CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216578Orig1s000

SUMMARY REVIEW

Division Director / Office Director Summary Review for Regulatory Action

Date	(electronic stamp)
From	May 12, 2023
Subject	Division Director / Office Director Summary Review
NDA/BLA # and Supplement #	216578
Applicant	Astellas Pharma Global Development, Inc.
Date of Submission	June 22, 2022
PDUFA Goal Date	February 22, 2023 (Extended to May 22, 2023)
Proprietary Name	Veozah
Established or Proper Name	Fezolinetant
Dosage Form(s)	45 mg tablet
Applicant Proposed Indication(s)/Population(s)	Treatment of moderate to severe vasomotor symptoms (VMS) associated with menopause
Action or Recommended Action:	Approval
Approved/Recommended Indication(s)/Population(s) (if applicable)	Treatment of moderate to severe vasomotor symptoms (VMS) due to menopause

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Theresa van der Vlugt, MD, MPH; Regina Zopf, MD, MPH
Statistical Review	Juan C. Vivar, PhD; Solomon Chefo, PhD, Daphne Lin, PhD COA Statistical Review Team: Yun Tang, PhD, Lili Garrard PhD
Pharmacology Toxicology Review	Miyun Tsai-Turton, PhD; Andrea Benedict, PhD; Kimberly Hatfield, PhD; Mukesh Summan, PhD
OPQ Review	Drug Substance: Friedrich Burnett, PhD; Lawrence Perez, PhD Drug Product: Baoqing Ma, PhD; Hamid Shafiei, PhD Manufacturing: Loqman Mohamed, PhD; Vaikunth Prabhu, PhD Biopharmaceutics: Kalpana Paudel, PhD; Tapash Ghosh, PhD
Microbiology Review	Loqman Mohamed, PhD; Vaikunth Prabhu, PhD
Clinical Pharmacology Review	Lin Zhou, PhD; Yaning Sun, PhD; Junshan Qiu, PhD; Jingyu (Jerry) Yu, PhD; Manuela Grimstein, PhD; Yuching Yang, PhD; Yanhui Lu, PhD; Shirley Seo, PhD
OPDP	Elvy Varghese, PharmD; James Dvorsky, PharmD

OSI	Michele Fedowitz, MD; Jenn Sellars, MD, PhD
CDTL Review	Shelley Slaughter, MD, PhD
OSE/OPE	Baoguang Wang, MD, DrPH
OSE/DEPII	Huei-Ting Tsai, PhD; Adebola Ajao, PhD; Dave Moeny, RPh, MPH
OSE/DPV II	Graca Dores, MD, MPH; Miriam Chehab, PharmD; Chris Jones, PharmD, MPH, MS
OSE/DMEPA	Justine Kalonia, PharmD; Stephanie DeGraw, PharmD; Danielle Harris, PharmD
Other	Controlled substance staff: Dominic Chiapperino, PhD, Chad J. Reissig, PhD Division of Clinical Outcome Assessment: Jing (Julia) Ju, PharmD, PhD, Selena Daniels, PharmD, PhD, David Reasner, PhD
Regulatory	OND: Samantha Bell; Margie Kober, RPh, MPA OSE: Mammah Borbor-Lebbie, MS, MBA, PMCP

OND=Office of New Drugs
OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
CDTL=Cross-Discipline Team Leader
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DPV= Division of Pharmacovigilance
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

1. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

Menopause is a natural process in a woman's life that marks the decline of ovarian hormone production and cessation of reproductive capacity. This process is associated with profound physiological changes, resulting in symptoms such as vasomotor symptoms (VMS, or hot flashes) and symptoms of vulvovaginal atrophy (VVA, vaginal dryness, irritation, and pain with intercourse). In the United States, nearly 63 million women are past the average age of natural menopause of 51 years of age (as of July 1, 2021).[1] VMS are experienced by up to 80% of women during menopause.[2] It is estimated that 20 to 30% of women with VMS seek medical attention for treatment.[3] Although not life-threatening, menopausal symptoms, such as vasomotor symptoms, can negatively affect women's daily activities and quality of life. In addition, menopausal symptoms can persist for long periods in some individuals.

FDA has approved numerous postmenopausal hormone therapy products, both estrogens alone for use in a woman without a uterus, and estrogens plus progestogens products for use in a woman with a uterus. In addition, FDA has approved one non-hormonal product for the treatment of moderate to severe VMS. Hormone therapy has been the predominant treatment for moderate to severe VMS. Risks of estrogen plus progesterone therapy include deep venous thrombosis, pulmonary emboli, stroke, myocardial infarction, and breast cancer. Risks of estrogen-alone therapy include endometrial cancer, stroke, and deep venous thrombosis. Although hormone therapy is effective, these products are contraindicated in women who have breast cancer or a history of breast cancer, venous thromboembolism (or a history of venous thromboembolism) or thrombophilia, and those with a history of stroke or myocardial infarction. Since some women cannot take or choose not to take hormone therapy, it is desirable to have additional non-hormonal treatments available to manage menopausal symptoms.

Fezolinetant is being proposed for the treatment of moderate to severe vasomotor symptoms (VMS) associated with menopause. Fezolinetant (Veozah) is a small molecule, neurokinin 3 (NK3) receptor antagonist that blocks neurokinin B (NKB) binding on the kisspeptin/neurokinin B/dynorphin (KNDy) neurons in the thermoregulatory center in the hypothalamus. KNDy neurons signal to the thermoregulatory center of the brain and modulate the output to heat dissipating mechanisms in response to input from peripheral temperature sensing neurons. By antagonizing NKB/NK3-mediated signal, fezolinetant modulates NKDy neuronal activity in the thermoregulatory center resulting in attenuated vasomotor symptoms associated with menopause.

The efficacy of fezolinetant 45 mg orally once daily was demonstrated in two phase 3 trials (Trial 2693-CL-0301 (301) and Trial 2693-CL-0302 (302)) in postmenopausal women with moderate to severe VMS. The first 12 weeks of trials 301 and 302 were placebo-controlled, followed by a 40 week extension

[1] http://www.census.gov.
[2] 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.
[3] Santen RJ, Loprinzi CL, Casper RF. Menopausal hot flashes. UptoDate, accessed February 8, 2023. https://www.uptodate.com/contents/menopausal-hot-flashes?search=menopause&source=search_result&selectedTitle=3~150&usage_type=default&display_rank=3

phase during which all patients received fezolinetant. These trials showed the efficacy of fezolinetant for the treatment of moderate to severe VMS based on a statistically significant improvement (reduction in VMS) when comparing fezolinetant to placebo, in the frequency and severity of vasomotor symptoms at Week 4 and Week 12 for both the fezolinetant 30 mg and 45 mg dose groups. Only the 45 mg dose 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.

The primary safety evaluation for fezolinetant was based on trials 301 and 302 and trial 2593-CL-0304 (304), which was a 52-week placebo-controlled trial that included the 30 mg and 45 mg doses of fezolinetant. A notable safety finding was the association between fezolinetant and elevation in hepatic transaminases. This safety finding did not appear to be dose-dependent for the 30 mg and 45 mg doses. There were no cases of Hy's Law seen. To mitigate this risk, the labeling will specify monitoring hepatic function/injury prior to drug initiation and every 3 months during treatment (at 3, 6, and 9 months after initiation of therapy). In addition, Astellas has agreed to enhanced pharmacovigilance 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. Another safety consideration was an imbalance in malignancies in the fezolinetant treatment groups compared to placebo. This finding did not appear to be clinically relevant as many of the cases of malignancy appeared to be pre-existing, there was a short time to onset to the development of malignancy, there was a lack of biological plausibility, there were no concerning findings in the nonclinical studies, and there was a variety of cancers without a clear pattern. This imbalance appeared to be a chance finding and given the lack of a reasonable likelihood of a causal association, it will not be included in labeling.

Based on the submitted data, the benefit-risk profile of fezolinetant for the treatment of moderate to severe VMS associated with menopause is favorable to support approval of Astellas' proposed 45 mg daily dose. In terms of benefit, both 30 mg and 45 mg were tested in phase 3 and both doses showed significant improvements in the frequency and severity of vasomotor symptoms at Week 4 and Week 12. However, only the 45 mg dose 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. In general, the safety of the 30 mg and 45 mg doses appeared similar. Astellas has only requested approval of the 45 mg daily dose. We agree with all review disciplines that the available data support approval of fezolinetant 45 mg for the treatment of moderate to severe VMS due to menopause.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Menopause is a natural biological process marking the end of fertility because of permanent ovarian failure. • Symptoms of menopause include hot flashes [vasomotor symptoms (VMS)] and vulvar and vaginal atrophy symptoms [(VVA) including the symptoms of vaginal dryness, vaginal irritation/itching, and dyspareunia (pain with sexual activity)].	• Although not life-threatening, menopausal symptoms, such as vasomotor symptoms, can negatively affect women's daily activities and quality of life. In addition, menopausal symptoms can persist for long periods in some individuals.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• While the symptoms of menopause are not life-threatening, they can negatively impact quality of life and work productivity.[4] Hot flashes are the most common symptom among women entering menopause. Hot flashes due to menopause usually begin with a sensation of heat on the upper body that becomes generalized. VMS can persist on average 7 to 10 years.[5,6] • Menopause typically occurs between the age of 40 years of age to the mid-50s (mean age in the United States is 51 years of age). In the United States, nearly 63 million women are past the mean age of natural menopause (50 years of age and older as of July 1, 2021).[7]	• Given the large menopausal population in the United States, VMS represent a significant public health burden.
Current Treatment Options	• FDA has approved numerous postmenopausal hormone therapy products, both estrogens alone for use in a woman without a uterus, and estrogens plus progestogens products for use in a woman with a uterus. In addition, FDA has approved one non-hormonal product for the treatment of moderate to severe VMS. • Hormone therapy has been the predominant treatment for moderate to severe VMS. Approved treatment options include various routes of administration, including oral, topical, and vaginal system products. These products are contraindicated in women who have breast cancer (or a history of breast cancer), venous thromboembolism (or a history of venous thromboembolism), or thrombophilia, and those with a history of stroke or myocardial infarction. Currently, women who pursue treatment for VMS and are unable to take hormone therapy have one approved treatment option (Brisdelle).	• While there are numerous hormone therapy products for the treatment of vasomotor symptoms associated with menopause, there is only one non-hormonal option currently approved. Since some women cannot take or choose not to take hormone therapy, it is desirable to have additional non-hormonal treatments available to manage menopausal symptoms.

[4] Whiteley J, et al. J Womens Health (Larchmt). 2013 Nov;22(11):983-90.
[5] Avis NE, et al. JAMA Intern Med. 2015;175:531-539.
[6] Freeman EW, et al. Obstet Gynecol. 2011;117:1095-1104.
[7] https://www.census.gov

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• The efficacy of fezolinetant 45 mg orally once daily was demonstrated in two adequate and well-controlled phase 3 trials (301 and 302) in postmenopausal women with moderate to severe VMS. • A total of 1022 women (522 in trial 301 and 500 in trial 302) who had a minimum average of 7 moderate to severe vasomotor symptoms per day were randomized to fezolinetant 30 mg, 45 mg, or placebo. • The trials showed statistically significant improvement (reduction) when comparing fezolinetant to placebo in the frequency and severity of vasomotor symptoms at Week 4 and Week 12 for both the fezolinetant 30 mg and 45 mg dose groups. Only the 45 mg dose 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.	• In phase 3 clinical trials, fezolinetant 45 mg demonstrated substantial evidence of effectiveness for the treatment of moderate to severe vasomotor symptoms due to menopause.
Risk and Risk Management	• The primary safety evaluation for fezolinetant was based on trials 301 and 302 and trial 2593-CL-0304 (304), which was a 52-week placebo-controlled trial that included the 30 mg and 45 mg doses of fezolinetant compared to placebo. Across the three clinical trials, a total of 2203 women received fezolinetant, with 1100 women taking the 45 mg dose. • Common adverse reactions included abdominal pain, diarrhea, insomnia, back pain, hot flush, and hepatic transaminase elevation. • A notable safety finding was the association between fezolinetant and elevation in hepatic transaminases. This safety finding did not appear to be dose-dependent for the 30 mg and 45 mg dose groups. There were no cases of Hy's Law seen. To mitigate this risk, the labeling will specify monitoring hepatic function/injury prior to drug initiation and every 3 months during	• The safety profile of fezolinetant is well-characterized and the submitted safety data are supportive of the proposed 45 mg dose. • Fezolinetant exposure was associated with elevation in hepatic transaminases, which could be substantial (>20x ULN) and the post-market exposure population may be quite large. However, there were no cases of Hy's Law and several liver injury cases improved despite continued fezolinetant exposure. • Labeling and enhanced pharmacovigilance will be used to mitigate the risk of hepatic

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	treatment (at 3, 6, and 9 months). In addition, Astellas has agreed to enhanced pharmacovigilance 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. • There was an imbalance in malignancies in the fezolinetant treatment groups and placebo, however this appeared to be a chance finding without evidence of a causal relationship between fezolinetant and malignancy. This finding did not appear to be clinically relevant as many of the cases of malignancy appeared to be pre-existing, there was a short time to onset to the development of malignancy, there was a lack of biological plausibility, there were no concerning findings in the nonclinical studies, and there was a variety of cancers without a clear pattern.	transaminase elevation. • The malignancy imbalance appeared to be a chance finding and given the lack of a reasonable likelihood of a causal association, it will not be included in labeling.

