CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216578Orig1s000

CLINICAL REVIEW(S)

M E M O R A N D U M

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

FROM: Jamie Brewer, MD
Clinical Team Lead, Division of Oncology 3 (DO3)

THROUGH: Lola Fashoyin-Aje, MD, MPH
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TO: Christina Chang, MD
Director, Division of Urology, Obstetrics, and Gynecology (DUOG)

SUBJECT: NDA 216578- ESN364 (fezolinetant) tablets for the treatment of moderate to severe vasomotor symptoms (VMS) associated with menopause.

CONSULT DATE: June 22, 2022

DATE: January 23, 2023

BACKGROUND

Astella Pharma Global Development, Inc., (Astellas) submitted an original NDA for fezolinetant, a small molecule, non-hormonal selective neurokinin 3 (NK3) receptor antagonist that blocks neurokinin B (NKB) binding. NKB is a hypothalamic neuropeptide that binds preferentially to the neurokinin 3 receptor. Expression of the gene encoding NKB is elevated in postmenopausal women. NKB/NK3R signaling plays an important role in the pathophysiology of hot flushes through inappropriate activation of heat dissipation responses via the thermoregulatory centers in the hypothalamus. While attenuation of the NKB/NK3R signaling pathway has emerged as a potential therapeutic target for the treatment of menopausal hot flushes (potentially without the need for estrogen replacement), the safety profile of agents targeting this pathway has not been established. (Jayasena CN, et al. 2015) If approved, fezolinetant will be the first selective NK3 receptor antagonist in the US.

Astellas submitted three randomized controlled trials (Trial 2693-CL-0301, Trial 2693-CL-0302, Trial 2693-CL-0304) to support FDA's assessment of the safety and effectiveness of fezolinetant for the proposed indication. These trials evaluated the

efficacy of 30 mg and 45 mg of fezolinetant or placebo, and the safety of both doses of the drug. Across these trials, over 3000 participants were exposed to fezolinetant. The Division of Urology, Obstetrics, and Gynecology (DUOG) requested a consult to obtain the Division's assessment of whether there is a potential safety signal of malignancy in women taking fezolinetant.

The DUOG provided, as a part of the consult request, the results of an analysis of Trials 2693-CL-0301 2693-CL-0302, and 2693-CL-0304, shown in **Table 1**.

Table 1: Cases of Malignancy Across Trial 2693-CL-0301, Trial 2693-CL-0302, and Trial 2693-CL-0304

Study ID	AEDECOD	ARM			
		ASP2693 30mg QD	ASP2693 45mg QD	Placebo QD	Placebo QD + ASP2693 30mg or 45mg QD (40-week extension cross-over)
2693-CL-301	Apocrine breast carcinoma				1
	Lung neoplasm		1		
	Squamous cell carcinoma of skin				1
2693-CL-302	Squamous cell carcinoma of skin		1		
	Invasive breast carcinoma				1
	Keratoacanthoma		1		
2693-CL-0304	Basal cell carcinoma	2			
	Bone cancer		1		
	Colon cancer		2		
	Endometrial adenocarcinoma	1	2		
	Malignant melanoma in situ		1		
	Non-small cell lung cancer		1		
	Squamous cell carcinoma of skin	1			
	Squamous cell carcinoma of the oral cavity		1	1	
TOTAL		4	11	1	3

Source: *Copied from Consult Request Form*

DO3 RESPONSE TO CONSULT REQUEST

The DUOG requests DO3 input on the following questions.

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

DO3 Response: From a clinical perspective, interpreting the clinical findings shown in Table 1 is challenging. There is insufficient data to support a definitive conclusion of an increased risk of malignancy in patients who received fezolinetant. While there exists a background risk of malignancy in the general population which increases with age, it is unclear what effect, if any, exposure to fezolinetant may have on this risk. It would be challenging to conclude an increased risk over the baseline rate without a baseline assessment of the history of malignancy (or of an increased risk for example due to presence of pre-cancerous lesions or risk factors for cancer, etc.,) in patients who enrolled in the trial. The post-exposure follow-up and the stage of the malignancy should also be considered in the assessment of the likelihood that the observed malignancies are attributable to the drug. For example, most cancers have a long latency from pre-malignant lesion to early malignant tumor, to invasive cancer. It is unclear whether the malignancy events were early stage, in-situ lesions or whether they represented more advanced disease. For these reasons, it is challenging to comment on whether any association exists between exposure to fezolinetant and increased risk of malignancy, or alternatively in an increased risk of progression in patients who have pre-existing neoplastic lesions.

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

Based on available data that describes the molecular pathways involved in tumorigenesis across the observed cancer types that have distinct histologies, it is unclear whether there is a unifying factor that explains the findings. Preclinical data may help elucidate a mechanistic association between fezolinetant exposure and the risk of malignancy (or progression of malignancy) across these diverse tumor types, if one exists. DO3 therefore recommends that the pharmacology toxicology team review the available data and provide input on the mechanistic potential of increased risk. Additionally, consider requesting input from the Office of Surveillance Epidemiology (OSE) to provide an assessment of the rate of malignancy observed in the trials submitted in the NDA, considering the background incidence of malignancy. OSE may also be able to provide guidance with respect to what signals have resulted in changes in labeling for other drugs with non-oncological indications (e.g., including JAK inhibitors, HCTZ, SLGT2i, and potentially others).

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

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

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

DO3 Response: Refer to DO3 response to Question 1 and Question 2. FDA defers to the review team whether to describe the study findings in product labeling considering the uncertainty with respect to the finding but acknowledging

the difference between arms and consideration for whether to be transparent with respect to the finding.

REFERENCES

1. Jayasena, C., Comninos, A., Stefanopoulou, E. et al. Neurokinin B Administration Induces Hot Flushes in Women. Sci Rep 5, 8466 (2015). https://doi.org/10.1038/srep08466
2. Obata K, Shimo T, Okui T, et al. A: Tachykinin Receptor 3 Distribution in Human Oral Squamous Cell Carcinoma. Anticancer Res 36: 6335-6341, 2016. https://ar.iiarjournals.org/content/37/11/6119
3. Obata K, Shimo T, Okui T, et al. Role of Neurokinin 3 Receptor Signaling in Oral Squamous Cell Carcinoma. Anticancer Research, Vol 37; November 2017, 37 (11) 6119-6123.

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/s/

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CLINICAL REVIEW

Application Type	505(b)(1)
Application Number(s)	NDA 216578
Priority or Standard	Priority
Submit Date(s)	June 22, 2022
Received Date(s)	June 22, 2022
PDUFA Goal Date	February 22, 2022
Division/Office	Division of Urology, Obstetrics, and Gynecology (DUOG) Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine (ORPURM)
Reviewer Name(s)	Theresa H. van der Vlugt, M.D., M.P.H. Regina Zopf, M.D., M.P.H.
Review Completion Date	November 23, 2022
Established/Proper Name	Fezolinetant
(Proposed) Trade Name	TRADENAME
Applicant	Astellas Pharma Global Development, Inc.
Dosage Form(s)	Tablet
Applicant Proposed Dosing Regimen(s)	45 mg tablet once daily with or without food
Applicant Proposed Indication(s)/Population(s)	Treatment of moderate to severe vasomotor symptoms due to menopause.
Recommendation on Regulatory Action	Pending an acceptable or positive recommendation from OSI, *Approval* of the 45 mg fezolinetant dosage strength is recommended from a clinical standpoint.
Recommended Indication(s)/Population(s) (if applicable)	Postmenopausal Women

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Glossary

AC	advisory committee
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Council for Harmonization
IND	Investigational New Drug Application
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat

NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1. Executive Summary

1.1. Product Introduction

TRADENAME (fezolinetant) 45 mg tablets, for oral use, is a neurokinin 3 (NK3) receptor antagonist (pharmacologic class) that blocks neurokinin B (NKB) binding on the kisspeptin, neurokinin, dynorphin (KNDy) neuron to modulate neuronal activity in the thermoregulatory center of the brain proposed for the treatment of moderate to severe vasomotor symptoms (VMS) associated with menopause. The applicant refers to fezolinetant as a *non-hormonal* and *selective* NK3 receptor antagonist. The thermoregulatory center in the hypothalamus is innervated by KNDy neurons, which are inhibited by estrogen and stimulated by the neuropeptide NKB. Through the menopausal transition, declining estrogen levels disrupts the balance with NKB. Unopposed, NKB signaling increases KNDy neuronal activity leading to hypertrophy of the KNDy neuron and altered activity on the thermoregulatory center, resulting in VMS.[1,2]

On March 22, 2022, Astellas Pharma Global Development, Inc. (hereafter referred to as Astellas) notified FDA (under IND 130277 Serial/Seq 0126) of their intent to use a Rare Pediatric Disease Priority Review Voucher (PRV), and the PRV user fee was provided via wire transfer on May 18, 2022. NDA 216578 is reviewed under a Priority Review designation with a PDUFA date of February 22, 2022.

On December 14, 2021, Astellas submitted a request for review of the proposed proprietary name, (b) (4) (under IND 130277 Serial/Seq 0118). June 12, 2022 was the FDA goal date for the proposed proprietary name review. On June 8, 2022, FDA informed Astellas that the June 12, 2022 goal date could not be met, and no estimated completion date was provided. Astellas, therefore, submitted the same proprietary name request ((b) (4) in the NDA 216578 application. On September 15, 2022, the proposed proprietary name (b) (4) was denied.

On September 26, 2022, Astellas submitted to the NDA, a request for review of the proposed proprietary name, (b) (4). On October 3, 2022, Astellas withdrew their September 26, 2022

[1] Skorupskaite K, George JT, Veldhuis JD, et. al. Neurokinin B Receptor Antagonism Decreases LH Secretion and Sensation of Hot Flashes in Postmenopausal Women. GJOG. 2016; 132-137.
[2] Prague JK, Roberts RE, Comninos AN, et. al. Neurokinin 3 Receptor Antagonism Rapidly Improves Vasomotor Symptoms with Sustained Duration of Action. Lancet. 2017; 389:1809-1820.

request following a September 28, 2002 teleconference with the Division of Medication Error and Prevention Analysis 2 (DMEPA 2).

On October 11, 2022, Astellas submitted a request for review of the proposed preferred proprietary name VEOZAH for 45 mg fezolinetant tablets. On October 30, 2022, Astellas was advised that the user fee goal date, for review of the proposed proprietary name VEOZAH, was January 9, 2023.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The clinical reviewers conclude that substantial evidence of overall efficacy for TRADENAME (fezolinetant) tablets, 45 mg, is demonstrated, based on successfully achieving the primary protocol-defined co-primary endpoints of: 1) a statistically significant mean change from baseline in the frequency of moderate to severe VMS at Week 4 when compared to placebo; 2) a statistically significant mean change from baseline in the frequency of moderate to severe VMS at Week 12 when compared to baseline; 3) a statistically significant mean change from baseline in the severity of moderate to severe VMS at Week 4 when compared to placebo; and 4) a statistically significant mean change from baseline in the severity of moderate to severe VMS at Week 12, when compared to placebo. In addition, the 45 mg fezolinetant tablets demonstrated a clinically meaningful threshold difference in the frequency of hot flashes (which compared to placebo is superiority of at least 2 hot flashes per day, or 14 per week) at Week 4 that is maintained through Week 12.

1.3. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

Menopause is a natural and inevitable physiological process marking the decline of reproductive capacity in females. Vasomotor symptoms (VMS) are common during menopause and can negatively impact the quality of life for women. A decrease in estrogen at the time of menopause is associated with vasomotor symptoms (hot flashes/hot flushes). VMS is characterized by problems with sleep, mood, concentration, energy and sexual activity[3,4], and individuals often also report feelings of physical discomfort, depression, anxiety, stress, self-consciousness and embarrassment.[5,6]

Although hormone therapy (estrogens given alone in a woman without a uterus and estrogens plus progestogens in a woman with a uterus) historically has been the predominant treatment for moderate to severe hot flashes, hormone therapy has contraindications to use and certain serious adverse health risks, most notably the risk of endometrial cancer with unopposed estrogen therapy and the risk of breast cancer with estrogen plus progestogen therapy.

Fezolinetant is a neurokinin 3 (NK3) receptor antagonist which mimics estrogens inhibitory effect on KNDy neurons in the thermoregulatory center in the hypothalamus, and thus balances out the stimulatory effects of NKB on KNDY neurons (unopposed stimulation results in hypertrophy of the KNDy neuron and increased activity of the thermoregulatory center). Thus, based on its physiologic actions, fezolinetant is a candidate for treatment of VMS that is not in the class of hormone therapy products. In the current NDA, the efficacy of fezolinetant is evaluated and demonstrated during the first 12 weeks of two phase 3, 52-week trials (Trial 2693-CL-0301 and Trial 2693-CL-0302) in postmenopausal women with moderate to severe hot flashes, while the safety of fezolinetant has been demonstrated in these same clinical trials and a third 52-week clinical trial (Trial 2593-CL-0304). Increased hepatic transaminases, abdominal pain, and insomnia have been

[3] Kagan R, et. al. Impact of sleep disturbances on employment and work productivity among midlife women in the US SWAN database: a brief report. Menopause. 2021; 28:1176-1180.
[4] Williams RE, et. al. The Hot Flush Beliefs Scale: a tool for assessing thoughts and beliefs associated with the experience of menopausal hot flushes and night sweats. Maturitas. 2008; 60:158-169.
[5] Whiteley J, et. al. The impact of menopausal symptoms on quality of life, productivity, and economic outcomes. J Womens Health (Larchmt). 2013; 22:983-90.
[6] Williams RE, et. al. Menopause-specific questionnaire assessment in US population-based study shows negative impact on health-related quality of life. Maturitas. 2009; 62:153-159.

identified as adverse reactions for fezolinetant. WARNINGS AND PRECAUTIONS will state that hepatic transaminase evaluations are to be performed prior to first use of fezolinetant, and each month for the first nine months to assure safe use.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Menopause is a natural and inevitable physiological process marking the decline of reproductive capacity in females. • In the US, nearly 63 million women are past the average age of natural menopause of 51 years of age (50 years of age and older as of July 1, 2021.[7] • Symptoms of menopause, such as vasomotor symptoms (VMS; hot flashes/hot flushes) and vulvar and vaginal atrophy (VVA) symptoms [vaginal dryness, vaginal irritation/itching, and pain with sexual activity (dyspareunia)] can be debilitating with respect to a woman's ability to accomplish her normal activities including sleep. However, menopause is not directly a life-threatening condition. • VMS are experienced by up to 80% of individuals during menopause.[8] The prevalence of moderate to severe VMS associated with menopause was 34% in the US, 40% in Europe and 16% in	• Although menopause is a natural and inevitable physiological process, VMS associated with menopause can persists for long periods in some individuals, with a substantial impact on quality of life. • Menopause symptoms, though not life-threatening, constitute a significant public health concern often requiring medical intervention.

[7] https://www.census.gov
[8] 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.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	Japan.[9] • Hot flashes involve sudden sensations of heat in the upper body, particularly in the head, neck, chest and upper back. These symptoms occur as episodes that usually last 1 to 5 minutes and are characterized by perspiration, flushing, chills, clamminess, anxiety and on occasion heart palpitations.[10,11] • An individual's experience can vary based on a combination of genetic background, psychological and socio-economic factors and other health conditions and/or treatments.[10] • The duration of VMS from the time of symptom onset is typically 7.4 years[12] and symptoms commonly persist for nearly a decade.[13]	

[9] Nappi RE, et. al. Global cross-sectional survey of women with vasomotor symptoms associated with menopause: prevalence and quality of life burden. Menopause. 2021; 28:875-882.
[10] Stuenkel CA, et. al. Treatment of Symptoms of the Menopause: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2015; 100:3975-4011.
[11] American College of Obstetrics and Gynecology (ACOG) Clinical Management Guidelines, 2014.
[12] Avis NE, et. al. Duration of menopausal vasomotor symptoms over the menopause transition. JAMA Intern Med. 2015; 175: 531-539.
[13] Hunter MS, et. al. Prevalence, frequency and problem rating of hot flushes persist in older postmenopausal women: impact of age, body mass index, hysterectomy, hormone therapy use, lifestyle and mood in a cross-sectional cohort study of 10,418 British women aged 54-65. BJOG. 2012; 119:40-50.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current Treatment Options	• Current approved treatment options for an indication for the treatment of moderate to severe vasomotor symptoms include multiple oral, transdermal systems, topical gels/emulsion/spray, vaginal system products with estrogen-alone for use in a woman without a uterus or in combination with a progestogen for use in a woman with a uterus. One non-hormonal product is approved. These approved products offer a range of dosage strengths allowing titration of dose to relieve vasomotor symptoms based on treatment goals and risk for the individual woman.	• Estrogens-alone in a woman without a uterus and estrogens plus progestogens in a women with a uterus is standard treatment for the relief of bothersome moderate to severe hot flashes.[9,14] • Symptomatic postmenopausal women may have a medical history or current medical condition preventing the use of estrogens with or without progestogens. • Fezolinetant reduces the frequency and severity of moderate to severe vasomotor symptoms at Week 4 and Week 12. Fezolinetant is not in the class of hormonal therapy products.
Benefit	• Fezolinetant 45 mg achieved statistical significance versus placebo consistently across the four co-primary VMS endpoints (mean change in VMS frequency and severity at Weeks 4 and 12) in two confirmatory, 12-week, placebo-controlled clinical trials. • Fezolinetant 45 mg achieved a clinically meaningful threshold reduction of hot flash frequency (defined as a reduction in hot flash frequency that exceeds placebo by at least 2 per day or 14 per week) at Week 4 maintained through Week 12.	• Non-hysterectomized and hysterectomized women using TRADENAME can expect a reduction in the frequency and severity of moderate to severe vasomotor symptoms. • VMS associated with menopause have repercussions on the daily lives of affected individuals, and negatively impact their quality of life. Management of these

[14] North American Menopause Society (NAMS) Position Statement, 2017.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Fezolinetant 45 mg achieved a ≥ 50% frequency reduction in moderate to severe VMS at Weeks 4 and 12. • Nonhormonal 45 mg fezolinetant tablets can be used by non-hysterectomized and hysterectomized postmenopausal women.	symptoms is essential for effective outcomes.
Risk and Risk Management	• The most common exposure adjusted adverse reactions (incidence ≥ 1%) with 45 mg fezolinetant are elevated hepatic transaminases, abdominal pain, and insomnia. • Hepatic transaminase elevations > 3 x ULN were observed that were approximately 2-fold greater in 45 mg fezolinetant compared with placebo. These hepatic transaminase elevations occurred at various timepoints in the 12-month clinical trials, were generally transient, and resolved while on 45 mg fezolinetant or shortly after discontinuation. No cases of Hy's law were observed. • There was an imbalance in overall serious adverse reactions driven by an imbalance in the exposure adjusted incidence rate (EAIR) fir non-benign neoplasms (high level group term) in TRADENAME versus placebo in three clinical trials. The EAIR was 0.2 per 100 person-years in the placebo group versus 1.2 per 100 person years in TRADENAME. Half of the non-benign neoplasms in TRADENAME were noted to be pre-existing.	• Risks associated with 45 mg fezolinetant are well characterized in the application. • Contraindications to be identified in TRADENAME labeling including 1) Known cirrhosis, 2) Severe renal impairment or end-stage renal disease, and 3) Concomitant use with strong CYP1A2 inhibitors. • The Warning and Precautions section of TRADENAME labeling recommends 1) Perform baseline hepatic transaminase evaluation, 2) Do not start TRADENAME therapy if baseline hepatic transaminase concentration is ≥ 2 x upper limit of normal (ULN), 3) Perform follow-up evaluation of hepatic transaminase concentration on a monthly basis up to nine months from the start of TRADENAME.

1.4. Patient Experience Data

The fezolinetant clinical development program consisted of 18 completed trials conducted over approximately 8.5 years: 11 phase 1 trials, 4 phase 2 trials, and 3 phase 3 clinical trials. The 18 completed trials have been conducted globally: North America, Europe and Asia. Per the application, all clinical trials were conducted according to Good Clinical Practice as defined by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. The completed fezolinetant clinical trials treated a total of 295 healthy participants in phase 1 trials, and 3,291 menopausal participants with moderate to severe VMS across the phase 1 to phase 3 clinical development program.

Primary evidence for the efficacy of fezolinetant in the treatment of moderate to severe VMS associated with menopause comes from Trial 2693-CL-0301 and Trial 2693-CL-0302. These two primary, phase 3, randomized trials included a 12-week placebo-controlled period followed by a 40-week extension period of fezolinetant exposure only (52-weeks in total). Both primary phase 3 efficacy and safety trials were conducted in the US, Canada and Europe.

The following primary clinical outcome assessment data (trial endpoints for phase 3, 52-week Trial 2593-CL-0301 and Trial 2693-CL-0302), for the 45 mg fezolinetant tablets, requested for approval, was submitted in the NDA 216578 application received June 22, 2022. These clinical endpoints comply with the Agency's 2003 draft Guidance for Industry entitled, "Estrogen and Estrogen/Progestin Drug Products to Treat Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms – Recommendations for Clinical Evaluation", hereafter, referred to as the Agency's 2003 draft Clinical Evaluation Guidance for Industry:

- Mean change in frequency of moderate to severe VMS from baseline to Week 4 in an active treatment group compared with placebo.
- Mean change in frequency of moderate to severe VMS from baseline to Week 12 in an active treatment group compared with placebo.
- Mean change in severity of moderate to severe VMS from baseline to Week 4 in an active treatment group compared with placebo.
- Mean change in severity of moderate to severe VMS from baseline to Week 12 in an active treatment group compared with placebo.

Patient Experience Data Relevant to this Application (check all that apply)

☒	The patient experience data that was submitted as part of the application include:		Section where discussed, if applicable
	☒	Clinical outcome assessment (COA) data, such as	[e.g., Sec 6.1 Study endpoints]

		☒	Patient reported outcome (PRO)	Section 6 Review of Relevant Individual Trials Used to Support Efficacy
		☐	Observer reported outcome (ObsRO)	
		☐	Clinician reported outcome (ClinRO)	
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		[e.g., Sec 2.1 Analysis of Condition]
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify)		
☐	Patient experience data that were not submitted in the application, but were considered in this review:			
		☐	Input informed from participation in meetings with patient stakeholders	
		☐	Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Current Treatment Options]
		☐	Observational survey studies designed to capture patient experience data	
		☐	Other: (Please specify)	
☐	Patient experience data was not submitted as part of this application.			

2. Therapeutic Context

2.1. Analysis of Condition

Menopause is a natural biological process and marks the end of fertility because of permanent ovarian failure. Symptoms of menopause, such as vasomotor symptoms [(VMS) referred to as hot flashes/hot flushes) and vulvar and vaginal atrophy symptoms [(VVA) including the symptoms of vaginal dryness, vaginal irritation/itching, and dyspareunia (pain with sexual activity)] can be debilitating with respect to a woman's ability to accomplish her normal

activities, including sleep. However, menopause is not a life-threatening condition. In the US, nearly 63 million women are past the average age of natural menopause of 51 years of age (50 years of age and older as of July 1, 2021).[7]

2.2. Analysis of 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, as well as a non-hormonal product, for the treatment of moderate to severe VMS. Treatment options for estrogen-alone and estrogens plus progestogens products are presented in Table 1, Table 2, and Table 3, and a non-hormonal option in Table 4.

Table 1 Estrogen-Alone Products Approved for the Treatment of Moderate to Severe Vasomotor Symptoms due to Menopause

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 m, 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 pouch 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

* Discontinued

Table 2 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

Table 3 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

Table 4 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

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

TRADENAME, a first in class new molecular entity (NME) product containing fezolinetant, a NK3 receptor antagonist, is not currently marketed in the U.S. or internationally.

3.2. Summary of Presubmission/Submission Regulatory Activity

March 22, 2016: Ogeda S.A., Belgium, opened IND 130277 for ESN364 (fezolinetant) for the treatment of moderate to severe vasomotor symptoms associated with menopause.

March 22, 2017: Type C meeting was held with Ogeda S.A. to discuss nonclinical and clinical development plans for the treatment of moderate to severe hot flashes in postmenopausal women. Ogeda S.A. also sought feedback on (b) (4)

April 17, 2017, FDA Type C Meeting Minutes conveyed, but not limited to, the following:

- Pending review of final nonclinical study reports for the 6-month rat and 9-month monkey studies to be submitted, there appears to be sufficient nonclinical information to proceed with phase 2b clinical Trial ESN 364_HF_205.
- There is sufficient data for assessing metabolite ES259564 safety.
- Provide a table of safety margins, based on animal exposure data (i.e., AUC and Cmax) to the IND.
- The trial primary efficacy analyses should show a clinically and a statistically significant reduction, within 4 weeks of initiation of treatment and maintained throughout 12 weeks of treatment, in both the frequency and severity of hot flashes in the treated groups compared with the control groups. A clinically significant reduction in frequency is identified as a reduction of at least two moderate to severe hot flashes above placebo per day at Week 4 and Week 12.
- Your proposal to (b) (4) Calculate severity as follows:
    - [(number of mild hot flashes/day × 1) + (number of moderate hot flashes/day × 2) + (number of severe hot flashes/day × 3)]/total number of daily (or weekly) mild/moderate/severe hot flashes
- The assessment of endometrial histology is recommended both for phase 3 clinical trial efficacy and safety evaluation and long-term (minimum 12-months) general and endometrial safety, and drug exposure trials.
- We considers ESN364 to be a new molecular entity. Two confirmatory 12-week phase 3 efficacy and safety clinical trials, and a long-term (minimum 12-months) general and endometrial safety trial should be conducted in support of this product.
- Your phase 2b dose finding trial should enroll only women that you intend to evaluate at phase 3, which are identified as postmenopausal women experiencing hot flashes due

to menopause. (b) (4)

- We generally follow the ICH E1 guidelines for patient exposure when a drug product is used on a chronic basis. These guidelines recommend exposure in 1500 patients overall, 300-600 patients for six months, and 100 patients for one year at the dose or dose range believed to be efficacious.

October 24, 2017: Ogeda S.A. submits two Special Protocol Assessment (SPA) protocols to FDA to obtain agreement on the 2-year rat carcinogenicity study ((b) (4) Study 8375967) and the 26-week mouse carcinogenicity study ((b) (4) Study 8375970). On December 6, 2017, the Executive Carcinogenicity Assessment Committee (ECAC) meeting minutes were sent to Ogeda S.A. Ogeda S.A. submitted the final FDA agreed-upon protocols on March 1, 2018.

May 1, 2018: General Correspondence: Transfer of IND from Ogeda S.A. to Astellas letter was received indicating, "Effective May 1, 2018, the Ogeda IND 130277 has transferred to Astellas Pharma Global Development, Inc. (Astellas), which has accepted all sponsor responsibilities and obligations pertaining to Ogeda IND 130277 with the exception of the ongoing 'Phase 2B Study ESN_HF_205'. Ogeda will remain the study sponsor of 'Phase 2B Study ESN364_HF_205'."

June 7, 2018: FDA provided Astellas Type C Written Responses Only related to findings of transient elevation of liver enzymes in the phase 2b Trial ESN364_HF_205. The FDA Written Responses Only conveyed, but not limited to, the following:

- "Discontinue (pause) enrollment in Trial ESN364_HF_205 if ≥ one additional woman is withdrawn because she meets the previously agreed-to patient withdrawal criteria.
- Women currently enrolled in Trial ESN364_HF_205 may continue with implementation of close observation, including more frequent serum liver biochemistry evaluation for women who develop transaminase abnormalities that do not meet the trial or individual participant stopping criteria, if enrollment is paused.
- Participating women should also have serial serum alkaline phosphatase and prothrombin (PT)/international normalized ratio (INR) evaluated in addition to transaminase and total bilirubin. Obtain these tests every week when a woman has been found to have any abnormal liver function test.
- Obtain a baseline fractionation of the serum bilirubin (direct and indirect fractions) when abnormal transaminases are reported as defined above, as some women will have Gilbert's syndrome. Repeat bilirubin measurements simultaneously with all liver biochemistry tests until all elevations have returned below the ULN.

- Investigate promptly with biochemical and physical evaluation and interrupt trial drug administration for any woman with symptoms of abdominal pain, worsening or new fatigue, anorexia, nausea, rash, vomiting or diarrhea. Discontinue investigational drug immediately if prompt evaluation is not possible.
- Conduct a thorough evaluation of each woman who develops asymptomatic ALT and/or AST abnormalities >3 x ULN (or 2 x baseline, but not more than 5 x ULN in trial participants that are enrolled with elevations at baseline) in the absence of hyperbilirubinemia and/or elevated INR.
- Provide the curriculum vitae of each member of the Liver Safety Monitoring Panel (LSMP) that you establish for Trial ESN364_HF_205, for our review.
- Masked and unblinded safety data for ongoing and future clinical trials should be reviewed at three month intervals by the Data Safety Monitoring Board (DSMB).
- Provide datasets of all women enrolled in all ESN364 trials to date, including clinical studies/trials conducted outside the United States, using eDISH data plotting attached, to better assist you in your ESN364 development program."

July 3, 2018: FDA provided Astellas an Advice/Information Request (A/IR) letter regarding the sponsor's finding of two additional cases of transient elevation of liver enzymes, and reiterated the advice provided in the June 7, 2018, Written Responses Only communication.

October 16, 2018: Astellas requested a Special Protocol Assessment (SPA) for a mouse Carcinogenicity Study. FDA responded on November 29, 2018. On January 16, 2019, Astellas submitted the SPA final protocol.

October 24, 2018: FDA provided Type C Written Responses Only related to endometrial health assessment, bone safety assessment, and breast cancer treatment-related VMS development strategy. The FDA Written Responses Only conveyed, but not limited to, the following:

- "All non-hysterectomized women enrolled in planned phase 3 clinical trials should undergo a baseline endometrial biopsy before beginning trial medication. Non-hysterectomized woman with an endometrial diagnosis of endometrial hyperplasia and/or endometrial cancer should not be enrolled. A transvaginal ultrasound (TVU) examination should also be performed.
- Repeat the endometrial biopsy at completion of all 12-week trials and all 52-week trials or for vaginal bleeding at any time during the course of drug therapy.
- Endometrial tissue obtained by endometrial biopsy prior to trial enrollment, during the conduct of the clinical trial, and at the End-of-Trial (EOT) should be processed in the same manner by a central laboratory.
- We recommend concurrent reading by three independent expert pathologists from institutions with independent fiduciary and organizational reporting for the evaluation

of the endometrium in a woman with a uterus. Each pathologist should be blinded to the treatment group and to the readings of the other pathologists. The concurrence of two of the three pathologists is accepted as the final diagnosis. If there is no agreement among the three pathologists, the most severe pathologic diagnosis should be used as the final diagnosis.

- The same standardized criteria for the diagnosis of endometrial hyperplasia or endometrial cancer should be used by the three independent pathologists, and endometrial polyps should be fully characterized as to glandular proliferation and atypia.
- Emerging research suggests that tachykinins may have a role in bone homeostasis. Therefore, a direct effect of ESN364 on bone turnover in postmenopausal women cannot be ruled out. The data from phase 2a Trial ESN364_HF_204 are insufficient to evaluate ESN364's effect on bone. Include BMD endpoints in your phase 3 development.
- All BMD measurements should be interpreted at a central read facility and analyses should include areas where there are standardized DXA placement procedures and normative data available for assessment (i.e. lumbar spine, femoral neck, and total hip). Analyses should be based on scans with standard (supine) patient positioning. Adequate quality control measures should be established for any multicenter trial that include bone density endpoints (Faulkner et al., 1995).
- (b) (4)

April 17, 2019: Type B "End-of-Phase 2 (EOP2)" meeting was held with Astellas to discuss their nonclinical, clinical pharmacology, and clinical development plans for phase 3 development of fezolinetant. On May 16, 2019, FDA Meeting Minutes conveyed, but not limited to, the following:

- "Submit all nonclinical final study reports to IND 130277, with a summary table of safety margins based on animal exposure data for both fezolinetant and ES259564 as discussed at the March 2017 Type C meeting. Based on the proposed duration of the phase 3 clinical trial, the 39-week toxicology study report must be submitted and reviewed by FDA prior to the initiation of the phase 3 clinical trials.
- The array of clinical pharmacology trials, completed or planned, appear to be reasonable. However, the adequacy of these trials to support the NDA submission will be a review issue and will depend on the quality of trial conduct and results.
- Your proposal to allow concomitant administration of weak CYP1A2 inhibitors (e.g., caffeine) with 30 mg fezolinetant daily in your phase 3 trials appears acceptable.

- We cannot agree at this time that a thorough QT/QTc (TQT) study can be waived. We request that you submit the following data for our integrated nonclinical and clinical assessment:
    - The proposed approach for justifying the supra-therapeutic exposures by combining the effects of strong CYP1A2 inhibition (~2-fold), the lowest body weight (1.44-fold), the to-be-marketed tablet formulation (1.225-fold), and an Asian patient population (1.25-fold) appears reasonable. Use the expected increase in Cmax of fezolinetant with concomitant administration of a strong CYP1A2 inhibitor at steady-state for representing the worst-case scenario.
    - Submit the following items for our further review:
        - The study report for the drug interaction Trial 2693-CL-0006.
        - The safety data from ongoing clinical trials.
        - Trial report(s) for any other clinical trial that you have conducted, that evaluates the effect of product administration on the QT interval.
- Reported results for completed phase 2b Trial ESN364_HF_205 show that the daily 30 mg fezolinetant dose demonstrated a clinically meaningful and statistically significant reduction in the frequency of hot flashes at Week 4 and Week 12, and demonstrated a statistically significant reduction in the severity of hot flashes at Week 4. However, a statistically significant reduction in the severity of hot flashes at Week 12 was not demonstrated for the daily 30 mg fezolinetant dose. You may be at risk of not identifying an effective dose of fezolinetant for a VMS indication in your proposed phase 3 development program.
- Your proposal to conduct a long-term, 52-weeks clinical trial of which the first 12-weeks will be placebo-controlled and followed by a 40-week open-label extension (representing a total of 52-weeks of trial medication exposure), is acceptable.
- Perform an endometrial biopsy in any participating woman with a uterus who completes the 12-week, placebo-controlled period in proposed Trial 2693-CL-0301 (and similar Trial 2693-CL-0302) who declines participation in the proposed open-label 40-weeks trial extension. A diagnosis of disordered proliferative endometrium, endometrial hyperplasia, or endometrial cancer must be appropriately followed-up by Astellas until resolution.
- We do not distinguish between moderate to severe hot flashes experienced during nighttime hours (commonly referred to as night sweats) and those experienced during the daytime hours. Count hot flashes experienced at night the same as those experienced during daytime hours.
- Reported results for proposed secondary and exploratory objectives/endpoints (for example, the PROMIS® SD SF 8b, PROMIS® SRI SF 8a, PGI-C, PGI-SSD, PGI-CSD, MENQOL, EuroQOL 5D-5L, and WPAI-VMS questionnaires), in your proposed phase 3 Trials 2693-CL-0301 and similar Trial 2693-CL-0302, (b) (4)

(b) (4)

- Reported results of the proposed secondary and exploratory objectives/endpoints in clinical Trials 2693-CL-0301 and similar Trial 2693-CL-0302 (b) (4) .
- Repeat the screening endometrial biopsy reported as insufficient tissue for evaluation to rule out the presence of disordered proliferative endometrium, endometrial hyperplasia, or endometrial cancer.
- Do not enroll a postmenopausal woman with a uterus and a screening endometrial biopsy reported as: disordered proliferative endometrium, endometrial hyperplasia, or endometrial cancer in proposed Trial 2693-CL-0301 and similar Trial 2693-CL-0302.
- The proposed sample sizes for Trials 2693-CL-0301 and similar Trial 2693-CL-0302 appear to be reasonable to detect treatment differences between active drug and placebo. We generally follow the ICH E1 guidelines for patient exposure for drug products intended for chronic use. These guidelines recommend exposure in 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures should occur at the dose or dose range anticipated to be efficacious. Note that larger exposures may be needed if there are safety concerns that emerge during drug development that need further characterization prior to approval.
- Your proposed schedule of laboratory and clinical assessments appears reasonable to monitor the potential for liver injury with incorporation of the following:

    - Evaluate liver biochemistry at 2 weeks and then every 4 weeks for the entire duration of the trial and approximately 2 to 4 weeks after the trial drug is discontinued for both trials.
- Postmenopausal women with mild elevations in serum transaminases <1.5 x the upper limit of normal (ULN) may be included, however, such participants must have a normal total bilirubin (TB) and direct bilirubin (DB) at enrollment.
- Postmenopausal women with Gilbert's syndrome may be enrolled in clinical trials. These women may have elevated total bilirubin, but their direct bilirubin, reticulocyte count, and hemoglobin should be normal.
- Evaluate a postmenopausal woman with elevated alkaline phosphatase (ALP) at baseline, for cholestatic liver disease prior to trial enrollment.
- Immediately discontinue drug in trial participants with persistent elevations in AST/ALT >3 x ULN accompanied by sign or symptoms consistent with drug-induced liver injury [(DILI) for example, fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (> 5% above pretreatment levels)].
- FDA and Astellas agreed upon the criteria for drug-induced liver injury (DILI):

  - ALT or AST >8 X ULN
  - ALT or AST >5 X ULN for more than 2 weeks
  - ALT or AST >3 X ULN and (TB >2 X ULN or INR >1.5 X ULN)
  - ALT or AST >3 X ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (> 5% above pretreatment levels).
- FDA agreed with the establishment of a Liver Safety Monitoring Panel (LSMP), the general plan for the blinded and unblinded assessments, and the composition of the panel. FDA also agreed with the role of the Data Safety Monitoring Board (DSMB) in interacting with the LSMP.
- FDA agreed that the nonclinical data and the adverse event (AE) data from clinical trials with fezolinetant do not provide a signal warranting further abuse-related studies with fezolinetant. However, if a signal of abuse potential arises in future clinical trials, additional abuse-related information or studies may be requested.
- Submit separately an Initial Pediatric Study Plan (iPSP) within 60 days of an End-of-Phase-2 (EOP2) meeting.
- FDA agreed that the study data standardization plan (SDSP) for the nonclinical studies, clinical pharmacology trials, and clinical trials, appears reasonable. However, the reported results of the proposed secondary and exploratory objectives/endpoints in clinical Trials 2693-CL-0301 and similar Trial 2693-CL-0302, (b) (4) . You may proceed with your analysis for PROMIS® SD SF 8b for exploratory purposes at your own discretion.
- For electronic data capture, perform usability testing of the selected devices with patient cognitive interviews to assess device functionality, questionnaire comprehension, and ease of use in the patient population. This would minimize the likelihood of having poor quality data due to patients' misunderstanding or incomplete understanding of how to use the device."

May 31, 2019: Astellas submitted a TQT/QT_c Study Waiver request. On December 20, 2019, FDA provided the following response via email/electronic communication to the IND, "From our QT Interdisciplinary Review Team: No significant QTc prolongation was detected in our QT assessment performed using data from the sponsor's single- / multiple- ascending dose study (Study # ESN364-CPK-102). Yes, we agree that a dedicated QT study is not needed. The submitted data was found to be adequate to support the substitution request of thorough QT study."

July 22, 2019: Astellas requested a Type C meeting to discuss and agree on the designation of the regulatory starting materials, the biopharmaceutics classification system (BCS) designation for fezolinetant and the CMC strategy for the development of fezolinetant immediate release

tablets for commercial use based on ICH M9 draft guideline. Written Responses Only were provided on October 4, 2019. See the FDA Office of Pharmaceutical (OPQ) Written Responses Only, dated October 4, 2019.

September 20, 2019: The Agency's A/IR letter regarding phase 3, 12-month Trials 0301 and 0302, conveyed the following to Astellas:

- "Do not enroll a postmenopausal woman who has a screening endometrial biopsy reported as insufficient tissue for diagnosis and a screening transvaginal ultrasound (TVU) double wall thickness of greater than 4 mm in the proposed phase 3, 52-week efficacy and safety clinical trials without further evaluation.
- Repeat any screening endometrial biopsy reported as insufficient tissue for diagnosis to rule out the presence of disordered proliferative endometrium, endometrial hyperplasia, or endometrial cancer in a postmenopausal woman with a uterus.
- Do not enroll any postmenopausal woman with a uterus and a screening endometrial biopsy reported as disordered proliferative endometrium, endometrial hyperplasia, or endometrial cancer.
- Have the histologic determination of the endometrial biopsy slides collected during the conduct of proposed Trials 2693-CL-0301 and 2693-CL-0302, made by three independent expert pathologists ((b) (4)), blinded to treatment and each other's readings.
- We do not distinguish between moderate to severe hot flashes experienced during the nighttime hours (commonly referred to as night sweats) and those experienced during the daytime hours.
- Reported results for proposed secondary and exploratory objectives/endpoints (for example, the PROMISR SD SF 8b, PROMISR SRI SF 8a, PGI-C, PGI-SSD, PGI-CSD, MENQOL, EuroQOL5D-5L, and WPAI-VMS questionnaires), in your proposed phase 3 Trials 2693-CL-0301 and 2693-CL-0302, (b) (4)
- The reported results of the proposed secondary and exploratory objectives/endpoints in clinical Trials 2693-CL-0301 and 2693-CL-0302 (b) (4)
- The primary efficacy analysis in phase 3 Trials 2693-CL-0301 and 2693-CL-0302 should demonstrate a statistically significant and clinically meaningful reduction in the frequency and statistically significant reduction in the severity of hot flashes in the treated group(s) compared with placebo. This reduction in frequency and severity

should occur at 4 weeks from initiation of treatment and be maintained through 12 weeks of treatment.
- We identify a clinically meaningful reduction in frequency as a reduction of at least two moderate to severe hot flashes above placebo at Week 4 and Week 12."

November 15, 2019: The Agency's A/IR letter, regarding phase 3, 12-month Trial 0304 conveyed the following to Astellas:

- "Do not enroll any postmenopausal woman with a uterus who has a screening endometrial biopsy reported as insufficient tissue for diagnosis and a screening transvaginal ultrasound (TVU) double-wall thickness greater than 4 mm in your proposed phase 3, 52-week safety clinical trial without further evaluation (exclusion criterion # 7 in the proposed protocol for Trial 2693-CL-0304).
- Repeat any screening endometrial biopsy that is reported as insufficient tissue for diagnosis to rule out the presence of disordered proliferative endometrium, endometrial hyperplasia, or endometrial cancer in a postmenopausal woman with a uterus.
- Assess endometrial safety, i.e., rates of endometrial cancer and endometrial hyperplasia as a primary endpoint. Assess the rate of disordered proliferative endometrium in the same way as the primary endpoint.
- Power proposed Trial 2693-CL-0304 based on the ability to demonstrate a rate of hyperplasia (as a surrogate for endometrial cancer) that is ≤ 1 percent with an upper bound of the one-sided 95 percent confidence interval for the rate, that does not exceed 4 percent."

January 7, 2020: The Agency submitted a Written Responses Only to the Astellas submission, dated November 19, 2019, containing a meeting request to discuss and obtain Agency's agreement on the design of fish full lifecycle study for Environmental Assessment (EA). FDA agrees with the proposed study design of the fish study for the EA for fezolinetant.

March 2, 2020: The Agency responded to IND 130277 protocol amendment, dated May 16, 2019, containing Astellas' Agreed Initial Pediatric Study Plan (Agreed iPSP) for the Treatment of Moderate to Severe Vasomotor Symptoms Associated with Menopause. "We have completed our review of your submission. We agree with your Agreed iPSP and have no further comments at this time. The attached copy of your Agreed iPSP serves as the official copy of this document and must be included in the appropriate section of an application for marketing approval for ESN364 (fezolinetant). Your Agreed iPSP may be amended at your initiative or at FDA's initiative at any time before you submit a marketing application. However, FDA must agree to any amendments to an Agreed iPSP."

July 14, 2020: The Agency submitted Written Responses Only to the Astellas submission, dated May 18, 2020, containing a Type C meeting request to obtain feedback and obtain Agency's agreement on the designation of a regulatory starting material (RSM) (b) (4) in the fezolinetant drug substance synthesis route. The Agency's Written Responses Only conveyed the following to Astellas. The Agency agreed that:

- (b) (4) complies with the definition of a "commercially available chemical" in ICH Q11.
- The impurity spike and purge studies demonstrate that impurities of (b) (4) other than (b) (4) and (b) (4) do not contribute to the impurity profile of fezolinetant drug substance.
- The revised specification proposed for (b) (4) appears to mitigate any risk of carryover of impurities through the manufacturing process of fezolinetant drug substance.
- Based upon revised control strategy for (b) (4) and in accordance with ICH Q11 and Q11 Q&A guidances, the designation of (b) (4) as a regulatory starting material is reasonable. The final determination on the acceptability of the regulatory starting materials for the commercial manufacturing of fezolinetant drug substance will be made during the review of your proposed NDA.

September 18, 2020: The Agency provided Written Responses Only to the Astellas submission, dated July 7, 2020, containing a Type C meeting request to obtain the Agency's feedback and agreement on (b) (4) in phase 3 Trials 0301 and 0302. The Agency's Written Responses Only conveyed, but not limited to, the following:

- (b) (4)
- You may propose as your primary analysis of clinical meaningfulness, meaningful within-patient change: change from the patients' perspective using your anchor-based measure in the ongoing phase 3 clinical trials, the patient reported outcome instrument Patient Global Impression of Change for Vasomotor Symptoms (PGIC-VMS) in lieu of the between-group determination that the reduction of the frequency of VMS in the fezolinetant treatment group exceeds that of placebo by the clinical meaningful threshold reduction of 2 moderate to severe hot flushes per day or 14 per week.

- PGI-C VMS has limitations for this use including, though not necessarily limited to, the following:

    1. The PGI-C VMS does not measure the concept of interest in the VMS diary (i.e., hot flash frequency). The anchor's concept should be the same as the specific concept being assessed by the clinical outcome assessment (COA) endpoint of interest.
    2. The PGI-C VMS scale is susceptible to recall error; therefore, it is not a reliable measure for change from baseline data.
- We do not object to a pooled analysis for the evaluation of clinically meaningful within-patient change from the phase 3 trials should you choose to proceed with assessment of the clinical meaningfulness of the frequency in the primary analyses based solely on within-patient change external anchors. We recommend that you blindly pool a subset (e.g., 100) of participating women in each trial to establish a meaningful change threshold(s), or a range of threshold(s), and then confirm using blinded, pooled data from remaining participating women in each study.
- Submit the proposed meaningful change threshold(s) (e.g., a range of score changes) to the IND prior to data unblinding.
- We recommend that you utilize a blinded, independent (external) statistician to conduct the analysis in order to maintain the integrity of the trial conduct prior to unblinding."

July 28, 2021: The Agency provided Written Responses Only to the Astellas submission, dated May 14, 2021, containing a Type C meeting request to obtain guidance on efficacy, safety, and dataset strategies for fezolinetant. The Agency's Written Responses Only conveyed to Astellas, but not limited to, the following:

- Based on reported results in your pre-meeting package, from evaluation of efficacy of fezolinetant vs placebo in the first 12 weeks of treatment in 52-weeks Trials 2603-CL-0301 (henceforth referred to as Trial 0301) and 2693-CL-0302 (henceforth referred to as Trial 0302):
    - The fezolinetant 30 mg dosage strength group and the fezolinetant 45 mg dosage strength group appear to demonstrate statistically significant improvement in the frequency and severity of moderate to severe vasomotor symptoms when compared to placebo groups at Weeks 4 and 12.
    - The statistically significant decrease in frequency for the fezolinetant 45 mg dosage strength group exceeds the Agency's recommended clinical meaningful frequency threshold reduction of 2 per day above placebo at Weeks 4 and 12 in both Trials 0301 and 0302.
    - The statistically significant decrease in frequency for the fezolinetant 30 mg dosage strength group failed to meet the clinical meaningful frequency threshold reduction of 2 per day above placebo at Week 4 in either Trial

0301 or 0302 and at Week 12 in Trial 0302.
    - The statistically significant decrease in frequency for the fezolinetant 30 mg dosage strength group exceeds the clinical meaningful frequency threshold reduction of 2 per day above placebo at Week 12 in Trial 0301.
- We do not agree that (b) (4)
    - The Patient Global Impression of Change for Vasomotor Symptoms (PGI-C VMS) has limitations for the determination of clinical meaningfulness including, though not necessarily limited to, the following:
        - The PGI-C VMS does not measure the concept of interest in the VMS diary (i.e., hot flush frequency). The anchor's concept should be the same as the specific concept being assessed by the clinical outcome assessment COA) endpoint of interest.
        - The PGI-C VMS scale is susceptible to recall error. Therefore, it is not a reliable measure for change from baseline data and interpretation of data.
    - Using PGI-C VMS may be problematic. A patient global impression of severity (PGIS) scale is generally the preferred anchor scale over the patient global impression of change scale. That said, we acknowledge there is no perfect anchor scale.
    - Clarify whether the PGI-C VMS was administered in all subjects in Trials 0301 and 0302 at both time points of primary endpoint collections (Weeks 4 and 12).
    - Confirm the number of subjects who have completed the PGI-C VMS in Trials 0301 and 0302 at both primary time points (Weeks 4 and 12).
    - Provide evidence to support that the "moderately better" response category represents a meaningful change in the PGI-C VMS.
    - Submit a revised Psychometric Analysis Plan (PAP) for review as soon as possible prior to your planned NDA submission. The revised PAP should contain detailed information showing how you derived the meaningful change threshold(s), or a range of thresholds for each trial.
    - For empirical cumulative distribution function (eCDF) and probability density function (PDF) curves (e.g., figures A-2 and A-3 in your psychometric analysis plan), include the curve for each anchor category at Week 4 and Week 12.
- Your NDA application in support of an indication for the treatment of moderate to severe VMS due to menopause, if filed, will be based on the separate analyses of efficacy data for each of the two independent, phase 3, 12-week, placebo-controlled confirmatory clinical trials. Provide this data separately. You may provide an Integrated Summary of Efficacy (ISE)/Summary of Clinical Efficacy (SCE) as

supportive documentation.

- Provide efficacy data for each individual phase 3 trial (Trial 0301 and Trial 0302) for the agreed upon co-primary efficacy endpoints as follows:

    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.

- Provide the weekly (Week 1 through Week 12) assessment of the mean change from baseline in frequency and severity of moderate to severe vasomotor symptoms for the treatment and placebo groups for the two phase 3 trials. Include mean change difference between the treatment group and placebo and the statistical significance.
- Submit the pooled safety analysis for POP2 from the three 52-week phase 3 Trials 0301, 0302 and 2693-CL-0304 (henceforth referred to as 0304) in postmenopausal women with VMS associated with menopause conducted in North America and Europe.
- We agree with the proposed approach to present the Integrated Summary of Safety (ISS) text portion in Module 2.7.4 and provide the associated ISS Tables, Listings, Figures (TLF) s in Module 5.3.5.3?
- We agree with the proposed selection of medical events for which narratives will be provided.
- Your proposed approach for the datasets and TLFs of clinical study reports 2693-CL-0301 and 2693-CL-0302 appears acceptable.
- Your proposed approach for submission of datasets in a future NDA application as specified in the SDSP appears acceptable."

January 28, 2022: A pre-NDA teleconference was conducted to discuss the fezolinetant completed nonclinical and clinical studies and other general information for the submission of a new drug application for fezolinetant tablets with a submission target as early as June 2022.

February 24, 2022: The FDA pre-NDA Meeting Minutes conveyed, but not limited to, the following:

- The completed nonclinical studies appear adequate to submit the NDA.
- The nonclinical data appear to be supportive of the mechanism of action.

- The human absorption, metabolism, and excretion Study ESN364_CPK_103 showed that the renal clearance of ES259564, i.e., the major metabolite of fezolinetant, had a mean renal clearance of 11.3 L/h, which is beyond the normal glomerular filtration rate and may be indicative of renal secretion. In Study ESN364_CPK_103, the exposure for the metabolite was 2-fold higher than the parent and the Agency is concerned that the accumulation of the metabolite may have a clinical impact.
- FDA requested that Astellas conduct studies to test whether metabolite ES259564 is a substrate of OATP1B3, and P-glycoprotein, prior to the NDA submission.

  Meeting Discussion:
  Astellas explained that they have profiled the metabolite ES259564, which has been shown to be pharmacologically and toxicologically inactive, and referenced selected results from the meeting package:

  1. "From a pharmacology perspective, the metabolite has approximately 20-fold lower potency on the target NK3 receptor compared to the parent fezolinetant, contributing to approximately 5% of the overall pharmacologic activity, which is substantially less than 50%."
  2. "From a toxicology perspective, the metabolite has shown no off-target activities. The 39-week toxicology study in female primates (cynomolgus monkey) provided a 26-fold higher AUC of the metabolite compared to the AUC in human at a dose of 45 mg. These data indicate the metabolite does not adversely impact the safety profile of fezolinetant."
  3. "Therefore, the drug-drug interaction (DDI) of the metabolite due to transporters is unlikely to result in clinically meaningful alteration of efficacy or safety in vivo, which is consistent with the most recent regulatory guidance."
  4. Astellas asked if the additional DDI studies could be submitted in the NDA at the time of the 120-day Safety Update. FDA stated that the NDA should be complete upon submission.
  5. Astellas intends to include data from a dedicated renal impairment study in the NDA and asked the FDA if this would address the Agency's concerns.
- The projected exposures in completed/ongoing clinical trials conducted during your development program, as represented in your meeting briefing document [1100 and 1140 participants with overall exposure to 45 mg and 30 mg, respectively of fezolinetant once daily, 920 and 900 participants exposed to 45 mg and 30 mg, respectively of fezolinetant once daily for 24 weeks (6 months) and approximately 570 and 560 participants exposed to 45 mg and 30 mg, respectively of fezolinetant once daily for 52 weeks (12 months)], appears to meet the ICH E1 criteria regarding participant exposure to assess clinical safety for drugs intended for chronic use in the treatment of non-life-threatening conditions.

- Your proposed approach including the assessment of hepatic safety and the presentations/displays appears reasonable at a high level.
- We agree with your proposed areas of medical focus which include, are not limited to:

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

    Address in your NDA application, as additional areas of medical focus. 1) glucose impairment, and 2) creatinine phosphokinase (CPK) increase.
- [redacted] (b) (4)
- Provide the following information in your NDA application:

    1. Define.xml should be compatible to the current version of Internet Explorer (Version 11.0 or later).
    2. Clearly list which versions of CDISC ADaM (and ADaMIG), and SDTM (and SDTMIG), and define.xml are used for the study data in your analysis data reviewer's guide and study data reviewer's guide.
- Provide detailed information regarding the changes made in the to-be-marketed compared to the clinical phase 3 formulations.

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

March 22, 2022: NOTIFICATION OF INTENT TO SUBMIT AN APPLICATION WITH A RARE PEDIATRIC DISEASE PRIORITY REVIEW VOUCHER received from Astellas indicating:

"In accordance with section 529(b)(2) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), [redacted] (b) (4) transferred the ownership of a rare pediatric disease priority review voucher (PRV) with tracking number [redacted] (b) (4) to Astellas US, LLC (Astellas) on 20 April 2021."

"In accordance with section 529(b)(4)(B)(i) of FD&C Act, Astellas hereby informs the Agency that we intend to redeem [redacted] (b) (4) for fezolinetant NDA 216578, with

the estimated NDA submission date of 22 June 2022."

June 22, 2022: NDA 216578 submitted to FDA requesting approval of 45 mg fezolinetant for the treatment of moderate to severe vasomotor symptoms associated with menopause.

July 21, 2022: Astellas responds to the July 19, 2022 Agency's IR to submit Word copies of the Prescribing Information (PI) and Patient Information (PPI labeling. Word copies of the PI and PPI are provided.

July 28, 2022: Astellas responds to the July 26, 2022 Agency's IR and resubmits all the proposed carton and container labels ensuring the proposed images contain all the proposed labeling information and reflect the intend-to-market labels and labeling.

August 11, 2022: Astellas responds to the FDA's Information Request letter, dated 27 July 2022, for Information on the Drug Substance, Drug Product, and Facility section(s) of the NDA. In summary:

- The (b) (4) used as the primary packaging for fezolinetant drug substance is compliant with 21 CFR (b) (4).
- The analytical method transfer reports from (b) (4) (validation site) to Astellas Pharma Tech Co., Ltd., (b) (4) (currently Astellas Pharma Inc., (b) (4), product release test site) are provided.
- The results of the (b) (4) identified in fezolinetant tablets are summarized.
- Astellas confirms that all registration stability data listed in [Module 3.2.P.8] conform to the proposed product specification listed in [Module 3.2.P.5.1], and commits to evaluate the existing and subsequent stability results based on the agreed product specification at the time of approval.
- Astellas does not intend to market the blister package; it will be made available for sample use only and therefore is not listed in section 16 of the label.
- Certificate of compliances (COCs) for bottle and closure are provided.

August 16, 2022: Astellas responds to the August 4, 2022 Agency's IR, updated August 8, 2022, and provides:

1. The location of the line listing(s) in the NDA application for endometrial biopsy specimen diagnosis, as determined by each individual pathologist 1, 2, and 3 and the final consensus diagnosis, for each non-hysterectomized participant in phase 3 clinical Trials 2693-CL-0301, 2693-CL-0302, and 2693-CL-0304.
2. All data for women with 40 weeks total of exposure derived from pooled Trials 0301,

0302 and 0304, all data for women with 52 weeks total of exposure from pooled Trials 0301, 0302 and 0304 in a single pooled analysis (not separated).

August 17, 2022: FILING COMMUNICATION – NO FILING REVIEW ISSUES IDENTIFIED letter to applicant stating, but not limited to:

"We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is Priority. Therefore, the user fee goal date is February 22, 2023. This application is also subject to the provisions of "the Program" under the Prescription Drug User Fee Act (PDUFA) VI."

"If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by November 22, 2022. In addition, the planned date for our internal mid-cycle review meeting is September 22, 2022. We are not currently planning to hold an advisory committee meeting to discuss this application."

"At this time, we are notifying you that, we have not identified any potential review issues. Note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

Reviewer's Comments:
The goals of "the Program" are to increase the efficiency and effectiveness of the first review cycle and decrease the number of review cycles necessary for approval so that patients have timely access to safe, effective, and high quality new drugs and biologics.

August 19, 2022: Astellas provides response to an August 15, 2022 Agency IR, and provides the requested related program and data files for the Dose Response Analysis Report based on the phase 2b Trial ESN364_HF_205. Astellas confirms that responses to questions 1 through 4 in the August 15, 2022 IR would be subsequently submitted by September 5, 2022, as requested.

August 24, 2022: Astellas provides response to an August 23, 2022 Agency IR, and provides the requested narrative for participant # (b) (6) in Trial 2693-CL-0301. This participant was screened on two separate occasions due to COVID 19 pause in enrollment activities. She returned and was re-screened and randomized under # (b) (6). Location of narrative was identified.

August 26, 2022: Astellas provides response to an August 10, 2022 Agency IR, and provides the

requested programming codes used for the Summary of Clinical Safety/Integrated Summary of Safety (SCS/ISS) analyses with clear variable definitions. Astellas also submits updated Analysis Data Reviewer's Guides (ADRGs) for 12 and 52 week SCS/ISS (not requested).

August 29, 2022: Astellas provides response to an August 24, 2022 Agency IR, and provides the requested tumor.xpt files for the carcinogenicity studies in the rat (Study 8375967) and transgenic mouse (Study 8375970). These tumor.xpt files were also submitted to fezolinetant IND 130277.

August 30, 2022: Astellas provides response to an August 24, 2022 Agency IR seeking clarification with respect to Trial 2693-PK-0011. Astellas specifically responded that the Agency's inability to verify the output from "run112d_mod.txt" and dataset "hf-phase3-12wk-22jul2021-total.csv" for exposure-response analysis for VMS severity in Table 12 was due to the Agency's evaluation of the model using NONMEM Version 7.5.0, a different version of the NONMEM software.

August 31, 2022: Astellas provides response to an August 25, 2022 Agency IR, and provides tables showing treatment-emergent adverse events (TEAEs) which occurred at a rate greater than or equal to 1% in the exposure arms by system organ class (SOC) and preferred term (PT) for Population 2 (52 weeks) by treatment arm, and a separate similar table for all TEAEs occurring at a rate greater than or equal to 2% in the exposure arms by SOC and preferred term for Population 2 (52 weeks) by treatment arm, and exposure-adjusted incidence rate (EAIR) along with statistical and confidence interval testing ($p<.05$) for all TEAEs.

September 2, 2022: Astellas provides response to an August 15, 2022 Agency IR requested by Clinical Pharmacology, specifically Questions 1 through 4. See Section 4.5 Clinical Pharmacology in this review.

September 6, 2022: Astellas provides response to an August 24, 2022 Agency IR, and provides the requested information related to the Patient Global Impression of Change for Vasomotor Symptoms (PGI-C VMS).

September 6, 2022: Astellas provides response to an September 1, 2022 Agency IR, aand provides the requested tables including all TEAEs with exposure-adjusted incidence rate (EAIR), treatment difference in EAIR, 95% CI and p-values and including the SOC of neoplasms benign, malignant and unspecified (incl cysts and polyps). These tables also included all TEAEs without applying any thresholds to select (PTs), e.g., >1% or >2%.

September 7, 2022: Astellas provides response to the September 6, 2022 Agency IR and identifies the locations of the audit certificates in the NDA application.

