Safety Analysis Set); 52-week Period; Trial 2693-CL-0301

Category	Placebo (n = 23)	Placebo/ Fezolinetant 30 mg (n = 76)	Placebo/ Fezolinetant 45 mg (n = 76)	Fezolinetant 30 mg (n = 174)	Fezolinetant 45 mg (n = 173)	Total (n = 522)
Overall protocol deviations	5 (21.7%)	19 (25.0%)	11 (14.5%)	36 (20.7%)	33 (19.1%)	104 (19.9%)
Entered into the study even though they did not satisfy entry criteria (PD1)	5 (21.7%)	17 (22.4%)	10 (13.2%)	27 (15.5%)	31 (17.9%)	90 (17.2%)
Developed withdrawal criteria during the study and was not withdrawn (PD2)	0	0	0	0	0	0
Received wrong treatment or incorrect dose (PD3)	0	1 (1.3%)	0	7 (4.0%)	3 (1.7%)	11 (2.1%)
Received excluded concomitant treatment (PD4)	0	1 (1.3%)	1 (1.3%)	4 (2.3%)	0	6 (1.1%)

Definitions: PD = Protocol deviation.

Source: Clinical Review Table 13, page 96 and NDA 216578, Trial 2693-CL-0301 Final Trial Report, Table 5, page 33.

Table 36 Major Protocol Deviations (Safety Analysis Set); 52-week Period; Trial 2693-CL-0302

Category	Placebo (n=16)	Placebo/ Fezolinetant 30 mg (n = 76)	Placebo/ Fezolinetant 45 mg (n = 75)	Fezolinetant 30 mg (n = 166)	Fezolinetant 45 mg (n = 167)	Total (n = 500)
Overall protocol deviations	2 (12.5%)	18 (23.7%)	17 (22.7%)	43 (25.9%)	33 (19.8%)	113 (22.6%)
Entered into the study even though they did not satisfy entry criteria (PD1)	2 (12.5%)	15 (19.7%)	14 (18.7%)	36 (21.7%)	29 (17.4%)	96 (19.2%)
Developed withdrawal criteria during the study and was not withdrawn (PD2)	0	0	0	1 (0.6%)	0	1 (0.2%)
Received wrong treatment or incorrect dose (PD3)	1 (6.3%)	0	2 (2.7%)	6 (3.6%)	4 (2.4%)	13 (2.6%)
Received excluded concomitant treatment (PD4)	1 (6.3%)	3 (3.9%)	1 (1.3%)	2 (1.2%)	3 (1.8%)	10 (2.0%)

Safety Analysis Set: All randomized participants who took at least 1 dose of trial medication.

Participants in the placebo/fezolinetant groups were re-randomized in a 1:1 ratio to 30 mg or 45 mg of fezolinetant after 12 weeks of placebo and only data from the active treatment extension period are shown in the placebo/fezolinetant columns (fezolinetant exposure).

Source: Clinical Review **Table 28**, page **128** and NDA 216578, Trial 2693-CL-0302 Final Trial Report, **Table 5**, page **35**.

Table 37 Major Protocol Deviations (Safety Analysis Set); 52-week Trial 2693-CL-0304

Category	Placebo (n = 610)	Fezolinetant 30 mg (n = 611)	Fezolinetant 45 mg (n = 609)	Total (n = 1830)
Overall protocol deviations	107 (17.5%)	106 (17.3%)	108 (17.7%)	321 (17.5%)
Entered into the study even though they did not satisfy entry criteria (PD1)	79 (13.0%)	75 (12.3%)	76 (12.5%)	230 (12.6%)
Developed withdrawal criteria during the study and was not withdrawn (PD2)	0	3 (0.5%)	1 (0.2%)	4 (0.2%)
Received wrong treatment or incorrect dose (PD3)	27 (4.4%)	22 (3.6%)	21 (3.4%)	70 (3.8%)
Received excluded concomitant treatment (PD4)	12 (2.0%)	18 (2.9%)	18 (3.0%)	48 (2.6%)

Definitions: PD = protocol deviation

PD3 included participants who took an incomplete dose.

Source: NDA 216578, Trial 2693-CL-0302 Final Trial Report, **End-of-text Table 9.1.1.5**

The major protocol deviations for POP2 appear to be related to participants who were allowed to enroll in each trial without meeting eligibility criteria. The most common eligibility criteria deviations were related to the exclusion criterion related to blood pressure (enrolled despite blood pressure greater than 130/80) and participants enrolling who were unwilling to complete

study procedures. In response to the clinical team's inquiry regarding allowing subjects to enroll who did not strictly meet enrollment criteria, the applicant responded:

1. If participants had a history of hypertension that was well controlled, they could be enrolled into the trial at the discretion of the investigator. The blood pressure deviations were minimal and not clinically significant based on the investigator's determination. The applicant considered that given the slight deviation, the enrollment of these participants would not affect the safety of fezolinetant or participant safety in the trial.
2. Forty-three (43) of 230 participants missed a pregnancy test at the time of enrollment; however, these participants were post-menopausal. No participants were found to have a positive pregnancy test in future visits.
3. Twenty-nine (29) participants had a protocol deviation related to an endometrial abnormality at the time of baseline biopsy or were enrolled without an evaluable endometrial sample if the TVUS showed an endometrial stripe <4mm (allowed in early versions of the protocol).
4. Seventy (70) participants had deviations related to receiving an incorrect dose. This was caused by a misunderstanding of dosing instruction and participants were dosed from only 1 blister pack in error instead of taking 1 pill from each blister pack for each dose. These deviations occurred during the first treatment period and most of them were identified and resolved within that treatment period. However, there were 10 participants with interruptions from 35 to 96 days. There were also 18 participants who erroneously received a kit that was not the kit assigned by the interactive response technology due to site personnel error, and the maximum amount of time those participants dosed erroneously was for 35 days. Ultimately participants received a lower dose than they should have and therefore this did not result in safety concerns.

Drs. van der Vlugt and Zopf opined that the applicant's responses were reasonable and concurred that the protocol deviations were unlikely to have any substantial effect on the safety outcome. I agree with their assessment.

Table 38 presents the clinical reviewers' assessments of discontinuations by treatment arm for the POP2 population. The causes of those discontinuations are presented Table 39.

Table 38: Reviewer's Assessment of Discontinuations by Treatment Arm, POP2 Population

Actual Treatment Arm	End of Study Status 12 weeks		End of Study Status 52 weeks	
	Discontinued	Completed	Discontinued	Completed
Fezolinetant 30 mg daily	111 (11.7%)	840 (88.3%)	251 (26.4%)	700 (73.61%)
Fezolinetant 45 mg daily	91 (9.6%)	858 (90.4%)	230 (24.2%)	719 (75.8%)
Placebo daily	134 (15.6%)	818 (85.9%)	287 (32.8%)	665 (69.9%)
Placebo/Fezolinetant 30 mg daily	0	152 (100%)	27 (17.8%)	125 (82.2%)
Placebo/Fezolinetant 45 mg daily	0	151 (100%)	21 (13.9%)	130 (86%)

Source: Clinical Review, **Table 46, page 175**, reviewer generated JMP table, ISS ADSL 52-week dataset, POP252FL=Y, variables: EO12STT, EO52STT.

Approximately 11% of POP2 participants in the fezolinetant arms discontinued by the end of 12 weeks, while approximately 25% of participants discontinued by the end of 52 weeks. Approximately 33% of participants in the placebo arm discontinued by the end of 52 weeks.

Table 1 Reviewer’s Assessment of Cause and Percent of Total for Discontinuation, POP2 Population

Discontinuation Reason	Number	Percent of Discontinuation
Withdrawal by Subject	411	53.5%
Adverse Event	144	18.7%
Lost to Follow-Up	126	16.4%
Other	60	7.81%
Protocol Deviation	28	3.65%
Death	1	0.13%
All	770	100%

Source: Clinical Review, **Table 47, page 175 176**, reviewer generated JMP table, ISS ADSL 52-week dataset, POP2FL=Y, EOTSTT=Discontinued

Of the participants that discontinued around half were coded as due to “subject withdrawal”. Reasons for withdrawal did not differ significantly by treatment arm. Around 15% of participant withdrawals were due to reasons related to the COVID-19 pandemic. There is a higher-than-expected number of “withdrawal by subject” because this study was being conducted as the COVID-19 pandemic unfolded over the course of 2020. Treatment withdrawal was balanced across treatment arms which is reassuring from a safety standpoint.

There were 144 participants that discontinued the study due to an adverse event. The most common adverse events that led to treatment withdrawn was liver function test increased (n=17) [with terms combined were alanine aminotransferase increased, aspartate aminotransferase increased, hepatic enzyme increased, liver function test increased, and transaminases increased. This was followed by headache (n=15), nausea (n=11), and fatigue (n=11).

Table 40 presents the Demographics and Targeted Baseline Information for the POP2 (52-Week) Safety Population.

Table 40: Demographics and Targeted Baseline Information for the POP2 (52-Week) Safety Population

Characteristic	Category/ Statistic	Placebo (n=952)	Fezolinetant 30 mg total (n=1100)	Fezolinetant 45 mg total (n=1103)
Age (years)	n	952	1100	1103
	Mean (SD)	54.8 (4.8)	54.6 (5.0)	54.5 (4.8)
	Median	55.0	54.0	54.0
	Min, Max	41, 65	40, 65	40, 65
BMI (kg/m ²)	n	952	1098	1102
	Mean (SD)	28.21(4.58)	28.23 (4.61)	28.34 (4.63)
	Median	27.94	27.98	28.05
	Min, Max	18.3, 38.0	18.0, 38.0	18.0, 38.0
Hysterectomy	No	723 (75.9%)	826 (75.1%)	843 (76.4%)
	Yes	229(24.1%)	274 (24.9%)	260 (23.6%)
Isolated NAFLD	No	939 (98.7%)	1093 (99.4%)	1088 (98.6%)
	Yes	8 (0.8%)	7 (0.6%)	15 (1.4%)
NASH	No	949 (99.7%)	1098 (99.8%)	1101 (99.8%)
	Yes	3 (0.3%)	2 (0.2%)	2 (0.2%)
Diabetes	No	880 (92.4%)	1007 (91.5%)	1018 (92.3%)
	Yes	72 (7.6%)	93 (8.5%)	85 (7.7%)
Smoking Status	Current	174 (18.3%)	196 (17.8%)	197 (17.9%)
	Former/never	778 (81.7%)	904 (82.2%)	906 (82.1%)
Alcohol history	Current	562(59.0%)	623 (56.6%)	636 (57.7%)
	Former/never	390(41.0%)	477 (43.4%)	467 (42.3%)
Geographical region/Country	Europe/Czech Republic	15 (1.6%)	18 (1.6%)	13 (1.2%)
	Europe/Hungary	12 (1.3%)	20 (1.8%)	10 (0.9%)
	Europe/Latvia	8 (0.8%)	9 (0.8%)	11 (1.0%)
	Europe/Poland	159 (16.7%)	193 (17.5%)	185 (16.8%)
	Europe/Spain	8 (0.8%)	12 (1.1%)	15 (1.4%)
	Europe/Ukraine	10 (1.1%)	12 (1.1%)	14 (1.3%)
	Europe/United Kingdom	37 (3.9%)	26 (2.4%)	29 (2.6%)
	North America/ Canada	79 (8.3%)	99 (9%)	69 (6.3%)
	North America/ United States	624 (62.5%)	711 (64.6%)	757 (68.6%)

Source: Clinical Review **Table 43**, **page 162** and NDA 216578, SCS/ISS, Sponsor **Table 7**, **page 33**.

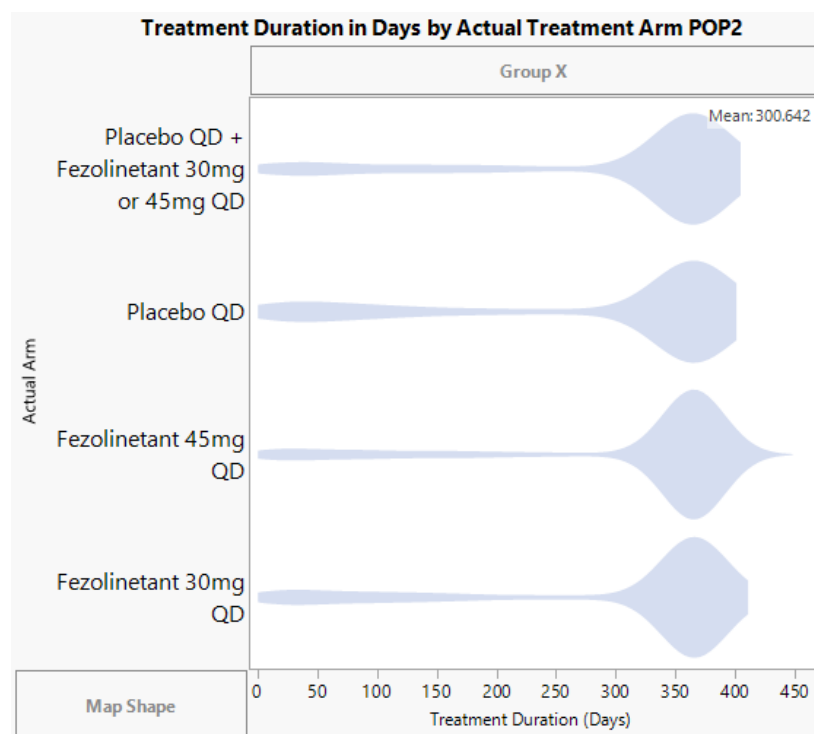
The average age was 55 years of age, with a range of 40 to 65 years of age. 80% of participants in POP2 self-identified as White and 17% self-identified as Black/African American. Eight percent of Black participants and twenty-five percent of White participants reported Hispanic ethnicity. The average BMI was 28.21 and around 80 percent were former or never smokers. Most of the participants enrolled were from the United States and Canada while around one

quarter of participants enrolled were from Europe (mostly Poland).

The demographics of the POP2 phase 3 trials population in line with and represent that of a US population. Considering that the US population is 18.9% Hispanic ethnicity and 13.6% Black race (2020 US Census Bureau Data), the clinical trials had good representation of minority populations.

Figure 7 is a graphic presentation of exposure by treatment group in POP2 and Table 41 presents exposure information by treatment group for the POP2 52-week population.