2. Background

Astellas Pharma US, Inc (Astellas) submitted a new drug application (NDA) 216578 on June 22, 2022 for the new molecular entity (NME) fezolinetant being proposed for the treatment of moderate to severe vasomotor symptoms (VMS) associated with menopause. Fezolinetant is a small molecule, neurokinin 3 (NK3) receptor antagonist that blocks neurokinin B (NKB) binding on the kisspeptin/neurokinin B/dynorphin (KNDy) neurons in the thermoregulatory center in the hypothalamus. KNDy neurons signal to the thermoregulatory center of the brain and modulate the output to heat dissipating mechanisms in response to input from peripheral temperature sensing neurons. By antagonizing NKB/NK3-mediated signal, fezolinetant modulates NKDy neuronal activity in the thermoregulatory center resulting in attenuated vasomotor symptoms associated with menopause.

The drug is not currently marketed in the U.S. or internationally. The proposed dose is 45 mg orally daily.

On March 22, 2022, Astellas notified FDA (under IND 130277) of their intent to use a Rare Pediatric Disease Priority Review Voucher (PRV). NDA 216578 was reviewed under a Priority Review designation with a PDUFA date of February 22, 2022. On January 27, 2023, Astellas submitted information that constituted a major amendment to this application. Thus, the goal date was extended to May 22, 2023.

Analysis of Current Treatment Options
Women with mild symptoms of VMS (sensation of heat without sweating) typically do not require pharmacologic therapy. FDA has approved numerous postmenopausal hormone therapy products, both estrogens alone for use in a woman without a uterus, and estrogens plus progestogens products for use in a woman with a uterus, as well as one non-hormonal product, for the treatment of moderate to severe VMS (Table 1). Hormone therapy has been the predominant treatment for moderate to severe VMS. Risks of estrogen plus progesterone therapy include deep venous thrombosis, pulmonary emboli, stroke, myocardial infarction, and breast cancer. Risks of estrogen-alone therapy include endometrial cancer, stroke, and deep venous thrombosis. Although hormone therapy is effective, these products are contraindicated in women who have breast cancer or a history of breast cancer, venous thromboembolism (or a history of venous thromboembolism) or thrombophilia, and those with a history of stroke or myocardial infarction. Currently, women who pursue treatment for VMS and are unable to take hormone therapy may try Brisdelle (paroxetine), but additional options would be desirable.

Table 1: Products Approved for the Treatment of Moderate to Severe Vasomotor Symptoms due to Menopause

Estrogen-alone products	
Oral Estrogen-Alone Products	**Available dosage strengths**
Cenestin® (synthetic conjugated estrogens, A)*	0.45 mg, 0.625 mg, 0.9 mg, or 1.25 mg once daily
Enjuvia® (synthetic conjugated estrogens, B)*	0.3 mg, 0.45 mg, 0.625 mg, 0.9 mg, or 1.25 mg once daily
Menest® (esterified estrogens)	0.3 mg, 0.625 mg, 1.25 mg, or 2.5 mg once daily
Ogen (estropipate)	0.625 mg, 1.25 mg, or 2.5 mg once daily
Premarin® (conjugated estrogens) Tablets	0.3 mg, 0.45 mg, 0.625 mg, 0.9 mg, or 1.25 mg once daily
Various Generics (estradiol) Tablets	0.5 mg, 1.0 mg, 2.0 mg
Transdermal Products	**Available Dosage Strengths**
Alora® (estradiol matrix patch)	0.05 mg, 0.075 mg, or 0.1 mg; patch applied twice weekly
Climara® (estradiol matrix patch)	0.025 mg, 0.0375 mg, 0.05 mg, 0.075 mg, or 0.1 mg; patch applied once weekly
Estraderm® (estradiol reservoir patch)	0.05 mg or 0.1 mg; patch applied twice weekly
VivelleDot® (estradiol matrix patch)	0.0375 mg, 0.05 mg, 0.075 mg, or 0.1 mg; patch applied twice weekly
Minivelle® (estradiol matrix patch)	0.0375 mg, 0.05 mg, 0.075 mg, or 0.1 mg; patch applied twice weekly
Various Generics (estradiol matrix patch)	0.05 mg or 0.1 mg; patch applied once or twice weekly
Topical Products	**Available Dosage Strengths**
Divigel (estradiol gel) 0.1%	0.25 mg, 0.5 mg, or 1.0 mg; 0.25 gram, 0.5 gram or 1.0 gram applied once daily
Elestrin® (estradiol gel)	0.87 gram containing 0.52 mg or 1.7 gram containing 1.04 mg applied once daily
Estrasorb® (estradiol topical emulsion)	0.05 mg; two 1.74-gram pouches applied once daily
EstroGel® 0.06% (estradiol gel)	1.25 grams containing 0.75 mg estradiol applied once daily
Evamist® (estradiol transdermal spray)	1, 2 or 3 spray(s) 90 mcL containing 1.53 mg estradiol applied once daily
Vaginal Rings	**Available Dosage Strengths**
Femring® (estradiol acetate)	Release of 0.05 mg estradiol or 0.10 mg estradiol; ring worn for 90 days
Estrogen Plus Progestogen Products Approved for the Treatment of Moderate to Severe Vasomotor Symptoms due to Menopause	
Oral Estrogen Plus Progestogen Products	**Available Dosage Strengths**
Activella® (estradiol [E2] plus norethindrone acetate [NETA])	0.5 mg E2 plus 0.1 mg NETA taken daily or 1 mg E2 plus 0.5 mg NETA taken daily
Angeliq® (drospirenone [DRSP] plus estradiol [E2])	0.25 mg DRSP plus 0.5 mg E2 or 0.5 mg DRSP plus 1 mg E2 taken daily
femhrt® (norethindrone acetate [NETA] plus ethinyl estradiol [EE])	0.5 mg NETA plus 2.5 mcg EE taken daily or 1 mg NETA plus 5 mcg EE taken daily
Prefest® (estradiol [E2] plus norgestimate)	1 mg E2 taken daily for 3 days, then 1 mg E2 plus 0.09 mg norgestimate taken daily for 3 days, repeated continuously
Premphase® (conjugated estrogens [CE] plus medroxyprogesterone acetate [MPA])	0.625 mg CE taken daily for 14 days, then 0.625 mg CE plus 5.0 mg MPA taken daily on days 15-18
Prempro® (conjugated estrogens [CE] plus medroxyprogesterone acetate [MPA])	0.3 mg or 0.45 mg CE plus 1.5 mg MPA taken daily or 0.625 mg CE plus 2.5 mg or 5.0 mg MPA taken daily
Bijuva® (estradiol [E2] and progesterone [P4])	0.5 mg estradiol/100 mg progesterone taken daily or 1 mg estradiol/100 mg progesterone taken daily
Transdermal Estrogen Plus Progestogen Products	**Available Dosage Strengths**
ClimaraPro® (estradiol [E2] plus levonorgestrel)	0.045 mg E2 plus 0.015 mg levonorgestrel; patch applied once weekly

CombiPatch® (estradiol [E2] plus norethindrone Acetate [NETA])	Release of 0.05 mg E2 plus 0.14 mg NETA; patch applied twice weekly or 0.05 mg E2 plus 0.25 mg NETA; patch applied twice weekly
Estrogen Plus Estrogen Agonist/Antagonist Products Approved for the Treatment of Moderate to Severe Vasomotor Symptoms due to Menopause	
Oral Tablet or Capsule	**Available Dosage Strengths**
Duavee® (conjugated estrogens/bazedoxifene)	0.45 mg CE plus 20 mg bazedoxifene taken daily
Non-Hormonal Products Approved for the Treatment of Moderate to Severe Vasomotor Symptoms due to Menopause	
Oral Non-Hormonal Tablet or Capsule	**Available Dosage Strengths**
Brisdelle™ (paroxetine) capsules	7.5 mg at bedtime daily

Based on information in clinical review dated 11/23/22; tables 1-4; pages 23-24

Regulatory interactions between the Agency and Astellas[8]

The development program for fezolinetant for the treatment of moderate to severe VMS associated with menopause was conducted under IND 130277, which was open on March 22, 2016. A high-level overview of regulatory interactions is included below:

- March 22, 2017: Type C meeting was held to discuss the nonclinical and clinical development plans, wherein the FDA provided general guidance on the design of phase 2b/phase 3 clinical trials.
- March 1, 2018: Ogeda S.A. submitted agreed-upon protocols for two nonclinical protocols – a 2-year rat carcinogenicity study and a 26-week mouse carcinogenicity study. These protocols had been reviewed under Special Protocol Assessment by the Executive Carcinogenicity Assessment Committee (ECAC).
- May 1, 2018: General correspondence submitted to outline the transfer of the IND from Ogeda S.A. to Astellas.
- October 24, 2018: FDA provided Type C Written Response guidance pertaining to endometrial health assessment, bone safety assessment, and breast cancer treatment-related VMS development strategy.
- April 19, 2019: End-of-Phase 2 meeting was held to discuss the nonclinical, clinical pharmacology, and phase 3 clinical programs, including dose selection.
- December 20, 2019: FDA informed Astellas that a dedicated QT study was not needed.
- March 2, 2020: FDA agreed to the full pediatric waiver proposed in the initial pediatric study plan (iPSP).
- January 28, 2022: Pre-NDA meeting was held to discuss the submission of the NDA.

See medical officers' and CDTL's reviews for additional details.

3. Product Quality

The NDA contains information on two dosage strengths of fezolinetant immediate release tablets: 30 mg and 45 mg. Astellas did not request approval for marketing of the 30 mg strength. Astellas has submitted all data to support the quality and manufacture of the product,

[8] The original sponsor of the IND was Ogeda S.A., Belgium. Ownership of the IND was transferred to Astellas on May 1, 2018.

and expiry period of 30 months. All manufacturing and testing facilities associated with the drug product have acceptable establishment evaluation status.

In a review dated November 25, 2022, the Product Quality review team recommended approval of this NDA, pending successful labeling discussion.

4. Nonclinical Pharmacology/Toxicology

Astellas conducted a complete and adequate toxicology program that included general toxicology studies in rodent and non-rodent species (rat for 26 weeks and cynomolgus monkeys for 39 weeks), central nervous system and drug dependency studies, reproductive and developmental toxicology studies (in rats and rabbits), and carcinogenicity studies (in transgenic mice and rats). In general, the 26-week rat study, there were no adverse effects on in-life parameters, clinical pathology, or microscopic changes 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. In the 39-week monkey study, 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 due to decreased production of bone marrow resulted in hemorrhage and regenerative anemia. However, the decrease was reversible. The NOAEL was the mid-dose of 25 mg/kg/day, with an AUC24=166000 ng●h/mL (43X MRHD).

Fezolinetant was found to have no potential to induce seizures and did not induce physical dependency.

The nonclinical mutagenicity and carcinogenicity studies (2-year study in female rats and 6-month carcinogenicity study in transgenic mice) conducted with fezolinetant did not indicate a potential risk or mechanism for drug-related genetic toxicity or tumorigenesis. Review of the published literature did not indicate a potential biological mechanism for an increased risk of malignancy with fezolinetant or NK3 antagonism.

In a safety assessment using pooled data from the three Phase 3 clinical trials (i.e., 2693-CL-0301, 2693-CL-0302, and 2693-CL-0304), a numeric dose-dependent imbalance in malignancy was identified during the review. The nonclinical review team conducted further assessment on the biological plausibility of fezolinetant as a potential cancer promotor, including internal consultation with Division of Applied Regulatory Science (DARS) Computational Toxicology Consultation Service (CTCS). Upon an exhaustive evaluation of structural alerts relevant to DNA-reactivity, carcinogenicity signal in the nonclonal bioassays, potential mechanisms of tumorigenesis or tumor promotor activity with fezolinetant or its metabolites, the nonclinical team concluded that fezolinetant was not associated with an increased risk of tumor promotor activity.

In the fertility study in female rats, fezolinetant did not affect fertility at doses up to 100 mg/kg/day, although there was altered estrous cyclicity and reduced reproductive organ weight, which were exaggerated pharmacological effects of fezolinetant.

In rat and rabbit embryo-fetal development studies, total litter loss was observed in both rats and rabbits at 100 and 125 mg/kg/day (128X and 174X MRHD, respectively). In addition, rabbits also showed increased late resorption and reduced fetal weight at 75 mg/kg/day (28X MRHD). Fezolinetant did not show teratogenic potential in either rats or rabbits. The NOAELs for the rat and rabbit embryo-fetal development studies based on embryotoxicity were 50 mg/kg/day (62X MRHD) and 45 mg/kg/day (16X MRHD), respectively.