September 29, 2022: Astellas provides a response to the September 27, 2022 Agency IR, and provides the requested dataset and SAS code used to create Tables 12 and 13 in the study report for Trial 2693-CL-0007.

October 3, 2022: Astellas provides a response to the Agency September 27, 2022 IR, Astellas confirms that fezolinetant tablets contain no sodium, potassium, or phosphorus as constituents of active and inactive drug ingredients.

October 3, 2022: Astellas provides response to an September 27, 2022 Agency IR, and provides the 2693-ME-004 Addendum 1 to the Validation Report, Validation of a UHPLC/MS/MS method for the determination of ESN364 and its metabolite ES259564 in lithium heparinized human plasma. The requested datasets and SAS codes supporting the September 2, 2022 response are also provided.

October 7, 2022: Astellas submits the 120-Day Safety Update Report (Sequence # 0022) to the NDA.

October 10, 2022: Astellas provides a response to the October 3, 2022 Agency IR, and provides the requested updates to CMC Modules 3.2.P.2, 3.2.P.3, and 3.2.P.4.

October 10, 2022: Astellas provides a response to the September 12, 2022 Agency IR, and provides the requested spreadsheets with fish toxicity data.

October 12, 2022: Astellas responds to an Agency October 5, 2022 IR, and provides the requested updated figures and tables using the simplified severity model described in their August 31, 2022 response. Astellas concludes that the reported results are consistent with the results originally reported for Trial 2693-PK-0011.

October 12, 2022: Astellas provides response to an Agency October 11, 2022 IR, and provides the requested Informed Consent Forms utilized in Trials 0301, 0302, and 0304.

October 13, 2022: Astellas provides response to an Agency October 6, 2022 IR, and provides the tabular listings of adverse events arranged by severity and treatment for POP2 52-week participants who also took concomitant weak, moderate, or strong CYP1A2 inhibitors including 1) 42 participants (1.9%) with mild concomitant CYP1A2 inhibitor; 2) 4 participants (0.2%) with moderate concomitant CYP1A2 inhibitor; and 34 (1.5%) with strong concomitant inhibitor.

October 13, 2022: Astellas provides response to an Agency October 6, 20222 IR, and provides a single physiological-based pharmacokinetic analysis (PBPK) model for Trial 2693-PK-0014,

including a single intrinsic clearance value for CYP1A2. The submission includes 1) the model predictive performance for the DDI effect with the strong CYP1A2 inhibitor fluvoxamine on the PK of fezolinetant in nonsmoking women [Trial 2693-CL-0006] using a single PBPK model of fezolinetant, and 2) an update to the application's predictions of Cmax and AUC ratios of fezolinetant in the presence of mexiletine (moderate CYP1A2 inhibitor) or cimetidine (weak CYP1A2 inhibitor) using a single PBPK model of fezolinetant.

October 17, 2022: Astellas provides response to an Agency October 11, 2022 IR, and provides the exposure-adjusted incidence rate (EAIR) for serious adverse events for POP2 52-weeks, safety analysis set.

October 19, 2022: Astellas provides response to an Agency September 21, 2022 IR and subsequent October 18, 2022 IR, and provides the datasets and program used to generate Figure 2 in a previous September 2, 2022 IR response regarding trial participants who used weak concomitant CYP1A2 inhibitors in POP2 52-week.

October 20, 2022: Astellas submits an undated 120-Day Safety Update Report (Sequence # 0033) to the NDA.

October 20, 2022: Astellas provides response to an Agency October 17, 2022 IR, and provides the updates to CMC Modules 3.2.P.3 and 3.2.P.4 including (b) (4) added to the list of in process control (IPC).

November 1, 2022: Astellas provides response to an Agency October 27, 2022 IR regarding clinical pharmacology considerations, and provides 1) the fraction of dose metabolized, and the percentages of dose excreted in feces as unchanged parent drug and as metabolite ES259564, 2) the calculate steady-state concentration (Css, mean ± SD), accumulation ratio (Rac), and terminal half-life (T1/2, mean ± SD) after 45 mg once daily dosing in the intended population, and 3) the requested dataset and program related to calculation of the above parameters.

November 2, 2022: Astellas receives the Agency's Mid-Cycle Communication letter with a record of the teleconference held on October 5, 2022.

November 7, 2022: Astellas provides response to an Agency November 4, 2022 IR, and provides a complete, formatted table is MS Word for all AEs ≥ 1% by treatment group for POP2 52-week which included n (%, EAIR)].

3.3. Foreign Regulatory Actions and Marketing History

TRADENAME (fezolinetant), a NK3 receptor antagonist, is a first in class new molecular entity (NME) product, which is not marketed in the US or internationally.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

Per the application, the three phase 3, 52-weeks, clinical trials were "conducted in accordance with the protocol and consensus ethical principles derived from international guidelines including the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and CIOMS International Ethical Guidelines
- Applicable ICH GCP Guidelines
- Applicable laws and regulations"

To ensure compliance with these procedures, and to assess the adequacy of quality control

procedures, Astellas undertook a good GCP independent audit program. Audit certificates are provided in the individual trial report for the following sites audited:

Trial 2693-CL-0301:

1. Site # 10001 - Hessam Aazami, MD, Hope Clinical Research, Canoga Park, CA; date of audit: September 9, 2019.
2. Site # 10104 - Michael Akpeke, MD, Cornerstone Research Institute, Altamonte Springs, FL; date of audit: February 3-4, 2020.
3. Site # 10066 - Hugo Ferrara, MD, Vital Pharma Research, Hialeah, FL; date of audit: February 11-12, 2020.
4. Site # 48003 - Janusz Tomaszewski, MD, Klinika Polozniczo-Ginekologic, Bialystok, Poland; date of audit: May 19, 2020 to June 23, 2020.
5. Site # 10117 - Romero Basso, Sandor Andres, MD, American Research Inst. Inc., Cutler Bay, FL; date of audit: May 25-26, 2021.

Trial 2693-CL-0302:

1. Site # 10084 - Gregory Guell, MD, Suncoast Research Group LLC, Miami, FL; date of audit: May 22-30, 2020.
2. Site # 10061 - Valerie Sorkin-Wells, MD, Precision Trials, Phoenix, AZ; date of audit: March 9-10, 2021.
3. Site # 10094 - Jose Rodriguez, MD, GCP Clinical Research LLC, Tampa, FL; date of audit: April 6-7, 2021.
4. Site # 15002 - Ginette Girard, MD, Diex Research Sherbrooke Inc., Quebec, Canada; date of audit: April 6 & 9, 2021.
5. Site # 48005 - Katarzyna Oronowicz, Twoja Przychodnia-Szczecinskie. Zachodniopomorskie, Poland; date of audit: March 17-18, 2021.

Trial 2693-CL-0304:

1. Site # 10039 - Hessam Aazami, MD, Hope Clinical Research, Canoga Park, CA; date of audit: September 9, 2019.
2. Site # 10162 - Kevin Fleishman, MD, Clinical Physiology Associates, Fort Meyers, FL; date of audit: October 12, 2020 and November 13, 2020.
3. Site # 10192 - Gilberto Jimenez, MD, Spotlight Research Center, Miami, FL; date of audit: October 19-31, 2020.
4. Site # 48016 - Szymanowski Krysztol MD, Examen Sp. zo.o Ul. Skorzewo, Poland; date of audit: November 4, 2020 and January 14, 2021.
5. Site # 15002 - Andre Frechette, MD, Diex Recherche Quebec Inc., Quebec City, Quebec, Canada; date of audit: September 7-8, 2021.
6. Site # 10053 - Robert Heller, MD, Bayview Research Group, Valley Village, CA; date of audit: November 16-17, 2021.

Reviewer's Comment:
No corrective action appears to have resulted from these internal audits.

On August 4, 2022, the Agency's Office of Scientific Investigation (OSI), Division of Clinical Compliance Evaluation (DCCE) was requested to conducted the following inspections at the following clinical sites:

Trial 2693-CL-0301:

1. Site # 10117 - Romero Basso, MD and Sandor Andres, MD, American Research Institute, Inc., 18951 Southwest 106th Avenue, Suite B110, Cutler Bay, Florida 33157.
2. Site # 48013 - Krzysztol Wilk, MD, NZOZ Sanas, Siemianowicka 5a, Katowice, Poland 40-301.

Trial 2593-CL-0302;

3. Site # 10084 - Gregory Guell, MD, Suncoast Research Group LLC, 2128 West Flagler Street, 1st Floor, Miami, FL 33135.
4. Site # 48005 - Katarzyna Oronowicz, MD, Twoja Przychednia – Slowackiego 19, Szczecin, Zachodniopomorskie, Poland 71-434.

Trial 2693-CL-0304;

5. Site # 10053 - Robert J. Heller, MD, Bayview Research Group, Suite 404, 12626 Riverside Drive, Valley Village, California 91670.
6. Site # 10192 - Gilberto Jimenez, MD, Spotlight Research Center LLC, 9570SW 107th Ave., Suite 201, Miami, Florida 33176. This site also participated in Trial 2693-CL-0301.
7. Site # 15002 - Andre Frechette, MD, DIEX Research Quebec, 205 Rue Montmagny, Suite 103, Quebec City, Quebec, Canada G1N4V3. This site also participated in Trial 2693-CL-0301.

Reviewer's Comment:
On November 13, 2022, OSI/DCCE provided the following preliminary information via email communication:

1. Site # 10053, Robert J. Heller, MD, Valley Village, CA: Inspection completed, official report from the field received, preliminary findings = NAI.

2. Site # 10117, Romero Basso, MD and Sandor Andres, MD, Cutler Bay, FL: Inspection completed, official report from the field received, preliminary findings = NAI.
3. Site # 15002 - Andre Frechette, MD, Quebec City, Quebec, Canada: Inspection completed, official report from the field pending, preliminary findings = NAI.
4. Site # 10084 - Gregory Guell, MD, Miami, FL: Inspection completed, official report from the field received, preliminary findings = VAI. Per the preliminary information provided, "There does not seem to be anything in the VAI to affect data integrity – the primary endpoint is verifiable, however, the VAI is related to poor record keeping (AEs not dated properly, out of range labs not reviewed properly, and one concomitant medication not reported).
5. Three inspection are ongoing: Site # 48013 - Krzysztol Wilk, MD, Poland; Site # 48005 - Katarzyna Oronowicz, MD, Poland; and Site # 10192 - Gilberto Jimenez, MD, Miami, FL.

These preliminary findings do not raise concerns for NDA 216578.

At the time of archiving of this review, the final DSI report is pending.

4.2. Product Quality

ESN364 (fezolinetant) tablets , 45 mg, are round, light red, immediate release film-coated tablets. Fezolinetant has a molecular formula of C16H15FN6OS, and a chemical name as follows: (4-Fluorophenyl)[(8R)-8-methyl-3-(3-methyl-1,2,4-thiadiazol-5-yl)-5,6-dihydro[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl]methanone.

Fezolinetant is manufactured (b) (4) See Figure 1 in Module 2 Common Technical Document Summaries, Submodule 2.3.S.2 in the NDA application.

(b) (4)

Fezolinetant tablets are packaged in high-density polyethylene (HDPE) bottles with silica (b) (4) desiccant, and child resistant (CR) (b) (4) closures lined with induction seals. Fezolinetant tablets are also packaged in aluminum/aluminum blisters.

Fezolinetant is classified as highly soluble because the highest single therapeutic dose of fezolinetant, 45 mg, is soluble in no more than 250 mL of aqueous media over the pH range of 1.2 – 6.8. Fezolinetant is also classified as highly permeable as determined in permeability studies using Caco-2 cell monolayers and stability study in the gastrointestinal tract. Per the NDA application, fezolinetant can be classified as a "Biopharmaceutics Classification System (BCS) Class 1 drug, based on the following guidance: "ICH Harmonized Guideline M9: Biopharmaceutics Classification System-Based Biowaivers" as it is considered to have both high aqueous solubility and high permeability.

In the clinical trials, two oral dosage forms of fezolinetant were used:

1) Immediate release hard gelatin capsules (size 0, white opaque cap/white opaque body) for oral administration in fezolinetant dosage strengths of 3 mg, 10 mg, 15 mg, 30 mg, 60 mg, 90 mg, 120 mg, and 180 mg. Common excipients (pregelatinized starch, croscarmellose sodium, silicon dioxide, and magnesium stearate) were used. These capsules were used in the phase 1 and 2 clinical trials.
2) Immediate release film-coated tablets were used in phase 3 clinical trials. A phase 3 formulation of fezolinetant tablets 15 mg, 30 mg, and 120 mg was developed. Common excipients (mannitol, hydroxypropyl cellulose, low-substituted hydroxypropyl cellulose, microcrystalline cellulose, magnesium stearate, and (b) (4)) were used. Tablet strengths of 30 mg and a combination of a 15 mg and a 30 mg tablet (total 45 mg) were used in phase 3 clinical trials.

The to-be-marketed tablet formulation was developed at the dosage strengths of 30 mg and 45 mg. This NDA application is only requesting approval of the 45 mg fezolinetant tablets for the indication sought.

(b) (4)

Reviewer's Comment:
Per the NDA application, the composition of the to-be-marketed tablet can be defined as proportionally similar between 30 mg and 45 mg fezolinetant dose strengths (b) (4) , based on the following FDA guidance, "Bioavailability Studies Submitted in NDAs or INDs -General Considerations, Guidance for Industry" and "Immediate-Release Solid Oral Dosage Forms: Scale-Up and Post-approval Changes: Chemistry, Manufacturing, and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation (SUPAC-IR)".

On November 21, 2022, the Office of Pharmaceutical Quality (OPQ) provided a draft Summary of Rationale for Recommendation as follows:

- The applicant of this 505(b)(1) new drug application has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug substance, fezolinetant and the drug product, Tradename (fezolinetant) Tablets, 45mg.
- The Office of Pharmaceutical Manufacturing Assessment has made the overall recommendation of adequate for the facilities involved in this application.
- The CMC recommended changes to the labeling have been communicated to the Clinical Review Team and is pending the successful labeling negotiations with the applicant.
- Based on the review of the applicant's environmental assessment report, the environmental assessment review team has concluded that no significant adverse environmental impacts are expected from the approval of this NDA.

"Therefore, this NDA is recommended for approval from the OPQ perspective the drug product expiration dating period of 30 months pending successful labeling negotiations."

4.3. Clinical Microbiology

Microbial quality of the fezolinetant drug substance was evaluated during development and stability studies. Microbiological limits specified in USP (United States Pharmacopeia) are routinely tested for mannitol, microcrystalline cellulose and magnesium stearate, which are used for the manufacturing of the fezolinetant drug product.

During the fezolinetant manufacturing process, (b) (4)

(b) (4)

With respect to the manufacturing of fezolinetant tablets, per the application, procedures are in place for cleaning of the manufacturing equipment and routine environmental microbiological monitoring.

The microbial limits results of nine (9) batches of fezolinetant tablets (to-be-marketed formulation) at release met the acceptance criteria for microbiological quality in compendial methods USP <61> and <62>. Likewise, the primary stability studies also met the acceptance criteria for microbiological quality in compendial methods USP <61> and <62>.

> Reviewer's Comment:
> Based on the reported results, the risk of microbiological quality of fezolinetant tablets is low. However, Astellas notes that only limited manufacturing experiences were in place during phase 3 development, and that the microbiological quality of fezolinetant tablets will continue to be monitored by including microbial limits in the specification for future manufactured batches.
>
> See the Clinical Microbiology Review for additional comments and recommendations. At the time of archiving of this review, the Clinical Microbiology review is pending.

4.4. Nonclinical Pharmacology/Toxicology

Rats and cynomolgus monkeys were selected as the nonclinical safety species based on the following:

- Fezolinetant has a similar affinity for hNK3 and the rhesus monkey NK3 receptor orthologs (Ki values for hNK3: 19.9 to 22.1 nmol/L; rhesus monkey NK3: 26.9 to 34.7 nmol/L), and lesser potency for the rat NK3 receptor ortholog (Ki value for rat NK3: 183 to 379 nmol/L).
- The major fezolinetant metabolite in rats and cynomolgus monkeys is ES259564, also the major metabolite in humans.
- The cynomolgus monkey was selected as the relevant nonrodent species because nonhuman primates are anatomically and functionally similar to humans in the reproductive system, which is known to be affected by LH change.

Nonclinical safety of fezolinetant was evaluated in the following studies, administered orally:

1. Repeated-dose toxicity studies in rats and cynomolgus monkeys [4-, 13- and 26-week (female animals only) administrations in rats; 5-, 13- and 39-week (female animals only) administrations in cynomolgus monkeys].
2. Genotoxicity studies using bacteria, cultured human lymphocytes and rats.
3. Carcinogenicity studies [104-week administration in rats (female animals only), 26-week administration in mice (female and male animals)].
4. Reproductive and developmental toxicity studies in rats and rabbits.
5. Other toxicity studies (a mechanistic study in rats, drug dependency studies in rats, genotoxicity studies of the major metabolite, a repeated-dose toxicity study of an impurity in cynomolgus monkeys, and a phototoxicity study using cultured mammalian cells).

104-Week Carcinogenicity Study:

Per the application, fezolinetant had no effect on survival rate in the 104-week carcinogenicity study utilizing oral doses of 10, 30 and 100 mg/kg per day. An increased incidence of follicular adenomas were noted in the thyroid at 100 mg/kg per day (statistically significant trend at 5% level [$P \leq 0.05$]). Thyroid follicular adenoma were considered to be related to thyroid follicular cell hypertrophy observed in the same dose range as hepatocyte hypertrophy in oral repeated-dose toxicity studies in rats up to 26 weeks.

> Reviewer's Comment:
> Thyroid follicular cell hypertrophy is considered to be an adaptive change correlated with hepatic enzyme induction. Astellas concluded that thyroid follicular adenoma is specific to rodents and not relevant to humans.

Additional findings were reported in the 104-week carcinogenicity study as follows:

- decreased incidence of carcinoma in the mammary gland at ≥ 10 mg/kg per day;
- decreased incidence of pars distalis adenoma in the pituitary at 100 mg/kg per day;
- liver, uterus, mammary gland, ovary, cervix and adrenal nonneoplastic findings including:
    - centrilobular hepatocyte hypertrophy at 100 mg/kg per day;
    - increased incidence of atrophy in the uterus at ≥ 30 mg/kg per day;
    - decreased incidence of hyperplasia in the mammary gland at ≥ 10 mg/kg per day;
    - atrophy in the ovary at ≥ 10 mg/kg per day;
    - squamous metaplasia in the cervix at ≥ 10 mg/kg per day; and
    - cystic degeneration in the adrenal cortex at ≥ 10 mg/kg per day.

Reviewer's Comment:
Per the NDA application, the decreased incidences of neoplastic and the nonneoplastic findings in female reproductive organs were considered to be associated with pharmacological effects of fezolinetant. At 30 mg/kg per day, the AUC_{24} of fezolinetant at week 26 was 75-fold the human AUC_{24} at the maximum recommended human dose (MRHD). At 30 mg/kg per day, the AUC_{24} of ES259564 was 10-fold the human AUCinf at the MRHD.

Per the Pharmacology/Toxicology Review of the 104-Week Carcinogenicity Study, dated October 28, 2022, "There was a statistically significant dose response relationship in tumor incidences for benign follicular cell adenomas in the thyroid with increased ESN364 dose across the vehicle control and the treated groups of female rats (trend; p-value = 0.0094, which is < 0.01 for common tumors). No pairwise significance was identified for this tumor. Since benign thyroid follicular cell adenoma was found to be statistically significant by trend analysis only, it is therefore considered a negative finding. Additionally, there was no statistically significant ESN364-related change in tumor incidence for the combination of benign follicular cell adenomas and malignant follicular cell carcinomas by either trend (p=0.0299, > 0.01 for common tumor) or pairwise analysis.

The Division considers the rat study an adequate assessment of carcinogenic potential because the high dose of ESN364 was based on mortality at 300 mg/kg/day and AUC exposure > 25-fold the clinical exposure."

The Executive Carcinogenicity Assessment Committee (CAC) Final Study Minutes, dated October 27, 2022, state "The Committee concluded that the 2-year carcinogenicity study in Sprague Dawley rat was adequate and negative for drug-related neoplasms."

<u>26-Week Carcinogenicity Study:</u>
Per the NDA application, fezolinetant did not affect survival rate and induce neoplasms in the 26-week carcinogenicity study (oral doses of 50, 150 and 450 mg/kg per day) in rasH2 [001178-T (hemizygous), CByB6F1-Tg (HRAS)2Jic] mice (Tg mice). Nonneoplastic findings occurred in the liver, ovary and vagina including:

- Increased vacuolation in the liver of males at 450 mg/kg per day and females at ≥ 150 mg/kg per day.
- Centrilobular hepatocellular hypertrophy in both sexes at 450 mg/kg per day.
- Decreased numbers of corpora lutea in the ovary and an increased incidence and/or severity of mucosal cornification in the vagina at 450 mg/kg per day.

Reviewer's Comment:
Per the NDA application, at 450 mg/kg per day, the AUC_{24} of fezolinetant at week 26 was 91-fold (350 000 ng·h/mL) in males and 47-fold in females the human AUC_{24} at the MRHD. At 450 mg/kg per day, the AUC_{24} of ES259564 were 130-fold (334 000 ng·h/mL) in males and 142-fold in females the human AUCinf at the MRHD.

Per the Pharmacology/Toxicology Review of the 26-Week Carcinogenicity Study, dated October 28, 2022, "There were no statistically significant neoplastic findings. Non-neoplastic lesions were observed in the liver, ovary, and vagina in MD and HD females. There were no tumor types with a statistically significant dose response relationship in tumor incidences with increased ESN364. There were also no tumor types with a statistically significant increase in tumor incidences in ESN364 treated groups by the pairwise comparison test, when compared to the vehicle control group in either male or female mice."

The Executive CAC Final Study Minutes, dated October 27, 2022, state "The Committee concluded that the 26-week carcinogenicity study in Tg.rasH2 mouse was adequate and negative for drug-related neoplasms."

13-Week Oral Repeated-Dose Toxicity Study in Female Rats:
A 13-week oral repeated-dose toxicity study was conducted utilizing doses of 30, 100, and 200 mg/kg per day in female rats. Increased liver weight and centrilobular hepatocellular hypertrophy was observed at ≥ 100 mg/kg per day. At 200 mg/kg per day, increased alkaline phosphatase (ALP) levels, increased thyroid weight and thyroid follicular cell hypertrophy were observed. The following findings were considered as pharmacological action-related findings: decreased ovary weight and abnormal estrus cycle in the uterus at 200 mg/kg per day.

Reviewer's Comment:
In this 13-week oral repeated-dose toxicity study, the histopathological changes were associated with increased ALP at 200 mg/kg per day (148-fold the human AUC_{24} at the MRHD), but other biomarkers of liver injury, such as ALT and total bilirubin elevation, were reported as "not significantly different from those in control group." These changes in rats were not observed in cynomolgus monkeys toxicity studies. Per Astellas, "Hepatic enzyme induction in rodents is a well-known adaptive change observed in many nonclinical toxicity studies with various compounds." Astellas concludes that "increased liver weight and centrilobular hepatocellular hypertrophy only in rats represent a rodent specific adaptive effect and, as such, suggests no safety risk to patients."

26-Week Oral Repeated -Dose Toxicity Study in Female Rats:
A 26-week oral repeated-dose toxicity study was conducted in female rats. This study utilized doses of 30, 100 and 200 mg/kg per day. Findings reported include:

- Increased total cholesterol levels at ≥ 30 mg/kg per day.
- Increased liver weight and centrilobular hepatocellular hypertrophy at≥ 100 mg/kg per day.
- Increased ALP levels and increased thyroid (included parathyroid) weight at 200 mg/kg per day.
- Eosinophilic globules in the olfactory epithelium, infiltrates of macrophages in the alveolus of the lungs and hypertrophy of the follicular cells in the thyroid at ≥ 30 mg/kg per day.
- Atrophy of the uterus at ≥ 30 mg/kg per day, and mucification of the epithelium in the vagina at ≥ 30 mg/kg per day and in the cervix at ≥ 100 mg/kg per day.

  Reviewer's Comment:
  See the above Reviewer's Comment regarding centrilobular hepatocellular hypertrophy and increased ALP levels. Per the Pharmacology/Toxicology Review, dated October 28, 2022, "In the 26-week rat study (Study No 8331724), fezolinetant was administered orally by daily gavage to sexually mature rats at a dose of 0 (vehicle), 30, 100, or 200 mg/kg. No adverse effects on in-life parameters, clinical pathology, or microscopic changes were noted. Uterine atrophy and epithelial mucification of the vagina and cervix were attributed to pharmacological effects of fezolinetant, did not affect the general health of the animals, and were not adverse. The NOAEL was the high-dose of 200 mg/kg/day, with AUC24 = 569000 ng·h/mL (148X MRHD of 45 mg with AUC24 = 3855 ng·h/mL obtained from clinical Study 2693-PD-0010)."

  Per the Pharmacology/Toxicology Primary Review, dated November 22, 2022, "the 26-week repeat dose toxicity study: 1) increased liver weight at MD (100 mg/kg/day) and HD (200 mg/kg/day); 2) non-tumor findings include Liver: centrilobular hepatocellular hypertrophy at MD and HD (143X and 148X MRHD, respectively), attributed to a rodent specific adaptive effect."

13-Week Oral Repeated-Dose Toxicity Study in Female Cynomolgus Monkeys:
The 13-week oral repeated-dose toxicity study with a 4-week recovery period was conducted in female cynomolgus monkeys. This study utilized doses of 10, 25 and 50 mg/kg per day. Findings reported include:

- Two (2) of 6 animals showed a temporary marked decrease in platelet counts between days 52 and 86 at 50 mg/kg per day. In 1 animal, the decreased platelet counts and

anemia slowly recovered during the treatment period.
- Focally decreased cellularity of hematopoietic cells was present in the sternal bone marrow of 2 animals.
- Decrease in uterus weight, associated with stromal atrophy of the uterus and a lack of cyclic ovarian activity at ≥ 10 mg/kg per day, hemorrhages in the endometrial zona functionalis in the uterus at 10 mg/kg per day, decreased epithelium and increased mucous secretion of the cervix at ≥ 25 mg/kg per day, and hyalinization of the vascular wall of the myometrium and endometrium at 50 mg/kg.

39-Week Oral Repeated-Dose Toxicity Study in Female Cynomolgus Monkeys:
The 39-week oral repeated-dose toxicity study with a 4-week recovery period was conducted in female cynomolgus monkeys. This study utilized doses of 10, 25 and 40 mg/kg per day. This study reported that 1 animal at 40 mg/kg per day was sacrificed in a moribund condition on day 155 showing severe thrombocytopenia, anemia, leukopenia, a decreased myeloid and erythroid lineage including a reduced number of megakaryocytes in the bone marrow and, macroscopically, a large hematoma at the back. The microscopic findings in this moribund animal showed marked nephropathy in the kidneys, moderate hypocellularity in the bone marrow of the sternum, minimal to severe hemorrhages in the heart, ileum, stomach, gall bladder, skin and lymph nodes, and lymphoid atrophy in lymph nodes as well as in the spleen. The following was reported at the 40 mg/kg per day dose:

- Two (2) of 6 animals showed a mild to marked decrease in platelet counts.
- Thrombocytopenia in the 1 surviving animal recovery group showed reversibility by the end of the 4-week recovery period.
- Reduced body weight gain, body weight loss and low food consumption were observed at 40 mg/kg per day.

In addition, the following findings occurred at all doses: disturbed or interrupted menstrual cycles, ovarian inactivity (absence of corpora lutea and follicular cyst) and stromal atrophy of the uterus and decreased glands in the mammary gland.

Reviewer's Comment:
Per the NDA application, "the nephropathy observed in only 1 cynomolgus monkey is thought to be caused by deteriorated conditions rather than the direct effects of fezolinetant, and the risk of renal injury is considered low."

Per the Pharmacology/Toxicology Review of the 39-Week Oral Repeated-Dose Toxicity Study in Female Cynomolgus Monkeys, dated October 28, 2022, "In the 39-week monkey study (Study No 8331280), fezolinetant was administered orally by daily gavage to sexually mature female monkeys at a dose of 0, 10, 25, or 40 mg/kg. High doses of

fezolinetant resulted in weight loss and microscopic findings (hyperplasia of lymphocytes in lymph nodes, spleen, and lung, as well as perivascular inflammation in the kidney). Decreased platelet counts (at 40 mg/kg/day in the 39-week study) due to decreased production in bone marrow resulted in hemorrhage and regenerative anemia. This was recoverable. The NOAEL was the mid-dose of 25 mg/kg/day, with AUC24 = 166000 ng·h/mL (43X MRHD)."

Reproductive and Developmental Toxicity:
Per the NDA application, "fezolinetant (oral doses of 10, 30 and 100 mg/kg per day) had no effect on female fertility or early embryonic development up to 100 mg/kg per day in rats." "Fezolinetant did not show teratogenic potential in either rats or rabbits."

Reviewer's Comment:
Per the Pharmacology/Toxicology Primary and Secondary Reviews, dated November 22, 2022, "the risks to pregnancy and fetal development for this product is low" given the intended clinical population is postmenopausal women. "However, it could also be presumed that incorrect administration to a pregnant female could carry the risks of early pregnancy loss or delayed maturation of a male fetus. (b) (4) "

Other Toxicity Studies:
To evaluate the potential of fezolinetant to produce seizures, fezolinetant was orally (oral gavage) administered to 8 female Wistar Han rats, 15 weeks old, in Study 8306209, for 13 weeks (doses of 10, 30, 100 and 200 mg/kg per day); and evaluated by EEG data, EMG data and synchronized video recording used in support of EEG interpretation. In EEG analysis, no seizures were detected throughout the study. A single animal from the 200 mg/kg group was found dead on day 70. Necropsy revealed red fluid in the abdomen and clear fluid in the thorax, "suggesting that dosing error may be related to death."

Reviewer's Comment:
In this mechanistic study, clinical signs involved changes in muscle tone including twitching, intermittent tremors and rigid stance were observed, and these incidences increased dose-dependently. However, no seizures were detected throughout the study based on review of video-EEG records. Under the conditions of the study, there was no evidence that fezolinetant has a potential to cause seizure.

To investigate the potential to induce physical dependency in rats, fezolinetant was orally administered for 4 weeks (doses of 10, 30 and 100 mg/kg per day) to 6 male and 6 female Han rats, 7-8 weeks old, per group in Study 8416428. The control group received vehicle alone in the same way. An additional 6 males and 6 females were administered 150 mg/kg per day positive

control drug (codeine). Per the study report, oral administration of 10, 30 or 100 mg/kg per day fezolinetant for 28 days did not produce a withdrawal syndrome in male or female rats upon cessation of dosing. As anticipated, oral administration of 150 mg/kg per day codeine for 28 days, produced a marked withdrawal syndrome in the rat upon cessation of dosing.

> Reviewer's Comment:
> In this study, fezolinetant did not cause physical dependency in rats under the conditions of the study.

The potential to induce psychological dependency was also evaluated in male and female Lister Hooded rats with a lever-pressing behavior study (assessed by training rats to self-administer intravenous cocaine, and then substituting cocaine with fezolinetant) based on positive reinforcing effects. The control group or positive control group received vehicle or amphetamine (0.05 mg/kg per 0.2 mL) in the same way, respectively.

> Reviewer's Comment:
> Per the NDA application, "Intravenous self-administration of 0.25, 0.50, or 0.75 mg/kg per 0.2 mL fezolinetant did not result in a statistically significant difference in response patterns compared to the vehicle."
>
> Per the Pharmacology/Toxicology Primary Review, dated November 22, 2022, "The applicant conducted additional studies to investigate the potential for effects on seizure threshold and drug dependency. Fezolinetant was found to have no potential to induce seizures in a 13-week oral study in rats at doses up to 200 mg/kg/day (>100X MRHD) and did not induce physical dependency in a 4-week oral study in rats up to 100 mg/kg/day (108X MRHD)."
>
> On November 22, 2022, the Pharmacology/Toxicology Primary Review concludes, "Fezolinetant is a small molecule NK3 receptor antagonist which decreases the activity of KNDy neurons by antagonizing NKB/NK3 signaling with the outcomes of relief from VMS. The pharmacology, pharmacokinetics, and toxicology of fezolinetant were characterized in nonclinical studies to support this application for the treatment of moderate to severe VMS associated with menopause. Pharm/tox supports approval of this application."

4.5. Clinical Pharmacology

Fezolinetant was initially developed as immediate-release, hard gelatin capsules for oral administration of 3, 10, 15, 30, 60, 90, 120 and 180 mg strengths. This formulation was used in phase 1 and phase 2 clinical trials. For the phase 3 development program, including parallel

phase 1 trials, an immediate-release tablet formulation (15, 30 and 120 mg dose strengths) was developed for oral administration. The composition of the phase 3 tablet is proportionally similar among the dose strengths, of which the 15 mg and 30 mg strength tablets were used in the phase 3 trials. The 120 mg strength tablet was only used in the relative bioavailability Trial 2693-CL-0009. The phase 3 tablet formulation was also used in special population and drug-drug interaction studies.

The to-be-marketed tablet formulation at the dosage strengths of 30 mg and 45 mg was developed for commercial use. There were 2 minor adjustments in the formulation development of the to-be marketed tablets compared with the phase 3 tablets: 1) changes in (b) (4) tablet composition (b) (4), and 2) tablet color shade.

Relative Bioavailability Trial 2693-CL-0009:
Trial 2693-CL-0009 was a randomized, open-label, 2-period, 2-sequence, single dose crossover relative bioavailability trial in 16 healthy postmenopausal women who received a single oral dose of 120 mg fezolinetant as either a capsule (reference formulation) or tablet (test formulation) under fasted conditions, followed by the alternative formulation after a 4-day washout period. Pharmacokinetic samples were collected predose on day 1 of each period and at multiple time points postdose.

Results of the statistical assessment of relative bioavailability of fezolinetant for the tablet compared with capsule are presented in Table 5. Geometric LS means increased approximately 8% for AUCinf and AUClast, and approximately 23% for Cmax following tablet administration, relative to capsule administration.

Table 5 Trial 2693-CL-0009: Statistical Assessment of Relative Bioavailability of Fezolinetant (Pharmacokinetic Analysis Set)

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

Source: NDA 216578, Module 2.7 Clinical Summary, Submodule 2.7.1 Summary of Biopharmaceutics Studies and Analytical Methods, Table 10, page 14 of 69.
All randomized participants who took at least 1 dose of study drug for which concentration data were available to facilitate derivation of at least 1 primary pharmacokinetic parameter.
Assessment based on an analysis of variance performed on natural logarithmic-transformed parameters with formulation and period as fixed effects and participant as a random effect.
Definitions: CI = confidence interval; LS = least squares.

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

Reviewers' Comment:
In Table 5, the relative bioavailability of a single oral dose of 120 mg fezolinetant as a tablet was slightly higher than that reported for a single oral dose of 120 mg fezolinetant as a capsule (range in 90% CI for AUC and Cmax: 101 to 136). The 90% CI of AUC are contained in the bioequivalence criteria of 80-125%. However, the upper end of the CI for Cmax was above the bioequivalence criteria range.

See the Clinical Pharmacology Review, dated November 23, 2022, for a full description of Trial 2693-CL-0009.

Bioequivalence Trial 2693-CL-0010:
The bioequivalence between the to-be-marketed tablets (45 mg, the highest strength and the requested dose for approval in the NDA application) and the phase 3 tablets (15 mg and 30 mg strengths administered together) was investigated in dedicated bioequivalence Trial 2693-CL-0010. Trial 2693-CL-0010 was a randomized, open-label, 2-period, 2-sequence, single dose crossover trial in 22 healthy female participants. Both postmenopausal and premenopausal (with synchronized menstrual cycles) female participants were enrolled. Participants received a single oral dose of 45 mg fezolinetant to-be-marketed formulation (test formulation) or one 30 mg and one 15 mg fezolinetant phase 3 formulation (reference formulation) under fasting conditions on day 1 of each period. The 2 treatment periods were separated by a 5-day washout period. Pharmacokinetic samples were collected predose on day 1 of each period and at multiple time points postdose. The results of Trial 2693-CL-0010 are shown in Table 6.

Table 6 Trial 2693-CL-0010: Statistical Assessment of Bioequivalence for Fezolinetant (Pharmacokinetic Analysis Set)

Parameter	Treatment B		Treatment A		Geometric LS Mean Ratio† (%)	90% CI of Ratio†	Geometric Intra-participant %CV
	n	Geometric LS Mean	n	Geometric LS Mean			
AUC_{last} (h•ng/mL)	21‡	2950	22	3010	102.17	(96.53, 108.15)	10.7
AUC_{inf} (h•ng/mL)	14§	3720	14‡	3680	99.00	(92.45, 106.01)	9.3
C_{max} (ng/mL)	21‡	488	22	483	99.12	(85.54, 114.87)	28.3

Source: NDA 216578, Module 2.7 Clinical Summary, Submodule 2.7.1 Summary of Biopharmaceutics Studies and Analytical Methods, Table 11, page 16 of 69.
Definitions: A = One 45 mg fezolinetant to-be-marketed tablet (test formulation); B = 45 mg fezolinetant dose comprising one 30 mg and one 15 mg fezolinetant phase 3 tablet (reference formulation); CI = confidence interval;
CV = coefficient of variation; IP = investigational product; LS = least squares.
Assessment based on an analysis of variance performed on natural logarithmic-transformed parameters with period and treatment as fixed effects and participants as a random effect.

The pharmacokinetic analysis set comprised all randomized participants who received at least 1 dose of IP for which concentration data were available to facilitate derivation of at least 1 primary pharmacokinetic parameter.
† Ratios and confidence limits were transformed back to raw scale and values are expressed as percentages.
‡ One participant (treatment sequence AB) who received treatment B had concentrations that were below the level of quantification on all sample timepoints pre- and postdose for both fezolinetant and ES259564. This participant was excluded from the summary and parameter calculations.
§ AUCinf values from 7 participants were not reported and thus not included in the statistical assessment due to undefined elimination phase. AUClast including all evaluable participants, as well as AUCinf excluding these 7 participants.

Reviewer's Comment:
Table 6 shows that bioequivalence criteria were met between the test and reference formulations as geometric LS mean ratio and 90% CI of ratios were contained within the equivalence limits of 80% to 125% for Cmax, AUClast and AUCinf for fezolinetant.

See the Clinical Pharmacology Review, dated November 23, 2022, for a full description of Trial 2693-CL-0010.

Food Effect Trial 2693-CL-0012:

Trial 2603-CL-0012, a phase 1 trial conducted at 1 site in the US, was a randomized, open-label, 2-treatment period, 2-sequence (fasted and fed), single dose crossover study (washout of at least 5 days) in 16 healthy female participants (mean 33.6 years of age; range 22 to 46 years; 68.8% self-identified as Black/African American, 25.0% self-identified as White, 6.3% self-identified as Other) conducted to assess the effects of high-fat food on the systemic exposure of a single dose of 45 mg to-be-marketed formulation. Eligible participants were admitted to the clinical unit on day-1 of period 1 and were residential for periods 1 and 2 for a total of 10 days/9 nights. On day 1 of each treatment period (trial days 1 and 6), participants received a single oral dose of 45 mg fezolinetant followed by a 72-hour blood sampling period (fezolinetant in plasma: AUCinf, AUClast, Cmax and tmax). Participants remained awake, semirecumbent and avoided lying on either the left or right side for 4 hours postdose. Scheduled safety and tolerability assessments were conducted. Participants were discharged from the clinical unit on day 4 of period 2 (trial day 9) on the condition that all required assessments had been performed. Reported results of Trial 2693-CL-0012 are shown in Table 7.

Table 7 Trial 2593-CL-0012: Statistical Assessment of Food Effect on Fezolinetant (Pharmacokinetic Analysis Set)

	Fasted		Fed			
Parameter	n	Geometric LS Mean	n	Geometric LS Mean	Geometric LS Mean Ratio (%)†	90% CI of Ratio
AUC_{inf} (h•ng/mL)	9‡	2630	9‡	2540	96.57	(86.38, 107.96)
AUC_{last} (h•ng/mL)	16	2460	16	2350	95.53	(89.93, 101.49)
C_{max} (ng/mL)	16	428	16	328	76.70	(62.03, 94.83)

Source: NDA 216578, Trial 2693-CL-00012 Study Report, Table 13, page 31 of 35.
All randomized participants who received at least 1 dose of study drug for which concentration data were available to facilitate derivation of at least 1 primary pharmacokinetic parameter.
Assessment based on an analysis of variance performed on natural logarithmic-transformed parameters with period and food condition as fixed effects and participant as a random effect.
Definitions: CI = confidence interval = LS: least squares.
† Ratios and confidence limits were transformed back to raw scale and values are expressed as percentages.
‡ AUCinf values from 7 participants were not reported and thus not included in the statistical assessment due to undefined elimination phase.

Reviewer's Comment:
The statistical results in Table 7 show that the 90% CI for the ratio of population geometric means between fasted and fed is contained in the no-effect boundaries of 80% to 125% for AUCinf and AUClast, but not contained for Cmax. There was a decrease in geometric LS mean of Cmax (ratio of 76.70%; 90%CI [62.03, 94.83]) under fed conditions. A high-fat meal reduced fezolinetant Cmax by approximately 23%.

A high-fat meal also reduced the Cmax of the fezolinetant metabolite ES259564 (results not included in Table 7) by approximately 16%.

In addition, reported results for Trial 2693-CL-0012 showed that the median tmax of fezolinetant was delayed by 30 minutes and by 1 hour for the fezolinetant metabolite ES259564.

Astellas does not consider the decrease in Cmax and the delay in tmax "clinically relevant". All three of the phase 3 trials were conducted without regards to food intake.

See the Clinical Pharmacology Review, dated November 23, 2022, for a full description of Trial 2693-CL-0012.

Hepatic Impairment Trial 2693-CL-0007:
Trial 2693-CL-0007, an open-label, single oral dose (30 mg fezolinetant) trial in female participants (18 to 75 years of age, inclusive), was conducted to evaluate the pharmacokinetics

of fezolinetant and metabolite ES259564 in female participants with mild (Child-Pugh classification Class A, score 5 or 6; group 1.1, n=8) and moderate (Child-Pugh classification Class B, score 7 to 9; group 1.2, n=8) hepatic impairment compared to healthy female participants with normal hepatic function [group 1.3, n=8-16, matched 1:1 by age (± 10 years), BMI (± 20%), race and sex] based on hepatic function. The trial was conducted at 4 trial sites in the US. The relationship between hepatic function abnormalities at baseline (bilirubin, serum albumin concentration and prothrombin time) and pharmacokinetic parameters (CL/F and Vz/F) were investigated using a linear regression model after adjusting for possible covariates such as age, BMI and race. To evaluate the effect of hepatic impairment on the pharmacokinetics of fezolinetant and metabolite ES259564, an ANCOVA model with hepatic function group as a factor and controlling for relevant covariates were fitted on natural logarithm-transformed pharmacokinetic parameters (AUCinf, AUClast and Cmax). Within the ANCOVA, the LS mean differences between each hepatic function group along with 90% CIs for the differences were estimated. The LS means for each pharmacokinetic parameter were back-transformed to produce the geometric LS means and presented with the number of participants for each hepatic function group.

Results of the statistical assessment of the effect of hepatic impairment on the pharmacokinetics of fezolinetant are shown in Table 8.

Table 8 Trial 2693-CL-0007: Statistical Assessment of the Effect of Hepatic Impairment on the Plasma Pharmacokinetics of Fezolinetant (Pharmacokinetic Analysis Set)

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

Source: NDA 216578, Trial 2693-CL-0007 Clinical Study Report, Table 13, page 31 of 39.
All enrolled participants who received at least 1 dose of study drug for which concentration data were available to facilitate derivation of at least 1 primary pharmacokinetic parameter (pharmacokinetic analysis set).
Assessment based on an analysis of covariance performed on natural logarithmic-transformed parameters with hepatic function as a fixed effect and body mass index and race as covariates.
Definitions: LS = least squares.
† Ratios and confidence limits were transformed back to raw scale and values are expressed as percentages.

Reviewer's Comment:
As shown in Table 8, the geometric mean ratios of fezolinetant AUCinf and AUClast progressively increased in the mild and moderate hepatic impairment groups compared to the normal hepatic function group. The geometric mean ratio of fezolinetant Cmax increased in the mild hepatic impairment group but decreased in the moderate hepatic impairment group as compared to the normal hepatic function group. Table 8 demonstrates that the plasma AUC increases with the severity of hepatic impairment (approximately 56% and 95% for mild and moderate hepatic impairment, respectively.)

The proposed labeling in the NDA application includes the following information:

[redacted] (b) (4)

Reviewer's Comment:
Appropriate and accurate hepatic impairment information should be included in product labeling if 45 mg fezolinetant is approved for the treatment of moderate to severe vasomotor symptoms associated with menopause.

On August 15, 2022, Clinical Pharmacology requested additional information on Trial 2693-CL-0007. Astellas responded on September 2, 2022. For ease of review, the Clinical Pharmacology question is listed first, followed by the applicant's response:

Clinical Pharmacology Question: In the dedicated hepatic impairment study, compared to its respective normal hepatic function group, fezolinetant AUCinf and Cmax increased in the mild group by ~56% and ~23%, respectively. (b) (4) summarize treatment emergent adverse events by preferred term (MedDRA 23.0) reported in >= 2% of patients received placebo, fezolinetant 30 mg or fezolinetant 45 mg by hepatic

impairment subgroups (i.e., normal, mild, moderate, and severe impairment using Child-Pugh scale) for the pooled safety dataset POP2, as defined in Table 3 of module 2.7.4 summary of clinical safety.

Astellas Response (Summarized):

- Inclusion and exclusion criteria of all phase 3 trials did not use Child-Pugh criteria for screening, although liver biochemistry parameters were regularly obtained and monitored by the sponsor and the Liver Safety Monitoring Panel (LSMP).
- The following exclusion criteria were implemented in all phase 3 protocols:
  - Subject has a medical condition or chronic disease (including history of neurological [including cognitive], hepatic, renal, cardiovascular, gastrointestinal, pulmonary [e.g., moderate asthma], endocrine or gynecological disease) or malignancy that could confound interpretation of the trial outcome in the opinion of the investigator.
  - Subject has active liver disease, jaundice or elevated liver aminotransferases (ALT or AST), elevated total or direct bilirubin, elevated INR, or elevated alkaline phosphatase (ALP). Patients with mildly elevated ALT or AST up to 1.5 times the upper limit of normal (ULN) can be enrolled if total and direct bilirubin are normal. Patients with mildly elevated ALP (up to 1.5 x ULN) can be enrolled if cholestatic liver disease is excluded and no cause other than fatty liver is diagnosed. Patients with Gilbert's syndrome with elevated total bilirubin may be enrolled as long as direct bilirubin, hemoglobin and reticulocytes are normal.
- It is not feasible to summarize the data based on chronic hepatic impairment subgroups.

See the Clinical Pharmacology Review, dated November 23, 2022, for a full description of Trial 2693-CL-0007.

<u>Renal Impairment Trial 2693-CL-0008:</u>

Trial 2693-CL-0008, an open-label, single oral dose (30 mg fezolinetant) trial in female participants (18 to 75 years of age, inclusive), was conducted in 6 centers in the US, to evaluate the pharmacokinetics of fezolinetant and metabolite ES259564 in female participants with varying levels of renal impairment [mild (n=6), moderate (n=6), severe (n=6)] compared to healthy female participants with normal renal function [n=10, demographically matched (1:1) by age (± 10 years), BMI (± 20%) and race to the enrolled impairment participant(s)]. Trial 2693-CL-0008 was stopped after enrolling only 5 women with severe renal impairment. Astellas indicates "enrollment of the severe renal impairment participants was challenging" and they "determined the data to be sufficient to meet the study objectives." "This decision was not based on safety concerns."

Eligible participants with mild, moderate and severe renal function and healthy participants with normal renal function were admitted to the clinical unit on day -1 and were residential for a single period of 6 days/5 nights. On day 1, participants received a single oral dose of 30 mg fezolinetant under fasting conditions followed by a 96-hour in-house blood and urine sampling period. Participants were to remain awake, seated or semirecumbent, and avoided lying on either the left or right side for at least 4 hours postdose. Standard safety and tolerability assessments were conducted.

Reported results show that compared to respective normal renal function groups, "mild to severe renal impairment had no substantial effects on fezolinetant's pharmacokinetic exposure (GMR: 48.02% to 117.93% for AUCinf; and 68.84% to 90.44% for AUClast; with all 90% CIs including 100%, except AUCinf of the moderate impairment group). Cmax of fezolinetant was comparable between mild, moderate and severe renal impairment groups and their respective matching normal renal function group (GMR [90% CI]: 99.48% [75.35, 131.33] for mild, 104.28% [78.28, 138.92] for moderate and 105.94% [81.86, 137.12] for severe renal impairment, respectively)." See Table 9.

Table 9 Trial 2693-CL-0008: Statistical Assessment of the Effect of Renal Impairment on Plasma Pharmacokinetics of Fezolinetant (Pharmacokinetic Analysis Set)

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

Source: NDA 216578, Trial 2694-CL-0008 Clinical Study Report, Table 13, page 35 of 45.
All enrolled participants who received at least 1 dose of investigational product for which concentration data were available to facilitate derivation of at least 1 primary pharmacokinetic parameter (pharmacokinetic analysis set).
Assessment based on an analysis of covariance performed on natural logarithmic-transformed parameters with renal function as a fixed effect and body mass index as a covariate.
Normal participants may have been enrolled to match more than 1 impaired participant in different impairment groups; these participants were not re-treated.
Definitions: CI = confidence interval; LS = least squares.
† Ratios and confidence limits were transformed back to raw scale and values are expressed as percentages.

Reviewer's Comment:
As shown in Table 9, the geometric mean ratios (GMRs) of fezolinetant AUCinf and AUClast generally decreased in the renal impairment groups with the largest decrease observed in the moderate renal impairment group. The GMRs of fezolinetant Cmax were not meaningfully changed in the mild and moderate renal impairment groups but increased in the severe renal impairment group. Per the NDA application, "BMI was

identified as a significant covariate for the AUCinf (moderate impairment group vs matched group with normal renal function only) and was integrated in the model for final assessment, based on the prespecified analysis in the study protocol." The plasma concentrations of fezolinetant metabolite ES259564 also increased progressively with the severity of renal impairment, with the highest concentration observed in participants with severe renal impairment (data not shown in Table 9). Astellas concluded "Compared to their respective normal renal function groups, the moderate and severe renal impairment groups showed substantial increased concentrations while there was no discernable difference between the mild renal impairment group and matching group with normal renal function."

The proposed labeling in the NDA application includes the following information:

(b) (4)

(b) (4)

(b) (4)

Reviewer's Comment:
Appropriate and accurate renal impairment information should be included in product labeling if 45 mg fezolinetant is approved for the treatment of moderate to severe vasomotor symptoms associated with menopause.

On August 15, 2022, Clinical Pharmacology requested additional information on Trial 2693-CL-0008. Astellas responded on September 2, 2022. For ease of review, the Clinical Pharmacology question is listed first, followed by the Applicant's response:

Clinical Pharmacology Question: In the dedicated renal impairment study, compared to its respective normal renal function group, fezolinetant AUCinf decreased by ~40%-50% in the mild and moderate impairment groups. You proposed that no dose adjustment is recommended for patients with mild or moderate renal impairment. To support that the observed changes in mild and moderate renal impairment groups are not clinically meaningful, summarize efficacy results of the four coprimary endpoints for patients received placebo, fezolinetant 30 mg or fezolinetant 45 mg by renal impairment subgroups [i.e., normal, mild, moderate, and severe impairment based on estimated glomerular filtration rate (eGFR)] for Phase 3 studies CL-0301 and CL-0302.

Astellas Response (Summarized):
"No participants were enrolled that met the criteria for severe renal impairment (≥ 15 to < 30 mL/min per 1.73 m2), or end stage renal failure (< 15 mL/min per 1.73 m2), as participants with severe renal impairment at screening were excluded from studies 2693-CL-0301 and 2693-CL-0302. The specific protocol exclusion criteria #10 and 11 are as follows: Subject has a medical condition or chronic disease (including renal) that could confound interpretation of the study outcome in the opinion of the investigator; and subject has creatinine > 1.5 x ULN; or eGFR using the Modification of Diet in Renal Disease formula ≤ 59 mL/min per 1.73 m2 at screening."

Per the final draft Clinical Pharmacology Review, received via email communication on November 21, 2022, " The Office of Clinical Pharmacology, Division of Cardiometabolic and Endocrine Pharmacology, has reviewed the information contained in NDA 216578 and recommends approval of this NDA." See the final Clinical Pharmacology review for identified key review issues with specific recommendations and/or comments.

See the Clinical Pharmacology Review, dated November 23, 2022, for a full description of Trial 2693-CL-0008.

4.6. Devices and Companion Diagnostic Issues

There are no device and companion diagnostic tests with fezolinetant tablets.

4.7. Consumer Study Reviews

No label comprehensive, patient self-selection, or other human factor studies were evaluated during the fezolinetant tablets development program.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

Table 10 Table of Clinical Trials

Trial Identity	Trial Design	Regimen/ schedule/ route	Trial Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Trial Population
Trial 2693-CL-0301	Phase 3, multicenter clinical trial. Efficacy was evaluated in the first 12-week period, which was conducted in a double-blind, placebo controlled parallel group fashion. Participants randomized to placebo in the 12 week double-blind period, were then re-randomized (1:1) to fezolinetant 30 mg or 45 mg for an additional 40-week active treatment extension period. Participating trial sites were in the US, Canada and Europe .	Fezolinetant 30 mg, 45 mg tablets and placebo oral tablets once daily in a 1:1:1 ratio, with or without food. Doses were administered as tablets of 15 mg and/or 30 mg fezolinetant/ placebo.	Four co-primary endpoints: • Mean change in frequency at Week 4 • Mean change in frequency at Week 12 • Mean change in severity at Week 4 • Mean change in severity at Week 12	Total 52-weeks: 12-week placebo-controlled period and 40-week active treatment extension period	527 randomized participants: 176 in 30 mg fezolinetant, 176 in 45 mg fezolinetant, 175 in placebo	Healthy postmenopausal women
Trial 2693-CL-0302	Phase 3, multicenter clinical trial. Efficacy was evaluated in the first 12-week period, which was conducted in a double-blind, placebo controlled parallel group fashion. Participants randomized to placebo in the 12-	Fezolinetant 30 mg, 45 mg tablets and placebo oral tablets	Four co-primary endpoints: • Mean change in frequency at Week 4 • Mean change in	Total 52-weeks: 12-week placebo-controlled period and	501 randomized participants: 166 in 30 mg fezolinetant,	Healthy postmenopausal women

	week double-blind period, were then rerandomized (1:1) to fezolinetant 30 mg or 45 mg for an additional 40-week active treatment extension period. Participating trial sites were in the US, Canada and Europe.	once daily in a 1:1:1 ratio, with or without food. Doses were administered as tablets of 15 mg and/or 30 mg fezolinetant/ placebo.	frequency at Week 12 • Mean change in severity at Week 4 • Mean change in severity at Week 12	40-week active treatment extension period	167 in 45 mg fezolinetant, 168 in placebo	
Trial 2693-CL-0304	Phase 3, 52-week, randomized, placebo-controlled, double-blind, parallel-group, multicenter clinical trial. Participants were treated with placebo, fezolinetant 30 mg or fezolinetant 45 mg for the 52-week trial period. Participating trial sites were in the US, Canada and Europe.	Fezolinetant 30 mg, 45 mg tablets and placebo tablets oral once daily in a 1:1:1 ratio, with or without food. Doses were administered as tablets of 15 mg	Primary objective of the trial was to evaluate the long-term safety, including endometrial health, and tolerability of fezolinetant in women seeking treatment for relief of VMS associated with menopause	Total 52-weeks	1831 randomized participants: 611 in 30 mg fezolinetant, 609 in 45 mg fezolinetant, 611 in placebo	Healthy postmenopausal women

		and/or 30 mg fezolinetant/ placebo				
Trial 2693-CL-0006	Single center, phase 1, open-label, single sequence study. Drug-drug interaction with fluvoxamine and smoking; Germany	Single dose of fezolinetant 30 mg on Day 1 and Day 7, fluvoxamine 50 mg qd on Day 3 and Day 10 and bid on Days 4 to 9, under fasting conditions. Fezolinetant administered as capsules of 15 mg; fluvoxamine administered as tablets of 50 mg.	To evaluate the effect of concomitant administration of fluvoxamine, a strong CYP1A2 inhibitor, on the pharmacokinetics of a single oral dose of fezolinetant i • To evaluate the effect of smoking on the pharmacokinetics of fezolinetant with and without concomitant administration of fluvoxamine (secondary objective)	Single dose	18 participants	Healthy postmenopausal women
Trial 2603-CL-0007	Phase 1, open-label, single dose study. Special population (effect of mild and	Single dose of oral 30 mg fezolinetant,	To evaluate the pharmacokinetics of a single oral	Single dose	26 participants: 8 with mild	Group 1: Female participants

	moderate hepatic impairment). The trial was conducted in the US	administered as tablet, under fasting conditions.	dose of fezolinetant and ES259564 (fezolinetant metabolite) in female participants with mild and moderate hepatic impairment compared to healthy female participants with normal hepatic function		hepatic impairment, 8 with moderate hepatic impairment and 10 with normal hepatic function.	with mild hepatic impairment Group 2: Female participants with moderate hepatic impairment Group 3: Healthy female participants with normal hepatic function
Trial 2693-CL-0008	Phase 1, open-label, single dose study. Special population (effect of renal impairment). The trial was conducted in the US	Single dose of oral 30 mg fezolinetant, administered as tablet, under fasting conditions.	To evaluate the pharmacokinetics of a single oral dose of fezolinetant and ES259564 (fezolinetant metabolite) in female participants with varying levels of renal impairment (mild, moderate and severe) compared to	Single dose	27 participants: 6 with mild renal function, 6 with moderate renal function, 5 with severe renal function and 10 with normal renal function	Group 1: Female participants with mild renal function Group 2: Female participants with moderate renal function Group 3: Female participants with severe renal function

			healthy demographically matched (1:1) female participants with normal renal function			Group 4: Healthy female participants with normal renal function
Trial 2603-CL-0009	Single center, phase 1, randomized, open-label, 2-period, 2-sequence, single dose, crossover study. Relative bioavailability of phase 3 tablet vs capsule. The trial was conducted in the US	Single dose of oral 120 mg fezolinetant, administered as phase 3 tablet or as capsule, on Day 1 of period 1, with the other formulation given on Day 1 of period 2, under fasting conditions.	To assess the relative bioavailability of a single dose of 120 mg fezolinetant tablet (test formulation) compared to a single dose of 120 mg fezolinetant capsule (reference formulation) under fasting conditions in healthy postmenopausal female participants	Period 1: single dose Period 2: single dose	16 randomized participants: 8 in each sequence	Healthy postmenopausal women
Trial 2693-CL-0010	Single center, phase 1, randomized, open-label, 2-period, 2-sequence, single dose crossover study.	Single dose of oral 45 mg to-be marketed	To assess the bioequivalence of a single dose of one 45 mg	Period 1: single dose Period 2: single dose	22 randomized participants: 11 in each sequence	Healthy premenopausal and postmenopausal

	Bioequivalence of to-be-marketed tablet vs phase 3 tablet. The trial was conducted in the US	tablet (test formulation) compared to a single dose of one 30 mg and one 15 mg phase 3 tablet (reference-formulation), under fasting conditions.	fezolinetant to-be-marketed tablet (test formulation) compared to a single dose of one 30 mg and one 15 mg fezolinetant phase 3 tablet (reference formulation) under fasting conditions in healthy female participants			female participants
Trial 2693-CL-0012	Single center, phase 1, randomized, open-label, 2-period, 2-sequence, single dose crossover study. Food effect; US	Single center, phase 1, randomized, open-label, 2-period, 2-sequence, single dose crossover study.	To evaluate the effect of food on the pharmacokinetics of a single oral dose of fezolinetant under fasting and fed conditions in healthy female participants	Period 1: single dose Period 2: single dose	16 randomized participants: 8 in each sequence	Healthy female participants

Source: Adapted from NDA 216578, CTD Module 5.2 , Listing of Clinical Studies.

5.2. Review Strategy

The available clinical data in Trial 2693-CL-0301 and Trial 2693-CL-0302, two independent, confirmatory, phase 3 efficacy and safety trials, provided the basis for consideration regarding the efficacy of ESN364 (fezolinetant) oral tablets, 45 mg, for the treatment of moderate to severe vasomotor symptoms (VMS), associated with menopause. These two primary, phase 3, 52-week clinical trials each included an initial 12-week placebo-controlled period followed by a 40-week extension period of fezolinetant only (52-weeks in total). Participants initially randomized to placebo in the first 12-weeks, who agreed to continued participation in the 40-week extension period, were re-randomized to fezolinetant treatment only for an additional 40-weeks. Participants initially randomized to 30 mg or 45 mg fezolinetant in the first 12-weeks, remained on their assigned treatments if they agreed to continue participation in the 40-weeks extension period. Both primary efficacy and safety trials were conducted in the U.S., Canada, and Europe.