Figure 7: Contour Graphic of Exposure Duration POP2 52 Weeks



Source: Clinical Reviewer generated JMP contour graph **Figure 3, page 158**, ISS ADSL 52-week dataset, POP2FL=Y, TRTEDY (Day of Last exposure to treatment) variable

Table 41 Cumulative Exposure Duration by Treatment Group POP2 52-Week: Safety Analyses Set

	Placebo (n = 951)	Fezolinetant 30 mg (n = 951)	Fezolinetant 45 mg (n = 949)	Placebo/ Fezolinetant 30 mg (n = 152)	Placebo/ Fezolinetant 45 mg (n = 151)	Fezolinetant 30 mg Total† (n = 1103)	Fezolinetant 45 mg Total‡ (n = 1100)	Fezolinetant Total (n = 2203)
Cumulative duration (days)								
≥ 1	952 (100.0%)	951 (100.0%)	949 (100.0%)	152 (100.0%)	151 (100.0%)	1103 (100.0%)	1100 (100.0%)	2203 (100.0%)
≥ 7	942 (98.9%)	937 (98.5%)	933 (98.3%)	152 (100.0%)	151 (100.0%)	1089 (98.7%)	1084 (98.5%)	2173 (98.6%)
≥ 14	930 (97.7%)	925 (97.3%)	931 (98.1%)	152 (100.0%)	151 (100.0%)	1077 (97.6%)	1082 (98.4%)	2159 (98.0%)
≥ 21	911 (95.7%)	917 (96.4%)	918 (96.7%)	151 (99.3%)	151 (100.0%)	1068 (96.8%)	1069 (97.2%)	2137 (97.0%)
≥ 28	900 (94.5%)	905 (95.2%)	909 (95.8%)	150 (98.7%)	149 (98.7%)	1055 (95.6%)	1058 (96.2%)	2113 (95.9%)
≥ 42	866 (91.0%)	875 (92.0%)	886 (93.4%)	146 (96.1%)	148 (98.0%)	1021 (92.6%)	1034 (94.0%)	2055 (93.3%)
≥ 56	855 (89.8%)	864 (90.9%)	882 (92.9%)	144 (94.7%)	147 (97.4%)	1008 (91.4%)	1029 (93.5%)	2037 (92.5%)
≥ 84	747 (78.5%)	844 (88.7%)	859 (90.5%)	141 (92.8%)	143 (94.7%)	985 (89.3%)	1002 (91.1%)	1987 (90.2%)
≥ 168	467 (49.1%)	769 (80.9%)	799 (84.2%)	133 (87.5%)	135 (89.4%)	902 (81.8%)	934 (84.9%)	1836 (83.3%)
≥ 252	441 (46.3%)	731 (76.9%)	757 (79.8%)	128 (84.2%)	131 (86.8%)	859 (77.9%)	888 (80.7%)	1747 (79.3%)
≥ 365	235 (24.7%)	393 (41.3%)	416 (43.8%)	0	0	393 (35.6%)	416 (37.8%)	809 (36.7%)
Missing	0	0	0	0	0	0	0	0

Source: Clinical Review **Table 42, page 159** and NDA 216578, SS/ISS **Table 5, page 29**.

Around three-quarters of all participants in POP2 completed the full 52-week trials. The mean exposure duration was 300 days, with most participants discontinuing trial treatment between 252 and 365 days.

The safety database is considered adequate based on size and duration of treatment for evaluating the safety of fezolinetant. The safety database exceeded ICH E1A guideline recommendations for drugs intended for chronic use of 1500 patients overall, 300-600 patients for six months, and 100 patients for one year at the dose or dose range believed to be efficacious.

Deaths and Serious Adverse Events

There were 2 deaths reported, both in fezolinetant treatment arms, during the clinical development program. There were no deaths in the placebo groups in any of the phase 3 trials.

1. One motorcycle passenger accident in Trial 2693-CL-0302
Narrative: The participant in Trial 2693-CL-0302 (assigned to Placebo/fezolinetant 45 mg daily) died following a motorcycle accident where the participant was the passenger sitting behind the driver. She died instantly following multiple injuries. The accident occurred on **Day 193**.

The review teams concurs that this was an accident and unrelated to trial drug treatment.

2. One cardiac arrest with anoxic brain injury in Trial 2693-CL-0304).

Narrative: The participant in Trial 2693-CL-0304 (assigned to fezolinetant 30 mg daily) experience sudden cardiac arrest and brain anoxic injury on study **Day 123** and died subsequently on **Day 125**. This participant was 62 years of age, White race, non-Hispanic ethnicity, and had a history of diabetes mellitus (type 2), chronic obstructive pulmonary disease (active smoker), hypertension and a BMI of 36. Assessments leading up to the event such as ECG and labs were not available. Baseline lab assessments were normal aside from elevated glucose. On **Day 123**, the participant suddenly collapsed with cardiac arrest and remained hypoxic during transport with intubation in the emergency department. A head CT scan was performed and revealed anoxic brain injury.

On **Day 124**, laboratory results showed a troponin value of 0.90 ng/mL, which was consistent with the definition of acute myocardial infarction as described by the WHO (range: 0.60 to 1.50 ng/mL). Troponin peaked later the same day at 2.03 ng/mL. Blood lactic acid peaked at 2.5 mmol/L also on **Day 124**. A nuclear medicine flow study performed on **Day 125** and compared with CT on **Day 123** (admission) revealed no evidence of cerebral blood flow consistent with brain death; the participant was declared dead on **Day 125**. The applicant's assessment was that this death was unrelated to trial medication.

The reviewers concur with the applicant that this death is like unrelated to trial drug treatment. Given the lack of assessments available in this case, it is not possible to definitively determine that that this death was drug related. However, given multiple medical problems affecting the cardiovascular system, this participant was at high risk for cardiac events, and it is highly likely that her medical history of diabetes, hypertension, obesity, and smoking were the major contributors to her cause of death.

A summary with EAIRs for the serious adverse events (SAEs) that occurred on/after the first dose of trial medication for the POP2 52-week safety population by system organ class (SOC) and preferred term (PT) according to treatment group are presented in Table 42.

Table

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**Table 42 Serious Treatment-Emergent Adverse Events POP2 52-Week Data;
Exposure Adjusted Incidence Rates (EAIRs)**

MedDRA (v23.0) System Organ Class Preferred Term	Placebo (n = 952) n (% , EAIR)	Fezolinetant 30 mg Total (n = 1103) n (% , EAIR)	Fezolinetant 45 mg Total (n = 1100) n (% , EAIR)
Overall	15 (1.6%, 2.7)	41 (3.7%, 4.6)	45 (4.1%, 4.8)
Cardiac Disorders	1 (0.1%, 0.2)	5 (0.5%, 0.6)	0
Acute myocardial	0	1 (0.1%, 0.1)	0
Atrial fibrillation	1 (0.1%, 0.2)	2 (0.2%, 0.2)	0
Cardiac arrest	0	1 (0.1%, 0.1)	0
Cardiac failure	0	1 (0.1%, 0.1)	0
Coronary artery disease	0	1 (0.1%, 0.1)	0
Congenital, familial, and genetic disorders	0	1 (0.1%, 0.1)	0
Alpha-1 antitrypsin deficiency	0	1 (0.1%, 0.1)	0
Ear and labyrinth disorders	0	1 (0.1%, 0.1)	0
Deafness bilateral		1 (0.1%, 0.1)	
Endocrine disorders	0	1 (0.1%, 0.1)	1 (0.1%, 0.1)
Goiter	0	1 (0.1%, 0.1)	1 (0.1%, 0.1)
Gastrointestinal disorders and administration site conditions	1 (0.1%, 0.1)	1 (0.1%, 0.1)	3 (0.3%)
Abdominal Pain	0	1 (0.1%, 0.1)	2 (0.2%)
Pancreatitis	0	0	1 (0.1%, 0.1)
Small intestinal obstruction	1 (0.1%, 0.1)	0	0
Vomiting	0	0	1 (0.1%, 0.1)
General disorders and administration site conditions	0	1 (0.1%, 0.1)	3 (0.3%)
Chest pain	0	0	3 (0.3%)
Non-cardiac chest pain	0	1 (0.1%, 0.1)	0
Hepatobiliary disorders	3 (0.3%, 0.5)	2 (0.2%, 0.2)	3 (0.3%)
Biliary dyskinesia	0	0	1 (0.1%, 0.1)
Cholecystitis	1 (0.1%, 0.2)	2 (0.2%, 0.3)	0
Cholelithiasis	1 (0.1%, 0.2)	0	1 (0.1%, 0.1)
Hepatitis	0	1 (0.1%, 0.1)	0
Hepatotoxicity	0	0	1 (0.1%, 0.1)
Infections and infestations	3 (0.3%, 0.5)	6 (0.5%, 0.7)	5 (0.5%)
COVID-19	1 (0.1%, 0.2)	2 (0.2%, 0.2)	2 (0.2%)
COVID-19 Pneumonia	1 (0.1%, 0.2)	1 (0.1%, 0.1)	1 (0.1%, 0.1)
Influenza	1 (0.1%, 0.2)	0	1 (0.1%, 0.1)
Meningitis	0	0	1 (0.1%, 0.1)
Pneumonia	1 (0.1%, 0.2)	1 (0.1%, 0.1)	0
Tooth infection	0	1 (0.1%, 0.1)	0

MedDRA (v23.0) System Organ Class Preferred Term	Placebo (n = 952) n (% , EAIR)	Fezolinetant 30 mg Total (n = 1103) n (% , EAIR)	Fezolinetant 45 mg Total (n = 1100) n (% , EAIR)
Urinary tract infection	0	1 (0.1%, 0.1)	0
Injury, poisoning and procedural complications	3 (0.3%, 0.5)	4 (0.4%, 0.5)	7 (0.7%)
Animal bite	1 (0.1%, 0.2)	0	0
Ankle fracture	0	1 (0.1%, 0.1)	0
Fibula fracture	0	0	1 (0.1%, 0.1)
Joint dislocation	1 (0.1%, 0.2)	0	0
Limb injury	0	0	1 (0.1%, 0.1)
Limb traumatic amputation	0	1 (0.1%, 0.1)	0
Lumbar vertebral fracture	0	0	1 (0.1%, 0.1)
Multiple injuries	0	0	1 (0.1%, 0.1)
Posterior tibial nerve injury	0	0	1 (0.1%, 0.1)
Radius fracture	0	1 (0.1%, 0.1)	0
Skin laceration	0	0	1 (0.1%, 0.1)
Stab wound	0	0	1 (0.1%, 0.1)
Tendon rupture	1 (0.1%, 0.2)	0	0
Tibia fracture	0	0	1 (0.1%, 0.1)
Investigations	1 (0.2%, 0.2)	3 (0.3%, 0.3)	3 (0.3%, 0.3)
Blood pressure increased	0	0	1 (0.1%, 0.1)
Gamma-glutamyl transferase increased	1 (0.1%, 0.2)	0	0
Liver function test increased*	1 (0.1%, 0.2)	3 (0.3%, 0.3)	2 (0.2%, 0.2)
Metabolism and nutrition disorders	0	2 (0.2%, 0.2)	1 (0.1%, 0.1)
Dehydration	0	1 (0.1%, 0.1)	0
Diabetic ketoacidosis	0	0	1 (0.1%, 0.1)
Hypercholesterolemia	0	1 (0.1%, 0.1)	0
Musculoskeletal and connective tissue disorders	0	3 (0.3%)	1 (0.1%, 0.1)
Intervertebral disc protrusion	0	1 (0.1%, 0.1)	0
Lumbar spinal stenosis	0	1 (0.1%, 0.1)	0
Rhabdomyolysis	0	1 (0.1%, 0.1)	0
Tendonitis	0	0	1 (0.1%, 0.1)
Neoplasms benign, malignant, and unspecified (incl cysts and polyps)	2 (0.2%, 0.4)	7 (0.6%, 0.8)	13 (1.5%, 1.4)
Apocrine breast carcinoma	0	0	1 (0.1%, 0.1)
Basal cell carcinoma	0	1 (0.1%, 0.1)	0
Benign breast neoplasm	0	1 (0.1%, 0.1)	0
Bone cancer	0	0	1 (0.1%, 0.1)
Chronic lymphocytic leukemia	0	1 (0.1%, 0.1)	0
Colon cancer	0	0	2 (0.2%, 0.2)
Endometrial adenocarcinoma	0	1 (0.1%, 0.1)	2 (0.2%, 0.2)

MedDRA (v23.0) System Organ Class Preferred Term	Placebo (n = 952) n (% , EAIR)	Fezolinetant 30 mg Total (n = 1103) n (% , EAIR)	Fezolinetant 45 mg Total (n = 1100) n (% , EAIR)
Hemangioma of liver	0	0	1 (0.1%, 0.1)
Hepatic cancer	0	0	1 (0.1%, 0.1)
Invasive breast carcinoma	0	1 (0.1%, 0.1)	0
Keratoacanthoma	0	0	1 (0.1%, 0.1)
Lung neoplasm	0	0	1 (0.1%, 0.1)
Malignant melanoma in situ	0	0	1 (0.1%, 0.1)
Neurolemmoma benign	1 (0.1%, 0.2)	0	0
Non-small cell lung cancer	0	0	1 (0.1%, 0.1)
Squamous cell carcinoma of skin	1 (0.1%, 0.2)	2 (0.2%, 0.2)	1 (0.1%, 0.1)
Squamous cell carcinoma of oral cavity	0	0	1 (0.1%, 0.1)
Uterine leiomyoma	0	0	1 (0.1%, 0.1)
Nervous system disorders	0	1 (0.1%, 0.1)	3 (0.3%, 0.3)
Brain injury	0	1 (0.1%, 0.1)	0
Headache	0	0	1 (0.1%, 0.1)
Hemiparesis	0	0	1 (0.1%, 0.1)
Paresthesia	0	0	1 (0.1%, 0.1)
Transient ischemic attack	0	0	1 (0.1%, 0.1)
Psychiatric disorders	1 (0.1, 0.2)	2 (0.2%, 0.2)	0
Alcohol abuse	0	1 (0.1%, 0.1)	0
Anxiety	0	1 (0.1%, 0.1)	0
Depression	1 (0.1%, 0.2)	0	0
Suicidal ideation	1 (0.1%, 0.2)	0	0
Renal and urinary disorders	0	0	2 (0.2%0.2)
Acute kidney injury	0	0	1 (0.1%, 0.1)
Renal colic	0	0	1 (0.1%, 0.1)
Ureteric stenosis	0	0	1 (0.1%, 0.1)
Reproductive system and breast disorders	0	3 (0.3%, 0.3)	2 (0.2%, 0.2)
Pelvic pain	0	0	1 (0.1%, 0.1)
Postmenopausal hemorrhage	0	1 (0.1%, 0.1)	0
Uterine hemorrhage	0	1 (0.1%, 0.1)	0
Uterine polyp	0	1 (0.1%, 0.1)	0
Vaginal hemorrhage	0	0	1 (0.1%, 0.1)
Respiratory, thoracic, and mediastinal disorders	1 (0.1%, 0.2)	1 (0.1%, 0.1)	1 (0.1%, 0.1)
Acute respiratory	1 (0.1%, 0.2)	1 (0.1%, 0.1)	1 (0.1%, 0.1)
Hypoxia	0	1 (0.1%, 0.1)	0
Pulmonary embolism	0	0	1 (0.1%, 0.1)
Pulmonary edema	0	1 (0.1%, 0.1)	0

MedDRA (v23.0) System Organ Class Preferred Term	Placebo (n = 952) n (% , EAIR)	Fezolinetant 30 mg Total (n = 1103) n (% , EAIR)	Fezolinetant 45 mg Total (n = 1100) n (% , EAIR)
Surgical and medical procedures	0	1 (0.1%, 0.1)	0
Fracture treatment	0	1 (0.1%, 0.1)	0
Vascular disorders	0	0	1 (0.1%, 0.1)
Varicose vein	0	0	1 (0.1%, 0.1)

*Alanine aminotransferase increased, Liver function test abnormal, Liver function test increased, Transaminases increased combined

Note: At each level of summation (Overall, SOC, PT) participants reporting more than one adverse event are counted only once.

