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Office of Surveillance and Epidemiology (OSE) Integrated Review

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Reviewers: Graça Dore, MD, MPH (Hematologist/Oncologist)
Division of Pharmacovigilance II (DPV II)

Adebola Ajao, PhD
Division of Epidemiology II

Division Directors: S. Christopher Jones, PharmD, MPH, MS
Director, DPV II

David Moeny, RPh, MPH
Director, Division of Epidemiology II

Product Name: Fezolinetant ((b) (4))

Subject: Assessment of Malignancy Cases and Imbalance in
Fezolinetant Clinical Trial Data

Application Type/Number: NDA 216578

Applicant/Sponsor: Astellas Pharma US, Inc

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EXECUTIVE SUMMARY

On June 22, 2022, Astellas Pharma Global Development, Inc (Astellas) submitted NDA 216578 for ESN364 (fezolinetant), 45 mg oral tablet, for treatment of moderate to severe vasomotor symptoms (VMS) associated with menopause. In the three individual (2693-CL-0301, 2693-CL-0302 and 2693-CL-0304) and pooled 52-week phase-3 studies, a dose-dependent numeric imbalance in the incidence of malignancy was observed in fezolinetant arms versus placebo.

On January 30, 2023, the Division of Urology, Obstetrics, and Gynecology (DUOG) consulted the Division of Pharmacovigilance II (DPV II) and the Division of Epidemiology (DEPI) to review and assess if the malignancy cases at various primary sites represented a signal for general malignancy with the product and to characterize the signal strength.

DPV II reviewed study documents for inclusion/exclusion criteria related to neoplasms in clinical trial protocols, protocol deviations related to neoplasms, and individual case details of neoplasm cases. DEPI attempted to calculate and compare general and site-specific cancer incidence in the fezolinetant trials to a general population of US women in a similar age group using data from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program.

Assessment of incident neoplasms across all three 52-week, phase-3 studies was limited by 1) lack of source documentation on relevant risk factors (e.g., ultraviolet radiation (UVR) exposure), physical exam findings, laboratory and imaging study results; 2) protocol deviations; 3) underreporting of past medical history (e.g., prior cancer history); 4) abnormal and/or nondiagnostic (insufficient sample for evaluation) laboratory and pathologic studies at screening visits or early in the study period; 5) detection bias (e.g., skin cancers, intrathoracic tumors) due to concurrent clinical conditions or imaging studies performed for unrelated reasons; and 6) alternate established cancer risk factors. In combination, these factors make it less likely that exposure to fezolinetant contributed to or accounted for cancer development in these studies. Short drug exposure time and detection of cancers across multiple primary sites (and histologic subtypes) further make it unlikely that fezolinetant was associated with tumor development. The inability to establish incident cancer rates and the small number of site-specific cancer cases in the three trials made it impossible to reliably calculate cancer incidence in the fezolinetant trial. Different study populations (international clinical trials vs. US-based SEER data), lack of data collection on most noninvasive neoplasms and nonmelanoma skin cancers (e.g., basal cell carcinoma, squamous cell carcinoma) in SEER make it impossible to compare cancer incidence in the fezolinetant trial to SEER.

Based on this case review, the evidence for implicating fezolinetant in the development of malignancy is weak and any causal association between fezolinetant exposure and neoplasm could not be established with certainty based on the data provided by the Applicant. This clinical information should be interpreted in the context of overall study quality, pre-clinical studies, and pharmacologic data that provide information on potential mechanisms by which fezolinetant might plausibly contribute to a carcinogenic process (e.g., initiator, promotor). Based on what we know today, we attribute the numeric imbalance in the clinical trials, which prompted this analysis, to most likely be a chance finding.

1 INTRODUCTION

The Division of Urology, Obstetrics, and Gynecology (DUOG) consulted the Division of Pharmacovigilance II (DPV II) and the Division of Epidemiology (DEPI) on January 30, 2023 to review and assess the imbalance in neoplasm in the fezolinetant clinical trial data. This integrated review provides DPV II and DEPI's joint assessment of a potential safety signal for malignancy in a general population of women taking fezolinetant for vasomotor symptoms.

1.1 Background

On June 22, 2022, Astellas Pharma Global Development, Inc (Astellas) submitted NDA 216578 for ESN364 (fezolinetant), 45 mg oral tablet, for the proposed indication of treatment of moderate to severe vasomotor symptoms (VMS) associated with menopause. Fezolinetant is a new molecular entity, small molecule, non-hormonal selective neurokinin (NK)₃ receptor antagonist that blocks neurokinin B (NKB) binding on the kisspeptin/neurokinin/dynorphin (KNDy) neuron to modulate neuronal activity in the thermoregulatory center. In the phase 2 nonclinical carcinogenicity and genotoxicity studies, there was no concern of malignancy, but in the three individual (2693-CL-0301, 2693-CL-0302, and 2693-CL-0304) and pooled 52-week phase-3 studies, a dose-dependent numeric imbalance in the incidence of malignancy was observed in the fezolinetant arms compared to placebo. Studies 2693-CL-301 and 2693-CL-302 are both randomized, placebo-controlled, 12-week double-blind, followed by an active 40-week treatment extension period where the placebo groups were re-randomized to either fezolinetant 30 mg, or fezolinetant 40 mg at week 12. Study 2693-CL-0304 is a 52-week, randomized, double-blind, parallel-group phase-3 study where participants were randomized 1:1:1 to receive placebo, fezolinetant 30 mg, or fezolinetant 45 mg once daily. The pooled phase 3 studies consist of all randomized individuals who received at least one dose of study drug from the three 52-week phase 3 studies. An overview of completed VMS fezolinetant clinical studies that contributed to pooled analyses of safety is shown in **Appendix A**.

Menopause is a natural biological process and marks the end of fertility because of permanent ovarian failure. Menopause occurs at a median age of 51.4 years and can occur in a woman's 40's or earlier.^{1,2} In the US, nearly 63 million women are past the average age of natural menopause of 51 years as of July 1, 2021. Prevalence of moderate/severe VMS is 46% among women who reached natural menopause during 1996-2012.³ VMS and hot flashes were the most common symptoms (45% and 40%, respectively) among women aged 45-65 years.⁴ The median duration of VMS is 10.2 years.³

1.2 Questions from DUOG

Given the higher incidence of some of these malignancies 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 REVIEW METHODS AND MATERIALS

2.1 DEPI Methods

DEPI attempted to calculate and compare general and site-specific cancer incidence in the individual and pooled 52-week phase 3 studies (Table 1) to the general population of women ages 50 – 64 years using the National Cancer Institute Surveillance, Epidemiology and End Results Program (SEER).^a The SEER Program of the National Cancer Institute (NCI) is an authoritative source of information on cancer incidence and survival in the United States. SEER currently collects and publishes cancer incidence and survival data from population-based cancer registries covering approximately 48 percent of the U.S. population. In SEER, age-adjusted cancer incidence is calculated by dividing the number of new cases by the total population in a specific age group over a period of time.

Table 1: Summary of Number and Incidence of Neoplasms for Studies 2693-CL-0301, 2693-CL-0302 and 2693-CL-0304 52-Week Data *			
Number and Incidence of Neoplasm for Study 2693-CL-0301			
MedDRA (v23.0) System Organ Class Preferred Term	Placebo N = 175 PY= 37.6	Fezolinetant 30mg N = 250 PY= 188.2	Fezolinetant 45mg N = 249 PY= 209.3
Apocrine breast carcinoma	0	0	1
Lung neoplasm	0	0	1
Squamous cell carcinoma of the skin	0	1	0
Cancer incidence	0/175 (0%)	1/250 (0.4%)	2/249 (0.8%)
Number and Incidence of Neoplasms for Study 2693-CL-0302			
MedDRA (v23.0) System Organ Class Preferred Term	Placebo N = 167 PY=36.3	Fezolinetant 30mg N = 242 PY=194.2	Fezolinetant 45mg N = 242 PY= 198.4
Invasive breast carcinoma	0	1	0
Keratoacanthoma	0	0	1
Squamous cell carcinoma of the skin	0	0	1
Cancer incidence	0/167 (0%)	1/242 (0.4%)	2/242 (0.8 %)
Number and Incidence of Neoplasms for Study 2693-CL-0304			
MedDRA (v23.0) System Organ Class Preferred Term	Placebo N=610 PY: 474.9	Fezolinetant 30mg N=611 PY: 503.8	Fezolinetant 45mg N=609 PY: 504.2
Basal Cell Carcinoma	0	1	0
Chronic lymphocytic leukemia	0	1	0
Colon cancer	0	0	2
Endometrial adenocarcinoma	0	1	2
Malignant melanoma, in situ	0	0	1
Non-small cell lung cancer	0	0	1

^a <https://seer.cancer.gov/statistics-network/explorer/>

Table 1: Summary of Number and Incidence of Neoplasms for Studies 2693-CL-0301, 2693-CL-0302 and 2693-CL-0304 52-Week Data*			
Squamous cell carcinoma of the skin	1	1	0
Squamous carcinoma of the oral cavity with bony metastasis	0	0	1
Cancer incidence	1/610 (0.1%)	4/611 (0.6%)	7/609 (1.1%)
Cancer incidence across three pooled studies	1/953 (0.1%)	6/1103 (0.5%)	11/1100 (1%)
* Table 1 excludes two benign neoplasms (schwannoma and papillary apocrine metaplasia (breast)) included in Table 7 below.			

2.2 DPV II Methods

DPV II reviewed the following documents to undertake the assessment of neoplasms:

- Sequence No. 0045: 1.11.3 Response to Information Request (IR) [23Jan2023]
- Sequence No. 0034: 5.3.5.3 Study Report Body Chapter
- Sequence No. 0001: 2.7.4 Summary of Clinical Safety; 4.2. Nonclinical Study Reports, 4.2.3.4 Carcinogenicity; 5.2 Tabular Listing of All Clinical Studies; 5.3 Clinical Study Reports, including Appendices and Case Report Forms
- FDA multidisciplinary reviews for NDA 216578: Clinical Review, Pharmacology/Toxicology Review and Addendum, Biostatistics Review

3 RESULTS

3.1 DEPI Results

According to data from the SEER Program, overall cancer incidence in women aged 50 – 64 years in the United States was 803.3 cases/100,000 persons (95% CI: 798 – 807 cases/100,000) in 2019. A number of challenges presented when DEPI attempted to calculate and compare overall and site-specific cancer incidence in women exposed to fezolinetant to the general population of US women in a similar age group. First, it was difficult to accurately calculate cancer incidence in the fezolinetant trial as we could not fully determine if cancer cases observed in the trial were pre-existing or new cases of cancer due to poor source documentation and protocol deviations. Second, the number of site-specific cancer cases in the fezolinetant trial were very small making any site-specific cancer estimates unstable. Third, SEER does not collect information on many of the site-specific cancers observed in the fezolinetant trial such as non-melanoma skin cancers (squamous cell carcinoma (SCC) and basal cell carcinoma (BCC)) and most non-invasive tumors (keratoacanthoma, schwannoma, leiomyoma, hemangioma, benign breast neoplasms) making it impossible to obtain or compare specific cancer incidence rates. Fourth, SEER collects information on invasive cancers (excluding SCC and BCC of skin) but only some in situ neoplasms, while the trial collected information on all benign, in situ, and invasive neoplasms. Fifth, SEER represents the US population, while these studies were international studies.

3.2 DPV II Results

DPV II reviewed study documents for inclusion/exclusion criteria related to neoplasms in clinical trial protocols, protocol deviations related to neoplasms, and individual case details of neoplasm cases.

3.2.1 Fezolinetant Studies: Inclusion/Exclusion Criteria

3.2.1.1 Phase 2 and Phase 3 Studies

Table 2 provides an overview of select inclusion criteria and duration of fezolinetant or placebo exposure for phase 2 and phase 3 studies.

Table 2. Overview of Phase 2 and Phase 3 Studies of Fezolinetant		
Study (No. participants)	Select inclusion criteria	Exposure duration
Phase 2		
ESN364_HF_204 (n=87 participants: 43 fezolinetant, 44 placebo)	Early postmenopausal females (45 to 60 years)	12 weeks
ESN364_HF_205 (n=356 participants: 312 fezolinetant, 44 placebo)	Postmenopausal women (>40 to ≤65 years)	12 weeks
Phase 3		
2693-CL-0301*	Postmenopausal women (≥40 years to ≤65 years)	52 weeks (30 mg) 52 weeks (45 mg) Placebo 16 weeks followed by treatment 36 weeks (30 mg or 45 mg)
2693-CL-0302*	Postmenopausal women (≥40 years to ≤65 years)	52 weeks (30 mg) 52 weeks (45 mg) Placebo 16 weeks followed by treatment 36 weeks (30 mg or 45 mg)
2693-CL-0304*	Postmenopausal women (≥40 years to ≤65 years)	52 weeks (30 mg) 52 weeks (45 mg) 52 weeks placebo
* Please refer to Table 1 for details on number of participants.		

3.2.1.2 Phase 3 Studies: 2693-CL-0301, 2693-CL-0302 and 2693-CL-0304

Inclusion criteria for the phase 3 fezolinetant studies relevant to the System Organ Class (SOC) of *Neoplasms benign, malignant, and unspecified (including cysts and polyps)* included the following:

- Documentation of a normal/negative or no clinically significant findings on 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.
- Willingness to undergo a transvaginal ultrasound (TVU) to evaluate the uterus and ovaries at screening, at Week 52 [end of treatment (EOT)], and at early

withdrawal/discontinuation for participants who are withdrawn/discontinued from the trial prior to Week 52.

- Willingness 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 trial prior to Week 52. The endometrial biopsy obtained at screening must be considered evaluable.
- Documentation of a normal or not clinically significant Papanicolaou (PAP) test (or equivalent cervical cytology) in the opinion of the investigator within the previous 12 months or at screening.

Some of the study **exclusion criteria** relevant to the SOC of *Neoplasms benign, malignant, and unspecified (including cysts and polyps)* included the following:

- Previous or current history of a malignant tumor, except for basal cell carcinoma.
- 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).
- 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.
- History within the last 6 months of undiagnosed uterine bleeding.

3.2.2 Protocol Deviations

Some protocol deviations relevant to the SOC of *Neoplasms benign, malignant, and unspecified (including cysts and polyps)* included the following:

Three patients with a history of neoplasm [other than basal cell carcinoma (BCC)] enrolled in the study:

- (b) (6): received placebo/fezolinetant and was included in Study 2693-CL-0301 despite a past medical history of Bowen's disease [(SCC, in situ)] in 2019. There is no notation that this patient was listed as a protocol deviation.
- (b) (6): received fezolinetant 45 mg and was included in Study 2693-CL-0302 despite a past medical history of cutaneous SCC (cSCC) in 2018. This patient was listed as a protocol deviation.
- (b) (6): received placebo and was included in Study 2693-CL-0304 despite a past medical history of cSCC (nose) in 2012. This patient was not listed as a protocol deviation.

Reviewer's comments: *These three patients were ineligible for study due to a prior history of SCC (invasive or in situ), and only one of the three was included as a protocol deviation. This finding suggests that there may have been under ascertainment of cancer history at study entry, particularly of nonmelanoma skin cancers (NMSC), the vast majority of which are curable with excision.⁵ In addition, the absence of reporting of two*

of the three cases, albeit small number of cases, suggests that protocol deviations were underreported. This situation may have gone undetected or unreported in other study participants, thereby potentially affecting risk of subsequent cancer with additional follow-up during the study period.

In Study 2693-CL-0304 (1,830 total participants), there were 16 (0.9%) protocol deviations related to exclusion criteria based on results of endometrial biopsy, and 13 (0.7%) protocol deviations related to endometrial biopsy inclusion criteria. These protocol deviations are detailed in **Table 3** according to study treatment.

Table 3. Select Protocol Deviations, Inclusion/Exclusion Criteria Relating to Endometrial Biopsy (Study 2693-CL-0304)					
Criteria Number	Criteria Text	Placebo (n = 610)	Fezolinetant 30 mg (n = 611)	Fezolinetant 45 mg (n = 609)	Fezolinetant Total (n = 1220)
Exclusion criterion 7	For subjects with a uterus: Subject 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. A biopsy with insufficient material for evaluation or unevaluable material is acceptable provided the endometrial thickness is < 4 mm	3 (0.5%)	9 (1.5%)	4 (0.7%)	13 (1.1%)
Inclusion criterion 7a	Subject 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	5 (0.8%)	3 (0.5%)	5 (0.8%)	8 (0.7%)
Source: Adapted from Midcycle Table 2.1 submitted on 24 Oct 2022 (sequence number 0034) and Information Request 23Jan2023.					

Reviewer's comments: *Although based on small numbers, there was an imbalance related to exclusion criterion 7 with more (1.1% total, n=13) protocol deviations among fezolinetant-treated participants compared to those treated with placebo (0.5%, n=3). Protocol deviations related to inclusion criterion 7a were nearly equal among fezolinetant-treated participants (0.7%, n=8) and those receiving placebo (0.8%, n=5).*

3.2.3 Cancer Screening Tests

Additional information on cancer screening tests relevant to the SOC of *Neoplasms benign, malignant, and unspecified (including cysts and polyps)* included the following:

3.2.3.1 PAP Test

The Applicant indicated that the phase 3 protocols specified that PAP tests should be performed at the screening visit [days -35 to -1 (visit 1)] only in the event that the participant did not have documentation of a normal/negative result or no clinically significant findings within the prior 12 months of study enrollment (changed from prior nine months of study enrollment in version 2.1 of 2693-CL-0301, 2693-CL-0302 and 2693-CL-0304 study protocols). There was documentation of meeting inclusion criteria, but no collection of source documentation.

Based on the information the Applicant provided in the IR response (23Jan2023), the proportion of participants with an abnormal PAP test assessment was similar across the treatment groups. Of those participants with a PAP test result, an abnormal result was not exclusionary if it was deemed not clinically significant by the investigator.

Table 4 shows the PAP test result availability for participants in Studies 2693-CL-0301, 2693-CL-0302 and 2693-CL-0304. A ‘Yes’ reflects participants who had a PAP specifically at screening to enable entry into the study. Per the protocol, participants with a ‘No’ may have had a PAP test in the preceding months which permitted study entry or a hysterectomy.

The Applicant noted that 55.8% to 58.2% of participants in each treatment group had a PAP test at screening, and among those with a PAP test at screening, 5.7% to 7.5% had an abnormal result and 0.5% to 1.4% had a quality comment with no result (**Table 4**).

Table 4. Distribution of Participants for PAP Test During Screening (Safety Analysis Set)				
PAP Test Category	Placebo (n = 952)	Fezolinetant 30 mg (n = 951)	Fezolinetant 45 mg (n = 949)	Fezolinetant Total (n = 1900)
Yes	554/952 (58.2%)	532/951 (55.9%)	530/949 (55.8%)	1062/1900 (55.9%)
Negative	474/952 (49.8%)	457/951 (48.1%)	471/949 (49.6%)	928/1900 (48.8%)
Abnormal	71/952 (7.5%)	62/951 (6.5%)	54/949 (5.7%)	116/1900 (6.1%)
Quality comment and no result	9/952 (0.9%)	13/951 (1.4%)	5/949 (0.5%)	18/1900 (0.9%)
No*	398/952 (41.8%)	419/951 (44.1%)	419/949 (44.2%)	838/1900 (44.1%)
Hysterectomy	115	122	119	241
Source: Information Request 23Jan2023. All randomized participants who took at least 1 dose of study intervention (Safety Analysis Set). PAP=Papanicolaou. * Participants with a ‘No’ may have had a PAP test in the preceding months which permitted study entry, or a hysterectomy, per the protocol				

Reviewer’s comments: *Several of the frequencies in the Applicant table underestimate the actual occurrence of events because the denominator is not limited to patients at-risk. The denominator for the subcategories of “Yes” should be based on the numerator in the “Yes” row, and similarly, the denominator for the subcategories in the “No” row, should be based on the numerator in the “No” row, as depicted in **Table 5** below (shaded rows are changed from **Table 4**).*

Table 5 calculations are limited to at-risk patients. Among study participants with a PAP test at screening, 10.2% to 12.8% had an abnormal result and 0.9% to 2.4% had a

quality comment with no result. In addition, among participants without a PAP performed, 70.9% to 71.7% “may have had a PAP test in the preceding months.”

Table 5. Revised Applicant Table 3 with distribution of participants for PAP test during screening based on at-risk populations (Safety Analysis Set)*				
PAP Test Category	Placebo (n = 952)	Fezolinetant 30 mg (n = 951)	Fezolinetant 45 mg (n = 949)	Fezolinetant Total (n = 1900)
Yes	554/952 (58.2%)	532/951 (55.9%)	530/949 (55.8%)	1062/1900 (55.9%)
Negative	474/554 (85.6%)	457/532 (85.9%)	471/530 (88.9%)	928/1062 (87.4%)
Abnormal	71/554 (12.8%)	62/532 (11.7%)	54/530 (10.2%)	116/1062 (10.9%)
Quality comment and no result	9/554 (1.6%)	13/532 (2.4%)	5/530 (0.9%)	18/1062 (1.7%)
No	398/952 (41.8%)	419/951 (44.1%)	419/949 (44.2%)	838/1900 (44.1%)
Hysterectomy	115 (28.9%)	122 (29.1%)	119 (28.4%)	241 (28.8%)
May have had a PAP test in the preceding months	283/398 (71.1%)	297/419 (70.9%)	300/419 (71.6%)	838 (71.2%)
* Refer to footnotes in Table 7. Shaded cells reflect changes from Applicant’s original Table.				

Reviewer’s comments: *Notably the study protocol specified that a normal/negative result or no clinically significant findings on Pap testing was required. With more than 10% of patients in each study arm having an abnormal result or a quality comment and no result, this raises concern that some of the lesions were clinically significant and source documentation verification would be important to clarify this point. The assessment that patients without hysterectomy “may have had” a Pap test in the preceding months, seems tenuous given the specified study inclusion criteria. Source document verification would alleviate concerns that some patients may not have had the stated testing or may have had results that would exclude them from study participation.*

3.2.3.2 Mammograms

Table 6 includes some of the reported protocol deviations related to mammograms (inclusion criterion 7).

Table 6. Select Protocol Deviations, Inclusion/Exclusion Criteria Relating to Mammograms (Study 2693-CL-0304)					
Criteria Number	Criteria Text	Placebo (n = 610)	Fezolinetant 30 mg (n = 611)	Fezolinetant 45 mg (n = 609)	Fezolinetant Total (n = 1220)
Inclusion criterion 7	Subject has documentation of a normal/negative or no clinically significant mammogram findings (obtained at Screening or within the prior 12 months of trial enrollment). Appropriate documentation includes a written report or an electronic	3 (0.5%)	2 (0.3%)	4 (0.7%)	6 (0.5%)

Table 6. Select Protocol Deviations, Inclusion/Exclusion Criteria Relating to Mammograms (Study 2693-CL-0304)					
Criteria Number	Criteria Text	Placebo (n = 610)	Fezolinetant 30 mg (n = 611)	Fezolinetant 45 mg (n = 609)	Fezolinetant Total (n = 1220)
	report indicating normal/negative or no clinically significant mammographic findings				

Mammograms at study entry

The Applicant indicated that mammograms were to be performed only in the event that the participant did not have documentation of a normal/negative or no clinically significant findings evaluation within the prior 12 months of study enrollment (changed from prior nine months of study enrollment in version 2.1 of 2693-CL-0301, 2693-CL-0302 and 2693-CL-0304 study protocols). The study protocol included documentation of meeting inclusion criteria, but there was no collection of source documentation at screening.