In the pre- and post-natal development toxicity rat study, delayed parturition and embryo-lethality were observed at 100 mg/kg/day (with material AUC24=788000 ng●h/mL, 204X MRHD). In addition, F1 males at 100 mg/kg/day showed decreases in mating and fertility associated with incomplete balanopreputial separation. The NOAEL for maternal toxicity and embryotoxicity was 30 mg/kg/day, 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) and was 10 mg/kg/day (F1 males) based on changes in fertility mainly due to incomplete balanopreputial separation in MD and HD males. Thus, the pharmacology/toxicology review team concluded that incorrect administration to a pregnant female could carry the risks of early pregnancy loss or delayed maturation of a male fetus. Notably, the intended population for fezolinetant is post-menopausal women, thus the risks for pregnancy and fetal loss are low. (b) (4)

For detailed pharmacology/toxicology assessment, see the following reviews: primary review by Dr. Miyun Tsai-Turton and secondary review by Dr. Andrea Benedict, both dated November 22, 2022; the tertiary review by Dr. Mukesh Summan, dated January 23, 2023; the addendum reviews by Dr. Benedict and Dr. Kimberly Hatfield, dated January 27, and April 21, 2023, respectively. The pharmacology/toxicology team supports the approval of fezolinetant for the treatment of moderate to severe VMS due to menopause. There are no nonclinical safety concerns for the safety of fezolinetant 45 mg orally once daily in the general population of individuals with moderate to severe VMS due to menopause.

5. Clinical Pharmacology

Clinical pharmacology program:
Fezolinetant is selective NK3 receptor antagonist that blocks neurokininB (NKB) binding on the kisseptin/neurokinin B/dynorphin (KNDy) neuron to modulate neuronal activity. Astellas conducted 11 Phase 1 studies that evaluated the pharmacokinetics (PK) and/or pharmacodynamics (PD) in healthy male and female adult participants and special populations. Drug-drug interactions of fezolinetant were evaluated in both in vitro and in vivo studies and further supported by physiologically based PK (PBPK) modeling analyses. Food effect and relative bioavailability of different formulations were also evaluated in Phase 1 studies.

ADME:

Astellas also assessed the absorption, distribution, metabolism, and elimination of fezolinetant. The PK of fezolinetant is dose-proportional between 20 to 60 mg once daily. The PKs of fezolinetant were similar between healthy female subjects and patients with moderate to severe vasomotor symptoms associated with menopause. The effective half-life (t1/2) of fezolinetant is 9.6 hours in women with vasomotor symptoms. Fezolinetant is the active moiety; the major metabolite (ES259564) is approximately 20-fold less potent against human NK3 receptor and considered not pharmacologically active.

Food effect:
No clinically significant differences in fezolinetant pharmacokinetics were observed following administration with a high-calorie, high-fat meal. Therefore, fezolinetant may be taken without regard to food.

Special population:
In the renal impairment study (2693-CL-0008), female subjects with normal, mild, moderate, and severe renal impairment had comparable Cmax after a single oral administration of 30 mg fezolinetant. Subjects with mild or moderate renal impairment had 19.2% and 31.2% lower total exposure (AUClast), respectively, compared to healthy normal subjects. Despite lower exposure in patients with mild (19.2% decrease in AUClast) or moderate renal impairment (31.2% decrease in AUClast) in the dedicated renal impairment study, the population PK model predicted exposure in patients with mild or moderate renal impairment had comparable exposure to patients with normal renal function. The clinical pharmacology team recommends no dose adjustment for patients with mild or moderate renal impairment. The team also recommends that fezolinetant be contraindicated in patients with severe renal impairment or end-stage renal disease.

Based on the hepatic impairment study in female participants, mild hepatic impairment led to approximately 56% increase in fezolinetant AUC and 23% increase in Cmax. Moderate hepatic impairment led to 94 to 96% increase in fezolinetant AUC (Study 2693-CL-0007). The PKs of fezolinetant have not been evaluated in patients with severe hepatic impairment. (b) (4) , the review team, in consultation with the Drug Induced Liver Injury experts, concluded that labeling language based on cirrhosis ((b) (4)) would be (b) (4) appropriate. Therefore, labeling will state that fezolinetant is contraindicated in patients with cirrhosis.

Pharmacodynamics:
Treatment with fezolinetant did not show any clear trends in sex hormones measured (follicle-stimulating hormone, testosterone, estrogen, and dehydroepiandrosterone sulfate) in menopausal women. Transient decrease of luteinizing hormone (LH) levels was observed at peak concentrations of fezolinetant. These findings will be reflected in labeling.

Potential for QT prolongation:
Per ICH revised E14 Q&A (R3) Guidance, Astellas conducted concentration-QTc modeling as the primary analysis for assessing the QTc interval prolongation risk of fezolinetant. At a dose

20 times the maximum recommended dose (i.e., 900 mg), fezolinetant was not found to prolong the QT interval to any clinically relevant extent.

Drug Interactions:
In a dedicated DDI study, concomitant use of fluvoxamine (a strong CYP1A2 inhibitor) resulted in a 9.4-fold increase in fezolinetant AUCinf and 1.8-fold increase in Cmax. There are no clinical data to support such high exposure in postmenopausal women. Based on PBPK modeling, weak CYP1A2 inhibitors are predicted to increase fezolinetant exposure by 1.6- to 2-fold. In the phase 3 trials, only 22 women received 45 mg fezolinetant had concomitant use of weak CYP1A2 inhibitors. Although treatment emergent adverse events in these women were generally mild and resolved, the clinical pharmacology review team recommended against concomitant use of fezolinetant 45 mg with weak CYP1A2 inhibitors. Due to these considerations, labeling will contraindicate use of fezolinetant with concomitant use of any CYP1A2 inhibitors.

Upon reviewing the clinical pharmacology information contained in this application, the Office of Clinical Pharmacology, Division of Cardiometabolic and Endocrine Pharmacology recommends approval of this application. For details of the clinical pharmacology assessment, see the Office of Clinical Pharmacology Review dated November 23, 2022.

6. Clinical Microbiology

Not applicable

7. Clinical/Statistical-Efficacy

Overview of the clinical program:
Two pivotal Phase 3 trials with identical design, Trial 2693-CL-0301 (hereafter referred to as Trial 301) and 2693-CL-0302 (hereafter referred to as Trial 302) serve as the primary evidence of efficacy of fezolinetant in the treatment of moderate to severe VMS associated with menopause (Table 3). In addition, two phase 2 trials (ESN364_HF_204 and ESN364_HF_205) were performed (Table 2). Astellas completed a 52-week controlled trial (2693-CL-0304) to evaluate safety. This trial (referred to as Trial 304) is further discussed in Section 8.

Table 2: Relevant Phase 2 controlled clinical trials with fezolinetant in VMS

ID Date	Study Characteristics	Treatment groups	N	Efficacy Variables	Regions and Countries
Phase 2					
ESN364_HF_204 Sept 2015-Oct 2016	12-week, R, DB, PC, PG, MC, POC study - Healthy postmenopausal women - ≥ 45 years and ≤ 60 years of age - moderate to severe VMS associated with menopause	Fezo 90 mg Placebo **Total**	43 44 **87**	1º endpoint: ● Change in mean weekly HFS from baseline to week 12	Belgium (100%)
ESN364_HF_205 Jul 2017-Sep 2018	12-week, R, DB, PC, dose-ranging, PG, MC study - Healthy postmenopausal women - ≥ 40 years and ≤ 65 years of age - moderate to severe VMS associated with menopause - Seeking treatment or relief for VMS associated with menopause - confirmed as menopausal - At least 50 moderate to severe VMS per week (i.e., 7 consecutive days), as recorded in the daily diary during the screening period;	Fezo 15 mg bid Fezo 30 mg bid Fezo 60 mg bid Fezo 90 mg bid Fezo 30 mg daily Fezo 60 mg daily Fezo 120 mg daily Placebo **Total**	45 44 45 44 45 45 44 44 **356**	4 co-1º endpoints: ● Mean change in the frequency of moderate to severe VMS from baseline to wk 4 ● Mean change in the frequency of moderate to severe VMS from baseline to wk 12 ● Mean change in the severity of moderate to severe VMS from baseline to wk 4 ● Mean change in the severity of moderate to severe VMS from baseline to wk 12	United States (100%)

DB=double-blind; fezo=Fezolinetant; HFS=hot flash severity score; ID=identification; MC=multicenter; PC=placebo-controlled; PG=parallel-group; POC=proof of concept; R=randomized; VMS=vasomotor symptoms; wk=week

Table 3: Relevant Phase 3 controlled clinical trials with fezolinetant in VMS

ID Date	Trial Characteristics	Treatment groups	N	Efficacy Variables	Regions and Countries
Phase 3					
2693-CL-0301 Skylight 1 NCT04003155 Jul 2019-Aug 2021	R, MC, 12-week PC, DB study, followed by a NC period of 40 weeks of fezo exposure - Healthy postmenopausal women - ≥ 40 years and ≤ 65 years of age - moderate to severe VMS associated with menopause - Seeking treatment or relief for VMS associated with menopause - confirmed as menopausal - 7 to 8 moderate to severe HFs (VMS) per day within the 10 days prior to randomization - screening endometrial biopsy had to be considered evaluable	Fezo 30 mg Fezo 45 mg Placebo* **Total**	173 174 175 **522**	4 co-1º endpoints: ● Mean change in the frequency of moderate to severe VMS from baseline to wk 4 ● Mean change in the frequency of moderate to severe VMS from baseline to wk 12 ● Mean change in the severity of moderate to severe VMS from baseline to wk 4 ● Mean change in the severity of moderate to severe VMS from baseline to wk 12 Key 2º endpoint: ● Mean change in PROMIS SD SF 8b total score from baseline to week 12	United States, Canada, United Kingdom, Spain, Poland, Czech Republic and Hungary
2693-CL-0302 Skylight 2 NCT04003142 Jul 2019-Aug 2021	R, MC, 12-week PC, DB study, followed by a NC period of 40 weeks of fezo exposure - Healthy postmenopausal women - ≥ 40 years and ≤ 65 years of age - moderate to severe VMS associated with menopause - Seeking treatment or relief for VMS associated with menopause - confirmed as menopausal - 7 to 8 moderate to severe HFs (VMS) per day within the 10 days prior to randomization - screening endometrial biopsy had to be considered evaluable	Fezo 30 mg Fezo 45 mg Placebo* **Total**	166 167 167 **500**	4 co-1º endpoints: ● Mean change in the frequency of moderate to severe VMS from baseline to wk 4 ● Mean change in the frequency of moderate to severe VMS from baseline to wk 12 ● Mean change in the severity of moderate to severe VMS from baseline to wk 4 ● Mean change in the severity of moderate to severe VMS from baseline to wk 12 Key 2º endpoint: ● Mean change in PROMIS SD SF 8b total score from baseline to week 12	United States, Canada, United Kingdom, Spain, Poland, Czech Republic and Latvia
2693-CL-0304 Skylight 4 NCT04003389 Jul 2019 – Jan 2022	R, MC, 52-week PC, DB study - Healthy postmenopausal women	Fezo 30 mg Fezo 45 mg Placebo **Total**	611 609 611 **1831**	Long-term safety, including endometrial health, and tolerability of fezolinetant in	United States, Canada, Spain, Latvia, Ukraine, Czech Republic, United Kingdom and Poland

	- ≥ 40 years and ≤ 65 years of age - Seeking treatment or relief for VMS associated with menopause			women seeking treatment for relief of VMS associated with menopause	

In addition to these trials, there are 2 ongoing phase 3 studies (2693-CL-0305 and 2693-CL-0307) and 1 ongoing phase 2 study (2693-CL-0206) to support registrations in Asia, and 1 ongoing phase 3b study (2693-CL-0312) which is being conducted in Europe and Canada in participants considered unsuitable for HT (also commonly referred to as hormone replacement therapy or HRT)

[#] Full Analysis Set
*After completing 12 weeks of treatment, participants on placebo were re-randomized to fezolinetant 30 mg or 45 mg once daily for a further 40 weeks. Participants remained blinded from the end-of-the 12 week efficacy collection period into and through the 40-week extension period for safety data collection.

DB=double-blind; fezo=Fezolinetant; HFS=hot flash severity score; ID=identification; MC=multicenter; NC=non-controlled; NCT=National Clinical Trial; PC=placebo-controlled; PG=parallel-group; R=randomized; PROMIS SD SF 8b=Patient-Reported Outcomes Measurement Information System Sleep Disturbance-Short Form 8b; VMS=vasomotor symptoms; wk=week;

Design and conduct of the trials:

The primary evidence of efficacy is from Trials 301 and 302. The trials had identical designs and inclusion/exclusion criteria. Both trials were conducted in healthy postmenopausal women, 40 to 65 years of age, with at least 7 to 8 moderate to severe hot flashes per day within the 10 days prior to randomization. The first 12 weeks of the trials were randomized, double-blinded and placebo-controlled and participants were randomized to placebo, fezolinetant 30 mg, or fezolinetant 45 mg. Participants were randomized in a 1:1:1 ratio to a treatment group according to the randomization schedules and stratified by smoking status (active smoker or nonsmoker). After completing 12 weeks of treatment, participants on placebo were re-randomized (1:1) to fezolinetant 30 mg or 45 mg once daily for a further 40 weeks (i.e., 52 study weeks of treatment total). Evidence of efficacy of fezolinetant is primarily from the 12-week placebo-controlled period.

Within the 10 days prior to randomization, participants had to have a minimum average of 7 to 8 moderate to severe HFs (VMS) per day, or 50 to 60 per week. Participants were to record their VMS via their electronic diary on a daily basis from screening through the follow-up visit. Site-based PRO measures were to be self-administered via an electronic device.