Abbreviations: EAIR=Exposure adjusted incidence Rate, per 100 Person Years

Source: Clinical Review **Table 45, page 174** and NDA 216578, SCS/ISS report, Sponsor **Table 23, pages 60-65.**

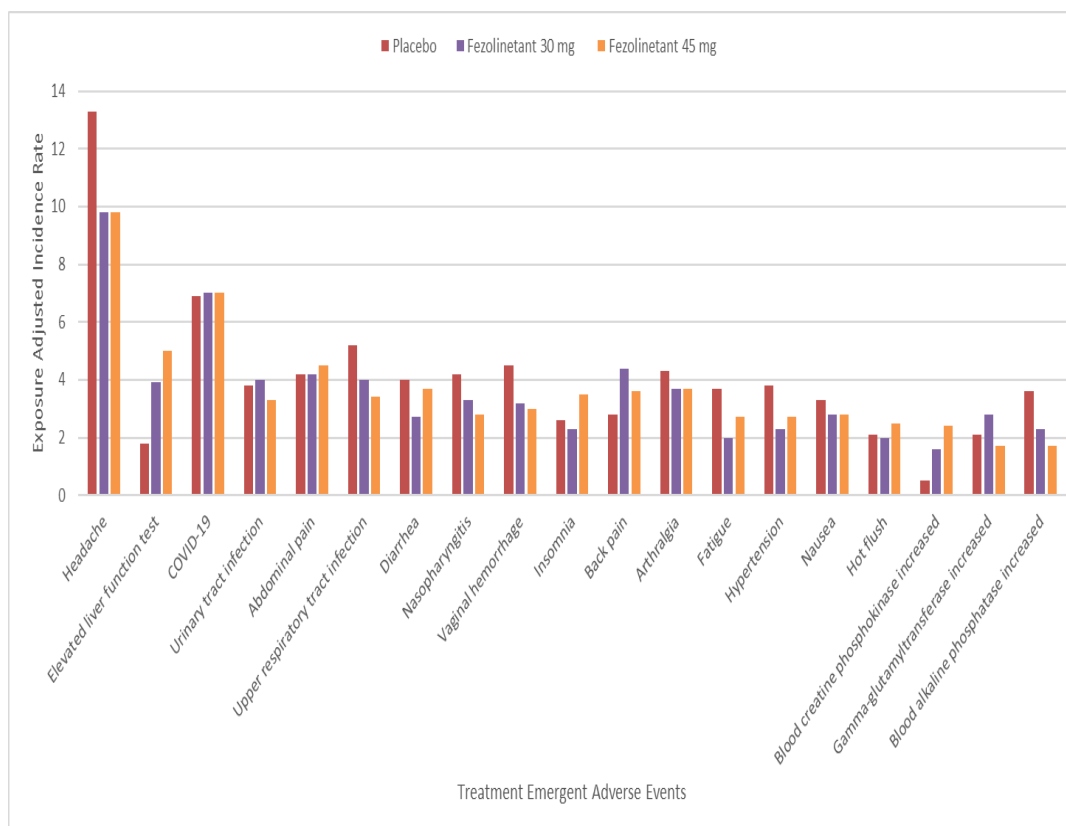
In Table 42, participants reporting more than one adverse event are counted only once. SAEs that occurred more than up to 21 days after the last dose of trial medication are denoted in the same table. Investigators reported one SAE of hepatotoxicity in the placebo/fezolinetant 45 mg arm on exposure day 54.

There was a numerical difference in the prevalence of overall SAEs in the treatment arms versus the placebo arm for POP2 at 12 and 52 weeks which was also reflected in the EAIR. The EAIR for the fezolinetant 45 mg arm was 4.8 per 100 PY versus 2.7 per 100 PY in the placebo. The differences in overall SAEs were *primarily driven by the differences in the SOC neoplasms benign, malignant, and unspecified (including cysts and polyps)*. These are addressed below in this review. The SAEs that occurred were primarily singular in nature except for liver function test increased (discussed below in this review). Hepatobiliary SAEs were balanced across all arms. The case of hepatotoxicity was similar to other participants in the trial given the mild rise in LFTs which were resolving on study drug and no elevations in bilirubin or development of jaundice

Treatment Emergent Adverse Events/Reactions:

Figure 8 presents the clinical reviewer's assessment of treatment emergent adverse events of any severity occurring in >2% of participants POP2 (52 Weeks), by treatment group.

Figure 8 Reviewer's Assessment of Exposure Adjusted Incidence Rate of Treatment Emergent Adverse Events (Any Severity) by Treatment Group, POP2 (52 Weeks) Occurring in $\geq 2\%$ of Participants



In the above analysis, like terms for common treatment emergent adverse event were combined as follows:

- abdominal pain: included abdominal pain, abdominal pain upper, and abdominal pain lower
- vaginal hemorrhage: included uterine hemorrhage, vaginal hemorrhage, and dysfunctional uterine bleeding
- liver function test increased: included alanine aminotransferase increased, and aspartate aminotransferase increased.

Headache was the most common TEAE in the placebo, and 30 and 45 mg dosage strengths groups. The next most common TEAEs were related to the COVID-19 pandemic (balanced across all groups) and elevated hepatic function test, for which there was an imbalance in the fezolinetant treatment groups compared to placebo.

The most common treatment emergent adverse reactions reported in greater than or equal to 1% of women treated with Veozah and greater than placebo in the POP2 population by exposure adjusted incident rate per 100 person-years are presented in

Table (sent to the applicant on November 22, 2022, as FDA's initially proposed labeling).

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Table 43: Adverse Reactions Reported in Greater Than or Equal to 1% of Women Treated with TRADENAME and Greater than Placebo in POP2 population ^a, Exposure Adjusted Incidence Rate per 100 person-years

Adverse Reaction	TRADENAME 45 mg (n=1103) n (% , EAIR)	Placebo (n=952) n (% , EAIR)
Total person-years	912.1	549.1
Hepatic transaminase elevation	48 (4.4%, 5.0)	11 (1.2%, 1.8)
Abdominal pain	42 (3.8%, 4.6)	19 (2.0%, 3.5)
Insomnia	33 (3.0%, 3.6)	15 (1.6%, 2.7)
Hot flush	24 (2.2%, 2.6)	12 (1.3%, 2.2)
Blood creatine phosphokinase increased	23 (2.1%, 2.5)	3 (0.3%, 0.5)
Anxiety	20 (1.8%, 2.2)	8 (0.8%, 1.5)
Dizziness	19 (1.7%, 2.1)	10 (1.1%, 1.8)
Gastroesophageal reflux disease	16 (1.5%, 1.8)	5 (0.5%, 0.9)
Ear infection	12 (1.1%, 1.3)	6 (0.6%, 1.1)
Osteoarthritis	12 (1.1%, 1.3)	4 (0.4%, 0.7)
Sciatica	11 (1.0%, 1.2)	5 (0.5%, 0.9)
Tooth abscess	11 (1.0%, 1.2)	3 (0.3%, 0.5)
Blood glucose increased	10 (0.9%, 1.1)	3 (0.3%, 0.5)
Vomiting	10 (0.9%, 1.1)	3 (0.3%, 0.5)
Pain	9 (0.8%, 1.0)	4 (0.4%, 0.7)

a. Data generated in POP 2 population. Trial 2693-CL-0301 and Trial 2693-CL-0304 were placebo-controlled for the first 12 weeks, followed by cross-over of participants previously receiving placebo to TRADENAME (participants on TRADENAME remained on TRADENAME) for an additional 40 weeks. Trial 2693-CL-0304 was placebo-controlled for 52-weeks for all participants.

Source: FDA Proposed labeling, November 22, 2022. Labeling negotiations are ongoing at the time of this review.

Hepatic transaminase elevation, abdominal pain, insomnia, hot flashes, and increased blood creatine phosphokinase were the most common adverse reaction. In addition to Table X, the following was proposed to be included in the product labeling, (b) (4)

[REDACTED]

I agree with Drs. van der Vlugt and Zopf that the ‘Overall Safety’ is reassuring for Veozah. The majority of adverse events (AE) are balanced between fezolinetant treatment and placebo. However, there are some (potential) safety risks that were identified in the clinical review (and discussed below); these are included in the proposed labeling.

Adverse Outcomes of Special Interest/Concern Identified in the Review

Evaluation of hepatic injury

During early clinical development up through phase 2, nine cases of aminotransferase elevations were reported occurring at fezolinetant doses ranging from 60 mg daily to a single 900 mg dose. Hepatic enzyme elevations characteristically occurred between 1 to 2 months on treatment and rapidly resolved with discontinuation of treatment. Some correlation was observed between exposure to fezolinetant (AUC) and the serum aminotransferase elevations. Astellas conducted Quantitative Systems Toxicology (QST) modeling (DILIsym) which predicted the adverse hepatic findings observed at phase 2 dosing. Based on these reported findings, phase 3 fezolinetant development was limited to 30 and 45 mg fezolinetant dosage strengths.

Prior to phase 3 development, Astellas and the Agency agreed upon the following hepatic transaminase evaluations, participant discontinuation criteria, and enhanced hepatic transaminase monitoring in phase 3 clinical trials:

1. Phase 3 clinical trials participants has laboratory evaluations (including hepatic transaminases) preformed at screening, randomizations (Visit 2, Day 1), Visit 2b (Week 2), Visits 3 (Week 4), Visit 4 (Week 8), Visit 5 (Week 12), Visit 5b (Week 14), Visits 6 through 15 (Weeks 16 through Week 52), and Visit 16 (Week 55, follow-up).
2. Weekly monitoring of serum aminotransferases (ALT and AST), total bilirubin, direct bilirubin, alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT) were assessed when a woman with non-elevated aminotransferase at baseline was found to have a hepatic transaminase elevation that did not meet the trial or individual participant stopping criteria.
3. Any participant enrolled in any fezolinetant clinical study who has an increase in serum aminotransferases of $> 3 \times \text{ULN}$ or in bilirubin $> 2 \times \text{ULN}$ during the trial underwent detailed testing for hepatic enzymes. Testing was repeated within 72 hours of notification of the test results. Automatic alerts were generated by the central laboratory regarding moderate to severe hepatic abnormalities to inform the investigator and trial team. Participants were asked if they have any symptoms suggestive of hepatobiliary dysfunction.
4. Confirmed abnormalities were characterized as moderate (ALT or AST $> 3 \times \text{ULN}$ or TBL $> 2 \times \text{ULN}$) or severe (ALT or AST $> 3 \times \text{ULN}$ and TBL $> 2 \times \text{ULN}$).
5. In the absence of an explanations for increase hepatic transaminases, such as viral hepatitis, preexisting or active liver disease, or exposure to other agents associated with liver injury, trial treatment was discontinued if:
 - Development of severe hepatic abnormality defined as ALT or AST $> 8 \times \text{ULN}$.
 - Confirmed (within 72 hours from the notification of test results) severe hepatic abnormality defined as any of the following:
 - ALT or AST $> 5 \times \text{ULN}$ for more than 2 weeks
 - ALT or AST $> 3 \times \text{ULN}$ **and** TBL $> 2 \times \text{ULN}$ **or** INR > 1.5
 - ALT or AST $> 3 \times \text{ULN}$ with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia ($> 5\%$ increase above baseline).
6. Moderate liver test abnormalities as defined above were repeated 2 to 3 times weekly, and then weekly or less if abnormalities stabilize or the trial drug had been discontinued

and the participant was asymptomatic.

7. Confirmed moderate and severe abnormalities in hepatic tests were thoroughly characterized by obtaining appropriate expert consultations, detailed pertinent history, physical examination, and laboratory tests. The site staff completed the liver abnormality case report form (LA-CRF). Astellas was contacted immediately of all participants for whom severe hepatic liver function abnormalities possibly attributable to study drug were observed.

Per the NDA application, relevant objective liver clinical laboratory results, TEAEs, independent Liver Safety Monitoring Panel (LSMP) assessments (see below), and the reported treatment-emergent adverse events of special interest, relative to hepatic safety, were combined into a comprehensive assessment of hepatic safety to inform the safety profile of fezolinetant. The data were assessed at the integrated pooled safety data level, at the study level in each of the 3 phase 3 trials, and at the individual participant level.

The following liver safety information is available in the NDA application:

- The number and percentage of participants meeting predefined categories of liver biochemistry elevations by treatment group for POP1 through POP5. See page 156 in this review for the safety population descriptions.
- Exposure-adjusted incidence rate, defined as number of participants with event per 100 participant-years for each categorical liver biochemistry finding, are presented by treatment group for POP2 and POP4.
- The categorical liver biochemistry listing is available for POP1 through POP5.
- An evaluation of drug-induced serious hepatotoxicity (eDISH) plot assessing the hepatic safety profile for placebo, 30 mg total fezolinetant groups and 45 mg total fezolinetant groups in POP 2 52-week is presented. For Trials 2693-CL-0301 and 2693-CL-0302, the participants who were initially randomized to placebo and then re-randomized to fezolinetant at the beginning of the extension treatment period have 2 values on the eDISH plot: a peak value from the 12-week placebo-controlled period, and a second peak value from the fezolinetant exposure 40-week extension period.

Table 44 present the applicants assessment of the number of participants with liver biochemistry findings by category in the 52-week, placebo-controlled safety Trial 2693-CL-0304 POP4 population.

Table 44 **Applicant's Reported Number (%) of Participants with Categorical Liver Biochemistry Findings (Safety Analysis Set); POP4; Trial 2693-CL-0304**

Parameter	Criteria	Placebo (n = 610)	Fezolinetant 30 mg (n = 611)	Fezolinetant 45 mg (n = 609)	Fezolinetant Total (n = 1220)
ALT	> 3 x ULN	5/583 (0.9%)	7/590 (1.2%)	11/589 (1.9%)	18/1179 (1.5%)
	> 5 x ULN	3/583 (0.5%)	2/590 (0.3%)	3/589 (0.5%)	5/1179 (0.4%)
	> 8 x ULN	1/583 (0.2%)	0/590	0/589	0/1179
	> 10 x ULN	0/583	0/590	0/589	0/1179
	> 20 x ULN	0/583	0/590	0/589	0/1179
AST	> 3 x ULN	3/583 (0.5%)	5/590 (0.8%)	5/589 (0.8%)	10/1179 (0.8%)
	> 5 x ULN	2/583 (0.3%)	1/590 (0.2%)	1/589 (0.2%)	2/1179 (0.2%)
	> 8 x ULN	0/583	0/590	0/589	0/1179
	> 10 x ULN	0/583	0/590	0/589	0/1179
	> 20 x ULN	0/583	0/590	0/589	0/1179
ALT or AST	> 3 x ULN	6/583 (1.0%)	8/590 (1.4%)	12/589 (2.0%)	20/1179 (0.2%)
	> 5 x ULN	4/583 (0.7%)	3/590 (0.5%)	3/589 (0.5%)	6/1179 (0.5%)
	> 8 x ULN	1/583 (0.2%)	0/590	0/589	0/1179
	> 10 x ULN	0/583	0/590	0/589	0/1179
ALP	> 1.5 x ULN	14/583 (2.4%)	8/591 (1.4%)	14/589 (2.4%)	22/1180 (1.9%)
TBL	> 2 x ULN	0/583	0/591	1/589 (0.2%)	1/1180 (1.9%)
(ALT or AST) and TBL†	ALT or AST > 3 x ULN and TBL > 1.5 x ULN	0/583	0/590	0/589	0/1179

All randomized participants who took at least 1 dose of trial drug (Safety Analysis Set).