Reviewer's comments: *Based on the lack of source documentation, it is not possible to determine if mammogram abnormalities detected during the study as a treatment-emergent adverse event (TEAE) may have been present on prior mammogram(s), nor is it possible to assess whether protocol deviations may have occurred (e.g., no mammogram performed during the required time frame). In addition, it is plausible to consider that study participants who underwent mammogram testing during the study may have had more than a 1-year period elapse since the prior mammogram, depending on the timing of the mammogram prior to study entry and the timing of the subsequent mammogram. For example, a study participant with a mammogram completed 11 months prior to study entry who had a subsequent mammogram after 250 days on study, would have had an interval of approximately 19 months in between mammograms, thereby exceeding the recommended annual frequency for average-risk women ≥ 50 years (or ≥ 40 years, depending on guidelines followed), with a previously normal mammogram.*

3.2.3.3 Other Screening Visit Exams

Per the phase 3 study protocols, bimanual pelvic exam and clinical breast examinations were to be performed at the screening visit (visit 1). Only abnormalities noted on examinations were recorded.

Reviewer's comments: *Additional details on screening visit examinations were requested for study participants who developed breast or uterine neoplasms during the study, but the Applicant could not provide additional information due to this information not being collected.*

Per the phase 3 study protocols, a full physical examination was performed at screening visit (visit 1). Investigators were instructed to document any abnormality found on the screening physical examination as part of the participant's medical history. There was no specific

instruction for a skin examination and no dedicated recording system for physical examination findings other than height, weight, and waist circumference.

Reviewer's comments: *Data on documentation of skin type (e.g., Fitzpatrick scale to assess susceptibility to UV exposure) was requested but the Applicant could not provide this information. Only abnormalities noted on skin examinations were recorded. Regarding study participants who developed TEAE related to neoplasm of the skin, the Applicant could not provide additional information regarding skin examination, and one cannot distinguish between a “negative” exam (no skin abnormalities) vs. a skin exam that was not done.*

3.2.4 Neoplasms

The Applicant noted a numeric imbalance in the incidence of serious TEAEs in the SOC of *Neoplasms benign, malignant, and unspecified (including cysts and polyps)* between fezolinetant and placebo groups reported in the Phase 3 studies. Although smaller in enrollment, no concern for malignant neoplasms was recognized in phase 2 studies (ESN364_HF_204 and ESN364_HF_205) with a total of one TEAE of squamous cell carcinoma of the skin (with fezolinetant 60 mg once daily) in the latter study. Importantly, duration of fezolinetant exposure in each of these studies was limited to 12 weeks.

Table 7 represents a tabular summary of the cases with a benign or malignant neoplasm reviewed by DPVII. A more detailed synopsis and reviewer assessment of each case is included in **Appendix B**. The Applicant included multiple PTs for a patient with multiple sites of disease (e.g., lung cancer with liver metastases included PTs for lung cancer and liver cancer). In the DPV II review, a malignancy associated with local invasion of surrounding structures or metastatic lesions was considered as a single neoplasm (e.g., primary lung cancer with metastases to the liver) and not two neoplasms.

Table 7. Summary of Neoplasms, Total Exposure Days to Fezolinetant, and Fezolinetant Dose*					
ID/Study	Primary neoplasm/Age	Total exposure-days at time of diagnosis [placebo days, if applicable]	Dose	Comments	Association with fezolinetant
Omit from assessment due to lack of exposure to fezolinetant					
(b) (6) / 2693-CL-0304	cSCC (forehead)/ 56 years	None	N/A	Placebo-days = 192	Unlikely based on absence of exposure to fezolinetant; omit from assessment
(b) (6) / 2693-CL-0304	Schwannoma/ 58 years	None	N/A	Placebo-days = 272; incidental finding on imaging	Unlikely based on absence of exposure to fezolinetant; omit from assessment
Lesions not generally considered a neoplastic precursor					
(b) (6) / 2693-CL-0301	Atypical apocrine metaplasia (breast)/ 62 years	11 [placebo D1-84]	45 mg	Nonproliferative lesions are not typically associated with increased cancer risk	Not a neoplastic precursor
(b) (6) / 2693-CL-0304	Papillary apocrine metaplasia (breast)/ 49 years	231	30 mg	Nonproliferative lesions are not typically associated with increased cancer risk	Not a neoplastic precursor
(b) (6) / 2693-CL-0301	Pulmonary hamartoma/ 56 years	<319	45 mg	Lesion incidentally detected on “lung screening test” (specific exam and date not specified). PET-CT confirmed presence of lesion on Day 319 (last dose of study drug, Day 353)	Not a neoplastic precursor
Neoplastic process likely pre-existing prior to study entry					
(b) (6) / 2693-CL-0304	NSCLC (with liver metastases)/ 65 years	72	45 mg	ED 58: onset upper quadrant abdominal pain; tobacco abuse (with imaging study findings suggesting chronic exposure); post-operative changes in the right apex of the lung on imaging study	Unlikely based on abnormal and persistent elevation in alkaline phosphatase (and GGTP) from time of screening visit (Day-32); also short TTO

Table 7. Summary of Neoplasms, Total Exposure Days to Fezolinetant, and Fezolinetant Dose *					
ID/Study	Primary neoplasm/Age	Total exposure-days at time of diagnosis [placebo days, if applicable]	Dose	Comments	Association with fezolinetant
				(unknown if represents history of resected lung neoplasm)	
(b) (6) / 2693-CL-0304	Endometrial adenocarcinoma/ 50 years	79	45 mg	Screening (Day -33) endometrial biopsy with complex hyperplasia (abnormal); Day 29 uterine hemorrhage noted. Study exclusion criteria: “endometrial biopsy confirming presence of disordered proliferative endometrium, endometrial hyperplasia ...”	Unlikely based on abnormal endometrial biopsy at screening
(b) (6) / 2693-CL-0304	Endometrial adenocarcinoma/ 58 years	107	45 mg	Screening (Day -20) abnormal endometrial thickness of 5.49 mm (abnormal) that was not evaluated at that time. Study exclusion criteria: “Has an unacceptable result from the TVU assessment at screening”	Unlikely based on abnormal endometrial thickness at screening that warranted follow-up evaluation prior to study entry
(b) (6) / 2693-CL-0304	Endometrioid adenocarcinoma/ 51 years	357	30 mg	Uterine biopsy at screening (D -28) inadequate for assessment: “tissue unsatisfactory for diagnosis, too scant for reliable diagnosis.” Study exclusion criteria: “the endometrial biopsy obtained at screening must be considered evaluable.”	Unlikely based on unsatisfactory endometrial biopsy at screening (D -28) that warranted follow-up evaluation prior to study entry
(b) (6) / 2693-CL-0304	Colon cancer (sigmoid)/ 55 years	168	45 mg	ED 24: onset of GI symptoms	Unlikely based on symptom onset on ED 24, further shortening an already short TTO
(b) (6) / 2693-CL-0304	Colon cancer (right colon)/ 52 years	233	45 mg	ED 185: Fecal occult blood test positive (abnormal)	Unlikely based on laboratory abnormalities present on ED 185; decline in hemoglobin from baseline beginning ED 1, notable on ED 57,

Table 7. Summary of Neoplasms, Total Exposure Days to Fezolinetant, and Fezolinetant Dose*					
ID/Study	Primary neoplasm/Age	Total exposure-days at time of diagnosis [placebo days, if applicable]	Dose	Comments	Association with fezolinetant
					and frank anemia on ED 226 further shortening an already short TTO
(b) (6) / 2693-CL-0304	CLL/ 51 years	225	30 mg	ED 1: evidence of lymphocytosis and lymphocytosis which persisted over study period	Unlikely based on laboratory abnormalities supporting a diagnosis of CLL being present on ED1 (short TTO)
Documented relevant risk factor					
(b) (6) / 2693-CL-0302	Breast cancer/ 60 years	130 [placebo D1-85]	30 mg	Family history of breast cancer in first-degree relative (mother)	Unlikely based on alternate risk factor (family history) and short TTO
Neoplasms associated with longstanding UVR exposure (likely ubiquitous exposure) for study population					
(b) (6) / 2693-CL-0301	cSCC (nose)/ 65 years	63 [placebo D1-83]	30 mg		Unlikely based on short TTO
(b) (6) / 2693-CL-0302	cSCC (skin, face) / 60 years	104	45 mg	Possible may have been detected on ED 25 at time of face laceration (and excised ED 104)	Unlikely based short TTO with further shortened TTO based on likelihood of initial detection on ED 25
(b) (6) / 2693-CL-0304	cSCC (cheek)/ 56 years	186	30 mg	ED 197 actinic keratoses	Unlikely based on concomitant marker of past UVR exposure and short TTO
(b) (6) / 2693-CL-0302	Keratoacanthoma, skin (tibial area)/ 55 years	213	45 mg		Cannot be excluded
(b) (6) / 2693-CL-0304	BCC, skin (chest, right shoulder)/ 63 years	239	30 mg	At least one BCC with onset >20 years prior to study entry	Unlikely based on prior BCC suggesting exposure to known risk factors (e.g., UVR, tobacco)
Other neoplasms with unlikely association based on TTO					
(b) (6) / 2693-CL-0304	Malignant melanoma in situ,	55	45 mg	Limited information on potential risk factors for melanoma	Unlikely based on short TTO

Table 7. Summary of Neoplasms, Total Exposure Days to Fezolinetant, and Fezolinetant Dose *

ID/Study	Primary neoplasm/Age	Total exposure-days at time of diagnosis [placebo days, if applicable]	Dose	Comments	Association with fezolinetant
	skin (sole of foot)/ 56 years				
(b) (6) / 2693-CL-0304	Head and neck cancer, SCC (oral cavity)/ 52 years	137	45 mg	ED 47: evaluated for oral abscess	Unlikely based on clinical signs and symptoms ED 47, further shortening an already short TTO
Abbreviations: BCC, basal cell carcinoma; CLL, chronic lymphocytic leukemia; cSCC, cutaneous squamous cell carcinoma; D, day; ED, exposure-day; GGTP, gamma-glutamyl transpeptidase; GI, gastrointestinal; NSCLC, non-small cell lung cancer; SCC, squamous cell carcinoma; TTO, time to onset. * See Appendix B for more detailed case assessments. In this table, neoplasms are grouped into mutually exclusive categories for ease of assessment; however, some neoplasms may have been included in more than one category. Exposure-days exclude periods where there may have been a gap in therapy and for this reason may not correlate with Study Day number.					

4 DISCUSSION

Most cancers in adults are characterized by a multiple-step process of progressive accumulation of abnormal phenotypes: hyperplasia to adenoma to dysplasia to carcinoma in situ to invasive cancer that has the ability to metastasize.⁶ For most cancers, these changes occur over a prolonged period of time, usually many years. In addition, there is considerable complexity in the mutational origins of cancer with cancer-causing genes varying across and within tumor types and with multiple genes contributing to tumorigenesis.⁷ In common solid tumors e.g., those derived from the colon or breast, an average of 33 to 66 genes demonstrate subtle somatic mutations that would be expected to alter their protein products.⁶ However, certain tumor types display many more or fewer mutations than average.⁶ For example, melanomas and lung tumors, tend to contain more mutations reflecting the involvement of potent mutagens – ultraviolet radiation (UVR) and cigarette smoke, respectively.⁶

The International Agency for Research on Cancer (IARC) Monographs on the Evaluation of Carcinogenic Risks to Humans have classified almost 500 chemical, physical, and biological agents as carcinogenic (Group 1), probably carcinogenic (Group 2A), or possibly carcinogenic (Group 2B) to humans.⁸ Some important factors that characterize carcinogens and the carcinogenic process include:

- **Characteristics of carcinogens:** Mechanisms associated with carcinogens include that they may (be):⁸
 - Electrophilic or metabolically activated to electrophiles
 - Genotoxic
 - Alter DNA repair or cause genomic instability
 - Induce epigenetic alterations
 - Induce oxidative stress
 - Induce chronic inflammation
 - Immunosuppressive
 - Modulate receptor-mediated effects
 - Cause immortalization
 - Alter cell proliferation, cell death, or nutrient supply

Among the Group 1 agents – those with sufficient evidence of carcinogenicity in humans – nearly all exert their effects through genotoxic effects; however, most agents act through multiple mechanisms. The Pharmacology/Toxicology review (addendum) of nonclinical information, Applicant's responses, and chemistry assessments did not identify potential mechanisms of tumorigenesis or tumor promoter activity.^b

- **Multiplicity of cancer sites with a single exposure**

Ionizing radiation and tobacco smoke have been identified by IARC as having sufficient evidence (Group 1 carcinogens) to establish that they are carcinogenic to humans. Both radiation and tobacco smoke are associated with cancers at multiple sites, including cancers of the esophagus, stomach, colon, lung, kidney, urinary bladder, and

^b NDA 216578_SDN 1 and 55_Addendum Review (FINAL)_DARRTS.pdf Reference ID: 5161532

hematopoietic system (acute myeloid leukemia, chronic myeloid leukemia)].⁸ Briefly, radiation is a DNA-damaging agent (genotoxic), and risk of neoplasms following therapeutic radiation (e.g., for a first primary malignancy) is related to multiple factors, including type of radiation, site of radiation (radiation field), radiation quality, dose of radiation, organ sensitivity, co-exposures (e.g., cytotoxic chemotherapy, tobacco), genetic factors, and hormonal status. Tobacco smoke is comprised of more than 4000 chemical compounds, and more than 60 of these are known carcinogens.⁹ Most carcinogens in tobacco products require metabolic activation before they are able to react with DNA, although some are capable of reacting with DNA directly.⁹

Among pharmaceuticals classified by IARC as carcinogenic to humans (Group 1), most are associated with cancers as at a single site, with some exceptions (**Table 8**).¹⁰ Of the pharmaceutical agents associated with multiple cancer sites, there is generally a unifying mechanism, e.g., hormonally mediated cancer sites are associated with pharmaceuticals acting through hormonally mediated events. Agents associated with immunosuppression are linked with several cancer sites, given the important role of immunosuppression in the development of multiple different cancers.

Table 8. Select Pharmaceuticals Classified by IARC as Carcinogenic to Humans According to Cancer Site, Drug, and Mechanism(s)*			
Cancer site	Select carcinogenic agents associated with sufficient evidence in humans (Group 1)	Established mechanistic events	Other likely mechanistic events
Lung	MOPP and other combined chemotherapy including alkylating agents	Genotoxicity	
Skin	Azathioprine Cyclosporine	Immunosuppression	
Breast	Estrogen–progestogen oral contraceptives (combined) Estrogen–progestogen menopausal therapy (combined)	Estrogen receptor-mediated events	
Uterine cervix	Estrogen–progestogen oral contraceptives (combined)	Receptor-mediated events	
Endometrium	Estrogen therapy, postmenopausal Estrogen–progestogen menopausal therapy (combined) Tamoxifen	Estrogen receptor-mediated events	Genotoxicity, estrogen genotoxicity
Ovary	Estrogen therapy, postmenopausal	Estrogen receptor-mediated events	Genotoxicity
Vagina	Diethylstilbestrol (exposure in utero)	Estrogen receptor-mediated events, genotoxicity	Epigenetic programming

Table 8. Select Pharmaceuticals Classified by IARC as Carcinogenic to Humans According to Cancer Site, Drug, and Mechanism(s)*			
Cancer site	Select carcinogenic agents associated with sufficient evidence in humans (Group 1)	Established mechanistic events	Other likely mechanistic events
Renal pelvis/ureter	Phenacetin and analgesic mixtures containing phenacetin	Genotoxicity, cell proliferation	
Urinary bladder	Cyclophosphamide	Genotoxicity	Thru metabolites (acrolein, phosphoramidate mustard)
Acute myeloid leukemia	Busulfan Chlorambucil Cyclophosphamide Etoposide in combination with cisplatin and bleomycin Melphalan MOPP and other combined chemotherapy including alkylating agents Semustine	Genotoxicity (alkylating agent or metabolism to alkylating agent); translocations involving MLL gene (etoposide)	
Leukemia, all subtypes combined	Thiotepa	Genotoxicity	
Non-Hodgkin lymphoma, all subtypes combined	Azathioprine Cyclosporine	Genotoxicity (azathioprine), immunosuppression	
Multiple sites (unspecified)	Cyclosporine	Immunosuppression	
* Adapted from Pharmaceuticals IARC Monographs on the Evaluation of Carcinogenic Risks to Humans Volume 100A; Lyon, France, 2012 and Grosse et al. ¹¹ Abbreviations: MOPP, mechlorethamine, vincristine, procarbazine, prednisone.			

Pharmaceuticals that presently are not considered carcinogens per IARC classification [e.g., Janus kinase inhibitors (JAKi)] have reported cancers at multiple sites occurring after drug exposure when compared to control patients. JAKi (e.g., tofacitinib, baricitinib) are targeted synthetic disease-modifying antirheumatic drugs that suppress multiple cytokine and growth factor receptor signaling pathways.¹² JAKs phosphorylate and activate Signal Transducers and Activators of Transcription (STATs) which modulate intracellular activity including gene expression.¹³ Tofacitinib was approved in the U.S on November 6, 2012, for treatment of adult patients with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response or intolerance to methotrexate.¹³ In the original labeling (11/2012), tofacitinib included a *Warning and Precaution* for “malignancy and lymphoproliferative disorders” related to a finding of a

numeric imbalance in malignancies observed in tofacitinib compared to placebo during the first 12 months of exposure, as specified below:

In the seven controlled rheumatoid arthritis clinical studies, 11 solid cancers and one lymphoma were diagnosed in 3328 patients receiving XELJANZ with or without DMARD, compared to 0 solid cancers and 0 lymphomas in 809 patients in the placebo with or without DMARD group during the first 12 months of exposure.

Based on two Phase 2 and five Phase 3 double-blind, controlled, multicenter trials of tofacitinib as monotherapy or as part of combination therapy (total patients: 1336 received 5 mg twice daily; 1349 received 10 mg twice daily; 809 received placebo), the 2012 USPI also includes the following description (section 6.1):

In the seven controlled trials, during the 0 to 3 months exposure, malignancies excluding NMSC were reported in 0 patients who received placebo and 2 patients (0.3 events per 100 patient-years) [...] During the 0 to 12 months exposure, malignancies excluding NMSC were reported in 5 patients (0.4 events per 100 patient-years) who received 5 mg twice daily of XELJANZ and 7 patients (0.6 events per 100 patient-years) who received 10 mg twice daily of XELJANZ. [...] The most common types of malignancy, including malignancies observed during the long-term extension, were lung and breast cancer, followed by gastric, colorectal, renal cell, prostate cancer, lymphoma, and malignant melanoma.

Rheumatoid arthritis is a clinical syndrome involving several inflammatory cascades which all lead to a final common pathway that results in synovial inflammation and associated damage to articular cartilage and underlying bone.¹⁴ Pharmacologic treatments include nonsteroidal anti-inflammatory agents, corticosteroids, biologic agents, and disease-modifying antirheumatic drugs, all of which act through diverse mechanisms, directly or indirectly modifying upregulated immunologic pathways involved in RA.^{14,15,16} The immune system is thought to play an important role in immune surveillance and protection from development of malignancy. Indeed, patients with RA are at increased risk of malignancy compared to the general population with risk attributed to underlying chronic inflammation of RA, immunosuppressive treatments administered for RA, and shared environmental and genetic risk factors.^{15,17} At least two plausible mechanisms of carcinogenesis specified by IARC are likely involved in cancer risk in RA patients, whether related to the disease and or its treatment: chronic inflammation and immunosuppressive effects. It is plausible to consider that in a population of patients with an increased baseline risk of malignancy, drugs that affect immunologic pathways may further affect that risk and potentially impact cancer latency and the spectrum of associated cancers.

- **Time to onset (latency)**

Most neoplasms in adults are associated with a long latency period (years). Much information on time to cancer onset has been derived from studies of long-term cancer survivors exposed to radiation and chemotherapy who develop subsequent neoplasms. Notably, risk of subsequent neoplasms is affected not only by treatment-related factors (e.g., type of treatment, treatment dose, cumulative exposure, duration of exposure) but also by factors relevant to the general population, including host characteristics (e.g., age at exposure); hormonal, environmental and lifestyle factors; and genetic susceptibility.¹⁸ Radiation-related solid tumors among adults generally begin to emerge 10 years or more after exposure and risk persists for years.^{19,20,21} Treatment-related myeloid neoplasms (t-MNs), particularly acute myeloid leukemia (AML), are a well-recognized sequelae of radiation and chemotherapy exposure.^{22,23,24,25} Drugs classically associated with t-MNs include alkylating agents and topoisomerase inhibitors, and while classification of AML by these drug classes is impractical and no longer recommended due to patients frequently receiving agents from both classes, topoisomerase II inhibitor-associated AML is typically associated with shorter time to onset (median: 2-3 years) than alkylating agent-associated AML (4-7 years).^{22,23} Cytotoxic chemotherapy also has been associated with solid neoplasms, including cancers of the lung, stomach, bladder, breast, thyroid, and bone.^{21,26,27,28,29} With the exception of lung cancer, most solid tumor risks following cytotoxic chemotherapy exposure (second primary neoplasms) begins to increase above that in the general population five or more years after initial exposure, with risks varying by first primary cancer site, duration of therapy, cumulative exposure, other co-exposures and genetic factors.

Etoposide, a topoisomerase II inhibitor implicated in the development of a treatment-related neoplasm (AML), is associated with among the shortest latency periods reported for drug-induced neoplasms. Etoposide was approved in the U.S. for treatment of testicular cancer in 1983.³⁰ However, it was introduced in clinical trials in 1973 and was commercially available in Europe for several years prior to approval in the U.S.³¹ By 1984, etoposide had been evaluated for treatment of several tumor sites (e.g., lymphoma, acute leukemia, and cancers of the lung, breast, ovary, esophagus, colon and rectum, and kidney), with more than 1000 total patients exposed.³¹ Etoposide was shown to be mutagenic, embryotoxic, and teratogenic in cell culture and in animal models in the 1970s.^{32,33} At the time of approval, myelosuppression was identified as a dose-limiting toxicity, with no cumulative hematopoietic toxicity reported.³¹ Reports of AML following etoposide (often in combination with other agents) began to appear in the literature in the late 1980s and later.^{34,35,36} Thus, despite a short latency period characterizing AML related to etoposide, at the time of drug approval, AML was not recognized as a treatment sequelae.

While an in-depth review of carcinogenesis is beyond the scope of this assessment, points to be acknowledged include the multiple carcinogenic pathways involved in pharmaceutical-related

neoplasms; importance of duration of exposure; generally few associated cancer sites linked with specific pharmaceuticals, and for multiple cancer sites associated with a pharmaceutical or carcinogen, there is a plausible underlying mechanism(s) linking the multiple cancer sites; and a generally characteristic long latency period associated with tumorigenesis.^{7,37} Effects of age at exposure, co-exposures, and gene-environment interactions are also important considerations for risk assessments, but in randomized clinical trials, theoretically these factors would be balanced between treatment and placebo arms.

Neoplasms diagnosed in clinical studies of fezolinetant demonstrate a short latency period from time of drug exposure (less than 371 days), involve multiple anatomic sites, and are associated with higher cancer incidence than placebo across individual studies and pooled study data. While no concern for malignant neoplasms was noted in phase II studies, the duration of exposure was brief (12 weeks), thereby limiting comparisons with studies with exposures of longer duration (52 weeks). Given the multiplicity of cancer sites noted, it is difficult to implicate a mechanism by which various malignancies developed based on the mechanism of action of fezolinetant (NK3R antagonism). Unlike cyclosporine and JAK inhibitors that have been associated with cancers at multiple sites, fezolinetant is not recognized to cause chronic immunosuppression,^c and the treated population was not generally chronically immunosuppressed from drug therapy and/or underlying chronic inflammatory conditions (e.g., rheumatoid arthritis, inflammatory bowel disease).