Primary evidence for the safety assessment of fezolinetant comes from the 52-week, primary efficacy and safety Trials 2693-CL-0301 and 2693-CL-0302, and from 52-weeks, placebo-controlled, long-term safety and chronic use exposure Trial 2693-CL-0304. Trial 2693-CL-0304 was conducted in support of the general and endometrial safety and long-term drug exposure safety for fezolinetant for use in a postmenopausal woman with a uterus and a postmenopausal woman without a uterus.

NDA 216578 is jointly reviewed by Theresa H. van der Vlugt, M.D., M.P.H. and Regina Zopf, M.D., M.P.H., Medical Officer's in the Division of Urology, Obstetrics, and Gynecology (DUOG).

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. Trial 2693-CL-0301

6.1.1. Study Design

Overview and Objective

Trial 2693-CL-0301 (Skylight 1, NCT04003155) titled "A Phase 3, Randomized, Placebo-controlled, 12-week Double-blind Study, followed by a Non-controlled Extension Treatment Period, to Assess the Efficacy and Safety of Fezolinetant in Women Suffering from Moderate to Severe Vasomotor Symptoms (Hot Flashes) Associated with Menopause" was phase 3, 52-weeks clinical trial, which was adequate and well-controlled for the first 12-weeks utilizing a

placebo-controlled, followed by a 40-week extension open-label period of active treatment only. Five hundred twenty-seven (527) healthy postmenopausal women, 40 to 65 years of age (average of 54.4 years of age), with at least 7 to 8 moderate to severe hot flashes per day, were randomized in a 1:1:1 ratio to placebo, 30 mg fezolinetant, or 45 mg fezolinetant given orally, once daily, with or without food. After completing 12-weeks of treatment, participants on placebo who agreed to continue trial participation in the 40-weeks extension period, were re-randomized in a 1:1 ratio to 30 mg fezolinetant or 45 mg fezolinetant treatment groups. Participants who completed treatment with 30 mg fezolinetant or 45 mg fezolinetant in the 12-week double-blind period, who agreed to continue trial participation in the 40-weeks extension period, continued to receive the same fezolinetant dose during the active treatment extension period.

> Reviewer's Comment:
> The primary objectives of Trial 2693-CL-0301 were to evaluate the efficacy of 30 mg or 45 mg fezolinetant versus placebo on the frequency and severity of moderate to severe vasomotor symptoms during the first 12-weeks of treatment, and to assess the chronic use and long-term safety of fezolinetant.

Per the NDA application, the following was a key secondary objectives in Trial 2693-CL-0301:

- To evaluate the efficacy of fezolinetant versus placebo on patient-reported sleep disturbance.

Secondary objectives in this trial included the following:

- To evaluate the effect of fezolinetant versus placebo on the frequency and severity of moderate to severe VMS at weekly time points.
- To evaluate the safety and tolerability of fezolinetant.

Trial 2693-CL-0301 included the following, but not limited to, exploratory objectives:

- To evaluate pharmacokinetics of fezolinetant and metabolite ES259564.
- To evaluate the effect of fezolinetant on pharmacodynamic markers.
- To evaluate the efficacy of fezolinetant versus placebo on the frequency and severity of mild, moderate to severe VMS.
- To evaluate the short-term and sustained effects of fezolinetant versus placebo on patient-reported sleep disturbance.
- To evaluate the effect of fezolinetant versus placebo on the following PROs: global assessments of VMS and sleep disturbance, overall sleep-wake function, quality of life and work productivity.

Efficacy analyses were conducted on the full analysis set (FAS), which consisted of all participants who were randomized and received at least 1 dose of trial medication. This was the primary efficacy analysis set. Five hundred twenty-two (522) participants in Trial 2693-CL-0301 took at least 1 dose of trial medication. Primary efficacy endpoints were analyzed using the mixed model repeated measures (MMRM) model. The MMRM model included treatment group, week (week 1 through week 12), and smoking status (current versus former/never) as factors, with baseline weight and baseline measurement as covariates, as well as an interaction of treatment by week and an interaction of baseline measurement by week. The family-wise type 1 error rate for the 2 active dose groups compared with placebo for the 4 co-primary endpoints was controlled using a Hochberg approach. Sensitivity analyses were conducted using the per protocol set (PPS), which consisted of the subsets of the full analysis set who met the following criteria 1) measurement of the primary efficacy endpoint available at Weeks 4 or 12; 2) ≥ 85% interactive diary compliance during Week 4 or Week 12 treatment period; and 3) treatment compliance > 85% between randomization and Week 4 or Week 12. The following prespecified subgroup analyses were performed at the study level: age, race, BMI and smoking status.

Study Design

Trial 2693-CL-0301 was a phase 3, 52-week, multicenter (96 clinical sites randomized at least 1 postmenopausal woman) trial, which included a randomized, double-blind, placebo-controlled, and parallel group (placebo, 30 mg fezolinetant, and 45 mg fezolinetant) trial design for the first 12-weeks only,. The trial population consisted of hysterectomized and non-hysterectomized postmenopausal women who met the trial inclusion criteria and none of the trial exclusion criteria.

Following informed consent procedures, trial participants completed initial screening procedures that included: demographics, medical/gynecological history, concomitant medications, physical examination [including height, weight, and body mass index (BMI) calculation], pregnancy test, vital signs, pelvic and breast examinations, laboratory measurements, 12-lead ECG, Pap smear, mammography, transvaginal ultrasound (TVU), and endometrial biopsy. An endometrial biopsy was also performed at Week 52/end-of-trial (EOT), for participants with uterine bleeding, and for women who were withdrawn from the trial prior to completion. If a woman discontinued from the trial, an endometrial biopsy was to be performed at the discontinuation visit along with all other EOT procedures. During treatment, any woman with an abnormal endometrial biopsy reported as disordered proliferative endometrium, endometrial hyperplasia or endometrial cancer was referred to standard of care clinical management and followed to resolution, and the report of any medical or surgical procedures and the resultant pathology would be obtained. A mammogram at Week

52/EOT/early discontinuation (ED) was obtained if it coincided with the regularly scheduled routine screening mammogram of the participant.

All trial participants were provided with an electronic hand-held diary to self-assess the frequency and severity of their vasomotor symptoms. Within the 10 days prior to randomization, screening participants had to have a minimum average of 7 to 8 moderate to severe hot flashes per day, or 50 to 60 per week. The electronic diary was reviewed by trial site staff at randomization (Visit 2) to confirm trial eligibility.

Clinical evaluations were performed at the following time points:

- Visit 1 (Screening): Day -35 to Day -1
- Visit 2 (Randomization): Day 1
- Visit 3 (Interim): Day 29 (Week 4)
- Visit 4 (Interim): Day 57 (Week 8)
- Visit 5 (Interim): Day 85 (Week 12)
- Visit 6 - 15 (Interim): Day 113 - 365 (Week 16 - 53)
- Visit 16 (Follow-up): Day 386 (Week 55)

Study Endpoints

Co-primary Endpoints:
The protocol defined primary efficacy objective required the evaluation of 4 co-primary endpoints:

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

Key Secondary Endpoint:
The protocol defined key secondary objective examined the effect of fezolinetant versus placebo on the following:

- Mean change in the Patient-reported Outcomes Measurement Information System Sleep Disturbance – Short Form 8b (PROMIS SD SF 8b) total score from baseline to Week 12.

Secondary Endpoints:
The protocol defined secondary objectives examined the effect of fezolinetant versus placebo

on the following:

- Mean change in the frequency of moderate to severe VMS from baseline to each week up to Week 12.
- Mean change in the severity of moderate to severe VMS from baseline to each week up to Week 12.
- Mean percent reduction in the frequency of moderate to severe VMS from baseline to each week up to Week 12.
- Percent reduction ≥ 50% and at 100% in the frequency of moderate to severe VMS from baseline to each week up to Week 12.
- Score on the Patient Global Impression of Change in Vasomotor Symptoms (PGI-C VMS) at each visit.

In addition, the following secondary endpoints described the effect of fezolinetant for the 40-week active treatment only extension period:

- Mean change in the frequency of moderate to severe VMS from baseline to Week 24. Per the NDA application, assessments after the 12-week placebo-controlled period were descriptive only because there was no placebo control.
- Mean change in the severity of moderate to severe VMS from baseline to Week 24.

Exploratory Endpoints:

- Mean change in the frequency of mild, moderate to severe VMS from baseline to each week up to Week 12.
- Mean change in the severity of mild, moderate to severe VMS from baseline to each week up to Week 12.
- Mean percent reduction in the frequency of mild, moderate to severe VMS from baseline to each week up to Week 12.
- Percent reduction ≥ 75% and ≥ 90% in the frequency of moderate to severe VMS from baseline to each week up to Week 12 (VMS responder).
- Percent reduction ≥ 50%, ≥ 75%, ≥ 90% and at 100% in the frequency of mild, moderate to severe VMS from baseline to each week up to Week 12 (VMS responder).
- Mean change in the frequency and severity of moderate to severe VMS from baseline to each visit in the active treatment extension period and the follow-up visit.
- Change in serum concentrations of sex hormones and sex hormone binding globulin (SHBG) from baseline to each visit.
- Mean change in serum concentrations of bone-specific alkaline phosphatase (BSAP), procollagen type 1 amino-terminal propeptide (P1NP) and carboxy-terminal telopeptide of type I collagen (CTX) from baseline to each visit.
- Plasma concentrations of fezolinetant and metabolite ES259564 at prespecified time

points.

- Mean change on the PROMIS SD SF 8b total score from baseline to each visit.
- Mean change on the Patient-reported Outcomes Measurement Information System Sleep Related Impairment – Short Form 8a (PROMIS SRI SF 8a) total score from baseline to each visit.
- Score on Patient Global Impression of Severity in Sleep Disturbance Patient Global Impression of Severity in Sleep Disturbance (PGI-S SD) at each visit.
- Score on Patient Global Impression of Change in Sleep Disturbance (PGI-C SD) at each visit.
- Mean change on the Menopause-Specific Quality of Life (MENQOL) total score from baseline to each visit.
- Mean change on the MENQOL domain scores from baseline to each visit.
- Mean change on the Euro-Qol 5D-5L (EQ-5D-5L) total score and Visual Analog Scale (VAS) from baseline to each visit.
- Mean change on the Work Productivity and Activity Impairment questionnaire specific
- to vasomotor symptoms (WPAI-VMS) domain scores from baseline to each visit.
- Mean change in the severity of moderate to severe VMS from baseline to each week up to Week 12 (excluding mild events postbaseline).
- Mean and mean change from baseline in the daily frequency of moderate to severe VMS for the first week.

Reviewer's Comment:
On April 17, 2019, and September 20, 2019, in the pre-NDA submission clinical development period, Astellas was advised of the following:

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

Safety Endpoints:
Safety evaluations included the following endpoints and other safety-related assessments:

- Frequency and severity of adverse events (AEs).
- Transvaginal ultrasound (TVU) and endometrial biopsy findings.
- Change from baseline to each time point in vital signs: sitting systolic and diastolic blood pressure and pulse rate.
- Change from baseline to each time point in ECG parameters.
- Change from baseline to each time point in laboratory tests: hematology, biochemistry and urinalysis.

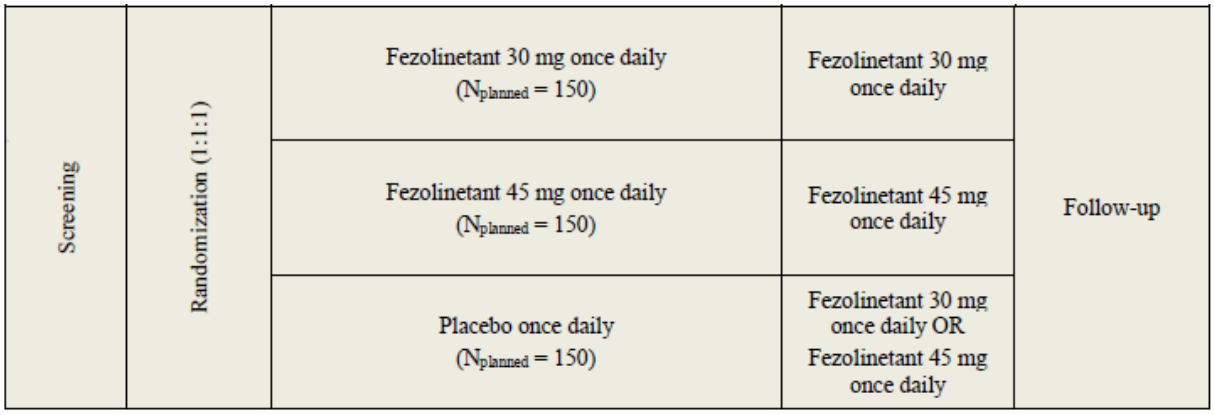
  Reviewer's Comment:
  The reported safety outcomes in phase 3 clinical trials are discussed in Section 8 Review of Safety in this review.

Trial Investigational Products:
Placebo tablets and two different fezolinetant tablets (fezolinetant 15 mg tablets and 30 mg tablets) were used in Trial 2693-CL-0301. Each of these tablets were identical in physical appearance. The method used for blinding of doses follows:

- Fezolinetant 30 mg dosage strength: one 30 mg fezolinetant tablet and one placebo tablet, orally, once daily
- Fezolinetant 45 mg dosage strength: one 15 mg fezolinetant tablet and one 30 mg fezolinetant tablet, orally, once daily
- Placebo: two placebo tablets

Trial 2693-CL-0301, conducted at 96 centers that enrolled participants in 8 countries (US, Canada, Spain, Hungary, Ukraine, Czech Republic, UK, Poland), was performed on an outpatient basis, and consisted of a screening period [days -35 to -1, including the screening visit (Visit 1) and collection of VMS frequency and severity assessments] and a 52-week treatment period [day 1 (Visit 2) to Week 52 (visit 15)]. See Figure 1.

Figure 1 Trial Schema



Source: Adapted from NDA 216578, Trial 2693-CL-0301 Study Report, Figure 1 Study Schema, page 18 of 3190.
Definitions: N = number; V = visit.
Screening was performed up to 35 days prior to randomization, with a minimum of 10 days to allow for baseline collection of VMS frequency and severity.

Inclusion Criteria:

Participants who met all of the following criteria were eligible to participate in the trial; waivers to the inclusion criteria were not allowed:

1. Institutional Review Board (IRB)/Independent Ethics Committee (IEC)-approved written informed consent and privacy language as per national regulations were obtained from the woman or legally authorized representative prior to any trial-related procedures.
2. Born female, ≥ 40 years of age and ≤ 65 years of age at the screening visit.
3. Has a body mass index ≥ 18 kg/m^2 and ≤ 38 kg/m^2.
4. Seeking treatment or relief for VMS associated with menopause and confirmed as menopausal per one of the following criteria at the screening visit:
    - Spontaneous amenorrhea for ≥ 12 consecutive months;
    - Spontaneous amenorrhea for ≥ 6 months with FSH > 40 IU/L; or
    - Had a bilateral oophorectomy ≥ 6 weeks prior to the screening visit.
5. Have a minimum average of 7 to 8 moderate to severe hot flashes per day, or 50 to 60 per week within 10 days prior to randomization.
6. In good general health as determined on the basis of medical history and general physical examination, including a bimanual clinical pelvic examination and clinical breast examination devoid of relevant clinical findings, performed at the screening visit; hematology and biochemistry parameters, pulse rate and/or blood pressure and ECG

within the reference range for the population studied, or showing no clinically relevant deviations, as judged by the investigator.

7. Documentation of a normal/negative or no clinically significant findings mammogram (obtained at screening or within the prior 12 months of trial enrollment). Appropriate documentation included a written report or an electronic report indicating normal/negative or no clinically significant mammographic findings.
8. Is willing to undergo a transvaginal ultrasound (TVU) to evaluate the uterus and ovaries at screening, at Week 52 (EOT), and at early withdrawal/discontinuation for participants who are withdrawn/discontinued from the trial prior to Week 52.
9. Is willing to undergo an endometrial biopsy at screening, at Week 52 (EOT), for evaluation of uterine bleeding during trial conduct, and at early withdrawal/discontinuation for participants who are withdrawn/discontinued from the trial prior to Week 52. The endometrial biopsy obtained at screening must be considered evaluable.
10. Has documentation of a normal or not clinically significant Pap test (or equivalent cervical cytology) in the opinion of the investigator within the previous 12 months or at screening.
11. Has a negative urine pregnancy test at screening.
12. Has a negative serology panel (i.e., negative hepatitis B surface antigen, negative hepatitis C virus antibody and negative human immunodeficiency virus antibody screens) at screening.
13. Agrees not to participate in another interventional trial while participating in the present trial.

Reviewer's Comment:
The inclusion criteria in Trial 0301 were comprehensive and complete, and considered appropriate for this phase 3 clinical trial.

Exclusion Criteria:

Participants who met any of the following criteria were excluded from participation in the trial; waivers to the exclusion criteria were not allowed:

1. Uses a prohibited therapy [strong or moderate CYP1A2 inhibitors, hormone therapy, hormonal contraceptive or any treatment for VMS (prescription, over the counter or herbal)] or is not willing to wash out and discontinue use of such drugs for the full duration of trial conduct.
2. Has known substance abuse or alcohol addiction within 6 months of screening, as assessed by the investigator.
3. Has previous or current history of a malignant tumor, except for basal cell carcinoma.
4. Systolic blood pressure is ≥ 130 mmHg or diastolic blood pressure is ≥ 80 mmHg based

on the average of 2 to 3 readings, on at least 2 different occasions within the screening period.

- Participants who do not meet these criteria may, at the discretion of the investigator, be re-assessed after initiation or review of antihypertensive measures.
- Participants with a medical history of hypertension can be enrolled at the discretion of the investigator once they are medically clear (stable and compliant).

5. Has a history of severe allergy, hypersensitivity or intolerance to drugs in general, including the trial drug and any of its excipients.
6. Has an unacceptable result from the TVU assessment at screening (i.e., full length of endometrial cavity cannot be visualized or presence of a clinically significant finding).
7. Has an endometrial biopsy confirming presence of disordered proliferative endometrium, endometrial hyperplasia, endometrial cancer or other clinically significant findings in the opinion of the investigator at screening.
8. Has a history within the last 6 months of undiagnosed uterine bleeding.
9. Has a history of seizures or other convulsive disorders.
10. Has a medical condition or chronic disease [including history of neurological (including cognitive), hepatic, renal, cardiovascular, gastrointestinal, pulmonary (e.g., moderate asthma), endocrine or gynecological disease] or malignancy that could confound interpretation of the trial outcome in the opinion of the investigator.
11. Has active liver disease, jaundice, elevated liver aminotransferases (ALT or AST), elevated total or direct bilirubin, elevated INR, or elevated alkaline phosphatase (ALP). Participants with mildly elevated ALT or AST up to 1.5 times the upper limit of normal (ULN) can be enrolled if total and direct bilirubin are normal. Participants with mildly elevated ALP (up to 1.5 x ULN) can be enrolled if cholestatic liver disease is excluded and no cause other than fatty liver is diagnosed. Participants with Gilbert's syndrome with elevated total bilirubin may be enrolled as long as direct bilirubin, hemoglobin, and reticulocytes are normal.
12. Has creatinine > 1.5 x ULN; or estimated glomerular filtration rate (eGFR) using the Modification of Diet in Renal Disease formula ≤ 59 mL/min per 1.73 m^2 at screening.
13. Has a history of suicide attempt or suicidal behavior within the last 12 months or has suicidal ideation within the last 12 months [a response of "yes" to question 4 or 5 on the suicidal ideation portion of the Columbia Suicide Severity Rating Scale (C-SSRS)], or who is at significant risk to commit suicide, as assessed by the investigator at screening and at Visit 2 (randomization).
14. Has previously been enrolled in a clinical trial with fezolinetant.
15. Is participating concurrently in another interventional study or participated in an interventional study within 28 days prior to screening, or received any investigational drug within 28 days or within 5 half-lives prior to screening, whichever is longer.

16. Is unable or unwilling to complete the study procedures.
17. Has any condition, which in the investigator's opinion, makes the participant unsuitable for trial participation.

    Reviewer's Comment:
    The exclusion criteria in Trial 0301 were comprehensive and complete, and considered appropriate for this phase 3 clinical trial.

Statistical Analysis Plan

In Trial 2693-CL-0301, the treatment groups for the 12-week analysis included placebo, 30 mg fezolinetant, and 45 mg fezolinetant. The treatment groups for the 52-week analysis included 30 mg fezolinetant, 45 mg fezolinetant for participants who received fezolinetant for 52-weeks, and placebo/30 mg fezolinetant and placebo/45 mg fezolinetant for participants who received placebo during the 12-week placebo-controlled period who were re-randomized to a fezolinetant group during the active treatment extension period. Therefore, the 52-week data included data from the 12-week double-blind period for fezolinetant treatment groups and data from the active treatment extension period for the placebo/fezolinetant treatment groups.

The primary analysis method for the co-primary efficacy endpoints of frequency and severity of moderate to severe VMS at Weeks 4 and 12, in the 12-week double-blind period, was an MMRM with change from baseline as dependent variable, treatment group, week (week 1 through week 12) and smoking status (current vs former/never) as factors, with baseline weight and baseline measurement as covariates. The family-wise type 1 error rate for the 2 active dose groups compared with placebo for the 4 co-primary efficacy endpoints was controlled using a Hochberg approach. All 4 co-primary endpoints must be statistically significant for a given dose to be considered successful.

Trial 2693-CL-0301 had 2 planned database locks, one at the end of 12-week double-blind period, for primary placebo-controlled efficacy and safety, and another lock at 52-weeks. Per the application, during the conduct of the 40-week active treatment extension period, some data fields from the 12-week period were updated. Pre-planned, sensitivity analyses of selected 12-week endpoints were conducted on the final locked 52-week database, including the co-primary endpoints, key secondary endpoint, summary of TEAEs and liver laboratory assessments, to ensure the robustness of the results at 12-weeks. Therefore, 12-week results include the data from the initial lock while the 52-week results include the data that was updated.

Per the NDA application, additional analyses were conducted to provide context for interpretation of change in the frequency of moderate to severe VMS. Thresholds for clinically

meaningful within-subject change in VMS frequency to Weeks 4 and 12 were calculated according to the prespecified analysis plan.

The consistency of treatment effects on the co-primary endpoints across subgroups was evaluated at the study level in this trial. The following prespecified subgroup analyses were performed at the study level: age, race, BMI and smoking status.

Efficacy analyses were conducted on the full analysis set (FAS), which consisted of all participants who were randomized and received at least 1 dose of trial intervention; this was the primary analysis set. Sensitivity analyses were conducted using the per protocol set (PPS), which consisted of the subsets of the FAS who met the following criteria:

1) measurement of the primary efficacy endpoint available at Weeks 4 or 12;
2) ≥ 85% interactive diary compliance during the 4-week or 12-week treatment period; and
3) treatment compliance > 85% between randomization and Week 4 or between randomization and Week 12.

COVID-19 Impact Summary:
The conduct of Trial 2693-CL-0301 included the period during which the COVID-19 pandemic occurred. The trial was paused on March 31, 2020 and restarted on June 1, 2020. Enrollment in the trial was paused in all sites from the 8 participating countries.

Per the NDA application, all attempts were made to conduct the protocol-defined scheduled visits. In cases where a participant was unable to visit the clinic due to site closure related to the COVID-19 pandemic, alternative measures were implemented to ensure participant safety and continuity of care while participating in the trial:

- Telemedicine conferences (telephone visits) to evaluate changes in a participant's medical condition or medications and completion of electronic PRO questionnaires.
- Safety laboratory tests were collected at a local lab to include biochemistry, hematology, liver biochemistry and coagulation panel testing.
- Participants were instructed to continue entering their daily hot flash frequency and severity in the handheld diary regardless of site closure.
- A COVID-19 login workaround for the eCOA device tablets was implemented to be available for in the event the site was closed, participants were unable to come in for their visit, or the site was unable to share the device with the participant.
- Home healthcare services were available in cases where arrangements were made in advance by the site upon request from the participant(s).

Reviewer's Comment:

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

Datasets Analyzed:

- Full Analysis Set (FAS): All participants who were randomized and received at least 1 dose of trial medication. The randomized treatment for each participant was used for summaries by treatment group based on the FAS, even if participant erroneously received a different treatment.
- Per Protocol Set (PPS): All randomized participants from the FAS who were treated according to the protocol without any major deviations at the Week 4 endpoint and the Week 12 endpoint. Reasons for exclusion from PPS Weeks 4 or 12 included 1) no measurement of the primary efficacy endpoint available at Week 4 or Week12; 2) <85% interactive diary compliance during the 4-week or 12-week treatment period; 3) treatment compliance less than or equal to 85% between randomization and Week 4 or Week 12.
- Safety Analysis Set (SAF): All randomized participants who took at least 1 dose of trial medication. A participant erroneously receiving a treatment different from their randomized treatment was assigned to the treatment group that the participant received as first dose.

Liver Safety Monitoring Panel (LSMP):
An independent panel of 3 clinical hepatic experts, experienced in the assessment of drug-induced liver injury (DILI), conducted a review of individual participant cases that met the criteria pertaining to elevated transaminases or other liver health markers. The primary objectives of the LSMP were to:

1. Conduct an independent review of available clinical data, i.e., blinded individual cases pertaining to elevated transaminases or other liver health markers.
2. Conduct a cumulative review of unblinded aggregate liver safety data every 3-6 months, in alignment with the Data Monitoring Committee (DMC) meetings. A DMC was established for the fezolinetant development program to safeguard the interests of trial participants and assess the safety of the trial treatment and procedures.
3. Determine whether the individually reviewed cases meet the criteria of a potential drug-induced liver injury.

Any participant who experienced alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 3 x upper limits of normal (ULN) or total bilirubin > 2 x ULN was evaluated for potential

DILI by the LSMP.

All trial participants were monitored for DILI from randomization up to their final trial visit through central (and local, if applicable) laboratory results. The data analysis center (consisting of independent unblinded statisticians and programmers external to the applicant) provided blinded participant data packages in the form of participant profiles to the LSMP for causality assessment. The LSMP also received ad-hoc blinded participant data packages anytime a participant met the aforementioned criteria and provided an evaluation of individual cases. The LSMP also reviewed aggregate liver safety data on a quarterly basis, in an unblinded fashion. Meetings were held with panel members to discuss these data and provide the panel recommendations. Blinded ad-hoc cases that were under the panel's review were completed prior to receiving the aggregate data.

Causal relationship to trial intervention was assessed for each case according to the DILI network scoring categories[15] as presented below in Table 11.

Table 11 Liver Safety Monitoring Panel's Categorization of Drug Product Causality of DILI

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

The final assessment/recommendation from the panel was based upon consensus (agreement by 3 members) or if lack of agreement, the simple majority vote (agreement by at least 2 members).

Reviewer's Comment:
The LSMP was a panel of the following three independent, well-recognized US hepatologists, experienced in the assessment of drug-induced liver injury:

1. (b) (4)
2.

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

3. (b) (4)

The NDA application includes a summary statement from the LSMP, dated May 26, 2022, regarding liver safety for fezolinetant. See the safety section of this review for additional information on liver safety for fezolinetant.

Endometrial Safety/Endometrial Biopsy Classification:
An endometrial biopsy was obtained at screening for determination of eligibility and at end-of-trial (EOT) or early discontinuation (ED) for the assessment of endometrial safety. Endometrial biopsies were also obtained during the trial for participants with reported uterine bleeding.

Endometrial biopsies were reviewed by three independent expert pathologists from institutions with independent fiduciary and organizational reporting as follows (b) (4) All reviewers are board certified pathologists. These pathologists did not meet to review slides or images before or during the conduct of the trials. Each pathologist was blinded to treatment group information, as well as other pathologist's results.

After the initial safety evaluation of the biopsy was completed by the primary pathologist, digital images of the biopsy were uploaded to a database which were then assessed by secondary and tertiary pathologists independently. The independent pathologists did not have access to any other clinical case data. All 3 pathologists used the same standardized criteria for the diagnosis of endometrial hyperplasia or endometrial cancer and endometrial polyps were fully characterized as to glandular proliferation and atypia.

Reviewer's Comment:
The fezolinetant clinical development program used the standardized criteria for histologic evaluation as recommended in the Agency's 2003 draft Guidance for Industry "Estrogen and Estrogen/Progestin Drug Products to Treat Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms – Recommendations for Clinical Evaluation": Blaustein's Pathology of the Female Genital Tract.

Per the NDA application, for screening biopsies, participants were excluded if the endometrial biopsy specimen confirmed the presence of disordered proliferative endometrium, endometrial hyperplasia, endometrial cancer or other clinically significant findings in the opinion of the investigator. However, in this clinical trial, participants could be enrolled based on the results of the primary pathologist. Participants whose biopsies were subsequently evaluated to be

exclusionary by the secondary or tertiary pathologist were then to be withdrawn from the trial.

> Reviewer's Comment:
> In Trial 2693-CL-0301, the screening endometrial biopsy specimen was usually read by two pathologist and sometimes all three pathologists. As noted, a participant could be enrolled based on the results of the primary pathologist reading. If the second, or third, pathologist's reading disagreed with the first pathologist, or confirmed the presence of an abnormal finding, for example hyperplasia or cancer, that participant was to be withdrawn for the trial. However, this did not always occur, per the NDA application.
>
> See the safety section of this review for additional information on endometrial safety for fezolinetant.

Protocol Amendments

The original protocol for Trial 2693-CL-0301 was submitted May 30, 2019 (Version 1.0, dated January 28, 2019). Overall, three (3) protocol amendments were submitted: Amendment 1 (Version 2, dated May 17, 2019); Amendment 1 (Version 2.1, dated December 5, 2019); and Amendment 2 (Version 3.0. dated July 2020). The Clinical Study Report for Trial 2693-CL-0301 included in the NDA application is dated February 24, 2022.

6.1.2. Study Results

Compliance with Good Clinical Practices

Per the application, Trial 2693-CL-0301 was "conducted in accordance with the protocol and consensus ethical principles derived from international guidelines including the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and CIOMS International Ethical Guidelines
- Applicable ICH GCP Guidelines
- Applicable laws and regulations"

Financial Disclosure

Pursuant to 21 CFR 54, Astellas provided financial certification and disclosure information for all covered clinical trials submitted in support of this application. Form FDA 3454 (4/21), signed by Judith Kannenberg, Vice President, RA, TA Head, Medical Specialties, Astellas Pharma US, 1 Astellas Way, Northbrook, IL 60062, dated June 6, 2022, indicates "There were no investigators with financial arrangements, payments, or interests requiring disclosure under 21 CFR

54.4(a)(3)" and confirms, "As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f))."

Patient Disposition

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

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

1) No measurement of primary efficacy endpoint available (highest exclusion for 30 mg fezolinetant at Weeks 4 and 12).
2) < 85% interactive diary compliance (highest exclusion for 30 mg fezolinetant at Week 4 and 45 mg fezolinetant at Week 12.
3) ≤ 85% treatment compliance (highest exclusion for 45 mg fezolinetant at Week 4 and 30 mg fezolinetant at Week 12).

Reviewer's Comment:
Overall, the reasons for exclusions from the PPS were similar across the treatment groups in Trial 2693-CL-0301.

A total of 455 participants completed the 12-week double-blind period. Of these participants, 452 participants entered the 40-week active treatment extension period; 396 participants completed the 52-week period.

(b) (4)

Trial 2693-CL-0301 was affected by a (b) (4) affecting their ability to deliver electronic Clinical Outcome Assessment results (eCOA) and electrocardiogram (ECG) central reading services to sites and study participants. (b) (4). At the time (b) (4), enrollment for this study had been completed.

> Reviewer's Comment:
> Per the NDA application, no protocol deviations related to (b) (4) or management of the incident were reported.

Protocol Violations/Deviations

A protocol deviation is defined in this NDA as generally an unplanned excursion from the protocol that is not implemented or intended as a systematic change. A major protocol deviation is one that may potentially impact the completeness, accuracy or reliability of data contributing to the primary endpoint or affect the rights, safety or well-being of a participant.

Major protocol deviation criteria was summarized at the end of each phase 3 trial as follows:

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

A total of 96 participants (18.2%; 96 of 527 randomized participants) had a major protocol deviation during the 12-week double-blind period, and 104 participants (19.9%; 104 of 522 participants in the SAF) had a major protocol deviation during the whole 52-week treatment period in Trial 2693-CL-0301. See Table 12 and Table 13.

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

Category	Placebo (n = 175)	Fezolinetant 30 mg (n = 176)	Fezolinetant 45 mg (n = 176)	Total (n = 527)
Overall protocol deviations	29 (16.6%)	33 (18.8%)	34 (19.3%)	96 (18.2%)
Entered into the study even though they did not satisfy entry criteria (PD1)	28 (16.0%)	26 (14.8%)	31 (17.6%)	85 (16.1%)
Developed withdrawal criteria during the study and was not withdrawn (PD2)	0	0	0	0
Received wrong treatment or incorrect dose (PD3)	1 (0.6%)	5 (2.8%)	4 (2.3%)	10 (1.9%)
Received excluded concomitant treatment (PD4)	0	3 (1.7%)	0	3 (0.6%)

Source: NDA 216578, Trial 2593-CL-0301 Final Study Report, Table 4, page 33 of 3190.
PD = Protocol deviation.

Table 13 Major Protocol Deviations (Safety Analysis Set); 52-week Period; Trial 2693-CL-0301

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

Source: Adapted from NDA 216578, Trial 2693-CL-0301 Final Study Report, Table 5, page 33 of 3190.
PD = Protocol deviation.

Reviewer's Comment:
As shown in Table 12 and Table 13, the most common major protocol deviation in all treatment groups was PD1 (participants who entered the trial but did not satisfy entry criteria). The 3 most common eligibility criteria deviations were:

1) Inclusion criterion # 4: Seeking treatment or relief for VMS associated with menopause and confirmed as menopausal per one of the following criteria at the

screening visit:

- Spontaneous amenorrhea for ≥ 12 consecutive months;
- Spontaneous amenorrhea for ≥ 6 months with FSH > 40 IU/L; or
- Had a bilateral oophorectomy ≥ 6 weeks prior to the screening visit. (related to the criteria for participants seeking treatment or relief).

2) Exclusion criterion # 4: Systolic blood pressure is ≥ 130 mmHg or diastolic blood pressure is ≥ 80 mmHg based on the average of 2 to 3 readings, on at least 2 different occasions within the screening period.
3) Exclusion criterion # 7: Has an endometrial biopsy confirming presence of disordered proliferative endometrium, endometrial hyperplasia, endometrial cancer or other clinically significant findings in the opinion of the investigator at screening.

Reviewer's Comment:
Overall, there were no important differences in frequencies of major protocol deviations between treatment groups.

Table of Demographic Characteristics

Demographics and baseline characteristics were similar between treatment groups. See Table 14. Slightly more than half of participants were less than 55 years of age (53.8%), with a median age of 54.0 years of age. Most participants were White (82.7%), not Hispanic or Latino (73.9%) and were either former or never smokers (87.4%). In addition, only 18.4% of participants had received prior treatment with hormone therapy.

Table 14 Demographic and Selected Baseline Characteristics (Safety Analysis Set)

Demographic Parameters	Treatment Group			
	Control Group (N=175) n (%)	30 mg Fezolinetant Treatment Group (N= 174) n (%)	45 mg Fezolinetant Treatment Group (N=173) n (%)	Total (N= 522) n (%)
Age (Years)				
Mean (SD)	54.7 (4.8)	54.2 (4.9)	54.2 (5.1)	54.4 (4.9)
Median	54.0	53.5	54.0	54.0
Min, Max	41, 65	42, 65	40, 65	40, 65
Age Category				
< 55 years	91 (52.0%)	63 (53.4%)	97 (56.1%)	281 (53.8%))
> 55 years	84 (48.0%)	81 (46.6%)	76 (43.9%)	241 (46.2%)
Race				

	Treatment Group			
White	142 (81.1%)	148 (85.5%)	141 (81.5%)	431 (82.7%)
Black or African American	28 (16.0%)	21 (12.1%)	26 (15.0%)	75 (14.4%)
American Indian or Alaska Native	2 (1.1%)	0	1 (0.6%)	3 (0.6%)
Asian	3 (1.7%)	3 (1.7%)	3 (1.7%)	9 (1.7%)
More Than One Race	0	1 (0.6%)	1 (0.6%)	2 (0.4%)
Missing	0	1	0	1
Ethnicity				
Hispanic or Latino	46 (26.4%)	43 (24.7%)	47 (27.2%)	136 (26.1%)
Not Hispanic or Latino	128 (73.6%)	131 (75.3%)	126 (72.8%)	385 (73.9%)
Missing	1	0	0	1
Weight (kg) (n)				
Mean (SD)	74.41 (12.14)	75.24 (14.07)	75.50 (12.66)	75.05 (12.97)
Median	73.60	74.20	74.30	73.85
Min, Max	NC	NC	NC	NC
BMI (kg/m^2) (n)				
Mean (SD)	28.19 (4.28)	28.17 (4.83)	28.28 (4.35)	28.20 (4.49)
Median	28.23	27.90	27.87	27.96
Min, Max	18.1, 37.7	17.0, 37.8	18.4, 37.9	18.0, 37.9
BMI Category (kg/m^2)				
< 18.5	0	1 (0.6%)	1 (0.6%)	2 (0.4%)
≥ 18.5 to < 25	44 (25.1%)	50 (28.7%)	40 (23.3%)	134 (25.7%)
≥ 25 to < 30	71 (40.6%)	60 (34.5%)	79 (45.9%)	210 (40.3%)
≥ 30	60 (34.3%)	63 (36.2%)	52 (30.2%)	175 (33.6%)
Missing	0	0	1	1 (0.6%)
Smoking Status Stratification factor†				
Current	22 (12.6%)	22 (12.6%)	22 (12.7%)	66 (12.6%)
Former/never	153 (87.4%)	152 (87.4%)	151 (87.3%)	456 (87.4%)
Prior Hormone Therapy				
Yes	33 (19.4%)	31 (18.0%)	30 (17.9%)	94 (18.4%)
No	137 (80.6%)	141 (82.0%)	138 (82.1%)	415 (81.6%)
Missing	5	2	5	12

Source: Adapted from NDA 216578, Trial 2693-CL-0301 Study Report, Table 8, page 36 of 3190.
All randomized participants who took at least 1 dose of trial medication (Safety Analysis Set)
† = Current vs former or never smoking status was a stratification factor for randomization; NC = Not calculated.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

The only pertinent baseline characteristic in phase 3 Trial 2693-CL-0301 population is the time since onset of amenorrhea. The median months since onset of amenorrhea was 61.1 months for 511 total participants, with a mean (SD) of 86.1 (81.1) and a range of 2 months (min) to 443

months (max).

> Reviewer's Comment:
> Overall, postmenopausal women participating in Trial 2693-CL-0301 were recently menopausal.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment compliance with the dosing schedule was examined for participants in the SAF whose total study drug count and first and last days of treatment were known. Compliance was calculated compared to the actual treatment period of dosing (first to last day of the double-blind treatment period), not to the planned treatment period.

Compliance was verified by the accounting of study drug at each monthly visit after baseline. Treatment compliance, for the co-primary efficacy assessments, was defined as at least 80% of trial drug usage over the 12 weeks of VMS evaluation. Per the trial protocol, participants who were less than 80% compliant with the dosage regimen for any 2 consecutive visit period during the trial were encouraged to be more compliant and if a positive outcome was not rendered were considered for withdrawal from the trial.

The reported mean treatment duration with trial intervention (placebo or fezolinetant) was 78.5 days with a mean overall treatment compliance (total number of tablets actually taken x 100/[days x 2]) of 98.5% at Week 4 and at Week 12. A similar trend was observed for compliance with fezolinetant treatment at Week 52: mean treatment duration was 291.0 days with a mean overall treatment compliance of 98.8%.

> Reviewer's Comment:
> Relatively good treatment compliance was observed in Trial 2693-CL-0301.

Results – Co-Primary Endpoints

For the co-primary efficacy endpoints, frequency and severity of moderate to severe VMS endpoints in the 12-week double-blind period, the primary analysis method was a mixed model of repeated measures (MMRM) with change from baseline as dependent variable, treatment group, week (week 1 through week 12) and smoking status (current vs former/never) as factors, with baseline weight and baseline measurement as covariates, as well as an interaction of treatment by week and an interaction of baseline measurement by week. The family-wise type 1 error rate for the 2 active dose groups compared with placebo for the 4 co-primary efficacy endpoints was controlled using a Hochberg approach.

All 4 co-primary endpoints were met in both fezolinetant groups (30 mg and 45 mg) for Trial

2693-CL-0301. Participants treated with either 30 mg or 45 mg fezolinetant had a statistically significant reduction relative to placebo in the frequency of moderate to severe VMS from baseline to Weeks 4 and 12. See the applicant's frequency Table 15 below, submitted in the NDA application.

Table 15 Applicant's Primary Analysis of Co-primary Endpoints: Change from Baseline in Mean Frequency of Moderate to Severe Vasomotor Symptoms Over 24 Hours (Full Analysis Set); 12-week Double-blind Period; Trial 2693-CL-0301

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

Source: NDA 216578, Trial 2693-CL-0301 Final Study Report, Table 11, page 43 of 3190.
Full Analysis Set = All participants who were randomized and received at least 1 dose of trial intervention.
The LS means, SE, CI, and P values come from a MMRM analysis of covariance model with change from baseline as the dependent variable and treatment group, week and smoking status (current vs former/never) as factors, with baseline measurement and baseline weight as covariates, as well as an interaction of treatment by week and an interaction of baseline measurement by week.

Definitions: CI = confidence interval; LS = least squares; Max = maximum; Min = minimum; MMRM = mixed model repeated measures; NA = not applicable.
† A negative change indicated a reduction/improvement from baseline.
‡ Differences were calculated by subtracting the LS mean of placebo group from the LS mean of fezolinetant group.
§ P value is for comparison of fezolinetant with placebo from the above described MMRM model.
¶ Largest p-value within each dose compared to placebo.
†† Statistically significant adjusting for multiplicity using the Hochberg procedure at the 5% significance level (statistical significance of the 4 co-primary endpoints).

Participants treated with 30 mg and 45 mg fezolinetant also had a statistically significant reductions from baseline in the severity of moderate to severe VMS relative to placebo at Weeks 4 and 12. See the applicant's severity Table 16 below, submitted in the NDA application.

Table 16 Applicant's Primary Analysis of Co-primary Endpoints: Change from Baseline in Mean Severity of Moderate to Severe Vasomotor Symptoms Over 24 Hours (Full Analysis Set); 12-week Double-blind Period; Trial 2693-CL-0301

Analysis Visit	Statistic	Placebo (n = 175)	Fezolinetant 30 mg (n = 173)	Fezolinetant 45 mg (n = 174)
Baseline	n	175	173	174
	Mean (SD)	2.43 (0.35)	2.39 (0.34)	2.40 (0.35)
	Median	2.35	2.33	2.36
	Min, Max	1.8, 3.0	1.8, 3.0	1.8, 3.0
Week 4	n	166	157	164
	Mean (SD)	2.13 (0.58)	1.95 (0.60)	1.95 (0.64)
	Median	2.05	2.00	2.00
	Min, Max	0.0, 3.0	0.0, 3.0	0.0, 3.0
	Change from Baseline†			
	n	166	157	164
	Mean (SD)	-0.28 (0.50)	-0.43 (0.56)	-0.45 (0.61)
	Median	-0.11	-0.24	-0.25
	Min, Max	-2.4, 0.6	-2.4, 0.4	-3.0, 0.4
	LS mean (SE)	-0.27 (0.04)	-0.42 (0.04)	-0.46 (0.04)
	95% CI (2-sided)	-0.35, -0.19	-0.50, -0.34	-0.54, -0.37
	Difference in LS Means‡: Fezolinetant vs Placebo			
	LS mean (SE)	NA	-0.15 (0.06)	-0.19 (0.06)
	95% CI (2-sided)		-0.27, -0.03	-0.30, -0.07
	P value (2-sided unadjusted) §		0.012	0.002
	P value (2-sided adjusted) ¶		0.012††	0.007††
Week 12	n	139	131	146
	Mean (SD)	2.06 (0.59)	1.79 (0.69)	1.83 (0.75)
	Median	2.00	2.00	1.97
	Min, Max	0.0, 3.0	0.0, 3.0	0.0, 3.0
	Change from Baseline†			
	n	139	131	146
	Mean (SD)	-0.35 (0.58)	-0.57 (0.73)	-0.58 (0.75)
	Median	-0.18	-0.31	-0.33
	Min, Max	-3.0, 0.6	-3.0, 0.4	-2.9, 0.7
	LS mean (SE)	-0.37 (0.05)	-0.60 (0.05)	-0.57 (0.05)
	95% CI (2-sided)	-0.47, -0.26	-0.71, -0.50	-0.67, -0.47
Week 12	**Difference in LS Means‡: Fezolinetant vs Placebo**			
	LS mean (SE)	NA	-0.24 (0.08)	-0.20 (0.08)
	95% CI (2-sided)		(-0.39, -0.09)	-0.35, -0.06
	P value (2-sided unadjusted) §		0.002	0.007
	P value (2-sided adjusted) ¶		0.012††	0.007††

Source: NDA 216578, Trial 2693-CL-0301, Final Study Report, Table 12, page 44 of 3190.
Baseline includes moderate to severe incidences. Postbaseline includes mild, moderate and severe incidences.
Full Analysis Set = All participants who were randomized and received at least 1 dose of study intervention.
The LS means, SE, CI, and P values come from a MMRM analysis of covariance model with change from baseline as the dependent variable and treatment group, week and smoking status (current vs former/never) as factors, with baseline

measurement and baseline weight as covariates, as well as an interaction of treatment by week and an interaction of baseline measurement by week.
Definitions: CI = confidence interval; LS = least squares; Max = maximum; Min = minimum; MMRM = mixed model repeated measures; NA = not applicable.
† A negative change indicated a reduction/improvement from baseline.
‡ Differences were calculated by subtracting the LS mean of placebo group from the LS mean of fezolinetant group.
§ P value is for comparison of fezolinetant with placebo from the above described MMRM model.
¶ Largest p-value within each dose compared with placebo.
†† Statistically significant adjusting for multiplicity using the Hochberg procedure at the 5% significance level (statistical significance of the 4 co-primary endpoints).

The Biometric Reviewer verified and replicated the applicant's change from baseline in the mean frequency of moderate to severe vasomotor symptoms in Trial 2693-CL-0301 as shown in Table 17.

Table 17 Biometric Reviewer's Primary Analysis of Change from Baseline in the Mean Frequency of Moderate to Severe Vasomotor Symptoms at Week 4 and Week 12 for the Full Analysis Set in Trial 2693-CL-0301

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

Source: Biometric Review, dated November 21, 2022.

The Biometric Reviewer also verified and replicated the applicant's change from baseline in the mean severity of moderate to severe vasomotor symptoms in Trial 2693-CL-0301 as shown in Table 18.

Table 18 Biometric Reviewer's Primary Analysis of Change from Baseline in the Mean Severity of Moderate to Severe Vasomotor Symptoms at Week 4 and Week 12 for the Full Analysis Set in Trial 2693-CL-0301

	Trial 2693-CL-0301		
	Placebo	Fezolinetant 30 mg	Fezolinetant 45 mg
Baseline (N)	175	173	174
Mean Severity (SD)	2.43 (0.35)	2.39 (0.34)	2.40 (0.35)
Week 4 (N)	166	157	164
Mean Severity Change (SD)	-0.28 (0.50)	-0.43 (0.56)	-0.45 (0.61)
Mean Difference from Placebo (SE)	--	-0.15 (0.06)	-0.19 (0.06)
(95% CI)	--	(-0.27, -0.03)	(-0.30, -0.07)
p-value		0.012	0.002
Week 12 (N)	139	131	146
Mean Severity Change (SD)	-0.35 (0.58)	-0.57 (0.73)	-0.58 (0.75)
Mean Difference from Placebo (SE)	--	-0.24 (0.08)	-0.20 (0.08)
(95% CI)	--	(-0.39, -0.09)	(-0.35, -0.05)
p-value		0.002	0.007

Source: Biometric Review, dated November 21, 2022.

Reviewer's Comment:
In Tables 17 and 18, the 30 mg and 45 mg fezolinetant doses both demonstrate a statistically significant reduction in the frequency and severity of hot flashes at Week 4 and Week 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 addition to a statistically significant reduction in the frequency and severity of hot flashes at Week 4 and Week 12 as co-primary measures of the effectiveness of their drug product, the Agency has communicated to the applicant that the change in hot flash frequency demonstrated for their product also represent a clinically meaningful change over that of placebo by achieving a clinically meaningful frequency threshold reduction of a mean change of 2 moderate to severe vasomotor symptoms per day or 14 per week above placebo at Week 4 that is maintained through Week 12.

The applicant evaluated and analyzed clinically meaningfulness as a secondary endpoint in Trial 2693-CL-0301. The results of these analyses for each week from Week 4 through Week 12 are presented in Table 19.

Table 19 Applicant's Analyses of Change in Mean Frequency of Moderate to Severe VMS Over 24 Hours at Week 4 Through Week 12 in Trial 2693-CL-0301, Full Analysis Set

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

Source: Adapted from NDA 216578, Trial 2693-CI-0301 Clinical Study Report, Table 9.3.2.1.1, page 404 of 3190.
The LS Means and standard errors come from a mixed model repeated measurements (MMRM) analysis of covariance model with change from baseline as the dependent variable and treatment group, week and smoking status (current vs former/never) as factors, with baseline measurement and baseline weight as covariates, as well as an interaction of treatment by week and an interaction of baseline measurement by week.
Definitions: LS = least squared, SE = standard error.

Reviewer's Comment:
It is evident in Table 19, using the application LS mean (SE) change from placebo, that the 45 mg fezolinetant dosage strength produces a clinical meaningful frequency threshold difference of two above placebo at Week 4 that is maintained through Week 12. The 30 mg fezolinetant dosage strength, not proposed for approval, does not show a LS mean (SE) change from placebo greater than two hot flashes until Week 5 which is then maintained through Week 12.

Subgroup Analyses/Smoking Status:

In Trial 2693-CL-0301, participants were stratified for smoking status (current smoker vs former/never smoker). Reported results on the frequency and severity of vasomotor symptoms and the corresponding subgroup analyses are presented in the following Table 20.

Table 20 Applicant's Subgroup Analyses of Co-primary Endpoints Over 24 Hours: Smoking Status (Full Analysis Set); 12-week Double-blind Period; Trial 2693-CL-0301

Analysis Visit	Smoking Status	Statistic	Placebo (n = 175)	Fezolinetant 30 mg (n = 173)	Fezolinetant 45 mg (n = 174)
Frequency of moderate to severe VMS					
Baseline	Current	N	22	21	23
		Mean (SD)	11.08 (4.50)	11.79 (3.64)	9.88 (3.26)
	Former/never	n	153	152	151
		Mean (SD)	10.43 (3.68)	10.49 (4.85)	10.52 (4.01)
Week 4	Current	n	20	19	21
		Change from baseline mean (SD) †	-3.87 (4.11)	-6.40 (4.20)	-4.44 (4.33)
	Former/never	n	146	138	143
		Change from baseline mean (SD) †	-3.19 (4.20)	-5.20 (5.73)	-5.31 (4.04)
Week 12	Current	n	19	13	17
		Change from baseline mean (SD) †	-3.52 (4.30)	-8.52 (5.33)	-5.81 (3.86)
	Former/never	n	120	118	129
		Change from baseline mean (SD) †	-3.69 (4.18)	-6.21 (6.21)	-6.46 (4.57)
Severity of moderate to severe VMS					
Baseline	Current	n	22	21	23
		Mean (SD)	2.52 (0.31)	2.48 (0.35)	2.43 (0.37)
	Former/never	n	153	152	151
		Mean (SD)	2.41 (0.36)	2.38 (0.34)	2.39 (0.35)
Week 4	Current	n	20	19	21
		Change from baseline mean (SD) †	-0.48 (0.79)	-0.35 (0.49)	-0.70 (0.87)
	Former/never	n	146	138	143
		Change from baseline mean (SD) †	-0.25 (0.44)	-0.44 (0.57)	-0.41 (0.55)
Week 12	Current	n	19	13	17
		Change from baseline mean (SD) †	-0.38 (0.68)	-0.60 (0.71)	-0.93 (0.87)
	Former/never	n	120	118	129
		Change from baseline mean (SD) †	-0.34 (0.56)	-0.56 (0.73)	-0.53 (0.72)

Source: NDA 216578, Trial 2693-CL-0301 Study Report, Table 15, page 49 of 3190.
All participants who were randomized and received at least 1 dose of study intervention (Full Analysis Set).
Definitions: VMS = vasomotor symptoms, SD = standard deviation.
† A negative change indicated a reduction/improvement from baseline.

Reviewer's Comment:

In Trial 2693-CL-0301, the majority of participants were former/never smokers. At Weeks 4 and 12, both current smokers and former/never smokers demonstrated a greater change from baseline for fezolinetant vs placebo in both frequency and severity of moderate to severe VMS. One exception is noted for the 30 mg fezolinetant dose which did not show a greater reduction compared to placebo in severity at Week 4 in current smokers. The applicant is not requesting approval of the 30 mg fezolinetant dose.

Trial 2693-CL-0301 was not powered to show a difference in smoking status. Therefore, the interpretation of these results is limited. This information should not appear in product labeling should 45 mg fezolinetant be approved for the indication sought.

Subgroup Analyses/Age Status:

In Trial 2693-CL-0301, subgroup analysis of age (< 55 years of age vs ≥ 55 years of age) was performed for the co-primary endpoints of frequency and severity at Weeks 4 and 12. Reported results for frequency and severity of VMS and the corresponding age subgroup analyses are presented in the following Table 21.

Table 21 Applicant's Subgroup Analysis of Co-primary Endpoints Over 24 Hours: Age Status (Full Analysis Set); 12-week Double-blind Period, Trial 2693-CL-0301

Analysis Visit	Age Status	Statistic	Placebo (n = 175)	Fezolinetant 30 mg (n – 173)	Fezolinetant 45 mg (n = 174)
Frequency of Moderate to Severe VMS					
Baseline	< 55 years	n	91	93	97
		Mean (SD)	10.54 (3.33)	10.54 (3.70)	10.80 (4.61)
	≥ 55 years	N	84	80	77
		Mean (SD)	10.48 (4.25)	10.78 (5.72)	9.98 (2.77)
Week 4	< 55 years	n	86	82	93
		Mean SD	7.08 (4.41)	5.44 (3.71)	5.47 (4.67)
		Mean Change from Baseline (SD)	-3.42 (4.03)	-5.09 (4.51)	5.30 (4.25)
		LS Mean Change from Baseline (SE)	-3.49 (0.40)	-5.12 (0.40)	-5.31 (0.39)
		Difference in LS Means (SE)	--	-1.63 (0.57)	-1.82 (0.56)
	≥ 55 years	n	80	75	71
		Mean SD	7.43 (4.19)	5.27 (3.85)	4.85 (4.23)
		Mean Change from Baseline (SD)	-3.11 (4.35)	-5.62 (6.56)	-5.07 (3.85)
		LS Mean Change from Baseline (SE)	-3.07 (0.42)	-5.23 (0.44)	-5.56 (0.44)
		Difference in LS Means (SE)	--	-2.15 (0.61)	-2.47 (0.61)
Week 12	< 55 years	n	69	72	80
		Mean SD	6.68 (4.35)	1.48 (3.60)	4.09 (3.53)

Analysis Visit	Age Status	Statistic	Placebo (n = 175)	Fezolinetant 30 mg (n – 173)	Fezolinetant 45 mg (n = 174)
		Mean Change from Baseline (SD)	-4.01 (4.19)	-6.14 (5.05)	-6.70 (4.48)
		LS Mean Change from Baseline (SE)	-4.19 (0.42)	-6.17 (0.41)	-6.58 (0.39)
		Difference in LS Means (SE)	--	-1.97 (0.59)	-2.38 (0.57)
	≥ 55 years	n	70	56	66
		Mean SD	7.02 (4.97)	4.44 (3.90)	4.01 (4.22)
		Mean Change from Baseline (SD)	-3.34 (4.17)	-6.81 (7.30)	-6.00 (3.93)
		LS Mean Change from Baseline (SE)	-3.52 (0.46)	-6.41 (0.48)	-6.34 (0.47)
		Difference in LS Means (SE)	--	-2.90 (0.66)	-2.82 (0.66)
Severity of Moderate to Severe VMS					
Baseline	< 55 years	n	91	93	97
		Mean (SD)	2.47 (0.35)	2.43 (0.36)	2.42 (0.36)
	≥ 55 years	n	84	80	77
		Mean (SD)	2.37 (0.35)	2.35 (0.32)	2.37 (0.34)
Week 4	< 55 years	n	86	82	93
		Mean SD	2.12 (0.63)	1.99 (0.62)	1.99 (0.64)
		Mean Change from Baseline (SD)	-0.34 (0.55)	-0.42 (0.57)	-0.42 (0.58)
		LS Mean Change from Baseline (SE)	-0.32 (0.06)	-0.41 (0.06)	-0.43 (0.06)
		Difference in LS Means (SE)	--	-0.08 (0.08)	-0.11 (0.08)
	≥ 55 years	n	80	75	71
		Mean SD	2.15 (0.53)	1.90 (0.58)	1.89 (0.65)
		Mean Change from Baseline (SD)	-0.22 (0.44)	-0.44 (0.54)	-0.49 (0.65)
		LS Mean Change from Baseline (SE)	-0.21 (0.06)	-0.43 (0.06)	-0.49 (0.06)
		Difference in LS Means (SE)	--	-0.22 (0.08)	-0.28 (0.09)
Week 12	< 55 years	n	69	72	80
		Mean SD	2.04 (0.68)	1.81 (0.75)	1.87 (0.80)
		Mean Change from Baseline (SD)	-0.43 (0.68)	-0.59 (0.77)	-0.57 (0.75)
		LS Mean Change from Baseline (SE)	-0.45 (0.08)	-0.60 (0.08)	-0.56 (0.08)
		Difference in LS Means (SE)	--	-0.15 (0.11)	-0.12 (0.11)
	≥ 55 years	n	70	59	66
		Mean SD	2.08 (0.48)	1.77 (0.63)	1.79 (0.70)
		Mean Change from Baseline (SD)	-0.26 (0.44)	-0.54 (0.67)	-0.58 (0.75)
		LS Mean Change from Baseline (SE)	-0.29 (0.07)	-0.61 (0.07)	-0.57 (0.07)
		Difference in LS Means (SE)	--	-0.32 (0.10)	-0.29 (0.10)

Source: Adapted from NDA 216578, Trial 2693-CL-0301 Study Report, Table 9.3.1.7.7, page 380 of 3190 and Table 9.3.1.7.8, page 384 of 3190.
All participants who were randomized and received at least 1 dose of study intervention (Full Analysis Set).
Definitions: VMS = vasomotor symptoms, SD = standard deviation, SE = standard error.

Reviewer's Comment:
Trial 2693-CL-0301 was not powered to show a difference in age subgroups. Therefore, the interpretation of these results is limited. This information should not appear in product labeling should 45 mg fezolinetant be approved for the indication sought.

Nonetheless, the reported results appear to show similar reductions in frequency and severity at Weeks 4 and 12 that is greater than placebo for both age subgroups.

Subgroup Analyses/Race Status:

In Trial 2693-CL-0301, subgroup analysis of race (African American vs non-African American, Asian vs non-Asian, White vs non-White) were performed for the co-primary endpoints of frequency and severity of VMS at Weeks 4 and 12. However, the interpretation of these results are limited due to the small number of participants in some of these subgroups. Reported VMS frequency and severity results for only those participants who self-identified as Black/African America or White are presented in the following Table 22.