Endpoints:

The primary protocol objective included four co-primary endpoints:

1) Mean change in the frequency of moderate to severe vasomotor symptoms from baseline to Week 4
2) Mean change in the frequency of moderate to severe vasomotor symptoms from baseline to Week 12
3) Mean change in the severity of moderate to severe vasomotor symptoms from baseline to Week 4
4) Mean change in the severity of moderate to severe vasomotor symptoms from baseline to Week 12

Severity of vasomotor symptoms was defined in the usual manor—mild (sensation of heat without sweating), moderate (sensation of heat with sweating but able to continue activity) or

severe (sensation of heat with sweating causing cessation of activity). The severity score for mild, moderate, and severe VMS was coded as 1, 2, and 3, respectively.

Calculations and endpoint definitions are included in Table 4.

Table 4: Endpoint Definitions

Calculation at	Frequency	Severity Score at Individual Days
Baseline	Average of the non-missing values in the 10 days before randomization	$\frac{[\#Mo/day \times 2] + [\#Se/day \times 3]}{\#(Mo + Se)/day}$
Post-baseline	Average of the non-missing values over a 7-day period	$\frac{[\#Mi/day \times 1] + [\#Mo/day \times 2] + [\#Se/day \times 3]}{\#(Mi + Mo + Se)/day}$

Mo=moderate; Se=severe; Mi=mild
Source: Statistical Review; Table 4; page 10; dated 11/21/2022

In addition, each trial included numerous secondary endpoints. (b) (4)

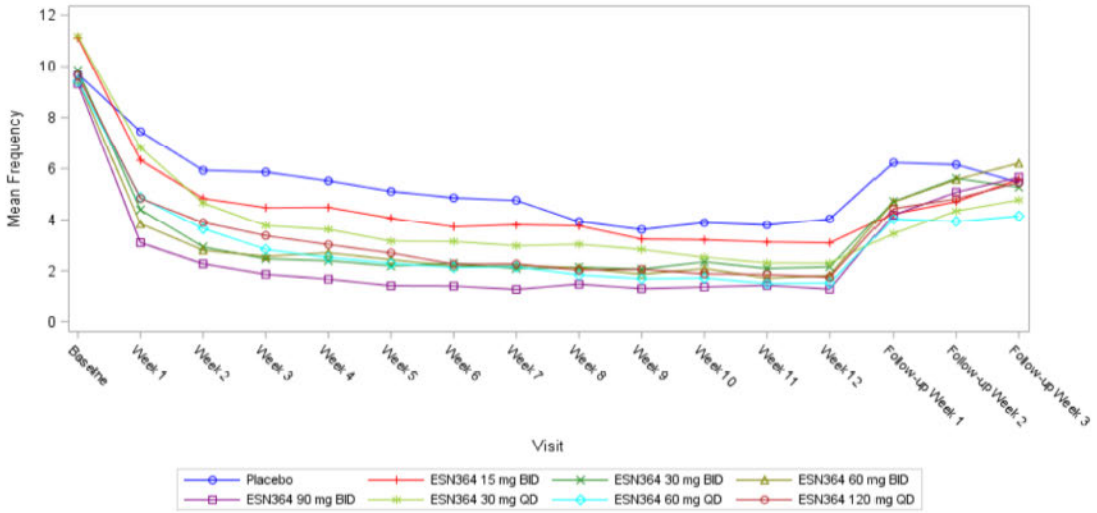
The design of the Phase 3 trials was consistent with the FDA Guidance for Industry—Estrogen and Estrogen/Progestin Drug Products to Treat Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms—Recommendations for Clinical Evaluation. Further, the clinical development program incorporated the Division's recommendation to assess whether the change from baseline in frequency met a clinical threshold determination of two hot flashes per day or 14 hot flashes per week superiority of the evaluated drug over placebo.

Dose Selection for Phase 3: Trials ESN364_HF_204 and ESN364_HF_205
ESN364_HF_204 was a phase 2a, 12-week double-blind, placebo-controlled, parallel group, multicenter, proof of concept study assessing fezolinetant 90 mg in 87 postmenopausal women suffering from hot flashes. The mean weekly general Hot Flash Score (HFS) in the ITT population (OC approach) decreased (improved) from 28.76 and 25.76 at baseline to 2.69 and 14.36 at Week 12, for the fezolinetant and placebo groups, respectively, corresponding to a mean decrease of 26.51 and 12.19, respectively. There were statistically significant decreases in the mean weekly general HFS in the fezolinetant group compared to the placebo group from the first timepoint of assessment (Week 1) onwards. Mildly elevated (i.e., <3x ULN) values for alanine aminotransferase (ALT) were observed more frequently in the fezolinetant group (11.9%) than the placebo group (2.3%). Aspartate aminotransferase (AST) increases were more frequent in the placebo group (9.1%) than in the fezolinetant group (4.8%).

Following completion of ESN364_HF_204, Astellas completed SN364_HF_205, a phase 2b, 12-week double-blind, placebo-controlled, parallel-group, multicenter, dose-ranging study to assess the effect of administration of fezolinetant in 356 postmenopausal women suffering from hot flashes. The doses tested included 15, 30, 60 and 90 mg bid and 30, 60, and 120 mg

daily. Participants were healthy postmenopausal women between 45 and 65 years old with moderate to severe VMS. All 4 co-primary endpoints (mean change from baseline in the frequency of moderate to severe VMS to week 4 and to week 12; mean change from baseline in the severity of moderate to severe VMS to week 4 and to week 12) were significantly different from placebo for the 90 mg bid, 60 mg bid and 60 mg daily fezolinetant dose groups. In addition, all fezolinetant dose groups were significantly different from placebo with respect to mean change in the frequency of moderate to severe VMS at both weeks 4 and 12 (Figure 1). All groups were significantly different from placebo with respect to mean change in the severity of moderate to severe VMS from baseline to week 4, but only 60 mg bid, 90 mg bid and 60 mg daily demonstrated significance with respect to mean change in severity at week 12.

Figure 1: Plot of Weekly Mean Frequency of Moderate and Severe VMS per 24 h: Full Analysis Set



Subset of the safety analysis set who had a baseline and at least one postbaseline efficacy evaluation (Full Analysis Set).

Note: Baseline was the average frequency of 24 h vasomotor symptom from 7 non-missing days prior to day 1.

VMS: vasomotor symptoms

Source: Figure 12.3.1.4

Study SN364_HF_205; Page 75; submitted 6/22/22

Astellas also developed dose-response and concentration-response analyses to support dose selection. These analyses, and the data from ESN364_HF_205, did not show a clinically relevant difference in efficacy for daily and bid treatment groups given the same total daily dose.

In terms of safety in ESN364_HF_205, there were 9 participants with transaminase elevations. Of these, 3 patients had ALT or AST > 8 x upper limit of normal (ULN) (60 mg BID, 90 mg BID, and 60 mg QD). Notably, there were no cases of ALT or AST > 8 x ULN with 15 mg BID, 30 mg BID, or 30 mg daily, suggesting that the elevations in ALT and AST were dose related over this wide dose range. In all dose groups, there were no cases of total bilirubin > 2 x ULN, and consequently no Hy's law cases. As discussed below, the hepatic transaminase elevations did not appear dose related when comparing a narrower dose range of 30 and 45 mg daily.

Astellas used a mechanistic, mathematical model of drug-induced liver injury to better characterize the transaminase elevations seen. Astellas stated that "ALT elevations were predicted to be dose dependent. The phase 3 doses, 30 mg QD and 45 mg QD, were selected with minimal risk of ALT elevation. Reduced hepatotoxicity was predicted with clinical monitoring (i.e., dosing stopped if ALT > 8 x ULN, with weekly monitoring). The model predicted that both parent and metabolite contributed to the simulated hepatotoxicity with the parent being slightly more potent than the metabolite." Astellas considered 30 mg daily to be the lowest effective dose and decided to evaluate 30 mg and 45 mg daily in phase 3. Notably, the 45 mg dose had not been studied in phase 2. Based on the safety and efficacy results, it was reasonable for Astellas to evaluate 30 mg and 45 mg daily in Phase 3.

Results from phase 3 trials:

Demographics:

In Trials 301 and 302, the subjects had a mean age of 54 years (range: 40 to 65 years). Most subjects in both trials were White (81%), not Hispanic or Latino (76%), and were either former smokers or had never smoked (83%). Both studies enrolled menopausal women with prior hormone therapy use (20%), with history of oophorectomy (22%), or with history of hysterectomy (32%). Most subjects in both trials completed the 12-week double blind treatment period (87% in 301 and 92% in 302). In trial 301, 8 (1.6%) participants discontinued treatment due to COVID-19. In trial 302, 4 (0.8%) participants discontinued treatment due to COVID-19. Thus, the impact of COVID-19 appeared minimal and did not impact the integrity and interpretation of the results.

Primary efficacy endpoints:

In both trials, the primary efficacy analysis for each of the 4 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 VMS as covariates, as well as an interaction of treatment by week and an interaction of baseline measurement by week. The Applicant proposed (b) (4) . All four co-primary endpoints had to be statistically significant for a given dose to be considered successful. During development, FDA communicated to Astellas that all four co-primary efficacy endpoints should be tested at a significance level of 0.05. Missing data were implicitly imputed assuming a missing at random (MAR) missing data mechanism. Sensitivity analyses were performed using different techniques for handling missing data.

In both trials, subjects had an average of approximately 11 moderate to severe hot flashes per day at baseline. In both trials, fezolinetant 30 mg and 45 mg was associated with statistically significant mean reductions from baseline in the frequency (Table 5) of moderate to severe vasomotor symptoms compared to placebo at weeks 4 and 12. At week 4, subjects in fezolinetant 30 mg and 45 mg had a mean reduction of approximately 5 to 6 moderate to

severe hot flashes per day from baseline compared to a mean reduction of approximately 3 to 4 hot flashes for subjects in the placebo group. Similarly, at week 12, subjects in fezolinetant 30 mg and 45 mg groups had a mean reduction of approximately 6 and 7 moderate to severe hot flashes per day from baseline, respectively, compared to a mean reduction of approximately 4 to 5 hot flashes for subjects in the placebo group. Changes over time are shown graphically in Figure 2 and Figure 3.

In both trials, the 45 mg group (but not the 30 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 at Week 4 that was maintained through Week 12. Astellas has only requested approval of the 45 mg fezolinetant dose for the treatment of moderate to severe vasomotor symptoms due to menopause.

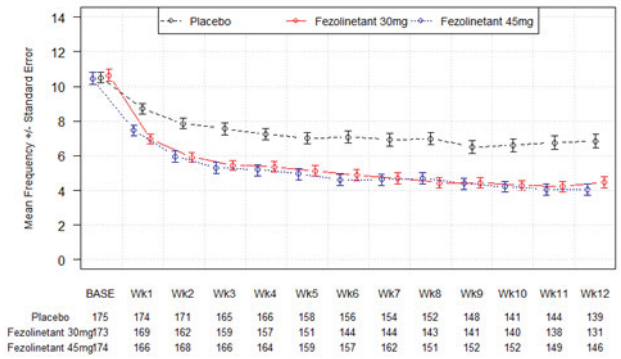
Table 5: Change from Baseline in the Mean Frequency of Moderate to Severe Vasomotor Symptoms per 24 Hours at Week 4 and Week 12

	SKYLIGHT 1			SKYLIGHT 2		
	Placebo	**Fezolinetant 30 mg**	**Fezolinetant 45 mg**	**Placebo**	**Fezolinetant 30 mg**	**Fezolinetant 45 mg**
Baseline (N)	175	173	174	167	166	167
Mean (SD)	10.51 (3.79)	10.65 (4.73)	10.44 (3.92)	11.59 (5.02)	11.23 (4.88)	11.79 (8.26)
Week 4 (N)	166	157	164	151	155	155
Mean (SD) change from baseline	-3.27 (4.18)	-5.35 (5.57)	-5.20 (4.07)	-3.64 (4.15)	-5.52 (4.23)	-6.24 (4.78)
LS Mean (SE) difference from placebo		-1.87 (0.42)	-2.07 (0.42)		-1.82 (0.46)	-2.55 (0.46)
95% CI		(-2.69, -1.05)	(-2.89, -1.25)		(-2.73, -0.91)	(-3.45, -1.64)
p-value		< 0.001	< 0.001		< 0.001	< 0.001
Week 12 (N)	139	131	146	140	133	145
Mean (SD) change from baseline	-3.67 (4.18)	-6.44 (6.15)	-6.38 (4.48)	-4.57 (5.14)	-6.43 (4.77)	-7.43 (6.47)
LS Mean (SE) difference from placebo		-2.39 (0.44)	-2.55 (0.43)		-1.86 (0.55)	-2.53 (0.55)
95% CI (2-sided)		(-3.25, -1.52)	(-3.40, -1.70)		(-2.94, -0.78)	(-3.60, -1.46)
p-value		< 0.001	< 0.001		< 0.001	< 0.001

Source: Table 11, Study Reports for SKYLIGHT 1 and SKYLIGHT 2.
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; dated 11/21/22