While the incidence of neoplasms in women treated with fezolinetant is substantially higher than placebo (based on approximately 1000 women in each of the three study arms from the 52-week studies detailed in **Table 1**), the data have limitations which potentially affect various aspects of the cancer diagnoses. The primary concern is that cancer diagnoses may have been present prior to start of fezolinetant. The lack of source documentation on relevant risk factors (e.g., UV exposure), physical exam, laboratory studies, and imaging studies limits the assessment of cancer risks and causality. The assessment of neoplasms is complicated by numerous protocol deviations (not all of which were recorded) that suggest participants entered on study despite not meeting cancer screening eligibility criteria. Furthermore, apparent underreporting of past medical history (e.g., prior cancer history) is suggested based on review of Case Report Forms and this may have resulted from patient/investigator accidental omission (e.g., skin cancer removal) or underreporting of these procedures so that patients would not be excluded from the clinical trial. In addition, several patients had evidence of relevant exposures or family history that are strongly implicated in specific cancer types, such as skin cancers and UVR exposure, lung cancer and tobacco, breast cancer and genetic factors (breast cancer in a first degree relative). Lastly, one cannot exclude the possibility that drug exposure might contribute to future cancer risk (e.g., with additional follow-up time post-exposure) given the short follow-up time (approximately one year) in relation to typical cancer outcomes that develop over years.

Furthermore, the inability to establish incident cancers and small number of site-specific cancer cases in the trial made it impossible to reliably calculate cancer incidence in the fezolinetant

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trials. While different study populations and absence of many site-specific cancers in SEER, made it impossible to compare cancer incidence in the fezolinetant trials to SEER.

5 CONCLUSION

Based on this case review, the evidence for implicating fezolinetant in development of malignancy is inadequate and a causal association between fezolinetant exposure and neoplasm could not be established or refuted with the data provided by the Applicant. Postmarketing studies with cancer outcomes are generally long-term studies, given the latency period associated with most known carcinogens. In the case of fezolinetant, the cancer incidence in fezolinetant-exposed women (whether 30 mg or 45 mg dose) is increased above placebo and within approximately one year of exposure (short term follow-up). Although a plausible mechanism of carcinogenesis was not evident, the latency period associated with cancer development was unusually short relative to established carcinogens, and the spectrum of multiple neoplasms associated with one pharmaceutical is unusual, it is important to assess these findings in the context of the quality of data collection in the fezolinetant studies and the potential exposure of millions of women with a non-life-threatening indication for treatment.

6 RECOMMENDATIONS

Based on this case review, the evidence for implicating fezolinetant in the development of malignancy is weak and any causal association between fezolinetant exposure and neoplasms could not be established with certainty based on the data provided by the Applicant. This clinical information should be interpreted in the context of overall study quality as well as pre-clinical and pharmacologic data that may provide additional information on potential mechanisms by which fezolinetant might contribute to a carcinogenic process (e.g., initiator, promotor). Based on what we know today, we attribute the numeric imbalance in the clinical trials, which prompted this analysis, to most likely be a chance finding.

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8 APPENDICES

8.1 APPENDIX A. OVERVIEW OF COMPLETED VMS FEZOLINETANT CLINICAL STUDIES CONTRIBUTING TO POLLED ANALYSIS OF SAFETY

Study Number, Region(s) Involved, Location within CTD	Study Design	Study Population	Dosing Regimens, Number in Safety Set, and Formulation	Treatment Period
Phase 2				
ESN364_HF_204 Eur (Belgium) Module 5.3.5.1	Proof of Concept / randomized, multicenter, double-blind, placebo-controlled	Early postmenopausal participants suffering from VMS	Fezolinetant 90 mg bid n = 43 Placebo bid n = 44 Capsule	12-week
ESN364_HF_205 US Module 5.3.5.1	Randomized, multicenter, double-blind, dose-ranging, placebo-controlled	Postmenopausal participants suffering from VMS	Fezolinetant 15 mg bid n = 45 Fezolinetant 30 mg bid n = 43 Fezolinetant 60 mg bid n = 45 Fezolinetant 90 mg bid n = 44 Fezolinetant 30 mg qd n = 43 Fezolinetant 60 mg qd n = 45 Fezolinetant 120 mg qd n = 44 Placebo bid n = 43 Capsule	12-week
Phase 3				
2693-CL-0301 US, Canada and Europe Module 5.3.5.1	Randomized, multicenter, placebo-controlled, 12-week double-blind, followed by an active treatment extension period	Female participants suffering from moderate to severe VMS associated with menopause	Fezolinetant 30 mg qd n = 174 Fezolinetant 45 mg qd n = 173 Placebo qd n = 175 Placebo/fezolinetant 30 mg qd n = 76 † Placebo/fezolinetant 45 mg qd n = 76 † Tablet	52-week
2693-CL-0302 US, Canada and Europe Module 5.3.5.1	Randomized, multicenter, placebo-controlled, 12-week double-blind, followed by an active treatment extension period	Female participants suffering from moderate to severe VMS associated with menopause	Fezolinetant 30 mg qd n = 166 Fezolinetant 45 mg qd n = 167 Placebo qd n = 167 Placebo/fezolinetant 30 mg qd n = 76 † Placebo/fezolinetant 45 mg qd n = 75 † Tablet	52-week
2693-CL-0304 US, Canada and Europe Module 5.3.5.1	Randomized, multicenter, placebo-controlled, double-blind, 52-week long-term safety study	Female participants suffering from VMS associated with menopause	Fezolinetant 30 mg qd n = 611 Fezolinetant 45 mg qd n = 609 Placebo qd n = 610 Tablet	52-week

CTD: common technical document; US: United States; VMS: vasomotor symptoms.

8.2 APPENDIX B. SYNOPSIS AND REVIEWER ASSESSMENT OF NEOPLASM CASES

Select details of individual cases and reviewer assessments are included in this Appendix. In these case descriptions, reference to a potential role of fezolinetant in carcinogenesis refers to an initiating and/or promoting role.

ID (b) (6): Cutaneous squamous cell carcinoma (cSCC), nose

- Country: (b) (6)
- 65-year-old, white, non-Hispanic female
- Factors for consideration in risk assessment: Age, former smoker
- Placebo Days 1-83; fezolinetant 30 mg Days 84-281
- cSCC Day 146 (146 – 83 placebo days = 63 exposure-days)

Reviewer comment: No information was available from the Applicant on the screening visit physical exam of the skin, including signs of sun exposure and Fitzpatrick skin type [to assess susceptibility to ultraviolet radiation (UVR) exposure], thereby limiting this assessment. Exposure of the skin to UVR targeting DNA is the primary factor in skin cancer development.² Keratinocyte cancers [basal cell carcinoma (BCC) and SCC] are the most frequently observed malignancies in Caucasians, with solar UVR being the

predominant causative agent.³ Epidemiological data indicate that excessive or cumulative UVR exposure takes place over years and decades before the resulting malignancies arise.²

Potential risk factors for NMSC in this patient include age and former smoking status. Although there is no information on UVR exposure, this is an important risk that is ubiquitous to some degree, although duration and intensity of exposure varies among individuals. There is no indication that the participant had a past history of nonmelanoma skin cancer (NMSC). Based on the long latency and important role of UVR in NMSC and the limited number of fezolinetant exposure-days (63 days) proximal to the diagnosis of cSCC, this suggests that fezolinetant had an unlikely role in the development of the identified cSCC.

ID (b) (6): Atypical apocrine metaplasia of right breast

- Country: (b) (6)
- 62-year-old, white female
- Factors for consideration in risk assessment: Age, prior use of hormone replacement therapy (HRT; no other details) with hysterectomy in (b) (6) but no report of oophorectomy, and hot flashes since (b) (6) to ongoing; former smoker
- Placebo Day 1 (b) (6) - 84; fezolinetant 45 mg Days 85 (b) (6) - 281
- Atypical apocrine metaplasia with atypia diagnosed Day 95 (95 – 84 placebo days = 11 exposure-days)

Reviewer comment: No information was available from the Applicant on the screening visit physical exam nor the report and date of the baseline mammogram at/prior to study entry thereby limiting this assessment. However, apocrine metaplasia is a nonproliferative lesion typically associated with a breast cyst or inflammation. Nonproliferative lesions are typically not associated with increased risk of breast cancer. The additional description of “atypia” is uncertain with respect to breast cancer risk. There is limited information on breast cancer risk factors other than age, prior use of hormone replacement therapy (type and duration not specified), and smoking history. Based on the 11 days of exposure proximal to the diagnosis of atypical apocrine metaplasia, this suggests that fezolinetant was unlikely to have contributed to this nonproliferative lesion.

ID (b) (6): Breast cancer

- Country: (b) (6)
- 60-year-old, African American female with known family history of breast cancer in a first-degree relative (mother).

- Factors for consideration in risk assessment: Never smoker, no HRT (it is noted that health care provider advised against HRT due to family history of breast cancer). No report of oophorectomy (or hysterectomy); hot flashes since (b) (6) and amenorrhea since (b) (6)
- Placebo Days 1 ((b) (6)) - 85; fezolinetant 30 mg Days 86 – 214
- Day 236 (236 – 85 placebo days = 151 days; minus days 215-236 = 21 days; 151 – 21 = 130 exposure-days)
- On day 236 the patient complained of left breast tenderness and follow-up medical procedures revealed grade II invasive mammary carcinoma.

Reviewer comment: No information was available from the Applicant on the screening visit physical exam nor the report and date of the baseline mammogram at/prior to study entry thereby limiting this assessment. The patient's risk factors for breast cancer include age and family history of breast cancer in a first degree relative, but there is little other information that can be gleaned with regard to reproductive risk factors. The absence of HRT is a favorable finding as it does not contribute to increased breast cancer risk. Based on the limited exposure (130 days) proximal to the diagnosis of breast cancer this suggests that fezolinetant was unlikely to have contributed to the breast cancer risk.

ID (b) (6): cSCC (face)

- Country: (b) (6)
- 60-year-old, white, non-Hispanic female
- Fezolinetant 45mg Day 1 ((b) (6)) - Day 297 ((b) (6))
- Factors for consideration in risk assessment: Age, former smoker, prior history of BCC right foot (b) (6) (excision (b) (6)), solar lentigo (b) (6) to (b) (6).
- Day 25 laceration of face, treated with mupirocin and resolved Day 39.
- Day 104 ((b) (6)) diagnosis of cutaneous SCC (face).

Reviewer comment: No information was available from the Applicant on the screening visit physical exam of the skin, including additional signs of sun exposure and Fitzpatrick skin type (to assess susceptibility to UV exposure), thereby limiting this assessment. Exposure of the skin to UVR targeting DNA is the primary factor in skin cancer development.² Keratinocyte cancers (BCC and SCC) are the most frequently observed malignancy in Caucasians, with solar UV radiation being the predominant causative agent.³ Epidemiological data indicate that excessive or cumulative UV exposure takes place over years and decades before the resulting malignancies arise.²

This patient had history of BCC and solar lentigo (present for 20 years) supporting a history of prior UVR exposure, a shared risk factor for cSCC. In addition, it is uncertain whether the patient's laceration on Day 25 may have led to the initial detection of the cSCC that was subsequently treated (Day 104), thereby raising the possibility that the SCC may have been present on Day 25. Based on the limited exposure to fezolinetant

(conservatively estimated at 130 days) proximal to the diagnosis of cSCC, fezolinetant was unlikely to have contributed to the development of this cSCC.

ID (b) (6): Schwannoma (mediastinum)

- Country: (b) (6)
- 58 white Hispanic Female
- Placebo Day 1-366
- Pt had a fall with rib fracture (Day 281); during work up (Day 272), a mediastinal cyst was found and excised on day 319
- Day 319: Glandular schwannoma with focal squamous metaplasia, and cystic and ancient changes. There were four negative lymph nodes. The tumor was adjacent to several peripheral and well circumscribed by a capsule

Reviewer comment: Of note, the history indicates that a mediastinal cyst was discovered during work-up of a rib fracture sustained after patient fell on study day 281. The mediastinal cyst is stated to have been detected on Day 272, and the Applicant indicates that this day preceded the fall due to imputation of the date (only month and year were available).

Schwannomas (or neurilemmomas) are the most common tumor of peripheral nerves in adults.⁴ Most are incidentally diagnosed, slow growing, encapsulated, solitary tumors that, aside from some atypical varieties, rarely undergo malignant transformation. Longstanding schwannomas can develop degenerative changes that were previously referred to as “ancient schwannomas”.⁵ The clinical presentation in this patient supports that the schwannoma was as an incidental finding discovered on imaging when the patient presented after a fall. The pathology of the schwannoma included localized disease (negative lymph nodes) and “ancient changes,” the latter supporting that the schwannoma had been a longstanding abnormality. This patient received placebo, and the clinical and pathologic description of the schwannoma does not support that an (approximate) 280-day course of placebo had a role in the development of the schwannoma.

ID (b) (6): cSCC, forehead

- Country: (b) (6)
- 56 African American female
- Placebo Day 1 ((b) (6)) - 361
- Factors for consideration in risk assessment: Age, past history of BCC 2010; never smoker
- Day 192: cSCC (forehead)

Reviewer comment: No information was available from the Applicant on the screening visit physical exam of the skin, including additional signs of sun exposure and Fitzpatrick

skin type (to assess susceptibility to UV exposure), thereby limiting this assessment. Exposure of the skin to UVR targeting DNA is the primary factor in skin cancer development.² Keratinocyte cancers (BCC and SCC) are the most frequently observed malignancy in Caucasians, with solar UVR being the predominant causative agent.³ Epidemiological data indicate that excessive or cumulative UV exposure takes place over years and decades before the resulting malignancies arise.² Women of African American descent typically have Fitzpatrick skin type III or higher, and lower incidence of BCC and SCC than Caucasian women.⁶ This patient developed cSCC after 192 days of receiving placebo. Based on the generally long latency associated with BCC and SCC, the patient's age, and history of BCC, it is more likely that UVR exposure contributed to the development of cSCC and less likely that a 192-day course of placebo contributed to the development of this cSCC.

ID (b) (6): Endometrioid adenocarcinoma (stage IA)

- Country: (b) (6)
- 51 white, non-Hispanic female
- Fezolinetant 30 mg Day 1 ((b) (6)) – Day 357; 357 exposure-days
- Current smoker; no prior HRT; BMI at entry 29.4
- Screening (Day -28) endometrial biopsy diagnoses by 3 pathologists: 1) limited surface endometrium; 2) no diagnosis (tissue unsatisfactory for diagnosis, too scant for reliable diagnosis); 3) limited surface endometrium, inactive. TVU at baseline on day -16 revealed an endometrial thickness of 1.43 mm.
- Day 370 Endometrioid adenocarcinoma, stage IA
- On day 368, the post-baseline TVU revealed an endometrial thickness of 3.777 mm. On the same day, an endometrial biopsy performed revealed the following diagnoses by 3 pathologists: 1) malignant, carcinoma/endometrioid adenocarcinoma is present; 2) limited surface endometrium; inactive/atypical glandular epithelium with abundant acute inflammation, favor endocervical microglandular hyperplasia; however, cytologic atypia and mitosis raise possibility of carcinoma; 3) malignant, carcinoma/adenocarcinoma with mucinous features, possibly endocervical but can't exclude uterine origin; final diagnosis of malignant, carcinoma.

Reviewer comment: No information was available from the Applicant on the screening visit physical exam, specifically in relation to the pelvic exam (no abnormality was recorded). The results of the endometrial biopsy performed at the screening visit (Day -28) were nondiagnostic due to limited specimen available for review. As such, it is not possible to determine if the endometrial tumor was present at screening but not detected due to the inadequacy of the specimen. This finding raises the question of whether the patient met entry criteria for the study given the specification that “the endometrial biopsy obtained at screening must be considered evaluable.” This patient is not listed as a major protocol deviation for study 2693-CL-0304 (Mid-Cycle Appendix 4). In addition to inadequate tissue sampling at screening, this patient's risks for uterine cancer include

age and overweight status (BMI 29.4; although duration of elevated BMI is unknown). It is also noted that this patient had a normal hemoglobin and hematocrit from Day -32 (screening) through the end of study (“Day 390/LD+23”) [“Table A1” below]. However, her red blood cell count was low ($4.0 \times 10^{12}/L$) at screening and remained low-normal or low throughout the study period. This finding supports an iron depleted (but not iron deficient) state at study entry, consistent with chronic blood loss. While there are too few details to implicate longstanding iron depletion related to undetected uterine cancer, the findings are not inconsistent. Despite 357 exposure-days, this timeframe is short for the generally lengthy carcinogenic process. While the role of fezolinetant cannot be definitively excluded, this patient’s nondiagnostic endometrial biopsy at study entry confounds the entire assessment, and the presence of decreased red blood cell counts supports the diagnosis being present at study entry (screening).

Table A1. Complete Blood Count Parameters and Normal Ranges for Participant (b) (6) (Study 2693-CL-0304)

Date of examination (Day)	Hemoglobin (g/L)	Hematocrit (fraction of 1)	Red Blood Cell Count ($10^{12}/L$)	Reticulocyte Count ($10^9/L$)
(b) (6) (-32)	138	0.4	4.0L	83
(1)	142B	0.42B	4.1B	76B
(25)	145	0.41	4.2	72
(57)	137	0.41	4.1	89
(85)	143	0.43	4.2	84
(112)	150	0.44	4.4	75
(141)	148	0.42	4.2	68
(169)	137	0.41	4.0L	81
(204)	146	0.43	4.2	103
(225)	138	0.42	4.1	75
(256)	141	0.41	4.0L	80
(278)	136	0.38	4.0L	90
(309)	145	0.43	4.3	90
(337)	140	-	4.1	72
(368/LD+1)	152	0.44	4.4	83
(390/LD+23)	148	0.4	4.2	80

Reference ranges are presented for the appropriate age group of the participant (51 years).

Hemoglobin: 116-164 g/L; hematocrit: 0.34-0.48 fraction of 1; red blood cell count: $4.1-5.6 \times 10^{12}/L$; reticulocyte count: $30-120 \times 10^9/L$.

B: baseline; L: below central laboratory range; LD: last dose.

Source: Study 2693-CL-0304 CSR, Appendix 10.2.8.1.1.1.1, 10.2.8.1.1.1.5 and 10.1.10.1

ID (b) (6): Endometrial adenocarcinoma (stage 1)

- Country: (b) (6)
- 58-year-old, white, non-Hispanic, female
- Never smoker; no prior HRT; BMI 32.2 at entry
- Fezolinetant 45mg Day 1 (b) (6) – Day 107 (discontinued due to fatigue and anxiety); 107 exposure-days

- Day -30: Endometrial biopsy performed at screening revealed the following diagnoses by 2 pathologists: 1) inactive; 2) limited surface endometrium, atrophy. A TVU at baseline on day -20 revealed an endometrial thickness of 5.49 mm.
- On Day 112 the patient underwent early discontinuation protocol assessments. On day 122 (15 days after stopping the study drug), the early discontinuation post-baseline TVU revealed endometrial polyp and a derived endometrial thickness of 2.295 mm. An endometrial biopsy was not performed at the early discontinuation visit due to subject refusal.
- Day 247 repeat TVU confirmed the presence and growth of the polyp; a derived endometrial thickness of 2.355 mm was reported. A hysteroscopy was performed on day 309 to remove the endometrial polyp; no malignancy was visualized during the hysteroscopy. The event of uterine polyp was considered resolved with sequelae on day 309. The polyp was biopsied, and the biopsy report showed endometrial adenocarcinoma (stage 1).

Reviewer comment: This patient's risks for uterine carcinoma include her age and elevated BMI (32.2; obese), although duration of elevated BMI is unknown. No information was available from the Applicant on the screening visit physical exam, specifically in relation to the pelvic exam (no abnormality was recorded). The results of the TVU performed on Day -20 revealed an endometrial thickness of 5.49 mm, reflecting an abnormal result. The question arises as to whether this patient was eligible for study (exclusion criterion: "Has an unacceptable result from the TVU assessment at screening"), or at a minimum, whether this abnormal finding should have been evaluated prior to considering eligibility for study participation. This participant's hemoglobin, hematocrit, red blood cell number, and retic count did not demonstrate any values outside the normal range.

In total, this patient had 107 fezolinetant exposure-days, which is an unusually short time frame for the carcinogenic process. Although her ultimate diagnostic evaluation was delayed until Day 309, an abnormality on TVUS was detected on Day 122 (endometrial polyp), a short interval for tumor development. This case is confounded by the abnormal endometrial thickness noted on TVUS prior to study entry, given that evaluation of this abnormality may have yielded a diagnosis of endometrial polyp with endometrial adenocarcinoma prior to study entry. Notably, this case is not included in the list of protocol deviations (Mid-Cycle Appendix 4, Major Protocol Deviations with Description: 2693-CL-0304).

ID (b) (6): Endometrial adenocarcinoma

- Country: (b) (6)
- 50-year-old, white, non-Hispanic, female
- Fezolinetant 45 mg Day 1 ((b) (6)) - Day 74
- Never smoker; no prior HRT; BMI 27.4; amenorrhea since (b) (6)
- Uterine hemorrhage started on exposure day 29, carcinoma diagnosis day 79 (but uterine abnormalities present pre-exposure)

- Day -33: TVU at baseline revealed an endometrial thickness of 3.545 mm. An endometrial biopsy performed at screening 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 crowded back-to-back atypical endometrial glands, consistent with atypical complex hyperplasia/endometrioid intraepithelial neoplasia; the cells are large and plump; 3) complex hyperplasia without atypia.
- Day 29 - 38 uterine hemorrhage
- Day 38: Due to the event of uterine hemorrhage, an endometrial biopsy was performed 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.
- Day 54 - 61 uterine hemorrhage
- Day 79: Endometrial biopsy revealed the following diagnoses by 3 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. Based on the pathological diagnosis, the final diagnosis was complex hyperplasia with atypia.

Reviewer comment: Based on the exclusion criterion - “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,” this patient did not meet eligibility criteria for study. The presence of abnormal findings on endometrial biopsy at the screening visit, makes it unlikely that fezolinetant contributed to the development of this endometrial adenocarcinoma. This case is not included in the list of protocol deviations (Mid-Cycle Appendix 4, Major Protocol Deviations with Description: 2693-CL-0304).

ID (b) (6): Colon cancer (right colon)

- Country: (b) (6)
- 52-year-old, white, non-Hispanic, female; BMI 34
- Current smoker
- Fezolinetant 45mg, Day 1 (b) (6) – Day 234
- Hypertension, hypercholesterolemia, gastroesophageal reflux disease, diabetes mellitus, chronic obstructive pulmonary disease (since (b) (6)). No report of hysterectomy/oophorectomy; amenorrhea since (b) (6).
- Cologuard (fecal occult blood test) – positive day 185 (185 exposure-days).
- Colon cancer: Day 233 colonoscopy (Day 234 path available).
- Day 246: right hemicolectomy showed invasive moderately differentiated colon carcinoma. The cancer invaded the muscularis propria with peritumoral tumor budding arising in a

tubulovillous adenoma with high grade dysplasia. The proximal and distal mucosal margins were negative for malignancy or adenomatous change. A total of 22 peri-colonic lymph nodes were negative for malignancy.

Reviewer comment: At screening (Day – 49) Hgb 141 g/L and on Day 1 Hgb 129 g/L. While the hemoglobin fluctuates slightly throughout the study period, on day 57 despite absence of anemia, hemoglobin is 20 g/l lower than at screening visit and on Day 226 there is evidence of anemia (hemoglobin 112 g/L, low). The hemoglobin pattern supports that the patient may have had intermittent blood loss, e.g., from the gastrointestinal tract.

There is no information on whether screening examination included rectal exam or testing for occult blood. Although the diagnosis of colon cancer was established on Day 247, the positive fecal occult blood testing on Day 185 (with 185 exposure-days) suggests that this finding was a manifestation of the underlying malignancy. In addition, despite fluctuation in hemoglobin, by Day 57 a 20 g/L decline in hemoglobin was noted (**Table A2**), potentially prompting the subsequent fecal occult blood test. The long latency usually associated with colon carcinogenesis and limited exposure time to detection of positive fecal blood testing suggest that the patient's colon cancer may have been present at study entry and makes it less likely that fezolinetant contributed to the development of this colon carcinoma.