Table 22 Applicant's Subgroup Analysis by Self-identified Racial Group of Change in Mean Frequency and Severity of Moderate to Severe VMS Over 24 Hours from Baseline to Week 4 and Week12: Reported Results for Black/African American and White Subgroups; Trial 2693-CL-0301 (Full Analysis Set)

Analysis Visit	Statistic	Placebo (n = 175)	Fezolinetant 30 mg (n = 173)	Fezolinetant 45 mg (n = 174)
Self-identified Race Subgroup: Black/African American				
Frequency of Moderate to Severe VMS				
Baseline	n	28	21	26
	Mean (SD)	11.06 (5.35)	10.93 (4.42)	10.19 (3.03)
Week 4	n	26	20	26
	Mean SD	6.47 (3.68)	5.68 (4.35)	4.16 (4.06)
	Mean Change from Baseline (SD)	-4.86 (6.14)	-5.40 (4.88)	-6.03 (3.28)
	LS Mean Change from Baseline (SE)	-4.31 (0.72)	-5.10 (0.85)	-6.36 (0.75)
	Difference in LS Means (SE)	--	-0.79 (1.11)	-2.05 (1.04)
Week 12	n	20	16	23
	Mean SD	6.81 (4.62)	4.81 (4.25)	2.89 (3.30)
	Mean Change from Baseline (SD)	-3.81 (4.98)	-6.66 (5.34)	-6.98 (2.31)
	LS Mean Change from Baseline			

Analysis Visit	Statistic	Placebo (n = 175)	Fezolinetant 30 mg (n = 173)	Fezolinetant 45 mg (n = 174)
	(SE)	-4.28 (0.73)	-6.36 (0.86)	-7.36 (0.73)
	Difference in LS Means (SE)	--	-2.08 (1.12)	-3.07 (1.03)
Self-identified Race Subgroup: White				
Frequency of Moderate to Severe VMS				
Baseline	n	142	147	142
	Mean (SD)	10.43 (3.46)	10.65 (4.86)	10.40 (1.09)
Week 4	n	135	133	133
	Mean SD	7.46 (4.40)	5.46 (3.64)	5.41 (4.57)
	Mean Change from Baseline (SD)	-2.93 (3.65)	-5.22 (5.73)	-4.96 (4.24)
	LS Mean Change from Baseline (SE)	-3.06 (0.32)	-5.07 (0.32)	-5.17 (0.33)
	Difference in LS Means (SE)	--	-2.01 (0.46)	-2.11 (0.46)
Week 12	n	116	112	118
	Mean SD	9.87 (4.05)	4.50 (3.60)	4.25 (3.93)
	Mean Change from Baseline (SD)	-3.67 (4.05)	-6.37 (6.34)	-6.21 (4.85)
	LS Mean Change from Baseline (SE)	-3.80 (0.35)	-6.20 (0.35)	-6.25 (0.34)
	Difference in LS Means (SE)	--	-2.40 (0.49)	-2.45 (0.49)
Self-identified Race Subgroup: Black/African American				
Severity of Moderate to Severe VMS				
Baseline	n	28	21	26
	Mean (SD)	2.47 (0.31)	2.28 (0.32)	2.33 (0.34)
Week 4	n	26	20	26
	Mean SD	2.18 (0.42)	1.89 (0.58)	4.86 (0.72)
	Mean Change from Baseline (SD)	-0.29 (0.33)	-0.41 (0.55)	-0.48 (0.64)
	LS Mean Change from Baseline (SE)	-0.27 (0.10)	-0.42 (0.12)	-0.48 (0.10)
	Difference in LS Means (SE)	--	-0.15 (0.15)	-0.21 (0.14)
Week 12	n	20	16	23
	Mean SD	2.13 (0.49)	1.67 (0.76)	1.71 (0.73)
	Mean Change from Baseline (SD)	-0.34 (0.44)	-0.62 (0.86)	-0.63 (0.70)
	LS Mean Change from Baseline (SE)	-0.36 (0.14)	-0.63 (0.16)	-0.64 (0.14)
	Difference in LS Means (SE)	--	-0.27 (0.22)	-0.28 (0.20)
Self-identified Race Subgroup: White				
Baseline	n	142	147	142
	Mean (SD)	2.41 (0.36)	2.41 (0.35)	2.41 (0.35)
Week 4	n	136	133	133
	Mean SD	2.13 (0.59)	1.98 (0.59)	1.96 (0.62)
	Mean Change from Baseline			

Analysis Visit	Statistic	Placebo (n = 175)	Fezolinetant 30 mg (n = 173)	Fezolinetant 45 mg (n = 174)
	(SD)	-0.27 (0.50)	-0.41 (0.56)	-0.45 (0.06)
	LS Mean Change from Baseline (SE)	-0.27 (0.05)	-0.40 (0.56)	-0.45 (0.60)
	Difference in LS Means (SE)	--	-0.13 (0.06)	-0.18 (0.06)
Week 12	n	115	112	118
	Mean SD	2.03 (0.61)	1.84 (0.65)	1.85 (0.74)
	Mean Change from Baseline (SD)	-0.35 (0.60)	-0.53 (0.68)	-0.57 (0.74)
	LS Mean Change from Baseline (SE)	-0.37 (0.06)	-0.57 (0.06)	-0.56 (0.06)
	Difference in LS Means (SE)	--	-0.21 (0.08)	-0.19 (0.08)

Source: Adapted from NDA 216578, Trial 2693-CL-0301 Study Report, Frequency from Table 9.3.1.7.3.1, page 344 of 3190 and Table 9.3.1.7.3.3, page 353 of 3190; Severity from Table 9.3.1.7.4.1, page 356 of 3190 and Table 9.3.3.1.4.3, page 364 of 3190.
The LS Means, standard errors, and confidence intervals come from a mixed model repeated measurements (MMRM) analysis of covariance model with change from baseline as the dependent variable and treatment group and week as factors, with baseline measurement as a covariate, as well as an interaction of treatment by week and an interaction of baseline measurement by week.
Differences are calculated by subtracting the LS mean of placebo group from the LS mean of fezolinetant group.
Definitions: VMS = vasomotor symptoms, SD = standard deviation, SE = standard error.

Reviewer's Comment:
As shown in Table 22, the mean change in VMS frequency and severity at Weeks 4 and 12 were consistently similar for 45 mg fezolinetant in participants who self-identified as either Black/African American or White. However, Trial 2693-CL-0301 was not powered to show a difference in race subgroups. This information should not appear in product labeling should 45 mg fezolinetant be approved for the indication sought.

Subgroup Analyses/BMI Status:

In Trial 2693-CL-0301, subgroup analysis of BMI (≥ 18.5 kg/m^2 to < 25 kg/m^2; ≥ 25 kg/m^2 to < 30 kg/m^2; ≥ 30 kg/m^2) were performed for the co-primary endpoints of frequency and severity of VMS at Weeks 4 and 12. Reported VMS frequency results are presented in the following Table 23.

Table 23 Applicant's Subgroup Analyses by Body Mass Index (BMI) for the Change from Baseline to Week 4 and Week 12 in Mean Frequency of Moderate to Severe Vasomotor Symptoms Over 24 Hours

Analysis Visit	Statistic	Placebo (n = 175)	Fezolinetant 30 mg (n = 173)	Fezolinetant 45 mg (n = 174)
BMI Subgroup: ≥ 18.5 kg/m^2 to < 25 kg/m^2				
Frequency of Moderate to Severe VMS				
Baseline	n	44	50	40
	Mean (SD)	10.71 (4.60)	10.50 (3.24)	10.31 (3.07)
Week 4	n	42	43	39
	Mean SD	4.28 (4.68)	5.48 (3.60)	4.74 (3.39)
	Mean Change from Baseline (SD)	-3.52 (3.69)	-4.99 (4.10)	-5.55 (3.86)
	LS Mean Change from Baseline (SE)	-3.29 (0.52)	-4.81 (0.50)	-5.65 (0.55)
	Difference in LS Means (SE)	--	-1.52 (0.72)	-2.36 (0.75)
Week 12	n	35	36	33
	Mean SD	7.41 (5.77)	4.57 (3.42)	3.77 (2.96)
	Mean Change from Baseline (SD)	-3.55 (3.86)	-5.93 (4.19)	-6.23 (3.14)
	LS Mean Change from Baseline (SE)	-3.59 (0.56)	-5.92 (0.55)	-6.56 (0.58)
	Difference in LS Means (SE)	--	-2.32 (0.79)	-2.97 (0.81)
BMI Subgroup: ≥ 25 kg/m^2 to < 30 kg/m^2				
Frequency of Moderate to Severe VMS				
Baseline	n	71	60	79
	Mean (SD)	10.15 (2.56)	10.28 (2.86)	10.42 (4.58)
Week 4	n	69	56	74
	Mean SD	7.17 (4.19)	5.63 (3.74)	5.53 (4.96)
	Mean Change from Baseline (SD)	-2.95 (3.94)	-4.68 (3.54)	-4.95 (4.44)
	LS Mean Change from Baseline (SE)	-3.18 (0.45)	-4.68 (0.50)	-5.01 (0.43)
	Difference in LS Means (SE)	--	-1.50 (0.67)	-1.83 (0.63)
Week 12	n	57	46	69
	Mean SD	6.47 (4.63)	4.67 (3.59)	3.98 (3.48)
	Mean Change from Baseline (SD)	-3.77 (4.23)	-5.85 (4.19)	-6.64 (5.41)
	LS Mean Change from Baseline (SE)	-4.02 (0.48)	-5.96 (0.53)	-6.31 (0.45)
	Difference in LS Means (SE)	--	-1.94 (0.71)	-2.29 (0.66)
BMI Subgroup: BMI Subgroup: ≥ 30 kg/m^2				
Frequency of Moderate to Severe VMS				
Baseline	n	60	62	53
	Mean (SD)	10.80 (4.34)	11.17 (6.80)	10.65 (3.49)
Week 4	n	56	57	49

Analysis Visit	Statistic	Placebo (n = 175)	Fezolinetant 30 mg (n = 173)	Fezolinetant 45 mg (n = 174)
	Mean SD	7.32 (4.19)	4.99 (3.98)	5.29 (3.74)
	Mean Change from Baseline (SD)	-3.47 (4.80)	-6.31 (7.74)	-5.19 (3.74)
	LS Mean Change from Baseline (SE)	-3.44 (0.53)	-5.99 (0.53)	-5.70 (0.56)
	Difference in LS Means (SE)	--	-2.55 (0.74)	-2.25 (0.77)
Week 12	n	47	48	43
	Mean SD	6.91 (3.75)	4.15 (4.16)	4.59 (4.90)
	Mean Change from Baseline (SD)	-3.64 (4.43)	-7.45 (8.54)	-6.03 (3.86)
	LS Mean Change from Baseline (SE)	-3.97 (0.55)	-6.97 (0.55)	-6.48 (0.58)
	Difference in LS Means (SE)	--	-3.00 (0.78)	-2.51 (0.80)

Source: Adapted from NDA 216578, Trial 2693-CL-0301 Study Report, Table 9.3.1.7.5, page 369 of 3190.
The LS Means, standard errors, and confidence intervals (CI) come from a mixed model repeated measures (MMRM) analysis of covariance model with change from baseline as the dependent variable and treatment group and week as factors, with baseline measurement as a covariate, as well as an interaction of treatment by week and an interaction of baseline measurement by week.
A negative change indicates a reduction/improvement from baseline.
Differences are calculated by subtracting the LS mean of placebo group from the LS mean of fezolinetant group.

See the NDA application for the reported results of the mean change in VMS severity at Weeks 4 and 12 for BMI subgroup analyses in Trial 2693-CL-0301.

> Reviewer's Comment:
> As shown in Table 23, similar numbers of participants were enrolled in each BMI subgroup in Trial 2693-CL-0301. Reported frequency reduction results appear stronger at Week 12 vs Week 4. Participants with a BMI ≥ 30 kg/m^2 appear to show the stronger differences in LS means (SE) in both fezolinetant dosage strengths. Trial 2693-CL-0301 was not powered to show a difference in BMI subgroups. Therefore, the interpretation of these results is limited. This information should not appear in product labeling should 45 mg fezolinetant be approved for the indication sought.

Data Quality and Integrity

Trial 2693-CL-0301 protocol and protocol amendments were reviewed and approved by the IRB/IEC before the trial was initiated and prior to authorization of drug shipment to the trial site. The endpoints used in this trial (e.g., efficacy, immunogenicity, pharmacokinetics, pharmacodynamics, safety and other endpoints) were standard, generally reliable and relevant to the objectives set forth in the protocol.

Astellas implemented and maintained quality assurance and quality control systems with

written standard operating procedures to ensure that Trial 2693-CL-0301 was conducted and data were generated, documented, recorded and reported in compliance with the protocol, GCP and applicable regulatory requirements.

Trial centers were monitored by the contract research organization ((b) (4)). Monitors were responsible for reviewing adherence to the protocol; compliance with GCP and applicable regulatory requirements; and the completeness, accuracy and consistency of the data. Audits of this trial were included as part of the independent quality assessment performed by the applicant. See Section 4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety, Subsection 4.1. Office of Scientific Investigations (OSI) for additional information on the audits conducted by the applicant.

Efficacy Results – Secondary and other relevant endpoints

Sensitivity Analyses:
The applicant conducted sensitivity analyses of the PPS to support the primary analyses on the co-primary endpoints. See Table 24.

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

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

Source: NDA216578, Trial 2693-CL-0301 Clinical Study Report, Table 13, page 46 of 3190.
All randomized participants from the Full Analysis Set who were treated according to the protocol without any major deviations at Week 4 and Week 12 endpoints (Per Protocol Set).
The LS means, SE, confidence interval, and P values come from a MMRM analysis of covariance model with change from baseline as the dependent variable and treatment group, week and smoking status (current vs former/never) as factors, with baseline measurement and baseline weight as covariates, as well as an interaction of treatment by week and an interaction of baseline measurement by week.
The number of participants (n) is different for baseline measurements by week 4 and week 12 due to a different proportion of participants being excluded from PPS. Excluded participants could have more than one reason of exclusion.
Definitions: CI = confidence interval; LS = least squares; MMRM = mixed model repeated measures; NA = not applicable; PPS = per protocol set; VMS = vasomotor symptoms.
† A negative change indicated a reduction/improvement from baseline .
‡ Differences were calculated by subtracting the LS mean of placebo group from the LS mean of fezolinetant group.
§ P value is for comparison of fezolinetant with placebo from the above described MMRM model.

Reviewer's Comment:
As shown in Table 24, sensitivity analyses performed for the PPS support the primary analysis for the co-primary endpoints in Trial 2693-CL-0301. The 30 mg and 45 mg fezolinetant doses are both statistically significant for frequency and severity at Weeks 4 and 12.

Responder Analyses:
The percent reduction ≥ 50% and at 100% in the frequency of moderate to severe VMS from baseline to each week up to Week 12 was also calculated as a secondary objective in Trial 2693-CL-0301. The following Table 25 shows the reported results for both the ≥ 50% reduction from baseline and the ≥ 100% reduction from baseline at Weeks 4 and 12.

Table 25 Applicant's Responder Analyses of Change from Baseline in Frequency of Moderate to Severe Vasomotor Symptoms at Week 4 and Week 12 in Trial 2693-CL-0301; Full Analysis Set

Responder Criteria/Week	Placebo N = 175	30 mg Fezolinetant N = 173	45 mg Fezolinetant N = 174
≥ 50% Reduction			
- Week 4	49 (28.0%)	77 (44.5%)	94 (54.0%)
- Week 12	52 (29.7%)	77 (44.5%)	99 (56.7%)
≥ 100% Reduction			
- Week 4	5 (2.9%)	6 (3.5%)	8 (4.6%)
- Week 12	6 (3.4%)	12 (6.9%)	18 (10.3%)

Source: Adapted from NDA 216578, Trial 2593-CL-0301 Clinical Study Report, Table 18, page 55 0f 3190.
Full Analysis Set: All participants who were randomized and received at least 1 dose of trial medication. Participants with missing VMS at an analysis visit were considered non-responders.

Reviewer's Comment:
A higher proportion of participants had a ≥ 50% reduction and a ≥ 100 % reduction in the frequency of moderate to severe VMS in the 30 mg and 45 mg fezolinetant groups

than in the placebo group at Week 4 and Week 12. The 45 mg fezolinetant group showed a higher reduction in frequency than the 30 mg fezolinetant group for both responder criteria (≥ 50% and ≥ 100%).

Per the application, the ≥ 50% reduction differences were statistically different for both doses at Week 4 and Week 12 (p= 0.001 and p=0.005, respectively, for 30 mg fezolinetant; and p< 0.001 and p<0.001, respectively, for 45 mg fezolinetant). However, only Week 12 for the 45 mg fezolinetant dose was statistically different for ≥ 100% reduction (p=0.015 at Week 12).

See Table 9.3.3.6.1 in the Clinical Study Report (page 464 of 3190) for the reported finding for each week during the 12-week double-blind period.

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

The reported results for the 12-week double-blind period are shown in Table 26.

Table 26 Applicant's Analyses of Patient Global Impression of Change – Vasomotor Symptoms (PGI-C VMS)

12-week Double-blind Period (Full Analysis Set)				
Visit	**Response**	**Placebo (n = 175)**	**Fezolinetant 30 mg (n = 173)**	**Fezolinetant 45 mg (n = 174)**
Week 4	Much better	32/160 (20.0%)	50/150 (33.3%)	72/160 (45.0%)
	Moderately better	21/160 (13.1%)	33/150 (22.0%)	24/160 (15.0%)
	A little better	44/160 (27.5%)	42/150 (28.0%)	35/160 (21.9%)
	No change	55/160 (34.4%)	23/150 (15.3%)	28/160 (17.5%)
	A little worse	1/160 (0.6%)	1/150 (0.7%)	0
	Moderately worse	1/160 (0.6%)	1/150 (0.7%)	1/160 (0.6%)
	Much worse	6/160 (3.8%)	0	0
	p-value†	NA	< 0.001	< 0.001
Week 12	Much better	35/149 (23.5%)	49/135 (36.3%)	74/157 (47.1%)
	Moderately better	24/149 (16.1%)	24/135 (17.8%)	30/157 (19.1%)
	A little better	40/149 (26.8%)	41/135 (30.4%)	35/157 (22.3%)
	No change	37/149 (24.8%)	19/135 (14.1%)	11/157 (7.0%)
	A little worse	6/149 (4.0%)	1/135 (0.7%)	2/157 (1.3%)
	Moderately worse	4/149 (2.7%)	1/135 (0.7%)	4/157 (2.5%)
	Much worse	3/149 (2.0%)	0	1/157 (0.6%)
	p-value†	NA	< 0.001	< 0.001

Source: Adapted from NDA 216578, Trial 2693-CL-0301 Study Report, Table 21, page 60 of 3190.
All participants who were randomized and received at least 1 dose of fezolinetant during either the 12-week double-blind or the active treatment extension periods (Full Analysis Set, Fezolinetant).
† P-value was obtained using Cochran-Mantel-Haenszel test with modified ridit scores. The association between response and treatment group (fezolinetant 30 mg vs placebo and fezolinetant 45 mg vs placebo) ateach analysis visit was tested.

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

On May 24, 2022, Astellas received the Agency's A/IR letter regarding the revised Psychometric Analysis Plan (PAP) and the PAP Summary Report submitted to IND 130277 on March 3, 2022, with requests for information to be submitted at the time of the NDA application including, but not limited to, providing evidence to support that the "moderately better" response category in the PGI-C VMS constitutes a meaningful change in the anchor scale.

In the NDA application, however, Astellas clarifies that PGI-C VMS reported results are considered *exploratory and only intended as supplementary evidence of efficacy*. Per the information provided in the NDA application:

> "Astellas understands that the primary assessment of clinically meaningful change will be in accordance with the Agency's prior communications that fezolinetant must

> demonstrate a mean reduction of 2 hot flashes per day compared to placebo in each pivotal study, at both 4 and 12 weeks. Astellas is not proposing that the PAP analyses are alternative criteria for demonstrating clinically meaningful change.
>
> As communicated by the FDA to Astellas in the 20 Sep 2019 Advice Letter and the Type C meetings dated 18 Sep 2020 and 28 July 2021, Astellas is in agreement that to obtain an indication for the treatment of moderate to severe vasomotor symptoms (VMS) due to menopause, we would need to demonstrate a statistically significant decrease from baseline in the frequency and severity of moderate to severe VMS at Weeks 4 and 12 for fezolinetant compared to placebo and the magnitude of the reduction from baseline in frequency of moderate to severe VMS at Weeks 4 and 12 exceed that of placebo at these timepoints by at least 2 moderate to severe hot flushes per day.
>
> Astellas fully agrees and is aligned with the Agency's approach to use this criterium when assessing the clinical efficacy of fezolinetant during the NDA review."

On July 29, 2022, the Division of Clinical Outcome Assessment (DCOA) was consulted regarding the information available in the NDA application as reported in the above Reviewer's Comments. DCOA was requested to respond to the following requests and questions:

1. Do you have additional comments and/or recommendations regarding the Psychometric Analysis Plan (PAP) and Astellas' responses included in the NDA application?

2. As secondary endpoint, please evaluate the applicant's assessment of meaningful within subject change of frequency of vasomotor symptoms. Discuss the strengths and weakness of the applicant's assessment.

On November 22, 2022, the DCOA Biometric Reviewer for NDA 216578 concludes, "In the NDA submission, in addition to the "14/2 Concept" (Applicant's primary assessment of clinically meaningful reduction in VMS frequency), the Applicant conducted additional exploratory analyses using clinically meaningful within-patient change thresholds derived from anchor-based analyses to interpret the change in the frequency of moderate to severe VMS. DCOA team has concluded that the selected primary anchor PGIC-VMS has limitations which make it difficult to interpret the results of the anchor-based analyses. Acknowledging the limitations of PGIC-VMS as the only available anchor included in the studies for the VMS frequency, we observed a clear and consistent separation between the treatment group eCDF curves (fezolinetant 30 mg vs. placebo and fezolinetant 45 mg vs. placebo) across the entire range of score change, including both FDA- and Applicant-derived meaningful change thresholds as determined by PGIC-VMS at both Week 4 and Week 12 for both phase 3 trials."

Reviewer's Comment:
See the DCOA final consult response, dated November 22, 2022, for information on the limitations of the PGI-C VMS anchor.

Dose/Dose Response

The results reported in phase 3 Trial 2693-CL-0301 show an incremental benefit in VMS frequency and severity for 45 mg fezolinetant when compared with the 30 mg fezolinetant dose. Fezolinetant 45 mg achieved statistical significance vs placebo more consistently across the frequency and severity efficacy endpoints analyzed than the 30 mg fezolinetant group.

Durability of Response

A 12-week, placebo-controlled, clinical Trial 2693-CL-0301 was conducted to demonstrate effectiveness of the fezolinetant drug product for the indication of the treatment of moderate to severe vasomotor symptoms, due to menopause.

Persistence of Effect

Per the NDA application, secondary efficacy analyses during the active treatment 40-week extension period in this trial "support the treatment effect of fezolinetant with no evidence of reduced effect size suggestive of tachyphylaxis." The NDA application states:

- "The effect of fezolinetant on VMS frequency and severity observed during the 12-week double-blind period was sustained during the active treatment extension period in participants treated with 30 mg and 45 mg fezolinetant for the entire 52-weeks."
- "Participants on placebo when re-randomized to active fezolinetant also demonstrated additional and sustained benefit from fezolinetant treatment on VMS frequency and severity throughout the 40-week extension period."

In addition, the following individual secondary endpoints are reported for the 40-weeks active treatment extension period:

- Mean change in the frequency of moderate to severe VMS from baseline to Week 24.
- Mean change in the severity of moderate to severe VMS from baseline to Week 24.

Reviewer's Comment:
The above reported results of the change from baseline to Week 24 in Trial 2693-CL-0301 in the frequency and severity of hot flashes are secondary endpoints and the presented data is descriptive only without a placebo comparator. This data is not relevant to the co-primary efficacy endpoints, and will not appear in product labeling

should the 45 mg fezolinetant dose be approved for the treatment of moderate to severe VMS due to menopause.

Additional Analyses Conducted on the Individual Trial

Patient-reported Outcomes Measurement Information System Sleep Disturbance – Short Form 8b (PROMIS SD SF 8b):
In Trial 2693-CL-0301, the protocol defined key secondary objective examined the effect of fezolinetant versus placebo on the mean change in the Patient-reported Outcomes Measurement Information System Sleep Disturbance – Short Form 8b (PROMIS SD SF 8b) total score from baseline to Week 12. Participants treated with both 30 mg and 45 mg fezolinetant had a numerical decrease in this defined key secondary analyses. However, the difference relative to placebo was not statistically significant (30 mg fezolinetant p-value = 0.489; 45 mg fezolinetant p-value = 0.155).

Reviewer's Comment:
The above reported result of a numerical decrease in the PROMIS SD SF 8b total score is a secondary endpoint in Trial 2693-CL-0301. Astellas was advised on April 17, 2019 and September 20, 2019 that reported results for proposed secondary and exploratory objectives/endpoints (for example, the PROMIS® SD SF 8b) (b) (4) .

6.2 [Trial 2603-CL-0302]

6.2.1 Study Design

Trial 2693-CL-0302 (Skylight 2, NCT04003142) titled "A Phase 3, Randomized, Placebo-controlled, 12-week Double-blind Study, followed by a Non-controlled Extension Treatment Period, to Assess the Efficacy and Safety of Fezolinetant in Women Suffering from Moderate to Severe Vasomotor Symptoms (Hot Flashes) Associated with Menopause" was phase 3, 52-weeks clinical trial with an adequate and well-controlled first 12-week period which utilized a double-blind, placebo-controlled trial design, followed by an open-label 40-week extension period of active treatment only.

Five hundred one (501) healthy postmenopausal women, 40 to 65 years of age (average of 54.3 years of age), with at least 7 to 8 moderate to severe hot flashes per day, were randomized in a 1:1:1 ratio to placebo, 30 mg fezolinetant, or 45 mg fezolinetant given orally, once daily, with or

without food. After completing 12-weeks of treatment, participants on placebo who agreed to continue trial participation in the 40-week extension period, were re-randomized in a 1:1 ratio to 30 mg fezolinetant or 45 mg fezolinetant treatment groups. Participants who completed treatment with 30 mg fezolinetant or 45 mg fezolinetant in the 12-week double-blind period, who agreed to continue trial participation in the 40-week extension period, continued to receive the same fezolinetant dose during the active treatment extension period.

> Reviewer's Comment:
> The primary objectives of Trial 2693-CL-0302 were to evaluate the efficacy of 30 mg or 45 mg fezolinetant versus placebo on the frequency and severity of moderate to severe vasomotor symptoms (VMS) during the first 12-weeks of treatment, and to assess the chronic use and long-term safety of fezolinetant.

Trial 2693-CL-0302 was identical in design to Trial 2693-CL-0301 with the same key secondary/secondary and exploratory objectives, trial endpoints including safety endpoints, inclusion/exclusion criteria, procedures and evaluations, and statistical analysis plan.

> Reviewer's Comment:
> Because Trials 2693-CL-0301 and 2693-CI-0302 are identical in trial design this information is not repeated for Trial 2693-CL-0302. The reader is referred to the information provided for Trial 2693-CL-0301 in this review

Protocol Amendments

The original protocol for Trial 2693-CL-0302 was submitted May 30, 2019 (Version 1.0, dated January 28, 2019). Overall, three (3) protocol amendments were submitted: Amendment 1 (Version 2, dated May 17, 2019); Amendment 1 (Version 2.1, dated December 5, 2019); and Amendment 2 (Version 3.0. dated July 1, 2020). The Clinical Study Report for Trial 2693-CL-0302 included in the NDA application is dated February 23, 2022.

6.2.2 Study Results

Compliance with Good Clinical Practice

Per the application, Trial 2693-CL-0302 was "conducted in accordance with the protocol and consensus ethical principles derived from international guidelines including the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and CIOMS International Ethical Guidelines
- Applicable ICH GCP Guidelines

- Applicable laws and regulations"

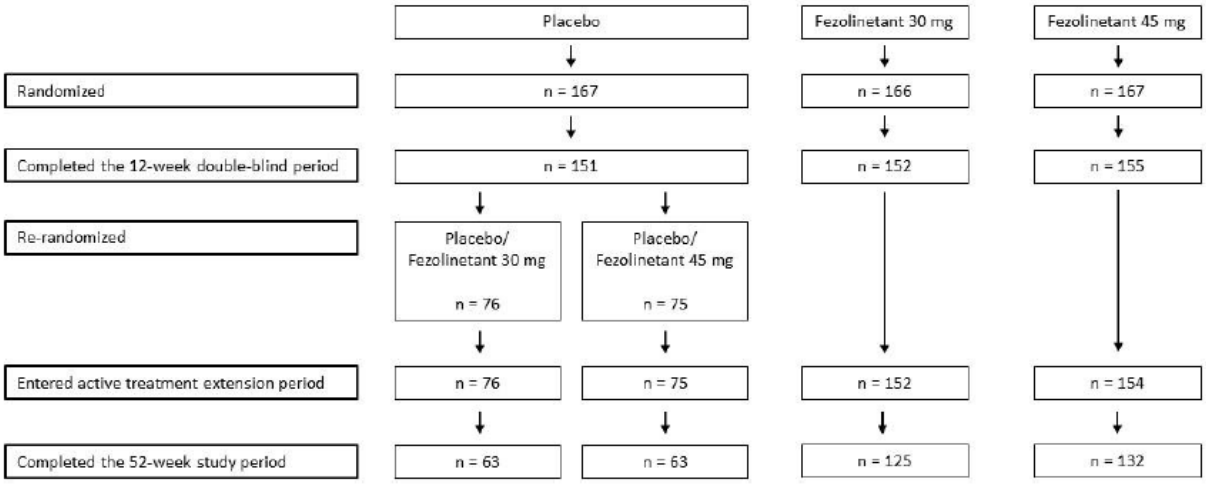
Financial Disclosures

Pursuant to 21 CFR 54, Astellas provided financial certification and disclosure information for all covered clinical trials submitted in support of this application. Form FDA 3454 (4/21), signed by Judith Kannenberg, Vice President, RA, TA Head, Medical Specialties, Astellas Pharma US, 1 Astellas Way, Northbrook, IL 60062, dated June 6, 2022, indicates "There were no investigators with financial arrangements, payments, or interests requiring disclosure under 21 CFR 54.4(a)(3)" and confirms, "As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f))."

Patient Disposition

Of the 501 participants randomized in this trial (168 to placebo, 155 to 30 mg fezolinetant, 156 to 45 mg fezolinetant, 500 took at least 1 dose of trial medication (1 placebo participant did not take any trial medication), and were included in the safety analysis set (SAF) and full analysis set (FAS). The following Figure 2 shows the treatment disposition for the safety analysis set.

Figure 2 Treatment Disposition in Trial 2693-CL-0302; Safety Analysis Set



Source: NDA 216578, Trial 2693-CL-0302 Study Report, Figure 2, page 33 of 2749.
Safety Analysis Set = All randomized participants who took 1 dose of trial medication.

Of the 500 participants who took the trial medication, a total of 458 completed the 12-week double-blind period; of these 457 entered the 40-weeks extension period. In total, 383 participant completed the full 52-weeks in Trial 2693-CL-0302.

Eighty-seven (87) participants were excluded from the per protocol set (PPS) at Week 4 and 139 at Week 12. The main reasons for exclusion from the PPS included:

1) No measurement of primary efficacy endpoint available (highest exclusion for placebo at Week 4 (9.5%) and 30 mg fezolinetant at Week 12 (19.9%).
2) < 85% interactive diary compliance (highest exclusion for 45 mg fezolinetant at Week 4 (13.8%) and 30 mg fezolinetant at Week 12 (24.1%).
3) ≤ 85% treatment compliance (highest exclusion for placebo and 45 mg fezolinetant at Week 4 (4.2% for both) and 30 mg fezolinetant at Week 12 (3.0%).

Reviewer's Comment:
Overall, the reasons for exclusions from the PPS was similar across the treatment groups in Trial 2693-CL-0302.

Protocol Violations/Deviations

As in Trial 2693-CL-0301, the major protocol deviation criteria was summarized at the end of Trial 2693-CL-0302 as follows:

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

A total of 104 randomized participants (20.8%; 104 of 501 randomized participants) had a major protocol deviation during the 12-week double-blind period, and 113 participants in the SAF (22.6%; 113 of 500 participants) during the whole 52-week treatment period in Trial 2693-CL-0302. See Table 27 and Table 28.

Table 27 Major Protocol Deviations (All Randomized Participants); 12-week Double-blind Period; Trial 2693-CL-0302

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

Source: NDA 216578, Trial 2693-CL-0302 Study Report, Table 4, page 35 of 2749.
Definitions: PD = Protocol deviation.

Table 28 Major Protocol Deviations (Safety Analysis Set); 52-week Period; Trial 2693-CL-0302

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

Source: NDA 216578, Trial 2693-CL-0302 Study Report, Table 5, page 35 of 2749.
Safety Analysis Set: All randomized participants who took at least 1 dose of trial medication.
Participants in the placebo/fezolinetant groups were re-randomized in a 1:1 ratio to 30 mg or 45 mg of fezolinetant after 12 weeks of placebo and only data from the active treatment extension period are shown in the placebo/fezolinetant columns (fezolinetant exposure).

Reviewer's Comment:
As shown in Table 27 and Table 28, the most common major protocol deviation in all treatment groups was PD1 (participants who entered the study but did not satisfy entry criteria). As in Trial 2693-CL-0301, the 3 most common eligibility criteria deviations in Trial 2693-CL-0302 were:

1) Inclusion criterion # 4: Seeking treatment or relief for VMS associated with menopause and confirmed as menopausal.
2) Inclusion Criterion # 11: Has a negative urine pregnancy test at screening.
3) Exclusion criterion # 4: Systolic blood pressure is ≥ 130 mmHg or diastolic blood pressure is ≥ 80 mmHg based on the average of 2 to 3 readings, on at least 2 different occasions within the screening period.

Overall, there were no important differences in frequencies of major protocol deviations between treatment groups in Trial 2693-CL-0302.

Table of Demographic Characteristics

Demographics and baseline characteristics were similar between treatment groups. See Table 29. Slightly more than half of participants were less than 55 years of age (52.8%), with a median age of 54.0 years of age. Most participants were White (79.4%), not Hispanic or Latino (78.6%)

and were either former or never smokers (79.4%). In addition, only 21.5% of participants had received prior treatment with hormone therapy.

Table 29 Demographic and Selected Baseline Characteristics, Safety Analysis Set; Trial 2693-CL-0302

Demographic Parameters	Treatment Group			
	Placebo Group (N=175) n (%)	30 mg Fezolinetant Treatment Group (N= 174) n (%)	45 mg Fezolinetant Treatment Group (N=173) n (%)	Total (N= 522) n (%)
Age (Years)				
Mean (SD)	54.7 (4.6)	53.9 (4.9)	54.3 (5.4)	54.3 (5.0)
Median	54.0	54.0	55.0	54.0
Min, Max	44, 65	42, 65	40, 65	40, 65
Age Category				
< 55 years	89 (53.3%)	93 (56.0%)	82 (49.1%)	264 (52.8%))
> 55 years	78 (46.7%)	73 (44.0%)	85 (50.9%)	236 (47.2%)
Race				
White	134 (80.2%)	131 (78.9%)	132 (78.0%)	397 (79.4%)
Black or African American	31 (18.6%)	35 (21.1%)	33 (19.8%)	99 (19.8%)
American Indian or Alaska Native	0	0	1 (0.6%)	1 (0.2%)
Asian	1 (0.6%)	0	0	1 (0.2%)
More Than One Race	0	1 (0.6%)	1 (0.6%)	2 (0.4%)
Ethnicity				
Hispanic or Latino	32 (19.3%)	34 (20.5%)	41 (24.6%)	107 (21.4%)
Not Hispanic or Latino	134 (80.7%)	132 (79.5%)	126 (75.4%)	392 (78.6%)
Missing	1	0	0	1
Weight (kg) (n)				
Mean (SD)	74.57 (14.68)	75.33 (14.09)	74.62 (12.45)	74.84 (13.75)
Median	71.70	74.05	73.00	73.00
Min, Max	NC	NC	NC	NC
BMI (kg/m^2) (n)				
Mean (SD)	28.16 (4.99)	27.94 (4.69)	27.91 (4.35)	28.00 (4.68)
Median	27.78	27.76	27.28	27.58
Min, Max	18.6, 38.0	18.1, 37.6	18.0, 37.5	18.0, 38.0
BMI Category (kg/m^2)				
< 18.5	0	1 (0.6%)	1 (0.6%)	2 (0.4%)
≥ 18.5 to < 25	53 (31.7%)	54 (32.5%)	45 (26.9%)	152 (30.4%)
≥ 25 to < 30	62 (37.1%)	58 (34.9%)	73 (43.7%)	193 (38.6%)

Demographic Parameters	Treatment Group			
	Placebo Group (N=175) n (%)	30 mg Fezolinetant Treatment Group (N= 174) n (%)	45 mg Fezolinetant Treatment Group (N=173) n (%)	Total (N= 522) n (%)
≥ 30	52 (31.1%)	53 (31.9%)	48 (28.7%)	153 (30.6%)
Smoking Status Stratification factor†				
Current	35 (21.0%)	34 (20.5%)	34 (20.4%)	103 (21.5%)
Former/never	132 (79.0%)	132 (79.5%)	133 (79.6%)	397 (79.4%)
Prior Hormone Therapy				
Yes	31 (18.5%)	37 (22.6%)	38 (23.3%)	106 (21.5%)
No	136 (81.4%)	127 (77.4%)	125 (76.7%)	388 (78.5%)
Missing	0	2	4	6

Source: NDA 216578, Trial 2693-CL-0302 Study Report, Table 8, page 38 of 2749.
Safety Analysis Set: All randomized participants who took at least 1 dose of trial intervention.
Definitions: BMI = body mass index (weight [kg]/height [m2]); Min = minimum; Max = maximum.

Reviewer's Comment:
Primary efficacy and safety Trials 2693-CL-0301 and 2693-CL-0302 had very similar participant populations. One noted difference between the two multi-countries, phase 3 trials, is race, particularly participants who self-identified as black or African American. Trial 2693-CL-0302 had more participants who self-identified as black or African American than in Trial 2693-CL-0301; 19.8% vs 14.4%, respectively.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

The medial time since onset of vasomotor symptoms was 56.3 months (range of 2 to 396 months) for 500 total participants in Trial 2693-CL-0302.

The median time to onset of amenorrhea in 500 total participants in Trial 2693-CL-0302 was 58.6 months (range 3 to 491 months).

Reviewer's Comment:
Overall, participants in Trial 2693-CL-0302 were recently menopausal.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Compliance of the trial drug was monitored and documented by the accounting of unused medication returned by the participant at site visits. If compliance was less than 80%, the investigator or designee was to counsel the participant to ensure steps were taken to improve compliance. Per the protocol, participants with less than 80% compliance with the dosage regimen for any 2 consecutive visits during the trial were considered for withdrawal from the study.

The mean treatment duration in Trial 2693-CL-0302 (placebo or fezolinetant) was 80.1 days with a mean overall treatment compliance (total number of tablets actually taken x 100/[days x 2]) of 99.0% at Week 4 and 99.3% at Week 12. A similar trend was observed for compliance with fezolinetant treatment at Week 52: mean treatment duration was 296.3 days with a mean overall treatment compliance of 99.1%.

> Reviewer's Comment:
> Relatively good treatment compliance was observed in Trial 2693-CL-0302.

Results – Co-Primary Endpoints

All 4 co-primary efficacy endpoints were met in both fezolinetant groups (30 mg and 45 mg) for Trial 2693-CL-0302. Participants treated with either 30 mg or 45 mg fezolinetant had a statistically significant reduction relative to placebo in the frequency of moderate to severe VMS from baseline to Weeks 4 and 12. See the applicant's frequency Table 30 below, submitted in the NDA application.

Table 30 Applicant's Primary Analysis of Co-primary Endpoints: Change from Baseline in Mean Frequency of Moderate to Severe Vasomotor Symptoms Over 24 Hours (Full Analysis Set); 12-week Double-blind Period; Trial 2693-CL-0302

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

Source: NDA 216578, Trial 2693-CL-0302, Final Study Report, Table 11, page 45 of 2749.
Full Analysis Set = All participants who were randomized and received at least 1 dose of trial intervention.
The LS means, SE, CI, and P values come from a MMRM analysis of covariance model with change from baseline as the dependent variable and treatment group, week and smoking status (current vs former/never) as factors, with baseline measurement and baseline weight as covariates, as well as an interaction of treatment by week and an interaction of baseline measurement by week.
Definitions: CI = confidence interval; LS = least squares; Max = maximum; Min = minimum; MMRM = mixed model repeated measures; NA = not applicable.
† A negative change indicated a reduction/improvement from baseline.
‡ Differences were calculated by subtracting the LS mean of placebo group from the LS mean of fezolinetant group.

§ P value is for comparison of fezolinetant with placebo from the above described MMRM model.
¶ Largest p-value within each dose compared to placebo.
†† Statistically significant adjusting for multiplicity using the Hochberg procedure at the 5% significance level (statistical significance of the 4 co-primary endpoints).

Participants treated with 30 mg and 45 mg fezolinetant also had a statistically significant reductions from baseline in the severity of moderate to severe VMS relative to placebo at Weeks 4 and 12. See the applicant's severity Table 31 below, submitted in the NDA application.

Table 31 Applicant's Primary Analysis of Co-primary Endpoints: Change from Baseline in Mean Severity of Moderate to Severe Vasomotor Symptoms Over 24 Hours (Full Analysis Set); 12-week Double-blind Period; Trial 2693-CL-0302

Analysis Visit	Statistic	Placebo (n = 167)	Fezolinetant 30 mg (n = 166)	Fezolinetant 45 mg (n = 167)
Baseline	n	167	166	167
	Mean (SD)	2.41 (0.32)	2.44 (0.33)	2.41 (0.34)
	Median	2.37	2.44	2.34
	Min, Max	2.0, 3.0	2.0, 3.0	1.9, 3.0
Week 4	n	151	155	155
	Mean (SD)	2.11 (0.56)	1.97 (0.65)	1.80 (0.74)
	Median	2.04	2.00	1.97
	Min, Max	0.0, 3.0	0.0, 3.0	0.0, 3.0
	Change from Baseline†			
	n	151	155	155
	Mean (SD)	-0.31 (0.48)	-0.47 (0.58)	-0.61 (0.63)
	Median	-0.14	-0.27	-0.42
	Min, Max	-2.1, 0.4	-3.0, 0.5	-2.7, 0.3
	LS mean (SE)	-0.32 (0.05)	-0.47 (0.05)	-0.61 (0.05)
	95% CI (2-sided)	-0.41, -0.23	-0.56, -0.38	-0.70, -0.52
	Difference in LS Means‡: Fezolinetant vs Placebo			
	LS mean (SE)	NA	-0.15 (0.06)	-0.29 (0.06)
	95% CI (2-sided)		-0.27, -0.02	-0.41, -0.16
	P value (2-sided unadjusted) §		0.021	< 0.001
	P value (2-sided adjusted) ¶		0.049 ††	< 0.001 ††
Week 12	n	140	133	145
	Mean (SD)	1.95 (0.68)	1.84 (0.79)	1.66 (0.79)
	Median	2.00	2.00	1.74
	Min, Max	0.0, 3.0	0.0, 3.0	0.0, 3.0
	Change from Baseline†			
	n	140	133	145
	Mean (SD)	-0.46 (0.65)	-0.60 (0.75)	-0.74 (0.71)
	Median	-0.28	-0.25	-0.61
	Min, Max	-3.0, 0.6	-3.0, 0.4	-2.8, 0.5
	LS mean (SE)	-0.48 (0.06)	-0.64 (0.06)	-0.77 (0.06)

Analysis Visit	Statistic	Placebo (n = 167)	Fezolinetant 30 mg (n = 166)	Fezolinetant 45 mg (n = 167)
Week 12	95% CI (2-sided)	-0.59, -0.36	-0.76, -0.53	-0.88, -0.65
	Difference in LS Means‡: Fezolinetant vs Placebo			
	LS mean (SE)	NA	-0.16 (0.08)	-0.29 (0.08)
	95% CI (2-sided)		-0.33, 0.00	-0.45, -0.13
	P value (2-sided unadjusted) §		0.049	< 0.001
	P value (2-sided adjusted) ¶		0.049 ††	< 0.001 ††

Source: NDA 216578, Trial 2693-CL-0302, Final Study Report, Table 12, page 46 of 2749.
Baseline includes moderate to severe incidences. Postbaseline includes mild, moderate and severe incidences.
Full Analysis Set = All participants who were randomized and received at least 1 dose of study intervention.
The LS means, SE, CI, and P values come from a MMRM analysis of covariance model with change from baseline as the dependent variable and treatment group, week and smoking status (current vs former/never) as factors, with baseline measurement and baseline weight as covariates, as well as an interaction of treatment by week and an interaction of baseline measurement by week.
Definitions: CI = confidence interval; LS = least squares; Max = maximum; Min = minimum; MMRM = mixed model repeated measures; NA = not applicable.
† A negative change indicated a reduction/improvement from baseline.
‡ Differences were calculated by subtracting the LS mean of placebo group from the LS mean of fezolinetant group.
§ P value is for comparison of fezolinetant with placebo from the above described MMRM model.
¶ Largest p-value within each dose compared with placebo.
†† Statistically significant adjusting for multiplicity using the Hochberg procedure at the 5% significance level (statistical significance of the 4 co-primary endpoints).

The Biometric Reviewer verified and replicated the applicant's change from baseline in the mean frequency of moderate to severe vasomotor symptoms in Trial 2693-CL-0302 as shown in Table 32.

Table 32 Biometric Reviewer's Primary Analysis of Change from Baseline in the Mean Frequency of Moderate to Severe Vasomotor Symptoms at Week 4 and Week 12 for the Full Analysis Set in Trial 2693-CL-0302

	Trial 2693-CL-0302		
	Placebo	Fezolinetant 30 mg	Fezolinetant 45 mg
Baseline (N)	167	166	167
Mean Frequency (SD)	11.57 (5.02)	11.23 (4.88)	11.79 (8.26)
Week 4 (N)	151	155	155
Mean Frequency Change (SD)	-3.64 (4.15)	-5.52 (4.23)	-6.24 (4.78)
Mean Difference from Placebo (SE)	--	-1.82 (0.46)	-2.55 (0.46)
(95% CI)	--	(-2.73, -0.91)	(-3.45, -1.64)
p-value		<0.001	<0.001
Week 12 (N)	140	133	145
Mean Frequency Change (SD)	-4.57 (5.14)	-6.43 (4.77)	-7.43 (6.47)
Mean Difference from Placebo (SE)	--	-1.86 (0.55)	-2.53 (0.55)
(95% CI)	--	(-2.90 -0.78)	(-3.60, -1.46)
p-value		<0.001	<0.001

Source: Biometric Review, dated November 21, 2022.

The Biometric Reviewer also verified and replicated the applicant's change from baseline in the mean severity of moderate to severe vasomotor symptoms in Trial 2693-CL-0302 as shown in Table 33.

Table 33 Biometric Reviewer's Primary Analysis of Change from Baseline in the Mean Severity of Moderate to Severe Vasomotor Symptoms at Week 4 and Week 12 for the Full Analysis Set in Trial 2693-CL-0302

	Trial 2693-CL-0302		
	Placebo	Fezolinetant 30 mg	Fezolinetant 45 mg
Baseline (N)	167	166	167
Mean Severity (SD)	2.41 (0.32)	2.44 (0.33)	2.41 (0.34)
Week 4 (N)	151	155	155
Mean Severity Change (SD)	-0.31 (0.48)	-0.47 (0.58)	-0.61 (0.34)
Mean Difference from Placebo (SE)	--	-0.15 (0.06)	-0.29 (0.06)
(95% CI)	--	(-0.27, -0.02)	(-0.42, -0.16)
p-value		0.021	<0.001
Week 12 (N)	140	133	145
Mean Severity Change (SD)	-0.46 (0.65)	-0.60 (0.75)	-0.74 (0.71)
Mean Difference from Placebo (SE)	--	-0.16 (0.08)	-0.29 (0.08)
(95% CI)	--	(-0.33, -0.00)	(-0.45, -0.13)
p-value		0.049	<0.001

Source: Biometric Review, dated November 21, 2022.

Reviewer's Comment:

> In Tables 32 and 33, the 30 mg and 45 mg fezolinetant doses both demonstrate a statistically significant reduction in the frequency and severity of hot flashes at Week 4 and Week 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 addition to a statistically significant reduction in the frequency and severity of hot flashes at Week 4 and Week 12 as co-primary measures of effectiveness of their drug product, the Agency has communicated to the applicant that the change in hot flash frequency demonstrated for their product also represent a clinically meaningful change over that of placebo by achieving a clinically meaningful frequency threshold reduction of a mean change of 2 moderate to severe vasomotor symptoms per day or 14 per week above placebo at Week 4 that is maintained through Week 12.

The applicant evaluated and analyzed clinically meaningfulness as a secondary endpoint in Trial 2693-CL-0302. The results of these analyses for each week from Week 4 through Week 12 are presented in Table 34.

Table 34 Analysis of Change in Mean Frequency of Moderate to Severe VMS at Week 4 Through Week 12 in Trial 2693-CL-0302, Full Analysis Set

Visit/Statistics	Trial 2693-CL-0302		
	Placebo (N = 167)	Fezolinetant 30 mg (N = 166)	Fezolinetant 45 mg (N = 167)
Baseline Mean Frequency (SD)	11.59 (5.02)	11.23 (4.88)	11.79 (8.26)
Week 4 (N)	151	155	155
Mean Frequency Change (SD)	-3.64 (4.15)	-5.52 (4.23)	-6.24 (4.78)
LS Mean Change (SE)	-3.72 (0.33)	-5.53 (0.33)	-6.26 (0.33)
LS Mean Difference from Placebo (SE)	--	-1.82 (0.46)	-2.55 (0.46)
Week 5 (N)	152	152	154
Mean Frequency Change (SD)	-3.39 (4.40)	-5.68 (4.33)	-6.63 (4.79)
LS Mean Change (SE)	-4.05 (0.34)	-5.89 (0.34)	-6.71 (0.34)
LS Mean Difference from Placebo (SE)	--	-1.84 (0.48)	-2.66 (0.48)
Week 6 (N)	152	146	149
Mean Frequency Change (SD)	-4.21 (4.43)	-5.81 (4.35)	-6.79 (4.90)
LS Mean Change (SE)	-4.25 (0.33)	-6.03 (0.33)	-6.91 (0.33)
LS Mean Difference from Placebo (SE)	--	-1.78 (0.47)	-2.66 (0.47)
Week 7 (N)	149	143	147
Mean Frequency Change (SD)	-4.30 (4.35)	-5.93 (4.46)	-6.63 (5.01)
LS Mean Change (SE)	-4.44 (0.35)	-6.24 (0.35)	-6.78 (0.35)
LS Mean Difference from Placebo (SE)	--	-1.80 (0.49)	-2.34 (0.49)
Week 8 (N)	148	143	154
Mean Frequency Change (SD)	-4.29 (4.76)	-5.97 (4.59)	-6.81 (5.20)
LS Mean Change (SE)	-4.48 (0.37)	-6.25 (0.37)	-6.86 (0.37)
LS Mean Difference from Placebo (SE)	--	-1.76 (0.52)	-2.38 (0.52)
Week 9 (N)	145	140	148

Visit/Statistics	Trial 2693-CL-0302		
	Placebo (N = 167)	Fezolinetant 30 mg (N = 166)	Fezolinetant 45 mg (N = 167)
Mean Frequency Change (SD)	-4.59 (5.37)	-6.15 (4.45)	-7.24 (5.67)
LS Mean Change (SE)	-4.88 (0.38)	-6.54 (0.38)	-7.39 (0.38)
LS Mean Difference from Placebo (SE)	--	-1.65 (0.54)	-2.51 (0.54)
Week 10 (N)	139	138	149
Mean Frequency Change (SD)	-4.47 (5.22)	-6.41 (4.35)	-7.42 (6.04)
LS Mean Change (SE)	-4.83 (0.38)	-6.74 (0.38)	-7.47 (0.38)
LS Mean Difference from Placebo (SE)	--	-1.91 (0.54)	-2.65 (0.53)
Week 11 (N)	138	142	149
Mean Frequency Change (SD)	-4.46 (5.14)	-6.45 (4.52)	-7.43 (6.18)
LS Mean Change (SE)	-4.90 (0.38)	-6.76 (0.38)	-7.46 (0.37)
LS Mean Difference from Placebo (SE)	--	-1.86 (0.53)	-2.56 (0.53)
Week 12 (N)	140	133	145
Mean Frequency Change (SD)	-4.57 (5.14)	-6.43 (4.77)	-7.43 (6.47)
LS Mean Change (SE)	-4.97 (0.39)	-6.83 (0.39)	-7.50 (0.39)
LS Mean Difference from Placebo (SE)	--	-1.86 (0.55)	-2.53 (0.55)

Source: Adapted from NDA 216578, Trial 2693-CI-0301 Clinical Study Report, Table 9.3.3.1.1, page 364 of 2749.
The LS Means and standard errors come from a mixed model repeated measures (MMRM) analysis of covariance model with change from baseline as the dependent variable and treatment group, week and smoking status (current vs former/never) as factors, with baseline measurement and baseline weight as covariates, as well as an interaction of treatment by week and an interaction of baseline measurement by week.
Definitions: LS = least squares, SE = standard error.

Reviewer's Comment:
It is evident in Table 34, using the application LS mean (SE) change from placebo, that the 45 mg fezolinetant dosage strength produces a clinical meaningful frequency threshold difference of two above placebo at Week 4 that is maintained through Week 12. The 30 mg fezolinetant dosage strength, not proposed for approval, does not show a LS mean (SE) change from placebo greater than two hot flashes for any weeks between Week 4 and Week 12 in Trial 2693-CL-0302.

Subgroup Analysis/Smoking Status:

In Trial 2693-CL-0302, participants were stratified for smoking status (current smoker vs former/never smoker). Reported results on the frequency and severity of vasomotor symptoms and the corresponding subgroup analyses are presented in the following Table 35.

Table 35 Applicant's Subgroup Analyses of Co-primary Endpoints: Smoking Status (Full Analysis Set); 12-week Double-blind Period; Trial 2693-CL-0302

Analysis Visit	Smoking Status	Statistic	Placebo (n = 167)	Fezolinetant 30 mg (n = 166)	Fezolinetant 45 mg (n = 167)
Frequency of moderate to severe VMS					
Baseline	Current	n	35	34	34
		Mean (SD)	10.54 (3.44)	11.57 (4.23)	11.39 (8.05)
	Former/never	n	132	132	133
		Mean (SD)	11.86 (5.34)	11.15 (5.04)	11.89 (8.34)
Week 4	Current	n	28	31	31
		Change from baseline mean (SD) †	-3.82 (4.36)	-6.69 (3.78)	-7.91 (5.61)
	Former/never	n	123	124	124
		Change from baseline mean (SD) †	-3.61 (4.11)	-5.22 (4.30)	-5.82 (4.48)
Week 12	Current	n	25	26	28
		Change from baseline mean (SD) †	-4.09 (4.38)	-7.30 (4.94)	-8.45 (6.36)
	Former/never	n	115	107	117
		Change from baseline mean (SD) †	-4.67 (5.31)	-6.22 (4.73)	-7.19 (6.50)
Severity of moderate to severe VMS					
Baseline	Current	n	35	34	34
		Mean (SD)	2.42 (0.33)	2.42 (0.35)	2.37 (0.27)
	Former/never	n	132	132	133
		Mean (SD)	2.41 (0.32)	2.44 (0.32)	2.41 (0.35)
Week 4	Current	n	28	31	31
		Change from baseline mean (SD) †	-0.32 (0.59)	-0.58 (0.72)	-0.73 (0.68)
	Former/never	n	123	124	124
		Change from baseline mean (SD) †	-0.31 (0.46)	-0.44 (0.53)	-0.58 (0.62)
Week 12	Current	n	25	26	28
		Change from baseline mean (SD) †	-0.53 (0.79)	-0.77 (0.81)	-0.76 (0.68)
	Former/never	n	115	107	117
		Change from baseline mean (SD) †	-0.44 (0.62)	-0.56 (0.73)	-0.73 (0.72)

Source: NDA 216578, Trial 2693-CL-0302 Study Report, Table 15, page 15 of 2749.
All participants who were randomized and received at least 1 dose of study intervention (Full Analysis Set).
Definitions: VMS = vasomotor symptoms, SD = standard deviation.
† A negative change indicated a reduction/improvement from baseline.

Reviewer's Comment:
In Trial 2693-CL-0302, the majority of participants were former/never smokers. Trial 2693-CL-0302 was not powered to show a difference in subgroups by smoking status. Therefore, the interpretation of these results is limited. This information should not appear in product labeling should 45 mg fezolinetant be approved for the indication sought.

That said, the reported results at Weeks 4 and 12 appear to show that former/never smokers demonstrated a greater change from baseline vs placebo in both frequency and severity of moderate to severe VMS. Similar results are shown for current smokers.

Subgroup Analysis/Age Status:
In Trial 2693-CL-0302, subgroup analyses of age (< 55 years of age vs ≥ 55 years of age) was performed for the co-primary endpoints of frequency and severity at Weeks 4 and 12. Reported results for frequency and severity of VMS and the corresponding age subgroup analyses are presented in the following Table 36.

Table 36 Applicant's Subgroup Analysis of Co-primary Endpoints: Age Status (Full Analysis Set); 12-Week Double-blind Period, Trial 2693-CL-0302

Analysis Visit	Age Status	Statistic	Placebo (n = 157)	Fezolinetant 30 mg (n – 166)	Fezolinetant 45 mg (n = 168)
Frequency of Moderate to Severe VMS					
Baseline	< 55 years	n Mean (SD)	89 12.21 (6.17)	93 11.38 (4.19)	82 12.88 (11.00)
	≥ 55 years	N Mean (SD)	78 10.88 (3.14)	73 11.06 (5.66)	85 10.74 (4.77)
Week 4	< 55 years	n Mean SD Mean Change from Baseline (SD) LS Mean Change from Baseline (SE) Difference in LS Means (SE)	80 8.66 (7.70) -3.83 (4.47) -3.88 (0.50) --	87 5.54 (5.50) -5.99 (4.65) -5.97 (0.48) -2.09 (0.69)	76 5.99 (9.07) -7.03 (5.77) -6.93 (0.52) -3.05 (0.72)
	≥ 55 years	n Mean SD Mean Change from Baseline (SD) LS Mean Change from Baseline (SE) Difference in LS Means (SE)	71 7.41 (4.77) -3.44 (3.79) -3.55 (0.41) --	68 6.11 (6.66) -5.04 (3.60) -5.06 (0.42) -1.51 (0.59)	79 5.35 (5.04) -5.48 (3.46) -5.59 (0.39) -2.04 (0.57)
Week 12	< 55 years	n Mean SD Mean Change from Baseline	70 7.35 (9.28)	70 4.61 (4.95)	71 4.65 (5.90)

Analysis Visit	Age Status	Statistic	Placebo (n = 157)	Fezolinetant 30 mg (n – 166)	Fezolinetant 45 mg (n = 168)
		(SD)	-4.37 (5.88)	-6.76 (5.65)	-8.31 (8.26)
		LS Mean Change from Baseline (SE)	-5.02 (0.61)	-7.44 (0.59)	-8.30 (0.63)
		Difference in LS Means (SE)	--	-2.43 (0.84)	-3.28 (0.87)
	≥ 55 years	n	70	63	74
		Mean SD	6.12 (5.36)	5.01 (6.26)	4.34 (4.88)
		Mean Change from Baseline (SD)	-4.76 (4.32)	-6.08 (3.55)	-6.59 (3.97)
		LS Mean Change from Baseline (SE)	-4.87 (0.45)	-6.22 (0.47)	-6.65 (0.43)
		Difference in LS Means (SE)	--	-1.35 (0.65)	-1.78 (0.62)
Severity of Moderate to Severe VMS					
Baseline	< 55 years	n	89	93	82
		Mean (SD)	2.41 (0.32)	2.44 (0.36)	2.47 (0.33)
	≥ 55 years	n	78	73	85
		Mean (SD)	2.41 (0.32)	2.44 (0.31)	2.34 (0.33)
Week 4	< 55 years	n	80	87	76
		Mean SD	2.07 (0.56)	1.93 (0.68)	1.80 (0.82)
		Mean Change from Baseline (SD)	-0.34 (0.50)	-0.50 (0.61)	-0.66 (0.70)
		LS Mean Change from Baseline (SE)	-0.36 (0.07)	-0.50 (0.07)	-0.67 (0.07)
		Difference in LS Means (SE)	--	-0.14 (0.09)	-0.31 (0.10)
	≥ 55 years	n	71	68	79
		Mean SD	2.15 (0.55)	2.02 (0.62)	1.80 (0.66)
		Mean Change from Baseline (SD)	-0.28 (0.46)	-0.42 (0.53)	-0.55 (0.56)
		LS Mean Change from Baseline (SE)	-0.28 (0.06)	-0.43 (0.06)	-0.55 (0.06)
		Difference in LS Means (SE)	--	-0.16 (0.09)	-0.27 (0.08)
Week 12	< 55 years	n	70	70	71
		Mean SD	1.93 (0.70)	1.77 (0.82)	1.70 (0.81)
		Mean Change from Baseline (SD)	-0.47 (0.66)	-0.67 (0.82)	-0.76 (0.70)
		LS Mean Change from Baseline (SE)	-0.53 (0.09)	-0.72 (0.08)	-0.80 (0.09)
		Difference in LS Means (SE)	--	-0.19 (0.12)	-0.28 (0.12)
	≥ 55 years	n	70	63	74
		Mean SD	1.97 (0.67)	1.91 (0.75)	1.61 (0.77)
		Mean Change from Baseline (SD)	-0.44 (0.66)	-0.52 (0.66)	-0.72 (0.72)
		LS Mean Change from Baseline (SE)	-0.43 (0.08)	-0.56 (0.08)	-0.73 (0.08)
		Difference in LS Means (SE)	--	-0.12 (0.12)	-0.30 (0.11)

Source: Adapted from NDA 216578, Trial 2693-CL-0302 Study Report, Table 9.3.1.7.7, page 348 of 2749 and Table 9.3.1.7.8, page 352 of 2749.
All participants who were randomized and received at least 1 dose of study intervention (Full Analysis Set).
Definitions: VMS = vasomotor symptoms, SD = standard deviation.

Reviewer's Comment:
Trial 2693-CL-0302 was not powered to show a difference in age subgroups. Therefore, the interpretation of these results is limited. This information should not appear in product labeling should 45 mg fezolinetant be approved for the indication sought.

Nonetheless, the reported results appear to show similar reductions in frequency and severity at Weeks 4 and 12 that is greater than placebo for both age subgroups.