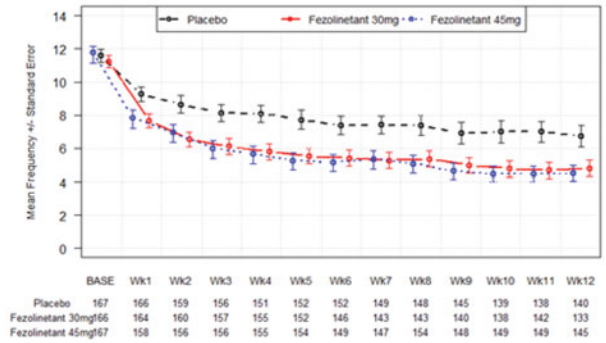
Figure 2: Mean Frequency of VMS by Week (Trial 301)



	BASE	Wk1	Wk2	Wk3	Wk4	Wk5	Wk6	Wk7	Wk8	Wk9	Wk10	Wk11	Wk12
Placebo	175	174	171	165	166	158	156	154	152	148	141	144	139
Fezolinetant 30mg	173	169	162	159	157	151	144	144	143	141	140	138	131
Fezolinetant 45mg	174	166	168	166	164	159	157	162	151	152	152	149	146

Source: Biometrics Review; Figure 2; page 19; dated 11/21/22

Figure 3: Mean Frequency of VMS by Week (Trial 302)



	BASE	Wk1	Wk2	Wk3	Wk4	Wk5	Wk6	Wk7	Wk8	Wk9	Wk10	Wk11	Wk12
Placebo	167	166	159	156	151	152	152	149	148	145	139	138	140
Fezolinetant 30mg	166	164	160	157	155	152	146	143	143	140	138	142	133
Fezolinetant 45mg	167	158	156	156	155	154	149	147	154	148	149	149	145

Source: Biometrics Review; Figure 3; page 19; dated 11/21/22

The baseline severity score was about 2.4 in the treatment groups in the two trials. In both trials, fezolinetant 30 mg and 45 mg was associated with statistically significant mean reduction from baseline in the severity (Table 6) of moderate to severe vasomotor symptoms compared to placebo at weeks 4 and 12. Changes over time are shown graphically in Figure 4 and Figure 5.

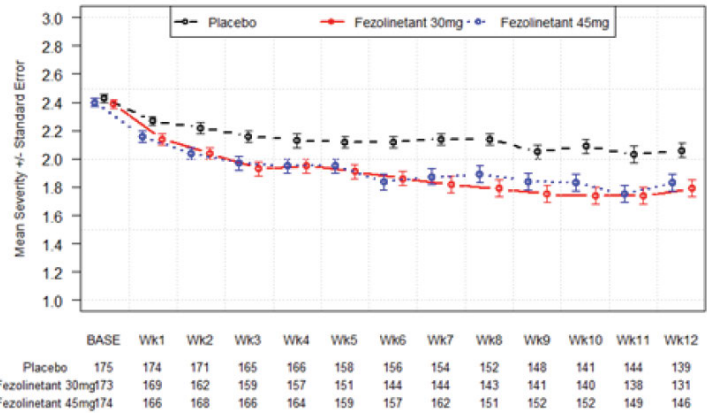
Table 6: Change from Baseline in the Mean Severity of Moderate to Severe Vasomotor Symptoms per 24 Hours, at Week 4 and Week 12

	SKYLIGHT 1			SKYLIGHT 2		
	Placebo	**Fezolinetant 30 mg**	**Fezolinetant 45 mg**	**Placebo**	**Fezolinetant 30 mg**	**Fezolinetant 45 mg**
Baseline (N)	175	173	174	167	166	167
Mean (SD)	2.43 (0.35)	2.39 (0.34)	2.40 (0.35)	2.41 (0.32)	2.44 (0.33)	2.41 (0.34)
Week 4 (N)	166	157	164	151	155	155
Mean (SD) change from baseline	-0.28 (0.50)	-0.43 (0.56)	-0.45 (0.61)	-0.31 (0.48)	-0.47 (0.58)	-0.61 (0.63)
LS Mean (SE) difference from placebo		-0.15 (0.06)	-0.19 (0.06)		-0.15 (0.06)	-0.29 (0.06)
95% CI (2-sided)		(-0.27, -0.03)	(-0.30, -0.07)		(-0.27, -0.02)	(-0.41, -0.16)
p-value		0.012	0.002		0.021	< 0.001
Week 12 (N)	139	131	146	140	133	145
Mean (SD) change from baseline	-0.35 (0.58)	-0.57 (0.73)	-0.58 (0.75)	-0.46 (0.65)	-0.60 (0.75)	-0.74 (0.71)
LS Mean (SE) difference from placebo		-0.24 (0.08)	-0.20 (0.08)		-0.16 (0.08)	-0.29 (0.08)
95% CI (2-sided)		(-0.39, -0.09)	(-0.35, -0.06)		(-0.33, 0.00)	(-0.45, -0.13)
p-value		0.002	0.007		0.049	< 0.001

Source: Table 12, Study Reports for SKYLIGHT 1 and SKYLIGHT 2. 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.

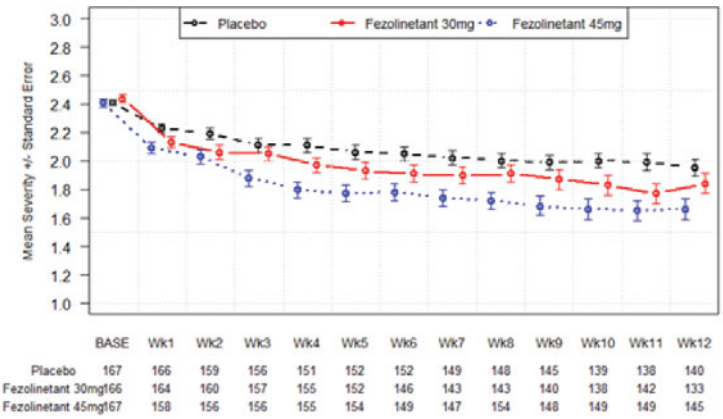
Source: Biometrics Review; Table 8; page 17; dated 11/21/22

Figure 4: Mean Severity of Moderate to Severe VMS by Week (Trial 301)



Source: Biometrics Review; Figure 4; page 20; dated 11/21/22

Figure 5: Mean Severity of Moderate to Severe VMS by Week (Trial 302)



Source: Biometrics Review; Figure 5; page 20; dated 11/21/22

Sensitivity analyses support these findings.

Please see the CDTL and the statistical reviews for assessment of the secondary endpoints, such as the Patient-Reported Outcomes Measurement Information System Sleep Disturbance – Short Form 8b (PROMIS SD SF 8b).

Subgroup analyses:

Subgroup analyses based on age, race, BMI, history of hysterectomy, history of oophorectomy, and prior hormone therapy use did not show any findings of concern. Efficacy was consistent across various subgroups.

Summary efficacy considerations:

The submitted data from two adequate and well-controlled phase 3 trials showed substantial evidence of efficacy of fezolinetant 45 mg daily for the treatment of moderate to severe vasomotor symptoms associated with menopause assessed by the frequency and severity of VMS. The 30 mg dose group and the 45 mg dose group were each statistically superior to placebo in mean reduction in the frequency and severity of moderate to severe VMS from baseline at week 4 and at week 12. Only the 45 mg dose 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. The clinical review team (review dated November 26, 2022 by Drs. van der Vlugt and Zopf), statistical review teams (review dated November 21, 2022), and the CDTL (review dated January 29, 2023 by Dr. Shelley Slaughter) agree that the collective efficacy evidence from the two adequate and well controlled trials (301 and 302) provide substantial evidence of efficacy of fezolinetant 45 mg tablet administered once daily for the treatment of moderate to severe VMS due to menopause.

8. Safety

- **Safety database:**

The safety assessment of fezolinetant for moderate to severe vasomotor symptoms associated with menopause is primarily based on 2 phase 3 trials that were placebo-controlled for the first 12 weeks followed by 40-week non-controlled extension phases when all patients received fezolinetant (301 and 302) and one phase 3 trial that was placebo-controlled for 52 weeks (304; Table 3). Study 304 enrolled healthy females aged ≥40 and ≤65 years seeking treatment for VMS associated with menopause.

The size and scope of the safety database were reasonable and consistent with the safety database expectations for long-term treatment of a non-life-threatening condition. In addition, the safety database was consistent with recommendations provided by the Division for this first in class NK3 receptor antagonist. The safety population includes all subjects who were randomized and received at least one dose of study drug or placebo. Among the five Applicant-defined pooled safety populations (Table 7), the populations of primary interest were the two populations (POP2 and POP4) that included the 52-week phase 3 trial. The pooled safety populations of interest are described as follows:

- POP2: all randomized subjects who received at least one dose of study drug from the three 52-week phase 3 studies (2693-CL-0301, 2693-CL-0302 and 2693-CL-0304). All three studies were placebo-controlled that assessed fezolinetant 30 mg and fezolinetant 45 mg. However, in studies 2693-CL-0301 and 2693-CL-0302, subjects randomized to placebo were re-randomized to either fezolinetant 30 mg or fezolinetant 40 mg at week 12. Therefore, the treatment duration for the two active treatment arms were 40 weeks and 52 weeks.

- POP4: all randomized subjects who received at least one dose of study drug in study 2693-CL-0304, a three-arm, placebo-controlled 52-week phase 3 study. The three arms were placebo, fezolinetant 30 mg, and fezolinetant 45 mg.

Table 7: Overview of Safety Populations and Pooling Strategies in NDA 216578 Fezolinetant VMS Program

Population	Studies	Treatment Groups Summarized
POP1 Phase 3 Pivotal Placebo-controlled 12-week	2693-CL-0301 2693-CL-0302	Placebo (n=342) Fezolinetant 30 mg (n=340) Fezolinetant 45 mg (n=340) Fezolinetant **total** (n=680) **Total N**=1022
POP2 Phase 3 52-week	2693-CL-0301 2693-CL-0302 2693-CL-0304	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) Fezolinetant **total** (n=2203) **Total** N=3155
POP3 VMS Phase 2 and 3 12-week	ESN364_HF_204 ESN364_HF_205 2693-CL-0301 2693-CL-0302 2693-CL-0304	Placebo (n=1039) Fezolinetant 30 mg total (n=1146) Fezolinetant 45 mg total (n=1100) Fezolinetant 15 mg bid (n=45) Fezolinetant ≥ 60 mg (including 60, 90 mg bid, 60, 120, 180 mg qd) (n=264) Fezolinetant **total** (n=2555) **Total** N=3594
POP4 Phase 3 Placebo-controlled 52-week	2693-CL-0304	Placebo (n=610) Fezolinetant 30 mg (n=611) Fezolinetant 45 mg (n=609) Fezolinetant **total** (n=1220) **Total** N=1830
POP5 VMS Phase 2 12-week	ESN364_HF_204 ESN364_HF_205	Placebo (n=87) Fezolinetant 30 mg qd (n=43) Fezolinetant 15 mg bid (n=45) Fezolinetant ≥ 60 mg (including 60, 90 mg bid, 60, 120, 180 mg qd) (n=264) Fezolinetant **total** n=352 **Total** N= 439

All randomized participants who took at least 1 dose of study intervention
Based on the clinical review, pages 156-157, dated 11/26/22

A total of 2,859 unique participants were originally randomized in Trials 301, 302, and 304. The Safety Analysis Set for POP2 includes those 2,859 women in Trials 301, 302, and 304 in addition to 303 women re-randomized from placebo to fezolinetant in the 40-week extension phase of Trials 301 and 302 (for a total of 3,162 randomized participants). Of the 3,162 randomized participants, 3,155 participants took at least 1 dose of study intervention (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. In Trial 304, a total of 1,831 participants were randomized: 611 in the placebo group, 611 in the fezolinetant 30 mg group, and 609 in the fezolinetant 45 mg group. In Trial 304, 71.3% of the subjects completed the trial. The trial occurred during the COVID-19 pandemic, but minimal modifications were needed and there was no significant impact on the study.

Given the cross-over study element of Trials 301 and 302 at week 12, comparing the placebo and fezolinetant arms at week 52 would violate the intention-to-treat (ITT) principle. In addition, by design, subjects re-randomized to fezolinetant arms at week 12 knew that they were on treatment. In contrast, Trial 304 was randomized and placebo-controlled for 52 weeks. These differences between Trials 301 and 302 compared to 304, limit the conclusions that can be drawn from the pooled Trials (301, 302, and 304). The focus of this safety review is on Trial 304 (POP4), with information incorporated from 301 and 302 to increase exposure and for descriptive purposes. The clinical review by Drs. van der Vlugt and Zopf and cross-disciplinary team leader review by Dr. Slaughter focus on POP2 as it contained the three controlled studies. POP2 was analyzed with exposure adjusted incidence rates (given the crossover design of Trials 301 and 302). Results of the safety analyses are similar even when utilizing different pooling and analysis strategies.

Safety findings and conclusions:

The submitted safety data are supportive of the proposed 45 mg dose.

Safety assessment in the clinical studies included evaluation of deaths, serious adverse events (SAEs), common adverse events (AEs), vital signs, physical examination, clinical laboratory measures, ECGs, transvaginal ultrasound (TVUS), endometrial biopsy, and mammograms. In Trial 304, dual energy X-ray Absorptiometry (DEXA) was performed. Adverse events of special interest for fezolinetant were:

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

Selection of these adverse events of special interest was based on laboratory and clinical findings in the fezolinetant program, nonclinical considerations, and safety considerations in postmenopausal women.