Table A2. Complete Blood Count Parameters and Normal Ranges for Participant (b) (6) (Study 2693-CL-0304)

Date of examination (Day)	Hemoglobin (g/L)	Hematocrit (fraction of 1)	Red Blood Cell Count (10 ¹² /L)	Reticulocyte Count (10 ⁹ /L)
(b) (6) (-49)	141	0.42	5.1	70
(1)	129B	0.39B	4.7B	74B
(50)	135	0.39	4.9	90
(57)	120	0.36	4.5	77
(85)	138	0.4	5.1	81
(114)	137	0.41	5.0	82
(143)	134	0.4	4.8	68
(169)	140	0.42	5.0	60
(199)	126	0.38	4.7	103
(226)	112L	0.35	4.3	92

Reference ranges are presented for the appropriate age group of the participant (52 years).

Hemoglobin: 116-164 g/L; hematocrit: 0.34-0.48 fraction of 1; red blood cell count: 4.1-5.6 x 10¹²/L; reticulocyte count: 30-120 x 10⁹/L.

B: baseline; L: below central laboratory range.

Source: [Study 2693-CL-0304 CSR, Appendix 10.2.8.1.1.1.1](#), [10.2.8.1.1.1.5](#) and [10.1.10.1](#)

ID (b) (6): Colon cancer (sigmoid colon)

- Country: (b) (6)
- 55-year-old, white, non-Hispanic, female; BMI 31

- Fezolinetant 45mg, Day 1 ((b) (6)) – Day 251 (interrupted Day 111 – Day 194 due to COVID = 83 days); 251 – 83 = 168 total exposure-days
- Current smoker (1 pack/day); no hysterectomy reported; oophorectomy (b) (6); amenorrhea since (b) (6)
- Day 24: flatulence (Day 128 resolved) and diarrhea (Day 131 resolved)
- Day 197: flatulence (2nd event)
- Day 209: anal incontinence
- Day 250: stopped diabetes medications due nausea/vomiting, developed diabetic ketoacidosis
- Day 252: admitted to hospital with elevation in glucose
- Day 253: CT abdomen revealed thickened sigmoid colon, no obstruction
- Day 260: endoscopy with tattooing, 18 cm sigmoid mass, biopsies confirmed sigmoid tumor
- Day 301: laparoscopic low anterior resection for carcinoma of sigmoid colon with obstruction

Reviewer comment: There is no information on whether screening examination included rectal exam or testing for occult blood. Despite colon cancer being detected on imaging on Day 253, a retrospective review of events suggests that sigmoid cancer manifestations began as early as Day 24 with flatulence and diarrhea, although these symptoms were attributed to fezolinetant. This patient had interruption in fezolinetant between Day 111 and Day 194 due to the COVID-19 pandemic, and flatulence and diarrhea persisted despite drug interruption, with flatulence resolving on Day 128 and diarrhea resolving on Day 131. In addition, there is a notable decrease in hemoglobin that is documented on Day 170, and on Day 177 anemia is noted and persists through Day 223 (last value available). It is noted that NK3 receptors are also expressed in the gut, and treatment with fezolinetant may have unmasked the colon cancer with precipitation of associated gastrointestinal symptoms.⁷ In combination, these findings support that colon cancer was present at study initiation and that fezolinetant was unlikely to have contributed to the carcinogenic process, based on limited exposure time.

ID (b) (6): Chronic lymphocytic leukemia (CLL)

- Country: (b) (6)
- 51-year-old African American female; never smoker
- Fezolinetant 30mg, Day 1 ((b) (6)) – Day 227 (227 exposure-days)
- Day 225: CLL diagnosis
- Day 1: WBC 14.3 with 11,150 ALC (these were the lowest levels); the mild leukocytosis (17-23K) and lymphocytosis (14K-21K) persisted throughout the study period. Day 22 WBC 22.9 and ALC 21,070

Reviewer comment: This patient had evidence of lymphocytosis with an absolute lymphocyte count >5000 sustained over >3 months (**Table A3**). This finding is consistent with a diagnosis of CLL. Leukocytosis is not required to establish a diagnosis of CLL, but this patient also manifested persisted leukocytosis throughout the study period.

While flow cytometry is needed to confirm the diagnosis of CLL, the persistent lymphocytosis (with leukocytosis) is the abnormality that would prompt subsequent flow cytometry testing. The laboratory data support a diagnosis of CLL being present on Study Day 1, making it unlikely that fezolinetant had a role in the development of CLL.

Table A3. Select hematology laboratory tests for case (b) (6)

Selected Hematology Laboratory Tests							
Study Day/ Date	Hemoglobin (g/L)	Leukocytes (10 ⁹ /L)	Neutrophils, Segmented (10 ⁶ /L)	Lymphocytes (10 ⁶ /L)	Monocytes (10 ⁶ /L)	Eosinophils (10 ⁶ /L)	Basophils (10 ⁶ /L)
1/ (b) (6)	137 (116 - 164)	14.3 H (3.8 - 10.7)	3000 (1960 - 7230)	11150 H (910 - 4280)	140 (120 - 920)	0 (0 - 570)	0 (0 - 200)
56/ (b) (6)	135 (116 - 164)	21.3 H (3.8 - 10.7)	3620 (1960 - 7230)	16800 H (910 - 4280)	210 (120 - 920)	0 (0 - 570)	0 (0 - 200)
84/ (b) (6)	131 (116 - 164)	17.5 H (3.8 - 10.7)	2390 (1960 - 7230)	14610 H (910 - 4280)	260 (120 - 920)	100 (0 - 570)	140 (0 - 200)
112/ (b) (6)	128 (116 - 164)	17.2 H (3.8 - 10.7)	2030 (1960 - 7230)	14810 H (910 - 4280)	220 (120 - 920)	90 (0 - 570)	40 (0 - 200)
140/ (b) (6)	135 (116 - 164)	18.6 H (3.8 - 10.7)	1670 L (1960 - 7230)	16000 H (910 - 4280)	190 (120 - 920)	190 (0 - 570)	0 (0 - 200)
168/ (b) (6)	141 (116 - 164)	21.7 H (3.8 - 10.7)	1520 L (1960 - 7230)	19330 H (910 - 4280)	220 (120 - 920)	0 (0 - 570)	0 (0 - 200)
228/ (b) (6)	129 (116 - 164)	22.9 H (3.8 - 10.7)	1600 L (1960 - 7230)	21070 H (910 - 4280)	230 (120 - 920)	0 (0 - 570)	0 (0 - 200)
Normal reference ranges are in parentheses. NR: not reported. H: above laboratory normal range; L: below laboratory normal range.							

Source: Study Report 2696-CL-0304 POP4.

ID (b) (6): Head and neck cancer, SCC (oral cavity)

- Country: (b) (6)
- 52-year-old, white, non-Hispanic, female; BMI 27.3
- Never smoker
- Fezolinetant 45 mg, Day 1 (b) (6) – Day 137 (137 exposure-days)
- Day 47: patient was evaluated for oral abscess (treated with antibiotics, oral rinse, hydrocodone/paracetamol).
- Day 138: SCC of the oral cavity (with involvement of left mandible) confirmed with biopsy and MRI. Based on the available information, this patient had a single primary oral cavity cancer, with apparent local extension to bone. The left mandible tumor was treated with surgical resection.

Reviewer comment: Although this patient is a never smoker (a risk factor for cancers of the head and neck), oropharyngeal cancers are also etiologically linked with human papilloma virus (HPV). Assuming this is an HPV-related cancer, this patient would be staged as having a T4 lesion based on involvement of the mandible, making the lesion at minimum stage III. This locally advanced stage at presentation suggests that the neoplastic process had been ongoing likely prior to fezolinetant exposure. This is further supported by the latency period typically associated with HPV-related cancers, with time from HPV exposure to carcinoma of >10 years.⁸ Even if one excludes the possibility of HPV-related oral cancer, the very short exposure period of 47 days (or conservatively 137 days) makes it unlikely that fezolinetant contributed to risk of this oral cavity cancer.

ID (b) (6): Non-small cell lung cancer (NSCLC), poorly differentiated, with liver metastases

- Country: (b) (6)
- 65-year-old, white, non-Hispanic, female; BMI 21.6
- Fezolinetant 45mg, Day 1 ((b) (6)) – Day 72 (72 exposure-days)
- Current smoker (15 cigarettes/day); family history of breast cancer
- Day 72 presented with 2-week history of pain in the upper abdomen (day 72 – 14 days = 58 exposure-days at start of symptoms) with nausea and vomiting starting the day before hospitalization.
- Day 72 CXR and CT chest/abdomen demonstrated a lower lung nodule and innumerable liver metastases. Biopsy of the liver confirmed a diagnosis of metastatic poorly differentiated NSCLC.
- Day 78: CT chest with contrast showed postoperative changes of the right apex, small right pleural effusion with sub-segmented atelectasis, centrilobular emphysematous changes, innumerable hepatic lesions, and suspected metastatic disease.
- GGTP and alkaline phosphatase remained consistently elevated throughout the study, from Day -32 (screening) through Day 58.

Reviewer comment: This patient’s past medical history includes ongoing pain (generalized body aches), chronic low back pain, hyperlipidemia, and tubal ligation. There is no indication of other surgical procedures. However, the CT scan of the lung from Day 78 describes “post-operative changes of the right apex” yet there is no mention of prior thoracic surgery. It is unknown if the surgery was undertaken for a benign or malignant process. In this 65-year-old smoker, the concern is whether the patient may have had a prior lung cancer resected and if so, whether the current NSCLC diagnosis reflects metastatic disease related to a prior diagnosis or a second primary NSCLC (distinct primary cancers). This question is not resolvable with the available information but suggests that the study Case Report Forms may be incomplete (underascertainment of information at study entry), thereby limiting a causality assessment. This patient is a smoker and while duration of tobacco abuse is unknown, the emphysematous changes

noted on CT chest would suggest that tobacco may have been a chronic exposure. A prior diagnosis of lung cancer would further increase her risk of another primary lung cancer (or metastatic disease from the first primary). This patient had a short exposure to fezolinetant making it less likely that it played a role in the etiology of the present NSCLC diagnosis. The presence of abnormal alkaline phosphatase (and GGTP) from time of screening visit (Day-32) to Day 58 (last values available), raise the possibility that metastatic liver disease was present prior to fezolinetant exposure, further decreasing the likelihood that fezolinetant had a role in this carcinogenic process.

ID (b) (6): BCC, skin (chest, right shoulder)

- Country: (b) (6)
- 63-year-old, white, non-Hispanic, female
- Past medical history includes BCC with onset (b) (6) - “recovered” (b) (6); former smoker
- Factors for consideration in risk assessment: Age, history of at least one prior BCC, former smoker
- Fezolinetant 30mg, Day 1 ((b) (6)) – Day 364
- Day 239 BCC, which upon microscopic diagnosis included solar keratosis (chest) and BCC right shoulder

Reviewer comment: No information was available from the Applicant on the screening visit physical exam of the skin, including signs of sun exposure and Fitzpatrick skin type (to assess susceptibility to UV exposure), thereby limiting this assessment. Exposure of the skin to UVR targeting DNA is the primary factor in skin cancer development.² Keratinocyte cancers (BCC and SCC) are the most frequently observed malignancy in Caucasians, with solar UVR being the predominant causative agent.³ Epidemiological data indicate that excessive or cumulative UV exposure takes place over years and decades before the resulting malignancies arise.²

This patient has risks for BCC, most importantly at least one prior BCC with onset >20 years in the past, age, and former tobacco use. The patient is noted to have developed two BCCs, but pathology reports indicate that the chest lesion was consistent with solar keratosis and there was only one BCC identified (right shoulder). The presence of solar keratosis (marker of chronic photodamage of the skin) further supports a history of UV exposure. While a role for fezolinetant exposure over 239 days cannot be excluded, the patient’s past history of BCC and other UV-related skin lesion suggest that a role for fezolinetant in carcinogenesis is less likely.

ID (b) (6): cSCC (left cheek)

- Country: (b) (6)
- 56-year-old, white, non-Hispanic, female

- Never smoker
- Factors for consideration in risk assessment: age
- Fezolinetant 30mg Day 1 ((b) (6)) – Day 366 (186 exposure-days)
- Day 186 SCC, left cheek
- Day 197 actinic keratoses

Reviewer comment: No information was available from the Applicant on the screening visit physical exam of the skin, including signs of sun exposure and Fitzpatrick skin type (to assess susceptibility to UV exposure), thereby limiting this assessment. Exposure of the skin to UV radiation (UV) targeting DNA is the primary factor in skin cancer development.² Keratinocyte cancers (BCC and SCC) are the most frequently observed malignancy in Caucasians, with solar UVR being the predominant causative agent.³ Epidemiological data indicate that excessive or cumulative UV exposure takes place over years and decades before the resulting malignancies arise.² This patient had evidence of SCC of the left cheek after 186 fezolinetant exposure-days and actinic keratosis (also referred to as solar keratosis and a marker of chronic photodamage of the skin) after 197 exposure days. In combination, these findings suggest a role for UVR exposure as a risk factor for SCC, and the relatively limited exposure time to fezolinetant makes it a less likely culprit.

ID (b) (6): In situ malignant melanoma, skin (right sole)

- Country: (b) (6)
- 56-year-old, white, non-Hispanic, female
- Never smoker
- Fezolinetant 45mg, Day 1 ((b) (6)) – Day 364; therapy interruption Day 33 – Day 75 = 42 days; exposure days prior to event: 97 – 42 = 55
- Day 97 malignant melanoma, in situ, right sole; another lesion close to the melanoma was removed as a precaution (benign), full body skin exam did not reveal other lesions.

Reviewer comment: No information was available from the Applicant on the screening visit physical exam of the skin, including signs of sun exposure and Fitzpatrick skin type (to assess susceptibility to UV exposure), thereby limiting this assessment. Exposure of the skin to UVR targeting DNA is the primary factor in skin cancer development.² Epidemiological data indicate that excessive or cumulative UVR exposure takes place over years and decades before the resulting cutaneous malignancies arise.² In this case, the patient developed malignant melanoma in situ in a typically sun unexposed site (sole of foot), raising the question of whether there may have been an underlying immunodeficiency (no such indication from information on CRF) or genetic predisposition. Although a role for fezolinetant cannot be excluded, the limited exposure of 55 days, makes this an unlikely contributor to the development of the in-situ melanoma.

ID (b) (6): Papillary apocrine metaplasia (right breast)

- Country: (b) (6)
- 49-year-old, white, Hispanic, female
- Never smoker; no prior HRT; BMI 22.2
- Fezolinetant 30mg Day 1 ((b) (6)) – Day 363
- PMH: uterine leiomyoma 2003 to ongoing; menopause (b) (6)
- Day 231: Benign microcysts with papillary apocrine metaplasia of the right breast

Reviewer comment: Papillary apocrine metaplasia is a benign, nonproliferative lesion of the breast, and breast cysts are common in pre-, peri, and postmenopausal women, with a peak incidence between 35-50 years of age.⁹ Simple cysts are bland or apocrine epithelium-lined, fluid-filled, round or oval structures that are thought to occur secondary to obstructed ducts.⁹ Clustered microcysts are a part of the spectrum of benign cystic change of the breast.⁹ Cysts are hormonally sensitive and can fluctuate with the menstrual cycle in premenopausal women. They are more common in postmenopausal women on HRT but also common in postmenopausal women not on HRT.⁹ The natural history of most cysts is to develop and regress. Asymptomatic breast cysts have been reported to spontaneously regress in more than half of cases at 1-year, nearly two-thirds of cases at 2 years and nearly 90% at 5 years.¹⁰

No information was available from the Applicant on the screening visit physical exam nor the report and date of the baseline mammogram at/prior to study entry thereby limiting this assessment. In addition, a radiographically “benign” finding at screening might have been considered as not a “clinically significant mammographic finding” (per inclusion criteria) and therefore not detailed in the patient record. Given the propensity of simple cysts to regress or remain stable over time, it would be important to determine if prior breast imaging had evidence of “benign findings” (e.g., cysts). Although it is plausible that this patient may not have had prior breast imaging based on age <50 years; however, it is presumed that she would have had a mammogram in the 12 (or 9) months prior to study entry in order to meet eligibility criteria. In the absence of comparator imaging, it is not possible to exclude a role for fezolinetant in the development of the reported benign breast finding after 231 exposure-days. However, since benign cysts do not predispose to malignancy (assuming correct radiologic interpretation of findings), the role of fezolinetant in this non-neoplastic process is not applicable.

ID (b) (6): Keratoacanthoma, skin (right tibia)

- Country: (b) (6)
- 55-year-old, white, non-Hispanic, female
- Never smoker
- Fezolinetant 45 mg Day 1 ((b) (6)) – Day 281

- Contact dermatitis (poison ivy), right shin: Day 215
- Keratoacanthoma, right tibia: Day 213, excision Day 313

Reviewer comment: Keratoacanthoma is a low-grade, rapidly growing tumor that originates in the pilosebaceous glands. It is histologically indistinguishable from (and likely a variant of) well-differentiated cutaneous squamous cell carcinoma (SCC) but has a distinct clinical behavior based on its ability to spontaneously regress.

Keratoacanthoma may occur as part of a hereditary syndrome (e.g., Muir-Torre syndrome), or it can occur sporadically (acquired). Risk factors for sporadic keratoacanthoma include a prior history of keratinocyte cancers, exposure to UVR, acquired or inherited immunodeficiency, cutaneous trauma (i.e., surgery, laser therapy, cryotherapy), occupational exposure to tar and other chemical carcinogens, exposure to drugs that affect the cell-cycle, or smoking.

No information was available from the Applicant on the screening visit physical exam of the skin, including signs of sun exposure and Fitzpatrick skin type (to assess susceptibility to UV exposure), thereby limiting this assessment. Exposure of the skin to UVR targeting DNA is the primary factor in skin cancer development.² There is limited information to assess risks for keratoacanthoma in this patient and it is unclear if detection was affected by the overlapping history of poison ivy (e.g., detection bias, underlying local inflammation). A role for fezolinetant (213 exposure days) cannot be excluded based on the limited information available.

ID (b) (6): Pulmonary hamartoma

- Country: (b) (6)
- 56-year-old, white, non-Hispanic, female
- Current smoker: ½ pack cigarettes/day
- Fezolinetant 45 mg Day 1 ((b) (6)) – Day 353

On an unspecified day, the patient had a lung screening test which revealed a neoplasm in the central lobe of the right lung. On Day 334, a PET-CT confirmed presence of the lesion and histology (date unspecified) was pulmonary hamartoma. On Day 353, the last dose of fezolinetant was administered (after the investigator reported a serious TEAE of lung neoplasm).

Reviewer comment: The World Health Organization defines pulmonary hamartomas as “benign mesenchymal neoplasms with variable amounts of at least two mesenchymal elements and entrapped respiratory epithelium.”¹¹ However, there remains uncertainty in the literature as to whether pulmonary hamartomas are neoplasms or malformations, but there is consensus that these are not congenital lesions.¹² Among the five subtypes of congenital pulmonary airway malformations, Type I lesions have been reported to undergo malignant transformation rarely, but an analogous finding is not reported for pulmonary hamartomas.^{11,12} Excision of pulmonary hamartomas is often therapeutic. Left untreated, hamartomas continue to increase in size “very slowly” and rarely cause significant morbidity.¹²

Pulmonary hamartoma was incidentally noted on a lung screening test, which is presumed to have been completed while patient was taking fezolinetant. There is no information on the size or appearance of the lesion detected on initial pulmonary imaging or PET-CT. The incidental nature of this finding suggests that the patient was asymptomatic from the pulmonary lesion. However, based on this information alone it is not possible to determine the length of time the lesion may have been present and one would need to compare findings on chest imaging fezolinetant (if available) prior to start of fezolinetant to determine if the lesion had been present previously. Based on the slow growing nature characterizing pulmonary hamartomas, it seems unlikely that this lesion would develop in less than one year and grow to a sufficiently large size to be detected on chest imaging (unknown if chest x-ray or CT imaging), but additional information is needed to make an assessment.

8.3 APPENDIX REFERENCES

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DAVID G MOENY
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**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: February 2, 2023

To: Samantha Bell, Regulatory Project Manager, Division of Urology,
Obstetrics, and Gynecology (DUOG)

Theresa H. Van Der Vlugt, Clinical Reviewer, DUOG

Regina R. Zopf, Clinical Reviewer, DUOG

From: Elvy Varghese, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: James Dvorsky, Team Leader, OPDP

Subject: OPDP Labeling Comments for VEOZAH™ (fezolinetant) tablets, for oral
use

NDA: 216578

Background:

In response to DUOG's consult request dated July 1, 2022, OPDP has reviewed the proposed Prescribing Information (PI), Patient Package Insert (PPI), and carton and container labeling for the original NDA submission for VEOZAH™ (fezolinetant) tablets, for oral use (Veoza).

PI/PPI:

OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on January 20, 2023, and our comments are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed for the proposed PPI/Medication Guide/IFU, and comments were sent under separate cover on January 27, 2023.

Carton and Container Labeling:

OPDP's review of the proposed carton and container labeling is based on the draft labeling submitted by the sponsor to the electronic document room on December 12, 2022, and our comments are provided below.

Thank you for your consult. If you have any questions, please contact Elvy Varghese at Elvy.Varghese@fda.hhs.gov.

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ELVY M VARGHESE
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**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: January 27, 2023

To: Samantha Bell
Regulatory Project Manager
Division of Urology, Obstetrics, and Gynecology (DUOG)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Sharon W. Williams, MSN, BSN, RN
Senior Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Elvy Varghese, PharmD.
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Patient Package Insert (PPI)

Drug Name (established name): VEOZAH (fezolinetant)

Dosage form: tablets, for oral use

Application Type/Number: NDA 216578

Applicant: Astellas Pharma US, Inc.

1 INTRODUCTION

On June 22, 2022, Astellas Pharma US, Inc. submitted for the Agency's review an Original New Drug Application for VEOZAH (fezolinetant) tablets, for oral use. The purpose of the submission is to seek approval for the proposed treatment of moderate and severe vasomotor symptoms (VMS) associated with menopause.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Urology, Obstetrics, and Gynecology (DUOG) on July 1, 2022, for DMPP and OPDP to review the Applicant's proposed PPI for VEOZAH (fezolinetant) tablets, for oral use.

2 MATERIAL REVIEWED

- Draft VEOZAH (fezolinetant) PPI received on June 22, 2022 and received by DMPP and OPDP on January 20, 2023.
- Draft VEOZAH (fezolinetant) Prescribing Information (PI) received on June 22, 2022, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on January 20, 2023.

3 REVIEW METHODS

In 2008, the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the PPI we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.

- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	January 9, 2023
Requesting Office or Division:	Division of Urology, Obstetrics, and Gynecology (DUOG)
Application Type and Number:	NDA 216578
Product Name and Strength:	Veozah (fezolinetant) tablets, 45 mg
Applicant/Sponsor Name:	Astellas Pharma US, Inc.
TTT ID #:	2022-707-1
DMEPA 2 Safety Evaluator:	Justine Kalonia, PharmD
DMEPA 2 Acting Team Leader:	Stephanie DeGraw, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received on December 12, 2022 for Veozah. The Division of Urology, Obstetrics, and Gynecology (DUOG) requested that we review the revised container labels and carton labeling for Veozah (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a

2 ASSESSMENT AND CONCLUSION

We note that in addition to our previous recommendations, the Applicant added the proposed proprietary name, Veozah, to the revised container labels and carton labeling following notification that we found the name conditionally acceptable on December 1, 2022.^b Further, we note the Applicant implemented most of our recommendations; however, the Applicant declined to add “per tablet” to the 45 mg strength statement on the 7-day professional sample carton and tray labeling. We acknowledge the sample container (blister pack) label denotes each tablet cell as a single daily dose (i.e., Day 1 through Day 7) and the carton and tray labeling state, “Take one tablet daily by mouth”. Thus, we determined the day-labeled blister cells and

^a Kalonia, J. Label and Labeling Review for Veozah (NDA 216578). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2022 SEP 16. TTT ID No.: 2022-707.

^b Kalonia, J. Proprietary Name Review for Veozah (NDA 216578). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2022 DEC 01. PNR ID No.: 2022-1044724803.

inclusion of the dosage instructions on the carton and tray labeling may help prevent confusion and wrong dose medication errors that may result from lack of clarity regarding the designated strength per unit. Therefore, we do not object to the Applicant's proposal to not include "per tablet" after the 45 mg strength statement.