Subgroup Analyses/Race Status:
In Trial 2693-CL-0302, subgroup analysis of race (African American vs non-African American, Asian vs non-Asian, White vs non-White) were performed for the co-primary endpoints of frequency and severity of VMS at Weeks 4 and 12. However, the interpretation of these results are limited due to the small number of participants in these subgroups. Reported VMS frequency and severity results for only those participants who self-identified as Black/African America and White are presented in the following Table 37.

Table 37 Applicant's Subgroup Analysis by Self-identified Racial Group of Change in Mean Frequency and Severity of Moderate to Severe VMS Over 24 Hours from Baseline to Week 4 and Week 12: Reported Results Black/African American or White Subgroups; Trial 2693-CL-0302 (Full Analysis Set)

Analysis Visit	Statistic	Placebo (n = 167)	Fezolinetant 30 mg (n = 166)	Fezolinetant 45 mg (n = 167)
Self-identified Race Subgroup: Black/African American				
Frequency of Moderate to Severe VMS				
Baseline	n	31	35	33
	Mean (SD)	12.22 (5.74)	11.32 (3.99)	12.60 (6.30)
Week 4	n	29	32	30
	Mean SD	9.94 (9.43)	5.72 (4.10)	6.45 (6.67)
	Mean Change from Baseline (SD)	-2.07(5.55)	-5.61 (4.41)	-6.41 (5.11)
	LS Mean Change from Baseline (SE)	-2.35 (1.03)	-5.84 (0.97)	-6.57 (1.01)
	Difference in LS Means (SE)	--	-3.49 (1.42)	-4.22 (1.44)
Week 12	n	27	26	26
	Mean SD	9.15 (12.94)	4.98 (5.26)	5.53 (7.03)
	Mean Change from Baseline (SD)	-3.27 (1.06)	-7.16 (1.02)	-7.74 (1.04)
	LS Mean Change from Baseline			

Analysis Visit	Statistic	Placebo (n = 167)	Fezolinetant 30 mg (n = 166)	Fezolinetant 45 mg (n = 167)
	(SE)	-4.28 (0.73)	-6.36 (0.86)	-7.36 (0.73)
	Difference in LS Means (SE)	--	-3.88 (1.47)	-4.47 (1.48)
Self-identified Race Subgroup: White				
Frequency of Moderate to Severe VMS				
Baseline	n	134	131	132
	Mean (SD)	11.25 (4.27)	11.21 (5.10)	11.26 (7.92)
Week 4	n	120	123	123
	Mean SD	7.44 (5.06)	5.81 (6.26)	5.27 (7.26)
	Mean Change from Baseline (SD)	-4.00 (3.69)	-5.49 (4.20)	-6.06 (4.27)
	LS Mean Change from Baseline (SE)	-4.05 (0.34)	-5.41 (0.34)	-6.11 (0.34)
	Difference in LS Means (SE)	--	-1.36 (0.48)	-2.06 (0.48)
Week 12	n	111	107	117
	Mean SD	5.91 (4.05)	4.76 (5.69)	4.14 (4.90)
	Mean Change from Baseline (SD)	-5.04 (4.07)	-6.40 (4.41)	-7.19 (6.16)
	LS Mean Change from Baseline (SE)	-5.34 (0.37)	-6.62 (0.37)	-7.24 (0.36)
	Difference in LS Means (SE)	--	-1.28 (0.52)	-1.90 (0.52)
Self-identified Race Subgroup: Black/African American				
Severity of Moderate to Severe VMS				
Baseline	n	31	35	33
	Mean (SD)	2.38 (0.31)	2.50 (0.37)	2.45 (0.33)
Week 4	n	29	32	30
	Mean SD	2.09 (0.75)	1.97 (0.74)	1.89 (0.75)
	Mean Change from Baseline (SD)	-0.29 (0.56)	-0.50 (0.76)	-0.55 (0.66)
	LS Mean Change from Baseline (SE)	-0.29 (0.13)	-0.55 (0.12)	-0.57 (0.12)
	Difference in LS Means (SE)	--	-0.27 (0.17)	-0.29 (0.17)
Week 12	n	27	26	26
	Mean SD	2.01 (0.88)	1.87 (0.88)	1.76 (0.81)
	Mean Change from Baseline (SD)	-0.39 (0.72)	-0.61 (0.87)	-0.66 (0.69)
	LS Mean Change from Baseline (SE)	-0.39 (0.15)	-0.67 (0.14)	-0.69 (0.15)
	Difference in LS Means (SE)	--	-0.28 (0.21)	-0.29 (0.21)
Self-identified Race Subgroup: White				
Baseline	n	134	131	132
	Mean (SD)	2.42 (0.38)	2.42 (0.32)	2.40 (0.34)
Week 4	n	120	123	123
	Mean SD	2.11 (0.51)	1.97 (0.63)	1.77 (0.74)
	Mean Change from Baseline			

Analysis Visit	Statistic	Placebo (n = 167)	Fezolinetant 30 mg (n = 166)	Fezolinetant 45 mg (n = 167)
	(SD)	-0.31 (0.46)	-0.46 (0.52)	-0.63 (0.62)
	LS Mean Change from Baseline (SE)	-0.33 (0.05)	-0.45 (0.05)	-0.63 (0.05)
	Difference in LS Means (SE)	--	-0.12 (0.07)	-0.30 (0.07)
Week 12	n	111	107	117
	Mean SD	1.93 (0.63)	1.83 (0.77)	1.62 (0.79)
	Mean Change from Baseline (SD)	-0.48 (0.64)	-0.60 (0.72)	-0.77 (0.71)
	LS Mean Change from Baseline (SE)	-0.50 (0.06)	-0.64 (0.06)	-0.79 (0.06)
	Difference in LS Means (SE)	--	-0.14 (0.09)	-0.29 (0.09)

Source: Adapted from NDA 216578, Trial 2693-CL-0302 Study Report, Frequency from Table 9.3.1.7.3.1, page 344 of 2749 and Table 9.3.1.7.3.3, page 353 of 3749; Severity from Table 9.3.1.7.4.1, page 356 of 2749 and Table 9.3.3.1.4.3, page 364 of 2749.
The LS Means, standard errors, and confidence intervals come from a mixed model repeated measures (MMRM) analysis of covariance model with change from baseline as the dependent variable and treatment group and week as factors, with baseline measurement as a covariate, as well as an interaction of treatment by week and an interaction of baseline measurement by week.
Differences are calculated by subtracting the LS mean of placebo group from the LS mean of fezolinetant group.
Definitions: VMS = vasomotor symptoms, SD = standard deviation, SE = standard error.

Reviewer's Comment:
As shown in Table 37, the mean change in VMS frequency and severity at Weeks 4 and 12 were consistently similar for 45 mg fezolinetant in participants who self-identified as either Black/African American or White. However, Trial 2693-CL-0302 was not powered to show a difference in race subgroups. This information should not appear in product labeling should 45 mg fezolinetant be approved for the indication sought.

Subgroup Analysis/ BMI Status:

In Trial 2693-CL-0302, subgroup analysis of BMI (≥ 18.5 kg/m^2 to < 25 kg/m^2; ≥ 25 kg/m^2 to < 30 kg/m^2; ≥ 30 kg/m^2) were performed for the co-primary endpoints of frequency and severity of VMS at Weeks 4 and 12. Reported VMS frequency results are presented in the following Table 38.

Table 38 Applicant's Subgroup Analysis of BMI Change from Baseline to Week 4 and Week 12 in Mean Frequency of Moderate to Severe Vasomotor Symptoms Over 24 Hours

Analysis Visit	Statistic	Placebo (n = 167)	Fezolinetant 30 mg (n = 166)	Fezolinetant 45 mg (n = 167)
BMI Subgroup: ≥ 18.5 kg/m^2 to < 25 kg/m^2				
Frequency of Moderate to Severe VMS				
Baseline	n	53	54	45
	Mean (SD)	11.23 (3.54)	9.94 (2.70)	10.66 (3.06)
Week 4	n	50	48	40
	Mean SD	7.41 (3.92)	4.63 (4.46)	4.43 (4.72)
	Mean Change from Baseline (SD)	-3.76 (3.31)	-5.47 (3.85)	-6.25 (3.20)
	LS Mean Change from Baseline (SE)	-3.75 (0.48)	-5.54 (0.48)	-6.55 (0.53)
	Difference in LS Means (SE)	--	-1.78 (0.69)	-2.79 (0.71)
Week 12	n	45	42	39
	Mean SD	5.80 (4.23)	3.72 (4.33)	3.86 (4.48)
	Mean Change from Baseline (SD)	-5.15 (3.05)	-6.03 (3.56)	-6.85 (2.75)
	LS Mean Change from Baseline (SE)	-4.43 (0.47)	-6.47 (0.47)	-7.15 (0.51)
	Difference in LS Means (SE)	--	-1.04 (0.67)	-1.72 (0.69)
BMI Subgroup: ≥ 25 kg/m^2 to < 30 kg/m^2				
Frequency of Moderate to Severe VMS				
Baseline	n	62	58	73
	Mean (SD)	11.03 (4.60)	12.23 (6.90)	12.19 (10.30)
Week 4	n	52	57	69
	Mean SD	7.46 (6.14)	6.36 (7.50)	6.12 (8.91)
	Mean Change from Baseline (SD)	-3.80 (4.24)	-5.85 (4.52)	-6.15 (4.69)
	LS Mean Change from Baseline (SE)	-4012 (0.54)	-5.80 (0.55)	-6.09 (0.49)
	Difference in LS Means (SE)	--	-1.68 (0.78)	-1.97 (0.74)
Week 12	n	50	44	63
	Mean SD	6.80 (7.43)	5.21 (7.16)	4.76 (5.63)
	Mean Change from Baseline (SD)	-4.32 (5.16)	-7.12 (5.29)	-7.66 (7.93)
	LS Mean Change from Baseline (SE)	-5.10 (0.65)	-7.11 (0.69)	-7.44 (0.59)
	Difference in LS Means (SE)	--	-2.01 (0.94)	-2.33 (0.88)
BMI Subgroup: BMI Subgroup: ≥ 30 kg/m^2				
Frequency of Moderate to Severe VMS				
Baseline	n	52	53	48
	Mean (SD)	12.61 (6.51)	11.52 (3.56)	12.28 (8.24)
Week 4	n	49	49	45
	Mean SD	9.41 (8.58)	6.31 (5.39)	5.98 (6.41)

Analysis Visit	Statistic	Placebo (n = 167)	Fezolinetant 30 mg (n = 166)	Fezolinetant 45 mg (n = 167)
	Mean Change from Baseline (SD)	-3.36 (4.83)	-5.19 (4.34)	-6.52 (5.99)
	LS Mean Change from Baseline (SE)	-3.24 (0.68)	-5.32 (0.67)	-6.46 (0.71)
	Difference in LS Means (SE)	--	-2.08 (0.95)	-3.22 (0.98)
Week 12	n	45	46	42
	Mean SD	7.60 (10.01)	5.45 (4.88)	4.63 (5.90)
	Mean Change from Baseline (SD)	-4.27 (6.65)	-6.16 (5.27)	-7.72 (6.65)
	LS Mean Change from Baseline (SE)	-4.53 (0.83)	-6.52 (0.82)	-7.98 (0.87)
	Difference in LS Means (SE)	--	-1.99 (1.17)	-3.45 (1.20)

Source: Adapted from NDA 216578, Trial 2693-CL-0302 Study Report, Table 9.3.1.7.5, page 336 of 2749.
The LS Means, standard errors, and confidence intervals (CI) come from a mixed model repeated measures (MMRM) analysis of covariance model with change from baseline as the dependent variable and treatment group and week as factors, with baseline measurement as a covariate, as well as an interaction of treatment by week and an interaction of baseline measurement by week.
A negative change indicates a reduction/improvement from baseline.
Differences are calculated by subtracting the LS mean of placebo group from the LS mean of fezolinetant group.

Reviewer's Comment:
As shown in Table 38, similar numbers of participants were enrolled in each BMI subgroup in Trial 2693-CL-0302. Trial 2693-CL-0302 was not powered to show a difference in BMI subgroups. Therefore, the interpretation of these results is limited. That said the reported results for frequency reduction appear to show stronger effect at Week 12 vs Week 4. Participants with a BMI ≥ 30 kg/m2 appear to show the stronger differences in LS means (SE) in the 45 mg fezolinetant dosage strength.

The NDA application reports results for the mean change in VMS severity at Weeks 4 and 12 for BMI subgroup analyses in Trial 2693-CL-0302.

Data Quality and Integrity

Trial 2693-CL-0302 was implemented and maintained under the same quality assurances and quality control systems as Trial 2693-CL-0301.

Audits of this trial were included as part of the independent quality assessment performed by the applicant. See Section 4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety, Subsection 4.1. Office of Scientific Investigations (OSI) for additional information on the audits conducted by the applicant.

Efficacy Results – Secondary and other relevant endpoints

Sensitivity Analyses:
The applicant conducted sensitivity analyses of the PPS to support the primary analyses on the co-primary endpoints in Trial 2693-CL-0302. See Table 39.

Table 39 Applicant's Conducted Per Protocol Set Sensitivity Analyses of Co-primary Endpoints; 12-week Double-blind Period; Trial 2693-CL-0302

Analysis Visit	Statistic	Placebo (n = 145)	Fezolinetant 30 mg (n = 138)	Fezolinetant 45 mg (n = 136)
Frequency of moderate to severe VMS				
Baseline for Week 4	n	145	138	136
	Mean (SD)	11.72 (5.25)	11.53 (5.15)	12.06 (9.02)
Baseline for Week 12	n	126	112	123
	Mean (SD)	11.56 (4.69)	11.39 (5.32)	12.29 (9.44)
Week 4	Mean (SD)	8.12 (6.53)	6.19 (6.11)	6.16 (7.55)
	Change from Baseline†			
	Mean (SD)	-3.60 (4.20)	-5.34 (4.28)	-5.90 (4.82)
	LS mean (SE)	-3.61 (0.35)	-5.39 (0.36)	-5.83 (0.36)

Analysis Visit	Statistic	Placebo (n = 145)	Fezolinetant 30 mg (n = 138)	Fezolinetant 45 mg (n = 136)
Week 4	**Difference in LS Means‡: Fezolinetant vs Placebo**			
	LS mean (SE)	NA	-1.77 (0.50)	-2.22 (0.50)
	95% CI (2-sided)		-2.76, -0.79	-3.21, -1.23
	P value (2-sided unadjusted) §		< 0.001	< 0.001
Week 12	Mean (SD)	7.19 (7.78)	5.35 (5.76)	4.92 (5.65)
	Change from Baseline†			
	Mean (SD)	-4.38 (5.29)	-6.04 (4.61)	-7.37 (6.92)
	LS mean (SE)	-4.45 (0.45)	-6.18 (0.48)	-7.17 (0.45)
	Difference in LS Means‡: Fezolinetant vs Placebo			
	LS mean (SE)	NA	-1.72 (0.65)	-2.72 (0.64)
	95% CI (2-sided)		-3.01, -0.44	-3.97, -1.46
	P value (2-sided unadjusted) §		0.009	< 0.001
Severity of moderate to severe VMS				
Baseline for Week 4	n	145	138	136
	Mean (SD)	2.42 (0.32)	2.44 (0.32)	2.40 (0.34)
Baseline for Week 12	n	126	112	123
	Mean (SD)	2.42 (0.31)	2.46 (0.33)	2.41 (0.34)
Week 4	Mean (SD)	2.12 (0.53)	2.04 (0.60)	1.89 (0.67)
	Change from Baseline†			
	Mean (SD)	-0.30 (0.45)	-0.40 (0.50)	-0.51 (0.53)
	LS mean (SE)	-0.30 (0.04)	-0.40 (0.04)	-0.51 (0.04)
	Difference in LS Means‡: Fezolinetant vs Placebo			
	LS mean (SE)	NA	-0.10 (0.06)	-0.21 (0.06)
	95% CI (2-sided)		-0.22, 0.02	-0.33, -0.09
	P value (2-sided unadjusted) §		0.090	< 0.001
Week 12	Mean (SD)	2.01 (0.64)	1.98 (0.70)	1.72 (0.73)
	Change from Baseline†			
	Mean (SD)	-0.41 (0.62)	-0.48 (0.68)	-0.69 (0.65)
	LS mean (SE)	-0.41 (0.06)	-0.47 (0.06)	-0.69 (0.06)
	Difference in LS Means‡: Fezolinetant vs Placebo			
	LS mean (SE)	NA	-0.06 (0.08)	-0.28 (0.08)
	95% CI (2-sided)		-0.22, 0.11	-0.44, -0.12
	P value (2-sided unadjusted) §		0.501	< 0.001

Source: NDA 216578, Trial 2693-CL-0302 Study Report, page 47 of 2749.
Per Protocol Set: All randomized participants from the Full Analysis Set who were treated according to the protocol without any major deviations at week 4 and week 12 endpoints.
The LS means, SE, CI and P values come from a MMRM analysis of covariance model with change from baseline as the dependent variable and treatment group, week and smoking status (current vs former/never) as factors, with baseline measurement and baseline weight as covariates, as well as an interaction of treatment by week and an interaction of baseline measurement by week.
The number of participants (n) is different for baseline measurements by week 4 and week 12 due to a different proportion of participants being excluded from PPS. Excluded participants could have more than one reason of exclusion.
Definitions: CI = confidence interval; LS = least squared; MMRM = mixed model repeated measurements; NA: = not applicable; PPS = per protocol set; VMS = vasomotor symptoms.
† A negative change indicated a reduction/improvement from baseline.
‡ Differences were calculated by subtracting the LS mean of placebo group from the LS mean of fezolinetant group.

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

Reviewer's Comment:
As shown in Table 39, sensitivity analyses performed for the PPS support the primary analysis for the co-primary endpoints in Trial 2693-CL-0302. Use of the 45 mg fezolinetant dose resulted in a statistically significant reduction in both the frequency and severity of hot flashes at Weeks 4 and 12. Use of the 30 mg dosage strength failed to demonstrate a statistically significant reduction in severity at Week 4 (p = 0.090) and Week 12 (p=0.501), but demonstrated a statistically significant reduction in frequency at Weeks 4 and 12.

The applicant is only requesting approval for the 45 mg fezolinetant dose for the treatment of moderate to severe vasomotor symptoms associated with menopause.

Responder Analysis:
The percent reduction ≥ 50% and at 100% in the frequency of moderate to severe VMS from baseline to each week up to Week 12 was also calculated as a secondary objective in Trial 2693-CL-0302. The following Table 40 shows the reported results for both the ≥ 50% reduction from baseline and the ≥ 100% reduction from baseline at Weeks 4 and 12.

Table 40 Applicant's Responder Analysis of Change from Baseline in Frequency of Moderate to Severe Vasomotor Symptoms at Week 4 and Week 12 in Trial 2693-CL-0302; Full Analysis Set

Responder Criteria/Week	Placebo N = 167	30 mg Fezolinetant N = 166	45 mg Fezolinetant N = 167
≥ 50% Reduction			
- Week 4	44 (26.3%)	84 (50.6%)	88 (52.7%)
- Week 12	71 (42.5%)	84 (50.6%)	101 (60.5%)
≥ 100% Reduction			
- Week 4	3 (1.8%)	10 (6.0%)	17 (10.2%)
- Week 12	9 (5.4%)	15 (9.0%)	25 (15.0%)

Source: Adapted from NDA 216578, Trial 2593-CL-0302 Study Report, Table 18, page 56 0f 2749.
Full Analysis Set: All participants who were randomized and received at least 1 dose of trial medication. Participants with missing VMS at an analysis visit were considered non-responders.

Reviewer's Comment:
A higher proportion of participants had a ≥ 50% reduction and a ≥ 100 % reduction in the frequency of moderate to severe VMS in the 30 mg and 45 mg fezolinetant groups than in the placebo group at Week 4 and Week 12. The 45 mg fezolinetant group showed a higher reduction in frequency than the 30 mg fezolinetant group for both responder criteria (≥ 50% and ≥ 100%).

Per the application, the ≥ 50% reduction difference was statistically significant for the 45 mg fezolinetant dose at Week 4 and Week 12 (p<0.001 for Weeks 4 and 12); the 30 mg fezolinetant dose showed inconsistent results (p<0.001 at Week 4 and p=0.152 at Week 12). The ≥ 100% reduction for the 45 mg fezolinetant dose was statistically significant at Weeks 4 and 12 (p=0.004 at Week 4 and p=0.006 at Week 12; the 30 mg fezolinetant dose was not statistically different at either weeks for the ≥ 100% reduction responder criteria.

See Table 9.3.3.6.1 in the Clinical Study Report (page 424 of 2749) for the reported finding for each week during the 12-week double-blind period.

Patient Global Impression of Change – Vasomotor Symptoms:

As with Trial 2693-CL-0301, supplemental prespecified analyses on the clinically meaningful within-subject change thresholds in the frequency of moderate to severe VMS were conducted according to the prespecified Psychometric Analysis Plan (PAP, Version 3.0, dated October 7, 2021). The anchor-based method was the primary approach, and the PGI-C VMS was proposed as the primary anchor measure. The score on the PGI-C VMS at Weeks 4 and 12 was provided in the NDA application. The PGI-C VMS is a patient-reported global outcome, designed to provide the participant's assessment of change in VMS experience from the start of the trial. The PGI-C VMS asks the following: "Compared to the beginning of this study, how would you rate your hot flushes/night sweats now?" Participant ratings are as follows: much better, moderately better, a little better, no change, a little worse, moderately worse, and much worse.

The reported results for the 12-week double-blind period are shown in Table 41.

Table 41 Applicant's Analysis of Patient Global Impression of Change – Vasomotor Symptoms (PGI-C VMS)

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

Source: Adapted from NDA 216578, Trial 2693-CL-0302 Study Report, Table 21, page 61 of 2749.
All participants who were randomized and received at least 1 dose of fezolinetant during either the 12-week double-blind or the active treatment extension periods (Full Analysis Set, Fezolinetant)
† P-value was obtained using Cochran-Mantel-Haenszel test with modified ridit scores. The association between response and treatment group (fezolinetant 30 mg vs placebo and fezolinetant 45 mg vs placebo) at each analysis visit was tested.

Reviewer's Comments:
A higher proportion of participants in the 30 mg and 45 mg fezolinetant groups compared with placebo reported a positive change in PGI-C VMS at Weeks 4 and 12 in this trial. Overall, participants in both the 30 mg and 45 mg fezolinetant groups had a statistically significant difference relative to placebo. The same findings were reported for comparator Trial 2693-CL-0301.

In the NDA application, Astellas clarifies that PGI-C VMS reported results are exploratory and only intended as supplementary evidence of efficacy. See the Clinical Reviewer's Comments, on page 120 of this review, for additional information

Dose/Dose Response

The results reported in phase 3 Trial 2693-CL-0302 show an incremental benefit in VMS frequency and severity for 45 mg fezolinetant when compared with the 30 mg fezolinetant dose. Fezolinetant 45 mg achieved statistical significance vs placebo more consistently across the frequency and severity efficacy endpoints analyzed than the 30 mg fezolinetant group.

Durability of Response
A 12-week, placebo-controlled, clinical Trial 2693-CL-0302 was conducted to demonstrate effectiveness of the fezolinetant drug product for the indication of the treatment of moderate to severe vasomotor symptoms, due to menopause

Persistence of Effect

Per the NDA application, secondary efficacy analyses during the active treatment 40-week extension period in this trial "support the treatment effect of fezolinetant with no evidence of reduced effect size suggestive of tachyphylaxis." The NDA application states:

- "The effect of fezolinetant on VMS frequency and severity observed during the 12-week double-blind period was sustained during the active treatment extension period in participants treated with 30 mg and 45 mg fezolinetant for the entire 52-weeks.
- Participants on placebo when re-randomized to active fezolinetant also demonstrated "additional and sustained benefit from fezolinetant treatment on VMS frequency and severity throughout the 40-week extension period."

In addition, the following secondary endpoints are reported for the 40-weeks active treatment extension period:

- Mean change in the frequency of moderate to severe VMS from baseline to Week 24.
- Mean change in the severity of moderate to severe VMS from baseline to Week 24.

  Reviewer's Comment:
  The above reported results of the change from baseline to Week 24 in Trial 2693-CL-0302 in the frequency and severity of hot flashes are secondary endpoints and the presented data is descriptive only without a placebo comparator. This data is not relevant to the co-primary analyses for efficacy, and will not appear in product labeling, should the 45 mg fezolinetant dose be approved for the treatment of moderate to severe VMS due to menopause.

Additional Analyses Conducted on the Individual Trial

Patient-reported Outcomes Measurement Information System Sleep Disturbance – Short Form 8b (PROMIS SD SF 8b):

In Trial 2693-CL-0302, the protocol defined key secondary objective examined the effect of fezolinetant versus placebo on the mean change in the Patient-reported Outcomes Measurement Information System Sleep Disturbance – Short Form 8b (PROMIS SD SF 8b) total score from baseline to Week 12. For participants treated with 30 mg fezolinetant, there was a numerical reduction from baseline in PROMIS SD 8b relative to placebo at Week 4 and Week 12 that was not statistically significant (p=0.082 at Week 4; p=0.381 at Week 12). The 45 mg fezolinetant dose showed a statistically significant difference in the mean total PROMIS SD SF 8b score at Weeks 4 and 12 (p<0.001 at week 4; p=0.007 at Week 12).

Reviewer's Comment:
Astellas was advised the following on April 17, 2019 and September 30, 2019:

1. Reported results for proposed secondary and exploratory objectives/endpoints (b) (4)
2. Reported results of proposed secondary and exploratory objectives/endpoints in clinical Trials 2693-CL-0301 and rial 2693-CL-0302 (b) (4)

Clinical Reviewer's Summary of Efficacy Findings:

The clinical reviewers conclude that substantial evidence of overall efficacy for TRADENAME (fezolinetant) tablets, 45 mg, is demonstrated in two randomized, comparative, 12-week, double-blind, placebo-controlled trials, Trial 2693-CL-0301 and Trial 2693-CL-0302. Results of the two trials successfully demonstrate achievement of the primary protocol-defined co-primary endpoints of 1) a statistically significant mean change in the frequency of moderate to severe vasomotor symptoms at Week 4, 2) a statistically significant mean change in the frequency of moderate to severe vasomotor symptoms at Week 12, 3) a statistically significant mean change in the severity of moderate to severe vasomotor symptoms at Week 4, and 4) a statistically significant mean change in the severity of moderate to severe vasomotor symptoms at Week 12. In addition, the 45 mg fezolinetant tablets demonstrated a clinically meaningful threshold difference in the frequency of hot flashes (at least 2 hot flashes above placebo per day, or 14 per week) at Week 4 that is maintained through Week 12.

> Fezolinetant, 45 mg, taken orally once daily with or without food, is recommended for approval for the treatment of moderate to severe vasomotor symptoms, due to menopause.

7 Integrated Review of Effectiveness

Data from the 2 primary phase 3 Trials 2693-CL-0301 and 2693-CL-0302 were pooled as follows in the NDA application:

1. POP 12-week: Phase 3 primary, placebo-controlled, 12 Weeks. This population included data from the 12-week placebo-controlled period of the 2 primary phase 3 trials. POP 12-week was defined as the main population used for the pooled efficacy analyses, as demonstration of efficacy to the data collected from evaluations performed during the first 12 weeks of treatment.
2. POP 24-week: Phase 3 primary, 24-week Persistence of Effect. This population included only the participants who were treated with fezolinetant up to 24 weeks from the 2 primary trials. POP 24-week was used to assess persistence of efficacy. Additional details on the effect of fezolinetant up to 52 weeks (total duration of primary trials) is included to further support the persistence of efficacy beyond 12 weeks.

Reviewers' Comment:
Analyses of pooled effectiveness data is not applicable for the primary demonstration of effectiveness for the indication of the treatment of moderate to severe vasomotor symptoms due to menopause. The following was conveyed to Astellas in the Written Responses Only communication, dated July 28, 2021:

> "Your NDA application in support of an indication for the treatment of moderate to severe VMS due to menopause, if filed, will be based on the separate analyses of efficacy data for each of the two independent, phase 3, 12-week, placebo-controlled confirmatory clinical trials. Provide this data separately. You may provide an Integrated Summary of Efficacy (ISE)/Summary of Clinical Efficacy (SCE) as supportive documentation."

As stated, the ISE/SCE is considered supportive.

7.1 Assessment of Efficacy Across Trial

Assessment of efficacy across trials is not applicable in this review.

7.1.1 Primary Endpoints

Not applicable.

7.1.2 Secondary and Other Endpoints

Not applicable.

7.1.3 Subpopulations

Not applicable.

7.1.4 Dose and Dose-Response

Not applicable

7.1.5 Onset, Duration, and Durability of Efficacy Effects

Not applicable.

7.2 Additional Efficacy Considerations

7.2.1 Considerations on Benefit in the Postmarket Setting

Fezolinetant, 45 mg, a nonhormonal, selective neurokinin 3 (NK3) receptor antagonist, which has demonstrated both a statistically significant reduction in frequency and severity of moderate to severe vasomotor symptoms, and a clinically meaningful threshold reduction in frequency at Weeks 4 and 12 (co-primary efficacy endpoints) can be used in non-hysterectomized and hysterectomized postmenopausal women.

7.2.2 Other Relevant Benefits

Not applicable.

7.3 Integrated Assessment of Effectiveness

Not applicable.

8. Review of Safety

8.1 Safety Review Approach

The pooled safety analysis for fezolinetant is comprised of three phase 3 clinical trials. Trials 2693-CL-0301 and 2693-CL-0302 employed a crossover study design where all participants were transitioned from 12 weeks of double-blind, double-dummy designed evaluation of fezolinetant versus placebo to an open-label fezolinetant exposure arm without a placebo control group for 40 weeks at dosage levels of 30 and 45 mg oral tablets. Therefore, half of the participants in studies 301 and 302 had up to 52 weeks of fezolinetant exposure and the other half had up to 40 weeks of exposure. By contrast, Trial 2693-CL-0304 was a double blind, placebo-controlled trial for the entire 52-weeks. Most of the participants in the safety database were in enrolled in Trial 2693-CL-0304. The Safety Analysis Set for each population consisted of all randomized participants (people with VMS associated with menopause) who took at least 1 dose of study intervention.

> Reviewer's Comment:
> When evaluating pooled data that includes variable duration of exposures to placebo and fezolinetant we used the exposure adjusted incidence rate (EAIR) of adverse events for statistical analysis of adverse events. When evaluating the results of Trial 2693-CL-304 alone, the rates of adverse event in placebo versus treatment can be compared along with the risk difference.

In phase 2 drug development, hepatic safety was identified as a potential safety concern. Therefore, drug induced liver injury (DILI) monitoring and analyses were performed throughout all phase 3 studies and will be reviewed here. In addition, endometrial and bone safety will be given close attention. Finally, there was an unanticipated imbalance in the incidence of malignancy the treatment versus the placebo groups that are reviewed in detail herein.

8.2 Review of the Safety Database

8.2.1 Overall Exposure

The applicant employed several pooled populations for analyses of safety which are summarized in below. Pooling strategies were presented in the statistical analysis plan submitted in the PreNDA phase and were reviewed and accepted by FDA statisticians and DUOG.

Safety Population Descriptions, Size, Denominators, and Rationale

AE:

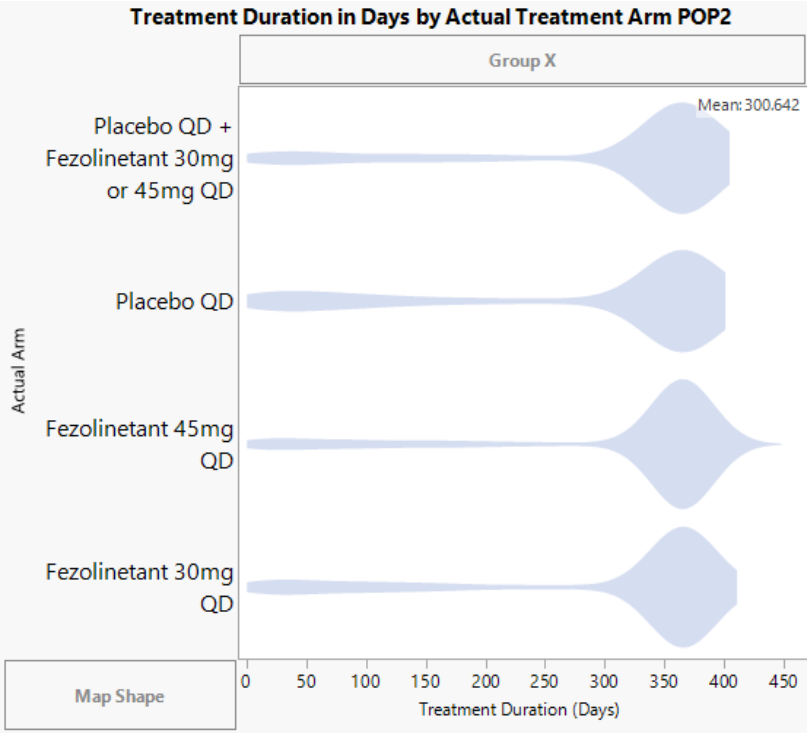
z	Studies	Treatment Groups Summarized	Rationale
POP1 Phase 3 Pivotal Placebo-controlled 12-week	2693-CL-0301 2693-CL-0302	• Placebo (n=342) • Fezolinetant 30 mg (n=340) • Fezolinetant 45 mg (n=340) • Fezolinetant total (n=680) • Total N=1022	• Assess the short-term safety profile of fezolinetant 30 mg and 45 mg doses relative to placebo for 12 weeks • The same subject population as for the efficacy profile for 12 weeks of exposure • The tablet formulation was administered
POP2† Phase 3 52-week	2693-CL-0301 2693-CL-0302 2693-CL-0304	• Placebo (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	• Assess the safety profile of fezolinetant 30 mg and 45 mg doses up to 52 weeks • Assess the 52-week endometrial health endpoints including TVU and endometrial biopsy findings • Varying exposure for fezolinetant and placebo, used for exposure-adjusted safety endpoints • The tablet formulation was administered
POP3 VMS Phase 2 and 3 12-week	ESN364_HF_204 ESN364_HF_205 2693-CL-0301 2693-CL-0302 2693-CL-0304	• Placebo (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	To accommodate difference in, formulations (capsule, tablet), dosing regimen (daily, twice daily) and doses within each set of dosing regimen, this population is used to assess the following: • The 12-week safety from all phase 2/3 studies in VMS subject population who were exposed to fezolinetant • The safety profile of fezolinetant doses that are lower than 30 mg and higher than 45 mg daily dose
POP4 Phase 3 Placebo-controlled 52-week	2693-CL-0304	• Placebo (n=610) • Fezolinetant 30 mg (n=611) • Fezolinetant 45 mg (n=609) • Fezolinetant total (n=1220) • Total N=1830	• Assess the long-term safety profile of fezolinetant 30 mg and 45 mg doses relative to placebo for 52 weeks • Perform additional analyses that may not have been planned in the study CSR

POP5 VMS Phase 2 12-week	ESN364_HF_204 ESN364_HF_205	• Placebo (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	• The 12-week safety from the phase 2 studies in VMS subject population who were exposed to fezolinetant (subset of POP3) • The safety profile of fezolinetant doses that are lower than 30 mg and higher than 45 mg daily dose.

AE: adverse event; TVU: transvaginal ultrasound; VMS: vasomotor symptoms. † In addition, POP2 was evaluated at 12 weeks (12-week POP2) to assess the placebo-controlled safety profile from the 3 phase 3 Studies 2693-CL-0301, 2693-CL-0302 and 2693-CL- 0304, specifically for AEs and categorical increases in liver parameters.
Source: Summary of Clinical Safety/Integrated Summary of Safety Table 3, page 19 of 152.

For POP2, 2,859 participants were randomized; the Safety Analysis Set (all participants that took at least one dose of drug or placebo, N=2,852) consisted of 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. The mean exposure duration was 300 days, with most participants discontinuing trial treatment between 252 and 365 days. Figure 3 presents a contour graphic of duration of treatment by actual treatment arm for the POP2 population.

Figure 3 Contour Graphic of Exposure Duration POP2 52 Weeks



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

Table 42 also presents exposure (cumulative measure) by treatment arm for the POP2 population.

Table 42 Cumulative Exposure Duration by Treatment Group POP2 52 Weeks

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

Source: NDA 216578, SS/ISS Table 5 Study Drug Exposure (Safety Analysis Set); POP2: Phase 3 52-week, page 29 of 152.
All randomized participants who took at least 1 dose of study intervention (Safety Analysis Set).

Reviewer's Comments:

- While the applicant has provided pooled data including phase 2 trial data, for purposes of the safety analysis, we focused primarily on data generated in the phase 3 trials. Population 2 (POP2, 52 weeks) is considered the primary safety analysis population for the purposes of this safety review and contains all pooled phase 3 data with up to 40 – 52 weeks of fezolinetant exposure data. Most of the data generated in POP2 was placebo-controlled
- Trials 2693-CL-301 and 2693-CL-302 contained 40 weeks of unmatched safety data. The sponsor provided 12-week placebo-controlled phase 3 pooled data, as well as pooled 52-week pooled phase 3 data for POP2.

8.2.2 Relevant characteristics of the safety population:

As shown in

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Figure 4 below, 80% of participants in POP2 self-identified as White and 17% self-identified as Black/African American. Eight percent of Black participants and twenty-five percent of White participants reported Hispanic ethnicity.

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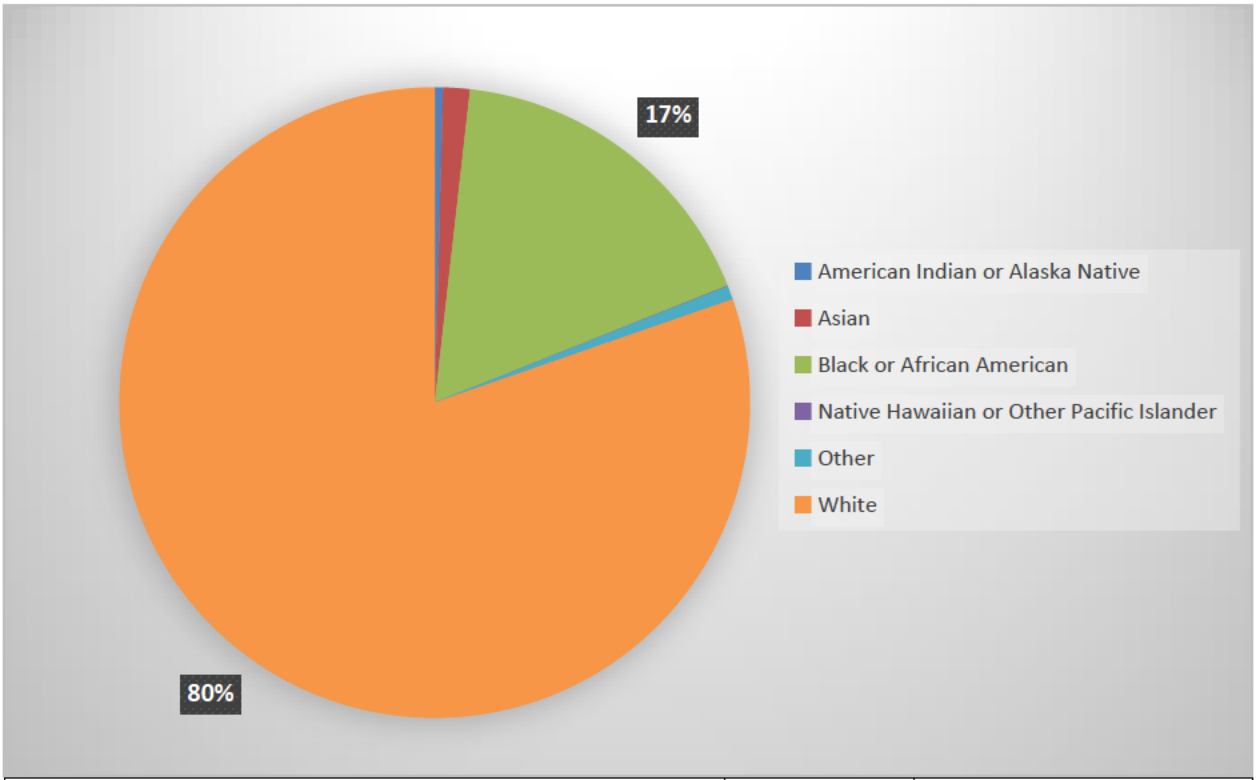
Figure 4 Racial Demographics POP2 (52 Weeks)



Race	N	% of Total
American Indian or Alaska Native	12	0.42%
Asian	39	1.37%
Black or African American	489	17.16%
Native Hawaiian or Other Pacific Islander	1	0.04%
Other	20	0.70%
White	2288	80.31%

Source: Reviewer generated Excel pie graph from ISS ADSL 52-week dataset, JMP generated tabulation POP2FL=Y, RACE

Approximately one-quarter of the participants in the study had a hysterectomy. Less than 1 percent had a history of non-alcoholic fatty liver disease or non-alcoholic steatohepatitis. Around 8 percent of participants had diabetes. The average age was around 55 years of age with a range of 40 to 65 years of age. The average BMI was 28.21 and around 80 percent were former or never smokers. Most of the participants enrolled were from the United States and Canada while around one quarter of participants enrolled were from Europe (mostly Poland). Refer to Table 43 for more detail.

Table 43 Demographic Characteristics and Targeted Medical History POP2 (52 Weeks)

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

Source: NDA 216578, SCS/ISS, Sponsor Table 7, page 33 of 152.

8.2.3 Adequacy of the safety database:

The demographics of the enrolled population (POP2) in phase 3 trials are representative of the US population. Considering that the US population is 18.9% Hispanic ethnicity and 13.6% Black race (2020 US Census Bureau Data), the clinical trials had good representation of minority populations. The safety database is considered adequate based on size and duration of treatment for evaluating the safety of fezolinetant and consistent with ICH E1A guideline recommendations.

8.3 Adequacy of Applicant's Clinical Safety Assessments

8.3.1 Issues Regarding Data Integrity and Submission Quality

The applicant's submission complied with the Division's pre-NDA advice and Statistical Analysis Plan (SAP) (January 2022). At that time, the FDA agreed that the Integrated Safety Summary (ISS) could include text portions in Module 2.7.4 of the Common Technical Document Summaries (CTSD) section with the table listings and figures in Module 5.3.5.3 of the Clinical Study Reports Section of the NDA application. The applicant designed and conducted the phase 3 clinical trials integrating FDA advice provided in the End-of-Phase 2 (meeting May 2019) and subsequent feedback provided in Advice/Information Requests (Nov 2019, Mar 2020, Apr 2020, May 2020 and Jan 2021).

The information provided in the NDA was consistently found to be complete and thorough. FDA biostatisticians were able to replicate sponsor results.

The Office of Computational Sciences (OCS) completed a Data Fitness assessment. The overall findings were satisfactory without data quality concerns however, there were some coding issues related to reason for patient withdrawal from the trial. A large proportion were categorized as "other" when they might have been better coded into existing categories consistent with CDISC standards.

The applicant responded within the allotted time frame for all IRs consistent with Good Review Management Principles (GRMP). Throughout the review, the data presented on Case Report Forms (CRFs) was consistent with what was identified in the database. There were minor issues identified related to data quality surrounding several participants with 1 Universal Subject ID having multiple different Subject IDs. The applicant explained that this was related to participants screening for early trials that they did not meet eligibility criteria for and subsequently being enrolled in a later trial.

In Trial 2693-CL-0304, major protocol deviations were reported for around 17.5% of participants with the largest proportion of these being participants enrolled in trial without meeting eligibility criteria. However, the most common eligibility criteria deviations were related to the exclusion criterion related to blood pressure (enrolled despite blood pressure

greater than 130/80) or participants enrolled that were unwilling to complete study procedures. During the mid-cycle meeting DUOG requested that the applicant provide additional information to clarify the rationale behind the inclusion of participants not meeting eligibility criteria and how this could affect trial data integrity.

The applicant responded that the original protocol excluded participants with a systolic blood pressure of ≥130 mmHg or diastolic blood pressure as ≥ 80 mmHg based on an average of 2 to 3 readings at screening and randomization. If participants had a history of hypertension that was well controlled, they could be enrolled into the trial at the discretion of the investigator. The blood pressure deviations were minimal and not clinically significant based on the investigator's determination. The applicant deems that given the slight deviation, the enrollment of these participants would not affect the safety of fezolinetant or participant safety in the trial. Other deviations included missing a pregnancy test at the time of enrollment in 43 out of 230 participants however, participants were post-menopausal, and no participants were found to have a positive pregnancy test in future visits. Twenty-nine participants had a protocol deviation related to an endometrial abnormality at the time of baseline biopsy or were enrolled without an evaluable endometrial sample if the TVUS showed an endometrial stripe <4mm (allowed in early versions of the protocol). In 70 participants there were deviations related to receiving an incorrect dose. This was caused by a misunderstanding of dosing instruction and participants were dosed from only 1 blister pack in error instead of taking 1 pill from each blister pack for each dose. These deviations occurred during the first treatment period and most of them were identified and resolved within that treatment period. However, there were 10 participants with interruptions from 35 to 96 days. There were also 18 participants who erroneously received a kit that was not the kit assigned by the interactive response technology due to site personnel error, and the maximum amount of time those participants dosed erroneously was for 35 days. Ultimately participants received a lower dose than they should have and therefore this did not result in safety concerns.

> Reviewer's Comment:
> We concur with the applicant's assessment that the protocol deviations that occurred in this trial are unlikely to have had a significant impact on the safety analysis of fezolinetant and should not impact the integrity of the study data in any appreciable way.

8.3.2 Categorization of Adverse Events

The applicant defined an Adverse Event (AE) as any untoward medical occurrence in a participant administered a study drug, and which does not necessarily have to have a causal relationship with this treatment. AE collection (collected in open-ended, non-leading verbal questioning fashion) began after the signing of the informed consent and continued until 21

days after the last dose of study drug or if the participant was determined to be a screen failure. AE intensity was assessed as mild, moderate or severe.

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

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

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

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

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

- Plausible temporal relationship between exposure to the study drug and (S)AE onset and/or resolution. Has the subject actually received the study drug? Did the (S)AE occur in a reasonable temporal relationship to the administration of the study drug?
- Plausibility; i.e., could the event been caused by the study drug? Consider biologic and/or pharmacologic mechanism, half-life, literature evidence, drug class, preclinical and clinical study data, etc.
- Dechallenge/Dose reduction/Rechallenge:
    - Did the (S)AE resolve or improve after stopping or reducing the dose of the suspect drug?

    - Did the (S)AE reoccur if the suspected drug was reintroduced after having been stopped?
- Laboratory or other test results; a specific lab investigation supports the assessment of the relationship between the (S)AE and the study drug (e.g., based on values pre-, during and post-treatment)
- Available alternative explanations independent of study drug exposure; such as other concomitant drugs, past medical history, concurrent or underlying disease, risk factors including medical and family history, season, location, etc. and strength of the alternative explanation

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

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

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

8.3.3 Routine Clinical Tests

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

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

Participants that experienced unscheduled bleeding underwent an additional endometrial

biopsy. All endometrial biopsies were read concurrently by three independent expert pathologists from institutions with independent fiduciary and organizational reporting. Each pathologist was blinded to the treatment group and to the readings of the other pathologists. The concurrence of two of the three pathologists was accepted as the final diagnosis. If there was no agreement among the three pathologists, the most severe pathologic diagnosis would be used as the final diagnosis. Pathologists were instructed to use the standardized criteria for histologic evaluation as presented in the Draft FDA Guidance for Industry, Estrogen and Estrogen/Progestin Drug Products to Treat Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms – Recommendations for Clinical Evaluation, 2003.

The clinical laboratories collected are presented in Table 44 below.

Table 44 Laboratory Assessments for Phase 3 Clinical Trials

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

Urinalysis	Protein Glucose pH Blood
Coagulation Panel	International normalized ratio Activated partial thromboplastin time Prothrombin time
Serology	HBsAg HCV antibody HIV antibody
Hormone Levels	LH FSH Estradiol SHBG Testosterone Total/Free Androstenedione DHEA Estrone

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

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

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

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

> Reviewer's Comment:
> The sponsor followed FDA recommendations related to clinical assessments for evaluating the general safety of fezolinetant in the treatment of moderate to severe

VMS in healthy postmenopausal women.

8.4 Safety Results

8.4.1 Deaths

There were 2 deaths reported, both in fezolinetant treatment arms during the clinical development program (one motorcycle passenger accident in Trial 2693-CL-0302 and one cardiac arrest with anoxic brain injury in Trial 2693-CL-0304). There were no deaths in the placebo groups in any of the phase 3 trials.

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

Reviewer's Comment:
The reviewers concur with the applicant that this death was unrelated to treatment.

The participant in Trial 2693-CL-0304 (assigned to fezolinetant 30 mg daily) experience sudden cardiac arrest and brain anoxic injury on study Day 123 and died subsequently on Day 125. This participant was 62 years of age, White race, non-Hispanic ethnicity, and had a history of diabetes mellitus (type 2), chronic obstructive pulmonary disease (active smoker), hypertension and a BMI of 36. Assessments leading up to the event such as ECG and labs were not available. Baseline lab assessments were normal aside from elevated glucose. On Day 123, the participant suddenly collapsed with cardiac arrest and remained hypoxic during transport with intubation in the emergency department. A head CT scan was performed and revealed anoxic brain injury. On Day 124, laboratory results showed a troponin value of 0.90 ng/mL, which was consistent with the definition of acute myocardial infarction as described by the WHO (range: 0.60 to 1.50 ng/mL). Troponin peaked later the same day at 2.03 ng/mL. Blood lactic acid peaked at 2.5 mmol/L also on Day 124. A nuclear medicine flow study performed on Day 125 and compared with CT on Day 123 (admission) revealed no evidence of cerebral blood flow consistent with brain death; the participant was declared dead on Day 125.. The applicant's assessment was that this death was unrelated to trial medication.

Reviewer's Comment:
Given the lack of assessments available in this case, it is not possible to definitively determine that that this death was drug related. However, given multiple medical problems affecting the cardiovascular system, this participant was at high risk for cardiac events, and it is highly likely that her medical history of diabetes, hypertension, obesity, and smoking were the major contributors to her cause of death.

8.4.2 Serious Adverse Events

In the initial 12-week study period, there were a total of 33 treatment emergent severe adverse events (SAEs), 12 participants in the POP2 30 mg arm (1.0%), 15 participants in the 45 mg arm (1.3%) and 7 participants in the placebo arm (0.7%). In the 52-week study period, a total of 38 participants 45 mg arm (3.5%) experienced 50 treatment emergent SAEs, 31 participants in the POP2 30 mg arm (2.8%) experienced 49 SAEs, and 24 (2.5%) in the POP2 placebo arm experienced 18 SAEs. The majority of SAEs occurred in the treatment period with 7 SAEs occurring in 7 participants in the follow up period (1 in placebo, 4 in 30 mg, and 2 in 45 mg arm). A summary of SAEs that occurred on/after the first dose of trial medication for the safety population by SOC and PT and treatment group is presented in

Table 45In this Table 45, participants reporting more than one adverse event are counted only once. SAEs that occurred more than up to 21 days after the last dose of trial medication are denoted in the same table.

Table 45 Serious Treatment-Emergent Adverse Events POP2 52-Week Data

MedDRA (v23.0) System Organ Class Preferred Term	Placebo (n = 952) n (%, EAIR)	Fezolinetant 30 mg Total (n = 1103) n (%, EAIR)	Fezolinetant 45 mg Total (n = 1100) n (%, EAIR)
Overall	15 (1.6%, 2.7)	41 (3.7%, 4.6)	45 (4.1%, 4.8)
Cardiac Disorders	1 (0.1%, 0.2)	5 (0.5%, 0.6)	0
Acute myocardial	0	1 (0.1%, 0.1)	0
Atrial fibrillation	1 (0.1%, 0.2)	2 (0.2%, 0.2)	0
Cardiac arrest	0	1 (0.1%, 0.1)	0
Cardiac failure	0	1 (0.1%, 0.1)	0
Coronary artery disease	0	1 (0.1%, 0.1)	0
Congenital, familial, and genetic disorders	0	1 (0.1%, 0.1)	0
Alpha-1 antitrypsin deficiency	0	1 (0.1%, 0.1)	0
Ear and labyrinth disorders	0	1 (0.1%, 0.1)	0
Deafness bilateral		1 (0.1% ,0.1)	
Endocrine disorders	0	1 (0.1%, 0.1)	1 (0.1%, 0.1)
Goiter	0	1 (0.1%, 0.1)	1 (0.1%, 0.1)
Gastrointestinal disorders and administration site conditions	1 (0.1%, 0.1)	1 (0.1%, 0.1)	3 (0.3%)
Abdominal Pain	0	1 (0.1%, 0.1)	2 (0.2%)

MedDRA (v23.0) System Organ Class Preferred Term	Placebo (n = 952) n (%, EAIR)	Fezolinetant 30 mg Total (n = 1103) n (%, EAIR)	Fezolinetant 45 mg Total (n = 1100) n (%, EAIR)
Pancreatitis	0	0	1 (0.1%, 0.1)
Small intestinal obstruction	1 (0.1%, 0.1)	0	0
Vomiting	0	0	1 (0.1%, 0.1)
General disorders and administration site conditions	0	1 (0.1%, 0.1)	3 (0.3%)
Chest pain	0	0	3 (0.3%)
Non-cardiac chest pain	0	1 (0.1%, 0.1)	0
Hepatobiliary disorders	3 (0.3%, 0.5)	2 (0.2%, 0.2)	3 (0.3%)
Biliary dyskinesia	0	0	1 (0.1%, 0.1)
Cholecystitis	1 (0.1%, 0.2)	2 (0.2%, 0.3)	0
Cholelithiasis	1 (0.1%, 0.2)	0	1 (0.1%, 0.1)
Hepatitis	0	1 (0.1%, 0.1)	0
Hepatotoxicity	0	0	1 (0.1%, 0.1)
Infections and infestations	3 (0.3%, 0.5)	6 (0.5%, 0.7)	5 (0.5%)
COVID-19	1 (0.1%, 0.2)	2 (0.2%, 0.2)	2 (0.2%)
COVID-19 Pneumonia	1 (0.1%, 0.2)	1 (0.1%, 0.1)	1 (0.1%, 0.1)
Influenza	1 (0.1%, 0.2)	0	1 (0.1%, 0.1)
Meningitis	0	0	1 (0.1%, 0.1)
Pneumonia	1 (0.1%, 0.2)	1 (0.1%, 0.1)	0
Tooth infection	0	1 (0.1%, 0.1)	0
Urinary tract infection	0	1 (0.1%, 0.1)	0
Injury, poisoning and procedural complications	3 (0.3%, 0.5)	4 (0.4%, 0.5)	7 (0.7%)
Animal bite	1 (0.1%, 0.2)	0	0
Ankle fracture	0	1 (0.1%, 0.1)	0
Fibula fracture	0	0	1 (0.1%, 0.1)
Joint dislocation	1 (0.1%, 0.2)	0	0
Limb injury	0	0	1 (0.1%, 0.1)
Limb traumatic amputation	0	1 (0.1%, 0.1)	0
Lumbar vertebral fracture	0	0	1 (0.1%, 0.1)
Multiple injuries	0	0	1 (0.1%, 0.1)
Posterior tibial nerve injury	0	0	1 (0.1%, 0.1)
Radius fracture	0	1 (0.1%, 0.1)	0
Skin laceration	0	0	1 (0.1%, 0.1)

MedDRA (v23.0) System Organ Class Preferred Term	Placebo (n = 952) n (%, EAIR)	Fezolinetant 30 mg Total (n = 1103) n (%, EAIR)	Fezolinetant 45 mg Total (n = 1100) n (%, EAIR)
Stab wound	0	0	1 (0.1%, 0.1)
Tendon rupture	1 (0.1%, 0.2)	0	0
Tibia fracture	0	0	1 (0.1%, 0.1)
Investigations	1 (0.2%, 0.2)	3 (0.3%, 0.3)	3 (0.3%, 0.3)
Blood pressure increased	0	0	1 (0.1%, 0.1)
Gamma-glutamyltransferase increased	1 (0.1%, 0.2)	0	0
Liver function test increased*	1 (0.1%, 0.2)	3 (0.3%, 0.3)	2 (0.2%, 0.2)
Metabolism and nutrition disorders	0	2 (0.2%, 0.2)	1 (0.1%, 0.1)
Dehydration	0	1 (0.1%, 0.1)	0
Diabetic ketoacidosis	0	0	1 (0.1%, 0.1)
Hypercholesterolemia	0	1 (0.1%, 0.1)	0
Musculoskeletal and connective tissue disorders	0	3 (0.3%)	1 (0.1%, 0.1)
Intervertebral disc protrusion	0	1 (0.1%, 0.1)	0
Lumbar spinal stenosis	0	1 (0.1%, 0.1)	0
Rhabdomyolysis	0	1 (0.1%, 0.1)	0
Tendonitis	0	0	1 (0.1%, 0.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (0.2%, 0.4)	7 (0.6%, 0.8)	13 (1.5%, 1.4)
Apocrine breast carcinoma	0	0	1 (0.1%, 0.1)
Basal cell carcinoma	0	1 (0.1%, 0.1)	0
Benign breast neoplasm	0	1 (0.1%, 0.1)	0
Bone cancer	0	0	1 (0.1%, 0.1)
Chronic lymphocytic leukemia	0	1 (0.1%, 0.1)	0
Colon cancer	0	0	2 (0.2%, 0.2)
Endometrial adenocarcinoma	0	1 (0.1%, 0.1)	2 (0.2%, 0.2)
Hemangioma of liver	0	0	1 (0.1%, 0.1)
Hepatic cancer	0	0	1 (0.1%, 0.1)
Invasive breast carcinoma	0	1 (0.1%, 0.1)	0
Keratoacanthoma	0	0	1 (0.1%, 0.1)
Lung neoplasm	0	0	1 (0.1%, 0.1)
Malignant melanoma in situ	0	0	1 (0.1%, 0.1)
Neurolemmoma benign	1 (0.1%, 0.2)	0	0
Non-small cell lung cancer	0	0	1 (0.1%, 0.1)

MedDRA (v23.0) System Organ Class Preferred Term	Placebo (n = 952) n (%, EAIR)	Fezolinetant 30 mg Total (n = 1103) n (%, EAIR)	Fezolinetant 45 mg Total (n = 1100) n (%, EAIR)
Squamous cell carcinoma of skin	1 (0.1%, 0.2)	2 (0.2%, 0.2)	1 (0.1%, 0.1)
Squamous cell carcinoma of oral cavity	0	0	1 (0.1%, 0.1)
Uterine leiomyoma	0	0	1 (0.1%, 0.1)
Nervous system disorders	0	1 (0.1%, 0.1)	3 (0.3%, 0.3)
Brain injury	0	1 (0.1%, 0.1)	0
Headache	0	0	1 (0.1%, 0.1)
Hemiparesis	0	0	1 (0.1%, 0.1)
Paresthesia	0	0	1 (0.1%, 0.1)
Transient ischemic attack	0	0	1 (0.1%, 0.1)
Psychiatric disorders	1 (0.1, 0.2)	2 (0.2%, 0.2)	0
Alcohol abuse	0	1 (0.1%, 0.1)	0
Anxiety	0	1 (0.1%, 0.1)	0
Depression	1 (0.1%, 0.2)	0	0
Suicidal ideation	1 (0.1%, 0.2)	0	0
Renal and urinary disorders	0	0	2 (0.2%0.2)
Acute kidney injury	0	0	1 (0.1%, 0.1)
Renal colic	0	0	1 (0.1%, 0.1)
Ureteric stenosis	0	0	1 (0.1%, 0.1)
Reproductive system and breast disorders	0	3 (0.3%, 0.3)	2 (0.2%, 0.2)
Pelvic pain	0	0	1 (0.1%, 0.1)
Postmenopausal hemorrhage	0	1 (0.1%, 0.1)	0
Uterine hemorrhage	0	1 (0.1%, 0.1)	0
Uterine polyp	0	1 (0.1%, 0.1)	0
Vaginal hemorrhage	0	0	1 (0.1%, 0.1)
Respiratory, thoracic and mediastinal disorders	1 (0.1%, 0.2)	1 (0.1%, 0.1)	1 (0.1%, 0.1)
Acute respiratory	1 (0.1%, 0.2)	1 (0.1%, 0.1)	1 (0.1%, 0.1)
Hypoxia	0	1 (0.1%, 0.1)	0
Pulmonary embolism	0	0	1 (0.1%, 0.1)
Pulmonary edema	0	1 (0.1%, 0.1)	0
Surgical and medical procedures	0	1 (0.1%, 0.1)	0
Fracture treatment	0	1 (0.1%, 0.1)	0
Vascular disorders	0	0	1 (0.1%, 0.1)

MedDRA (v23.0) System Organ Class Preferred Term	Placebo (n = 952) n (%, EAIR)	Fezolinetant 30 mg Total (n = 1103) n (%, EAIR)	Fezolinetant 45 mg Total (n = 1100) n (%, EAIR)
Varicose vein	0	0	1 (0.1%, 0.1)

Source: NDA 216578, SCS/ISS report, Sponsor Table 23, pages 60-65 of 152.
*Alanine aminotransferase increased, Liver function test abnormal, Liver function test increased, Transaminases increased combined
Note: At each level of summation (Overall, SOC, PT) participants reporting more than one adverse event are counted only once.
EAIR=Exposure adjusted incidence Rate, per 100 Person Years

As shown in Table 45, investigators reported one SAE of hepatotoxicity in the placebo/fezolinetant 45 mg arm on exposure day 54. This participant reported 54 years of age, white race, not Hispanic ethnicity, less than one drink per week, and no history of non-alcoholic steatohepatitis. Her baseline ALT was elevated (62 U/L) at enrollment with all other hepatic function labs in the normal range. Following 12 weeks of placebo treatment, she was rerandomized to fezolinetant 45 mg on trial day 87. On trial day 141, the investigator reported a non-serious TEAE of special interest of ALT increased due to an elevated ALT level of 135 U/L and AST level of 59 U/L. All other hepatic laboratory values were normal on the same day: ALP (82 U/L), total bilirubin (4.0 µmol/L), direct bilirubin (2.0 µmol/L), INR (1.00), APTT (24 sec) and PT (11 sec). On Day 145, the ALT level was stable at 132 U/L and AST was slightly increased at 87 U/L. On day 155, the labs continued to trend down despite being on study drug with ALT 108 U/L and AST 67 U/L however on day 160 the participant was removed from the trial due to abdominal pain and nausea. The participant never developed jaundice or elevated bilirubin. Her maximum ALT and AST levels were 3.1 times the upper limit of normal and 1.5 times the upper limit of normal.