Maximum value on treatment was presented for each liver enzyme and total bilirubin.

The denominator was the number of participants who had at least 1 non-missing value during treatment.

† Combination of values measured within same day or within 1 day apart.

Definitions: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; TBL = total bilirubin; ULN = upper limit of normal range.

Source: Clinical Review **Table 64, page 212** and NDA 216578, Summary Clinical Safety (SCS)/Integrated Summary of Safety (ISS), **Table 36, page 99**.

In the Trial 2693-CL-0304 52-week POP4 population, ALT or AST elevations (as determined by laboratory data) of > 3 x ULN were observed in 1.0% of participants treated with placebo (6 of 583 participants), 1.4% of participants treated with 30 mg fezolinetant (8 of 590 participants), and 2.0% of participants treated with 45 mg fezolinetant (12 of 589 participants). There was a low and similar incidence of AST or ALT elevations > 5 x ULN across the treatment groups. Time to onset for ALT or AST elevations varied from week 2 through to week 52, with no difference between placebo and fezolinetant groups.

One participant in the 45 mg fezolinetant group had a bilirubin level > 2 x ULN. This participant had a medical history of Gilbert's syndrome (and was allowed participation under the enrollment criteria), and no ALT or AST elevations > 3 x ULN.

The EAIR (the number of participants with an event per 100 participant-years) results (data not presented in tabular form) of 1.3 per 100 participant-years in the placebo group, 1.6 per 100

participant-years in the 30 mg fezolinetant group, and 2.4 per 100 participant-years in the 45 mg fezolinetant group, were consistent with the unadjusted incidence data in POP4.

The applicant's assessment of the categorical findings of liver biochemistry for the 52-week POP2 population EAIR, is presented in Table 45.

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Table 45 **Participants with Categorical Findings of Liver Biochemistry POP2 52-week population: Trial 2693-CL-0301, Trial 2693-CL-0302, and Trial 2693-CL-0304; Exposure Adjusted Incidence Rates (EAIR)**

Parameter	Criteria	Placebo (N = 952)	Fezolinetant 30 mg (N = 951)	Fezolinetant 45 mg (N = 949)	Placebo/ Fezolinetant 30 mg (N = 152))	Placebo/ Fezolinetant 45 mg (N = 151)	Fezolinetant 30 mg Total (N = 1103)	Fezolinetant 45 mg Total (N = 1100)
		n (rate)	n (rate)	n (rate)	n (rate)	n (rate)	n (rate)	n (rate)
Total Subject Years		548.0	780.0	804.4	105.0	106.8	885.1	911.2
ALT or AST	> 3 x ULN	8 (1.5)	15 (1.9)	23 (2.9)	1 (1.0)	2 (1.9)	16 (1.8)	25 (2.7)
	> 5 x ULN	4 (0.7)	7 (0.9)	6 (0.7)	0	0	7 (0.8)	6 (0.7)
	> 8 x ULN	1 (0.2)	2 (0.3)	0	0	0	2 (0.2)	0
	> 10 x ULN	0	1 (0.1)	0	0	0	1 (0.1)	0
	> 20 x ULN	0	1 (0.1)	0	0	0	1 (0.1)	0

Number of subjects (n), and exposure adjusted rate per 100 subject-years (rate) are shown where rate = 100*n/Total subject-years.

Maximum value on treatment is presented for each liver biochemistry variable. For participants re-randomized to either 30 mg or 45 mg fezolinetant, the maximum value during the extension treatment period is presented. The denominator was the number of subjects who had at least one non-missing value during treatment.

Definitions: ALT = alanine transaminase, AST = aspartate aminotransferase, ULN = upper limit of normal range.

Source: Clinical Review **Table 66, page 216** and NDA 216578, Integrated Summary of Safety (ISS), **End-of-Text Table 12.5.7.1, page 4643**.

In the supportive POP2 52-week assessment (inclusive of re-randomized placebo participants in Trials 2693-CL-0301 and Trial 2693-CL-0302 in addition to Trial 2693-CL-0304), ALT or AST elevations of > 3 x ULN were observed in *0.9% of participants in the placebo group (8 in 917 participants), 1.5% of participants in the total 30 mg fezolinetant group (16 in 1069 participants), and 2.3% of participants in the total 45 mg fezolinetant group (25 in 1072 participants)*. ALT or AST elevations > 3 x ULN were occasionally accompanied ALP elevations. Time to onset for ALT or AST elevations varied from week 2 through to week 52, with no difference between placebo and fezolinetant groups.

The fezolinetant phase 3 clinical development program was monitored by a Liver Safety Monitoring Panel (LSMP), consisting of three independent board-certified well-recognized US hepatologists, experienced in the assessment of drug-induced liver injury (DILI), reviewed on an ongoing and regular basis, each potential case of DILI.

The LSMP was comprised of the following three independent, well-recognized US hepatologists, considered experts in the assessment of drug-induced liver injury:

1.

(b) (4)

2. [REDACTED] (b) (4)

3. [REDACTED] (b) (4)

Any participant who experienced criteria ALT or AST > 3 x ULN or total bilirubin > 2 x ULN was evaluated, using blinded data, for potential DILI by the LSMP. These data were considered along with other laboratory data including, but not limited to, ALP, GGT, and international normalized ration (INR).

The data analysis center (consisting of independent unblinded statisticians and programmers external to the applicant) provided blinded participant data packages in the form of participant profiles to the LSMP for causality assessment. The LSMP also received ad-hoc blinded participant data packages anytime a participant met the above criteria and provided an evaluation of individual cases. The LSMP also reviewed aggregate liver safety data on a quarterly basis, in an unblinded fashion. Meetings were held with panel members to discuss these data and provide the panel recommendations. Blinded ad-hoc cases that were under the panel's review were completed prior to receiving the aggregate data.

Causal relationship to trial intervention was assessed for each case according to the DILI network scoring categories⁸ as presented below in Table 46.

Table 46 Liver Safety Monitoring Panel's Categorization of Drug Product Causality of DILI

Causality Score	Likelihood	Description
1 (Definite)	>95%	Beyond any reasonable doubt
2 (Highly likely)	75%–95%	Clear and convincing data, but not definite
3 (Probable)	50%–74%	Majority of data supports causal relationship
4 (Possible)	25%–49%	Majority of data suggests no causal relationship, but possibility remains
5 (Unlikely)	<25%	Causal relationship very unlikely
6 (Insufficient data)	Not Determinable	Missing key data

Source: Clinical Review **Table 11, page 91.**

In the NDA application, Astellas provides for the assessment of DILI:

- A summary report of the LSMP findings:
 - “**Trial 2603-CL-0301:** *Of the 10 participants with ALT or AST levels > 3 x ULN, 4 participants were assessed by the LSMP as having possible causality (1 in the placebo group, 1 in the placebo/fezolinetant 30 mg group and 2 in the fezolinetant 45 mg group) and 2 as probable causality (both in the fezolinetant 30 mg group); the causality for the other 4 events was assessed as unlikely.*”
 - “**Trial 2693-CL-0302:** *Of the 12 participants with ALT or AST levels > 3 x ULN, 5*

⁸ Hayashi PH, Drug-Induced Liver Injury Network Causality Assessment: Criteria and Experience in the United States. *Int J Mol Sci.* 2016; 17(2): 201.

were assessed by the LSMP as having possible causality (3 participants in the fezolinetant 45 mg group and 2 in the placebo/fezolinetant 45 mg group) and 2 as probable causality (1 participant in the fezolinetant 30 mg group and 1 in the fezolinetant 45 mg group); the causality for the other 5 events was assessed as unlikely."

- **"Trial 2693-CL-0304:** Of the 26 participants with ALT or AST levels $> 3 \times \text{ULN}$, 12 were assessed by the LSMP as having possible causality (3 participants in the placebo group, 4 participants in the fezolinetant 30 mg group and 5 in the fezolinetant 45 mg group) and 5 as probable causality (0 participants in the placebo group, 1 in the fezolinetant 30 mg group and 4 in the fezolinetant 45 mg group); the causality for the other 9 events was assessed as unlikely (3 participants in each treatment group)."
2. A summary statement from the LSMP regarding liver safety for fezolinetant, dated May 26, 2022

The statement confirms that three independent experts assessed blinded participants experiencing serum ALT or AST elevations $>3 \times \text{ULN}$ or total serum bilirubin elevations $>2 \times \text{ULN}$ that occurred in the three phase 3 clinical trials. The LSMP findings, summary, and conclusion, provided in the LSMB May 26, 2022, summary statement, are provided below:

Findings:

"There were ***no serious liver injuries defined by international consensus criteria including no Hy's Law Cases***. We assessed the following 9 cases as probably related to study drug. Unblinding treatment assignment upon completion of the trials revealed that each was receiving active treatment at the doses listed:

Subject ID	Study	Dose
(b) (6)	0301	30 mg
	0301	30 mg
	0302	30 mg
	0302	45 mg
	0304	30 mg
	0304	45 mg
	0304	45 mg
	0304	45 mg
	0304	45 mg

These *events were generally hepatocellular* in nature, generally occurred during the first 3 months of treatment, and typically resolved rapidly whether study drug treatment was continued or stopped. We could find no patient characteristics (BMI, history of NAFLD or NASH, age, race, concomitant medications, or race/ethnicity) that clearly distinguished these nine cases from others in the clinical trials.

The graph depicting initial onset of serum ALT elevations > 3 X ULN vs time on study drug treatment in the 304 study showed increased incidence relative to placebo for the patients receiving 45 mg fezolinetant daily, but only during the first 3 months on treatment. No differences in incidence were evident at any time between the placebo treated patients and those receiving 30 mg fezolinetant daily.”

Summary:

“Fezolinetant treatment in the 301, 302, and 304 clinical trials was associated with a low incidence of elevations in serum aminotransferases, most evident at the 45 mg dose. These elevations have typically been asymptomatic, have occurred within the first 3 months of treatment, and have resolved rapidly with continued treatment or with discontinuing treatment. No serious liver injuries were observed in the 301, 302, and 304 clinical trials. It seems likely that the characteristic liver events reflect a direct effect on the liver without an innate or adaptive immune response. This is supported by the accuracy of the QST modeling results, the prior demonstration of an exposure-response relationship, and the rapid resolution of these events.”

Conclusions:

“Fezolinetant treatment at the dosing regimens employed in 301, 302, and 304 clinical trials is generally safe for the liver. However, it should be noted that active liver disease, very high BMI, and concomitant treatment with drugs that strongly inhibit fezolinetant metabolism were exclusion criteria in these studies. In addition, a few patients in the trials discontinued active drug treatment prior to spontaneous improvement in their serum aminotransferase levels. Although it seems likely that these biochemical abnormalities would also have resolved with continued fezolinetant treatment, protocol stopping criteria prevented demonstrating this. It is therefore not possible to exclude that fezolinetant could cause more serious and/or progressive liver injuries in a real-world setting, but it seems reasonable to conclude based on the available data that such events would be very rare.” The LSMB concludes that, “To mitigate this possible liver safety risk post-approval, routine liver chemistry monitoring could be considered, especially during the first 3 months when event rate was highest. However, given the rarity of the events, their relatively rapid onset, and the observation that the events typically resolved rapidly with or without discontinuation of treatment, we are skeptical of the value of routine liver chemistry monitoring here.”

The Division of Hepatology and Nutrition (DHN) was consulted to assess evidence of hepatic function and/or hepatic injury in the phase 3 clinical trials submitted under NDA 216578. Previous consultation for the fezolinetant IND 130277 was provided by DGIEP (now DHN) in responses, dated June 11, 2018, October 23, 2018, and March 29, 2019.

The DILI Team conducted detailed case level analysis of 14 participants with ALT or AST > 5 x ULN in concert with the LSMB findings. Of the 14 cases, the DILI Team assessed six as unlikely DILI, *four as possible DILI, and four as probable DILI*. Per the DILI Team, their assessment was similar to the LSMB's assessment. Table 47 shows the findings of the DILI Team assessments.

Table 2 DILI Team Consult Response: Summary of Cases with ALT or AST > 5 x ULN in the Fezolinetant Phase 3 Clinical Trials

#	Subject ID	Study	DILI Team Causality Score*	HAC Causality Score*	Alternate diagnosis	Age (yr)	Sex	Race	Symptoms	Hy's Law
1	(b) (6)	2693-CL-0301	3	3	NA	55	F	White	No	No
2		2693-CL-0302	3	4	NA	57	F	White	No	No
3		2693-CL-0301	3	3	NA	48	F	White	Yes	No
4		2693-CL-0304	3	3	NA	55	F	White	No	No
5		2693-CL-0304	4	3	Unknown	52	F	White	No	No
6		2693-CL-0304	4	3	APAP	52	F	White	No	No
7		2693-CL-0304	4	3	APAP	58	F	White	No	No
8		2693-CL-0304	4	4	Unknown	53	F	White	No	No
9		2693-CL-0301	5	5	Myopathy	64	F	White	No	No
10		2693-CL-0301	5	5	Unknown	54	F	White	No	No
11		2693-CL-0302	5	5	NASH	51	F	White	No	No
12		2693-CL-0304	5	5	Unknown	53	F	White	No	No
13		2693-CL-0301	5	4	Unknown	54	F	White	No	No
14		2693-CL-0301	5	5	Gallstones	53	F	White	No	No
	<i>mean</i> 54 <i>std dev</i> 3.6 <i>median</i> 54 <i>max</i> 64 <i>min</i> 48									

*1=definite, 2=highly likely, 3=probable, 4=possible, 5=unlikely, 6=indeterminate

NASH = non-alcoholic steatohepatitis

APAP = acetaminophen

Source: Clinical Review **Table 67, page 221** and DHN consult, **Table 5, page 10**.

DHN noted, "The greatest discrepancies [between the DHN review and the applicant's LSMP] were in the possible versus probable assessments. The LSMP tended to see resolution of liver injury on drug as probable DILI with adaptation while we assessed them as possible DILI."

DHN excluded seven participants from consideration because these cases were not assessed as probable by either the DILI Team or the LSMP. *The remaining seven participants had predominantly hepatocellular injury as assessed by R-value (R-value > 5 is considered hepatocellular) with median latency from drug start of 56 days, but with a wide range of 14 to 250 days.* These seven cases are presented in Table 48.