Our review of the revised container labels and carton labeling did not identify any new medication error concerns and we have no additional recommendations at this time.

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JUSTINE H KALONIA
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STEPHANIE L DEGRAW
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MEMORANDUM

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

Date: December 21, 2022

To: Christine Nguyen, M.D.
Division of Urology, Obstetrics, and Gynecology

Through: Dominic Chiapperino, Ph.D., Director
Controlled Substance Staff

From: Chad J. Reissig, Ph.D., Supervisory Pharmacologist
Controlled Substance Staff

Subject: **Drug:** Fezolinetant (Veoza)
NDA Number: 216578
Indication: moderate to severe vasomotor symptoms (VMS) associated with menopause
Dosage: 45 mg oral tablets
Sponsor: Astella Pharma Global Development Inc.
PDUFA Goal Date: February 22, 2023

Materials Reviewed: fezolinetant NDA submission (NDA 216578)
DARRTS review by J. Randall-Thompson (4/9/2019)
DARRTS review by Theresa H. van der Vlugt, M.D., M.P.H (11/26/2022)

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I. EXECUTIVE SUMMARY

1. Background

This memorandum responds to a consult request by the Division of Urology, Obstetrics, and Gynecology (DUOG) to evaluate the abuse potential of fezolinetant and input regarding labeling. The drug is being developed by Astella Pharma Global Development Inc. (Sponsor) and indicated for moderate to severe vasomotor symptoms (VMS) associated with menopause.

Fezolinetant is a first in class, small molecule, central nervous system (CNS) active drug. According to the Sponsor, fezolinetant is a selective, neurokinin-3 (NK₃) receptor antagonist and blocks the activity of neurokinin B (NKB) on kisspeptin/neurokinin B/dynorphin (KNDy) neurons. The result of this blockade is modulation of neuronal activity in the thermoregulatory center and a decrease in vasomotor symptoms (VMS), also known as “hotflashes” or “flushes.”

CSS previously reviewed fezolinetant under IND 130277 on April 9, 2019 (DARRTS review by J. Randall-Thompson). In the previous CSS review, CSS noted that fezolinetant did not bind to receptor sites associated with abuse and appeared to have a low potential for abuse.

2. Conclusions

- Fezolinetant appears to be selective for NK₃ receptors and does not bind with significant affinity for receptor subtypes or targets associated with abuse
- In nonclinical assessments, fezolinetant was not self-administered by rodents suggesting a lack of reinforcing effects and negligible potential for abuse
- In nonclinical assessments of physical dependence in rodents, fezolinetant did not produce a withdrawal syndrome
- In clinical studies, fezolinetant did not produce adverse events associated with abuse, even at doses well above the proposed therapeutic dose. These data suggest fezolinetant has no, or negligible potential for abuse

3. Recommendations

Based on our findings in the Conclusions section, we recommend the following:

- Fezolinetant does not appear to have a meaningful abuse potential and does not require scheduling under the Controlled Substances Act (CSA).
- Fezolinetant does not require section 9 (Drug Abuse and Dependence) in its label.

II. DISCUSSION

1. Chemistry

1.1 Substance Information

Fezolinetant tablets are round, (b) (4) film-coated tablets containing (b) (4) 45 mg of the active ingredient.

Name: fezolinetant

Chemical Properties

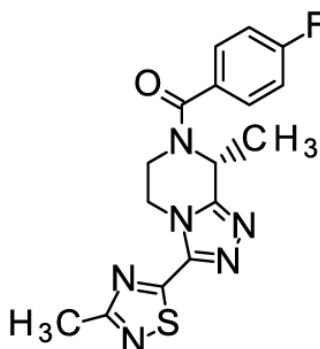
Chemical name: Methanone, [(8R)-5,6-dihydro-8-methyl-3-(3-methyl-1,2,4-thiadiazol-5-yl)-1,2,4-triazolo[4,3-a]pyrazin-7(8H)-yl](4-fluorophenyl)-

(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

Chemical formula: C₁₆H₁₅FN₆OS

Molecular weight: 358.39

Molecular Structure:



2. Nonclinical Pharmacology

As described below (section 2.1), fezolinetant binds competitively and reversibly to NK₃ receptors and functions as an antagonist. Off target activity was not observed at receptor sites associated with abuse.

2.1 Receptor Binding and Functional Assays

The Sponsor performed an *in vitro* evaluation of the ability of fezolinetant (10 μmol/L) to bind to a variety of receptor subtypes and targets, including abuse-related receptor targets (48 receptors, 6 ion channels, 3 transporters, and 48 enzymes). The results of the study (study 100002171) showed that fezolinetant is highly selective for NK₃ receptors and is unlikely to produce abuse related effects at clinically relevant doses.

2.3 Findings from Safety Pharmacology and Toxicology Studies

Fezolinetant was orally administered to male and female Wistar Han rats at 25, 125, and 250 mg/kg to examine CNS activity. Observations were recorded at 1, 2.5, 5, 8, and 24 hours after dosing along with temperature assessments. According to the Sponsor, at the highest dose (250 mg/kg) signs of mild severity were observed in the animals. Animals (both sexes) displayed constricted pupils, decreased activity, touch escape response and changes in grip strength were observed between 1 and 8 hours postdose. Decreased visual placing, startle response and alertness were less frequently observed. These behavioral signs dissipated 24 hours postdose. These data suggest that at high doses (e.g., the highest 250 mg/kg dose) fezolinetant produces behavioral effects that may be indicative of CNS activity. However, given the selectivity of fezolinetant for NK₃ receptors, the CNS effects of fezolinetant may not be abuse-related per se.

2.4 Animal Behavioral Studies

As noted in the prior CSS review (April 9, 2019 DARRTS review by J. Randall-Thompson), because fezolinetant does not bind to receptor sites associated with abuse, has limited CNS activity, and does not appear to produce AEs associated with abuse potential, dedicated animal abuse potential studies were not required or requested by CSS (e.g., self-administration and drug discrimination studies). Nonetheless, fezolinetant was evaluated in a rodent self-administration study and a rodent study of withdrawal.

Self -administration

To directly examine the reinforcing effects of fezolinetant, a rodent self administration study was performed. Male and female Lister Hooded rats (n=7 per dose/cohort) were trained to self administer cocaine at a dose of 0.32 mg/kg/infusion beginning under an FR1 schedule of reinforcement and progressing to an FR10. Once rats were successfully trained to self administer cocaine, they underwent extinction via saline substitution to confirm stable responding for the training agent and to verify adequate training. After training was complete, substitution sessions began. During substitution sessions, fezolinetant doses of 0.25, 0.5, and 0.75 mg/kg/injection were tested and amphetamine (0.05 mg/kg/injection) was used as a positive control. According to the Sponsor, amphetamine was self administered and resulted in a significant increase in responding relative to saline. The Sponsor asserts that no dose of fezolinetant was self administered and responding was not significantly greater than saline. Overall, the data appear to support this finding and in the self administration paradigm, fezolinetant does not appear to be reinforcing, suggesting a low likelihood of abuse.

2.5 Tolerance and Physical Dependence Studies in Animals

To evaluate fezolinetant for physical dependence, male and female Wistar Han rats (n=12) were administered drug for 4 weeks (28 days) at 10, 30, and 100 mg/kg/day. Codeine (150 mg/kg/day) was used as a positive control. Withdrawal assessments occurred over an 8-day period at the end of oral dosing. During assessments, animals were examined for changes in body weight, food consumption, general observations, elicited responses (e.g., reactions to stimuli), location preference in the observation arena, body temperature, rearing, and locomotor activity. According to the Sponsor, administration of fezolinetant for 28 days did not produce a

withdrawal syndrome after cessation of dosing while (as expected) codeine elicited a marked withdrawal syndrome after cessation of dosing.

3. Clinical Pharmacology

According to the Sponsor, fezolinetant is highly soluble and bioavailable orally with a Tmax between 1-4 hours and half-life of about 9.6 hours. Absorption from the GI is rapid and described by the Sponsor as “essentially complete (>70%).” The metabolism of fezolinetant occurs primarily via CYP1A2 with minor contributions by CYP2C9 and CYP2C19.

4. Clinical Studies

A total of 18 clinical studies were performed in support of the fezolinetant NDA. This included eleven phase 1 studies, four phase 2 studies, and three phase 3 studies. A total of 3682 participants were included in the clinical program. In response to a CSS information request, the Sponsor summarized and tabulated abuse related AEs during each phase of development and these AEs are discussed below, beginning with phase 1 studies.

Phase 1 studies:

ESN364-CPK-101: “A Phase 1, Double-Blind, Placebo-Controlled, Single and Multiple Ascending Dose Study of ESN364 to Evaluate Pharmacokinetics, Pharmacodynamics, Safety and Tolerability in Healthy Male and Healthy Female Volunteers of Child Bearing Potential”

Table 1 Events of Interest from the FDA-recommended List of Abuse-related Treatment-emergent Adverse Events; Study ESN364-CPK-101: Part 1

SOC PT, n (%)	Pooled PB n = 14	PB Fed n = 2	3 mg Fezo n = 6	6 mg Fezo n = 6	12 mg Fezo n = 6	23 mg Fezo n = 6	46 mg Fezo n = 6	90 mg Fezo n = 6	180 mg Fezo n = 6	23 mg Fezo Fed n = 6
General Disorders and Administration Site Conditions										
Irritability	0	0	0	0	0	0	0	1 (16.7)	0	0

Fezolinetant is reported as ESN364 in the CSR for this study.

Fezo: fezolinetant; PB: placebo.

Source: [\[ESN364-CPK-101 CSR, Table 41\]](#)

Part two of this study (ESN364-CPK-101) utilized a multiple ascending dose administration in male participants and part three of the study was a multiple ascending dose response evaluation in female participants. No abuse-related AEs were reported in subsequent parts of the study (i.e., parts 2 and 3).

ESN364-CPK-102: “A Phase I, Double Blind, Placebo Controlled, Single and Multiple Ascending Dose Study of ESN364 to Evaluate Pharmacokinetics, Safety, Tolerability and Maximum Tolerated Dose in Healthy Female and Healthy Male Volunteers”

Table 2 Events of Interest from the FDA-recommended List of Abuse-related Treatment-emergent Adverse Events; Study ESN364-CPK-102: Part 1

SOC PT, n (%)	Pooled Placebo n = 12	180 mg Fezo n = 6	360 mg Fezo n = 6	540 mg Fezo n = 6	720 mg Fezo n = 6	900 mg Fezo n = 12	Fezo Total n = 16
Nervous System Disorders							
Disturbance in attention	0	0	0	1 (16.7)	0	0	1 (6.3)
Somnolence	0	0	0	0	1 (16.7)	0	1 (6.3)
Psychiatric Disorders							
Restlessness	0	0	0	0	0	1 (8.3)	1 (6.3)

Fezolinetant is reported as ESN364 in the CSR for this study.

Somnolence is coded as Somnolence in MedDRA version 23.0.

Fezo: fezolinetant.

Source: [\[ESN364-CPK-102 CSR, Table 13\]](#)

Part two of this study ESN364-CPK-102 was a multiple ascending dose administration in female subjects and the abuse related AEs from this portion of the study appear below in Table 3. Part three of this study administered a single dose of fezolinetant and no abuse related AEs were reported by the Sponsor.

Table 3 Events of Interest from the FDA-recommended List of Abuse-related Treatment-emergent Adverse Events; Study ESN364-CPK-102: Part 2

SOC PT, n (%)	Pooled Placebo n = 4	540 mg Fezolinetant n = 6	720 mg Fezolinetant n = 6	Fezolinetant Total n = 12
Nervous System Disorders				
Disturbance in attention	1 (25.0)	0	0	0

ESN364 CPK 103: “A Phase 1, Open-Label Study to Investigate the Absorption, Metabolism and Excretion of 14C-ESN-364 in Healthy Menopausal Female Volunteers”

Table 4 Events of Interest from the FDA-recommended List of Abuse-related Treatment-emergent Adverse Events; Study ESN364_CPK_103

SOC PT, n (%)	180 mg ¹⁴ C-Fezolinetant n = 5
Nervous System Disorders	
Somnolence	1 (20.0)

Fezolinetant is reported as ESN364 in the CSR for this study.

Source: [\[ESN364 CPK 103 CSR, Table 9\]](#)

2693-CL-0008: “A Phase 1 Open-label Study to Investigate the Effect of Renal Impairment on the Pharmacokinetics, Safety and Tolerability of Fezolinetant Compared to Subjects with Normal Renal Function”

Table 5 Events of Interest from the FDA-recommended List of Abuse-related Treatment-emergent Adverse Events; Study 2693-CL-0008

SOC PT, n (%)	Renal Function Group						
	Mild n = 6	Normal to Match Mild n = 6	Moderate n = 6	Normal to Match Moderate n = 6	Severe n = 5	Normal to Match Severe n = 5	Normal Total n = 10
Nervous System Disorders							
Somnolence	0	0	1 (16.7)	0	1 (20.0)	0	0

Source: [2693-CL-0008 CSR, Table 9]

2693-CL-0009: “A Phase 1 Crossover Study to Assess the Relative Bioavailability of ESN364 Following a Single Dose of Tablet Formulation Compared to a Single Dose of Capsule Formulation in Healthy Postmenopausal Female Subjects”

Table 6 Events of Interest from the FDA-recommended List of Abuse-related Treatment-emergent Adverse Events; Study 2693-CL-0009

SOC PT, n (%)	120 mg Fezolinetant		
	Tablet n = 16	Capsule n = 16	Total n = 16
Nervous System Disorders			
Somnolence	1 (6.3)	0	1 (6.3)

Fezolinetant is reported as ESN364 in the CSR for this study.

Source: [2693-CL-0009 CSR, Table 8]

2693-CL-0010: “A Phase 1 Crossover Study to Assess the Bioequivalence of Fezolinetant Following a Single Dose of Fezolinetant to-be-marketed Formulation (Test Formulation) Compared to a Single Dose of Fezolinetant Phase 3 Formulation (Reference Formulation) in Healthy Female Subjects”

Table 7 Events of Interest from the FDA-recommended List of Abuse-related Treatment-emergent Adverse Events; Study 2693-CL-0010

SOC PT, n (%)	Treatment A n = 22	Treatment B n = 22	Total n = 22
Nervous System Disorders			
Somnolence	0	1 (4.5)	1 (4.5)

A: one 45 mg fezolinetant to-be-marketed tablet (test formulation); B: 45 mg fezolinetant comprising one 30 mg and one 15 mg fezolinetant phase 3 tablet (reference formulation).

Source: [2693-CL-0010 CSR, Table 12]

2693-CL-0012: “A Phase 1 Crossover Study to Investigate the Effect of Food on the Pharmacokinetics of Fezolinetant in Healthy Female Participants”

Table 8 Events of Interest from the FDA-recommended List of Abuse-related Treatment-emergent Adverse Events; Study 2693-CL-0012

SOC PT, n (%)	Fed n = 16	Fasted n = 16	Total n = 16
Nervous System Disorders			
Somnolence	1 (6.3)	0	1 (6.3)

Source: [2693-CL-0012 CSR, Table 9]

For the remaining four, phase 1 studies (2693-CL-0006, 2693-CL-0007, 2693-CL-0020, and 2693-CL-0030), no abuse-related AEs were reported. Notably, the phase 1 studies included doses up to 900 mg, well beyond the proposed therapeutic dose (e.g., 20X the proposed therapeutic dose). As seen in the tables presented above, no more than one abuse related AE was observed in any phase 1 study, and there were no reports of euphoria. The most common abuse related AEs in the phase 1 program were somnolence and disturbance in attention. In the absence of euphoria, these AEs are not indicative of a signal of abuse.

The Sponsor pooled the safety assessment of fezolinetant for phase 2 and phase 3 studies. According to the Sponsor, in the largest population exposed to fezolinetant for 52 weeks (POP2), AEs of “feeling abnormal” and “mood altered” were reported at an incidence of < 0.5%. A search of the tabular listing of AEs for POP2 did not reveal any reports of “euphoria,” suggesting a low likelihood of abuse. The Medical Officer review (Theresa H. van der Vlugt, M.D., M.P.H, DARRTS 11/26/2022) summarized Treatment Emergent Adverse Events (TEAEs) of any severity occurring in greater than 1% of subjects in the POP2 database containing ~1100 subjects at each dose of fezolinetant (30 and 45 mg). “Anxiety” was the only potential abuse related TEAE reported and occurred in 1.6 % (n=18) of subjects dosed at 30 mg and 1.8% (n=20) of subjects dosed at 45 mg.

Collectively, abuse related AEs across the development program do not suggest a potential for abuse for fezolinetant.

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Clinical Inspection Summary

Date	12/13/2022
From	Michele Fedowitz, MD Primary Reviewer and (Acting) Team Leader Jenn Sellars, MD, PhD, Acting Branch Chief Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	Theresa Van Der Vlugt, MD, and Regina Zopf, MD, Clinical Reviewers Shelley Slaughter MD, Clinical Team Leader Samantha Bell, Regulatory Project Manager Division of Urology Obstetrics and Gynecology (DUOG)
NDA #	216578
Applicant	Astellas Pharma
Drug	Fezolinetant
NME (Yes/No)	Yes
Therapeutic Classification	Nonhormonal selective neurokinin 3 (NK3) receptor antagonist
Proposed Indication	Indicated for the treatment of moderate to severe vasomotor symptoms (VMS) associated with menopause.
Consultation Request Date	08/04/2022
Summary Goal Date	12/22/2022
Action Goal Date	02/22/2023
PDUFA Date	02/22/2023

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The Applicant, Astellas Pharma, submitted clinical data from Study 2693-CL-0301/SKYLIGHT 1 (NCT04003155), 2693-CL-0302/SKYLIGHT 2 (NCT04003142), and 2693-CL-0304/SKYLIGHT 4 (NCT04003389) to the Agency in support a New Drug Application (NDA 216578) for fezolinetant.

Seven clinical investigators were selected for Good Clinical Practice (GCP) inspections given they were high enrolling sites with good treatment effect. The sites were geographically diverse and comprised investigators from the U.S. (Drs. Heller, Romero, Guell, and Jimenez), Canada (Dr. Frechette), and Poland (Drs. Wilk and Oronowicz). All inspections were conducted on-site.

The inspections did not find significant concerns regarding the management of the clinical trials, GCP compliance, or data integrity. Data related to the primary efficacy endpoint for Studies SKYLIGHT 1 and SKYLIGHT 2, the frequency and severity of moderate to severe

vasomotor symptoms, were verified with the source records available at the inspected clinical sites.

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

II. BACKGROUND

Astellas Pharma seeks approval for a new drug application for fezolinetant. In support of the NDA, the Applicant submitted clinical data from three studies: Study 2693-CL-0301 (SKYLIGHT 1), Study 2693-CL-0302 (SKYLIGHT 2), and Study 2693-CL-0304 (SKYLIGHT 4). The following is a summary of study protocols and key study information relevant to the clinical inspections.

Study 2693-CL-0301 and Study 2693-CL-0302

These two pivotal studies are similarly designed phase 3 studies in menopausal women experiencing moderate to severe vasomotor symptoms (VMS) with prior hormone replacement therapy (HRT) use, oophorectomy, or hysterectomy. The first 12 weeks of the study were randomized, double-blinded, and placebo controlled, followed by a 40-week extension treatment period for a duration of treatment of 52 weeks. During the first 12 weeks, subjects were randomized 1:1:1 to placebo, fezolinetant 30 mg, or fezolinetant 45 mg and were stratified by smoking status (active smoker or nonsmoker). After completing 12 weeks, the subjects on placebo were re-randomized to fezolinetant 30 mg or 45 mg for 40 weeks; the subjects on either 30 or 45 mg of the study drug continued to receive fezolinetant at the same dose during the 40-week extension period.

Study Objectives

The primary objective for both studies was to evaluate the efficacy of fezolinetant vs. placebo on the frequency and severity of moderate to severe vasomotor symptoms (VMS). The 4 co-primary efficacy endpoints were:

- 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

Schedule of Assessments

Subjects were to be screened at least 35 days prior to randomization. If eligible, enrolled subjects were to be evaluated weekly until week 16, and then every 4 weeks from week 16 through 52. Subjects were to complete an end of treatment (EOT) visit and final safety follow-up visit 3 weeks after the last dose of study intervention was administered (week 55).

For the primary efficacy endpoint, daily symptom data was to be collected using an electronic diary which was to be completed daily by subjects. Subjects were to record their vasomotor

symptoms (VMS) via their electronic diary daily from screening through the follow-up visit. The diary data was to be transferred electronically to sponsor or designee at predefined intervals during the study by the vendor. The vendor was also to provide the investigator with a complete and clean copy of their site's data and was to provide the sponsor with a complete and clean copy of the study data.

Study Conduct and Status

In SKYLIGHT 1 and SKYLIGHT 2, a total of 1022 women were randomized. Endpoint data was captured on the subject's e-diary and directly submitted from the third-party vendor, (b) (4), to the sponsor. The e-diaries were provided by the sponsor to the clinical site.

Study 2693-CL-0304

This is a 52-week randomized, placebo-controlled, double-blind, parallel-group, multicenter clinical study to assess the safety and tolerability of fezolinetant in female individuals seeking treatment for VMS associated with menopause.

Study Objectives

To evaluate the safety of fezolinetant based on the following primary endpoints:

- Frequency and severity of adverse events (AEs)
- Percentage of subjects with endometrial hyperplasia
- Percentage of subjects with endometrial cancer

Schedule of Assessments

The subjects were to be screened (visit 1) at least 35 days prior to randomization. Subjects were then to be randomized 1:1:1 to placebo, fezolinetant 30 mg, or fezolinetant 45 mg for 52-weeks. Eligibility was assessed via physical examination, clinical laboratory testing, urine pregnancy test, vital signs, electrocardiogram (ECG), Pap test (or equivalent cervical cytology), mammography, transvaginal ultrasound (TVU) and endometrial biopsy.

Subjects were evaluated every 2 weeks until week 8 (visit 4) and then every 4 weeks until week 52 for adverse events. An endometrial biopsy was to be performed at screening and in the case of uterine bleeding during treatment. At the end of treatment (EOT), a TVU and a suction endometrial biopsy will be required.

Study Conduct and Status

SKYLIGHT 4 was conducted at 181 centers that enrolled participants in 8 countries (United States, Canada, Spain, Latvia, Ukraine, Czech Republic, United Kingdom, and Poland). A total of 1831 participants were randomized: Of those, 1830 received study intervention: 610 participants in the placebo group, 611 in the fezolinetant 30 mg group and 609 in the fezolinetant 45 mg group.

RESULTS

1. **Dr. Robert J. Heller (Site 10053)**

12626 Riverside Dr. Ste. 404
Valley Village, CA 91607-3456

Inspection Dates: October 3-7, 2022

This investigator was inspected as an onsite surveillance inspection for Study 2693-CL-0304/SKYLIGHT 4. This investigator has had one previous inspection in 7/2020 with no significant regulatory findings.

At the time of data cutoff, there were 119 subjects screened, 53 subjects enrolled and treated at the site; 15 subjects discontinued and 38 completed the study.

The source documents were reviewed for all 53 enrolled subjects for protocol adherence, adverse event reporting, concomitant medications, and eligibility; the reviewed records included informed consent forms, paper-based progress notes, medical records from external institutions, laboratory reports, EKGs, concomitant drugs, eligibility, AEs, and study drug records.

Study related documents were also reviewed including IRB approval letters and correspondence; monitoring reports; consent forms, subject medical records, financial disclosure reports, case report forms, delegation of responsibility logs, monitoring reports and site training documentation.

Dr. Heller followed the protocol with respect to subject selection, number of subjects enrolled, randomization scheme, blinding procedures, required procedures and evaluations, storage, maintenance, and administration of investigational product, and follow-up of subjects. The data included with the background material was complete and accurate as compared with the source documentation. Adverse events were monitored appropriately, and no unreported adverse events were identified. No unreported protocol deviations were identified. Study SKYLIGHT 4 did not evaluate efficacy.