Demographics: Study 304

Study 304 (POP4) included predominantly White (79.9%) participants with 20.1% of participants self-identifying as Hispanic or Latino. The mean age was 54.7 years and the median weight was 74.8 kg. A total of 18.6% of participants had undergone hysterectomy and 13.5% had undergone an oophorectomy. Prior hormone replacement therapy was taken by 17% of participants.

Deaths, SAEs, and discontinuations due to AEs:

There were two deaths reported in the fezolinetant program, both in the fezolinetant treatment arms. The causes of death were motorcycle passenger accident and cardiac arrest with anoxic brain injury. For both deaths, the reviewers concluded that they were unlikely to be related to study drug treatment.

In POP4 (Trial 304), the percentage of patients with SAEs was slightly higher in the fezolinetant groups compared to placebo (2.3% placebo, 3.3% fezolinetant 30 mg, and 3.8% fezolinetant 45 mg) (Table 8). The most frequent SAEs were abdominal pain (0% placebo, 0.2% fezolinetant 30 mg, and 0.3% fezolinetant 45 mg), COVID-19 (0.2% placebo, 0% fezolinetant 30 mg, and 0.3% fezolinetant 45 mg), and endometrial adenocarcinoma (0% placebo, 0.2% fezolinetant 30 mg, and 0.3% fezolinetant 45 mg). There was a greater percentage of participants with SAEs within the SOC of neoplasms benign, malignant and unspecified (incl cysts and polyps) in the fezolinetant groups than in the placebo group. Considerations related to malignancy are discussed below. Similar SAE findings were noted in POP2, but there was one case of hepatotoxicity in a participant who was in the placebo/fezolinetant 45 mg group. Considerations related to hepatic transaminase elevations are discussed below. The SAEs that occurred were primarily singular in nature, except for liver function test increased (discussed below).

In POP4 (Trial 304), the percentage of subjects with AEs leading to withdrawal was similar across groups (4.3% placebo, 5.6% fezolinetant 30 mg, and 4.6% fezolinetant 45 mg). No specific AE leading to withdrawal of study treatment (by preferred term) was reported for more than 2 participants in any treatment group, with the exception of fatigue (3 participants [0.5%] fezolinetant 45 mg), headache (3 participants [0.5%] placebo group and 4 participants [0.7%] fezolinetant 45 mg group) and nausea (4 participants [0.7%] fezolinetant 30 mg group). In POP2, the most common adverse event leading to treatment withdrawal was liver function tests increased (with terms combined, including ALT increased, AST increased, hepatic enzyme increased, liver function test increased, and transaminase increased). Elevations in hepatic transaminases are discussed further below.

Table 8: Serious Treatment-Emergent Adverse Events by System Organ Class in Trial 2693-CL-304

	Placebo N=610 n (%)	Fezolinetant 30 mg N=611 n (%)	Fezolinetant 45 mg N=609 n (%)
Overall	14 (2.3)	20 (3.3)	23 (3.8)
Cardiac disorders	1 (0.2)	2 (0.3)	0
Congenital, familial, and genetic disorders	0	1 (0.2)	0
Ear and labyrinth disorders	0	1 (0.2)	0
Endocrine disorders	0	1 (0.2)	1 (0.2)
Gastrointestinal disorders	1 (0.2)	1 (0.2)	3 (0.5)
General disorders and administration site conditions	0	0	1 (0.2)
Hepatobiliary disorders	2 (0.3)	1 (0.2)	0
Infections and infestations	3 (0.5)	3 (0.5)	4 (0.7)
Injury, poisoning and procedural complications	3 (0.5)	1 (0.2)	3 (0.5)
Investigations	1 (0.2)	0	2 (0.3)
Metabolism and nutrition disorders	0	2 (0.3)	1 (0.2)
Musculoskeletal and connective tissue disorders	0	1 (0.2)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (0.3)	5 (0.8)	7 (1.1)
Nervous system disorders	0	1 (0.2)	2 (0.3)
Psychiatric disorders	1 (0.2)	1 (0.2)	0
Renal and urinary disorders	0	0	1 (0.2)
Reproductive system and breast disorders	0	1 (0.2)	0
Respiratory, thoracic and mediastinal disorders	1 (0.2)	1 (0.2)	1 (0.2)
Surgical and medical procedures	0	1 (0.2)	0

Generated from Trial 2693-CL-0304; Table 9.6.1.7; Serious Treatment-Emergent Adverse Events (MedDRA v.23); pages 679-683; submitted 6/22/22

Common AEs:

In Trial 304, common adverse events were fairly balanced between treatment arms without suggestion of a dose response (64.1%: placebo; 67.9%: fezolinetant 30 mg; 63.9% fezolinetant 45 mg). The treatment-emergent AEs that occurred more commonly in the fezolinetant 45 mg group than the placebo group were back pain, diarrhea, arthralgia, nausea, insomnia, fatigue, and anxiety (Table 9).

Table 9: Treatment-emergent Adverse Events by Preferred Term ≥2% in the Fezolinetant Total Group (Safety Analysis Set); POP4; Trial 2693-CL-304

MedDRA (v23.0) Preferred Term	Placebo (n=610)	Fezolinetant 30 mg (n=611)	Fezolinetant 45 mg (n=609)
Overall	391 (64.1%)	415 (67.9%)	389 (63.9%)
Headache	56 (9.2%)	52 (8.5%)	55 (9.0%)
COVID-19	38 (6.2%)	38 (6.2%)	32 (5.3%)
Urinary tract infection	18 (3.0%)	29 (4.7%)	18 (3.0%)
Back pain	13 (2.1%)	27 (4.4%)	18 (3.0%)
Diarrhea	16 (2.6%)	21 (3.4%)	24 (3.9%)
Arthralgia	23 (3.8%)	15 (2.5%)	25 (4.1%)
Nausea	15 (2.5%)	18 (2.9%)	19 (3.1%)
Insomnia	11 (1.8%)	12 (2.0%)	24 (3.9%)
Upper respiratory tract infection	20 (3.3%)	15 (2.5%)	18 (3.0%)
Hypertension	18 (3.0%)	13 (2.1%)	18 (3.0%)
Nasopharyngitis	18 (3.0%)	15 (2.5%)	15 (2.5%)
Fatigue	16 (2.6%)	10 (1.6%)	17 (2.8%)
Anxiety	8 (1.3%)	13 (2.1%)	11 (1.8%)
Sinusitis	14 (2.3%)	13 (2.1%)	11 (1.8%)

All randomized participants who took at least 1 dose of study intervention (Safety Analysis Set)
Number of participants and percentage of participants are shown
Sorting order: descending by the number of participants of total fezolinetant group by preferred term. In case of ties, ascending order by preferred term code was applied
COVID-19: coronavirus disease 2019
MedDRA v23.0
Source: Summary of Clinical Safety; Table 15; page 49; submitted 6/22/22

Adverse events of special interest:

- Elevations of hepatic transaminases

Hepatic transaminase elevations and drug induced liver injury were of interest because of the reported aminotransferase elevations (ALT and AST) seen in the fezolinetant program beginning in phase 2 studies. In early fezolinetant development up to 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 were noted between 1-2 months on treatment, and rapidly resolved with discontinuation of treatment. Some correlation was observed between exposure to fezolinetant (AUC) and the serum aminotransferase elevations. The Division of Hepatology and Nutrition (DHN) Drug Induced Liver Injury (DILI) Team was consulted to assess the potential risk of liver injury.

In terms of other NK antagonists, there are two approved NK1 receptor antagonists that do not have significant hepatotoxicity signals. (b) (4)

The non-clinical evaluation did not suggest an elevated DILI risk. Excretion of fezolinetant is primarily through urine and the parent compound dominates excretion and serum profiles.

The phase 3 program included a Liver Safety Monitoring Panel (LSMP) that consisted of three independent hepatologists experienced in the assessment of drug induced liver injury (DILI).

The LSMP reviewed potential cases at the phase 3 program level and monitored the phase 3 program. Any participant who experienced criteria ALT or AST > 3 x ULN or total bilirubin > 2 x ULN was evaluated for potential DILI by the LSMP (blinded data were provided). The study features that were relevant to the DILI assessment included the following:

Relevant inclusion criteria:

- Negative serology panel (i.e., negative hepatitis B virus surface antigen, negative hepatitis C virus antibody and negative human immunodeficiency virus antibody screens).
- ALT/AST <1.5 x ULN if total bilirubin and direct bilirubin are normal. Alkaline phosphatase <1.5 x ULN if no cholestatic liver disease and no cause other than fatty liver is diagnosed.
- Gilbert's syndrome with elevated total bilirubin if direct bilirubin, hemoglobin, and reticulocytes are normal.
- Body mass index ≥18 kg/m^2 and ≤38 kg/m^2.

Relevant exclusion criteria:

- History of hepatic disease, active liver disease, jaundice or elevated liver ALT or AST, total or direct bilirubin, INR or alkaline phosphatase (≥ 1.5x ULN).

Relevant discontinuation of treatment criteria included:

- ALT or AST >8 x ULN
- ALT or AST >5 x ULN for more than 2 weeks
- ALT or AST >3 x ULN and TBili >2 x ULN or INR>1.5
- 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% increase above baseline)

Monitoring frequency:

- Labs were assessed at screening, randomization (day 1), week 2, week 4, week 8, week 12, week 14, week 16, week 20, week 24, week 28, week 32, week 36, week 40, week 44, week 48, week 52, and week 55

In Trial 304, there was a higher frequency of AST and ALT elevations (>3 x ULN) in the fezolinetant treatment groups compared to the placebo group, but the overall frequency of AST and ALT elevations was low (Table 10 and Figure 6). Specifically, in Trial 304 at 52 weeks ALT or AST elevations 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.

In all the phase 3 trials (POP2), there were 17 participants with ALT or AST >5 x ULN (0.4% (4/917) placebo, 0.7% (7/1069) fezolinetant 30 mg total, and 0.6% (6/1072) fezolinetant 45 mg total). There was a case of marked hepatic transaminase elevation, with a participant on fezolinetant 30 mg developing AST/ALT >20 x ULN. The phase 3 trials had no potential Hy's

law case. There was one subject with jaundice without aminotransferase or alkaline phosphatase elevation. There was no clear dose-response relationship with ALT or AST elevation for the 30 mg and 45 mg dose groups.

Table 10: Applicant's Reported Number (%) of Participants with Categorical Liver Biochemistry Findings (Safety Analysis Set); POP4 52-week; Trial 304

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%0
	> 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.

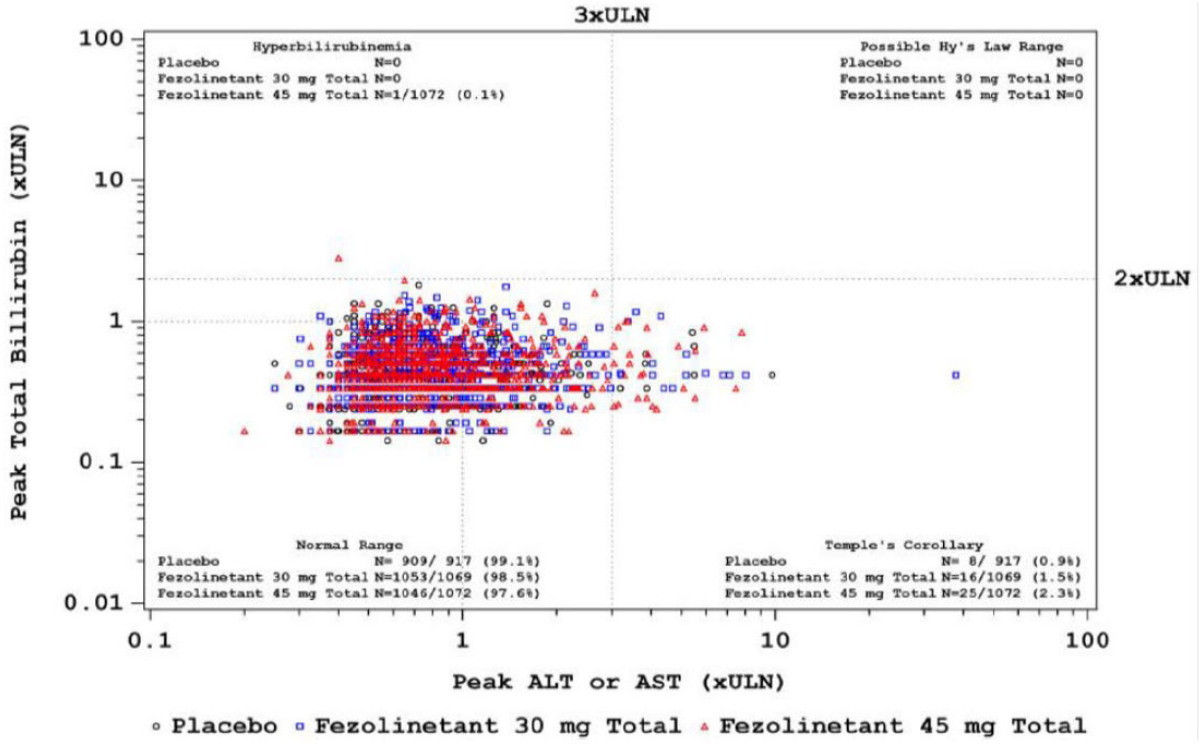
† Combination of values measured within same day or within 1 day apart.