Table 48 DILI Team Consult Response: Participants in POP2 52-week Assessed as Probable DILI by the DILI Team and/or Applicant's LSMP

#	Subject ID	Study	DILI Team Causality Score*	HAC Causality Score*	Alternate diagnosis	Age (yr)	Sex	Race	Symptoms	Hy's Law	Latency from start drug (da)	Latency from stop drug (da)#	ALT peak (U/L)	AST peak (U/L)	ALP peak (U/L)^	Bilirubin peak (mg/dL)	R value peak (ALT)	R value peak (AST)	
1	(b) (6)	2693-CL-0301	3	3	NA	55	F	White	No	No	84	-1	686	1515	153	0.5	13.71	30.29	
2		2693-CL-0302	3	4	NA	57	F	White	No	No	54	-51	322	158	104	0.4	9.47	4.65	
3		2693-CL-0301	3	3	NA	48	F	White	Yes	No	28	-8	293	194	104	0.3	8.62	5.71	
4		2693-CL-0304	3	3	NA	55	F	White	No	No	250	-62	270	189	116	1.17	7.12	4.98	
5		2693-CL-0304	4	3	Unknown	52	F	White	No	No	56	-36	336	203	104	0.7	9.88	5.97	
6		2693-CL-0304	4	3	APAP	52	F	White	No	No	114	-249	223	97	104	0.5	6.56	2.85	
7		2693-CL-0304	4	3	APAP	58	F	White	No	No	14	-352	219	172	172	3.4	3.89	3.06	
											mean	86	-108	336	361	122	1.0	8.5	8.2
											std dev	74	126	149	472	26	1.0	2.9	9.1
											median	56	-51	293	189	104	0.5	8.6	5.0
											max	250	-1	686	###	172	3.4	13.7	30.3
											min	14	-352	219	97	104	0.3	3.9	2.9

*1=definite, 2=highly likely, 3=probable, 4=possible, 5=unlikely, 6=indeterminate

^AP imputed as 104 (upper limit of normal) when peak value was <104

#Negative value indicates subject stayed on study drug for that many days after injury onset

R-value = AP/ULN ÷ ALT/ULN or AP/ULN ÷ AST/ULN; Hepatocellular: R value ≥ 5; Mixed/cholestatic: R value < 5

NA = not applicable

APAP = acetaminophen

Source: Clinical Review **Table 68, page 222** and DHN consult, **Table 6, page 11**.

The DHN notes their consideration of the influence of ADME (Table 49), Preclinical Toxicology (Table 50) and Enrollment Criteria (Table X) in their assessment:

Table 49: Summary of the Absorption, Distribution, Metabolism, and Elimination (ADME) of fezolinetant.

Item	Finding
Absorption	Rapid absorption and high bioavailability noted.
Distribution	High and rapid distribution to tissues. Plasma binding was higher in human than other species.
Metabolism	No extensive metabolism observed, with more than 16 metabolites, each at low level were seen in rats and monkeys.
Elimination	Mainly via urine and minor excretion in feces. Rapid elimination noted. A 7-day oral gavage of FZT (≥250 mg/kg/day) in rats caused liver weight increase. Following a 26-week oral study in female rats, increase liver weight at ≥100 mg/kg/dose was seen. NOAEL was 200 mg/kg/dose. A NOAEL was 25 mg/kg in a 39-week toxicity study with 4 weeks recovery in female monkeys.

Table 50: Summary of Preclinical Toxicology.

Item	Findings
In Vitro Studies	
Major CYPs	No information found.
Reactive metabolites (e.g., glutathione trapping)	No information found.
Mitochondria studies/inhibition	No information found.
Transporter (BSEP or MRP2 inhibition)	No information found.
Animal Studies	
Elevation in liver analytes (e.g., ALT, ALP, TB)	Slight elevation of transaminases and increase in ALP.
Liver histopathology findings (animal species)	Minimal centrilobular hepatocellular hypertrophy, minimal multifocal inflammatory cell foci and marked periportal hepatocyte pigment in rat livers.

Table 51 Specific Enrollment Criteria

Inclusion Criteria:
Negative serology panel (i.e., negative HBV surface antigen, negative HCV antibody and negative human immunodeficiency virus antibody screens)
ALT/AST <1.5 x ULN if total bilirubin (TB) and direct bilirubin (DB) are normal. ALP <1.5 x ULN if no cholestatic liver disease and no cause other than fatty liver is diagnosed
Gilbert's syndrome with elevated TB if DB, hemoglobin, and reticulocytes are normal.
Exclusion Criteria:
History of hepatic disease; active liver disease, jaundice, elevated ALT/AST ($\geq 1.5 \times$ ULN), TB, INR, or ALP ($\geq 1.5 \times$ ULN)

DHN concludes:

1. . *Non-clinical evaluation does not suggest an elevated DILI risk, but several in vitro studies (e.g., glutathione trapping, mitochondrial toxicity studies) were lacking. Excretion is primarily through urine and FZT parent compound dominates excretion and serum profiles. Several metabolites are generated from FZT but at low amounts.*

CDTL Note: In follow-up to this DHN conclusion, I asked for input from the Nonclinical Pharmacology/Toxicology Review Team regarding the significance of failure to perform the above noted in vitro studies. In a direct communication to me, dated January 19, 2023, Dr. Andrea Benedict stated, "based on our review and DILI team's review of the nonclinical data, there was no indication for the potential of substantial liver injury from either the in vitro or in vivo studies. In the animal studies, no liver effects were observed in the 39-week monkey study up to the highest dose tested (102X the MRHD on an AUC basis). In the 26-week rat study, minimal increases in liver weight, serum ALP, and microscopic findings of centrilobular hepatocellular hypertrophy at MD and HD (143X and 148X MRHD, respectively) were attributed to a rodent specific adaptive effect. We concur with the DILI review that the nonclinical data do not suggest a substantial liver injury risk. Therefore, the nonclinical studies do not provide a potential mechanism of action for elevated liver enzymes in the clinical trials."

Further, on January 19, 2023, Dr. Kim Hatfield noted in a separate email to me, “As for the information in the DILI review that was noted as missing, Andrea [Dr. Andrea Benedict] went back through the submission and she actually found the studies tucked away in the submission. They were submitted by the sponsor to the incorrect Module of the eCTD, and listed under clinical studies, which is not the usual spot where we would have known to look for them. And with a lack of nonclinical signal in the animals, we didn’t actively pursue any additional in-depth liver review. We thought to look at Lin’s [Dr. Lin Zhou] clin pharm review to see if she happened to cover some of these studies, and she does give a summary about the major CYPs (fezolinetant does not significantly induce or inhibit; see p 11 of her review), and information that in vitro data suggested no evidence for active uptake of fezolinetant by the transporters OATP1B, OATP1A2, OATP2B1 and PEPT1; and neither efflux by the transporters MRP2 and MRP3 (see p87 of her review).”

2. “Clinical trial data suggest *a mild increase incidence in ALT or AST elevation in subjects exposed to FZT compared to subjects on placebo, but there were no aminotransferase elevations with jaundice.*

There was no clear dose-response relationship regarding aminotransferases elevations in FZT 30 mg and 45 mg arms. Case level analyses yielded at least four subjects with probable DILI and three to four others with at least possible DILI.

Approximately, 2800 [different] VMS subjects were exposed to FZT in the phase 3 trials. DILI was predominantly hepatocellular with a median latency from drug start of 56 days, but the latency range was wide at 14 to 250 days. Many of the subjects considered to have possible DILI improved even with continued FZT use. Thus, FZT may cause some DILI, but it appears modest, and adaption may occur with continued exposure.

However, the number of women exposed post market could be large. One estimate suggests 40 to 50 million women in the United States have VMS. Only 20-30 percent may seek medical care; but if FZT is prescribed to just 1-5% of these women, then the number exposed could be 80,000 to 750,000. With such a potentially large exposure population, more severe cases of DILI could arise.”

3. “We can support approval if the need for FZT and its effectiveness are substantive. We generally agreed with the LSMP assessments and conclusions, although they tended to emphasize the probability of benign adaption after DILI more than we were willing to accept. If approved, we suggest a warning and precaution regarding hepatotoxicity in Section 5. Liver test should be checked at baseline. Monitoring may be justifiable in this non-life-threatening target disease, but the range of latency is long at up 250 days.”

DHN recommends:

1. Do not hold up approval for liver injury observed in the NDA.
2. Label for liver enzyme elevation in Warnings and Precautions.
3. Include a recommendation to perform baseline liver tests.
4. Consider a recommendation to perform routine liver test monitoring for the first several months of FZT use.

5. Consider requesting the sponsor to submit 15-day expedited reports to FAERS of all spontaneously reported post-market serious liver injury adverse events as well as those with new onset biochemical abnormalities consistent with Hy's Law.

The Clinical Reviewers are in complete agreement with the DHN recommendations. In response to these, we have the following recommendations for labeling to inform and address the risk for Drug Induced Liver Injury in patients receiving Veozah:

(b) (4)



Additionally, at this time we do not recommend a PMR or PMC before approval. On the recommendation of the Office Pharmacovigilance and Epidemiology and with input from DHN, we recommend an enhanced pharmacovigilance (EPV) to assess post-marketing adverse hepatic events occurring with the use of fezolinetant and provide expedited reporting, as well as summary analyses to be included in periodic safety reports as described below:

Elements of the ePV include the following:

1. Review all post-marketing reports of hepatic adverse events, including liver injury, with fezolinetant using recommended search terms. If follow-up information is needed to classify a report (as defined by the bulleted criteria in #2) as a hepatic adverse event, send an FDA-agreed upon hepatic adverse event follow-up questionnaire to the reporter for additional information. Structure the questionnaire such that you can obtain relevant clinical information including, but not limited to:
 - a. causality assessment
 - b. concomitant medications
 - c. dechallenge and rechallenge information, if available
 - d. description of the hepatic adverse event (e.g., signs and symptoms)
 - e. event outcome (e.g., liver transplant, lost to follow up, not resolved, resolved with or without sequelae, unknown)
 - f. patient's age
 - g. regulatory serious outcomes as defined by CFR 314.80
 - h. relevant laboratory data not captured by the initial report (e.g., albumin, autoimmune markers, coagulation parameters, endoscopic retrograde cholangiopancreatography, eosinophil count, liver biopsy, liver enzymes, liver imaging, viral serology)
 - i. relevant medical history (e.g., alcohol consumption, autoimmune disease, biliary tract disorders, blood transfusion, cardiac disorders-specifically right heart failure or hypotension, cirrhosis, connective tissue disease, family history of liver disease, recent tattoos, recent travel, viral illness, viral or alcoholic hepatitis)
 - j. time from fezolinetant initiation to occurrence of the hepatic adverse event
 - k. treatment for hepatic adverse event

Have the questionnaire query for the healthcare provider's specialty.

2. Expedite, as 15-Day alert reports, all initial and follow-up post-marketing hepatic adverse event reports including liver injury, from all post-marketing sources, including consumer reports, solicited reports, foreign reports, and ANY case with the following laboratory criteria:
 - a. ALT / AST > 8x ULN confirmed on repeat testing OR
 - b. ALT / AST > 3x ULN and total bilirubin > 2x ULN (new onset biochemical abnormalities consistent with possible Hy's law cases) OR
 - c. ALT / AST > 3x ULN associated with symptoms suggestive of hepatic disease such as: anorexia, dark urine, fatigue, fever, jaundice, nausea, vomiting, rash, right upper quadrant pain, etc., OR
 - d. Any liver adverse event leading to discontinuation OR
 - e. Any hepatic event preferred term (PT) denoting diagnosis, jaundice, liver injury, or non- infectious hepatitis. See Appendix A.
3. Using information from the hepatic adverse event follow-up questionnaire and all post-marketing reports of hepatic adverse events including liver injury, provide a summary analysis of these events in the periodic safety reports, submitted quarterly for the first 3 years after approval, as per 21 CFR 314.80(c)(1). We also request that a cumulative summary of these events since NDA approval be included in the periodic safety reports.

These summary analyses should include:

All adverse events which contain the MedDRA terms listed in Appendix A (or, where appropriate MedDRA terms currently do not exist, descriptions in the case narratives consistent with hepatic adverse events):

- a. a discussion of worldwide (if applicable) and domestic trends in reporting of hepatic adverse events including liver injury if/when applicable
 - b. causality assessment by you or your designee
 - c. recommendations for changes to the ePV system or product labeling if applicable.
4. Also provide in the periodic safety report, medical literature reviews for case reports/case series of hepatic adverse events including liver injury reported with **APPENDIX A**.

Appendix A: MedDRA Search Specifications**Search Terms for Hepatic Adverse Events including Liver Injury in the Enhanced Pharmacovigilance Program for Fezolinetant**

Any hepatic event (PT) diagnosis either from MedDRA SOC <i>Hepatobiliary Disorders</i> or MedDRA HLGT <i>Hepatobiliary Investigations</i> with fatal outcome
OR
Any of the following PTs denoting hepatic failure, hepatic encephalopathy, hepatic cirrhosis or fibrosis, liver injury or liver transplant
acute hepatic failure; asterixis; biliary cirrhosis; biliary cirrhosis primary; cholestatic liver injury; chronic hepatic failure; cirrhosis alcoholic; coma hepatic; cryptogenic cirrhosis; drug-induced liver injury; hepatic cirrhosis; hepatic encephalopathy; hepatic encephalopathy prophylaxis; hepatic failure; hepatic fibrosis; hepatic infiltration eosinophilic; hepatic necrosis; hepatocellular injury; hepatopulmonary syndrome; hepatorenal failure; hepatorenal syndrome; hepatotoxicity; liver and small intestine transplant; liver transplantation; liver operation; liver transplant; lupoid hepatic cirrhosis; mixed liver injury; nodular regenerative hyperplasia; renal and liver transplantation; Reye's syndrome; subacute hepatic failure
OR
Any of the following PTs denoting non-infectious hepatitis
acute graft versus host disease in liver; allergic hepatitis; autoimmune hepatitis; chronic graft versus host disease in liver; chronic hepatitis; graft versus host disease in liver; hepatitis; hepatitis acute; hepatitis alcoholic; hepatitis cholestatic; hepatitis chronic; hepatitis chronic persistent; hepatitis fulminant; hepatitis toxic; ischaemic hepatitis; lupus hepatitis; non-alcoholic steatohepatitis; radiation hepatitis; withdrawal hepatitis
OR
Any of the following PTs denoting jaundice
hyperbilirubinaemia; jaundice; jaundice cholestatic; jaundice hepatocellular; ocular icterus; yellow skin

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Imbalance in the incidence of malignancy in fezolinetant treated groups versus placebo

The review of safety noted an apparent dose dependent numeric imbalance in the incidence of malignancy in fezolinetant treatment groups when compared to placebo groups. The clinical team consulted the Division of Biometrics 7 (DB7) to assess: 1) whether participants with different exposure duration to study drug can be pooled (as is the case for the POP2 population; and 2) whether the placebo group from one trial can be compared to active treatment groups from another trial (i.e., to assess whether the placebo group in POP4 could be used to assess the non-controlled fezolinetant groups in POP2. DB7 was also asked to assess the potential for a malignancy signal.