2. **Sandor A. Romero (Site 10117)**

18951 SW 106th Ave
Cutler Bay, FL, 33157-7668

Inspection Dates: October 11-14, 2022

This investigator was inspected as an onsite surveillance inspection for Study 2693-CL-0301, SKYLIGHT 1. This was the third FDA inspection for this investigator. The first inspection,

which ended on 02/13/2018, was classified as Voluntary Action Indicated (VAI), a form FDA-483, Inspectional Observations was issued, citing failure to prepare or maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation. The most recent inspection, which ended on 12/19/2019, had no significant regulatory findings.

At the time of data cutoff, there were 161 subjects screened, 45 subjects enrolled and treated at the site, 41 have completed the study.

The informed consent forms were reviewed for all 45 enrolled subjects. The complete source documents were reviewed for 15 of the 45 enrolled subjects for eligibility, consent, general protocol adherence, adverse event (AE) reporting, and primary endpoint verification and were compared to the provided data line listings; the reviewed records included progress notes and previous medical records, ECGs, mammograms, transvaginal ultrasounds, endometrial biopsies, laboratory reports, study test article accountability, concomitant medications, and vital sign entries.

Study related documents were also reviewed including financial disclosure forms, FDA form 1572s, protocols, IRB submissions and correspondence, AE reporting, screening and enrollment log, monitoring records, delegation of responsibilities log, and investigational product (IP) accountability/disposition records.

The primary endpoint of frequency and severity of vasomotor symptoms (VMS) was recorded in a subject diary and sent directly to a central data base for evaluation. The source records for the primary endpoint were reviewed at the site and there were no discrepancies. No unreported adverse events were identified. No significant unreported protocol deviations were identified.

3. Gregory A. Guell (Site 10084)

Suncoast Research Group LLC,
2128 W Flagler St Ste 101,
Miami, FL, 33135-1687

Inspection Dates: October 19-31, 2022

This investigator was inspected as an onsite surveillance inspection for Study 2693-CL-0302, SKYLIGHT 2. This is the first FDA inspection for this investigator.

At the time of data cutoff, there were 122 subjects screened, 39 subjects enrolled and treated at the site; 31 completed the study; and one was lost to follow up and 6 withdrew consent.

The complete source documents were reviewed for 10 of the 39 enrolled subjects. The reviewed records included informed consent forms, medical history forms, medical records, EKGs, laboratory reports, past medical history, inclusion/exclusion information, AE log, concomitant medication log, mammogram reports, endometrial biopsy reports, and specific visit source records with progress notes. Records were reviewed to verify eligibility, consent, protocol adherence, adverse event (AE) reporting. The primary efficacy data was reviewed for all 39 randomized subjects. A review of only IP compliance only was done for 5 of the 39 randomized subjects.

Study related documents were also reviewed including financial disclosure forms, FDA form 1572s, protocols, IRB submissions and correspondence, training documents, AE reporting, screening and enrollment log, monitoring records, study staff curricula vitae and delegation of responsibilities log, and investigational product (IP) storage and accountability.

The primary endpoint of frequency and severity of vasomotor symptoms (VMS) was recorded in a subject diary and sent directly to a central data base for evaluation. The source records for the primary endpoint were reviewed at the site and there were no discrepancies.

The investigator did have discrepancies in maintaining accurate records with regards to adverse event reporting and concomitant medication reporting. There were 7 adverse events that were not documented correctly. The adverse event discrepancies largely included documentation issues [not capturing in eCRF (1), not including with an existing AE (4) and not capturing accurate dates (2)]. After review of the inspection report and the clinical investigator's (CI's) response, there is a single AE not reported to the Sponsor and not in the data listings: Subject (b) (6) had elevated Creatinine Kinase levels on (b) (6). This AE was noted in the AE log, but not transferred to the electronic case report form (eCRF) or reported to the sponsor.

Reviewer's Comment:

There was a single episode of an unreported AE of elevated creatinine kinase in subject (b) (6), this event is captured in the laboratory line listings submitted to the Agency.

There are six (6) instances of inaccurate record keeping: four (4) instances were in a single subject with elevated gamma-glutamyl transferase (GGT) levels that were part of a previous AE of elevated liver enzymes but not documented accurately as an existing AE; and Two (2) AEs in two subjects that had inaccurate start or end dates. In all cases, the AEs were not serious. The elevated GGT should have been included into the existing AE of elevated liver enzymes for the same lab results.

There was one concomitant medication discrepancy. Subject (b) (6) started taking Tizanidine 2 mg for fibromyalgia. This was captured in the concomitant medication log, but lacked a start date. There were multiple discrepancies in subject's investigational product (IP) accountability that included either an incorrect date being entered into the record or inaccurate accounting of lost pills.

Reviewer's Comment: There were multiple instances of inaccurate record keeping regarding IP accountability. In all cases, the drug was taken as directed and the instances of incorrect dates or lost pills were not documented correctly. None of the discrepancies affect the primary efficacy endpoint or the safety profile of the drug.

The CI responded to the regulatory violations on November 16, 2022, and his response and CAPA plan are adequate.

4. Gilberto Jimenez (Site 10098 for SKYLIGHT 1, 10192 for SKYLIGHT 4)

Spotlight Research Center LLC
9570SW 107th Ave. Suite 201
Miami, Florida 33176

Inspection Dates: November 14-18 and 21, 2022

This investigator was inspected as an onsite surveillance inspection for Study 2693-CL-0301, SKYLIGHT 1 and Study 2693-CL-0304, SKYLIGHT 4. This is the first FDA inspection for this investigator.

For both studies, study related documents were reviewed including financial disclosure forms, FDA form 1572s, protocols, IRB approvals and correspondence, training records, AE reporting, screening and enrollment log, monitoring records, study staff curricula vitae and delegation of responsibilities log, and investigational product (IP) storage and accountability. The electronic case report forms (eCRF), electronic diary data, and electronic questionnaire data were reviewed for a subset of subjects to determine Part 11 compliance.

Study 2693-CL-0301, SKYLIGHT 1

At the time of data cutoff, there were 130 subjects screened, 23 subjects enrolled and treated at the site. Of the enrolled subjects, 5 discontinued (1 terminated early, 3 withdrew consent and 1 was lost to follow-up) and 18 completed the study. The complete source documents were reviewed for 8 of the 23 enrolled subjects. The reviewed records included informed consent forms, inclusion/exclusion information, medical records including medical history forms, progress notes, laboratory reports, and ECGs. Records were reviewed to verify eligibility, consent, protocol adherence, adverse event (AE) reporting.

For Protocol SKYLIGHT 1, the raw data provided by the third-party vendor, (b) (4), was compared with the data listing in the background material to verify the primary efficacy endpoint data, frequency and severity of hot flashes, and there were no discrepancies.

No significant unreported adverse events were identified. No unreported protocol deviations were identified.

Study 2693-CL-0304, SKYLIGHT 4

At the time of data cutoff, there were 224 subjects screened, 104 subjects enrolled and treated at the site. Of the enrolled subjects, 26 discontinued (3 terminated early, 15 withdrew consent, and 8 were lost to follow-up) and 78 completed the study. The complete source documents were reviewed for 10 of the 104 enrolled subjects; the reviewed records included informed consent, medical records including specific visit source records with progress notes, mammogram reports, endometrial biopsy reports, laboratory reports, and ECGs. Records were reviewed to verify eligibility, consent, protocol adherence, adverse event (AE) reporting.

No unreported protocol deviations were identified. There were instances of discrepancies in documentation of adverse events; specifically, not capturing accurate end dates of three AEs in

three subjects. No significant adverse events were unreported. Skylight 4 did not evaluate efficacy.

5. Krzysztol Wilk (Site 48013)

NZOZ Sanas, Siemianowicka 5a
Katowice, Poland 40-301

Inspection Dates: October 31 – November 4, 2022

This investigator was inspected as an onsite surveillance inspection for Study 2693-CL-0301, SKYLIGHT 1. This is the first FDA inspection for this investigator. These results for Dr. Wilk are based on preliminary communication with the FDA site inspector.

At the time of data cutoff, there were 27 subjects screened, 21 subjects enrolled and treated at the site. The records of 19 subjects were reviewed.

The primary efficacy endpoints were recorded directly onto the take-home e-tablets. Data were uploaded directly to the sponsor. At the conclusion of the study the sponsor provided an encrypted thumb-drive to the site. The data on the thumb drive was compared with the data listing in the background material to verify the primary efficacy endpoint data, frequency and severity of hot flashes, and there were no discrepancies.

6. Katarzyna Oronowicz (Site 48005)

Twoja Przyszłość –Słowackiego 19 Szczecin,
Zachodniopomorskie, Poland 71-434

Inspection Dates: November 7-10, 2022

This investigator was inspected as an onsite surveillance inspection for Study 2693-CL-0302, SKYLIGHT 2. This is the first FDA inspection for this investigator. These results for Dr. Oronowicz are based on preliminary communication with the FDA site inspector.

At the time of data cutoff, there were 35 subjects screened, 26 subjects enrolled and treated at the site. The records of 16 subjects were reviewed.

The primary efficacy endpoints were recorded directly onto the take-home e-tablets. Data were uploaded directly to the sponsor. At the conclusion of the study the sponsor provided an encrypted thumb-drive to the site. The data on the thumb drive was compared with the data listing in the background material to verify the primary efficacy endpoint data, frequency and severity of hot flashes, and there were no discrepancies.

7. Andre Frechette (15001)

Place de la Cité
2600 Boul. Laurier

Suite 293 Québec
Canada G1V 4T3

Inspection Dates: October 17-21, 2022

This investigator was inspected as an onsite surveillance inspection for Study 2693-CL-0301, SKYLIGHT 1 and Study 2693-CL-0304, SKYLIGHT 4. This is the first FDA inspection for this investigator.

The source documents were reviewed for protocol adherence and overall conduct of the study, inclusion/exclusion criteria, informed consent, and data verification between source documentation and data line listings. The reviewed record included subjects' charts, case report forms, medical records, subject diaries, adverse events, and drug accountability records. Study related documents were reviewed including onsite study protocols, sponsor and IRB communications, investigator's agreements, financial disclosure forms, FDA form 1572s, monitoring records, investigational product storage and handling records, and training procedures and records.

Study 2693-CL- 0301, SKYLIGHT 1

At the time of data cutoff, there were 40 subjects screened, 6 subjects enrolled and treated at the site; 5 completed the study and one discontinued. All 6 records were reviewed.

The primary endpoint of frequency and severity of vasomotor symptoms (VMS) was recorded in a subject diary and sent directly to a central data base for evaluation. The source records for the primary endpoint were reviewed at the site and there were no discrepancies.

Protocol deviations and adverse events were reported to the IRB and sponsor accordingly. Consents were reviewed and all were consented prior to study activities being conducted and were reconsented appropriately. No unreported adverse events or protocol deviations were identified.

Study 2693-CL-0304, SKYLIGHT 4

At the time of data cutoff, there were 99 subjects screened, 47 subjects were enrolled and treated at the site; 43 subjects completed the study and 4 were discontinued. The source records for 43 of 47 subjects were reviewed.

Protocol deviations and adverse events appeared to be reported appropriately. No unreported adverse events or protocol deviations were identified. Data were verifiable and no discrepancies were noted.

{See appended electronic signature page}

Michele Fedowitz, M.D.
Primary reviewer and Acting Team Leader

Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{ See appended electronic signature page }

CONCURRENCE:

{ See appended electronic signature page }

Jenn Sellers, M.D., Ph.D.
Acting Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

cc:

Review Division /Division Director/Audrey Gassman, MD
Review Division /Project Manager/ Samantha Bell
Review Division/Cross Discipline Team Lead/Shelly Slaughter, MD
Review Division/Clinical Reviewer/ Theresa Van Der Vlugt, MD
Review Division/Clinical Reviewer/Regina Zopf, MD
OSI/Office Director/Dave Burrow
OSI/ GCP Program Analysts/Yolanda Patague

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MICHELE B FEDOWITZ
12/13/2022 11:19:38 AM

JENN W SELLERS
12/13/2022 11:47:39 AM

Division of Hepatology and Nutrition Consultation

Drug-induced Liver Injury Team

NDA	216578
Consultation Issue	Drug-induced liver injury (DILI)
Drug Product	Fezolinetant
Indication	Vasomotor symptoms
Applicant	Astellas Pharma US, Inc.
Requesting Division	DUOG; Samantha Bell, RPM
Primary Reviewer	Ling Lan, MD, PhD, Clinical Analyst, DILI Team, OND/DHN
Secondary Reviewer	Paul H. Hayashi, MD, MPH DILI Team Lead, OND/DHN
Other Reviewers	Edwige Chiogo Vouffo, PharmD, PhD, OND/DHN
Reviewer Office of Pharmacoepidemiology	Mark Avigan, MD, CM Associate Director, OPE/OSE
Signatory Authority	Frank A. Anania, MD Acting Director, OND/DHN
Assessment Date	11/18/2022

Context: Fezolinetant (FZT) is small molecule, neurokinin 3 (NK3) receptor antagonist under review for the treatment of vasomotor symptoms (VMS) of menopause. The phase 2 studies reported aminotransferase elevations in subjects on FZT under IND 130277. DHN (then DGIEP) provided consultations on Jun 11, 2018,¹ Oct 23, 2018,² and Mar 29, 2019.³ An independent Liver Safety Monitoring Panel (LSMP) oversaw the applicant's clinical program as the Agency recommended. The Division of Urology, Obstetrics and Gynecology (DUOG) requested the DILI Team's advice on the hepatic injury findings associated with FZT in the three phase 3 studies, the LSMP committee conclusions, FZT approvability, and labeling if approved.

Executive Summary: We do not see a liver injury risk that should hold up approval if the need for FZT and its effectiveness are substantive. There were no Hy's Law cases, several liver injury cases improved despite continued FZT use, and around 2800 subjects were exposed to FZT in the phase 3 trials. Nevertheless, the level of transaminase elevations could be substantial (> 20 x ULN), and the post-market exposure population may be quite large. We generally agreed with the applicant's LSMP's assessments and conclusions. If approved, we recommend labeling in the

¹ (First open the DARRTS homepage to allow the following link to work);

<https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af8049f649>

² (First open the DARRTS homepage to allow the following link to work);

<https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af804bf03a>

³ (First open the DARRTS homepage to allow the following link to work);

<https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af804e8035>

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 in Section 5.

Consultation Sections:

Section 1.0 – Target Disease and Rationale

Section 2.0 - ADME pertinent to DILI

Section 3.0 - Non-clinical data pertinent to DILI.

Section 4.0 - Clinical data

Section 5.0 – Assessment & Recommendations.

Appendix A: ADME and non-clinical data

Appendix B: Trial design schematics and eDISH plots

Abbreviations:

AP or ALP: alkaline phosphatase

ALT: alanine aminotransferase

AST: aspartate aminotransferase

BMI: body mass index

CPK: creatinine phosphokinase

CYP: cytochrome P450

DB: direct bilirubin

DILI: drug-induced liver injury

DUOG: Division of Urology, Obstetrics and Gynecology

FAERS: FDA Adverse Event Reporting System

FZT: fezolinetant

GGT: gamma-glutamyl transferase

HDS: herbal and dietary supplements

IP: investigational product

LSMP: Liver Safety Monitoring Panel

MRI: magnetic resonance imaging

CT: computerized tomography

R-value: $\text{ALT/ULN} \div \text{ALP/ULN}$

TB: total bilirubin

US: ultrasound

ULN: upper limit of normal

VMS: vasomotor symptoms

1.0 Target Disease and Rationale

1.1. Target disease is vasomotor symptoms (VMS) of menopause.

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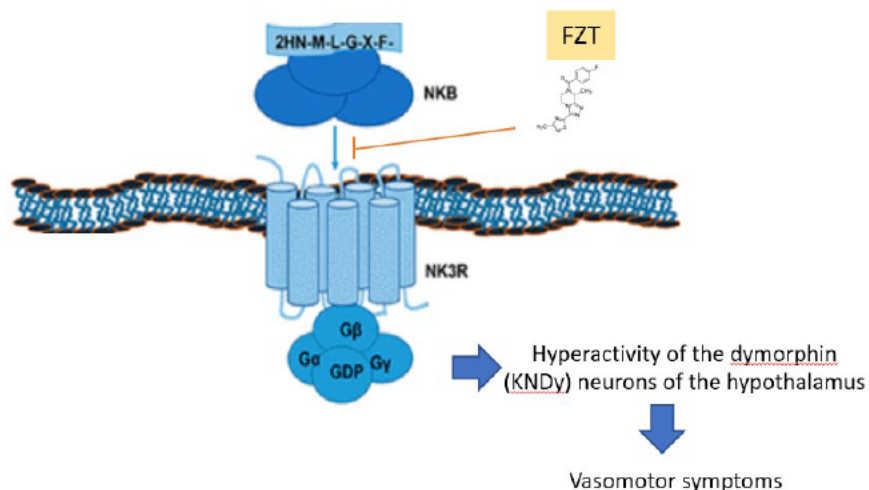
1.2 Mechanism of action:

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, for mechanism of action and rationale. FZT oral, small molecule, neurokinin 3 (NK3) receptor antagonist mechanism of action (**Figure 1**).

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Figure 1: FZT blocks neurokinin (NKB) binding of the NK3 receptor.⁵



2.0 ADME data

2.1 Structure of FZT (**Figure 2**):

Figure 2: Chemical formula and structure⁶

Compound Number: ESN364 Generic Name: Fezolinetant Molecular Formula: C₁₆H₁₅FN₆OS Chemical Name: (4-Fluorophenyl)[(8<i>R</i>)-8-methyl-3-(3-methyl-1,2,4-thiadiazol-5-yl)-5,6-dihydro[1,2,4]triazolo[4,3-<i>a</i>]pyrazin-7(8<i>H</i>)-yl]methanone	Chemical Structure:
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2.2 Absorption: Following administration by oral gavage to female rats, FZT was well absorbed with a T_{max} =0.5 hours at all doses (1, 3, and 10 mg/kg). The oral bioavailability was 91.9% and 115% for 1 mg/kg and 10 mg/kg respectively. Mean concentration of ES259564 (FZT's major metabolite) increased proportionally with increase dose of FZT. The increases in C_{max} and AUC values of FZT and ES259564 were also generally increased with increasing dose. In cynomolgus monkeys, mean oral bioavailability of FZT ranged from 74.6% to 103% at 1 mg/kg to 10 mg/kg respectively. Following a single PO administration of ¹⁴C-FZT in monkeys, the radioactivity in plasma peaked at

⁵ Adapted from Zhang W, et al. ACS Chemical Neuroscience, 2020; 11(19): 2935-43;

<https://pubs.acs.org/doi/full/10.1021/acscchemneuro.0c00421>

⁶ Seq 0001 (SDN 1), 2.4, Nonclinical Overview, p. 7; [NDA216578 \(216578 - 0001 - \(1\) - 2022-06-22 - ORIG-1 /Multiple Categories/Subcategories\) - Nonclinical Overview \(#7\)](#)

0.67 hours and decreased with a half-life of 5.4 hours. Hence, rapid absorption and high bioavailability occur with oral administration. The increases in parent drug and metabolites concentrations were dose dependent.

2.3 Distribution: Following intravenous (IV) administration of FZT, the volume of distribution in female rats exceeded total body water (668 mL/kg), demonstrating that FZT is highly distributed to tissues. Similarly wide and rapid distribution was seen after oral administration. In vitro plasma binding of FZT was higher in humans than in mice, rat, rabbits, and monkeys. Hence, FZT was rapidly and highly distributed into tissues. Plasma binding was higher in humans which may lead to lower bioavailability.

2.4 Metabolism: Studies suggest multiple metabolic pathways with many metabolites (**Appendix A, Figure A**). In rats and monkeys, the metabolic pathways of FZT include oxidation of methyl groups and glutathione conjugation of oxidative metabolites. However, such pathways are not highly utilized based on plasma metabolite concentrations. Following IV and oral administration to monkeys, the recovery of radioactivity at 96 hours was 98.5%, and most was parent compound. Following a single oral dose in rats, the parent compound comprised 94% of peak plasma concentration. The most common metabolite, ES259564, consistently accounted for <10%. The metabolic stability of FZT was similar in human and monkey liver microsomes. Thus, the metabolism of FZT may lead to numerous metabolites, but none were more than 10% of delivered dose by carbon-14 studies. Nevertheless, intra-hepatic amounts of these various metabolites could be more prominent than in plasma.

2.5 Elimination: Elimination is mainly via urine with minor to moderate elimination in feces. Following a single oral administration in monkeys, the excretion at two hours was 81.7% in urine and 14.6% in feces. The difference was less pronounced in rats with 52.3% in urine and 36.1% in feces. Thus, FZT elimination is expected to be more dependent on renal function, and elimination was rapid with normal renal function. The half-life was 3.4 to 6.8 hours in a 13-week oral delivery study in rats irrespective of dose. In female rats, clearance was 132 mL/hr/kg which is less than hepatic blood flow. Therefore, the applicant suggests that FZT was not highly extracted by the liver. Similar observations were reported in monkeys with a mean clearance of 262 mL/hr/kg. Low hepatic extraction makes drug elimination (and exposure) independent of changes in hepatic blood flow.⁷ Thus, any potential off-target effects on splanchnic circulation are unlikely to alter elimination or DILI risk.

3.0 Non-clinical data

3.1 In vitro data: The DILI Team found no in vitro data on glutathione trapping, transporter inhibition or mitochondrial toxicity.

3.2 Animal data: A seven-day oral gavage of FZT (≥ 250 mg/kg/day) in rats caused liver weight increase. Following a 26-week oral study, female rats had increase liver weight

⁷ Rodighiero V. Effects of liver disease on pharmacokinetics: An update, Clin Pharmacokinet, 1999; 37(5):399-431. <https://link.springer.com/article/10.2165/00003088-199937050-00004>

at ≥ 100 mg/kg/dose. NOAEL was 200 mg/kg/dose. A NOAEL was 25 mg/kg in a 39-week toxicity study with four-week recovery in female monkeys.

3.2.1 Liver Chemistry Data: 26-week oral toxicity study in rats showed an increase in ALP at the dose of ≥ 200 mg/kg/day. A 5-week oral toxicity study in monkeys indicated a slight increase in transaminases in some animals⁸ which the applicant attributed to muscular origin due to handling of those animals. Occasional modest increase in ALP was noted as well.⁹ Thus, there were no significant liver enzyme or bilirubin rises that would raise concerns for DILI.

3.2.2 Liver Histopathology: Following a 28-day oral gavage toxicity study in rats there was minimal centrilobular hypertrophy at the doses of 100 and 300 mg/kg/day. Some rats had minimal multifocal inflammatory cell foci and marked periportal hepatocyte pigment. In a 26-week, rat toxicity study, there was a dose-related increased incidence and severity of centrilobular hepatocellular hypertrophy in rats receiving ≥ 200 mg/kg/day which correlated with liver weight increase. Thus, minimal centrilobular hepatocellular hypertrophy was noted as well as minimal multifocal inflammation cell foci and marked periportal hepatocyte pigment in the liver. But no necrosis was seen despite pigment deposition. Thus, animal liver histopathology changes do not suggest a significant liver injury risk, though pigment deposition is unexplained and could represent prior missed injury.

ADME and Toxicology Summary tables

Table 1: ADME Summary 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	Hepatic metabolism occurs but is quantitatively low; more than 16 metabolites at low levels were seen in rats and monkeys.
Elimination	Mainly via urine and minor excretion in feces. Rapid elimination noted.

Table 2: Toxicology Summary pertinent to DILI

Item	Finding
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, AP, TB)	Slight elevation of transaminases and increase in ALP

⁸ Seq 0001 (SDN 1), 4.2.2.3, Study Report 8331280, pp. 634-45; [NDA216578 \(216578 - 0001 - \(1\) - 2022-06-22 - ORIG-1 /Multiple Categories/Subcategories\) - 8331280 Study Report \(#634\)](#)

⁹ Seq 0001 (SDN 1), 4.2.2.3, Study Report 8331280, pp. 646-51; [NDA216578 \(216578 - 0001 - \(1\) - 2022-06-22 - ORIG-1 /Multiple Categories/Subcategories\) - 8331280 Study Report \(#646\)](#)

Liver histopathology findings	centrilobular hepatocellular hypertrophy, minimal foci of multifocal inflammation and marked periportal hepatocyte pigment in rat livers
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Overall, non-clinical data do not suggest a substantial liver injury risk though the in vitro studies were sparse.