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**.

Source: CDTL review; Table 44; page 114

Figure 6: eDish Plot for Trials 301, 302, and 304 through Week 52



Source: Drug-induced liver injury team; consult; figure 4; page 8; dated 11/21/2022

The DILI team conducted a detailed case level analysis of 14 participants with ALT or AST >5 x ULN. Of the 14, the DILI team assessed six as unlikely DILI, four as possible and four as probable (Table 11). The assessments of the DILI team and the applicant's LSPM were similar. The LSMP tended to see resolution of liver injury on drug as probable DILI with adaptation while the DILI team assessed them as possible DILI. The DILI Team consult response notes that, "the greatest discrepancies 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."

The DILI team analyzed seven cases assessed as probable DILI by either the DILI Team or the LSMP (Table 12).

Table 11: Summary of Cases with ALT or AST >5x ULN

#	Subject ID	Study	DILI Team Causality Score*	LSMP 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	Gallstone	53	F	White	No	No
					mean	*54*				
					std dev	*3.6*				
					median	*54*				
					max	*64*				
					min	*48*				

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

NASH = non-alcoholic steatohepatitis

APAP = acetaminophen

NA = not applicable

Source: Drug-induced liver injury team; consult; table 5; page 10; dated 11/21/2022

Table 12: Seven subjects assessed as having probable DILI by the DILI Team and/or LSMP

#	Subject ID	Study	DILI Team Causality Score*	LSMP Causality Score*	Alternate diagnosis	Age (yr)	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	No	No	84	-1	686	1515	153	0.5	13.71	30.29
2		2693-CL-0302	3	4	NA	57	No	No	54	-51	322	158	104	0.4	9.47	4.65
3		2693-CL-0301	3	3	NA	48	Yes	No	28	-8	293	194	104	0.3	8.62	5.71
4		2693-CL-0304	3	3	NA	55	No	No	250	-62	270	189	116	1.17	7.12	4.98
5		2693-CL-0304	4	3	Unknown	52	No	No	56	-36	336	203	104	0.7	9.88	5.97
6		2693-CL-0304	4	3	APAP	52	No	No	114	-249	223	97	104	0.5	6.56	2.85
7		2693-CL-0304	4	3	APAP	58	No	No	14	-352	219	172	172	0.2	3.89	3.06
					mean	*54*			*86*	*-108*	*336*	*361*	*122*	*0.5*	*8.5*	*8.2*
					std dev	*3.2*			*74*	*126*	*149*	*472*	*26*	*0.3*	*2.9*	*9.1*
					median	*55*			*56*	*-51*	*293*	*189*	*104*	*0.5*	*8.6*	*5.0*
					max	*58*			*250*	*-1*	*686*	*1515*	*172*	*1.2*	*13.7*	*30.3*
					min	*48*			*14*	*-352*	*219*	*97*	*104*	*0.2*	*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 = ALT/ULN ÷ AP/ULN or AST/ULN ÷ AP/ULN; Hepatocellular: R value ≥ 5; Mixed/cholestatic: R value < 5

LSMP = Liver Safety Monitoring Panel

NA = not applicable

APAP = acetaminophen

Source: Drug-induced liver injury team; consult; table 6; page 11; dated 11/21/2022

In the cases, only one subject had symptoms (nausea) and the remainder were asymptomatic. The findings were primarily hepatocellular with a median latency from drug start of 56 days (range 14 to 250 days). Many of the subjects considered to have possible DILI improved even with continued use of fezolinetant. Please see the clinical, CDTL, and DHN reviews for additional details.

The clinical trial data suggest a mild increase in ALT or AST elevation in subjects exposed to fezolinetant compared to placebo and there were no aminotransferase elevations with jaundice. There were four subjects with probable DILI and three to four others with at least possible DILI out of approximately 2,800 subjects with VMS exposed to fezolinetant in the phase 3 trials. The 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. Notably, many of the subjects considered to have possible DILI improved despite continued use of fezolinetant, suggesting adaptation may occur with continued exposure. The DILI team concluded that fezolinetant "may cause DILI, but it appears modest, and adaptation may occur with continued exposure. However, the number of women exposed post market could be quite large." Given the potentially large exposure population, more severe cases of DILI could arise.

The DILI team's recommendations were incorporated, including adding a Warning and Precaution to the labeling, including a recommendation to perform baseline liver tests, performing routine liver tests during the first period of fezolinetant use, and performing enhanced pharmacovigilance (EPV). Consideration was given to inclusion of a Boxed Warning and this was discussed at the Medical Policy and Program Review Council (MPPRC). The majority of council members did not feel a Boxed Warning was indicated at

this time. Council members indicated that mild hepatic transaminase elevations would not be considered a serious adverse reaction. However, council members noted that it if serious adverse reactions occurred post-marketing, then a Boxed Warning should be considered. In addition, there was consideration of whether postmarketing studies would be required, but the team determined that EPV would be adequate to monitor the liver safety considerations post-approval. The team, including the DILI consult team, agreed that the risk of hepatic transaminase elevations can be adequately managed with labeling and EPV.

During the review, there was significant consideration of the optimal frequency of monitoring hepatic function. Initially, the team proposed baseline and monthly monitoring, which would have been similar to the frequency of hepatic function monitoring in the phase 3 trials. Astellas noted that monthly monitoring would create significant burdens, without anticipated enhancement of safe use given the timing and low occurrence of hepatic transaminase elevations without suggestion of serious hepatotoxic risk. After extensive discussion internally, including with DHN, it was determined that the frequency could be less than monthly given that the overall frequency of AST and ALT elevations was low, the limited duration of hepatic transaminase elevations, the lack of bilirubin elevations, and the resolution of hepatic transaminase elevations with either continuation or soon after discontinuation of fezolinetant. Intense monthly monitoring would be of limited value to reduce the risk of a rare event. Monitoring every three months was determined to be optimal in terms of ensuring safe use given the relatively early onset of hepatic transaminase elevations. In terms of the duration of monitoring, monitoring will occur for 9 months, which captures the maximum of the latency range (14 to 250 days) seen in the clinical trials.

As additional post-marketing data are available, FDA will continue to review and assess if modifications to risk mitigation measures are needed. For example, if additional safety concerns arise, additional monitoring or labeling (such as a Boxed Warning) may be indicated. Conversely, if the post-marketing data are reassuring, it is possible that the labeling could be updated to reflect a need for less frequent or prolonged hepatic transaminase monitoring.

Malignancy:

There was a dose-dependent numeric imbalance noted in the occurrence of malignancy in fezolinetant versus placebo arms in the system organ class (SOC) of neoplasms benign, malignant, and unspecified. The percentages of patients with malignancy in Trial 304 were 0.3%, 0.8%, and 1.1% in the placebo, fezolinetant 30 mg, and fezolinetant 45 mg arms, respectively (Table 13). As seen in Table 14, the exposure-adjusted incidence rate difference comparing fezolinetant 45 mg and placebo was greater than the null value of 0. Figure 7 displays the cumulative incidence of malignancy over time in Trial 304, which shows a separation over time, but is notable for an early separation for the fezolinetant 45 mg dose. It would be unusual for a drug related malignancy to happen at earlier time points after minimal drug exposure.

Table 13: Neoplasms benign, malignant, unspecified in Trial 304

	Placebo N=610 n (%)	Fezolinetant 30 mg N=611 n (%)	Fezolinetant 45 mg N=609 n (%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (0.3%)	5 (0.8%)	7 (1.1%)
Endometrial adenocarcinoma	0	1 (0.2%)	2 (0.3%)
Colon cancer	0	0	2 (0.3%)
Basal cell carcinoma	0	1 (0.2%)	0
Benign breast neoplasm	0	1 (0.2%)	0
Bone cancer	0	0	1 (0.2%)
Chronic lymphocytic leukemia	0	1 (0.2%)	0
Malignant melanoma in situ	0	0	1 (0.2%)
Squamous cell carcinoma of the Skin	1 (0.2%)	1 (0.2%)	0
Squamous cell carcinoma of the oral cavity	0	0	1 (0.2%)
Non-small cell lung cancer	0	0	1 (0.2%)
Hepatic cancer	0	0	1 (0.2%)
Neurilemmoma benign	1 (0.2%)	0	0

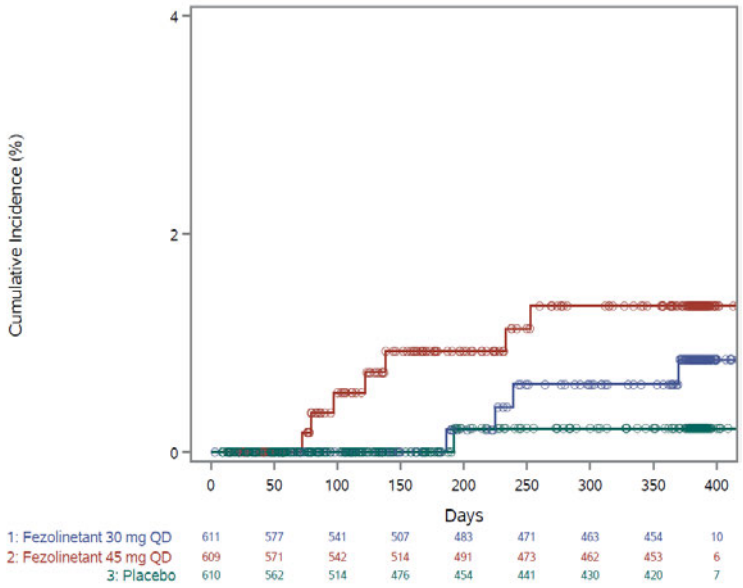
Source: Trial 2693-CL-0304 study report; Table 9.6.1.7; submitted 6/22/22

Table 14: Number of Subjects with Events (%) and Exposure-Adjusted Incidence Rates and Differences of Malignancy

	Placebo N=952 PY=599.4	Fezolinetant 30 mg N=1103 PY-941.0	Fezolinetant 45 mg N=1100 PY=966.0
POP2 (Trials 301, 302, and 304)			
Subjects with Events	1	6	11
Exposure-adjusted Incidence Rates (EAIR) per 100 PY, (95% CI)	0.20 (0.03, 1.39)	0.65 (0.29, 1.44)	1.15 (0.64, 2.07)
POP4 (Trial 304)			
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, %	--	0.49 (0.22, 1.21)	0.99 (0.08, 1.89)
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)

Source: Division of Biometrics VII Review; Table 4; page 6-7; dated 10/20/22

Figure 7: Cumulative Incidence Rate of Malignancy (POP4: CL-304)



Source: Division of Biometrics VII Review; Figure 1; page 7; dated 10/20/22

The Division of Oncology III (DO3) and the Division of Biometrics 7 (DB7) were consulted to assist in considering this potential safety signal. DO3 noted that pooling data across studies with different designs and patient follow-up could introduce heterogeneity to render interpretation of results difficult, and that there was insufficient information to support a definitive conclusion of increased risk of malignancy. DB7 noted that the duration of Trial 304 was 52 weeks, which may be too short to assess malignancy and that the small number of events resulted in uncertainty around the estimated risk difference. DO3 noted that from a clinical perspective, there is insufficient data to support a definitive conclusion of an increased risk of malignancy in patients who received fezolinetant. It is notable that there were a variety of cancer types that have distinct histologies (Table 13) and there were no nonclinical signals for malignancy. Further, several of the cancers appeared to be pre-existing. The CDTL memo notes that six of the participants (with 8/16 malignancies TEAEs in treatment arms) were likely preexisting before enrollment. If these malignancies were removed, the resultant incidence rate would be decreased approximately in half and would be consistent with the background rate of cancer in this age group.

A consult was also placed to the Office of Surveillance and Epidemiology (OSE)/ Division of Pharmacovigilance II (DPV II) and the Division of Epidemiology (DEPI) to further review and assess whether the imbalance indicated a safety signal. DPV II reviewed study documents for inclusion/exclusion criteria related to neoplasms in clinical trial protocols, protocol deviations related to neoplasms, and individual case details of neoplasm cases. DEPI attempted to calculate and compare general and site-specific cancer incidence in the fezolinetant trial to a general population of US women in a similar age group using data from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program. As outlined in their consult, assessment of incident cancer was severely limited by the lack of source documentation on relevant risk factors, presence of protocol deviations, underreporting of past medical history, abnormal and/or nondiagnostic laboratory and pathologic studies at screening visits or early in the study period, detection bias, and alternate established cancer risk factors. DPV noted that many, if not most, of the cancers were likely preexisting. DPV noted that detection bias, short drug exposure time, and detection of cancers across multiple primary sites made if unlikely that fezolinetant was associated with tumor development. The short drug exposure time and detection of cancers across multiple primary sites (and histologic subtypes) makes it unlikely that fezolinetant was associated with tumor development. Their consult notes that "the inability to establish incident cancer rates and the small number of site-specific cancer cases in the three trials made it impossible to reliably calculate incidence in the fezolinetant trial. Different study populations (international clinical trials vs. US-based SEER data), lack of collection on most noninvasive neoplasms and nonmelanoma skin cancers (e.g., basal cell carcinoma, squamous cell carcinoma) in SEER make it impossible to compare to cancer incidence in the fezolinetant trial in SEER." DPV concluded that "the evidence for implicating fezolinetant in development of malignancy is weak and any causal association between fezolinetant exposure and neoplasm could not be established with certainty based on the data provided by the Applicant." Based on the totality of the data, they concluded that the numeric imbalance was most likely a chance finding. An overview of the serious adverse events of malignancy is provided in Table 15. Notably, most of the cancers occurred before

250 days, and about half before 180 days) which is not consistent with a malignancy associated with drug exposure.