The consult reply from Dr. Lee indicated: “because of the cross-over study element of studies 2693-CL-301 and 2693-CL-302, comparing placebo and fezolinetant arms at 52 weeks would violate the intention-to-treat (ITT) principle. Furthermore, by design, subjects re-randomized to fezolinetant arm(s) at week 12 knew that they were on treatment, which might make studies 2693-CL-301 and 2693-CL-302 inherently too different from study 2693-CL-304 to make comparisons. Therefore, analyses for POP2 are presented for descriptive purposes and only POP4 should be used for comparative assessment at week 52.” Therefore, for POP2 the *analyses are descriptive*. The analyses include the number and exposure-adjusted incidence rates. Exposure-adjusted incidence rate, defined as number of subjects with an event per 100 subject-years, accounts for the differences in follow-up time, and drug-exposure time among studies or treatment arms. The exposure for each subject is the time from first dose to the first onset of an event for those who had event or to the date of last collection of AE (last dose + 21 days) for those who did not. A 95% confidence interval (CI) for the exposure-adjusted incidence rates were calculated using normal approximation.

For 52-week placebo-controlled Trial 2693-CL-0304, the descriptive analysis methods are the same as those for POP2. Comparisons are based on exposure-adjusted incidence rates difference (EAIRD) with the 95% confidence interval (normal approximation).

The requested assessments of potential malignancy safety signal are presented in Tables 52 and 53.

Table 52: Number of Subjects with Events (%) and Exposure-Adjusted Incidence Rates POP2 (52 weeks)

	Placebo N=952 PY=599.4	Fezolinetant 30 mg N=1103 PY=941.0	Fezolinetant 45 mg N=1100 PY=966.9
Participants with Events¹	1	6	11
Proportion % (95% CI)	0.11 (0.01, 0.74)	0.54 (0.24, 1.21)	1.0 (0.55, 1.80)
Exposure²-adjusted Incidence Rates, EAIR per 100 PY³ (95% CI)	0.20 (0.03, 1.39)	0.65 (0.29, 1.44)	1.15 (0.64, 2.07)

¹First event only²Exposure: (date of 1st onset of event minus date of 1st dose)+1 for those with event or (date of last dose +21 days minus date of 1st dose) + 1 for those with no event; PY person year = sum of exposure over all subjects /365.25.Source: Clinical Review **Table 55, page 191** and DB7 Consult Review **Table 4.****Table 53: Number of Subjects with Events (%) and Exposure-Adjusted Incidence Rates and Differences of Malignancy POP4 (52 weeks)**

POP 4 (CL-304)			
	Placebo N=610 PY=509.5	Fezolinetant 30 mg N=611 PY=537.9	Fezolinetant 45 mg N=609 PY=538.2
Subjects with Events	1	4	7
Proportion, % (95% CI)	0.16 (0, 0.91)	0.65 (0.18, 1.67)	1.15 (0.46, 2.35)
Crude Risk Difference, % (95% CI)	—	0.49 (-0.22, 1.21)	0.99 (0.08, 1.89)
Exposure-Adjusted Incidence Rates (EAIR) per 100 PY, (95% CI)	0.20 (0.0, 0.58)	0.74 (0.02, 1.47)	1.30 (0.33, 2.27)
EAIR Difference per 100 PY (95% CI)	—	0.55 (-0.28, 1.37)	1.10 (0.07, 2.14)

¹First event only²Exposure: (date of 1st onset of event minus date of 1st dose) +1 for those with event or (date of last dose+21 days minus date of 1st dose) + 1 for those with no event; PY³person year = sum of exposure over all subjects/365.25.Source: DB7 Consult Review **Table 4**

The *EAIR rates were 0.2, 0.65 and 1.15 in placebo, fezolinetant 30 mg dosage strength group and fezolinetant 45 mg dosage strength group, respectively in POP2*. The EAIR rate of malignancy outcome showed a dose-dependent increased risk in POP4. The lower bound of the 95% confidence interval of the exposure-adjusted incidence rate difference (EAIRD) comparing fezolinetant 45 mg and placebo arms was greater than the null value of 0.

On August 25, 2022, we consulted the Division of Oncology III for their input regarding following:

“We request your assistance in evaluating whether there is a potential safety signal of malignancy in women taking fezolinetant. In a pooled consideration of Trials 2693-CL-0301 2693-CL-0302, and 2693-CL-0304, there was 1 case of malignancy in placebo(a squamous cell carcinoma of the skin), 4 cases of malignancy in fezolinetant 30mg (1 squamous cell carcinoma of the skin, 1 squamous cell carcinoma of the oral cavity, and 2 basal cell carcinomas) and 10 cases of malignancy in fezolinetant 45 mg (1 squamous cell carcinoma of the skin, 1 squamous cell carcinoma of the oral cavity, 1 bone cancer, 2 colon cancer, 3 endometrial adenocarcinomas, 1 malignant melanoma in situ, 1 non-small cell carcinoma of the lung) and 3 cases of malignancy in the 40 week cross over extension (1 squamous cell cancer of skin, 1 apocrine cancer of breast, 1 invasive cancer of breast). Additionally, 1 case of unspecified lung neoplasm and 1 case of keratoacanthoma, a neoplasm with high malignant potential.

We have the following specific requests/questions:

1. Given the higher incidence of some of these malignancy in the older population of women in general (as compared to their younger counterparts), do you consider that these 18 to 19 cases of malignancies of various primary sites represent a signal for general malignancy with this product? If so, how would you characterize the strength, i.e., weak, moderate, or strong signal).
2. Is there a potential biologic mechanism by which an NK3 antagonist could lead to malignancy?
3. If you believe that this malignancy signal is of potential concern to patients that take this medication, do you have recommendations for wording of the related warnings and precautions in labeling.”

On January 23, 2023, the Division of Oncology III replied as follows

1. Given the higher incidence of some of these malignancy in the older population of women in general (as compared to their younger counterparts), do you consider that these 18 to 19 cases of malignancies of various primary sites represent a signal for general malignancy with this product? If so, how would you characterize the strength, i.e., weak, moderate, or strong signal).

DO3 Response:

“From a clinical perspective, interpreting the clinical findings shown in Table 1 is challenging. There is insufficient data to support a definitive conclusion of an increased risk of malignancy in patients who received fezolinetant. While there exists a background risk of malignancy in the general population which increases with age, it is unclear what effect, if any, exposure to fezolinetant may have on this risk. It would be challenging to conclude an increased risk over the baseline rate without a baseline assessment of the history of malignancy (or of an increased risk for example due to presence of pre-cancerous lesions or risk factors for cancer, etc.) in patients who enrolled in the trial. The post-exposure follow-up and the stage of the malignancy should also be considered in the assessment of the likelihood that the observed malignancies are attributable to the drug. For example, most cancers have a long latency from pre-malignant lesion to early malignant tumor, to invasive cancer. It is unclear whether the malignancy events were early stage, in-situ lesions or whether they represented more advanced disease. For these reasons, it is challenging to comment on whether any association exists between exposure to fezolinetant and increased risk of malignancy, or alternatively in an increased risk of progression in patients who have pre-existing neoplastic lesions.

Another limitation is that pooling of data across studies with different designs, and patient follow-up, can introduce heterogeneity such that interpretation of results can be difficult. It is unclear whether comparing rates of malignancy in participants randomized to fezolinetant versus those randomized to placebo across the -301 and -302 trials, is appropriate given that participants who were initially randomized to placebo were subsequently re-randomized to treatment following 12 weeks of placebo. These limitations can lead to falsely attributing a finding to a safety signal due to the drug due to potentially flawed comparisons (including limited follow-up timing for patients receiving placebo as compared to patients who received fezolinetant).

Based on available data that describes the molecular pathways involved in tumorigenesis across the observed cancer types that have distinct histologies, it is unclear whether there is a unifying factor that explains the findings. Preclinical data may help elucidate a mechanistic association between fezolinetant exposure and the risk of malignancy (or progression of malignancy) across these diverse tumor types, if one exists. DO3 therefore recommends that the pharmacology toxicology team review the available data and provide input on the mechanistic potential of increased risk. Additionally, consider requesting input from the Office of Surveillance Epidemiology (OSE) to provide an assessment of the rate of malignancy observed in the trials submitted in the NDA, considering the background incidence of malignancy. OSE may also be able to provide guidance with respect to what signals have resulted in changes in labeling for other drugs

with non-oncological indications (e.g., including JAK inhibitors, HCTZ, SLGT2i, and potentially others).

CDTL Comment:

There were no preclinical signals for malignancy noted in the NDA data. The reader is referred to Section 4 of this review and the statement, “The Pharmacology/Toxicology review team concludes that fezolinetant was found not to be carcinogenic...”

2. Is there a potential biologic mechanism by which an NK3 antagonist could lead to malignancy?

DO3 Response:

We cannot comment on the biological plausibility of whether NK3 antagonism can lead to malignancy. There are published reports evaluating the role of NK3 receptor expression in oral squamous cell carcinoma (Obata K et al, 2016; Obata K et al, 2017). DO3 strongly recommends consultation of pharmacology toxicology team for an assessment of the mechanism of action including the potential for malignancy.

CDTL Comment:

As noted in comment under the DO3 response to Questions 1, there were no preclinical signals for malignancy noted in the NDA data.

3. If you believe that this malignancy signal is of potential concern to patients that take this medication, do you have recommendations for wording of the related warnings and precautions in labeling.

DO3 Response:

Refer to DO3 response to Question 1 and Question 2. FDA defers to the review team whether to describe the study findings in product labeling considering the uncertainty with respect to the finding but acknowledging the difference between arms and consideration for whether to be transparent with respect to the finding.”

Before receiving the Oncology Consult response, Dr. Zopf undertook a through look at each of the 16 cases of reported malignancies in the POP2 population. Table 54 presents that evaluation.

Table 54: Clinical Reviewer - Assessed Individual Malignancy TEAEs in POP2 (52 weeks)

Patient ID #	Trial	Treatment Arm		Exposure						Comments
		(Phase 3 POP2)	AE Code	Day	Months	Age	Race	BMI	Smoker	
(b) (6)	2693-CL-0304	Placebo	Squamous cell carcinoma of skin	192	6.3	56	Black	33.8	Former/Never	
	2693-CL-0301	Placebo/45mg	Apocrine breast carcinoma	11	3.1	62	White	26.0	Former/Never	Completed 12 wks placeb. Rerandomized to 45 mg fez. Day 95 dx. Atypical apocrine metaplasia. Partial mastectomy Day 240
	2693-CL-0304	45mg	Non-small cell lung cancer	11	2.4	65	White	21.6	Current	The participant had metastasis to the liver
	2693-CL-0301	Placebo/30mg	Squamous cell carcinoma of skin	62	4.8	65	White	33.4	Former/Never	
	2693-CL-0304	45mg	Endometrial adenocarcinoma	79	2.6	50	White	27.4	Former/Never	Complex hyperplasia with atypia at baseline
	2693-CL-0304	45mg	Malignant melanoma in situ	97	3.2	56	White	22.5	Current	

Patient ID #	Trial	Treatment Arm		Exposure		Age	Race	BMI	Smoker	Comments
		(Phase 3 POP2)	AE Code	Day	Months					
(b) (6)	2693-CL-0302	45mg	Squamous cell carcinoma of skin	104	3.4	60	White	31.3	Former/Never	
	2693-CL-0304	45mg	Endometrial adenocarcinoma	122	4.0	58	White	32.2	Former/Never	
	2693-CL-0304	45mg	Squamous cell carcinoma of the oral cavity**	138	4.5	52	White	27.3	Former/Never	Oral lesion Day 47 not biopsied at on initial presentation
	2693-CL-0304	45mg	Bone cancer**	151	5.0	52	White	27.3	Former/Never	Oral cancer that spread locally to jaw bone
	2693-CL-0302	Placebo/30mg	Invasive breast carcinoma	152	7.8	60	Black	33.0	Former/Never	
	2693-CL-0304	30mg	Squamous cell carcinoma of skin	186	6.1	56	White	27.3	Former/Never	
	2693-CL-0302	45mg	Keratoacanthoma (precancerous)	213	7.0	55	White	30.0	Former/Never	

Patient ID #	Trial	Treatment Arm (Phase 3 POP2) AE Code	Exposure Day	Months	Age	Race	BMI	Smoker	Comments
(b) (6)	2693-CL-0304	30mg Chronic lymphocytic leukemia	225	7.4	51	Black	24.9	Former/Never	Baseline leuko and lymphocytosis
	2693-CL-0304	45mg Colon cancer	233	7.7	52	White	34.0	Current	
	2693-CL-0304	30mg Basal cell carcinoma	239	7.9	63	White	19.7	Former/Never	Recurrent case
	2693-CL-0304	45mg Colon cancer	253	8.3	55	White	31.0	Current	Symptomatic starting on Day 24 without evaluation
	2693-CL-0304	30mg Endometrial adenocarcinoma	370	12.2	51	White	29.4	Current	

*AEs occurred in same participant, ** AEs occurred in same participant

Source: Clinical Review **Table 56, page 193-194** , reviewer generated using NDA 216578 ISS ADAE database, JMP analysis.

The preceding Table 54 presents 18 cases overall representing 16 cases of cancer, one case of carcinoma in-situ, and one precancerous lesion. The cases of malignancy were not of a single cancer type or apparent associated cluster of cancer types. There was no obvious pattern or distribution by duration of drug exposure or body system. Most cancers were singularly occurring from disparate organ origins with the exception of two cases of colon cancer, three cases of squamous cell skin cancer three cases of endometrial cancer. This reviewer notes one error in Table 56 (pages 193 through 194) in the Clinical Review upon which Table 54 is based upon. The footnotes of Clinical Review Table 56 identify two cases of malignancy, an apocrine breast cancer and a non-small cell lung cancer, as occurring in the same participant. These two cancer cases occurred in different participants.

Based on the clinical review, six of the participants (8/16 malignancy TEAEs in treatment arms) were likely to have had preexisting malignancy that were undiagnosed at the time of enrollment. That number includes: 1) Participant # (b) (6) who was diagnosed following re-randomization to fezolinetant treatment (Day 11) after completing 12 weeks on placebo; 2) Participant # (b) (6) who had complex endometrial hyperplasia on a baseline endometrial biopsy, but was enrolled despite meeting a criterion for exclusion; 3) Participant # (b) (6) who had recurrent basal carcinoma (history of basal cell carcinoma allowed under the enrollment criteria); 4) Participant # (b) (6) who had oral lesions noted on enrollment which were not biopsied prior to her diagnosis of squamous cell carcinoma of the oral cavity; Participant # (b) (6) who had symptoms consistent with her ultimate diagnosis beginning on Day 24 of exposure and Participant # (b) (6) who had leuko and lymphocytosis at Baseline evaluation. If these six participants representing seven cases of malignancy were to be removed (because of history that suggests preexistent malignancy) from consideration, then the overall incidence rate of malignancy would be approximately halved. That resultant incident rate would approximate the normal background rate of cancer for the represented age group which is 5.6 per 1,000 for 50 – 59 years of age (75% of participants) according to SEER incidence rates by age at diagnosis of cancer in all races (years 2015 – 2019). Additionally, the placebo arm had lower than expected rate of malignancy as compared to the background rate.