Reviewer's Comment:
There was a numerical difference in the prevalence of overall severe adverse events in the treatment arms versus the placebo arm for POP2 at 12 and 52 weeks which was also reflected in the EAIR. The EAIR for the fezolinetant 45 mg arm was 4.8 per 100 PY versus 2.7 per 100 PY in the placebo. The differences in overall SAEs were primarily driven by the differences in the SOC neoplasms benign, malignant, and unspecified (including cysts and polyps) which is discussed in Section 8.5.1. The SAEs that occurred were primarily singular in nature except for liver function test increased [(5 SAEs), discussed in Section 8.5.4], COVID-19 (4 SAEs), squamous cell carcinoma of skin (2 SAEs), colon cancer (2 SAEs) and endometrial cancer [(3 SAEs), discussed in Section 8.5.3]. Hepatobiliary SAEs were balanced across all arms. The SAEs that occurred tended to be related to preexisting conditions in most cases or due to injuries unrelated to drug exposure and do not appear to be drug related in the opinion of the reviewers. The case

of hepatotoxicity was similar to other participants in the trial given the mild rise in LFTs which were resolving on study drug and no elevations in bilirubin or development of jaundice.

8.4.3 Dropouts and/or Discontinuations Due to Adverse Effects

Around 11% of POP2 participants in the fezolinetant arms discontinued by the end of 12 weeks, while around one quarter of participants stopped by the end of 52 weeks. Almost one third of participants in the placebo arm discontinued by the end of 52 weeks as shown in Table 46.

Table 46 Reviewer's Assessment of Discontinuations by Treatment Arm, POP2 Population

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

Source: Reviewer generated JMP table, ISS ADSL 52-week dataset, POP252FL=Y, variables: EO12STT, EO52STT.

Of the participants that discontinued around half were coded as due to "subject withdrawal". Reasons for withdrawal did not differ significantly by treatment arm.

There were 144 participants that discontinued the study due to an adverse event. The most common adverse events that led to treatment withdrawn was liver function test increased (n=17) [with terms combined were alanine aminotransferase increased, aspartate aminotransferase increased, hepatic enzyme increased, liver function test increased, and transaminases increased (See section 8.5.4)]. This was followed by headache (n=15), nausea (n=11), and fatigue (n=11). See additional AEs that led to discontinuation in 47, Figure 5 and Figure 6 below.

Table 47 Reviewer's Assessment of Cause and Percent of Total for Discontinuation, POP2 Population

Discontinuation Reason	Number	Percent of Discontinuation
Withdrawal by Subject	411	53.5%
Adverse Event	144	18.7%
Lost to Follow-Up	126	16.4%

Other	60	7.81%
Protocol Deviation	28	3.65%
Death	1	0.13%
All	770	100%

Source: Reviewer generated JMP table, ISS ADSL 52-week dataset, POP2FL=Y, EOTSTT=Discontinued

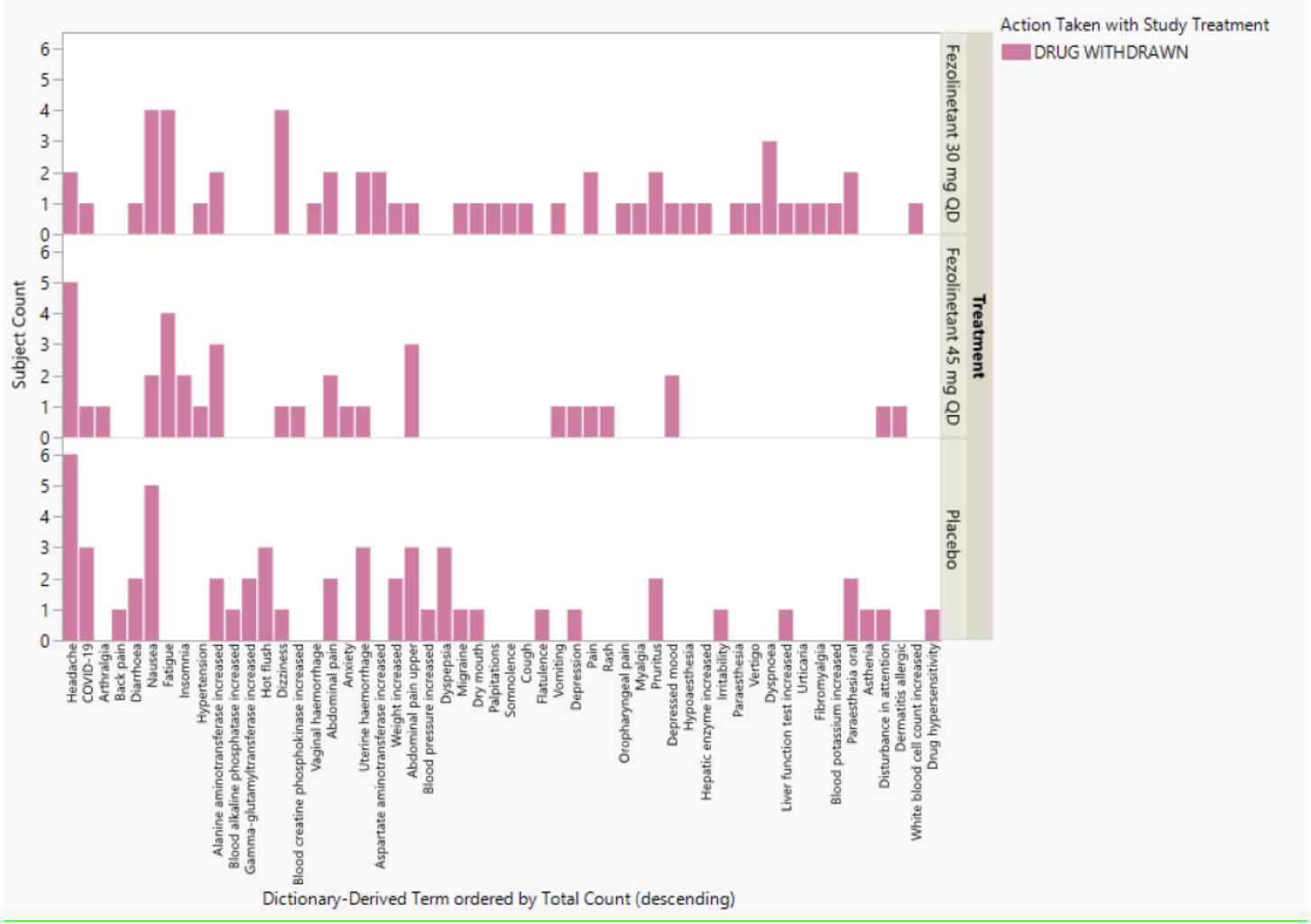
Table 48 Treatment-emergent Adverse Events Leading to Withdrawal of Treatment (> 1 Participant in Any Treatment Group) (Safety Analysis Set); POP2 (52-Week)

MedDRA (v23.0) System Organ Class Preferred Term	Placebo (n = 952)	Fezolinetant 30 mg Total (n = 1103)	Fezolinetant 45 mg Total (n = 1100)
Overall	37 (3.9%)	55 (5.0%)	47 (4.3%)
Gastrointestinal disorders	14 (1.5%)	7 (0.6%)	7 (0.6%)
Abdominal pain	2 (0.2%)	2 (0.2%)	2 (0.2%)
Abdominal pain upper	3 (0.3%)	1 (0.1%)	3 (0.3%)
Diarrhea	2 (0.2%)	1 (0.1%)	0
Dyspepsia	2 (0.2%)	0	0
Nausea	5 (0.5%)	4 (0.4%)	2 (0.2%)
Paresthesia oral	2 (0.2%)	2 (0.2%)	0
General disorders and administration site conditions	1 (0.1%)	7 (0.6%)	6 (0.5%)
Fatigue	0	4 (0.4%)	3 (0.3%)
Pain	0	2 (0.2%)	1 (0.1%)
Infections and infestations	2 (0.2%)	3 (0.3%)	1 (0.1%)
COVID-19	2 (0.2%)	1 (0.1%)	1 (0.1%)
Investigations	7 (0.7%)	9 (0.8%)	9 (0.8%)
Alanine aminotransferase increased	2 (0.2%)	2 (0.2%)	3 (0.3%)
Aspartate aminotransferase increased	0	2 (0.2%)	0
Gamma- glutamyl transferase increased	2 (0.2%)	0	0
International normalized ratio increased	0	0	2 (0.2%)
Liver function test abnormal	0	0	2 (0.2%)

Weight increased	2 (0.2%)	1 (0.1%)	0
Musculoskeletal and connective tissue disorders	1 (0.1%)	5 (0.5%)	2 (0.2%)
Arthralgia	0	0	2 (0.2%)
Nervous system disorders	9 (0.9%)	11 (1.0%)	7 (0.6%)
Dizziness	2 (0.2%)	4 (0.4%)	2 (0.2%)
Headache	6 (0.6%)	2 (0.2%)	5 (0.5%)
Paresthesia	0	2 (0.2%)	0
Psychiatric disorders	2 (0.2%)	4 (0.4%)	6 (0.5%)
Insomnia	0	0	2 (0.2%)
Reproductive system and breast disorders	3 (0.3%)	4 (0.4%)	1 (0.1%)
Uterine hemorrhage	2 (0.2%)	1 (0.1%)	1 (0.1%)
Respiratory, thoracic and mediastinal disorders	0	3 (0.3%)	1 (0.1%)
Dyspnea	0	2 (0.2%)	0
Skin and subcutaneous tissue disorders	2 (0.2%)	5 (0.5%)	3 (0.3%)
Pruritus	1 (0.1%)	2 (0.2%)	0
Vascular disorders	2 (0.2%)	1 (0.1%)	1 (0.1%)
Hot flush	2 (0.2%)	0	0

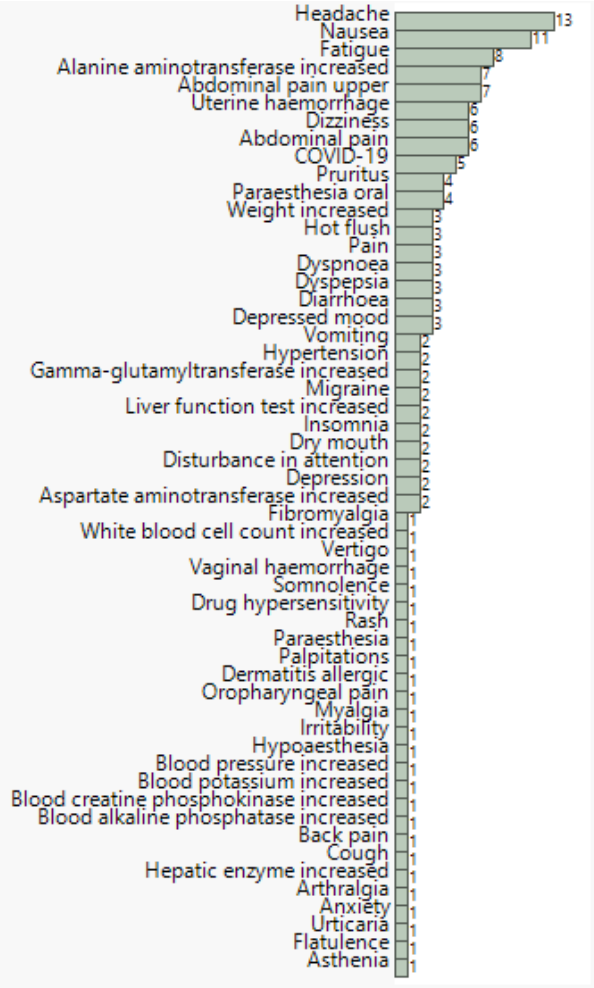
Source: NDA 216578 SCS/ISS, SDN 37.

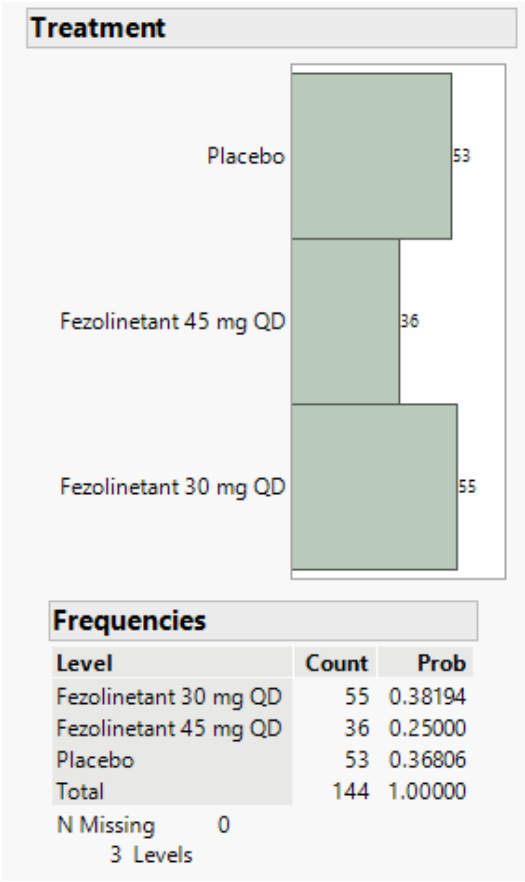
Figure 5 Frequency of drug withdrawn by actual treatment arm and MedDRA Preferred Term, POP2 (52-weeks)



Source: NDA 216578 ISS ADSL, ADAE datasets, JMP Clinical Adverse Events Distribution.

Figure 6 Treatment Withdrawal Frequency by MedDRA Preferred Term, POP2 (52-weeks)





Source: NDA 216578 ISS ADSL, ADAE datasets, JMP Clinical.

Reviewer's Comment:
Of note, around 15% of patient withdrawals were due to reasons related to the COVID-19 pandemic. There is a higher-than-expected number of "withdrawal by subject" because this study was being conducted as the COVID-19 pandemic unfolded over the course of 2020. Treatment withdrawal was balanced across treatment arms which is reassuring from a safety standpoint. It is notable that the most common TEAE leading to treatment withdrawal was due to liver function tests increased. This was not immediately evident as AEs were split among multiple like terms. The discontinuation rate by all preferred terms was balanced across treatment arms.

8.4.4 Significant Adverse Events Definitions

Adverse events that are considered significant refers to the definition in the ICH guideline for industry E3 Structure and Content of Clinical Study Reports and are those that include marked hematological and other laboratory abnormalities (other than those meeting the definition of serious) and any events that led to an intervention, including withdrawal of test drug/investigational product treatment, dose reduction, or significant additional concomitant therapy, other than those reported as serious adverse events.

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

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

8.4.5 Treatment Emergent Adverse Events and Adverse Reactions

The most common treatment emergent adverse events (TEAE) occurring in the POP2 population are presented in Figure 7 and Table 42. Headache, liver function test increased, COVID 19, urinary tract infection back pain, and abdominal pain were the most common TEAS. There was a dose related imbalance in the occurrence of liver function test increased. This is further discussed in section 8.5.4. Back pain, abdominal pain and insomnia were also increased in treatment versus placebo groups however they did not occur in a dose dependent fashion.

Headache was roughly equal in the placebo and fezolinetant 45 mg arm. Insomnia occurred more frequently in the fezolinetant 45 mg group as compared to the placebo group (EAIR 3.6 versus 2.5 per 100 PY).

Like terms for common treatment emergent adverse event were combined as follows:

- abdominal pain=abdominal pain, abdominal pain upper, abdominal pain lower

- vaginal hemorrhage=uterine hemorrhage, vaginal hemorrhage, dysfunctional uterine bleeding
- liver function test increased= alanine aminotransferase increased, aspartate aminotransferase increased

The TEAE "Blood creatinine phosphokinase (CPK) increased" occurred in a dose dependent fashion at a higher rate in treatment versus placebo groups. Most CPK elevations were mild in nature, spontaneously recovered and did not lead to drug withdrawal except in one case of rhabdomyolysis (SAE) which was a recurrence (first onset prior to trial involvement) following new onset of strenuous exercise (CrossFit program). Laboratory changes in CPK are discussed further in Section 8.4.6.3.

Table 49 Tabular listing of Treatment Emergent Adverse Event of Any Severity by Treatment, ≥1% in POP2 (52 weeks)

Preferred Term	Placebo (N=952) n (%, EAIR)	Fezolinetant 30 mg Total (N=1103) n (%, EAIR)	Fezolinetant 45 mg Total (N=1100) n (%, EAIR)
Total subject-years	549.1	886.3	912.1
Headache	73 (7.7%, 13.3)	75 (6.8%, 8.5)	90 (8.2%, 9.9)
COVID-19	39 (4.1%, 7.1)	64 (5.8%, 7.2)	67 (6.1%, 7.3)
Abdominal Pain*	19 (2.0%,3.5)	40 (3.6%, 4.5)	42 (3.8%, 4.6)
Arthralgia	25 (2.6%, 4.6)	32 (2.9%, 3.6)	35 (3.2%, 3.8)
Diarrhea	23 (2.4%, 4.2)	25 (2.3%, 2.8)	35 (3.2%, 3.8)
Back pain	16 (1.7%, 2.9)	41 (3.7%, 4.6)	34 (3.1%, 3.7)
Insomnia	15 (1.6%, 2.7)	22 (2.0%, 2.5)	33 (3.0%, 3.6)
Upper respiratory tract infection	30 (3.2%, 5.5)	31 (2.8%, 3.5)	32 (2.9%, 3.5)
Urinary tract infection	22 (2.3%, 4.0)	37 (3.4%, 4.2)	32 (2.9%, 3.5)
Elevated Liver Function Test*	11 (1.2%, 1.8)	37 (3.4%, 3.9)	48 (4.4%, 5.0)
Alanine aminotransferase increased	9 (0.9%, 1.6)	21 (1.9%, 2.4)	31 (2.8%, 3.4)
Nasopharyngitis	24 (2.5%, 4.4)	31 (2.8%, 3.5)	27 (2.5%, 3.0)
Nausea	19 (2.0%, 3.5)	26 (2.4%, 2.9)	27 (2.5%, 3.0)
Fatigue	21 (2.2%, 3.8)	19 (1.7%, 2.1)	26 (2.4%, 2.9)
Hypertension	22 (2.3%, 4.0)	22 (2.0%, 2.5)	26 (2.4%, 2.9)
Hot flush	12 (1.3%, 2.2)	19 (1.7%, 2.1)	24 (2.2%, 2.6)
Blood creatine phosphokinase increased	3 (0.3%, 0.5)	15 (1.4%, 1.7)	23 (2.1%, 2.5)
Anxiety	8 (0.8%, 1.5)	18 (1.6%, 2.0)	20 (1.8%, 2.2)
Dizziness	10 (1.1%, 1.8)	17 (1.5%, 1.9)	19 (1.7%, 2.1)
Sinusitis	18 (1.9%, 3.3)	20 (1.8%, 2.3)	18 (1.6%, 2.0)

Preferred Term	Placebo (N=952) n (%, EAIR)	Fezolinetant 30 mg Total (N=1103) n (%, EAIR)	Fezolinetant 45 mg Total (N=1100) n (%, EAIR)
Aspartate aminotransferase increased	2 (0.2%, 0.4)	16 (1.5%, 1.8)	17 (1.5%, 1.9)
Constipation	15 (1.6%, 2.7)	16 (1.5%, 1.8)	17 (1.5%, 1.9)
Blood alkaline phosphatase increased	21 (2.2%, 3.8)	22 (2.0%, 2.5)	16 (1.5%, 1.8)
Gamma-glutamyltransferase increased	12 (1.3%, 2.2)	26 (2.4%, 2.9)	16 (1.5%, 1.8)
Gastroesophageal reflux disease	5 (0.5%, 0.9)	5 (0.5%, 0.6)	16 (1.5%, 1.8)
Pain in extremity	14 (1.5%, 2.5)	18 (1.6%, 2.0)	15 (1.4%, 1.6)
Blood pressure increased	10 (1.1%, 1.8)	11 (1.0%, 1.2)	14 (1.3%, 1.5)
Glomerular filtration rate decreased	9 (0.9%, 1.6)	12 (1.1%, 1.4)	14 (1.3%, 1.5)
Dyspepsia	15 (1.6%, 2.7)	7 (0.6%, 0.8)	13 (1.2%, 1.4)
Ear infection	6 (0.6%, 1.1)	1 (0.1%, 0.1)	12 (1.1%, 1.3)
Osteoarthritis	4 (0.4%, 0.7)	7 (0.6%, 0.8)	12 (1.1%, 1.3)
Vaginal hemorrhage***	26 (2.7%, 4.5)	30 (2.7%, 3.2)	29 (2.6%, 3.0)
Abdominal pain upper	8 (0.8%, 1.5)	15 (1.4%, 1.7)	11 (1.0%, 1.2)
Sciatica	5 (0.5%, 0.9)	13 (1.2%, 1.5)	11 (1.0%, 1.2)
Tooth abscess	3 (0.3%, 0.5)	9 (0.8%, 1.0)	11 (1.0%, 1.2)
Blood glucose increased	3 (0.3%, 0.5)	20 (1.8%, 2.3)	10 (0.9%, 1.1)
Vomiting	3 (0.3%, 0.5)	13 (1.2%, 1.5)	10 (0.9%, 1.1)
Dry mouth	8 (0.8%, 1.5)	12 (1.1%, 1.4)	9 (0.8%, 1.0)
Pain	4 (0.4%, 0.7)	12 (1.1%, 1.4)	9 (0.8%, 1.0)
Bronchitis	6 (0.6%, 1.1)	12 (1.1%, 1.4)	8 (0.7%, 0.9)
Musculoskeletal pain	10 (1.1%, 1.8)	14 (1.3%, 1.6)	8 (0.7%, 0.9)
Weight increased	10 (1.1%, 1.8)	22 (2.0%, 2.5)	8 (0.7%, 0.9)
Flatulence	10 (1.1%, 1.8)	10 (0.9%, 1.1)	7 (0.6%, 0.8)
Myalgia	11 (1.2%, 2.0)	5 (0.5%, 0.6)	7 (0.6%, 0.8)
Neck pain	10 (1.1%, 1.8)	14 (1.3%, 1.6)	7 (0.6%, 0.8)
Spinal pain	10 (1.1%, 1.8)	5 (0.5%, 0.6)	3 (0.3%, 0.3)

Source: NDA 216578 SDN 37 Table 1.1 EAIR of TEAEs>1% POP2 (52 week), Safety Analysis Set.
*Grouping of like terms performed for elevated liver function test (Alanine aminotransferase increased and aspartate aminotransferase increased), **abdominal pain (abdominal pain, abdominal pain upper, abdominal pain lower) and ***vaginal hemorrhage (vaginal hemorrhage and uterine hemorrhage), EAIR=Exposure adjusted incidence Rate, per 100 Person Years

Figure 7 Reviewer Assessment of Exposure Adjusted Incidence Rate of Treatment Emergent Adverse Events (Any Severity) by Treatment Group, POP2 (52 Weeks) Occurring in ≥2% of Participants

SOURCE: Reviewer generated Excel Histogram generated from Table 50 data

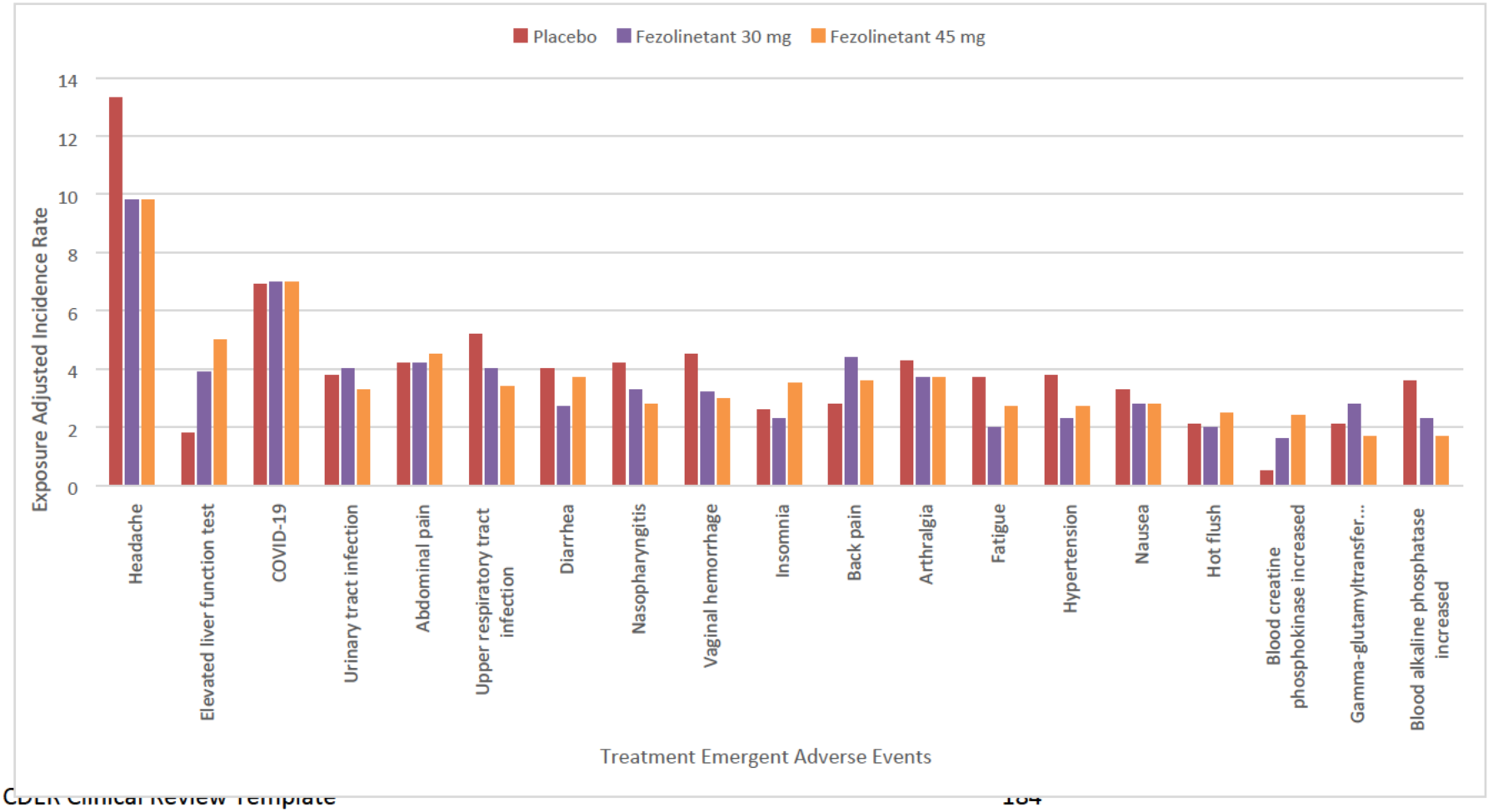


Table 50 Tabular listing of Treatment Emergent Adverse Event of Any Severity by Treatment, ≥2% in POP2 (52 week)

Preferred Term	Placebo n (%, EAIR) N=952	Fezolinetant 30 mg total n (%, EAIR) N=1103	Fezolinetant 45 mg total n (%, EAIR) N=1100
Total subject-years	549.1	886.3	912.1
Headache	73 (7.6%, 13.3)	75 (6.7%, 9.8)	90 (8.1%, 9.8)
Elevated Liver Function Test*	11 (1.2%, 1.8)	37 (3.4%, 3.9)	48 (4.4%, 5.0)
COVID-19	39 (4%, 6.9)	64 (5.8%, 7.0)	67 (6.1%, 7.0)
Urinary tract infection	22 (2.3%, 3.8)	37 (3.4%, 4.0)	32 (2.9%, 3.3)
Abdominal pain**	40 (4.2%, 4.2)	40 (3.6%, 4.2)	44 (4.0%, 4.5)
Upper respiratory tract infection	30 (3.1%, 5.2)	31 (2.8%, 4.0)	32 (2.9%, 3.4)
Diarrhea	23 (2.4%, 4.0)	25 (2.3%, 2.7)	35 (3.2%, 3.7)
Nasopharyngitis	24 (2.5%, 4.2)	31 (3.1%, 3.3)	27 (2.5%, 2.8)
Vaginal hemorrhage***	26 (2.7%, 4.5)	30 (2.7%, 3.2)	29 (2.6%, 3.0)
Insomnia	15 (1.6%, 2.6)	22 (2.0%, 2.3)	33 (3.0%, 3.5)
Back Pain	16 (1.7%, 2.8)	41 (3.7%, 4.4)	34 (3.1%, 3.6)
Arthralgia	25 (2.6%, 4.3)	32 (2.9%, 3.7)	35 (3.2%,3.7)
Fatigue	21 (2.2%, 3.7)	19 (1.7%, 2.0)	26 (2.4%, 2.7)
Hypertension	22 (2.3%, 3.8)	22 (2.0%, 2.3)	26 (2.4%, 2.7)
Nausea	19 (2.0%, 3.3)	26 (2.4%, 2.8)	27 (2.5%, 2.8)
Hot flush	12 (1.9%, 2.1)	19 (1.9%. 2.0)	24 (2.2%, 2.5)
Blood creatine phosphokinase increased	3 (0.3%, 0.5)	15 (1.4%, 1.6)	23 (2.1%, 2.4)
Gamma-glutamyltransferase increased	12 (1.3%, 2.1)	26 (2.4%, 2.8)	16 (1.5%, 1.7)
Blood alkaline phosphatase increased	21 (2.2%, 3.6)	22 (2.0%, 2.3)	16 (1.5%, 1.7)

Source: NDA 216578 SDN 10 Table 1.1 EAIR of TEAEs>1% POP2 (52 week), Safety Analysis Set.
*Grouping of like terms performed for elevated liver function test (Alanine aminotransferase increased and aspartate aminotransferase increased), **abdominal pain (abdominal pain, abdominal pain upper, abdominal pain lower) and ***vaginal hemorrhage (vaginal hemorrhage and uterine hemorrhage), EAIR=Exposure adjusted incidence Rate, per 100 Person Years

Reviewer's Comment:
Treatment emergent adverse event that should be included in labeling as adverse drug reactions in the opinion of the reviewers include insomnia, blood creatinine phosphokinase increased, and elevated liver function test. The 120-day Safety Update of

Clinical Safety reported similar TEAEs however, there were fewer AEs in the Neoplasms benign, malignancy and unspecified SOC.

8.4.6 Laboratory Findings

8.4.6.1 Thrombocytopenia

The applicant considered thrombocytopenia as a medical event of interest based on the occurrence of thrombocytopenia observed in monkeys in a nonclinical study. For purposes of this assessment, the applicant defined thrombocytopenia as platelet count <150X10^9/L. The occurrence of thrombocytopenia by this definition was similar across treatment groups in the 12 and 52-weeks trials for POP2 and POP4. The incidence of thrombocytopenia was rare overall occurring in 2.9% of participants in the placebo arm, 3.8% and 3.3% in the fezolinetant 30 and 45 mg arms respectively. The prevalence of thrombocytopenia in the general population is reported as 1.6% to 3.9% of the population.

Reviewer's Comment:
In humans, fezolinetant does not appear to be associated with thrombocytopenia.

8.4.6.2 Elevated Glucose

The applicant assessed the potential effect of fezolinetant on glucose metabolism. They accomplished this by evaluating the TEAEs related to carbohydrate intolerance (diabetes mellitus subtypes and hyperglycemic conditions (NEC) and by examining clinical laboratory data for mean and median changes from baseline and categorical shifts in values. Blood glucose samples were collected at various times of the day without respect to fasting. Shifts in glucose from missing, low (defined as ≤100.9 mg/dL), or normal (defined as 100.9 mg/dL) or to high (defined as <200 mg/dL) were similar across treatment groups in POP2 except for the placebo versus fezolinetant 45 mg arm at 4 and 20 weeks. In Trial 2693-CL-0304 there were no differences in glucose low, missing, or normal shifts to high across treatment arms.

TEAEs related to elevated glucose levels were uncommon in all treatment groups. In POP2 there was an imbalance in the incidence of hyperglycemia related TEAEs driven by TEAEs observed in Trial 2693-CL-0301, however the imbalance was not observed in Trial 2693-CL-0302 or the larger Trial 2693-CL-0304. In Trial 2693-CL-0301 during the 12-week double blind period, there were 6 reports (3.4 and 3.5% respectively) of "blood glucose increased" in both 30 and 45 mg arms and no reports in the placebo arm. For the 52-week study data from Trial 2693-CL-0301, there was a total of 12 reports (8.3%) in the fezolinetant 30 mg arm and 8 (4.6%) in the fezolinetant 45 mg arm versus none in the placebo arm. During the 12-week placebo-controlled portion of Trial 2693-CL-0302, there was 1 each (0.6%) in the incident of "blood glucose increased" in the placebo and fezolinetant 30 mg arm, respectively. In Trial 2693-CL-0304, the

largest safety trial, there were 2 (0.3%), 4 (0.5%), and 2 (0.3%) TEAE reports of blood glucose increased in placebo, fezolinetant 30 and 45 mg arms respectively (refer to Table 51.

Table 51 Incidence of TEAE MedDRA Preferred Term "Blood Glucose Increased"

Trial Number	Placebo	Fezolinetant 30 mg	Fezolinetant 45 mg
0301	0	12 (8.3%)	8 (4.6%)
0302	1 (0.6%)	1 (0.6%)	0
0304	2 (0.3%)	4 (0.5%)	2 (0.3%)
ISS	3 (0.3%)	20 (1.8%)	10 (0.9%)

Source: NDA216578 SCS/ISS

When evaluating the confounder of diabetes mellitus related to AEs of blood glucose elevations, diabetes mellitus did not appear to be a primary driver of the differences across treatment groups. There were more events in the treatment arms as compared to the placebo arm. However, this pattern did not occur in a dose dependent fashion and no patterns related to time to event emerged with an onset of events occurring from trial Day 4 to trial Day 377 with a median AE onset of trial Day 167 and a mean AE onset on trial Day 168.

In Table 52, TEAE related to diabetes are presented by diabetic status for population 2.

Table 52 TEAE of Elevated Glucose by Diabetic Status, Pop2 (52 Weeks)

Baseline diabetes diagnosis	TEAE Preferred Term	Placebo n=952	Fezolinetant 30 mg n=1103	Fezolinetant 45 mg n=1100
All	AE of Blood glucose elevation	11 (1.2%)	35 (3.2%)	30 (2.7%)
	Blood glucose increased	3 (0.3%)	20 (1.8%)	10 (0.9%)
	Diabetes mellitus	3 (0.3%)	4 (0.4%)	9 (0.8%)
	Diabetic ketoacidosis	0	1 (0.1%)	1 (0.1%)
	Glucose tolerance impaired	1 (0.1%)	0	1 (0.1%)
	Glycosuria	0	0	2 (0.2%)
	Hyperglycemia	1 (0.1%)	4 (0.4%)	5 (0.5%)
	Impaired fasting glucose	0	1 (0.1%)	2(0.2%)
	Insulin resistance	0	1 (0.1%)	1 (0.1%)
	Ketonuria	0	1 (0.1%)	0

	Type 2 diabetes mellitus	4 (0.4%)	7 (0.6%)	4 (0.4%)
Yes	AE of Blood glucose elevation	3 (0.3%)	12 (1.0%)	11 (1.0%)
	Blood glucose increased	1 (0.1%)	6(0.6%)	4 (0.4%)
	Diabetes mellitus	2 (0.2%)	3 (0.3%)	4 (04%)
	Diabetic ketoacidosis	0	0	1 (0.1%)
	Glycosuria	0	1 (0.1%)	1 (0.1%)
	Hyperglycemia 0	0	1 (0.1%)	2 (0.2%)
	Type 2 diabetes mellitus	0	1 (0.1%)	2 (0.2%)
No	AE of Blood glucose elevation	8 (0.9%)	24 (2.4%)	19 (1.9%)
	Blood glucose increased	2 (0.2%)	14 (1.4%)	6 (0.5^)
	Diabetes mellitus	1 (0.1%)	1 (0.1%)	5(0.5%)
	Glucose tolerance impaired	1 (0.1%)	0	1 (0.1%)
	Glycosuria	0	0	1 (0.1%)
	Hyperglycemia	1 (0.1%)	3 (0.3%)	3 (0.3%)
	Impaired fasting glucose	0	1 (0.1%)	2 (0.2%)
	Insulin resistance	0	1 (0.1%)	1 (0.1%)
	Ketonuria	0	1 (0.1%)	0
	Type 2 diabetes mellitus	4 (0.5%)	6 (0.6%)	2 (0.2%)

Source: NDA 215478. Table 12.4.21 POP2 TEAE of Elevated Glucose by Diabetic Status. Note: Correction of percent performed as applicant had incorrect percentage calculated for Diabetic Status Yes.

Reviewer's Comment:
The difference in the incidence of “blood glucose increased” in Trial 2693-CL-0301 versus Trials 2693-CL-0302 and 2693-CL- 0304 is unexplained and appears to be anomalous as it was not consistent in phase 3 trials. The data are limited in that the applicant did not evaluate the shift in HbA1C and that blood glucose levels were random in relation to fasting and therefore of limited clinical interpretation. The lack of shift to high in the mean glucose levels across all arms and studies is reassuring.

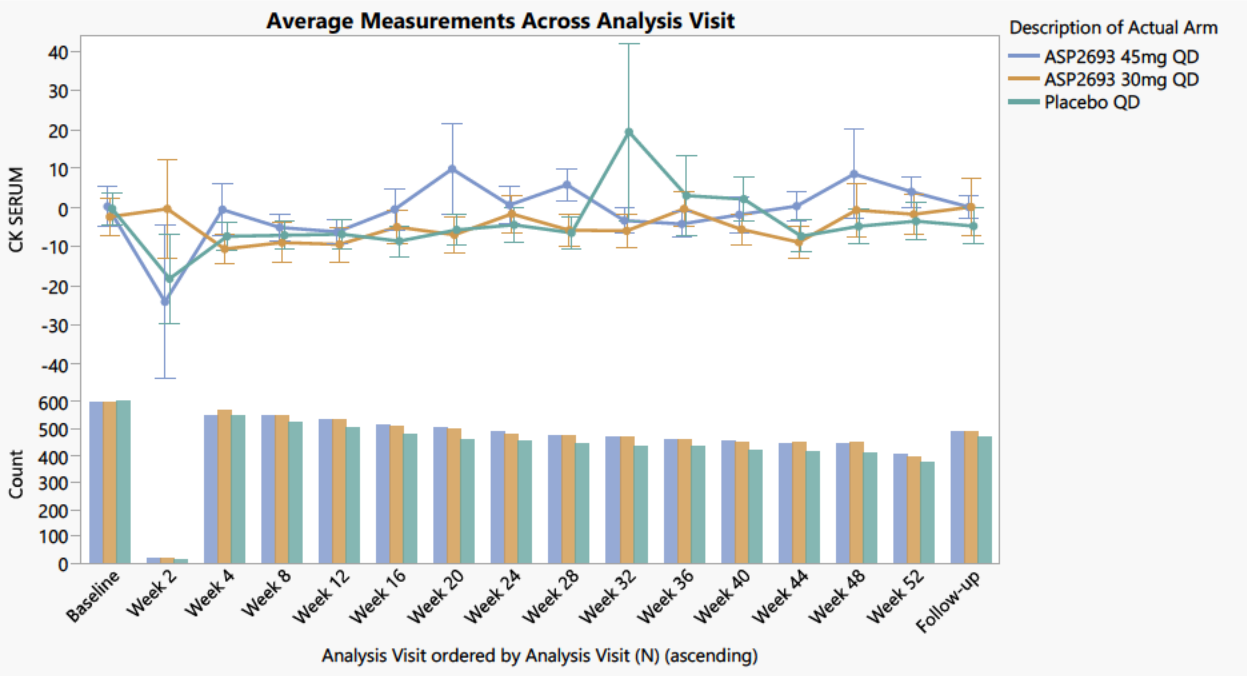
8.4.6.3 Elevated Creatinine Phosphokinase

The TEAE "Blood creatinine phosphokinase increased" occurred in a dose dependent fashion at a higher rate in treatment versus placebo groups. Most elevations were mild in nature, spontaneously recovered and did not lead to drug withdrawal except in one case of rhabdomyolysis (SAE) which was a recurrence (first onset prior to trial involvement) following new onset of strenuous exercise (CrossFit program). There were 45 participants that experienced 51 total TEAEs of increase in blood creatinine phosphokinase (CPK) in the phase 3 trials. Of these AEs, 43 were categorized as mild and 8 were categorized as moderate as shown in Table 53. One of the participants (Fezolinetant 45 mg, Trial 2693-CL-301) was discontinued due to a level of CPK that rose to 1423 U/L (ref normal 26 – 192 U/L) on Day 144. This participant also had a history of hypothyroidism which has been shown to be associated with some dysfunction in skeletal muscle metabolism and CK levels being inversely related to thyroid function. The investigator stopped the drug on Day 147 as they determined the reaction to be drug related. On Day 148, the level of CPK was 236 U/L and 141 U/L on Day 153. The TEAEs of increase in CPK were not echoed in laboratory data which did not show any difference by treatment versus placebo or dose dependent elevations in CPK as shown in Figure 8 and the shift tables in Table 54.

Table 53 Incidence of TEAE Preferred Term 'Increase in Blood Creatinine Phosphokinase' by Severity and Treatment Arm

Severity	Placebo N	Fezolinetant 30 mg total n (%)	Fezolinetant 45 mg total n (%)
Mild	10	26	17
Moderate	4	2	3
Total	14	28	20
Discontinuations due to AE	0	0	1

Figure 8 Change from Baseline for CREATINE KINASE (U/L) SERUM



Laboratory Test Results Shift Tables

Table 54 Reviewer Assessment of SERUM CK Baseline vs. SERUM CK Trial Mean Elevations, POP4 (52 weeks).

Actual Treatment for Period 01=Placebo								
	CK SERUM Baseline							
	Less than 2x ULN		**2x and 5x ULN**		**5x and 10x ULN**		**All**	
CK SERUM Trial Mean	**Count**	**%**	**Count**	**%**	**Count**	**%**	**Count**	**%**
Less than 2x ULN	598	98.0%	9	1.5%	1	0.2%	608	99.7%
2x and 5x ULN	2	0.3%	0	0.0%	0	0.0%	2	0.3%
All	600	98.4%	9	1.5%	1	0.2%	610	100.0%
Actual Treatment for Period 01=Fezolinetant 30 mg								
	CK SERUM Baseline							
	Less than 2x ULN		**2x and 5x ULN**		**5x and 10x ULN**		**All**	
Less than 2x ULN	599	98.0%	5	0.8%	2	0.3%	606	99.2%
2x and 5x ULN	0	0.0%	3	0.5%	1	0.2%	4	0.7%
Missing	1	0.2%	0	0.0%	0	0.0%	1	0.2%
All	600	98.2%	8	1.3%	3	0.5%	611	100.0%
Actual Treatment for Period 01=Fezolinetant 45 mg								
	CK SERUM Baseline							
	Less than 2x ULN		**2x and 5x ULN**		**5x and 10x ULN**		**All**	

Actual Treatment for Period 01=Placebo								
	CK SERUM Baseline							
	Less than 2x ULN		2x and 5x ULN		5x and 10x ULN		All	
CK SERUM Trial Mean	Count	%	Count	%	Count	%	Count	%
Less than 2x ULN	600	98.5%	7	1.1%	0	0.0%	607	99.7%
2x and 5x ULN	2	0.3%	0	0.0%	0	0.0%	2	0.3%
All	602	98.9%	7	1.1%	0	0.0%	609	100.0%

Source: NDA 216578 Trial 2693-CL-304, JMP Clinical, LB Dataset

Reviewer's Comment:
There were no differences in CK lab shifts to high in placebo versus fezolinetant 30 or 45 mg in Trial 2693-CL-304. There were no distinct patterns related to elevations over the course of the trial. The single case of clinically relevant recurrent rhabdomyolysis in the treatment group was associated with excessive exercise and a history of hypothyroid. There does not appear to be a signal or safety concern related to elevated CK.

8.4.7 Vital Signs

In POP2 and POP 4 study data 12 and 52-week vital sign data, there were no clinically relevant mean or median changes from baseline in systolic blood pressure, diastolic blood pressure and/or pulse rate for any treatment groups.

8.4.8 Electrocardiograms (ECGs)

In POP2 12 and 52-week safety populations, there were no clinically relevant changes in the quantitative interval measures of the ECG parameters in any of the treatment groups. In the POP2 12-week population, the majority of participants (> 97%) in all treatment groups had a QTcF $\leq$ 450 msec at baseline and at week 12 for POP2 no participants had a QTcF > 480 msec. In the POP2 52-week population, the majority of participants (> 97%) in all treatment groups had a QTcF $\leq$ 450 msec at baseline and at week 52. One participant had a QTcF > 480 but $\leq$ 500 msec at week 52 (fezolinetant 45 mg group) and 1 participant in the fezolinetant 30 mg group had a QTcF > 500 msec at week 52. Across the entire phase 3 program, there were no reported cases of ventricular tachycardia, ventricular fibrillation, electrocardiogram T wave abnormal, QT prolongation or Torsades de pointes.

8.4.9 QT

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

8.4.10 Immunogenicity

There were no cases of anaphylaxis or allergic response to fezolinetant reported in the development program. Fezolinetant does not appear to have significant immunogenicity.

8.5 Analysis of Submission-Specific Safety Issues

8.5.1 Malignancy

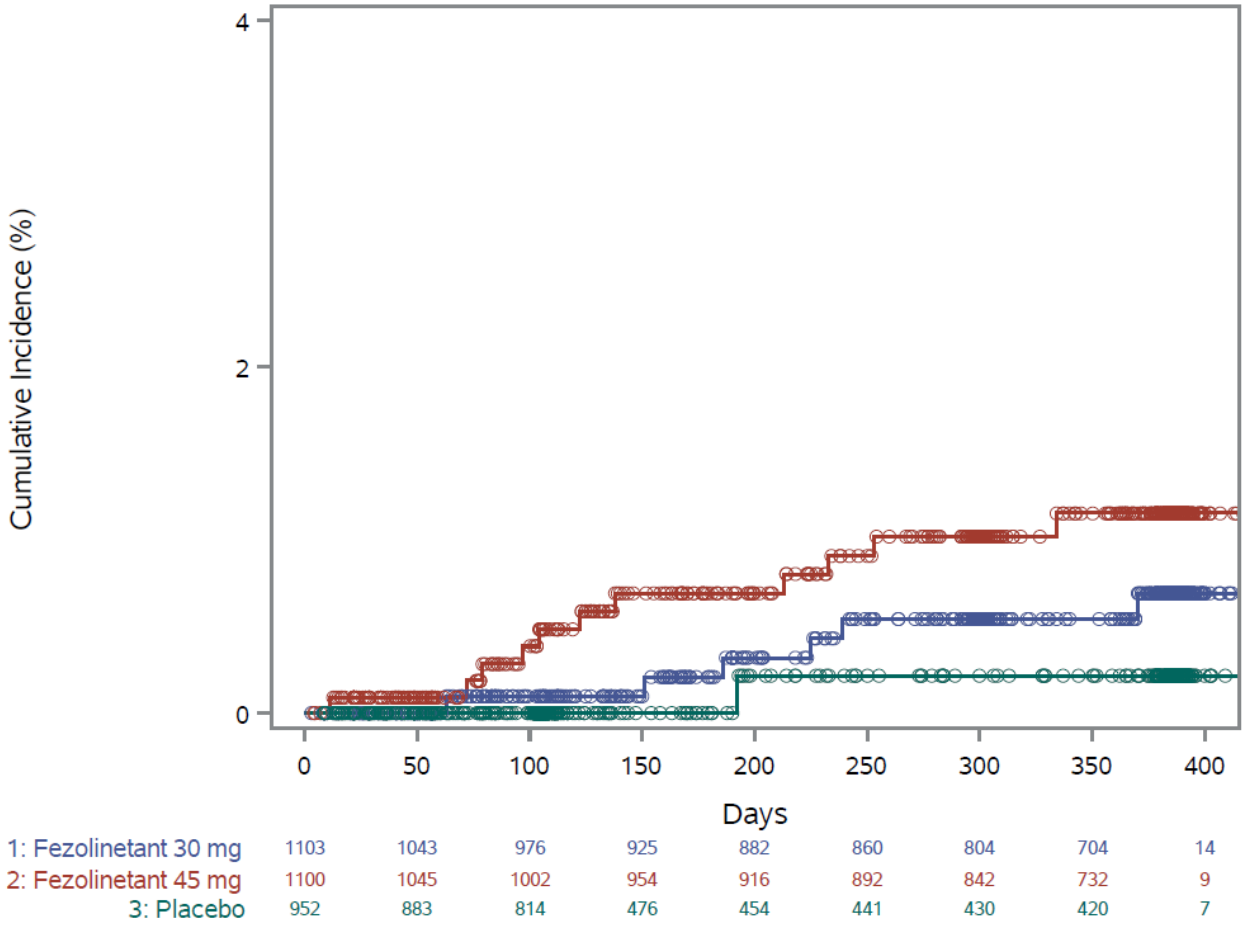
There was a dose dependent numeric imbalance noted in the incidence of malignancy in fezolinetant versus placebo arms in the SOC of neoplasms benign, malignant, and unspecified. All TEAEs in this SOC were upgraded to SAEs per the applicant in the case of malignancy and benign neoplasms not in remission. There was no previous concern of malignancy prior to initiating phase 3 trials based on nonclinical carcinogenicity, genotoxicity studies and phase 2 studies. The exposure adjusted incidence rates for non-benign neoplasms (high level group term) in POP2 (52 weeks) were 0.2, 0.7 and 1.2 per 100 participant years in placebo, total fezolinetant 30 mg and total fezolinetant 45 mg arms respectively.

Table 55 Reviewer-Assessed Malignancy TEAEs POP2 (52 weeks)

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

Source: DB7 reviewer generated data table; Reviewer notes: First event only, Exposure: (date of 1st onset of event – date of 1st dose)+1 for those with event or (date of last dose+21 days – date of 1st dose)+1 for those with no event; PY : person year = sum of exposure over all subjects / 365.25.

Figure 9 Reviewer-Assessed Cumulative Incidence Rate (%) of Malignancy POP2 (52 weeks)



Source: FDA Division of Biometrics 7 reviewer generated table; Joo-Yeon Lee

Table 56 Reviewer- Assessed Individual Malignancy TEAEs in POP2 (52 weeks)

Treatment Arm (Phase 3 POP2)	AE Code	Exposure Day	Months	Age	Race	BMI	Smoker	Notes
Placebo	Squamous cell carcinoma of skin	192	6.3	56	Black	33.8	Former/Never	
Placebo/45mg	Apocrine breast carcinoma*	11	3.1	62	White	26.0	Former/Never	Occured exposure day 11
45mg	Non-small cell lung cancer*	11	2.4	65	White	21.6	Current	Apocrine breast carcinoma metastatic to liver
Placebo/30mg	Squamous cell carcinoma of skin	62	4.8	65	White	33.4	Former/Never	
45mg	Endometrial adenocarcinoma	79	2.6	50	White	27.4	Former/Never	Complex hyperplasia with atypia at baseline
45mg	Malignant melanoma in situ	97	3.2	56	White	22.5	Current	
45mg	Squamous cell carcinoma of skin	104	3.4	60	White	31.3	Former/Never	
45mg	Endometrial adenocarcinoma	122	4.0	58	White	32.2	Former/Never	
45mg	Squamous cell carcinoma of the oral cavity**	138	4.5	52	White	27.3	Former/Never	Oral lesion day 47 not biopsied at on initial presentation
45mg	Bone cancer**	151	5.0	52	White	27.3	Former/Never	Oral cancer that spread locally to jaw bone
Placebo/30mg	Invasive breast carcinoma	152	7.8	60	Black	33.0	Former/Never	

Treatment Arm (Phase 3 POP2)	AE Code	Exposure Day	Months	Age	Race	BMI	Smoker	Notes
30mg	Squamous cell carcinoma of skin	186	6.1	56	White	27.3	Former/Never	
45mg	Keratoacanthoma (precancerous)	213	7.0	55	White	30.0	Former/Never	
30mg	Chronic lymphocytic leukemia	225	7.4	51	Black	24.9	Former/Never	Baseline leuko and lymphocytosis
45mg	Colon cancer	233	7.7	52	White	34.0	Current	
30mg	Basal cell carcinoma	239	7.9	63	White	19.7	Former/Never	Recurrent case
45mg	Colon cancer	253	8.3	55	White	31.0	Current	Symptomatic starting on Day 24 without evaluation
30mg	Endometrial adenocarcinoma	370	12.2	51	White	29.4	Current	

Source: Reviewer generated using NDA 216578 ISS ADAE database, JMP analysis. *AEs occurred in Same participant, ** AEs occurred in same participant.

Based on the apparent imbalance in the incidence of malignancy in treatment compared to placebo groups, the review team consulted the Division of Oncology III for their input regarding following questions:

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

At the time of archiving of this clinical review, the Oncology response is pending.

In the 120-day Safety Update of Clinical Safety submitted on October 6, 2022, there was 1 report of fibroadenoma of breast in placebo and 1 case of malignant neoplasm of thymus in fezolinetant 30 mg in a 24-week cross-over placebo-controlled trial in China (12 to 24 weeks of exposure, CL 0305, N=300). In a single arm, multicenter safety and tolerability 52-week study in China (CL 0307, N=150), there was 1 case of endometrial adenocarcinoma and one case of invasive breast carcinoma in the fezolinetant 30 mg arm.

> Reviewer's Comment:
> While there was the appearance of a dose response for malignancy in comparing the placebo, fezolinetant 30, and fezolinetant 45 mg treatment arms, malignancy cases were sporadically distributed without patterns related to duration of drug exposure, body system and/or cancer type. Most cancers were singular in nature and occurring in disparate systems and varied cancer types except for colon cancer (2 cases), squamous cell skin cancer (3 cases) and endometrial cancer (3 cases). Based on our clinical review, six of the participants (8/16 malignancy TEAEs in treatment arms) were likely to have had preexisting malignancy that were undiagnosed at the time of enrollment. This brings the incidence rate of malignancy TEAEs within the normal background rate of cancer for the age group of this population which is 5.6 per 1,000 for 50 – 59 years of age (75% of participants) according to SEER incidence rates by age at diagnosis of cancer in all races (years 2015 – 2019). Additionally, the placebo arm had lower than expected rate of malignancy as compared to the background rate. The data presented in the 120-day Safety Update of Clinical Safety are reassuring related to malignancy.

8.5.2 Bone Safety

The applicant conducted the following assessments to assess bone safety:

- Bone marker data in Trials 301 and 302 only
  - BSAP, P1NP, and CTX measured at baseline and at 52 weeks
- Dual-energy X-ray Absorptiometry (DEXA) in Trial 2693-CL-304 only
  - Bone mineral density (BMD) and TBS at hip and spine measured at baseline and 52 weeks

See Table 57 for the change from Baseline to Week 52 (POP2) in bone markers and Table 58 for the change from Baseline to Week 52 in bone density.

Table 57 Change from Baseline to Week 52 in Bone Markers (Safety Analysis Set); POP2 52-week, Trials 301 and 302

Parameter	Fezolinetant 30 mg (n = 242)	Fezolinetant 45 mg (n = 253)	Placebo/ Fezolinetant 30 mg (n = 113)	Placebo/ Fezolinetant 45 mg (n = 119)	Fezolinetant 30 mg Total† (n = 355)	Fezolinetant 45 mg Total‡ (n = 372)	Fezolinetant Total (n = 727)
BSAP (µg/L)							
n	242	253	113	119	355	372	727
Mean (SD)	0.39 (3.77)	0.24 (3.57)	0.00 (3.31)	0.15 (4.42)	0.27 (3.63)	0.21 (3.86)	0.24 (3.74)
Median	0.24	-0.09	-0.09	-0.20	0.06	-0.11	0.03
Min, Max	-10.3, 14.5	-9.1, 13.8	-10.5, 9.7	-12.9, 22.7	-10.5, 14.5	-12.9, 22.7	-12.9, 22.7
P1NP (µg/L)							
n	238	247	112	118	350	365	715
Mean (SD)	3.23 (25.86)	0.41 (29.11)	0.51 (22.91)	4.08 (26.26)	2.36 (24.95)	1.59 (28.24)	1.97 (26.66)
Median	3.00	-1.00	2.00	3.50	3.00	0.00	1.00
Min, Max	-127.0, 90.0	-275.0, 112.0	-97.0, 63.0	-57.0, 97.0	-127.0, 90.0	-275.0, 112.0	-275.0, 112.0
CTX (ng/L)							
n	225	241	108	112	333	353	686
Mean (SD)	55.6 (207.3)	53.4 (191.9)	38.8 (183.3)	57.7 (256.3)	50.1 (199.7)	54.8 (214.1)	52.5 (207.1)
Median	50.0	30.0	40.0	40.0	50.0	40.0	40.0
Min, Max	-680, 730	-390, 700	-670, 520	-930, 1070	-680, 730	-930, 1070	-930, 1070

Source: NDA SCC/ISS Page 115, Table 47. Safety analysis set. n is number of participants with non-missing value.
n is number of participants with non-missing value.
† Includes fezolinetant 30 mg and placebo/fezolinetant 30 mg in Trials 2693-CL-0301 and 2693-CL-0302.
‡ Includes fezolinetant 45 mg and placebo/fezolinetant 45 mg in Trials 2693-CL-0301 and 2693-CL-0302.

Table 58 Change from Baseline to Week 52 in Bone Density (Safety Analysis Set); POP2 52-week, Trial 2693-CL-304

Reading	Placebo (n = 610)	Fezolinetant 30 mg (n = 611)	Fezolinetant 45 mg (n = 609)
BMD Parameter: Bone Mineral Density (g/cm^2)			
Hip (Femoral Neck)			
n	246	221	234
LS mean change from baseline (SE)	-0.012 (0.003)	-0.006 (0.003)	-0.010 (0.003)
Difference in LS means (SE)†	-	0.006 (0.004)	0.001 (0.003)
95% CI	-	-0.001, 0.013	-0.006, 0.008
2-sided P value ‡	-	0.103	0.740
Hip (Femur)			
n	246	221	234
LS mean change from baseline (SE)	-0.011 (0.002)	-0.006 (0.002)	-0.008 (0.002)
Difference in LS means (SE)†	-	0.005 (0.003)	0.003 (0.003)
95% CI	-	-0.001, 0.011	-0.003, 0.009
2-sided P value ‡	-	0.116	0.330
Hip (Trochanter)			
n	246	221	234
LS mean change from baseline (SE)	-0.008 (0.002)	-0.004 (0.003)	-0.004 (0.003)
Difference in LS means (SE) †	-	0.004 (0.003)	0.004 (0.003)
95% CI	-	-0.002, 0.010	-0.002, 0.010
2-sided P value ‡	-	0.211	0.192
Spine			
n	253	225	242
LS mean change from baseline (SE)	-0.013 (0.003)	-0.011 (0.003)	-0.010 (0.003)
Difference in LS means (SE) †	-	0.001 (0.004)	0.003 (0.004)
95% CI	-	-0.007, 0.010	-0.006, 0.011
2-sided P value ‡	-	0.781	0.523

Source: NDA 216578, SCS/ISS, Table 116, page 116 of 152. Safety analysis set.
n is number of participants with non-missing value. The LS Means, SE, CI, and P values come from an ANCOVA model with change from baseline at the week 52 timepoint as response, treatment and smoking status (current vs former/never) as fixed effects with baseline weight and baseline as covariates. Records marked as poor image quality will be excluded from this analysis.
† Differences are calculated by subtracting the LS mean of placebo group from the LS mean of fezolinetant group.

‡ P value is for comparison of fezolinetant with placebo from the above described ANCOVA model.
ANCOVA: analysis of covariance; BMD: bone mineral density; CI: confidence interval; IQC: internal quality control; LS: least squares; XCAL: factor of uncertainty measurement for calibration.