4.0 Clinical data:

4.1 In class or near class data: See DILI Team consult logged in DARRTS on
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there were no Hy's law cases, no cases of jaundice and no definitive cases of liver injury in approximately 438 subjects exposed. Two anti-emetic, NK-1 receptor antagonists are on the market in the US, rolapitant, approved in Sep 2015, and aprepitant, approved in Mar 2006. Neither have liver injury in Warnings and Precautions section. Neither carry significant DILI signals by LiverTox®.¹¹ The DILI Team found no reports in post-marketing literature on DILI from these agents and no other NK receptor antagonists on the market.

4.2 Summary of studies: This review focuses on three phase 3 studies 301, 302 and 304 summarized in **Table 3**. In total, 2852 VMS subjects were exposed to FZT in phase 3 trials.

Table 3: Clinical Studies in VMS Patients

Study	Phase	Design and Duration	Participant Number	PBO
2693-CL-0301	3	Period 1: R (1:1:1), 12-week DB, PBO Period 2: 40-week OLE	N = 522 (35 mg: 40mg: PBO = 173:174:175)	Yes
2693-CL-0302	3	Period 1: R (1:1:1), 12-week DB, PBO Period 2: 40-week OLE	N = 500 (35 mg: 40mg: PBO = 166:167:167)	Yes
2693-CL-0304	3	52-weekk DB, PBO	N = 1830 (35 mg: 40mg: PBO = 611:609:610)	Yes

DB = double blind; OLE = open label extension; PBO = placebo; R = randomized;
Source: DILI Team

4.3 Study design features related to DILI 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 TB and 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.

¹⁰ (First open the DARRTS homepage to allow the following link to work)

<https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af806257c2>

¹¹ <https://www.ncbi.nlm.nih.gov/books/NBK547852/>

Exclusion criteria: history of hepatic disease; active liver disease, jaundice, elevated ALT/AST ($\geq 1.5 \times \text{ULN}$), TB, INR, or ALP ($\geq 1.5 \times \text{ULN}$).

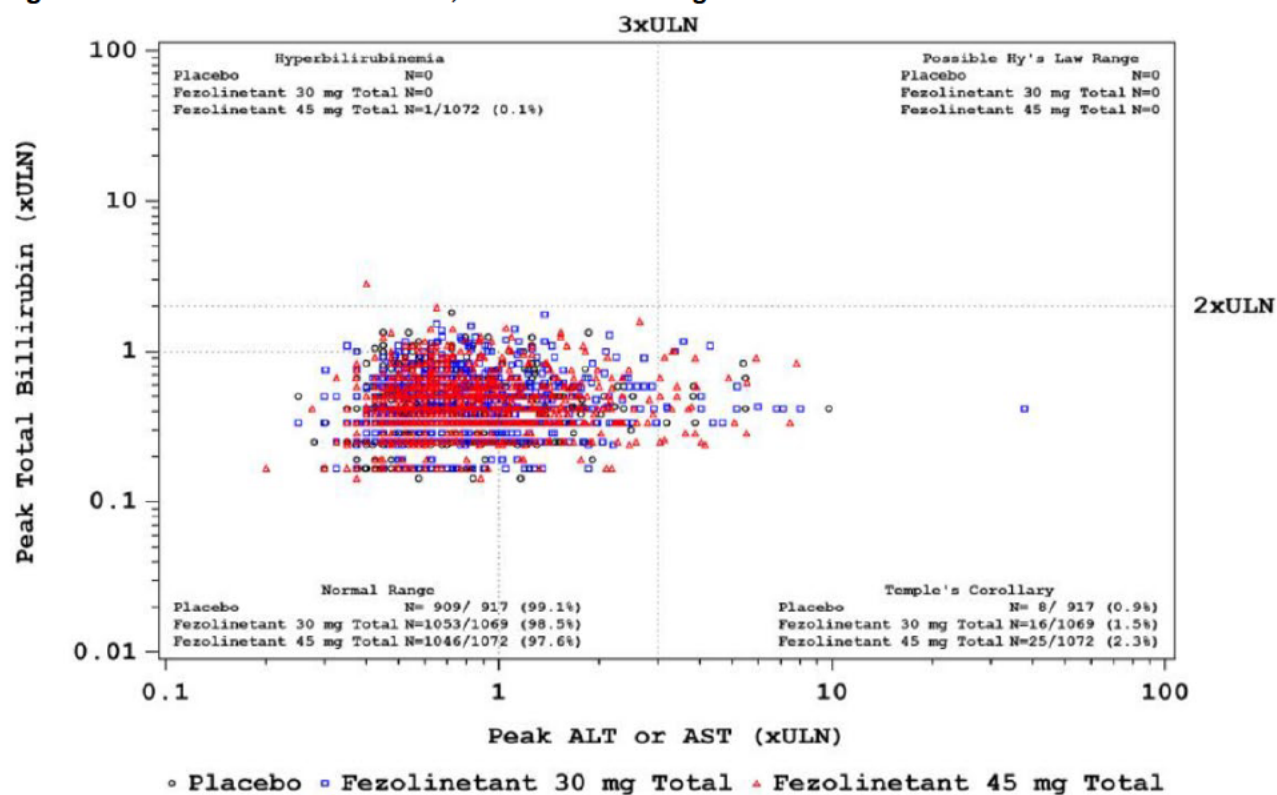
*Discontinuation of treatment:*¹²

- ALT or AST $> 8 \times \text{ULN}$
- ALT or AST $> 5 \times \text{ULN}$ for more than 2 weeks
- ALT or AST $> 3 \times \text{ULN}$ and TBL $> 2 \times \text{ULN}$ or INR > 1.5
- ALT or AST $> 3 \times \text{ULN}$ with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia ($> 5\%$ increase above baseline)

4.4 eDISH and liver enzymes elevations by treatment arm: The phase 3 studies had no potential Hy's law case. There was one subject with jaundice without aminotransferase or AP elevation. There was a higher incidence of subjects with ALT or AST elevation $> 3 \times \text{ULN}$ without hyperbilirubinemia with FZT use (**Figure 4, Temple's Corollary**). This higher incidence persisted at higher ALT or AST cut-off by Week 52, but the differences compared to placebo were smaller (**Table 4**). Similar pattern of transaminases elevations across treatment arms was observed for the 12-week periods in Studies 301 and 302, as well as 52-week period of Study 304 (**Appendix B, Section 2**). There was no clear dose-response relationship with ALT or AST elevation (i.e., FZT 30 mg versus 45 mg daily dosing).

¹² Seq 0002, SDN 2; [NDA216578 \(216578 - 0002 - \(2\) - 2022-07-21 - ORIG-1 /Multiple Categories/Subcategories\) - 16.1.1 Protocol Substantial Amendment 2 v3.0 \[2693-CL-0301\] \(#100\)](#)

Figure 4: eDish Plot for Studies 301, 302 and 304 *through Week 52* ¹³



¹³ Seq 0001 (SDN 1), 2.7.4, Summary of Clinical Safety, p. 94; [NDA216578 \(216578 - 0001 - \(1\) - 2022-06-22 - ORIG-1 /Multiple Categories/Subcategories\) - Summary of Clinical Safety \(#94\)](#)

Table 4: Liver Biochemistry Findings in Studies 301, 302 and 304 by Week 52 ¹⁴

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)	Fezolinetant Total (n = 2203)
ALT	> 3 x ULN	7/917 (0.8%)	13/917 (1.4%)	21/923 (2.3%)	1/152 (0.7%)	2/149 (1.3%)	14/1069 (1.3%)	23/1072 (2.1%)	37/2141 (1.7%)
	> 5 x ULN	3/917 (0.3%)	5/917 (0.5%)	6/923 (0.7%)	0/152	0/149	5/1069 (0.5%)	6/1072 (0.6%)	11/2141 (0.5%)
	> 8 x ULN	1/917 (0.1%)	1/917 (0.1%)	0/923	0/152	0/149	1/1069 (0.1%)	0/1072	1/2141 ($<0.1\%$)
	> 10 x ULN	0/917	1/917 (0.1%)	0/923	0/152	0/149	1/1069 (0.1%)	0/1072	1/2141 ($<0.1\%$)
	> 20 x ULN	0/917	0/917	0/923	0/152	0/149	0/1069	0/1072	0/2141
	> 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%)	20/2141 (0.9%)
AST	> 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%)	5/2141 (0.2%)
	> 8 x ULN	0/917	2/917 (0.2%)	0/923	0/152	0/149	2/1069 (0.2%)	0/1072	2/2141 (0.1%)
	> 10 x ULN	0/917	1/917 (0.1%)	0/923	0/152	0/149	1/1069 (0.1%)	0/1072	1/2141 ($<0.1\%$)
	> 20 x ULN	0/917	1/917 (0.1%)	0/923	0/152	0/149	1/1069 (0.1%)	0/1072	1/2141 ($<0.1\%$)
	> 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%)	41/2141 (1.9%)
	> 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%)	13/2141 (0.6%)
ALT or AST	> 8 x ULN	1/917 (0.1%)	2/917 (0.2%)	0/923	0/152	0/149	2/1069 (0.2%)	0/1072	2/2141 (0.1%)
	> 10 x ULN	0/917	1/917 (0.1%)	0/923	0/152	0/149	1/1069 (0.1%)	0/1072	1/2141 ($<0.1\%$)
	> 20 x ULN	0/917	1/917 (0.1%)	0/923	0/152	0/149	1/1069 (0.1%)	0/1072	1/2141 ($<0.1\%$)
	> 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%)	44/2142 (2.1%)
TBL	> 2 x ULN	0/917	0/918	1/923 (0.1%)	0/152	0/149	0/1070	1/1072 (0.1%)	1/2142 ($<0.1\%$)

4.5 Case level analyses: Fourteen subjects with ALT or AST >5x ULN were assessed in detail by the DILI team and the applicant's liver safety monitoring panel (LSMP). Of the 14, we assessed six as unlikely DILI, four as possible and four as probable (**Table 5**). Overall, our assessments were similar to the applicant's LSMP assessments. 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 the DILI Team assessed them as possible DILI.

¹⁴ Seq 0001 (SDN 1), 2.7.4, Summary of Clinical Safety, p. 95; [NDA216578 \(216578 - 0001 - \(1\) - 2022-06-22 - ORIG-1 /Multiple Categories/Subcategories\) - Summary of Clinical Safety \(#95\)](#)

Table 5: Summary of cases with ALT or AST 5x ULN¹⁵

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

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

NASH = non-alcoholic steatohepatitis

APAP = acetaminophen

NA = not applicable

We analyzed seven cases assessed as probable DILI by either the DILI Team or the LSMP. Such criteria excluded subjects in lines 8 through 14 in Table 5 above. The remaining seven subjects 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) (**Table 6**).

¹⁵ DILI Team, Microsoft Access database and Excel spreadsheet for NDA 216578

Table 6: Seven subjects assessed as having probable DILI by the DILI Team and/or LSMP¹⁶

#	Subject ID	Study	DILI Team Causality Score*	LSMP Causality Score*	Alternate diagnosis	Age (yr)	Symptoms	Hy's Law	Latency from start drug (da)	Latency from stop drug (da)#	ALT peak (U/L)	AST peak (U/L)	ALP peak (U/L)^	Bilirubin peak (mg/dL)	R value peak (ALT)	R value peak (AST)	
1	(b) (6)	2693-CL-0301	3	3	NA	55	No	No	84	-1	686	1515	153	0.5	13.71	30.29	
2		2693-CL-0302	3	4	NA	57	No	No	54	-51	322	158	104	0.4	9.47	4.65	
3		2693-CL-0301	3	3	NA	48	Yes	No	28	-8	293	194	104	0.3	8.62	5.71	
4		2693-CL-0304	3	3	NA	55	No	No	250	-62	270	189	116	1.17	7.12	4.98	
5		2693-CL-0304	4	3	Unknown	52	No	No	56	-36	336	203	104	0.7	9.88	5.97	
6		2693-CL-0304	4	3	APAP	52	No	No	114	-249	223	97	104	0.5	6.56	2.85	
7		2693-CL-0304	4	3	APAP	58	No	No	14	-352	219	172	172	0.2	3.89	3.06	
mean									54	86	-108	336	361	122	0.5	8.5	8.2
std dev									3.2	74	126	149	472	26	0.3	2.9	9.1
median									55	56	-51	293	189	104	0.5	8.6	5.0
max									58	250	-1	686	1515	172	1.2	13.7	30.3
min									48	14	-352	219	97	104	0.2	3.9	2.9

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

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

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

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

LSMP = Liver Safety Monitoring Panel

NA = not applicable

APAP = acetaminophen

Cases of interest:

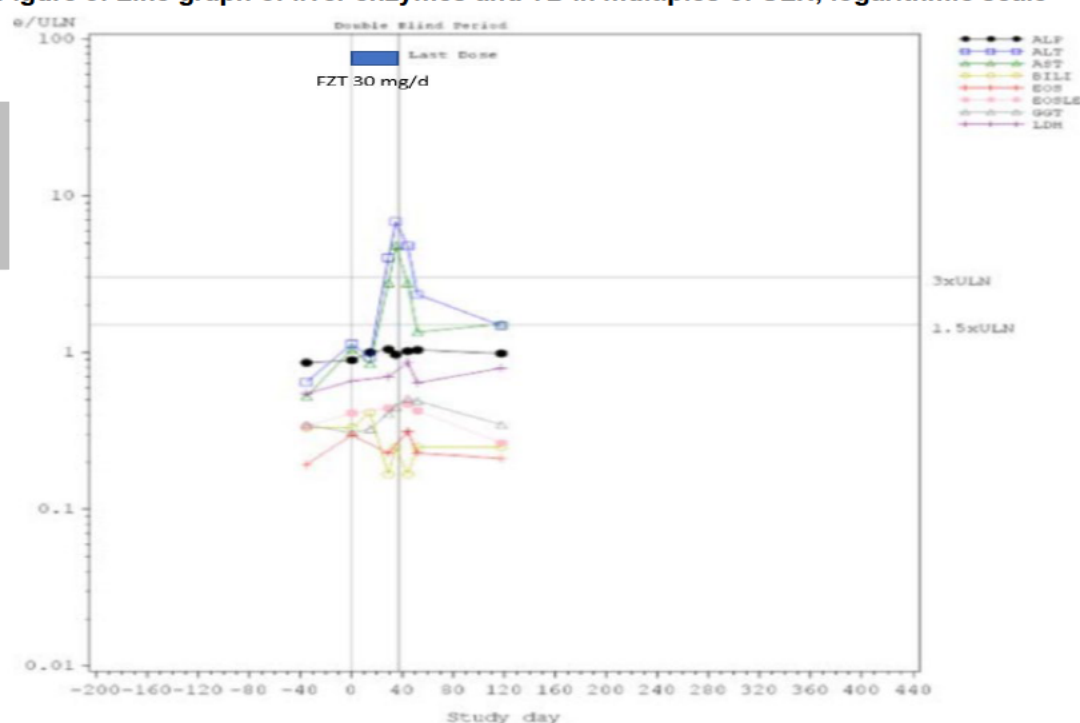
Subject (b) (6) (Study 2693-CL-0301)

Summary: This is a 48-year-old woman enrolled in the United States. At baseline, her BMI was 29.2 kg/m². Medical history included rheumatoid arthritis since 2000. Medications included oxycodone, paracetamol, taken for more than a year prior to study entry, and varenicline (Chantix) taken (b) (6), to (b) (6). ALT was 49 U/L, AST 42 U/L, AP 93 U/L and TB 0.4 mg/dL.

On (b) (6), she started FZT at 30 mg/d. She started varenicline on (b) (6), for smoking cessation. On (b) (6), her ALT was 173 U/L, AST 111 U/L and TB 0.2 mg/dL. FZT continued. ALT and AST peaked on (b) (6). She developed nausea, and FZT was stopped on (b) (6). Chantix was also stopped that day. Thereafter liver tests fell by 50% within 17 days and went to near baseline by (b) (6). (Figure 5). She had no eosinophilia, fever, lymphadenopathy or rash. Serologies for hepatitis B and C were negative. Ultrasound (US) was normal. No other evaluation test results were given.

¹⁶ DILI Team, Microsoft Access database and Excel spreadsheet for NDA 216578

Figure 5: Line graph of liver enzymes and TB in multiples of ULN, logarithmic scale¹⁷



Assessment: We assessed this case as probable DILI. The latency and washout are appropriate. Lack of adequate evaluation (e.g., HAV IgM, HCV RNA, HEV IgM) leave other etiologies competing, but HAV and HEV seem less likely in the United States, and no HCV risk factors were given. She did have symptoms of nausea, but no fever, lymphadenopathy or rash mentioned. Varenicline is in the right timeframe but is a rare cause of DILI. This case is similar to several other probable or possible liver injuries due to FZT

Subject (b) (6) **(Study 2693-CL-0304)**

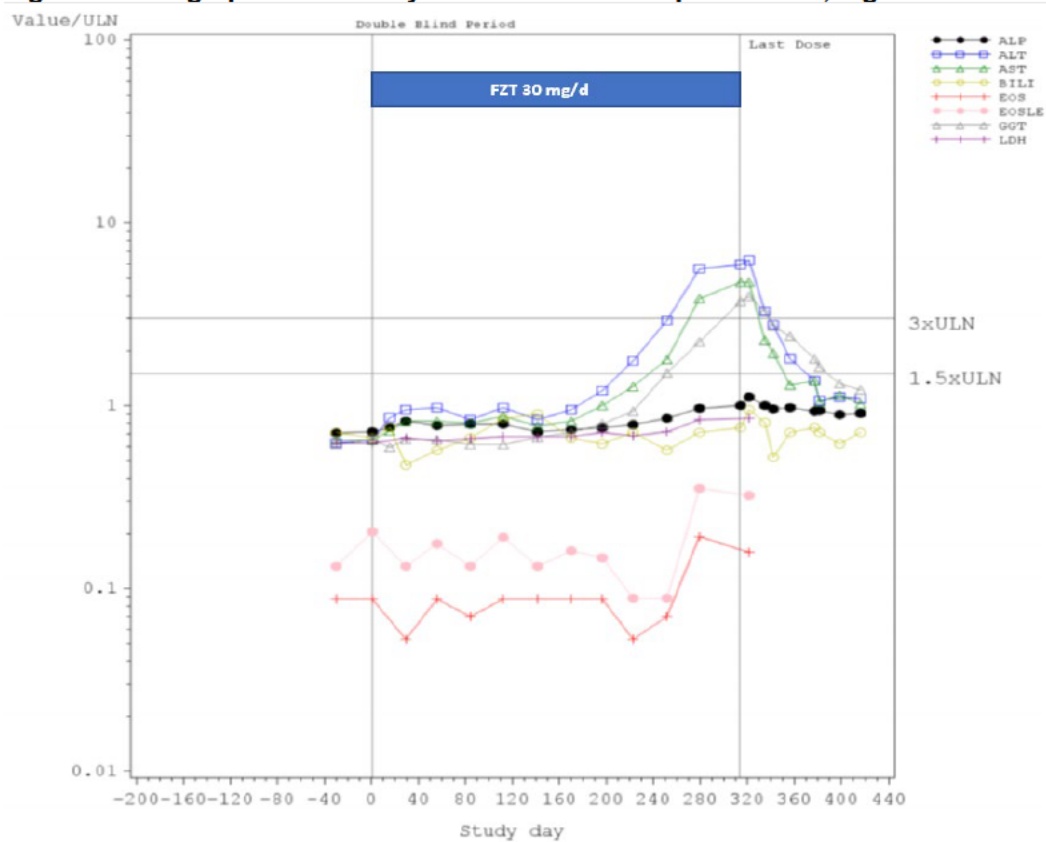
Summary: This is a 55-year-old white woman enrolled in (b) (6). At baseline, BMI was 23.3 kg/m². Medical history included hypothyroidism on replacement therapy. ALT was 28 U/L, AST 26 U/L, ALP 75 U/L, and total bilirubin was normal.

She started FZT at 45 mg/d on (b) (6). She did well except she had baseline and continued mild thrombocytopenia of unclear source. On (b) (6), her ALT was 126 U/L, AST 72 U/L with normal AP and TB. No symptoms were mentioned. No eosinophilia was reported. Liver tests continued to increase warranting FZT stop on (b) (6). ALT and AST would go on to peak at ALT 270 U/L and AST 189 U/L. Thereafter her aminotransferases fell by 50% in 14-21 days but took much longer to

¹⁷ Adapted from Seq 0006 (SDN 6), Study 2693-CL-0301 Clinical Safety Report, p. 1968; [NDA216578 \(216578 - 0006 - \(6\) - 2022-08-19 - ORIG-1 /Clinical/Response To Information Request\) - Study Report Body \[2693-CL-0301\] \(#1968\)](#)

return to normal. (**Figure 6**) Hepatitis B and C serologies were negative. US was normal. No other evaluation test data were given. CK and LDH were not elevated.

Figure 6: Line graph of liver enzymes and TB in multiples of ULN, logarithmic scale¹⁸



Assessment: This is probable DILI due to FZT. The case is remarkable for a long latency, persistence of a few days after the drug was stopped, and long washout followed by normal enzyme levels. HAV, HEV and HCV status were unknown to due to lack of screening.

5.0 Assessment & Recommendations

5.1 Assessment: Fezolinetant (FZT) is small molecule, neurokinin 3 (NK3) receptor antagonist with an indication for treating vasomotor symptoms (VMS) of menopause. 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.

¹⁸ Adapted from Seq 0006 (SDN 6), Study 2693-CL-0304 Clinical Safety Report, p. 2339; [NDA216578 \(216578 - 0006 - \(6\) - 2022-08-19 - ORIG-1 /Clinical/Response To Information Request\) - Study Report Body \[2693-CL-0304\] \(#2339\)](#)

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 compared to 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 DILI, but it appears modest, and adaptation may occur with continued exposure. However, the number of women exposed post market could be quite large. One estimate suggests 40 to 50 million women in the United States have VMS.¹⁹ Only 20-30 percent may seek medical care;²⁰ but if FZT is prescribed to just 1-5% of these women, then the number exposed could be 80,000 to 750,000.²¹ With such a potentially large exposure population, more severe cases of DILI could arise.

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

5.2 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.