In the 120-day Safety Update of Clinical Safety submitted on October 6, 2022, there was one report of fibroadenoma of breast in placebo and one case of malignant neoplasm of thymus in fezolinetant 30 mg in a 24-week cross-over placebo-controlled trial in China (12 to 24 weeks of exposure, CL 0305, N=300). In a single arm, multicenter safety and tolerability 52-week study in China (CL 0307, N=150), there was one case of endometrial adenocarcinoma and one case of invasive breast carcinoma in the fezolinetant 30 mg arm. The data presented in the 120-day Safety Update of Clinical Safety are reassuring related to malignancy.

Based on our review, *we opine that there is no signal for increased malignancy risk with Veozah*. Based on the nonclinical information provided by the applicant and available in the published literature, no biological mechanism was identified that indicated an increased risk of malignancy with fezolinetant or NK3R antagonism (See Section 4 of this review).

We have consulted Graca Does, M.D., an oncologist in the Office of Surveillance and Epidemiology (OSE)/ Division of Pharmacovigilance VII (DPVII), to support or refute this conclusions. As of the date of this review Dr. Does' evaluation is ongoing.

Endometrial Safety

Endometrial assessment was performed in all three phase 3 trials, Trials 2693-CL-0301, 2693-CL-0302 and 2693-CL-0304. In agreement with FDA, this assessment included endometrial biopsy specimen collection and histologic pathology diagnoses of the collected endometrial tissue. Transvaginal ultrasound (TVU) assessment was also performed.

The endometrial biopsy specimens were reviewed by three independent board-certified pathologists from institutions with independent fiduciary and organizational reporting. After the initial safety evaluation of the actual biopsy was completed by the primary pathologist, digital images of the biopsy specimen were uploaded to a database and then assessed by secondary and tertiary pathologists independently. Each pathologist was blinded to the treatment group information as well as other pathologist's results. The independent pathologists did not have access to any other clinical case data. The three pathologists used the same standardized criteria for the diagnosis of endometrial hyperplasia or endometrial cancer, and endometrial polyps were fully characterized as to glandular proliferation and atypia per FDA's draft 2003 HT Clinical Trial Guidance. For postbaseline endometrial biopsies, the concordance of two of the three pathologists' readings determined the final diagnosis endometrial specimen classification. If all 3-three individual pathologist readings were discordant, the final diagnosis was classified based on the worst diagnosis.

The endometrial health (EH) set consisted of all non-hysterectomized participants who were randomized and received at least 1 dose of trial drug, had the postbaseline endometrial biopsy done within 30 days after the last dose of trial drug, and who:

- had an acceptable biopsy at baseline (at least 1 endometrial biopsy with satisfactory tissue and no read of hyperplasia, disordered proliferative pattern or malignancy); and
- had a satisfactory endometrial biopsy result after or on day 326 or had a postbaseline final diagnosis of hyperplasia, disordered proliferative or malignancy prior to day 326.

In agreement with FDA, Astellas calculated the percentage of participants with 1) a final diagnosis of endometrial hyperplasia, 2) a final diagnosis of endometrial cancer, and 3) a final diagnosis of disordered proliferative pattern, using the exact (Clopper-Pearson) upper limit of the one-sided 95% confidence interval (CI).

Participants from Trials 2693-CL-0301 and 2693-CL-0302 initially randomized to fezolinetant and who satisfied the criteria for inclusion were eligible for the POP2 EH set. Per Astellas, participants who were initially randomized to placebo and re-randomized to 30 or 45 mg fezolinetant in these two trials were not included in the primary EH set for POP2 because of the differences in duration of fezolinetant treatment.

Per Astellas, POP4 was considered the primary population for analysis of endometrial health, since it was composed of 52-week, placebo-controlled Trial 2693-CL-0304, for which endometrial health was a primary trial objective.

In Trial 2693-CL-0304, no participant in the placebo or 30 mg fezolinetant treatment group was diagnosed with endometrial hyperplasia; 1 participant in the 45 mg fezolinetant treatment group

was diagnosed with simple hyperplasia without atypia. Likewise, in Trial 2693-CL-0304, no participant in the placebo or 45 mg fezolinetant treatment group was diagnosed with endometrial cancer; 1 participant in the 30 mg fezolinetant treatment group was diagnosed with endometrial adenocarcinoma. Table 55 presents the endometrial biopsy results for POP4:

**Table 55 Endometrial Biopsy Results; Hyperplasia or Malignancy
(Endometrial Health Set); POP4: Trial 2693-CL-0304**

Final Diagnosis	Placebo (n = 186)	Fezolinetant 30 mg (n = 210)	Fezolinetant 45 mg (n = 203)
Hyperplasia	0	0	1 (0.5%)
One-sided upper limit of 95% CI †	1.6%	1.4%	2.3%
Simple hyperplasia without atypia	0	0	1
Malignancy	0	1 (0.5%)	0
One-sided upper limit of 95% CI †	1.6%	2.2%	1.5%
Malignant, carcinoma	0	1	0

† CI obtained using the Clopper-Pearson exact method for binomial proportions.

Definition: CI = confidence interval.

Source: Clinical Review **Table 59, page 202** and NDA 216578, Summary Clinical Safety (SCS)/Integrated Summary of Safety (ISS), **Table 38, page 106**.

The point estimates for endometrial hyperplasia or malignancy were below the *prespecified 2003 draft HT Clinical Trial Guidance* recommended limits of $\leq 1\%$, and the upper limit of the one-sided 95% CI was $\leq 4\%$. Per Astellas Trial 2693-CL-0304 met its primary endpoints for endometrial safety.

Table 56 shows the disposition of endometrial biopsy results in the POP2 52-week analysis.

Table 56. Disposition of Endometrial Biopsy Results (Randomized Participants); POP2 52-week

Reason	Fezolinetant 30 mg (n = 953)	Fezolinetant 45 mg (n = 952)
Randomized †	953	952
Safety Analysis Set ‡	951	949
Had a hysterectomy	214	227
Postbaseline final diagnosis of hyperplasia, malignancy or disordered proliferative pattern before day 326 §	2	2
Acceptable biopsy at baseline AND satisfactory sample at postbaseline	344	338
< 326 days ¶	29	27
> last dose + 30 days ††	13	7
EH set †††	302	304

† Planned treatment of randomized participants.

‡ In Trial 2693-CL-0301, 1 participant who was randomized to 45 mg fezolinetant received 30 mg fezolinetant for the first 12 weeks.

§ These participants had an acceptable biopsy at baseline except for the 2 participants from the fezolinetant: 45 mg group: participant (b) (6) had disordered proliferative pattern and participant (b) (6) had hyperplasia at baseline, therefore these 2 participants were not included in the EH set.

¶ Participants who had an acceptable biopsy at baseline and a satisfactory postbaseline biopsy prior to day 326, but were not included in the EH set.

†† Participants who had an acceptable biopsy at baseline and a satisfactory postbaseline biopsy after last dose + 30 days, but were not included in EH set.

††† Participants who met the EH set definition in the statistical analysis plan (SAP).

Source: Clinical Review Table 60, page 201 and NDA 216578, Summary Clinical Safety (SCS)/Integrated Summary of Safety (ISS), Table 40, page 107.

Table 57 presents the endometrial biopsy results for POP2:

Table 57 Endometrial Biopsy Results; Hyperplasia or Malignancy (Endometrial Health Set¹); POP2 52-week

Final Diagnosis	Fezolinetant 30 mg (n = 302)	Fezolinetant 45 mg (n = 304)
Hyperplasia	0	1 (0.3%)
One-sided upper limit of 95% CI †	1.0%	1.6%
Simple hyperplasia without atypia	0	1
Malignancy	1 (0.3%)	0
One-sided upper limit of 95% CI †	1.6%	1.0%
Malignant, carcinoma	1	0

¹Endometrial Health Set consists of safety analysis participants with an acceptable biopsy baseline (per SAP), had postbaseline biopsy done within 30 days from last dose, and had satisfactory postbaseline on or after day 326 or had a hyperplasia, malignancy, or disordered proliferative pattern final diagnosis prior to day 326.

†CI calculated using Clopper-Pearson exact method for binomial proportions.

Definition: CI = confidence interval.

Source: Clinical Review **Table 61, page 203** and NDA 216578, Summary Clinical Safety (SCS)/Integrated Summary of Safety (ISS), **Table 41, page 107**.

In POP2, a total 302 participants were included in the fezolinetant 30 mg group, and 304 participants in the fezolinetant 45 mg group in the EH set. Per the NDA application, the rate of endometrial hyperplasia and malignancy in the fezolinetant groups in POP2 met the prespecified 2003 draft HT Clinical Trial Guidance recommended limits of $\leq 1\%$ with the upper bound of the one-sided 95% CI being $\leq 4\%$. The secondary results for the POP2 52-week are consistent with the primary results reported for POP4.

During the primary clinical review two additional cases of endometrial adenocarcinoma and an additional case of endometrial hyperplasia were noted as having been diagnosed in Trial 2693-CL-0304. These are described below:

1. **Participant Number** (b) (6), a self-identified as White woman, 50 years of age, was randomized to the 45 mg fezolinetant treatment group. Her relevant medical history included ongoing hypothyroidism and depressed mood, and concurrent medications included paroxetine hydrochloride and levothyroxine sodium. She had never smoked and *had not received previous hormone therapy*. Her baseline TVU on **Day -33** revealed an endometrial thickness of 3.545 mm. An endometrial biopsy performed on the same day (**Baseline**) revealed the following diagnoses by 3 pathologists: Pathologist 1 - complex hyperplasia with atypia/areas of squamous metaplasia; Pathologist 2 - complex hyperplasia with atypia and two foci with crowded back-to-back atypical endometrial glands, consistent with atypical complex hyperplasia/endometrioid intraepithelial neoplasia; and Pathologist 3 - complex hyperplasia without atypia. The Final diagnosis was **complex hyperplasia with atypia**.

On **Day 29**, she experienced uterine hemorrhage, which was moderate in intensity and considered related to trial drug by the investigator which resolved on **Day 38**. No action was taken with trial drug due to the event. An endometrial biopsy was performed on **Day 38** and revealed the following diagnoses by 3 pathologists: Pathologist 1 - limited surface endometrium; Pathologist 2 - tissue unsatisfactory for diagnosis; no endometrium present and Pathologist 3 - limited surface endometrium. The Final diagnosis was limited surface endometrium.

On **Day 54**, she again experienced uterine hemorrhage, which was moderate in intensity and considered related to trial drug by the investigator which resolved on **Day 61**. An endometrial biopsy was performed on **Day 79** and revealed the following diagnoses by three pathologists: Pathologist 1 – malignant, carcinoma/well differentiated endometrial adenocarcinoma in background of secretory endometrium; Pathologist 2 – secretory cyclic type, simple hyperplasia without atypia, functional polyp/there are areas with crowded glands with decreased intervening stroma and squamous metaplasia; no significant cytologic atypia is seen; the rest of the specimen shows secretory and polypoid changes; Pathologist 3 – functional polyp, complex hyperplasia with atypia. Per the 2003 draft HT Clinical Trial Guidance, when the three independent pathologists all disagree, the most severe diagnosis is the **final diagnosis**. and that diagnosis is **endometrial adenocarcinoma**.

Treatment with trial drug was withdrawn due to the event. No TVU was performed post-baseline. On **Day 119**, she was hospitalized and had a laparotomy, modified radical hysterectomy with adnexa resection. Histopathology: adenocarcinoma endometrioides endometrii G1. The investigator considered the 2 events of uterine hemorrhage to be related to trial drug, and the event of endometrial adenocarcinoma to be not related to trial drug. The applicant agreed with the investigator's assessments for all events, including the event of endometrial adenocarcinoma to be not related to study drug. This participant was not included in the endometrial health set as she did not fulfill one of the qualifying criteria (i.e., she had Baseline diagnosis of hyperplasia).

I agree with Dr. van der Vlugt's conclusion that this participant had a pre-existing complex hyperplasia with atypia at baseline which subsequently advanced to endometrial adenocarcinoma. She should not have been enrolled in Trial 2693-CL-0304 and should not be included under 45 mg fezolinetant for POP2 52-week population.

2. **Participant Number** (b) (6), a self-identified as White woman, 538 years of age, was randomized to the 45 mg fezolinetant treatment group. Her relevant medical history included ongoing arthralgia (right knee) and no relevant concurrent medications. She had never smoked and had not received previous hormone therapy. A TVU on Day -20 revealed an endometrial thickness of 5.49 mm. An endometrial biopsy performed on **Day - 30** revealed the following diagnoses by two pathologists: Pathologist 1 – inactive endometrium; and Pathologist 2 - limited surface endometrium, atrophy. The **final diagnosis** was **limited surface endometrium**.

On **Day 1**, she experienced severe fatigue and mild hot flush (resolved **Day 25**). Both events were considered related to trial drug by the investigator. No action was taken with the trial drug. On **Day 74**, her fatigue improved to moderate severity, but she then experienced moderate anxiety, considered related to trial drug by the investigator. The events of fatigue and anxiety led to withdrawal of trial drug, with the last dose on **Day 107**. She was discontinued from the trial on **Day 112** and underwent early discontinuation protocol assessments. On **Day 122** (15 days after stopping the trial drug), the early discontinuation post-baseline TVU revealed an endometrial polyp and a derived endometrial thickness of 2.295 mm. An endometrial biopsy was not performed at the early discontinuation visit due to participant refusal. On the same day (**Day 122**), the investigator reported a nonserious TEAE of uterine polyp considered related to trial drug by the investigator.

On **Day 247** after trial discontinuation, the investigator reported that a repeat TVU was performed which confirmed the presence and growth of the polyp first seen on **Day 122**; a TVU endometrial thickness of 2.355 mm was reported. A hysteroscopy was performed on day 309 to remove the endometrial polyp. The event of uterine polyp was considered resolved with sequelae on **Day 309**. The polyp biopsy report showed **endometrial adenocarcinoma (Stage 1)**. On **Day 351**, she underwent a robotic XI total lap hysterectomy bilateral salpingo-oophorectomy sentinel lymph node dissection. The event of endometrial adenocarcinoma (Stage 1) was not resolved at the time of reporting. Although requested, no histopathology report has been submitted thus far.

The investigator considered the events of fatigue (severe and moderate events), anxiety and endometrial adenocarcinoma to be related to trial drug. The sponsor agreed with the investigator's assessment for the events of fatigue (both events) and anxiety. The sponsor assessed the serious event of endometrial adenocarcinoma (Stage 1) as not related to trial drug.

This participant was not included in the endometrial health set as she did not fulfill one of the qualifying criteria (i.e., she did not have an acceptable postbaseline endometrial biopsy assessment).