Analyses in 57 and 58 did not reveal any statistically significant changes from baseline to Week-52 in bone density for participants in the fezolinetant arms vs placebo. Assessment of change from baseline in bone markers did not yield clinically concerning patterns.

> Reviewer's Comment:
> Fezolinetant does not appear to have an impact on bone safety after 12 months of exposure according to the data generated in the fezolinetant development program. We note that neither Trials 2693-CL-0301 nor 2693-CL-0302 standardized Vitamin D or calcium intake.

8.5.3 Endometrial Safety

In the NDA application, an assessment of endometrial safety was performed, inclusive of available data from transvaginal ultrasound (TVU) assessment; endometrial biopsy specimen collection and histologic pathology diagnoses of the collected endometrial tissue; and reported TEAE data across the phase 3 clinical trials, including Trials 2693-CL-0301, 2693-CL-0302 and 2693-CL-0304.

Endometrial biopsy specimens were reviewed by three independent board-certified pathologists from institutions with independent fiduciary and organizational reporting. After the initial safety evaluation of the actual biopsy was completed by the primary pathologist, digital images of the biopsy specimen were uploaded to a database and then assessed by secondary and tertiary pathologists independently. Each pathologist was blinded to the treatment group information as well as other pathologist's results. The independent pathologists did not have access to any other clinical case data. The three pathologists used the same standardized criteria for the diagnosis of endometrial hyperplasia or endometrial cancer, and endometrial polyps were fully characterized as to glandular proliferation and atypia per the Agency's draft 2003 Clinical Evaluation Guidance for Industry.

For postbaseline endometrial biopsies, the concordance of two of the three pathologists' readings determined the final diagnosis endometrial specimen classification. If all 3-three individual pathologist readings were discordant, the final diagnosis was classified based on the worst diagnosis.

In the NDA application, the satisfactory endometrial biopsy results were summarized for the endometrial health (EH) set. The EH set consisted of all non-hysterectomized participants who

were randomized and received at least 1 dose of trial drug, had the postbaseline endometrial biopsy done within 30 days after the last dose of trial drug, and who:

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

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

Participants from Trials 2693-CL-0301 and 2693-CL-0302 initially randomized to fezolinetant and who satisfied the criteria for inclusion were eligible for the POP2 EH set. Per Astellas, participants who were initially randomized to placebo and re-randomized to 30 or 45 mg fezolinetant in these two trials were not included in the primary EH set for POP2 because of the differences in duration of fezolinetant treatment. However, Astellas provided an additional supportive analysis for these re-randomized participants in Trials 2693-CL-0301 and 2693-CL-0302 who had a satisfactory endometrial biopsy result at end-of-treatment.

Per Astellas, POP4 was considered the primary population for analysis of endometrial health, since it was composed of 52-week, placebo-controlled Trial 2693-CL-0304, for which endometrial health was a primary trial objective. In Trial 2693-CL-0304, no participant in the placebo or 30 mg fezolinetant treatment group was diagnosed with endometrial hyperplasia; 1 participant in the 45 mg fezolinetant treatment group was diagnosed with simple hyperplasia without atypia. Likewise, in Trial 2693-CL-0304, no participant in the placebo or 45 mg fezolinetant treatment group was diagnosed with endometrial cancer; 1 participant in the 30 mg fezolinetant treatment group was diagnosed with endometrial adenocarcinoma.

Given that the point estimates for endometrial hyperplasia or malignancy were below the prespecified limits of ≤ 1%, and the upper limit of the one-sided 95% CI was ≤ 4%, Astellas points out that Trial 2693-CL-0304 met its primary endpoints for endometrial safety, as shown in the following Table 59.

Table 59 Endometrial Biopsy Results; Hyperplasia or Malignancy (Endometrial Health Set); POP4: Trial 2693-CL-0304

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

Source: NDA 216578, Summary Clinical Safety (SCS)/Integrated Summary of Safety (ISS), Table 38, page 106 of 152.
Definition: CI = confidence interval.
† CI obtained using the Clopper-Pearson exact method for binomial proportions.

In POP2, a total 302 participants were included in the fezolinetant 30 mg group, and 304 participants in the fezolinetant 45 mg group in the EH set. Table 60 shows the disposition of endometrial biopsy results in POP2 52-week.

Table 60 Disposition of Endometrial Biopsy Results (Randomized Participants); POP2 52-week

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

Source: NDA 216578, Summary Clinical Safety (SCS)/Integrated Summary of Safety (ISS), Table 40, page 107 of 152.
Definition: EH = endometrial health.
† Planned treatment of randomized participants.
‡ In Trial 2693-CL-0301, 1 participant who was randomized to 45 mg fezolinetant received 30 mg fezolinetant for the first 12 weeks.
§ These participants had an acceptable biopsy at baseline except for the 2 participants from the fezolinetant 45 mg group: participant (b) (6) had disordered proliferative pattern and participant (b) (6) had hyperplasia at baseline, therefore these 2 participants were not included in the EH set.
¶ Participants who had an acceptable biopsy at baseline and a satisfactory postbaseline biopsy prior to day 326, but were not included in the EH set.

†† Participants who had an acceptable biopsy at baseline and a satisfactory postbaseline biopsy after last dose + 30 days, but were not included in EH set.
‡‡ Participants who met the EH set definition in the statistical analysis plan (SAP).

Per the NDA application, in POP2 for the events of endometrial hyperplasia and malignancy, the rate of events in the fezolinetant groups was ≤ 1% with the upper bound of the one-sided 95% CI being ≤ 4%, as shown in Table 61.

Table 61 Endometrial Biopsy Results; Hyperplasia or Malignancy (Endometrial Health Set); POP2 52-week

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

Source: NDA 216578, Summary Clinical Safety (SCS)/Integrated Summary of Safety (ISS), Table 41, page 107 of 152.
Definition: CI = confidence interval.
EH set consists of safety analysis participants with an acceptable biopsy baseline (per SAP), had postbaseline biopsy done within 30 days from last dose, and had satisfactory postbaseline on or after day 326 or had a hyperplasia, malignancy, or disordered proliferative pattern final diagnosis prior to day 326.
POP2 is comprised of Trials 2693-CL-0301, 2693-CL-0302 and 2693-CL-0304.
Number of participants and percentage of participants (%) are shown.
†CI calculated using Clopper-Pearson exact method for binomial proportions.

Reviewer's Comment:
The reported results in the above table for POP2 52-week are consistent with the results reported for POP4.

However, the following two additional cases of endometrial adenocarcinoma were diagnosed in Trial 2693-CL-0304.

1. Participant Number (b) (6) was randomized to the 45 mg fezolinetant treatment group. Her relevant medical history included ongoing hypothyroidism and depressed mood, and concurrent medications included paroxetine hydrochloride and levothyroxine sodium. She had never smoked, and *had not received previous hormone therapy*. Her baseline TVU on Day -33 revealed an endometrial thickness of 3.545 mm. An endometrial biopsy performed on the same day revealed the following diagnoses by 3 pathologists:

1) Complex hyperplasia with atypia/areas of squamous metaplasia.
2) Complex hyperplasia with atypia and two foci with crowed back-to-back atypical endometrial glands, consistent with atypical complex hyperplasia/endometrioid intraepithelial neoplasia.
3) Complex hyperplasia without atypia.
   Final diagnosis: complex hyperplasia with atypia.

On Day 29, she experienced uterine hemorrhage, which was moderate in intensity and considered related to trial drug by the investigator which resolved on Day 38. No action was taken with trial drug due to the event. An endometrial biopsy was performed on Day 38 and revealed the following diagnoses by 3 pathologists:

1) Limited surface endometrium.
2) Tissue unsatisfactory for diagnosis; no endometrium present.
3) Limited surface endometrium.
   Final diagnosis: limited surface endometrium.

On Day 54, she again experienced uterine hemorrhage, which was moderate in intensity and considered related to trial drug by the investigator which resolved on Day 61. An endometrial biopsy was performed on Day 79 and revealed the following diagnoses by three pathologists:

1) Malignant, carcinoma/well differentiated endometrial adenocarcinoma in background of secretory endometrium.
2) Secretory cyclic type, simple hyperplasia without atypia, functional polyp/there are areas with crowded glands with decreased intervening stroma and squamous metaplasia; no significant cytologic atypia is seen; the rest of the specimen shows secretory and polypoid changes.
3) Functional polyp, complex hyperplasia with atypia.
   Final diagnosis: endometrial adenocarcinoma.

Treatment with trial drug was withdrawn due to the event. No TVU was performed post-baseline.

On Day 119, she was hospitalized and had a laparotomy, modified radical hysterectomy with adnexa resection. Histopathology: adenocarcinoma endometrioides endometrii G1.

The investigator considered the 2 events of uterine hemorrhage to be related to trial

drug, and the event of endometrial adenocarcinoma to be not related to trial drug. The sponsor agreed with the investigator's assessments for all events, including the event of endometrial adenocarcinoma to be not related to study drug.

This participant was not included in the endometrial health set as she did not fulfill one of the qualifying criteria (i.e., she had at least one acceptable endometrial biopsy result with a satisfactory tissue and a read of hyperplasia at baseline).

Reviewer's Comments:
We opine that this participant had a pre-existing complex hyperplasia with atypia at baseline which subsequently advanced to endometrial adenocarcinoma. She should not have been enrolled in Trial 2693-CL-0304.

2. Participant Number (b) (6) was randomized to the 45 mg fezolinetant treatment group. Her relevant medical history included ongoing arthralgia (right knee) and no relevant concurrent medications. She had never smoked, and *had not received previous hormone therapy*. A TVU on Day -20 revealed an endometrial thickness of 5.49 mm. An endometrial biopsy performed on Day -30 revealed the following diagnoses by two pathologists:

    1) Inactive.
    2) Limited surface endometrium, atrophy.

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

    On Day 247 after trial discontinuation, the investigator reported that a repeat TVU was performed which confirmed the presence and growth of the polyp first seen on Day 122; a TVU endometrial thickness of 2.355 mm was reported. A hysteroscopy was performed on day 309 to remove the endometrial polyp. The event of uterine

polyp was considered resolved with sequelae on Day 309. The polyp biopsy report showed endometrial adenocarcinoma (Stage 1). On Day 351, she underwent a robotic XI total lap hysterectomy bilateral salpingo-oophorectomy sentinel lymph node dissection. The event of endometrial adenocarcinoma (Stage 1) was not resolved at the time of reporting. Although requested, no histopathology report has been submitted thus far.

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

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

Reviewer's Comment:
We agree with the investigator's assessment of causality and disagree with the sponsor. This participant's polyp was confirmed by TVU on Day 122, 15 days after her last dose of trial medication.

This one case of endometrial adenocarcinoma should be added under 45 mg fezolinetant for POP2 52-week.

On September 28, 2022, Astellas was requested to recalculated the point estimate of the incident rate along with the one-sided 95% confidence interval for that rate for hyperplasia (participant # (b) (6)) and endometrial adenocarcinoma of polyp, Stage 1 (participant # (b) (6)) for the 45 mg fezolinetant dose. Astellas responded on October 3, 2022 providing the following information incorporated in Table 62.

Table 62 Primary Analysis of Participants with Endometrial Hyperplasia, Endometrial Carcinoma, Disordered Proliferative Pattern at Postbaseline; Endometrial Health Set; POP2 52-Week

Final Diagnosis	Fezolinetant 30 mg (n = 302)	Fezolinetant 45 mg (n = 305)
Hyperplasia and Carcinoma	1 (0.3%)	2 (0.7%)
One-sided upper limit of 95% CI	1.6%	2.0%
- Simple hyperplasia without atypia	0	1
- Simple hyperplasia with atypia	0	0
- Complex hyperplasia without atypia	0	0
- Complex hyperplasia with atypia	0	0
- Endometrial adenocarcinoma	0	1
- Malignant, carcinoma	1	0
Disordered Proliferative Pattern	4 (1.3%)	3 (1.0%)
One -sided upper limit of 95% CI	3.0%	2.5%

Source: Adapter from NDA 216578, Response to September 28, 2022 Information Request Received October 3, 2022.
Definition: CI = confidence interval.

Reviewer's Comment:
Table 62 above does not include the available endometrial safety information reported for the re-randomized placebo participants in Trials 2693-CL-0301 and 2693-CL-0302. Astellas provided this information as a supportive analysis. This analysis showed one case of complex hyperplasia without atypia occurring in the placebo/30 mg fezolinetant treatment group in POP2 52-week. Astellas is not requesting approval of 30 mg fezolinetant for the indication sought.

On September 28, 2022, the Division of Biometrics 7 (DB7) was consulted to analyze the reported endometrial safety information including the re-randomized placebo participants in the phase 3 clinical trials. Table 63 shows the DB7 analysis received in an electronic communication dated September 30, 2022.

Table 63 Division of Biometrics 7 Analysis of Participants with Endometrial Hyperplasia and Carcinoma at Postbaseline; POP2 52-week Including Re-randomized Participant in Trial 2693-CL-0301 and Trial 2693-CL-0302

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

Source: Division of Biometrics 7, Received September 30, 2022.

Reviewer's Comment:
The Table 63 analysis, prepared by Astellas following FDA's request, continues to demonstrate that the point estimates for endometrial hyperplasia or malignancy were below the prespecified limits of ≤ 1%, and the upper limit of the one-sided 95% CI was ≤ 4%. The Table 60 analysis, prepared by DB7 confirms these findings for the expanded safety data.

See Subsection 10.1 Prescription Drug Labeling, in this review, for the clinical reviewer's recommendations for the proposed fezolinetant labeling submitted.

Disordered Proliferative Endometrium:
Both disordered proliferative endometrium and endometrial hyperplasia are on a continuum of morphological endometrial alterations resulting from unopposed estrogenic stimulation, and these conditions may be considered precursors to endometrial carcinoma.[16]

In POP4, the percentage of non-hysterectomized participants with a final endometrial biopsy diagnosis of disordered proliferative pattern was higher in the placebo group (2.2%, 4 in 186 participants) than in the fezolinetant groups (1.4%, 3 in 210 participants in 30 mg fezolinetant group; 0 in 203 participants in the 45 mg fezolinetant group).

In POP2 52-week, the incidence of disordered proliferative pattern was similar in the

[16] Damle RP, et al. Clinicopathological spectrum of endometrial changes in peri-menopausal and post-menopausal abnormal uterine bleeding: a 2-year study. J Clin Diagn Res. 2013: 7; 2744-6.

fezolinetant 30 mg and fezolinetant 45 mg groups in the EH set (1.3%, 4 in 302 participants in 30 mg fezolinetant group; 1.0%, 3 in 304 participants in 45 mg group). The results of the POP2 52-week supportive analysis of the EH set plus the re-randomized placebo participants in POP2 52-week shows a higher percentage of cases of disordered proliferative endometrium in 30 mg fezolinetant than 45 mg fezolinetant (1.7%, 6 in 353 participants vs 1.4%, 5 in 349 participants, respectively).

> Reviewer's Comments:
> The POP2 52-week results of the supportive analysis of the EH set including the re-randomized participants in Trials 2693-CL-0301 and 2693-CL-0302 was concordant with and supportive of the primary analysis for the EH set in POP4. The occurrence of 5 cases of diagnosed disordered proliferative endometrium in the 45 mg fezolinetant treatment group, requested for approval in the NDA application, will appear in labeling in Section 14 Clinical Studies.
>
> See Subsection 10.1 Prescription Drug Labeling, in this review, for the clinical reviewer's recommendations for the proposed labeling submitted.

Transvaginal Ultrasound (TVU) Results:
In POP4, the placebo-controlled 52-week safety Trial 2693-CL-0304, the centrally read TVU data demonstrated there was no difference between fezolinetant and placebo in the change from baseline to Week 52 in endometrial thickness. The baseline endometrial thickness (mm) ranged from a mean (SD) of 3.51(2.99) for the 45 mg fezolinetant group to 3.59 (2.19) for the placebo group. The Week 52 endometrial thickness (mm) ranged from mean (SD) of 3.21 (2.01) for the 45 mg fezolinetant group to 3.52 (2.39) for the placebo group. The reported data support that fezolinetant has no impact on endometrial thickness after 1 year of chronic use treatment. See Table 45 on page 111 of 152 in the SCS/ISS in the NDA application.

In POP2 52-week, including the re-randomized placebo participants, change from baseline to week 52 in endometrial thickness as assessed by TVU showed no clinically relevant changes in any of the treatment groups. The POP2 52-week data support the assessment of TVU in POP4. See Table 46 on page 113 of 152 in the SCS/ISS in the NDA application.

> Reviewer's Comment:
> Based on the TVU data reported in the NDA application for POP4 and POP2 52-week, fezolinetant has no impact on endometrial thickness after 1 year of treatment.

Uterine Bleeding:
The exposure-adjusted incidence rate of uterine bleeding in POP2 52-week showed a higher rate of uterine bleeding in the placebo group than in the fezolinetant groups (6.0% in the

placebo group vs 4.1% in 30 mg fezolinetant group, 3.4% in the 45 mg fezolinetant group, 3.8% in the placebo/30 mg fezolinetant group, and 2.8% in placebo/45 mg fezolinetant group.

> Reviewer's Comment:
> Overall, the incidence of treatment-emergent uterine bleeding was low in the phase 3 clinical trials and greater in the placebo treatment group than in the fezolinetant treatment groups.

8.5.4 Hepatic Safety

Potential concern for the liver safety of fezolinetant arose during the conduct of phase 2 clinical trials when a greater incidence of alanine aminotransferase (ALT)/aspartate aminotransferase (AST) elevations were observed in participants receiving fezolinetant active treatment vs. placebo. In early fezolinetant development for VMS, and other Astellas/Ogeda SA programs, nine (9) 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. Prior to phase 3 development, Astellas conducted Quantitative Systems Toxicology (QST) modeling (DILIsym) which predicted the adverse hepatic findings observed at phase 2 dosing . Based on these reported findings, phase 3 fezolinetant development was limited to 30 and 45 mg fezolinetant dosage strengths.

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

1. Phase 3 clinical trials participants has laboratory evaluations (including hepatic transaminases) preformed at screening, randomizations (Visit 2, Day 1), Visit 2b (Week 2), Visits 3 (Week 4), Visit 4 (Week 8), Visit 5 (Week 12), Visit 5b (Week 14), Visits 6 through 15 (Weeks 16 through Week 52), and Visit 16 (Week 55, follow-up).
2. Weekly monitoring of serum aminotransferases (ALT and AST), total bilirubin, direct bilirubin, alkaline phosphatase (ALP), gamma-glutamyltransferase (GGT) were assessed when a woman with non-elevated aminotransferase at baseline was found to have a hepatic transaminase elevation that did not meet the trial or individual participant stopping criteria.
3. Any participant enrolled in any fezolinetant clinical study who has an increase in serum aminotransferases of > 3 x ULN or in bilirubin > 2 x ULN during the trial underwent detailed testing for hepatic enzymes. Testing was repeated within 72 hours of notification of the test results. Automatic alerts were generated by the central laboratory regarding moderate to severe hepatic abnormalities to inform the

investigator and trial team. Participants were asked if they have any symptoms suggestive of hepatobiliary dysfunction.

4. Confirmed abnormalities were characterized as moderate (ALT or AST > 3 x ULN or TBL > 2 x ULN) or severe (ALT or AST > 3 x ULN and TBL > 2 X ULN).
5. In the absence of an explanations for increase hepatic transaminases, such as viral hepatitis, preexisting or active liver disease, or exposure to other agents associated with liver injury, trial treatment was discontinued if:

    - Development of severe hepatic abnormality defined as ALT or AST > 8 x ULN.
    - Confirmed (within 72 hours from the notification of test results) severe hepatic abnormality defined as any of the following:

        - ALT or AST > 5 x ULN for more than 2 weeks
        - ALT or AST > 3 x ULN and TBL > 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).
6. Moderate liver test abnormalities as defined above were repeated 2 to 3 times weekly, and then weekly or less if abnormalities stabilize or the trial drug had been discontinued and the participant was asymptomatic.
7. Confirmed moderate and severe abnormalities in hepatic tests were thoroughly characterized by obtaining appropriate expert consultations, detailed pertinent history, physical examination and laboratory tests. The site staff completed the liver abnormality case report form (LA-CRF). Astellas was contacted immediately of all participants for whom severe hepatic liver function abnormalities possibly attributable to study drug were observed.

A Liver Safety Monitoring Panel (LSMP), consisting of 3 independent board-certified hepatologists, experienced in the assessment of drug-induced liver injury (DILI), reviewed each potential case at the phase 3 program level and monitored the fezolinetant phase 3 development program. Any participant who experienced criteria ALT or AST > 3 x ULN or total bilirubin > 2 x ULN was evaluated, using blinded data, for potential DILI by the LSMP. These data were considered in tandem with other laboratory data including, but not limited to, ALP, GGT, and international normalized ration (INR).

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

participant level.

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

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

In the 52-week, placebo-controlled safety Trial 2693-CL-0304 (POP4), *ALT or AST elevations* (as determined by laboratory data*) of > 3 x ULN were observed in 1.0% of participants treated with placebo (6 of 583 participants), 1.4% of participants treated with 30 mg fezolinetant (8 of 590 participants), and 2.0% of participants treated with 45 mg fezolinetant (12 of 589 participants).* There was a low and similar incidence of AST or ALT elevations > 5 x ULN across the treatment groups. One 45 mg fezolinetant group participant had a bilirubin level > 2 x ULN. This participant had a medical history of Gilbert's syndrome, and no ALT or AST elevations > 3 x ULN. Time to onset for ALT or AST elevations varied from week 2 through to week 52, with no difference between placebo and fezolinetant groups. Table 64 shows the categorial liver biochemistry findings in POP4.

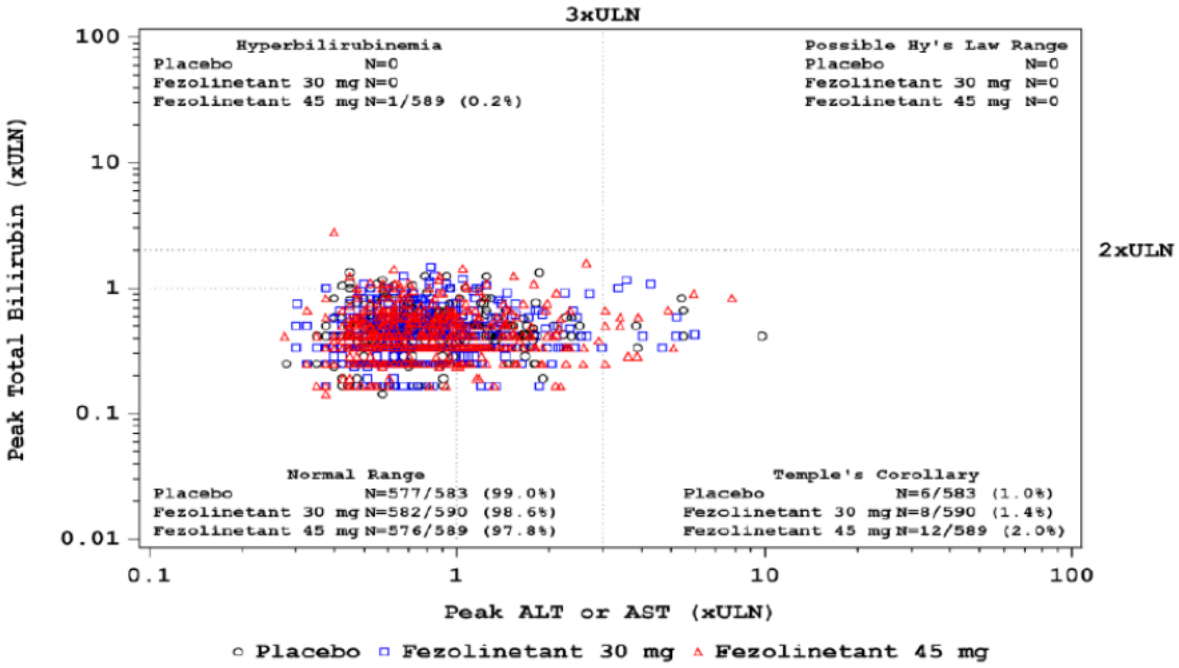
Table 64 Applicant's Reported Number (%) of Participants with Categorical Liver Biochemistry Findings (Safety Analysis Set); POP4; Trial 2693-CL-0304

Parameter	Criteria	Placebo (n = 610)	Fezolinetant 30 mg (n = 611)	Fezolinetant 45 mg (n = 609	Fezolinetant Total (n = 1220)
ALT	> 3 x ULN	5/583 (0.9%)	7/590 (1.2%)	11/589 (1.9%)	18/1179 (1.5%)
	> 5 x ULN	3/583 (0.5%)	2/590 (0.3%)	3/589 (0.5%)	5/1179 (0.4%)
	> 8 x ULN	1/583 (0.2%)	0/590	0/589	0/1179
	> 10 x ULN	0/583	0/590	0/589	0/1179
	> 20 x ULN	0/583	0/590	0/589	0/1179
AST	> 3 x ULN	3/583 (0.5%)	5/590 (0.8%)	5/589 (0.8%)	10/1179 (0.8%)
	> 5 x ULN	2/583 (0.3%)	1/590 (0.2%)	1 589 (0.2%)	2/1179 (0.2%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
	ALT or AST > 3 x ULN and TBL > 2 x ULN	0/583	0/590	0/589	0/1179

Source: NDA 216578, Summary Clinical Safety (SCS)/Integrated Summary of Safety (ISS), Table 36, page 99 of 152.
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.

The exposure-adjusted results (number of participants with an event per 100 participant-years) were consistent with the unadjusted incidence data in POP4; 1.3 per 100 participant-years in the placebo group, 1.6 per 100 participant-years in the 30 mg fezolinetant group, and 2.4 per 100 participant-years in the 45 mg fezolinetant group. The following Figure 10 is presented in the NDA application

Figure 10 Applicant's Drug-induced Serious Hepatotoxicity (eDISH) Plot: Maximum of (AST or ALT) vs Maximum Total Bilirubin Values (Safety Analysis Set); POP4: Trial 2693-CL-0304



Source: NDA 216578, Summary Clinical Safety (SCS)/Integrated Summary of Safety (ISS), Figure 2, page 98 of 153.
All randomized participants who took at least 1 dose of trial drug (Safety Analysis Set).
Peak ALT or AST (x ULN) = maximum of (maximum x ULN postbaseline value for ALT, maximum x ULN postbaseline value for AST).
Definitions: ALT = alanine transferase; AST: =aspartate transferase; ULN = upper limit of the normal range.

Reviewer's Comment:
As shown in Figure 10, there are no Hy's Law cases shown for POP4 in this eDISH plot. No participant in POP4 had ALT or AST elevations > 3 x ULN **AND** total Bilirubin > 2 x ULN.

In the supportive POP2 52-week plus re-randomized placebo participants assessment (includes all three phase 3 trials), ALT or AST elevations of > 3 x ULN were observed in 0.9% of participants in the placebo group (8 in 917 participants), 1.5% of participants in the total 30 mg fezolinetant group (16 in 1069 participants), and 2.3% of participants in the total 45 mg fezolinetant group (25 in 1072 participants). ALT or AST elevations > 3 x ULN were occasionally accompanied ALP elevations. Time to onset for ALT or AST elevations varied from week 2 through to week 52, with no difference between placebo and fezolinetant groups. Table 65 shows the categorial liver biochemistry findings in POP2 52-week.

Table 65 Applicant's Reported Number (%) of Participants with Categorical Liver Biochemistry Findings (Safety Analysis Set); POP2 52-week; Trial 2693-CL-0301. Trial 2693-CL-0302, and Trial 2693-CL-0304

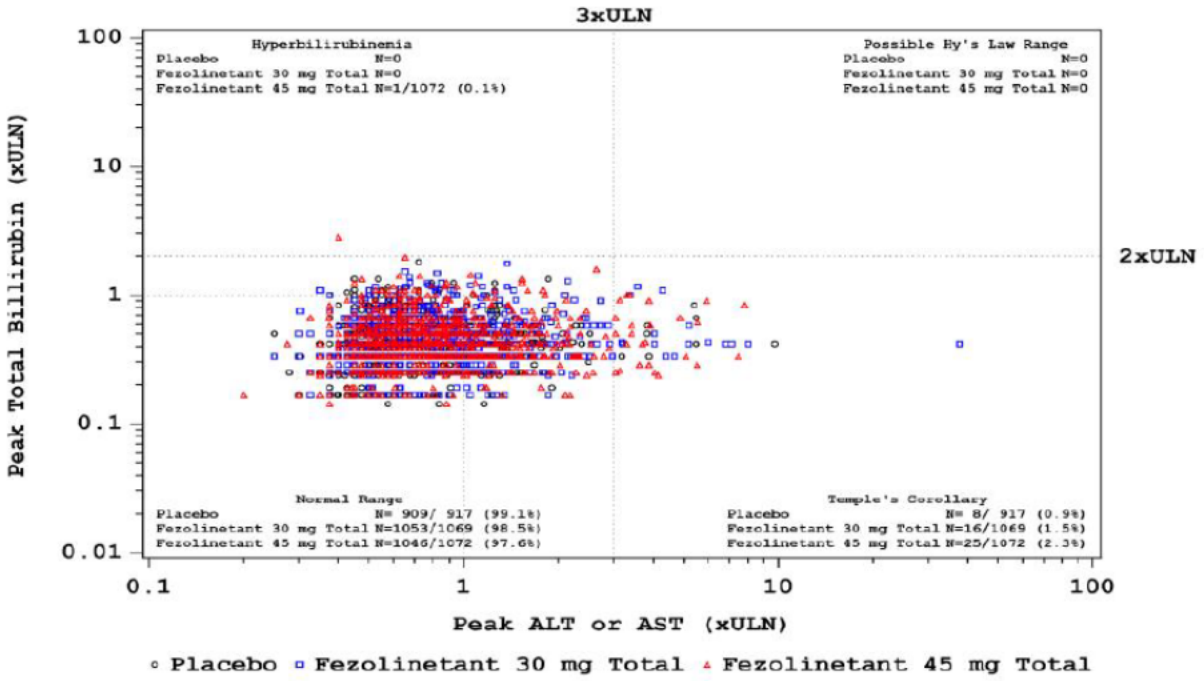
Parameter	Criteria	Placebo (n = 952)	Fezolinetant 30 mg (n = 951)	Fezolinetant 45 mg (n = 949)	Placebo/ Fezolinetant 30 mg (n = 152)	Placebo/ Fezolinetant 45 mg (n = 151)	Fezolinetant 30 mg Total (n = 1103)	Fezolinetant 45 mg Total (n = 1100)
ALT	> 3 x ULN	7/917 (0.8%)	13/917 (0.5%)	21/923 (2.3%)	1/152 (0.7%)	2/149 (1.3%)	14/1069 (1.3%)	23/1072 (2.1%)
	> 5 x ULN	3/917 (0.3%)	5/917 (0.5%)	9/923 (0.7%)	0/152	0/149	5/1069 (0.5%)	6/1072 (0.6%)
	> 8 x ULN	1/917 (0.1%)	1/917 (0.1%)	0/923	0/152	0/149	1/1069 (0.1%)	0/1072
	> 10 x ULN	0/917	1/917 (0.1%)	0/923	0/152	0/149	1/1069 (0.1%)	0/1072
	> 20 x ULN	0/917	0/917	0/923	0/152	0/149	0/1069	0/1072
AST	> 3 x ULN	4/917 (0.4%)	9/917 (1.0%)	11/923 (1.2%)	0/152	0/149	9/1069 (0.8%)	11/1072 (1.0%)
	> 5 x ULN	2/917 (0.2%)	3/917 (0.3%)	2/923 (0.2%)	0/152	0/149	3/1069 (0.3%)	2/1072 (0.2%)
	> 8 x ULN	0/917	2/917 (0.1%)	0/923	0/152	0/149	2/1069 (0.2%)	0/1072
	> 10 x ULN	0/917	1/917 (0.1%)	0/923	0/152	0/149	1/1069 (0.1%)	0/1072
	> 20 x ULN	0/917	1/917 (0.1%)	0/923	0/152	0/149	1/1069 (0.1%)	0/1072
ALT or AST	> 3 x ULN	8/917 (0.9%)	15/917 (1.6%)	23/923 (2.5%)	1/152 (0.7%)	2/149 (1.3%)	16/1069 (1.5%)	25/1072 (2.3%)
	> 5 x ULN	4/917 (0.4%)	7/917 (0.8%)	6/923 (0.7%)	0/152	0/149	7/1069 (0.7%)	6/1072 (0.6%)
	> 8 x ULN	1/917 (0.1%)	2/917 (0.2%)	0/923	0/152	0/149	2/1069 (0.2%)	0/1072
	> 10 x ULN	0/917	1/917 (0.1%)	0/923	0/152	0/149	1/1069 (0.1%)	0/1072
	> 20 x ULN	0/917	1/917 (0.1%)	0/923	0/152	0/149	1/1069 (0.1%)	0/1072
ALP	> 1.5 X ULN	21/918 (2.3%)	15/918 (1.6%)	17/923 (1.8%)	6/152 (3.9%)	6/149 (4.0%)	21/1070 (2.0%)	23/1072 (2.1%)
TBL	> 2 x ULN	0/917	0/915	1/923 (0.1%)	0/152	0/149	0/1070	1/1072 (0.1%)
ALT or AST and TBL†	ALT or AST > 3 x ULN and TBL > 2 x ULN	0/917	0/917	0/923	0/152	0/149	0/1069	0/1072
	ALT or AST > 3 x ULN and TBL > 1.5 x UN	0/917	0/917	0/923	0/152	0/149	0/1069	0/1072
ALT or AST and ALP and TBL†	ALT or AST > 3 x ULN and ALP < 2 x ULN and TBL > 2 x ULN	0/917	0/917	0/923	0/152	0/149	0/1069	0/1072

Source: NDA 216578, Summary Clinical Safety (SCS)/Integrated Summary of Safety (ISS), Table 35, page 96 of 152.
All randomized participants who took at least 1 dose of study intervention (Safety Analysis Set).
Maximum value on treatment is presented for each liver biochemistry variable. For participants re-randomized to either fezolinetant 30 mg or 45 mg, the maximum value during the extension treatment period is presented for each liver

biochemistry variable.
The denominator was the number of participants who had at least one 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.

There are no Hy's Law cases shown for POP2 52-week in the eDISH plot in Figure 11.

Figure 11 Applicant's Drug-induced Serious Hepatotoxicity (eDISH) Plot: Maximum of (AST or ALT) vs Maximum Total Bilirubin Values (Safety Analysis Set); POP2 52-week; Trial 2693-CL-0301, Trial 2693-CL-0302, and Trial 2693-CL-0304



Source: NDA 216578 Summary Clinical Safety (SCS)/Integrated Summary of Safety (ISS), Figure 1, page 94 of 152.
Log10 scale is used for both axes.
Peak ALT or AST (x ULN) = maximum x ULN postbaseline value of (ALT, AST) on treatment. For participants re-randomized to either fezolinetant 30 mg or 45 mg, the maximum value during the extension treatment period is also presented.
Definitions: ALT = alanine aminotransferase; AST = aspartate aminotransferase; ULN: upper limit of the normal range.

Reviewer's Comment:
No participant in POP2 52-week including the re-randomized placebo participants in Trials 2693-CL0301 and 2603-CL-0302 had ALT or AST elevations > 3 x ULN **AND** total bilirubin > 2 x ULN. There were no Hy's Law cases.

The exposure-adjusted reported results (number of participants with an ALT or AST > 3 x ULN

per 100 participant-years) in POP2 52-week was reported as 1.5 per 100 participant-years in the placebo group, 1.8 per 100 participant-years in the total 30 mg fezolinetant group, and 2.7 per 100 participant-years in the total 45 mg fezolinetant group. Exposure-adjusted incidence rates for elevations > 5 x ULN were balanced between treatment groups (0.8 in the 30 mg fezolinetant treatment group and 0.7 in the 45 mg fezolinetant treatment group), and elevations > 8 x ULN were rare [0.2 in the 30 mg fezolinetant treatment group (2 in 1069 participants) and none in the 45 mg fezolinetant treatment group). See Table 66.

Table 66 Number (%) of Participants with Categorical Findings of Liver Biochemistry: Exposure Adjusted Rates; POP2 52-week; Trial 2693-CL-0301. Trial 2693-CL-0302, and Trial 2693-CL-0304

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

Source: Adapted from NDA 216578, Integrated Summary of Safety (ISS), End-of-Text Table 12.5.7.1, page 4643 of 8061.
Number of subjects (n), and exposure adjusted rate per 100 subject-years (rate) are shown where rate = 100*n/Total subject-years.
Maximum value on treatment is presented for each liver biochemistry variable. For participants re-randomized to either 30 mg or 45 mg fezolinetant, the maximum value during the extension treatment period is presented. The denominator was the number of subjects who had at least one non-missing value during treatment.
Definitions: ALT = alanine transaminase, AST = aspartate aminotransferase, ULN = upper limit of normal range.

> Reviewer's Comment:
> Overall, the incidence of ALT or AST elevations in fezolinetant phase 3 development was low. After adjustment for exposure, similar incidence rates for treatment-emergent adverse events of special interest relating to hepatic enzyme elevations were compatible between placebo and fezolinetant-treated participants and between the 30 mg and 45 mg fezolinetant dosage strengths.
>
> Per the applicant, "hepatic enzyme elevations reflected asymptomatic abnormalities capture through protocol-specified routine testing."

Liver Safety Monitoring Panel (LSMP) Assessment:
The fezolinetant phase 3 clinical development program was monitored by an LSMP on an ongoing and regular basis through blinded review of individual participant cases that met the criteria of ALT or AST elevations > 3 x ULN and/or total bilirubin > 2 x ULN and other liver health markers, as well as an aggregate unblinded review across the phase 3 program. See page 90 of

this review for additional information regarding the LSMP. The LSMP supported continuation of phase 3 development at all timepoints during phase 3 clinical trials conduct.

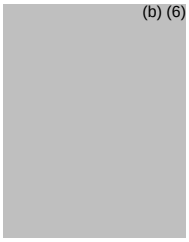
In the NDA application, Astellas provides the following summary report of the LSMP findings:

- "Trial 2603-CL-0301: Of the 10 participants with ALT or AST levels > 3 x ULN, 4 participants were assessed by the LSMP as having possible causality (1 in the placebo group, 1 in the placebo/fezolinetant 30 mg group and 2 in the fezolinetant 45 mg group) and 2 as probable causality (both in the fezolinetant 30 mg group); the causality for the other 4 events was assessed as unlikely."
- "Trial 2693-CL-0302: Of the 12 participants with ALT or AST levels > 3 x ULN, 5 were assessed by the LSMP as having possible causality (3 participants in the fezolinetant 45 mg group and 2 in the placebo/fezolinetant 45 mg group) and 2 as probable causality (1 participant in the fezolinetant 30 mg group and 1 in the fezolinetant 45 mg group); the causality for the other 5 events was assessed as unlikely."
- "Trial 2693-CL-0304: Of the 26 participants with ALT or AST levels > 3 x ULN, 12 were assessed by the LSMP as having possible causality (3 participants in the placebo group, 4 participants in the fezolinetant 30 mg group and 5 in the fezolinetant 45 mg group) and 5 as probable causality (0 participants in the placebo group, 1 in the fezolinetant 30 mg group and 4 in the fezolinetant 45 mg group); the causality for the other 9 events was assessed as unlikely (3 participants in each treatment group)."

Summary Statement from Liver Safety Monitoring Committee – May 26, 2022:
The NDA application includes a summary statement from the LSMB, dated May 26, 2022. The summary statement confirms that the 3 independent hepatologist assessed blinded participants experiencing serum ALT or AST elevations >3 x ULN or total serum bilirubin elevations >2 x ULN that occurred in the three phase 3 clinical trials. The following information on the LSMP findings, summary and conclusion is provided in the LSMB May 26, 2022 summary statement:

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

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



0302 – 45 mg
0304 – 30 mg
0304 – 45 mg
0304 – 45 mg
0304 – 45 mg
0304 – 45 mg

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

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

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

Conclusions:
"Fezolinetant treatment at the dosing regimens employed in 301, 302, and 304 clinical trials is generally safe for the liver. However, it should be *noted that active liver disease, very high BMI, and concomitant treatment with drugs that strongly inhibit fezolinetant metabolism were exclusion criteria in these studies*. In addition, a few patients in the trials discontinued active drug treatment prior to spontaneous improvement in their serum aminotransferase levels. Although it seems likely that these biochemical abnormalities would also have resolved with continued fezolinetant treatment, protocol stopping criteria prevented demonstrating this. It is *therefore not possible to exclude that fezolinetant could cause more serious and/or progressive liver injuries in a real-world setting, but it seems reasonable to*

> *conclude based on the available data that such events would be very rare*." *The LSMB concludes that, "To mitigate this possible liver safety risk post-approval, routine liver chemistry monitoring could be considered, especially during the first 3 months when event rate was highest.* However, given the rarity of the events, their relatively rapid onset, and the observation that the events typically resolved rapidly with or without discontinuation of treatment, we are skeptical of the value of routine liver chemistry monitoring here."

On July 26, 2022, the Division of Hepatology and Nutrition (DHN) was requested to provide consultative assessment to evaluate the evidence regarding hepatic function and/or hepatic injury findings in the phase 3 clinical trials submitted under NDA 216578. Previous consult responses were provided by DGIEP (now DHN) to IND 130277 on June 11, 2018, October 23, 2018, and March 29, 2019. The following requests and questions were included in the July 26, 2022 DHN consult request:

1. For ease of your review, do you need additional information, or data provided in an alternative presentation(s)?
2. Do you agree with the findings and conclusions provided in the Summary Statement from the Liver Safety Monitoring Committee, dated May 26, 2022?
3. Based on your review and conclusions with respect to hepatic safety evaluations and findings presented in NDA 216578, what is your recommendation on approvability of the NDA.
    a. If you opine that the NDA is not approvable from a hepatic safety standpoint, please provide your description of the complete response deficiency and the path forward for the applicant to address the deficiency.
    b. If you opine that the NDA is approvable with inclusion of certain labeling WARNINGS AND PRECAUTIONS, please provide these in the language you would put forward for the applicant's consideration."

On November 21, 2022, the DHN DILI Team responded providing the following response:

DILI Team Executive Summary:
We do not see a liver injury risk that should hold up approval if the need for fezolinetant (FZT) and its effectiveness are significant. There were no Hy's Law cases and many liver injury cases improved despite continued FZT use. Nevertheless, the level of transaminase elevations could be substantial (> 20 x ULN). We generally agreed with the applicant's LSMP's assessments and conclusions. *We recommend labeling in the WARNINGS AND PRECAUTIONS section for potential hepatotoxicity. Baseline liver chemistries should be checked and consideration given for monthly checks for several months. Our full assessment and recommendations are below in Section 5.*

DILI Team Consultation Sections:

In the DHN consult response, the DILI Team provided the following summary of the Absorption, Distribution, Metabolism, and Elimination (ADME) of fezolinetant pertinent to DILI.

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

A toxicology summary pertinent to Dili is also provided.

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

In addition, the following trial design features, incorporated in the protocols of each of the phase 3 clinical trials, were pertinent to the DILI Team assessment:

- Inclusion criteria: 1) negative serology panel (i.e., negative HBV surface antigen, negative HCV antibody and negative human immunodeficiency virus antibody screens), 2) ALT/AST <1.5 x ULN if total bilirubin (TB) and direct bilirubin (DB) are normal. ALP <1.5 x ULN if no cholestatic liver disease and no cause other than fatty liver is diagnosed, 3) Gilbert's syndrome with elevated TB if DB, hemoglobin, and reticulocytes are normal.
- Exclusion Criteria: 1) history of hepatic disease; active liver disease, jaundice, elevated ALT/AST (≥ 1.5 x ULN), TB, INR, or ALP (≥ 1.5 x ULN).
- Individual participant discontinuation Criteria: As stated above.

The DILI Team conducted detailed case level analysis of 14 participants with ALT or AST > 5 x

ULN in concert with the LSMB findings. Of the 14 cases, the DILI Team assessed six as unlikely DILI, four as possible DILI, and four as probable DILI. Per the DILI Team, their assessment were similar to the LSMB's assessment. Table 67 shows the findings of the DILI Team assessments.

Table 67 DILI Team Consult Response: Summary of Cases with ALT or AST > 5 x ULN in the Fezolinetant Phase 3 Clinical Trials

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

Clinical Reviewer's Comments:
Per the DILI Team consult response, "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."

Seven participants in the above table, rows 8 through 14, were excluded since these cases were not assessed as probable by either the DILI Team or the LSMP. The remaining seven participants had predominantly hepatocellular injury by R-value (R-value > 5 is considered hepatocellular) with median latency from drug start of 56 days, but the range was wide (14 to 250 days) as

shown in Table 68.

Table 68 DILI Team Consult Response: Participants in POP2 52-week Assessed as Probable DILI by the DILI Team and/or Applicant's LSMP

#	Subject ID	Study	DILI Team Causality Score*	HAC Causality Score*	Alternate diagnosis	Age (yr)	Sex	Race	Symptoms	Hy's Law	Latency from start drug (da)	Latency from stop drug (da)#	ALT peak (U/L)	AST peak (U/L)	ALP peak (U/L)^	Bilirubin peak (mg/dL)	R value peak (ALT)	R value peak (AST)
1	(b) (6)	2693-CL-0301	3	3	NA	55	F	White	No	No	84	-1	686	1515	153	0.5	13.71	30.29
2		2693-CL-0302	3	4	NA	57	F	White	No	No	54	-51	322	158	104	0.4	9.47	4.65
3		2693-CL-0301	3	3	NA	48	F	White	Yes	No	28	-8	293	194	104	0.3	8.62	5.71
4		2693-CL-0304	3	3	NA	55	F	White	No	No	250	-62	270	189	116	1.17	7.12	4.98
5		2693-CL-0304	4	3	Unknown	52	F	White	No	No	56	-36	336	203	104	0.7	9.88	5.97
6		2693-CL-0304	4	3	APAP	52	F	White	No	No	114	-249	223	97	104	0.5	6.56	2.85
7		2693-CL-0304	4	3	APAP	58	F	White	No	No	14	-352	219	172	172	3.4	3.89	3.06
					mean	*54*					*86*	*-108*	*336*	*361*	*122*	*1.0*	*8.5*	*8.2*
					std dev	*3.2*					*74*	*126*	*149*	*472*	*26*	*1.0*	*2.9*	*9.1*
					median	*55*					*56*	*-51*	*293*	*189*	*104*	*0.5*	*8.6*	*5.0*
					max	*58*					*250*	*-1*	*686*	*###*	*172*	*3.4*	*13.7*	*30.3*
					min	*48*					*14*	*-352*	*219*	*97*	*104*	*0.3*	*3.9*	*2.9*

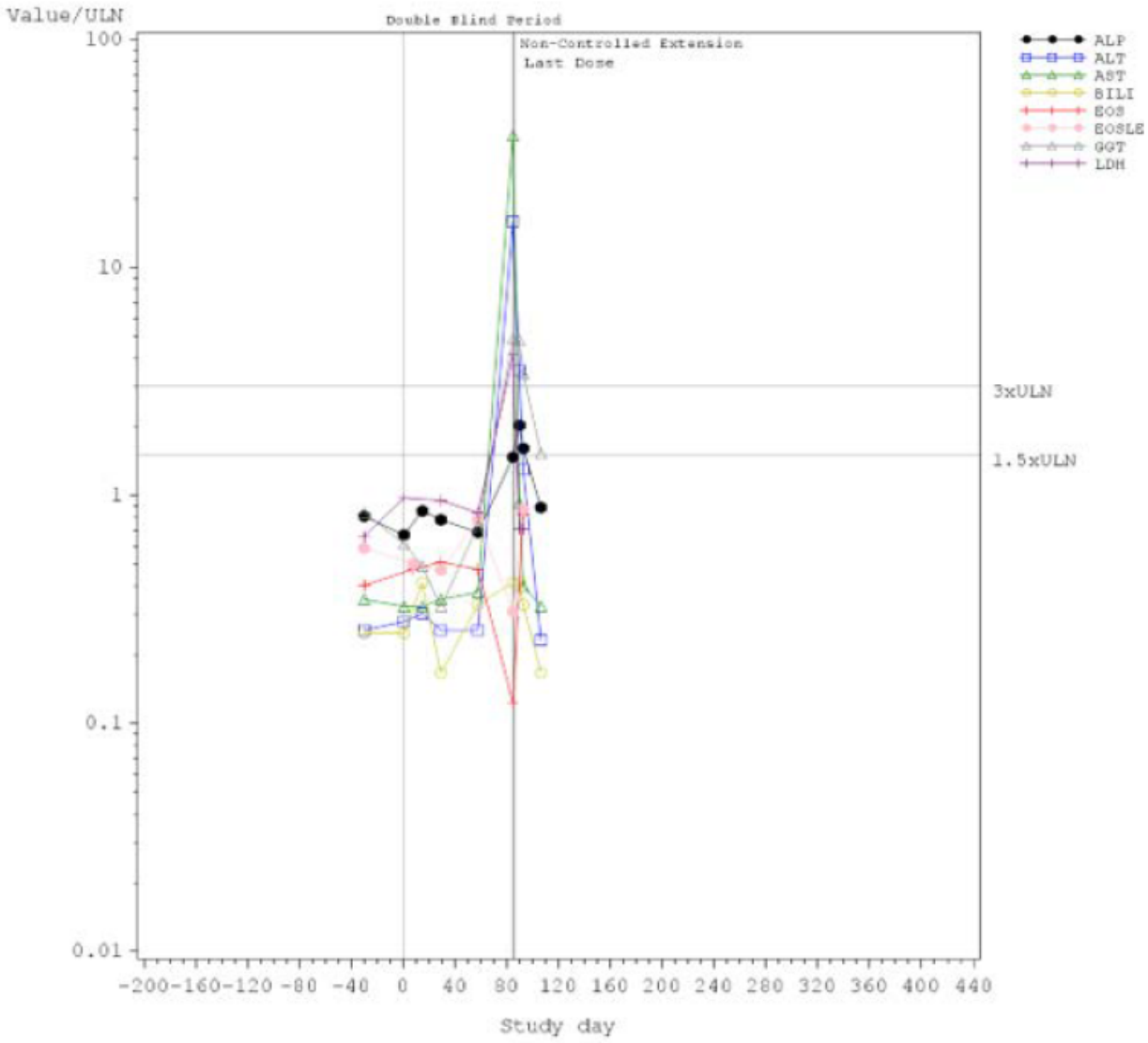
*1=definite, 2=highly likely, 3=probable, 4=possible, 5=unlikely, 6=indeterminate
^AP imputed as 104 (upper limit of normal) when peak value was <104
#Negative value indicates subject stayed on study drug for that many days after injury onset
R-value = AP/ULN ÷ ALT/ULN or AP/ULN ÷ AST/ULN; Hepatocellular: R value ≥ 5; Mixed/cholestatic: R value < 5
NA = not applicable
APAP = acetaminophen

Narratives on the above noted seven cases identified in Table 68 as probable DILI by the DILI Team and/or applicant's LSMP, and Participant # (b) (6), noted in Table 67 as possible by both, are as follows:

1. Participant (b) (6): This case involves a female 55 years of age, who self-identified as White, who was randomized to 30 mg fezolinetant in Trial 2603-CL-0301. Her relevant medical history included ongoing drug hypersensitivity (to doxycycline and sulfa), allergy to arthropod sting, rubber sensitivity, food allergy, depression, anxiety, hypothyroidism, gastroesophageal reflux disease and osteoarthritis. Her concomitant medications included levothyroxine sodium, pantoprazole sodium sesquihydrate, tramadol, escitalopram oxalate and paracetamol. Biochemistry and hepatic laboratory results were normal at baseline on Day 1. On **Day 81**, she experienced a mild AE of arthralgia (right knee pain) and received treatment with several analgesic drugs starting from Day 81 (orally: gabapentin, clonazepam and ketorolac tromethamine for 6 days, hydrocodone bitartrate/paracetamol for a day; intramuscularly for a day: morphine and ketorolac tromethamine) and oxycodone hydrochloride and paracetamol orally from Day 83 for 3 days. On **Day 85**, she was reassigned to continue treatment with 30 mg fezolinetant. **Day 85** laboratory tests showed elevated ALT 686 U/L (normal range: 4-43), AST 1515 U/L (normal range: 8-40), ALP 153 U/L (normal range: 35-104), GGT 239 U/L (normal range: 4-

49), and LDH 971 U/L (normal range: 53-234). Other hepatic laboratory results at Day 85 were normal: total bilirubin 8.6 µmol/L (normal range: 3.4208-20.5248), direct bilirubin 6.8 µmol/L (1.7104-6.8416), INR 0.90 (not reported). She was asymptomatic. She was withdrawn from trial drug with the last dose on Day 86. On Day 93, a liver ultrasound revealed borderline hepatomegaly with fatty infiltration. By Day 106, only GGT remained elevated (75 U/L) and was not clinically significant, and other relevant hepatic test results were normal. The investigator considered the serious TEAE of liver function test increased to be related to trial drug. The sponsor agreed with the investigator's assessment of causal relationship based on the temporal relationship and a positive dechallenge.

Selected liver values for participant Number (b) (6) are shown in the following eDISH plot included in the application.



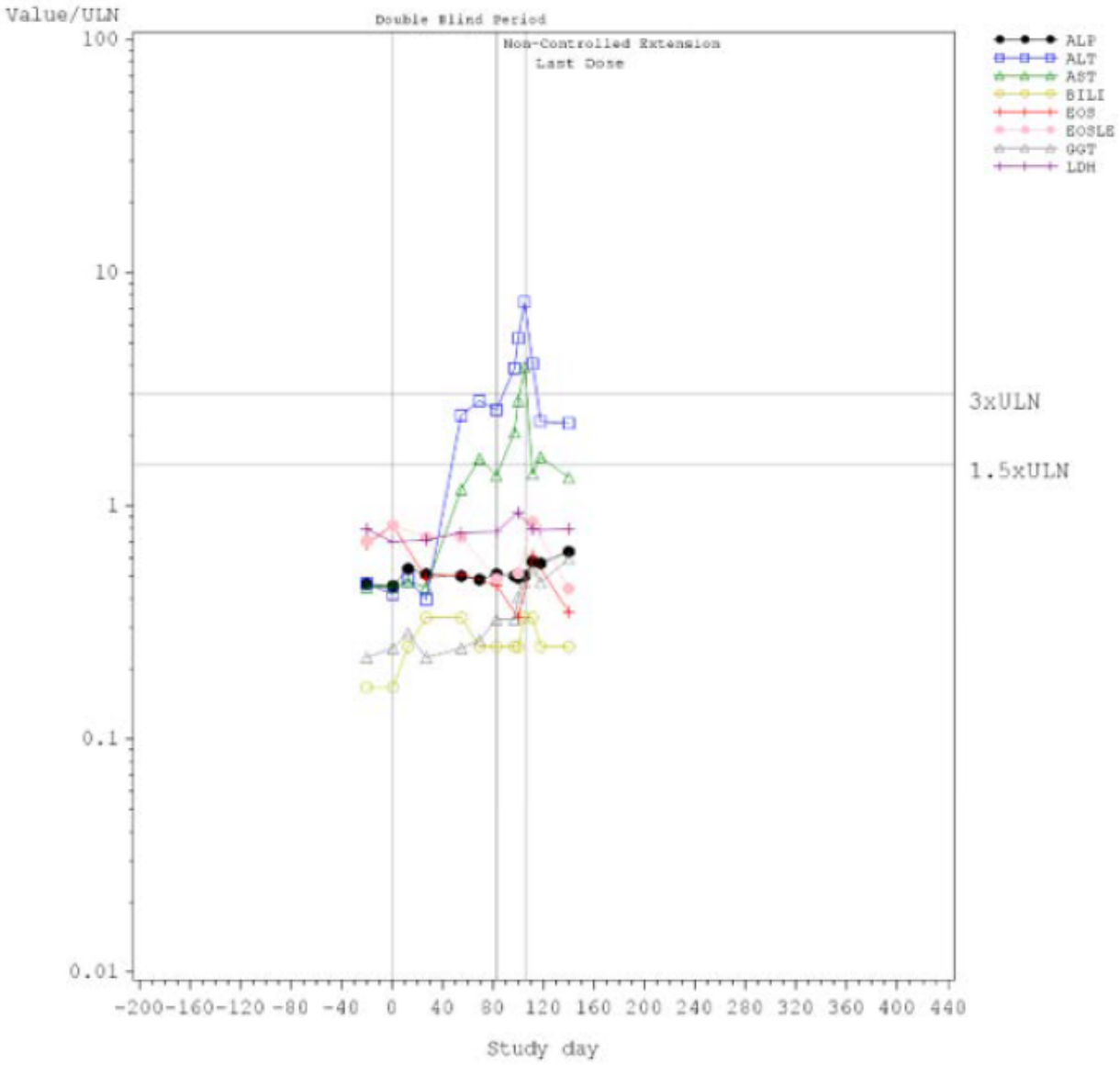
Source: NDA 216578, Trial 2693-CL-0301 Study Report, Attachment 1, Narratives, page 1948 of 2190.

Liver Safety Monitoring Panel Assessment of Participant Number [redacted] (b) (6):
"*The Liver Safety Monitoring Panel assessment was probable causality (comment: 55-year old woman with treated hypothyroidism who experienced a sharp spike in serum AST > ALT noted at week 12 of blinded study drug treatment.* The new information is that there was a rapid, positive dechallenge with both ALT and AST falling at approximately their serum half-lives indicating that ongoing liver injury had stopped by the time the study drug was discontinued. *This pattern is unusual for DILI with prolonged latency. The rapid fall in aminotransferases is consistent with passing a gall stone and this subject had a history of cholecystectomy and had an episode of pancreatitis at about that time suggesting gall stone*

pancreatitis, raising the possibility of a retain gall stone that passed to cause this event. However, there is no report of abdominal pain which would be expected. Transient liver ischemia can also do this, but there is no suggestion of cardiovascular compromise that would be required for this diagnosis [fall in hemoglobin is interesting but unlikely connected]. For right knee pain, she received an intramuscular injection of ketorolac as well as 1-day treatment with acetaminophen, 4 days before the elevation was noted, and at this same time, she was started on daily gabapentin and clonazepam for anxiety. *However, none of these drugs alone or in combination are likely to have caused such a high spike in aminotransferases. It must be assumed that the study drug had some role in the event unless new information becomes available. The association is rated as probable [> 50%] but not higher in view of the atypically rapid resolution and the possible, but admittedly less likely, role of the cocktail of drugs she received for her right knee pain).*"

2. Participant Number (b) (6): This case involves a female 57 years of age, who self-identified as White, who was randomized to 45 mg fezolinetant in Trial 2693-CL-0302. No relevant medical history was reported. Relevant concurrent medications included methylsulfonylmethane and ibuprofen. Her hematology, biochemistry, and hepatic laboratory results at baseline on day 1 were normal. On Day 55, hepatic laboratory tests showed elevated ALT (105 U/L) and AST (47 U/L), while other hepatic laboratory results were normal. Both ALT and AST levels continued to increase over time, reaching a maximum of 322 U/L and 158 U/L, respectively, at Day 105. Other hepatic laboratory results remained normal at Day 105. Her last dose of trial drug was on Day 106. She was discontinued from the trial on Day 111. Hepatic laboratory tests showed a reduction in ALT and AST levels on Days 111, 118 and 140; however, the levels remained above the reference range. The investigator considered the event of increased ALT to be related to trial drug. The sponsor agreed with the investigator's assessment.

   Selected liver values for participant Number (b) (6) are shown in the following eDISH plot included in the application.