Table 15: Serious Adverse Events of Malignancy Within the Neoplasms Benign, Malignant and Unspecified (incl Cysts and Polyps) System Organ Class (Safety Analysis Set): POP2

Patient ID	Treatment Duration (days)	Study	Malignancy type	Comments
Fezolinetant 45 mg				
(b) (6)	Placebo: 95 Fezolinetant 45 mg: 11	301	Apocrine breast carcinoma	Completed 12 weeks of placebo treatment and then re-randomized to fezo 45 mg; short TTO and not a neoplastic precursor
	72	304	Non-small cell lung cancer (NSCLC) Hepatic cancer (liver masses, malignant) Hepatic cancer (malignant liver lesions)	NSCLC that metastasized to the liver; likely pre-existing prior to study entry (per DPV review; baseline laboratory abnormalities; short TTO)
	79	304	Endometrial Adenocarcinoma	Likely preexisting prior to study entry (baseline abnormality; endometrial biopsy with complex hyperplasia at screening)
	97	304	Malignant melanoma in situ	DPV notes unlikely associated with fezo given short TTO
	104	302	Squamous cell carcinoma of the skin	DPV notes unlikely associated with fezo exposure based on short TTO and initial detection on ED 25
	122	304	Endometrial Adenocarcinoma	Likely preexisting based on abnormal endometrial thickness at screening per DPV review
	138 151	304	Squamous cell carcinoma oral Cavity (mandible) Bone cancer (mandible)	Oral cancer spread to the jaw bone; appeared to be pre-existing (oral lesions at enrollment) with clinical signs at ED 47 (short TTO)

(b) (6)	213		Keratoacanthoma (precancerous)	DPV notes that association with fezo cannot be excluded
	233	304	Colon cancer	Likely to be preexisting (laboratory abnormalities beginning on ED1 (decline in hemoglobin) with frank anemia on ED 226, shortening an already short TTO) per DPV review
	253	304	Colon cancer	Likely to be preexisting (GI symptom onset on exposure day 24) and already short TTO per DPV review
Fezolinetant 30 mg (b) (6)				
	Placebo: 83 Fezolinetant: 63	301	Squamous cell carcinoma of the skin	Completed 12 weeks of placebo treatment and then re-randomized to fezolinetant 30 mg; DPV notes short TTO
	Placebo: 85 Fezolinetant: 151	302	Invasive breast carcinoma	Completed 12 weeks of placebo treatment and then re-randomized to fezolinetant 30 mg; Family history of breast cancer in first-degree relative (mother); DPV felt unlikely related to fezo based on alternative risk factor and short TTO
	186	304	Squamous cell carcinoma of skin	Unlikely associated with fezo given short TTO and concomitant marker of past UV radiation exposure per DPV review
	225	304	Chronic lymphocytic leukemia	Likely to be preexisting per DPV review (baseline lab abnormalities)
	239	304	Basal cell carcinoma	Appeared to be preexisting/recurrent; unlikely to be associated with fezo
	370	304	Endometrial Adenocarcinoma	Uterine biopsy at screening was

				inadequate for assessment; DPV concluded that it was likely pre-existing. The exact timing of onset is unclear.
Placebo				
(b) (6)	192	304	Squamous cell carcinoma	Forehead
	272	304	Schwannoma (Neurilemomas)	Incidental finding on imaging

DPV=Division of Pharmacovigilance II; ED=exposure day; Fezo=fezolinetant; TTO=time to onset
For patients who were on placebo and then switched to fezolinetant, the treatment duration is shown for the time on placebo and then the time on fezolinetant
DPV considered the narrative (b) (6) but omitted from the assessment given that papillary apocrine metaplasia is not considered a neoplastic precursor. Also, (b) (6) was omitted as pulmonary hamartoma is not considered a neoplastic precursor.
Source: Summary of Clinical Safety; Table 50; pages 141-152, submitted 6/22/22 and DPV review dated 4/27/23

In addition, review of previous trials of similar duration in similar patient populations showed a fairly similar rate of adverse events associated with malignancy as to what was seen in the fezolinetant treatment arms. While there are significant limitations to cross-study comparisons, they suggest that there was not a distinct safety signal in the fezolinetant trials.

Based on extensive review of the clinical and nonclinical data, there were not data to implicate fezolinetant in the development of malignancy and a causal relationship between fezolinetant exposure and malignancy was not established. Key factors that were considered in this assessment included the lack of nonclinical data suggesting carcinogenetic potential, lack of clear mechanism or biologic plausibility, multiple types of cancer without a clear pattern, and short time to malignancy onset. Based on the currently available nonclinical information, no biological mechanism was identified that indicated an increased risk of malignancy or tumor promoter activity with fezolinetant or through NK3R antagonism. The pharmacology/toxicology team did not identify structural alerts relevant to DNA-reactivity, positive carcinogenicity signal in the nonclinical bioassays, or potential mechanisms of tumorigenesis or tumor promoter activity with fezolinetant or its metabolites.

An additional consideration was the multiple cancer sites with a single exposure. As noted in the DPV review, most pharmaceuticals classified as carcinogenic to humans are associated with cancers at a single site. Of the pharmaceuticals associated with multiple cancer sites, there is generally a unifying mechanism, such as hormonally mediated cancer sites. In addition, immunosuppressive drugs are associated with cancer at several sites given the role of immunosuppression in the development of multiple cancers, yet fezolinetant is not immunosuppressive. There is no clear mechanism of action for fezolinetant to cause cancers, including cancers at multiple sites.

Another consideration was the short latency from exposure to fezolinetant to the development of malignancy. Many of the cancers appeared to be pre-existing prior to fezolinetant exposure. For cancers that developed during the trials, the latency was short which is not consistent with fezolinetant associated cancer as most cancers are associated with long latency period that is usually many years. Thus, there is not definitive evidence of increased malignancy risk with fezolinetant. The review team considered whether to include the numeric imbalance in

labeling. Given that there was no evidence to believe there was a causal relationship between fezolinetant and malignancy, this information will not be included in product labeling.

Endometrial safety:

Given that the proposed indication is for postmenopausal women, endometrial hyperplasia and adenocarcinoma are adverse events of special interest. A comprehensive assessment of endometrial safety was performed that included transvaginal ultrasound (TVU), endometrial biopsies, and adverse events of special interest relative to endometrial safety. The rates of endometrial hyperplasia and malignancy were less than 1% with upper limits of a one-sided 95% CI $\leq$ 4%, which met the pre-specified criteria in the FDA guidance[9] in both POP2 and POP4. Similarly, the other assessments of endometrial safety did not reveal any concerns. Thus, the overall assessment of endometrial safety for fezolinetant was reassuring.

Abuse potential:

The controlled substance staff was consulted and evaluated the abuse potential of fezolinetant. CSS concluded that fezolinetant does not appear to have a meaningful abuse potential and does not require scheduling under the Controlled Substances Act (CSA). Further, fezolinetant does not require section 9 (Drug Abuse and Dependence) in its label.

Other selected adverse events of interest:

Drs. Slaughter, van der Vlugt, and Zopf also evaluated for other selected adverse events of interest, including cardiac safety, bone fractures, thrombocytopenia, depression, wakefulness, and effect on memory. In terms of cardiac safety, no significant QTc prolongation was detected in the QT assessment performed using data from the single- / multiple-ascending dose study and therefore a thorough QT study was not conducted. The FDA provided agreement that these studies were not required following a model-based approach to assess the QT prolongation potential of fezolinetant. In terms of bone safety, fezolinetant does not appear to have an impact on bone safety after 12 months of exposure. In terms of thrombocytopenia, this was an adverse event of special interest based on the occurrence of thrombocytopenia in monkeys in a nonclinical study. In POP4, the incidence of platelet count $<150 \times 10^9$/L was similar in the placebo and fezolinetant arms (4.1% placebo; 4.0% fezolinetant 30 mg; 3.9% fezolinetant 45 mg). There were no meaningful imbalances in the treatment arms for depression, wakefulness, and effect on memory. Thus, there were no safety concerns in the submitted data related to these selected adverse events of interest.

Safety conclusions:

The review team agreed that the overall safety of fezolinetant is acceptable to support approval and that the benefit-risk is favorable. There is a risk of drug induced liver injury, which was seen as elevations in hepatic transaminases in the clinical development program. Notably, most

[9] FDA's Draft Guidance for Industry—Estrogen and Estrogen/Progestin Drug Products to Treat Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms – Recommendations for Clinical Evaluation.

enzyme elevations were mild, there were no Hy's Law cases, several liver injury cases improved despite continued exposure to fezolinetant, and the frequency of elevations was low. However, given that the post-market exposure population could be large, there will be enhanced pharmacovigilance post-approval, and the labeling will include a Warning and Precaution for this risk, with monitoring of hepatic function at baseline and every 3 months for 9 months after drug initiation. The clinical team and DHN were in agreement on the strategy to mitigate this risk.

9. Advisory Committee Meeting

An Advisory Committee meeting was not held to discuss this application because there were no considerations that would warrant a discussion at an Advisory Committee meeting.

10. Pediatrics

On January 10, 2023, the Pediatric Review Committee (PeRC) agreed with the requested full waiver for pediatric studies 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)

No concerns were raised regarding questions of data reliability or application integrity.

Exclusivity or patent issues of concern

No issues were identified during the course of the review.

Office of Scientific Investigations (OSI) Audits

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). 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 Studies 301 and 3022, the frequency and severity of moderate to severe vasomotor symptoms, were verified with the source records available at the inspected clinical sites.

Financial Disclosure

No concerns were identified.

Other Good Clinical Practice (GCP) issues

There are no GCP issues with this application. All studies were conducted in accordance with accepted ethical standards.

Proprietary Name Review

On December 2, 2022, the 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 concluded that the proprietary name Veozah was conditionally acceptable.

12. Labeling

Prescribing Information: The product label was reviewed by various disciplines, and by other Divisions and Offices. Various changes were incorporated to ensure that the information ensures the safe and effective use of the drug. A high-level summary of key elements of the labeling include:

Indication and Usage
Veozah is indicated for the treatment of moderate to severe vasomotor symptoms due to menopause.

Dosage and Administration
The recommended dose is 45 mg daily. Baseline bloodwork is needed to evaluate for hepatic injury and function before initiating fezolinetant and during treatment.

Boxed Warning
A Boxed Warning is not included. See discussion of the elevated hepatic transaminases for further discussion.

Warnings and Precautions
A Warning and Precaution was added regarding the risk of elevations in hepatic transaminases associated with fezolinetant treatment. In addition, there is information regarding monitoring bloodwork to evaluate for hepatic function and injury at baseline and every three months during treatment for the first 9 months (i.e., at Month 3, Month 6, and Month 9) and for patients who experiencing symptoms related to liver damage, such as nausea, vomiting, or jaundice.

Adverse Reactions
Data are shown in tabular form from trial 3 (304) and pooled laboratory data for elevated hepatic transaminases are described for trials 1, 2, and 3 (301, 302, and 304).

Drug Interactions

Fezolinetant is a substrate of CYP1A2 and should not be used with any CYP1A2 inhibitors.

Use in Special Populations
Fezolinetant should not be used in individuals with cirrhosis, severe renal impairment, or end-stage renal disease.

Efficacy Information
Labeling will include information regarding the co-primary efficacy endpoints for both trials: mean change from baseline in moderate to severe vasomotor symptoms frequency and severity to Weeks 4 and 12.

13. Postmarketing

- Postmarketing Risk Evaluation and Mitigation Strategies

A REMS will not be required for this application. The information necessary to use fezolinetant safely and effectively will be provided through the prescribing information.

- Other Postmarketing Requirements and Commitments

No postmarketing requirements or commitments are needed. Astellas has agreed to 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. Specifically, for a period of 3 years, FDA requested that Astellas: (1) Implement a targeted questionnaire to obtain follow-up information for hepatic adverse events, including liver injury; (2) Submit all initial and follow-up postmarketing hepatic adverse drug experiences, including liver injury, as 15-day "Alert reports" (described under 21 CFR 314.80(c)(1)), from all postmarketing sources; (3) Provide a summary analysis of hepatic adverse events, including liver injury, in the required postmarketing periodic safety reports. The summary analyses should include interval and cumulative data relative to the date of approval of Veozah; and (4) Provide, in the postmarketing periodic safety report, a review of case reports/case series of hepatic adverse events, including liver injury, reported with Veozah identified in the medical literature.

The enhanced pharmacovigilance program will be reassessed 3 years after Veozah approval.

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CHRISTINA Y CHANG
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JANET W MAYNARD
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