Dr. van der Vlugt agreed with the investigator's assessment of causality and disagreed with the sponsor. This participant's polyp was confirmed by TVU on **Day 122**, 15 days after her last dose of trial medication. *I agree with Dr. van der Vlugt that this case of endometrial adenocarcinoma should be added under 45 mg fezolinetant for POP2 52-week population.*

3. **Participant Number** (b) (6), a self-identified as White woman, 53 years of age, was randomized to the 45 mg fezolinetant treatment group in Trial 2693-CL-0304 on September 28, 2020. On **Day -34**, her baseline transvaginal ultrasound (TVU) revealed an endometrial thickness of 3.665 mm. On **Day -18**, her **baseline endometrial biopsy** revealed a consensus diagnosis of **endometrial atrophy** by 3 pathologist. On Day 124, she experienced a right foot fracture considered not related to trial medication by the investigator. Her last dose of trial medication was on Day

361. On **Day 361**, her TVU revealed an endometrial thickness of 3.004. Her endometrial biopsy obtained the same day revealed the following diagnoses by 3 pathologists: Pathologist 1 - atrophy.; Pathologist 2 - polyp hyperplasia without atypia and Pathologist 3 - hyperplasia simple without atypia. The Final diagnosis was **hyperplasia simple without atypia**.

The investigator considered the event of right foot fracture to be not related to trial medication, and the event of simple hyperplasia without atypia to be related to trial medication. The sponsor agreed with the investigator's assessment with no additional comments. At the time of reporting, the event of simple hyperplasia without atypia was not resolved. *I agree with Dr. van der Vlugt that this case of simple hyperplasia without atypia should be added under 45 mg fezolinetant for POP2 52-week population*

On September 28, 2022, Astellas and DB7 were each requested to recalculate the point estimate of the incident rate of hyperplasia and cancer and the one-sided 95% confidence interval for that rate including the POP2 data on the re-randomized placebo group in Trials 0301 and 0302 [hyperplasia (participant # (b) (6)) and endometrial adenocarcinoma of polyp, Stage 1 (participant # (b) (6))] for the 45 mg fezolinetant dose. Astellas responded on October 3, 2022, but their response (**Table 62** in the Clinical Review) did not contain the information requested. The DB7 analysis (received September 30, 2022) of the requested information is presented in Table 58

Table 58 Division of Biometrics 7 Analysis of Participants with Endometrial Hyperplasia and Carcinoma at Postbaseline; POP2 52-week Including Re-randomized Participant in Trial 2693-CL-0301 and Trial 2693-CL-0302

Final Diagnosis	Fezolinetant 30 mg (n = 353)	Fezolinetant 45 mg (n = 350)
Hyperplasia and Carcinoma	2 (0.6%)	2 (0.6%)
One-sided upper limit of 95% CI	1.8%	1.8%
- Simple hyperplasia without atypia	0	1
- Simple hyperplasia with atypia	0	0
- Complex hyperplasia without atypia	1	0
- Complex hyperplasia with atypia	0	0
- Endometrial adenocarcinoma	0	1
- Malignant, carcinoma	1	0
Disordered Proliferative Pattern	6 (1.7%)	5 (1.4%)
One-sided upper limit of 95% CI	3.3%	3.0%

Source: Clinical Review **Table 63, page 208** and Division of Biometrics 7 Consult Response, received September 30, 2022.

The DB7 analyses for the expanded safety base of the rate for endometrial hyperplasia or malignancy met the prespecified 2003 draft HT Clinical Trial Guidance recommended limits of $\leq 1\%$ in the point estimate with the upper bound of the one-sided 95% CI being $\leq 4\%$.

I agree with Dr. van der Vlugt that the POP2 52-week supportive analysis of the Endometrial Health Set including the re-randomized participants in Trials 2693-CL-0301 and 2693-CL-0302 was consistent with and supportive of the primary analysis for the Endometrial Health Set in POP4. The POP4 52-week primary analyses and the POP2 52-week supportive analyses each met the prespecified 2003 draft HT Clinical Trial Guidance recommended limits of $\leq 1\%$ in the point estimate of rate of endometrial hyperplasia or malignancy with the upper bound of the one-sided 95% CI being $\leq 4\%$.

The reader is referred to the Clinical Review for presentation of transvaginal ultrasound findings in the assessment of endometrial health.

The exposure-adjusted incidence rate of uterine bleeding in POP2 52-week showed a higher rate of uterine bleeding in the placebo group than in the fezolinetant groups (6.0% in the placebo group vs 4.1% in 30 mg fezolinetant group, 3.4% in the 45 mg fezolinetant group, 3.8% in the placebo/30 mg fezolinetant group, and 2.8% in placebo/45 mg fezolinetant group.

The overall assessment of endometrial health provided in the data for NDA 216578 is reassuring.

Cardiac Safety Studies

The Interdisciplinary Review Team for Cardiac Safety Studies (IRT) indicated on October 4, 2022, that the applicant's "QT assessments for fezolinetant, including C-QT report and data, were previously reviewed by the IRT (See IRT review for IND130277 dated 11/21/2019 in DARRTS). In the previous review, the IRT determined that, based on a randomized, double-blind, placebo-controlled, 3-part (part-1: single ascending dose, part-2: multiple ascending doses, and part-3: single ascending dose) clinical study, fezolinetant did not cause concentration dependent QTc prolongation. However, at the time of the previous review, the maximum recommended dose was 30 mg QD and the highest tested dose in the trial provided > 2-fold margin over worst-case exposure and therefore justified waiving a positive control. Now, the applicant has revised fezolinetant dosage to 45 mg QD....Despite the higher dosage of 45 mg QD than previously recommended, given the new worst-case exposure scenario, the highest tested dose still covers > 2-fold margin of the anticipated worst-case exposure and therefore the study still meets the assay sensitivity requirements. Based on this assessment, the previous IRT review is applicable to the new proposed dosage regimen of 45 mg QD."

The IRT labeling recommendations are noted below. The proposed edits are highlighted (addition, deletion). Each section is followed by a rationale for the changes made. IRT states that their revisions are meant to be suggestion only and they defer final labeling decisions to the Division.

We propose to use labeling language for this product consistent with the “Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format” guidance.

CDTL Overall Conclusions on the Evidence of Safety for Veozah

This reviewer concludes that the overall safety of Veozah is acceptable, and no issues preclude approval. That said there appears to be a modest signal for the risk of drug induced liver injury with this product. As presented in 2,859 unique participants included in the POP2 population, only a small percentage had elevation of hepatic transaminases. Elevations in serum transaminase [alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST)] levels greater than three times the upper limit of normal (ULN) occurred in 2.3% (EAIR) of 2.7 per 100 person-years) of women receiving VEOZAH and 0.9% (EAIR of 1.5 per 100 person-years) of women receiving placebo in three clinical trials. No Hy's Law Cases.

Even though the findings, occurring in a relatively high number of participant exposures in the phase 3 clinical trials, were not acutely worrisome, there is concern that should the product be used in as low as 1% (approximately 100,000 women) of the available population of menopausal women seeking therapy for moderate to severe vasomotor symptoms in the postmarketing setting (estimated in the range of 10 to 13 million women), a higher proportion of more severe liver injury may become evident. The clinical team proposes monitoring of hepatic function/injury before the patient begins Veozah and while on Veozah for minimum of up to 9 months follow initiation of use.

Additionally, we also endorse an enhanced pharmacovigilance program, to involve the applicant in actively seeking (from the reporter) additional information (in the form of an approved FDA questionnaire), as needed, to provide full and complete 15-Day Safety Reports characterizing the risk of hepatic injury according to the following laboratory criteria:

- a. ALT / AST > 8x ULN confirmed on repeat testing OR
- b. ALT / AST > 3x ULN and total bilirubin > 2x ULN (new onset biochemical abnormalities consistent with possible Hy's law cases) OR
- c. ALT / AST > 3x ULN associated with symptoms suggestive of hepatic disease such as: anorexia, dark urine, fatigue, fever, jaundice, nausea, vomiting, rash, right upper quadrant pain, etc., OR
- d. Any liver adverse event leading to discontinuation OR

- e. Any hepatic event preferred term (PT) denoting diagnosis, jaundice, liver injury, or non- infectious hepatitis.

Further to use all post-marketing reports of hepatic adverse events including liver injury to provide a summary analysis of these events in the periodic safety reports, submitted quarterly for the first 3 years after approval, as per 21 CFR 314.80(c)(1) and a cumulative summary of these events since NDA.

Should evidence be presented of more severe liver injury, formal postmarketing required studies may be sought.

Efforts are ongoing to better define whether there is any signal for increased risk of malignancies with use of Veozah.

9. Advisory Committee Meeting

An Advisory Committee meeting was not considered necessary for the review of this NDA

10. Pediatrics

On January 10, 2023, the Pediatric Review Committee (PeRC) Review made a preliminary determination for Veozah agreeing with the request to grant full waiver for pediatrics because necessary studies are impossible or highly impracticable as the number of patients would be too small.

11. Other Relevant Regulatory Issues

Application Integrity Policy (AIP)

N/A for this NDA

Exclusivity or patent issues of concern

No issues were identified during the course of the review. The exclusivity summary will be completed just prior to approval.

Financial disclosures

Astellas submitted in the application Form 3454 noting that “as the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

Other Good Clinical Practice (GCP) issues

Proprietary Name Review:

On December 02, 2022, Division of Medication Error Prevention and Analysis 2, Office of Medication Error Prevention and Risk Management, Office of Surveillance and Epidemiology, Center for Drug Evaluation and Research provided a regulatory letter to the applicant concluding that the proprietary name Veozah was conditionally acceptable.

Office of Scientific Investigations (OSI) audits

On December 13, 2022, the OSI provided preliminary reporting on their audits of the clinical trial sites for NDA 216578. Seven clinical investigators were selected for Good Clinical Practice (GCP) inspections given they were high enrolling sites with good treatment effect. The sites were geographically diverse and comprised investigators from the U.S. (Drs. Heller, Romero, Guell, and Jimenez), Canada (Dr. Frechette), and Poland (Drs. Wilk and Oronowicz). All inspections were conducted on-site.

The inspections did not find significant concerns regarding the management of the clinical trials, GCP compliance, or data integrity. Data related to the primary efficacy endpoint for Trials 2693-CL-0301 and 2693-CL-0302, the frequency and severity of moderate to severe vasomotor symptoms, were verified with the source records available at the inspected clinical sites.

The inspection results for Drs. Wilk and Oronowicz in Poland are based on communications with the FDA site inspectors and are therefore preliminary. If significantly new or different information is contained in the final FDA Establishment Inspection Report, an addendum to this clinical inspection summary will be filed.

12. Labeling

Key elements of the proposed labeling are reproduced below:

Prescribing Information

(b) (4)

Other Labeling

Patient labeling (i.e., Medication Guide, Patient Information, Instructions for Use)

The Office of Medical Policy/Division of Medical Policy Programs (DMPP) review of Patient Labeling is outstanding. The clinical review team will review DMPP recommendations, for purposes of our concurrence or further Patient labeling recommendations, prior to sending to the applicant.

Carton and container labeling

In a memorandum dated January 9, 2022, the Division of Medication Error Prevention and Analysis 2 (DMEPA 2) noted that the revised container labels and carton labeling for Veozah, submitted by the applicant on December 12, 2022, was acceptable. They noted that they did not identify any new medication error concerns and had no additional recommendations for the applicant as of the timing of their memorandum.

13. Postmarketing Recommendations

As of the completion of this review, Drs. van der Vlugt, Zopf and I do not recommend a PMR or PMC before approval. We (relying on critical input from OSE/DPV and DHN) recommend an enhanced pharmacovigilance (EPV) to assess post-marketing adverse hepatic events occurring with the use of fezolinetant and provide expedited reporting, as well as summary analyses to be included in periodic safety reports.

Elements of the proposed ePV include the following:

1. Review all post-marketing reports of hepatic adverse events, including liver injury, with fezolinetant using recommended search terms. If follow-up information is needed to classify a report (as defined by the bulleted criteria in #2) as a hepatic adverse event, send an FDA-agreed upon hepatic adverse event follow-up questionnaire to the reporter for additional information. Structure the questionnaire such that you can obtain relevant clinical information including, but not limited to:
 - a. causality assessment
 - b. concomitant medications
 - c. dechallenge and rechallenge information, if available
 - d. description of the hepatic adverse event (e.g., signs and symptoms)
 - e. event outcome (e.g., liver transplant, lost to follow up, not resolved, resolved with or without sequelae, unknown)
 - f. patient's age
 - g. regulatory serious outcomes as defined by CFR 314.80
 - h. relevant laboratory data not captured by the initial report (e.g., albumin, autoimmune markers, coagulation parameters, endoscopic retrograde cholangiopancreatography, eosinophil count, liver biopsy, liver enzymes, liver imaging, viral serology)

- i. relevant medical history (e.g., alcohol consumption, autoimmune disease, biliary tract disorders, blood transfusion, cardiac disorders-specifically right heart failure or hypotension, cirrhosis, connective tissue disease, family history of liver disease, recent tattoos, recent travel, viral illness, viral or alcoholic hepatitis)
- j. time from fezolinetant initiation to occurrence of the hepatic adverse event
- k. treatment for hepatic adverse event

The applicant is requested to have the questionnaire query for the healthcare provider's specialty.

2. Expedite, as 15-Day alert reports, all initial and follow-up post-marketing hepatic adverse event reports including liver injury, from all post-marketing sources, including consumer reports, solicited reports, foreign reports, and ANY case with the following laboratory criteria:
 - a. ALT / AST > 8x ULN confirmed on repeat testing OR
 - b. ALT / AST > 3x ULN and total bilirubin > 2x ULN (new onset biochemical abnormalities consistent with possible Hy's law cases) OR
 - c. ALT / AST > 3x ULN associated with symptoms suggestive of hepatic disease such as: anorexia, dark urine, fatigue, fever, jaundice, nausea, vomiting, rash, right upper quadrant pain, etc., OR
 - d. Any liver adverse event leading to discontinuation OR
 - e. Any hepatic event preferred term (PT) denoting diagnosis, jaundice, liver injury, or non- infectious hepatitis. See Appendix A.
3. Using information from the hepatic adverse event follow-up questionnaire and all post-marketing reports of hepatic adverse events including liver injury, provide a summary analysis of these events in the periodic safety reports, submitted quarterly for the first 3 years after approval, as per 21 CFR 314.80(c)(1). We also request that a cumulative summary of these events since NDA approval be included in the periodic safety reports.

These summary analyses should include:

All adverse events which contain the MedDRA terms listed in Appendix A (or, where appropriate MedDRA terms currently do not exist, descriptions in the case narratives consistent with hepatic adverse events):

- a. a discussion of worldwide (if applicable) and domestic trends in reporting of hepatic adverse events including liver injury if/when applicable
 - b. causality assessment by you or your designee
 - c. recommendations for changes to the ePV system or product labeling if applicable.
4. Also provide in the periodic safety report, medical literature reviews for case reports/case series of hepatic adverse events including liver injury reported with fezolinetant.

14. Recommended Comments to the Applicant

Labeling discussions are ongoing.

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
01/29/2023 10:43:34 PM