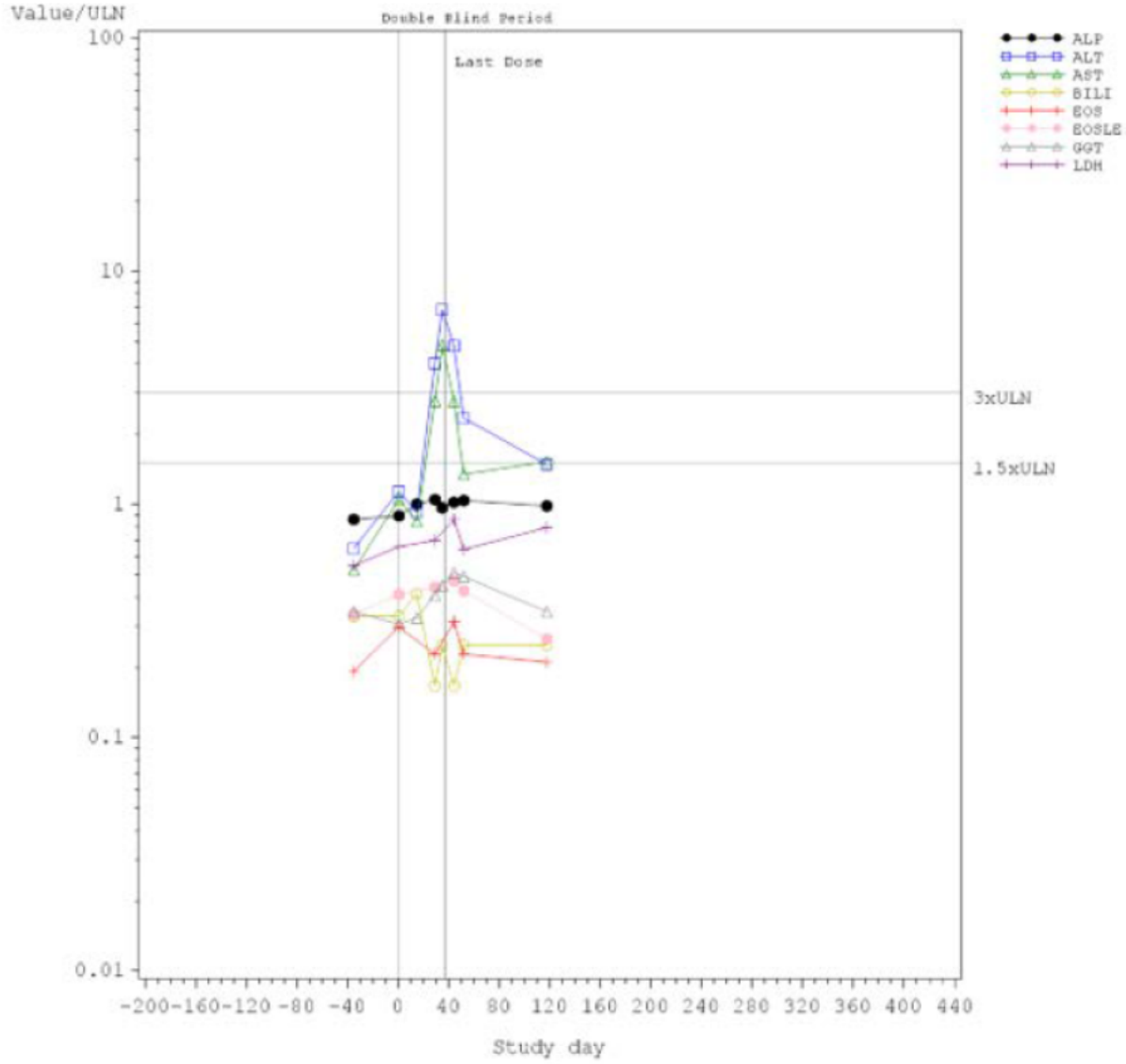
Source: NDA 216578, Trial 2693-CL-0302 Study Report, Attachment 1, Narratives, page 2110 of 2749.

Liver Safety Monitoring Panel Assessment of Participant Number [redacted](b) (6):
"*The Liver Safety Monitoring Panel assessment was possible causality (comment: positive dechallenge but not complete, plateaued)*."

3. Participant Number [redacted](b) (6): This case involves a female 48 years of age, who self-identified a White, who was randomized to 30 mg fezolinetant in Trial 2603-CL-0301. She had no relevant medical history. Her concomitant medications were oxycodone

hydrochloride and paracetamol which she continued throughout the trial. On Day 1, her hepatic laboratory results showed ALT 49 U/L and AST 42 U/L, slightly above ULN. Her other hepatic laboratory results were normal. On Day 27 she started varenicline tartrate for smoking cessation until day 37. Laboratory results on Day 29 showed elevated ALT (173 U/L), AST (111 U/L) and ALP (109 U/L. On Day 35, hepatic laboratory results showed a further increase in transaminases ALT 293 U/L) and AST (194 U/L). On Day 37, she also experienced mild nausea. Due to the nausea in addition to the transaminases increased, the study drug was stopped on Day 37. *The investigator considered the event of transaminase increased to be related to study drug. The sponsor agreed with the investigator's assessment based on temporal relationship with short latency, positive dechallenge results and lack of alternative causative factors reported.*

Selected liver values for participant Number (b) (6) are shown in the following eDISH plot included in the application.



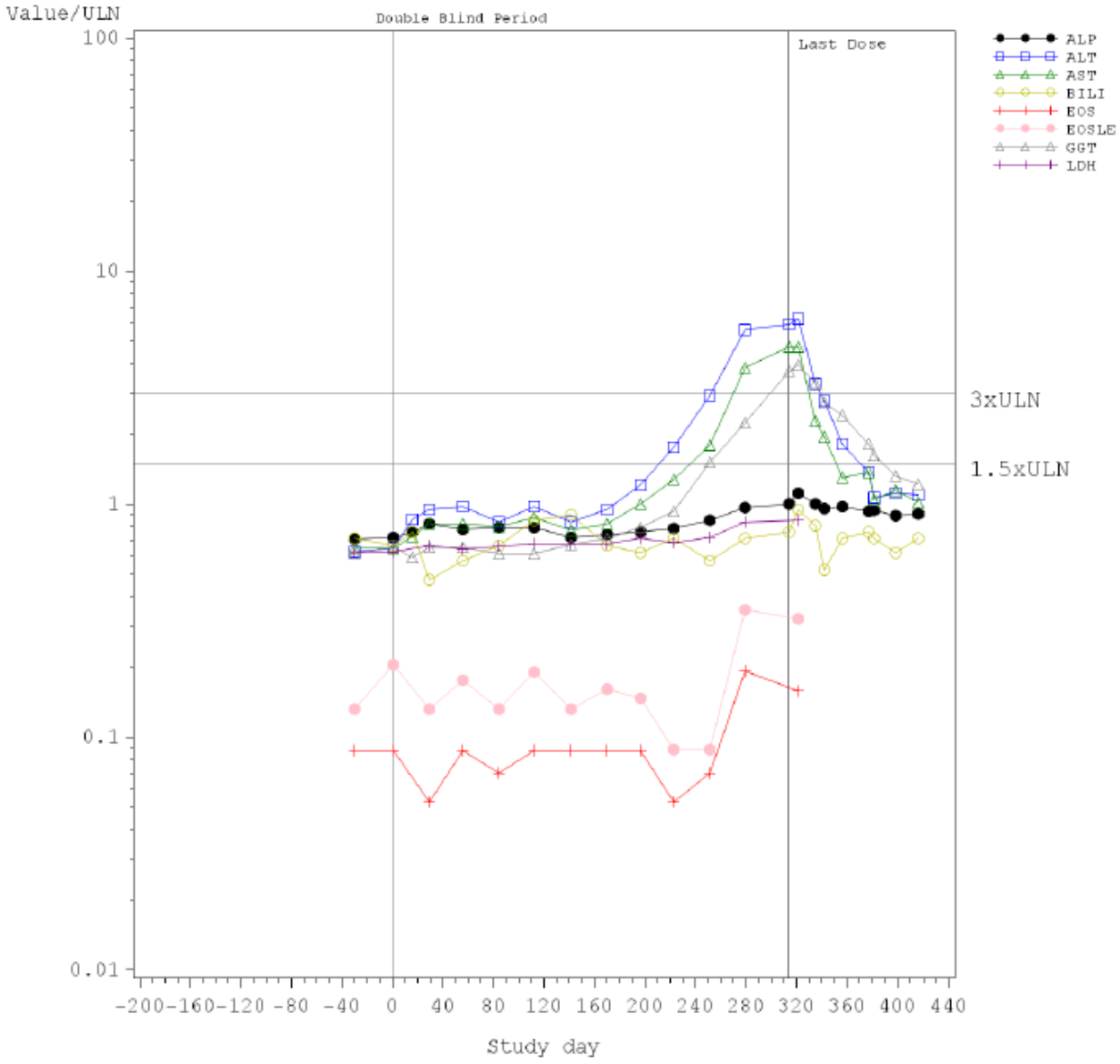
Source: NDA 216578, Trial 2693-CL-0301 Study Report, Attachment 1, Narratives, page 1968 of 3190.

Liver Safety Monitoring Panel Assessment of Participant Number (b) (6):
"The Liver Safety Monitoring Panel assessment was probable causality (comment: 48-year old woman with RA who experienced serum ALT to 6 x ULN at week 4 with positive dechallenge. *Taking APAP but profile of liver chemistries not characteristic of APAP, and had just started Chantix which liver tox state is a very rare if ever cause for DILI. Hepatitis B and C serologies negative as was ultrasound. This event has to be considered probably due to trial drug).*"

4. Participant Number (b) (6): This case involves a female, 55 years of age who

self-identified as White, who was randomized to 45 mg fezolinetant in Trial 2693-CL-0304. Her relevant medical history included ongoing hypothyroidism for which she was taking levothyroxine sodium. Her hematology and biochemistry laboratory results were normal at baseline on Day 1, except for low leukocytes (3.66 x 109/L) and neutrophils, segmented (1590 x 106/L). Platelet count at baseline on day 1 was <150000/µL (140 x 109/L). Her hepatic laboratory values at baseline on Day 1 were normal. On Day 29, laboratory results showed low platelet count (129 x 109/L; <150000/µL). No corresponding AEs were reported for the subject relating to platelet count. On Day 56, platelet count returned to normal. On Day 279, hepatic laboratory tests revealed elevated GGT (110 U/L), ALT (242 U/L; > 5 x ULN) and AST (154 U/L; > 3 x ULN), and the hematology laboratory tests revealed low platelets (128 x 109/L; <150000µL). Other hepatic laboratory results were normal. She was started on oral treatment with essential phospholipids (Essentiale Forte) from day 281 for the events. Hepatic laboratory tests were repeated on Day 314, which revealed worsening of GGT (182 U/L), ALT (255 U/L; > 5 x ULN) and AST (190 U/L; > 4 x ULN), and normal total bilirubin (16.0 µmol/L). These results revealed that ALT remained elevated to > 5 x ULN for more than 2 weeks, which met the trial drug discontinuation criteria. On Day 314, the investigator reported a serious TEAE of ALT increased, which was moderate in intensity and considered related to the trial drug. The event led to withdrawal of trial drug, with the last dose on Day 313. The participant reported no signs or symptoms. The event of AST increased was considered resolved with sequelae on Day 314. She was discontinued from the study on Day 321. Hepatic laboratory tests were repeated on Days 335, 342, 356, 377, 381, 398 and 416, which showed gradual improvements in the levels of GGT, ALT and AST. ALT (59 U/L) and AST (55 U/L) improved to < 1.5 x ULN from day 377 and GGT improved to < 1.5 x ULN from Day 398 (65 U/L). The event of ALT increased was considered resolved on Day 507. On the same day, GGT (41 U/L). ALT (34 U/L), and AST (35 U/L) were normal. The subject stopped treatment with essential phospholipids on the same day, and the serious event of ALT increased was considered resolved on Day 510. The investigator considered the events of special interest of ALT increased and AST increased to be related to trial drug. The sponsor notes that while there is no documented history of NAFLD, the (b) (6)-based investigator initiated treatment with oral essential phospholipids (Essentiale Forte) on Day 281, with use of essential phospholipids common practice in (b) (6) for treatment of non-acute fatty liver disease (NAFLD). As such, the treatment with essential phospholipids can be considered a cofounder in the assessment in terms of the LSMP referenced de-challenge effect as well in undiagnosed NAFLD.

Selected liver values for participant Number [redacted] (b) (6) are shown in the following eDISH plot included in the application.



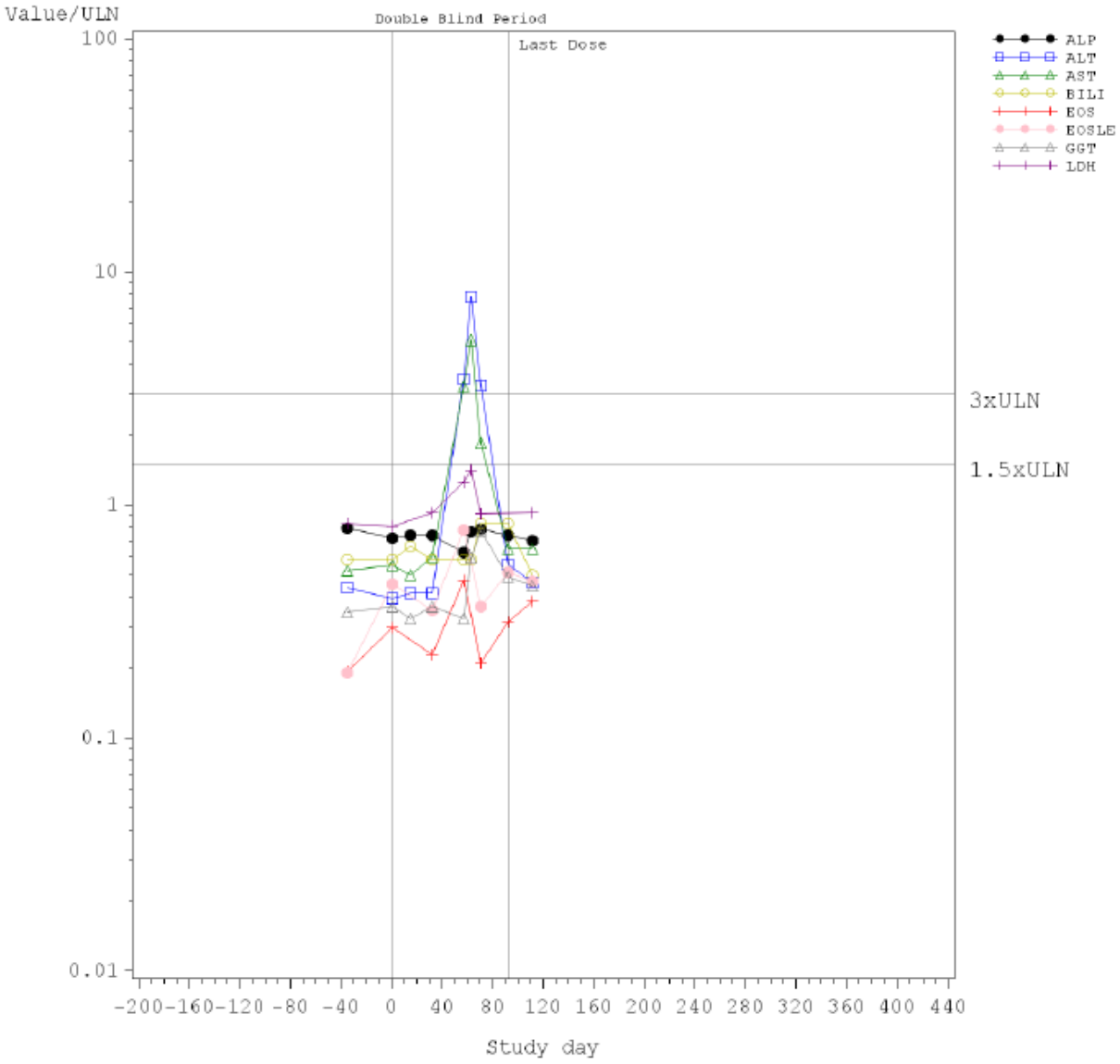
Source: NDA 216578, Trial 2693-CL-0304 Study Report, Attachment 1, Narratives, page 2327 of 6190.

Liver Safety Monitoring Panel Assessment of Participant Number [redacted] (b) (6):
"*The Liver Safety Monitoring Panel assessment for the event was probable causality. It was initially considered possibly related but changed to probable causality with follow-up laboratory results documenting positive de-challenge.* ALT started to increase week 28 to 1.2x and ALT/AST peaked at 6.3x / 4.7x, ALP 1.1x, normal total bilirubin. Study drug was

discontinued and values gradually declined to normal in 6 months. No symptoms were mentioned. Hepatitis B and hepatitis C were negative for active infection and HBcAb was positive. Probable DILI due to compatible latency and positive de-challenge without apparent alternative cause, albeit without full workup."

5. Participant Number (b) (6): This case involves a female 52 years of age, who self-identified as White, who was randomized to 45 mg fezolinetant in Trial 2693-CL-0304. Her relevant medical history included ongoing myalgia with no concurrent medications reported. Hematology, biochemistry and hepatic enzyme laboratory results were normal at baseline on day 1. On Day 57, laboratory results showed elevated LDH (294 U/L), CK 404 U/L (normal range: 26-192), ALT (149 U/L) and AST (129 U/L). Other hepatic laboratory values were normal. She denied any symptoms, increase in alcohol intake, use of any herbal supplements, new medications, travel, abnormal injury or needlestick injury On Day 63, laboratory results showed a further increase in LDH (329 U/L), ALT (336 U/L) and AST (203 U/L), and elevated glucose 5.66202 mmol/L (normal range: 3.8857-5.551). On Day 71, ultrasound of the abdomen right upper quadrant showed echogenic liver suggesting hepatic steatosis; no evidence for gallstones or biliary dilatation. Her LDH value returned to normal on Day 71, and her ALT and AST values returned to normal on Day 92. She was discontinued from the trial on Day 111. On Day 111, her LDH (216 U/L), ALT (20 U/L), AST (26 U/L), and ALP (73 U/L) values were normal. The investigator considered the event of liver function test abnormal to be related to trial drug. The sponsor agreed with the investigator's assessment based on the plausible temporal relationship and in the absence of medical history, co-suspect medication and any other alternative etiology. Ultrasound reports showed hepatic steatosis, for which the cause was unknown.

   Selected liver values for participant Number (b) (6) are shown in the following eDISH plot included in the application.



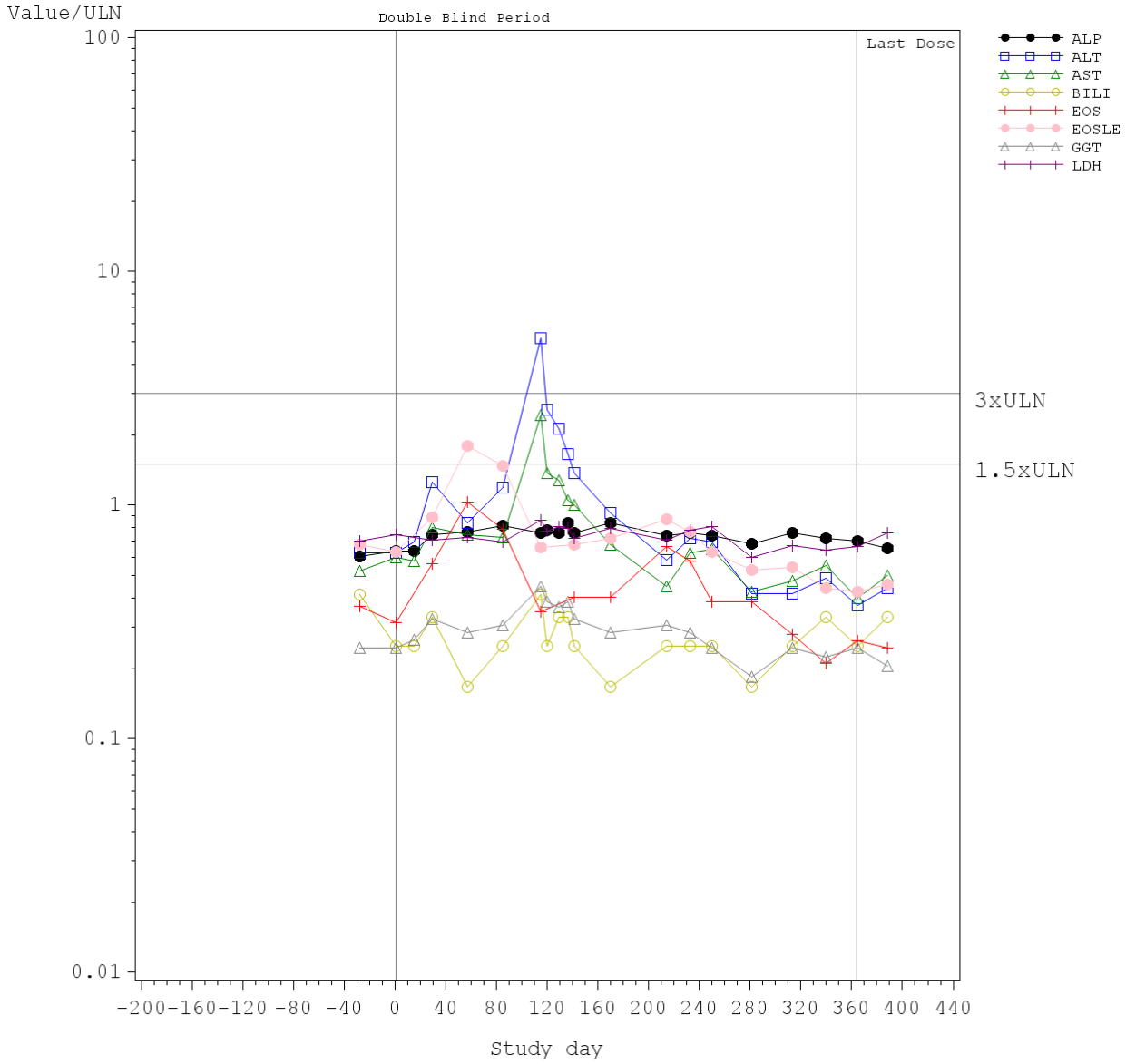
Source: NDA 216578, Trial 2693-CL-0304 Study Report, Attachment 1, Narratives, page 2340 of 6190.

Liver Monitoring Safety Panel Assessment of Participant Number [redacted] (b) (6):
"*The Liver Safety Monitoring Panel assessment was probable causality (comment: 52-year-old woman with ALT > AST elevation at week 8 with resolution on continued treatment. Hepatitis B and C serologies were unrevealing as was ultrasound. The event was probably attributable to study drug with adaptation)*."

6. Participant Number [redacted] (b) (6): This case involves a female 52 years of age, who self-identified as White, who was randomized to 30 mg fezolinetant in Trial 2693-CL-0304. Her

relevant medical history included ongoing gastroesophageal reflux disease, gastritis, nausea, fatigue, overweight and drug hypersensitivity. Relevant ongoing concurrent medications included ibuprofen, ondansetron hydrochloride and amitriptyline. Her hematology, biochemistry, and laboratory results were normal at baseline on Day 1. On Day 107, she experienced a TEAE of malaise, which was moderate in intensity and considered not related to trial drug by the investigator. She started oral treatment with paracetamol from Day 107 to 108 for the event. On Day 109, she experienced a TEAE of sciatica (bilateral sciatica), which was moderate in intensity and considered not related to trial drug by the investigator. No action was taken with trial drug due the events of malaise or sciatica On Day 115, hepatic laboratory results showed elevated ALT (223 U/L) and AST (97 U/L); other hepatic tests were normal. On Day 120, hepatic laboratory results showed a reduction in ALT (110 U/L; <3 x ULN) and AST (55 U/L); although values remained elevated. On Day 141, she experienced TEAEs of nausea and oropharyngeal pain, both events were moderate in intensity and considered not related to trial drug by the investigator. No action was taken with trial drug due to both events. The event of nausea resolved on Day 145 and the event of oropharyngeal pain resolved on Day 147.

Selected liver values for participant Number (b) (6) in the following eDISH plot included in the application.



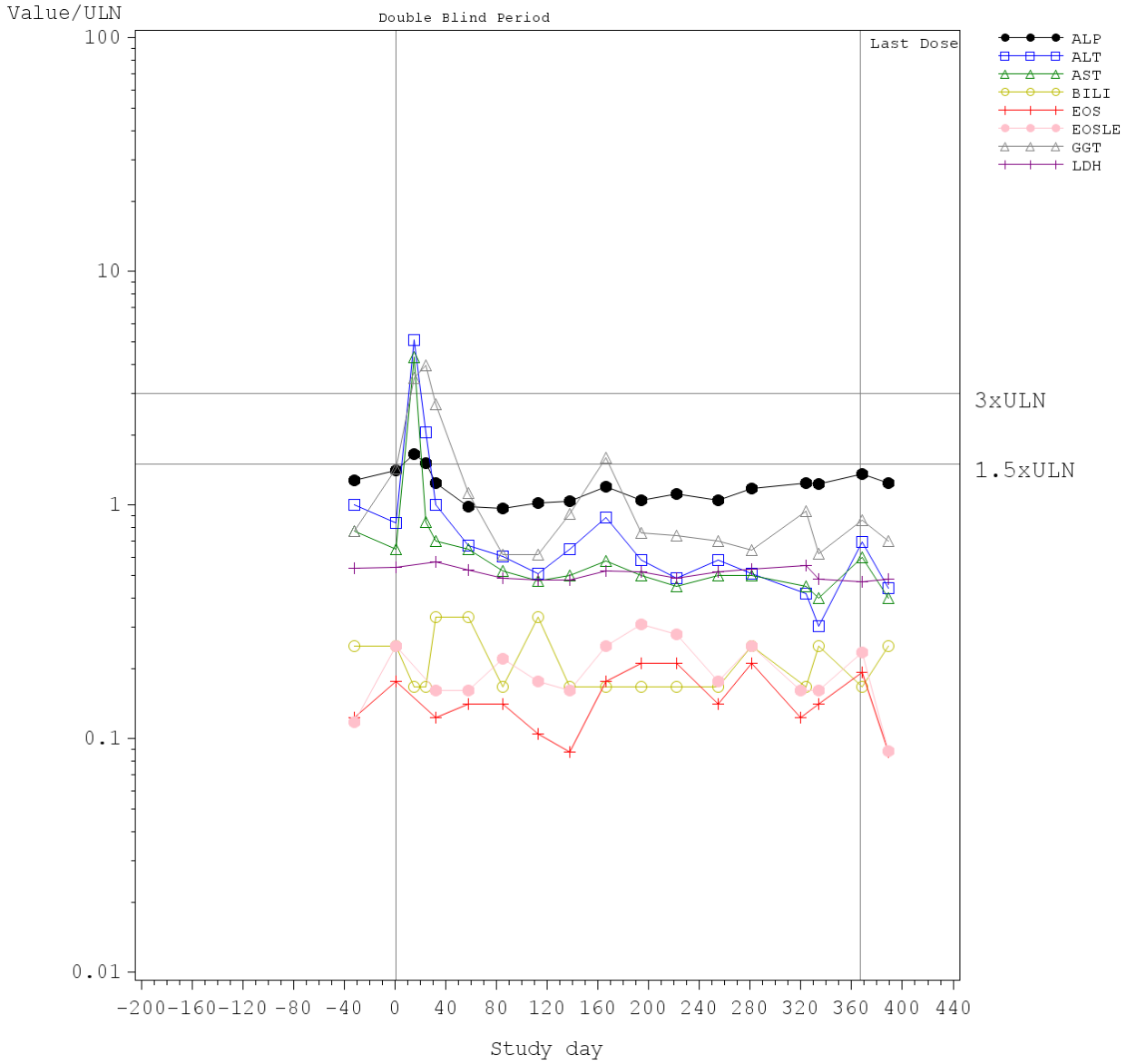
Source: NDA 216578, Trial 2693-CL-0304 Study Report, Attachment 1, Narratives, page 3714 of 6190.

Liver Safety Monitoring Panel Assessment of Participant Number [redacted] (b) (6):
"The Liver Safety Monitoring Panel assessment was *probable causality* (comment: 52-year old woman with elevation in serum ALT to 5 x ULN at week 16 of treatment [with mild eosinophilia] with resolution over the next month despite continuing study drug treatment. There was some acetaminophen intake, but duration of abnormalities makes this an unlikely cause. DILI due to study drug is probable)."

7. Participant Number [redacted] (b) (6): This case involves a female 58 years of age, who self-

identified as White, who was randomized to 45 mg fezolinetant in Trial 2603-CL-04304. She reported no relevant medical history or concurrent medications. Hematology and biochemistry laboratory values were normal at baseline on Day 1, with the exception of elevated platelets (416 x 109/L). Hepatic laboratory values were also normal at baseline on Day 1. On Day 15, laboratory tests showed elevated ALT (219 U/L; 5.09 x ULN), AST (172 U/L; 4.30 x ULN), ALP (172 U/L) and GGT (171 U/L). Other hepatic laboratory values on the same day were normal. On Day 24, a normal AST value was reported (34 U/L), while ALT improved but remained elevated until Day 32 when a normal ALT value was reported (43 U/L). Treatment with trial drug was interrupted due to the events from Days 24 to 42. On Day 36, ultrasound examination of the liver showed an abnormal – not clinically significant result (borderline enlargement of the liver). No action was taken with trial drug due to the event. Laboratory tests showed elevated ALP on Days 113, 138 and 166. The event of hepatomegaly was considered resolved on day 178. On Day 194, laboratory tests also showed elevated ALP (109 U/L). Other hepatic laboratory values on the same day were normal. ALP remained elevated throughout the remainder of the trial. The participant completed treatment with the last dose of trial drug on Day 367. On Day 368 and Day 389, laboratory tests still showed elevated ALP (142 U/L and 129 U/L, respectively). The investigator considered the events of ALT increased, AST increased, hepatomegaly and blood ALP increased to be not related to trial drug and provided the following comment: "subject was taking Tylenol 500 mg daily for 2 days prior the blood samples were collected; subject symptomatic; physical examination within normal limit". Per the sponsor, *"the elevated transaminases occurred within approximately 2 weeks of starting fezolinetant; importantly, the subject received multiple doses of paracetamol for 2 days prior to the elevated ALT and AST, which serves as an important alternative explanation for these events."*

Selected liver values for participant Number (b) (6) in the following eDISH plot included in the application.



Source: NDA 216578, Trial 2693-CL-0304 Study Report, Attachment 1, Narratives, page 3785 of 6190.

Liver Safety Monitoring Panel Assessment of Participant Number (b) (6):
"The Liver Safety Monitoring Panel assessment was *probable causality* (comment: 58-year-old woman with ALT elevation at 2 weeks and apparently a positive dechallenge but negative rechallenge. This event is probably related [with adaptation])."

8. Participant Number (b) (6): This case involves a female 53 years of age, who self-identified as White, who was randomized to 30 mg fezolinetant in Trial 2603-CL-04304. She reported no relevant medical history or concurrent medications.

Hematology, biochemistry and hepatic laboratory results were normal at baseline, with the exception of elevated LDH (258 U/L), albumin (54 g/L), ALT (54 U/L) and AST (43 U/L). On Day 113, laboratory results showed elevated ALT (96 U/L), AST (51 U/L) and GGT (54 U/L). Other hepatic laboratory values were normal on the same day. On the same day, the investigator reported a nonserious TEAE of special interest of ALT increased, which was mild in intensity and considered not related to trial drug by the investigator. On Day 141, laboratory results showed further elevated ALT (171 U/L), AST (86 U/L) and GGT (104 U/L). On Day 147, hepatic laboratory results showed elevated but improved ALT (121 U/L) and AST (53 U/L). On Day 148, the event of AST increased was considered resolved and the event of ALT increased was downgraded to mild intensity. The event of mild GGT increased was ongoing. On Day 195, hepatic laboratory results showed further elevated ALT (257 U/L), AST (135 U/L) and GGT (139 U/L). Other hepatic laboratory values were normal on the same day. On Day 204, hepatic laboratory results showed elevated but improved ALT (86 U/L), AST (42 U/L) and GGT (96 U/L). On Day 287, the investigator reported a nonserious TEAE of nonalcoholic steatohepatitis. No action was taken with the trial drug due to any of the above events. The participant completed treatment with the last dose of trial drug on day 363. On Days 364 and 386, ALT, AST and GGT remained elevated. The events of ALT increased, AST increased, and nonalcoholic steatohepatitis were considered resolving at the time of reporting.

Liver Safety Monitoring Panel Assessment of Participant Number (b) (6):
"The Liver Safety Monitoring Panel assessment was *possible causality* (comment: previously thought to be possibly related, now with follow-up laboratory work. BMI 28.7; baseline AST 1.1 x ULN; ALT/AST fluctuated between normal and 1.3 x ULN until rising to 2.2 x/1.3 x ULN. They then fluctuated between 2.6 x to 6.0 x ULN (ALT) and 1.3 x to 3.4 x ULN. (AST). ALP and total bilirubin were normal. Blinded study drug was continued. No relevant symptoms were reported. HBV and HCV serologies were negative for active infection. Possible background NAFLD but superimposed effect of study drug remains possible. DILI is possible due to compatible latency and continued abnormalities during constant study drug administration."

Sponsor's Interpretation and Comment:
"As noted by the Liver Safety Monitoring Panel assessment, the events of ALT increased, AST increased and GGT increased are possibly related but are confounded by the mild elevation of ALT and AST at baseline and the newly diagnosed nonalcoholic steatohepatitis."

DILI Team Assessment and Recommendations:
The November 21, 2022 DHN DILI Team consult response includes the following assessment and recommendations:

Assessment:

"Aminotransferase elevations were seen in phase 2 and 3 studies, but no Hy's Law cases. Non-clinical evaluation does not suggest an elevated DILI risk, but several in vitro studies (e.g., glutathione trapping, mitochondrial toxicity studies) were lacking. Excretion is primarily through urine and FZT parent compound dominates excretion and serum profiles. Several metabolites are generated from FZT but at low amounts."

"Clinical trial data suggest a mild increase incidence in ALT or AST elevation in subjects exposed to FZT compared to subjects on placebo, but there were no aminotransferase elevations with jaundice. There was no clear dose-response relationship regarding aminotransferases elevations in FZT 30 mg and 45 mg arms. Case level analyses yielded at least four subjects with probable DILI and three to four others with at least possible DILI. Approximately, 2800 VMS subjects were exposed to FZT in the phase 3 trials. DILI was predominantly hepatocellular with a median latency from drug start of 56 days, but the latency range was wide at 14 to 250 days. Many of the subjects considered to have possible DILI improved even with continued FZT use. Thus, FZT may cause some DILI, but it appears modest, and adaption may occur with continued exposure. However, the number of women exposed post market could be large. One estimate suggests 40 to 50 million women in the United States have VMS. Only 20-30 percent may seek medical care; but if FZT is prescribed to just 1-5% of these women, then the number exposed could be 80,000 to 750,000. With such a potentially large exposure population, more severe cases of DILI could arise."

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

Recommendations:

1. Do not hold up approval for liver injury observed in the NDA.
2. Label for liver enzyme elevation in Warnings and Precautions.
3. Include a recommendation to perform baseline liver tests.
4. Consider a recommendation to perform routine liver test monitoring for the first several months of FZT use.
5. Consider requesting the sponsor to submit 15-day expedited reports to FAERS of all spontaneously reported post-market serious liver injury adverse events as well as those

with new onset biochemical abnormalities consistent with Hy's Law.

Reviewer's Comment:
Overall, the Clinical Team concurs with the DHN DILI Team. See the recommended changes to proposed product labeling.

8.5.5 Central Nervous System/Psychiatric Safety

Given the fact that rapid withdrawal of central nervous system (CNS)-active drugs may result in rebound phenomenon, characterized by a rapid return of an individual's original symptoms at a greater intensity than before the treatment (e.g., Selective Serotonin Reuptake Inhibitors), the applicant was asked to evaluate mental health AEs following treatment cessation by treatment arm. The applicant provided the following Table 69 with this evaluation of adverse nervous and psychiatric events with onset date occurring after the last date of trial medication dosing for POP2.

Table 69 Adverse Events with Onset Date after Last Dose Date, POP2 (52-week) SOC: Nervous system disorders or Psychiatric disorders, Safety Analysis Set

MedDRA System Organ Class Preferred Term	Placebo (n = 952)	Fezolinetant 30 mg (n = 1103)	Fezolinetant 45 mg (n = 1100)
Overall Total	4 (0.4%)	8 (0.7%)	8 (0.7%)
Nervous system disorders	2 (0.2%)	3 (0.3%)	4 (0.4%)
Headache	1 (0.1%)	1 (0.1%)	2 (0.2%)
Syncope	0	1 (0.1%)	0
Sciatica	0	1 (0.1%)	0
Parosmia	0	0	1 (0.1%)
Myelopathy	0	0	1 (0.1%)
Facial paralysis	1 (0.1%)	0	0
Psychiatric disorders	2 (0.2%)	5 (0.5%)	3 (0.3%)
Depression	0	2 (0.2%)	1 (0.1%)

Insomnia	1 (0.1%)	2 (0.2%)	0
Nervousness	0	1 (0.1%)	0
Anxiety	1 (0.1%)	0	0
Mood swings	0	1 (0.1%)	1 (<0.1%)
Mental status changes	0	1 (0.1%)	1 (<0.1%)
Alcohol abuse	0	1 (0.1%)	0

Source: NDA 216578 SDN 34, Mid Cycle Communication Table 1.1, Safety Analysis Set. 21-day follow-up period.

Depression was reported at baseline in 2 participants (0.3%) in fezolinetant 30 mg group and 1 participant (0.2%) in fezolinetant 45 mg group and none in the placebo group. Of the 3 participants treated with fezolinetant, 1 participant discontinued treatment due to the event of depression while on fezolinetant (Participant ID # (b) (6)) and 1 participant had the event of depression after early discontinuation of fezolinetant (Participant ID # (b) (6)).

The applicant also performed a literature review in the databases Pubmed, Dialog and UpToDate to identify any potential literature data available on potential rebound effects after discontinuing a NK3 receptor antagonist in women known to have a psychiatric or neurologic disorder. Specifically, Astellas has searched on compounds (both INN names as well as compound codes) that have been studied in clinical trials, e.g., fezolinetant, elinzanetant, osanetant, pavinetant, talnetant.

The searches yielded no information regarding rebound effects of psychiatric or nervous system disorders occurring after withdrawal of NK 3 receptor antagonists.

> Reviewer's Comment:
> The incidence of mental health and nervous system disorders was rare overall and only slightly higher in treatment as compared to placebo. Except for insomnia and depression, all AEs were singular in presentation. The available evidence indicates that there are no rebound effects on the CNS system however, the dataset is limited considering the low prevalence of depression in this trial.

8.6 Safety Analyses by Demographic Subgroup

Age made little difference on safety in 12 or 52 weeks POP2 safety populations for overall TEAEs. Women 55 years of age and older had a slightly higher likelihood of having a serious TEAE (placebo arm: 2.3% in participants 55 years of age and older compared to 0.9% in participants younger than 55 years of age; fezolinetant arm total group: 4.3% in participants 55

years of age and older compared to 3.5% in participants younger than 55 years of age). Age had no difference on safety in Trial 2693-CL-0304 as measured by overall TEAEs and liver biochemistry.

Race had no discernable difference on safety for the 12-week POP2 population evaluation as measured by overall TEAEs, TEAEs related to study intervention, SAEs, SAEs related to study intervention, treatment-emergent AESIs and liver biochemistry.

Race had no clinically significant difference in safety outcomes for the 52-week POP2 population evaluation as measured by overall TEAEs, TEAEs related to study intervention, SAEs, SAEs related to study intervention, treatment-emergent AESIs and liver biochemistry. There was a slightly higher incidence of treatment-emergent AESIs in self-identified White participants compared to self-identified non-White participants (placebo group: 11.6% compared to 9.0% of participants; fezolinetant total group: 13.8% compared to 11.3%), with the incidence of treatment-emergent AESIs of hepatic transaminase elevations and those relating to endometrial pathology following the same pattern; however, this difference was not considered clinically relevant. In addition, race had no discernable difference on safety in POP4 as measured by overall TEAEs and hepatic biochemistry disturbance.

Ethnicity had no difference in safety outcomes for 12-week POP2 as measured by overall TEAEs, TEAEs related to study intervention, SAEs, SAEs related to study intervention, treatment-emergent AESIs and hepatic biochemistry evaluation. In the 52-week POP2 population there was a slightly higher incidence of treatment-emergent AESIs of hepatic transaminase elevations in Hispanic or Latino participants compared to non-Hispanic or Latino participants (placebo group: 4.7% versus 1.5%, fezolinetant total group: 4.0% versus 1.6%); however, there were no meaningful differences in the number of participants with categorical findings of hepatic biochemistry disturbance when grouped by ethnicity.

Overall, geographical region had no discernable difference on safety in POP2 as measured by overall TEAEs, TEAEs related to study intervention, SAEs, SAEs related to study intervention, treatment-emergent AESIs and liver biochemistry. There was a slightly higher incidence of TEAEs of liver test elevations in North American participants than in European participants (placebo group: 4.7% versus 2.4%, fezolinetant total group: 6.4% versus 3.9%), however, there were no meaningful differences in the number of participants with categorical findings of hepatic biochemistry disturbance when grouped by geographical region.

Reviewer's Comment:
Overall, the safety did not substantially differ by demographic subgroup.

8.7 Specific Safety Studies/Clinical Trials

Three phase 3 clinical trials were conducted. Trial 2693-CL-0301 and Trial 2693-CL-0302

provided efficacy and safety analyses. Trial 2693-CL-0304 provided long-term general safety and chronic drug exposure analyses.

8.8 Additional Safety Explorations

8.8.1 Human Carcinogenicity or Tumor Development

This is discussed in Section 8.5.1 above.

8.8.2 Human Reproduction and Pregnancy

No human reproductive and pregnancy safety explorations were conducted for fezolinetant product. No pregnancies were reported during the fezolinetant development program. There are no data on the presence of fezolinetant in human milk, the effects on the breastfed child or the effects on milk production.

8.8.3 Pediatrics and Assessment of Effects on Growth

No pediatric studies or assessments of effects on growth were conducted for fezolinetant. The fezolinetant development program addresses an indication which is applicable only to postmenopausal women.

8.8.4 Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Overdose, drug abuse potential, withdrawal and/or rebound potential were not demonstrated in the fezolinetant drug trials. NK3 receptors are not among the CNS receptors known to mediate abuse-related effects. It is highly unlikely that fezolinetant is associated with abuse potential given the absence of withdrawal type events, the lack of psychiatric adverse events suggesting altered mental state, the observed compliance rates and the evidence of lower concentrations in the CNS than in the plasma observed in nonclinical experiments.

8.8.5 120-Day Update Clinical Safety

The applicant submitted the 120-Day Update to Clinical Safety on October 7, 2022 with an update on October 20, 2022. There were no safety updates to data from completed studies discussed above. In the report, the applicant reported the following additional safety findings:

- Final safety and efficacy data from Trial 2693-CL-0305 (unblinded data)
    - Completed study of efficacy, safety and pharmacokinetics of fezolinetant 30 mg daily in China, Taiwan and South Korea in women with moderate to severe VMS.
    - 12 weeks of placebo control with additional 12 weeks of crossover safety data.
- Preliminary safety data from Trial 2693-CL-0307 (open-label)

    - Completed 52-week single arm multicenter study in China to assess safety and tolerability of fezolinetant 30 mg QD in women with moderate to severe VMS.
- Preliminary safety data from Trial 2693-CL-0312 (blinded data)
    - Ongoing, 2-arm randomized 24 week double-blind, placebo-controlled, parallel group, multicenter study in Europe and Canada to assess the efficacy and safety of fezolinetant 45 mg QD in women with moderate to severe VMS associated with menopause and considered unsuitable for HT.
- Preliminary safety data from Trial 2693-CL-0206 (blinded data)
    - Ongoing, randomized, double-blind, placebo-controlled, parallel group, multicenter clinical study in Japan to assess the efficacy and safety of (b) (4) or 30 mg dose of fezolinetant in female individuals with VMS associated with menopause.

(b) (4)

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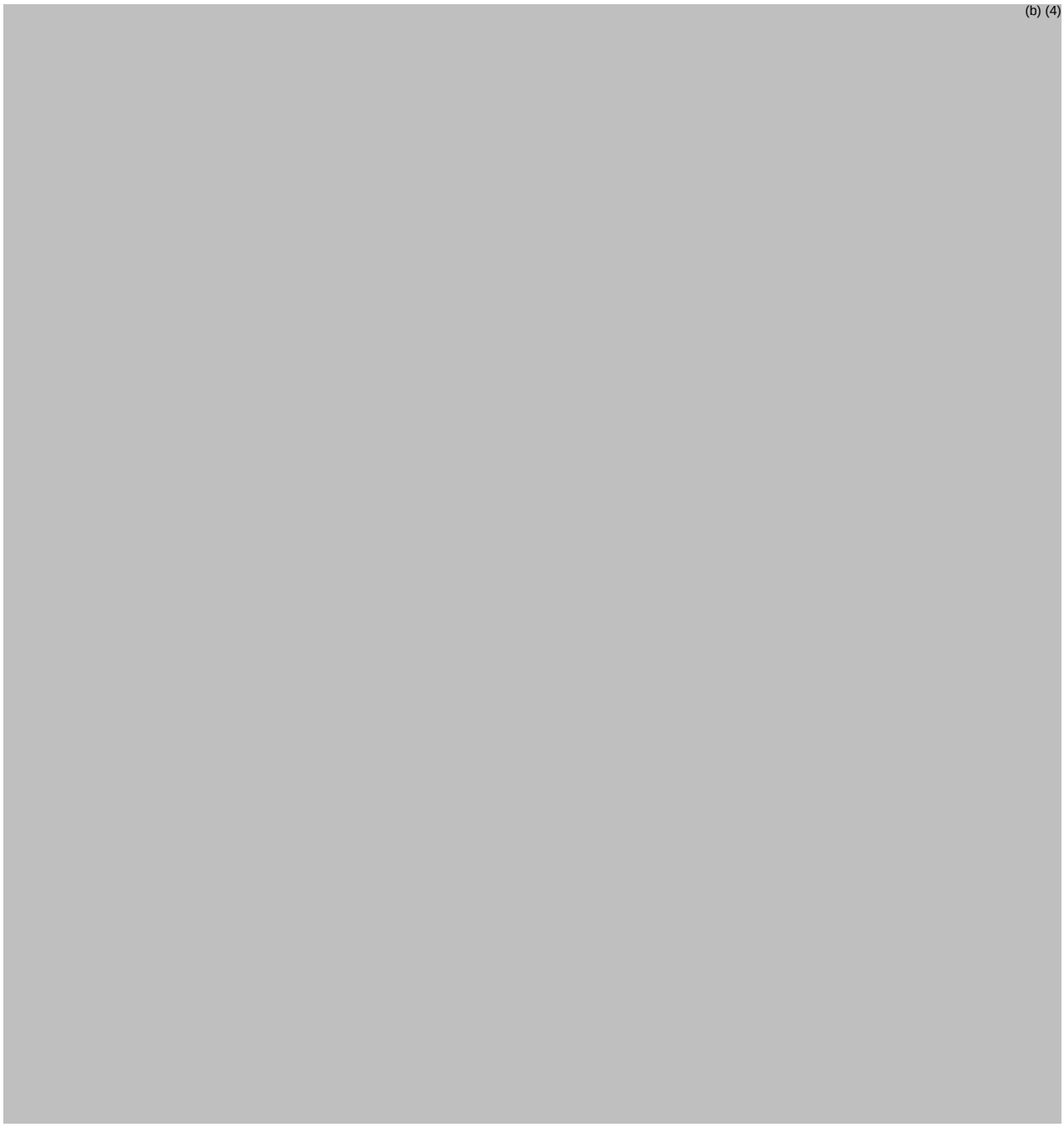

Reviewer's Comment:
The data generated in Trial 2693-CL-0305 did not reveal any new safety signals for fezolinetant. The 12% incidence of elevated hepatic transaminases as a TEAE was higher in the enrolled Asian population than in the trial data submitted for this application which had a significantly lower proportion of Asian participants.

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Reviewer's Comment:
Trial 2693-CL-0307 generated uncontrolled safety data where an incidence of 12% of participants experienced elevated LFTs (ALT increased or AST increased) similar to Trial 2693-CL-0305. There were 9 reports of blood creatinine phosphokinase increased reported.

Reviewer's Comment:
Overall, the 120-Day Safety Update of Clinical Safety revealed a higher level of elevated hepatic transaminases in the trials in Asia as compared to the US and European studies and trials. There are fewer malignancies and no apparent imbalance in malignancies in these trials. Otherwise, the safety data was consistent with the data generated in the fezolinetant development program presented in this NDA applications and no new safety signals are identified.

8.9 Safety in the Postmarket Setting

8.9.1 Safety Concerns Identified Through Postmarket Experience

Fezolinetant is not approved for use in the US or internationally. There is no safety data to evaluate from the postmarket environment.

8.9.2 Expectations on Safety in the Postmarket Setting

It is not anticipated that this drug will be used off-label in the post-market setting.

8.9.3 Additional Safety Issues From Other Disciplines

Clinical Pharmacology provided recommendation that people with mild hepatic impairment, renal impairment and/or people using mild CYP1A2 inhibitors be placed on a reduced dosage strength (e.g., one fezolinetant 30 mg tablet daily).

> Reviewer's Comment:
> Although the applicant studied fezolinetant in a 30 mg dosage form and women with mild hepatic impairment, mild renal impairment or use of mild CYP1A2 inhibitors were allowed to be enrolled in all treatment arms, including the 30 mg fezolinetant arm, the 30 mg fezolinetant arm did not meet all efficacy endpoints. Additionally, Astellas did not request approval of the 30 mg dosage strength in this application. Therefore, the Clinical Pharmacology recommendation to reduce the dosage strength to 30 mg dosage in women with mild hepatic impairment, mild renal impairment or use of mild CYP1A2 inhibitors is not feasible as the 30 mg dosage strength will not be marketed in the US drug market. Further, the 45 mg pill is not to be cut or chewed according to labeling and persons with mild hepatic impairment, severe renal impairment, or concomitant users of mild CYP1A2 should not take fezolinetant 45 mg.

8.10 Integrated Assessment of Safety

Fezolinetant is associated with a risk of elevated hepatic transaminases in women with and without baseline hepatic abnormalities. Fezolinetant did not lead to serious and/or sustained hepatic injury in assessed phase 3 trials assessed in the application and there were no Hy's law cases. The majority of hepatic enzyme elevations were transient in nature and resolved while on study drug. The label should indicate the importance of patient selection (for example inclusion of a contraindication in women with known cirrhosis and severe renal impairment or end-stage renal disease) as well as baseline and early serial monitoring for liver functions tests. Fezolinetant was generally well tolerated related to other side effects without clinically significant imbalances in serious adverse events or deaths in women with moderate to severe VMS.

Overall, Fezolinetant has a favorable safety profile and known safety risks related to elevated hepatic transaminases can be mitigated with baseline and monthly monitoring of hepatic transaminases.

9. Advisory Committee Meeting and Other External Consultations

No Advisory Committee was conducted for NDA 216578.

10. Labeling Recommendations

10.1 Prescription Drug Labeling

Reference to (b) (4)™ was removed throughout proposed labeling. On September 15, 2022, the proposed proprietary name (b) (4) was denied.

The format and content of the proposed labeling was updated for consistency with the Physician Labeling Rule (PLR) and the Pregnancy and Lactation Labeling Rule (PLLT). Labeling sections and content were revised as follows:

10.2 Nonprescription Drug Labeling

Not applicable.

11. Risk Evaluation and Mitigation Strategies (REMS)

No Risk Evaluation and Mitigation Strategies (REMS) are proposed for the 45 mg fezolinetant drug product. The clinical team recommends the risk mitigation measures for the risk of DILI to include labeling which advises prescribers to obtain hepatic transaminase assessment at baseline and monthly while the patient is on the drug for up to 9 months. The labeling recommendations are coupled with focused standard pharmacovigilance inclusive of a 15-Day alert report focused on incidence greater than anticipated of elevated liver transaminases, elevated bilirubin, and reports of jaundice or yellowing of the skin.

12. Postmarketing Requirements and Commitments

No postmarketing requirements or commitments are requested as of the archiving of this review. The clinical team recommends the risk mitigation measures for the risk of DILI to include labeling which advises prescribers to obtain hepatic transaminase assessment at baseline and monthly while the patient is on the drug for up to 9 months. The labeling recommendations are coupled with focused standard pharmacovigilance inclusive of a 15-Day alert report focused on incidence greater than anticipated of elevated liver transaminases, elevated bilirubin, and reports of jaundice or yellowing of the skin.

13. Appendices

13.1 References

See the references reviewed and discussed throughout this primary clinical review.

13.2 Financial Disclosure

Astellas adequately disclosed financial agreements for participating investigators in the primary clinical trials conducted to support the NDA application.

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/s/

THERESA H VAN DER VLUGT
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REGINA R ZOPF
11/23/2022 10:07:48 PM

SHELLEY R SLAUGHTER
11/26/2022 07:13:56 PM
I concur with Dr. van der Vlugt's and Dr. Zopf's conclusions and recommendations for this NDA.

Clinical Outcome Assessment Review Memorandum

From:	Julia Ju, PharmD., PhD. Clinical Outcome Assessment (COA) Reviewer Division of Clinical Outcome Assessment (DCOA) Selena Daniels, PharmD., PhD. COA Team Leader DCOA David Reasner, PhD. Division Director DCOA
To:	Division of Urology, Obstetrics and Gynecology
COA tracking ID:	C2022271
NDA#/Reference IND:	NDA 216578/IND 130277
Applicant:	Astellas Pharma Global Development, Inc.
Established Name /Trade Name:	fezolinetant
Indication:	Treatment of moderate to severe vasomotor symptoms (VMS) associated with menopause Please check all that apply: ☐ Rare Disease/Orphan Designation ☐ Pediatric
Instrument(s) reviewed:	1. Vasomotor symptoms (VMS) Diary ☒ Patient-reported outcome (PRO)

This memo is in response to the clinical outcome assessment (COA) consult request filed in DARRTS by Division of Urology, Obstetrics, and Gynecology (DUOG) on July 29, 2022 (DARRTS Reference ID: 5021559) for NDA 216578. In this submission, the applicant is seeking approval of fezolinetant for the treatment of moderate to severe vasomotor symptoms (VMS) associated with menopause. The specific COA-related labeling claims are related to reduction in the severity and frequency of moderate to severe symptoms derived from two clinical trials (Studies 2893-CL-0301 and 2693-CL-0302). The primary objective of this review is to evaluate from a COA perspective if the submitted information supports the COA-related labeling claims related to these concept(s) of interest, as well as the clinical meaningfulness of the target COA endpoints.

The co-primary efficacy endpoints proposed for labeling:

- Mean change in the frequency of moderate to severe VMS from baseline to week 4
- Mean change in the frequency of moderate to severe VMS from baseline to week 12
- Mean change in the severity of moderate to severe VMS from baseline to week 4
- Mean change in the severity of moderate to severe VMS from baseline to week 12

The data from Studies 2893-CL-0301 and 2693-CL-0302 demonstrated that fezolinetant 45mg had statistically significant improvement in the co-primary efficacy endpoints compared with placebo.

From a COA perspective, the VMS Diary and its corresponding endpoint(s) adequately supports labeling claims. However, based on the anchor-based analyses it is challenging to determine a range of meaningful within-patient change thresholds as there are limitations related to the primary anchor.

Review Conclusions

The Division had previously agreed to the VMS diary. As such, the VMS Diary was reviewed for meaningful within-patient change. The VMS Diary is adequate to support labeling claims.

Review Summary

The applicant attempted to use an anchor-based approach to interpret the target COA endpoints. However, the selected primary anchor (Patient Global Impression of Change for Vasomotor Symptoms [PGI-C VMS]) has limitations which make it difficult to interpret the results of the anchor-based analyses (see Key Issues Identified). Nonetheless, we note that change from baseline in VMS frequency showed a clear separation between the treatment (both 30 mg and 45 mg) and placebo arms across a range that likely includes a clinically meaningful change threshold (refer to the COA Statistical review).

Key Issues Identified

1. The PGI-C VMS has limitations which may impact the interpretability of the results of the anchor-based analyses. Specifically,
    - The concept of the primary anchor scale (hot flashes and night sweats) is not aligned to the concept measured in the VMS Diary (frequency and severity of hot flashes alone). For an endpoint measuring a specific aspect of the disease, an anchor scale measuring the same concept provides the most direct evidence.
    - The PGI-C VMS item stem is double-barreled (measures both hot flashes and night sweats). Combining these concepts into one question makes it unclear what is being measured. It is unclear which concept the respondents were thinking about when they answered the question.
    - The PGI-C VMS may be potentially susceptible to recall error (recall from Weeks 4 and 12 for the co-primary efficacy endpoints).

2. Lack of evidence to support that "moderately better" category response on the PGIC-VMS represents a meaningful change to patients.

Recommendations for Future Studies

For future clinical trials in this indication, we recommend that sponsors explore multiple anchors (e.g., current state global impression rating scale, global impression of change scale) to provide an accumulation of evidence to help interpret a clinically meaningful within-patient score change (can also be a range) in the clinical outcome endpoint score. Sponsors should submit exact copies of the anchor scales for Agency review and concurrence prior to

implementing them in the planned clinical trial(s). Sponsor should also provide evidence for what constitutes a meaningful change on the anchor scale(s).

Regulatory Background and Materials Reviewed

There have been several communications related to the applicant's COA measurement strategy, which included advice on the following:

- Final Written Response dated September 18, 2020
  - Disagreed with the proposal (b) (4)
  - Communicated that the primary analysis of clinical meaningfulness could be based on the meaningful within-patient change from the patients' perspective using external anchors and pooled treatment arms data in lieu of the between-group determination to demonstrate that the reduction of the frequency of the VMS in the fezolinetant treatment group exceeds that of placebo by the clinical meaningful threshold of 2 moderate to severe hot flushes per day or 14 per week.
  - Recommended the primary analyses based on external anchors should use a subset of blinded, pooled data in each trial to establish a meaningful change threshold(s), or a range of threshold(s). This data subsequently should be confirmed using blinded, pooled data from remaining participants in each study.
  - Identified limitations with PGI-C VMS anchor scale (i.e., concept of anchor does not measure hot flush frequency, susceptible to recall error).
  - Requested clarification regarding the calculation of baseline and post-baseline (e.g., Week 4 and Week 12) frequency and severity endpoint scores using different time periods, i.e., a 10-day period vs. a 7-day period, respectively.
  - Suggested the conduct of exit interviews to complement the anchor-based methods.

- Final Written Response dated July 28, 2021
  - Reiterated the limitations of the PGI-C VMS anchor scale.
  - Requested clarification regarding the administration of the PGI-C VMS scale in all participants in Studies 2693-CL-0301 and 2693-CL-0302 at both time points of primary endpoint collections (Weeks 4 and 12).
  - Requested confirmation of the number of participants who had completed the PGI-C VMS scale in Studies 2693-CL-0301 and 2693-CL-0302 at both primary time points.
  - Requested evidence to support that the "moderately better" response category in the PGI-C VMS represents a meaningful change in the measure.
  - Requested final quantitative summary report and revised psychometric analysis plan.

- FDA Advice/Information Request Letter dated May 24, 2022
  - Reiterated the recommendation on the use of qualitative methods to complement the anchor-based methods.

- Acknowledged that exit interviews were not conducted.
- Recommended stand-alone cognitive interviews to (1) provide evidence to support the patient comprehension of the PGI-C VMS and (2) provide evidence for what constitutes a meaningful change on the anchor scale.

The materials reviewed for this submission included the following:

- Sponsor's response to the FDA Advice/Information Request letter dated May 24, 2022 (SDN 1, eCTD 0001)
- NDA submission package (SDN 1, eCTD 0001)
- Previous COA review:
  - C2022106_IND 130277_Ju dated May 9, 2022 (DARRTS Reference ID: 4981149)

Trial Design and Study Endpoints

Studies 2693-CL-0301 and 2693-CL-0302 are identical randomized, placebo-controlled, 12-week double-blind phase 3 studies with an active-dose extension treatment period designed to assess the efficacy and safety of fezolinetant in adult women (40-65 years) with moderate-to-severe vasomotor symptoms associated with menopause. Eligible participants must have had a minimum of 7-8 moderate-to-severe VMS per day on average, or 50-60 VMS per week.

The study endpoints for both trials are as follows:

Co-primary efficacy endpoints

- Mean change in the frequency of moderate to severe VMS from baseline to week 4
- Mean change in the frequency of moderate to severe VMS from baseline to week 12
- Mean change in the severity of moderate to severe VMS from baseline to week 4
- Mean change in the severity of moderate to severe VMS from baseline to week 12

Secondary COA efficacy endpoint

- Mean change in the Patient-reported Outcomes Measurement Information System Sleep Disturbance – Short Form 8b (PROMIS SD SF 8b) total score from baseline to week 12

Reviewer's comment(s): *The baseline VMS frequency endpoint is the average of the daily simple count of moderate and severe VMS events across a 10-day period prior to randomization. The average values for weeks 4 and 12 are based on a 7-day period prior to the visit.*

Refer to the Clinical review for more details regarding the design of Studies 2693-CL-0301 and 2693-CL-0302.

COA Description(s)

Vasomotor Symptoms (VMS) Diary

The VMS Diary is a patient-reported outcome (PRO) instrument designed to assess the frequency and severity of hot flashes. Hot flash events are recorded as they occur (b) (4)

(b) (4)

. The VMS Diary was administered daily. A copy of the instrument is in Appendix A.

Anchor Scale(s)

Table 1 summarizes the PGI-C VMS anchor scale used in Studies 2693-CL-0301 and 2693-CL-0302. The PGI-C VMS was administered at weeks 4 and 12. A copy of the instrument is in Appendix B.

Table 1. Summary of PGI-C VMS

Endpoint concept/attribute (COA type/name if any)	Anchor (concept)	Anchor response scale	Recall period (target/anchor)	Timing (target/anchor)
VMS Diary (severity of hot flashes)	PGI-C VMS (hot flashes and night sweat)	7-point VRS: Much better, Moderately better, A little better, No change, A little worse, Moderately worse, Much worse	Momentary /Comparison of current state to earlier time period	Weeks 4 and 12
VMS Diary (frequency of hot flashes)	PGI-C VMS (hot flashes and night sweats)	7-point VRS: Much better, Moderately better, A little better, No change, A little worse, Moderately worse, Much worse	Momentary/ Comparison of current state to earlier time period	Weeks 4 and 12

PGI-C VMS= Patient Global Impression of Change -Vasomotor Symptoms
VRS= verbal rating scale

Appendices:

Appendix A. VMS diary
Appendix B. PGIC-VMS

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DAVID S REASNER
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