Paul H.
Hayashi -S

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Hayashi -S
Date: 2022.11.21 13:20:27
-05'00'

(Signing for and at the agreement of Dr. Lan)

Ling Lan, MD, PhD

¹⁹ Utian WH. Psychosocial and socioeconomic burden of vasomotor symptoms in menopause: A comprehensive review. Health and Quality of Life Outcomes, 2005, 47:1-10;
<https://hqlo.biomedcentral.com/articles/10.1186/1477-7525-3-47>

²⁰ UpToDate: https://www.uptodate.com/contents/menopausal-hot-flashes?search=vasomotor%20menopause%20epidemiology&source=search_result&selectedTitle=5~150&usage_type=default&display_rank=5#H3 (Last update: Oct 24, 2022; Accessed Nov 18, 2022)

²¹ (0.2 x 40 million x 0.01 = 80,000; 0.3 x 50 million x 0.05 = 750,000)

Clinical Analyst, DILI Team, Division of Hepatology and Nutrition
CDER/OND

**Paul H.
Hayashi -S**

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Hayashi -S
Date: 2022.11.21 13:21:23
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Paul H. Hayashi, MD, MPH
DILI Team Lead, Division of Hepatology and Nutrition
CDER/OND

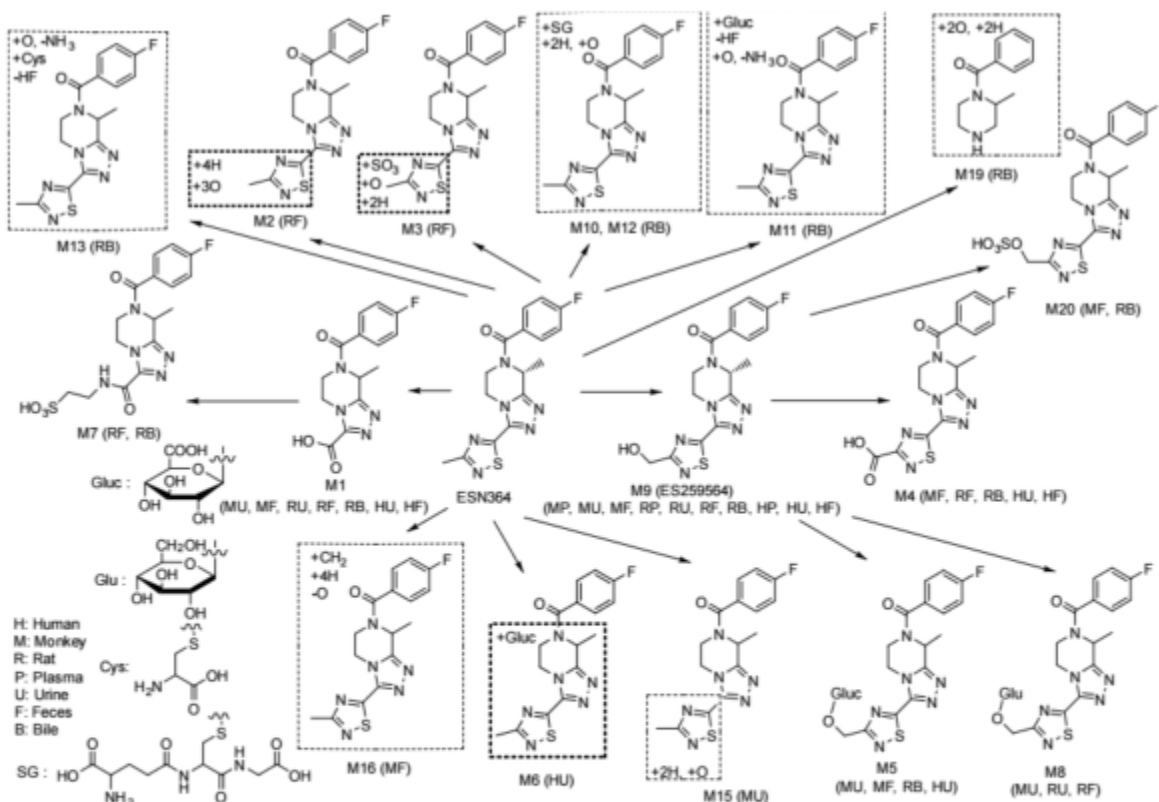
Frank A. Anania -S

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Date: 2022.11.21 13:25:53 -05'00'

Frank A. Anania, MD
Acting Director, Division of Hepatology and Nutrition
CDER/OND

Appendix A: ADME and non-clinical data

Figure A: In vivo postulated metabolic pathways for fezolinetant²²



ESN364: fezolinetant; M1: triazole carboxylic acid metabolite; M2: oxidized methylthiadiazole metabolite; M3: sulfuric acid conjugate of oxidized metabolite; M4: carboxylic acid metabolite; M5: glucuronic acid conjugate of M9; M6: glucuronic acid conjugate of fezolinetant; M7: taurine conjugate of M1; M8: glucose conjugate of M9; M9: hydroxylated metabolite (ES259564); M10: glutathione conjugate of oxidized metabolite; M11: glucuronic acid conjugate of oxidative deaminated and defluorinated metabolite; M12: glutathione conjugate of oxidized metabolite; M13: cysteine conjugate of oxidative deaminated and defluorinated metabolite; M15: oxidized methylthiadiazole metabolite; M16: methyl conjugate of deoxygenated and hydrogenated metabolite; M19: oxidized 1-benzoyl-2-methylpiperazine metabolite; M20: sulfuric acid conjugate of M9.

²² [NDA216578 \(216578 - 0001 - \(1\) - 2022-06-22 - ORIG-1 /Multiple Categories/Subcategories\) - Pharmacokinetics Written Summary \(#25\)](#)

Appendix B: Trial design schematics and additional eDISH plots

1. Schematics for phase 3 studies

Figure A: Study 2693-CL-0301 and 2693-CL-0302 (identical protocol schematics):^{23, 24}

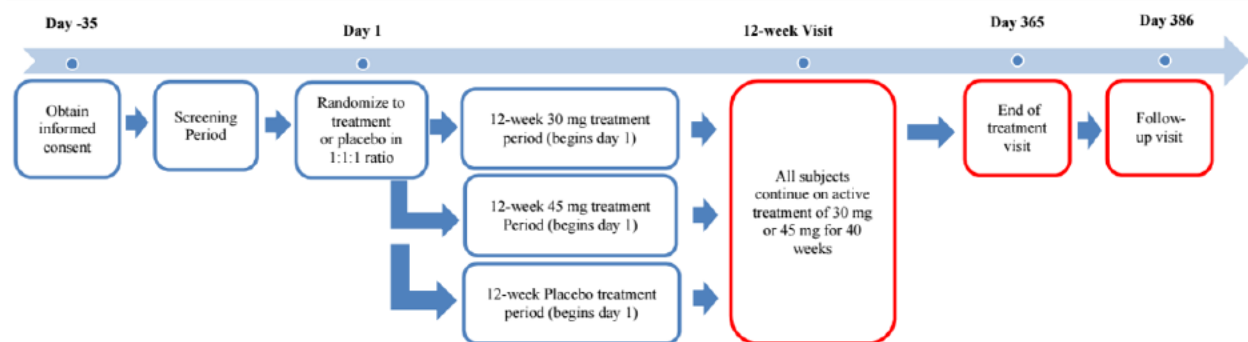
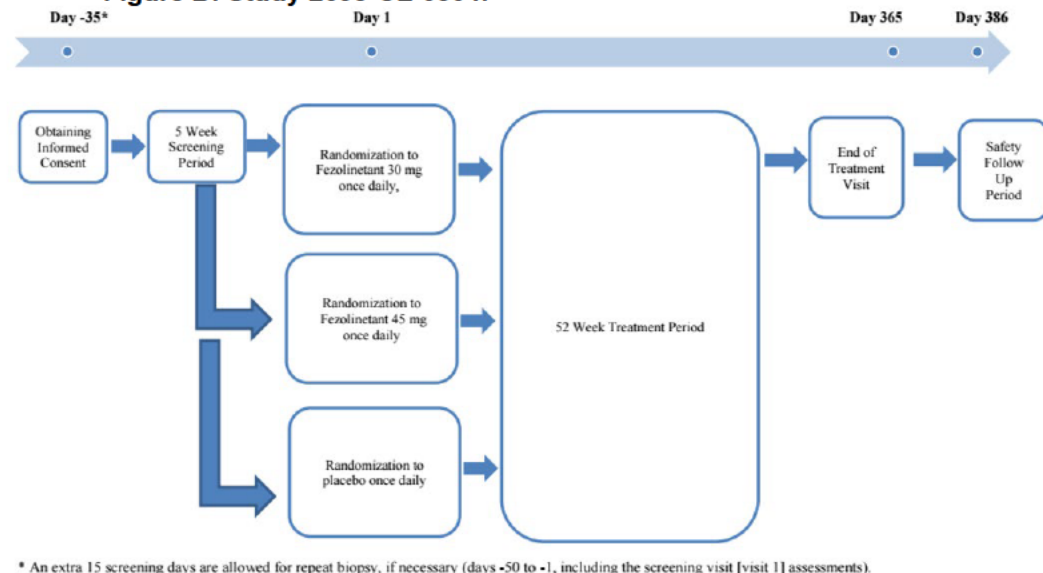


Figure B: Study 2693-CL-0304:²⁵



2. Additional eDISH plots

²³ [NDA216578 \(216578 - 0001 - \(1\) - 2022-06-22 - ORIG-1 /Multiple Categories/Subcategories\) - 16.1.1 Protocol Substantial Amendment 1 v2.0 \[2693-CL-0301\] \(#25\)](#)

²⁴ [NDA216578 \(216578 - 0001 - \(1\) - 2022-06-22 - ORIG-1 /Multiple Categories/Subcategories\) - 16.1.1 Protocol Substantial Amendment 1 v2.0 \[2693-CL-0302\] \(#25\)](#)

²⁵ [NDA216578 \(216578 - 0001 - \(1\) - 2022-06-22 - ORIG-1 /Multiple Categories/Subcategories\) - 16.1.1 Protocol Non-Substantial Amendment 3 v3.2 \[2693-CL-0304\] \(#24\)](#)

Figure C: eDISH plot for Study 301 by Week 12²⁶

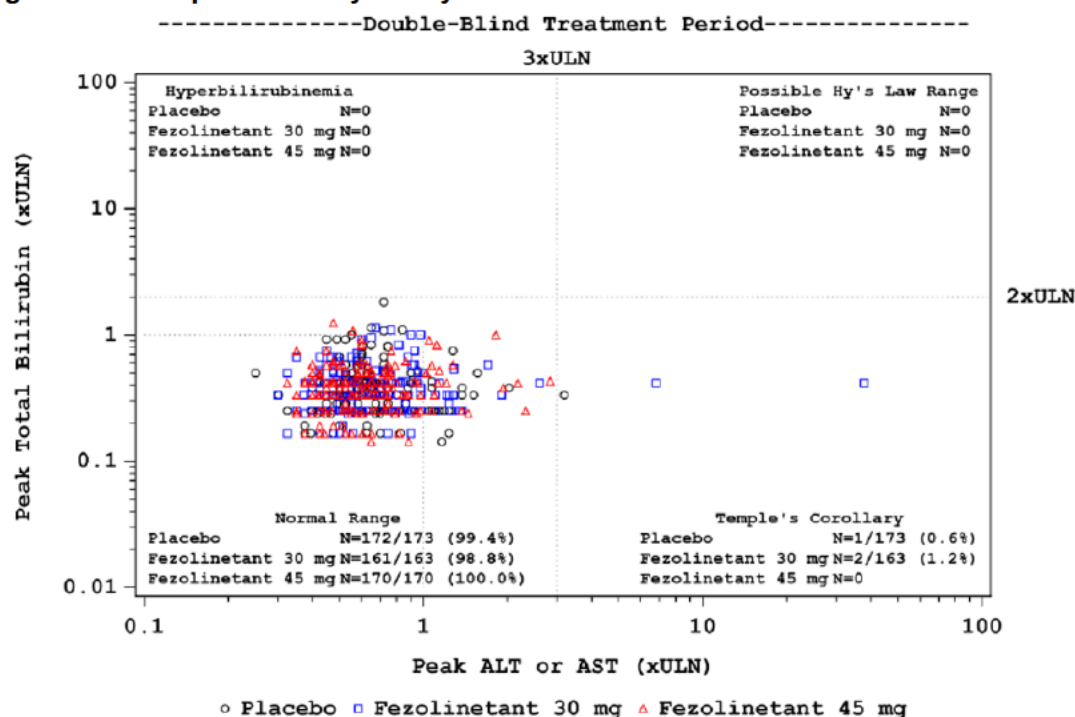
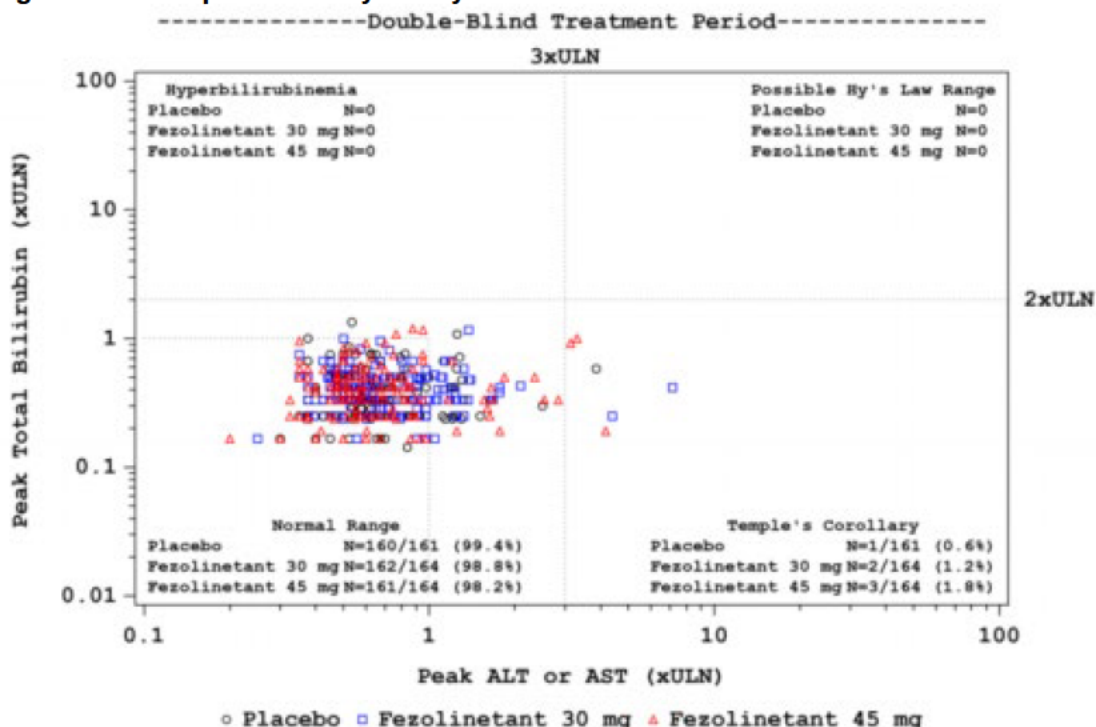


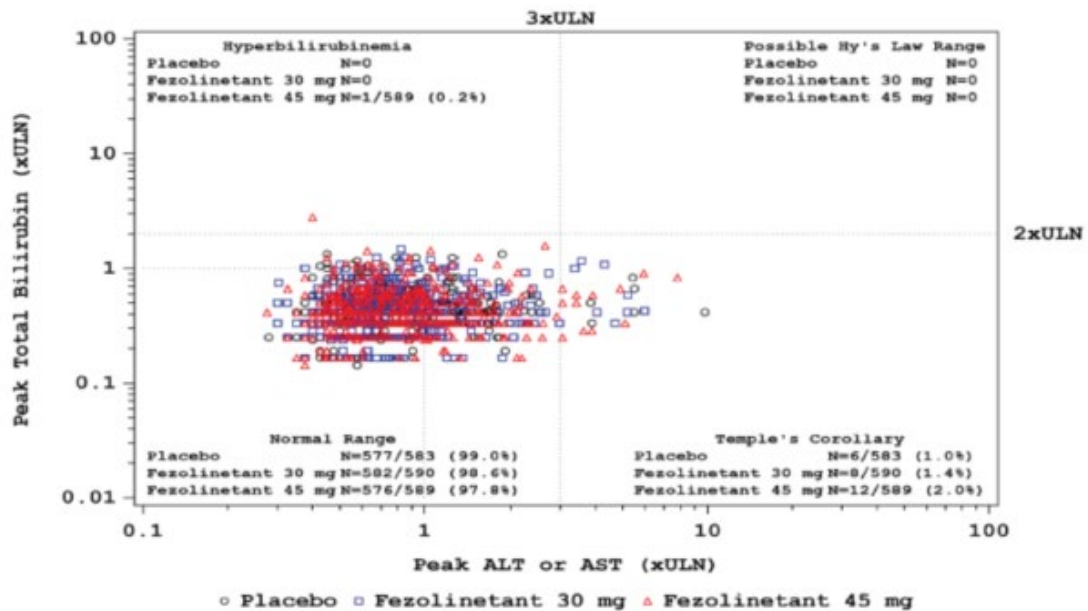
Figure D: eDISH plot for Study 302 by Week 12²⁷



²⁶ [NDA216578 \(216578 - 0001 - \(1\) - 2022-06-22 - ORIG-1 /Multiple Categories/Subcategories\) - Study Report Body \[2693-CL-0301\] \(#112\)](#)

²⁷ [NDA216578 \(216578 - 0001 - \(1\) - 2022-06-22 - ORIG-1 /Multiple Categories/Subcategories\) - Study Report Body \[2693-CL-0302\] \(#111\)](#)

Figure E: eDISH plot for Study 304 by Week 52²⁸



²⁸ [NDA216578 \(216578 - 0001 - \(1\) - 2022-06-22 - ORIG-1 /Multiple Categories/Subcategories\) - Study Report Body \[2693-CL-0304\] \(#67\)](#)

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

/s/

PAUL H HAYASHI
11/21/2022 02:58:41 PM

MEMORANDUM**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

DATE: 11/3/2022

TO: Division of Urology, Obstetrics, and Gynecology (DUOG)
Office of Rare Diseases, Pediatrics, Urology and Reproductive Medicine (ORPURM)

FROM: Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Decline to conduct an on-site inspection**

RE: NDA 216578

OSIS received an inspection request consult from the Division of Urology, Obstetrics, and Gynecology on August 3, 2022, for the below site. The requested review goal date is November 4, 2022, and the PDUFA date is February 22, 2023.

The Office of Study Integrity and Surveillance (OSIS) declines to conduct an inspection for the site listed on the consult. The rationale for this decision is noted below.

Rationale

An inspection of the site listed below is not able to be completed. Specifically, the requested review goal date of November 4, 2022, to meet the PDUFA date of February 22, 2023, does not provide sufficient time for the inspection to be completed and for OSIS to provide a review to the review.

We note that OSIS's inspection history for the site is listed below.

The Office of Regulatory Affairs (ORA) conducted an inspection of the site in October 2018. The inspection was conducted under the following submission: NDA 210874.

The following item was discussed with the site:

- Pharmacokinetic (PK) sampling deviations were noted during sample collection and the sample collections were not handled within the prescribed time window outlined in the clinical protocol.

After review of the inspectional findings, OSIS noted that the protocol deviations were already reported to the agency and concluded that data from the reviewed study were reliable.

Site

Facility Type	Facility Name	Facility Address
Clinical	PAREXEL Early Phase Clinical	MedStar Harbor Hospital, 3001 South Hanover Street, 7th Floor, Baltimore, MD

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/s/

WENDY NG
11/03/2022 07:13:03 PM



Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: October 4, 2022

From: Interdisciplinary Review Team for Cardiac Safety Studies

Through: Christine Garnett, PharmD
Team Lead Cardiac Safety IRT, DCN

To: Samantha Bell
DUOG

Subject: QT Consult to NDA216578 (SDN 001)

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

This memo responds to your consult to us dated 7/28/2022 regarding the Review Division's QT related question. We reviewed the following materials:

- Sponsor's TQT [study waiver summary \(NDA216578 / SDN001\)](#);
- Sponsor's [proposed fezolinetant label \(NDA216578 / SDN001\)](#);
- Sponsor's [summary of Clinical Pharmacology studies \(NDA216578 / SDN001\)](#);
- Sponsor's [proposed label \(NDA216578 / SDN001\)](#);
- Previous IRT review(s) for IND130277 dated [04/02/2019](#); [11/21/2019](#) in DARRTS;
- [Highlights of clinical pharmacology and cardiac safety \(NDA216578 / SDN001\)](#).

1 Responses for the Sponsor

Question from the Review Division: On June 22, 2022, Astellas Pharma Global Development, Inc (Astellas) submitted their NDA 216578 application for ESN364 (fezolinetant), 45 mg oral tablet, for the treatment of moderate to severe vasomotor symptoms (VMS) associated with menopause. Fezolinetant is a small molecule non-hormonal selective NK3 receptor antagonist that blocks neurokinin B (NKB) binding on the kisspeptin/neurokinin/dynorphin (KNDy) neuron to modulate neuronal activity in the thermoregulatory center.

Per FDA feedback at the April 17, 2019, End of Phase 2 meeting, the Applicant has submitted the requested information in a TQT waiver request package in their NDA for the Agency's review.

IRT's response: The Applicant's QT assessments for fezolinetant, including C-QT report and data, were previously reviewed by the IRT (See [IRT review for IND130277 dated 11/21/2019](#) in DARRTS). In the previous review, the IRT determined that, based on a randomized, double-blind, placebo-controlled, 3-part (part-1: single ascending dose, part-2: multiple ascending doses, and part-3: single ascending dose) clinical study, fezolinetant did not cause concentration-dependent QTc prolongation. However, at the time of the previous review, the maximum recommended dose was 30 mg QD and the highest tested dose in the study provided > 2-fold margin over worst-case exposure and therefore justified waiving a positive control. Now, the sponsor has revised fezolinetant dosage to 45 mg QD. In addition, the sponsor has recommended contraindication to patients with severe or end-stage renal impairment, (b) (4) and patients taking strong CYP1A2 inhibitors. Despite the higher dosage of 45 mg QD than previously recommended, given the new worst-case exposure scenario, the highest tested dose still covers > 2-fold margin of the anticipated worst-case exposure and therefore the study still meets the assay sensitivity requirements. Based on this assessment, the previous IRT review is applicable to the new proposed dosage regimen of 45 mg QD.

Proposed label:

Below are proposed edits to the label submitted to SDN 0001.

Our changes are highlighted ([addition](#), ~~deletion~~). Each section is followed by a rationale for the changes made. Please note that this is a suggestion only and that we defer final labeling decisions to the Division.

(b) (4)	
<i>We propose to use labeling language for this product consistent with the "Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format" guidance.</i>	

2 Internal Comments for the Division

- *None*

3 BACKGROUND

3.1 Product Information

Fezolinetant (MW = 358.39) is a non-hormonal antagonist of the selective neurokinin 3 (NK3) receptor. The sponsor (Astellas Pharma Inc.) is seeking FDA approval for fezolinetant for the indicated treatment of moderate to severe vasomotor symptoms (VMS) associated with

menopause. The recommended maximum therapeutic dose for this indication is 45 mg orally QD, with or without food.

A summary of fezolinetant clinical pharmacokinetics (PK) is presented in the [table of highlights of clinical pharmacology and cardiac safety](#). In brief, Fezolinetant is formulated as 45 mg film-coated tablets. It is rapidly absorbed after oral administration (Dose dependent median Tmax range between 1.25 – 4 hours, after 3 – 900 mg single dose). Fezolinetant is mainly metabolized by CYP1A2 to a major metabolite (ES259564) with mean AUC_{0-inf} ratio (metabolite/parent) of 1.84-fold. The metabolite is mainly eliminated through urine. Based on the sponsor's population PK model, the 45 mg QD dosage is projected to provide fezolinetant and ES259564 steady state geometric mean Cmax of 354 ng/mL and 350 ng/mL respectively. According to the sponsor, intrinsic and extrinsic factors with clinically relevant impact of fezolinetant and ES259564 PK are:

- i) Body weight: subjects < 45 Kg have 1.44-fold higher fezolinetant Cmax.
- ii) Race: Asian have 1.25-fold higher fezolinetant Cmax than Caucasian.
- iii) Renal impairment: ES259564 Cmax were 1.13-, 1.74-, and 2.3-fold higher in subjects with mild, moderate, and severe impairment, respectively, compared to normal function (See Summary of Clinical Pharmacology studies).
- iv) Hepatic impairment: fezolinetant AUC_{0-inf} were 1.55-, and 1.96- fold higher in subjects with mild and moderate impairment, respectively, compared to normal function. No clinically relevant increase in fezolinetant Cmax was observed (See Summary of Clinical Pharmacology studies).
- v) Drug interaction with CYP1A2 inhibitor: co-administration with a strong CYP1A2 inhibitor, fluvoxamine, increased fezolinetant Cmax by 1.82-fold while according to the sponsor's PBPK model, a weak CYP1A2 inhibitor, cimetidine, would increase fezolinetant Cmax by 1.4-fold.

According to the proposed label, fezolinetant is prohibited in subjects with severe or end-stage renal impairment and in subjects with (b) (4). Also, the drug should not be co-administered with strong CYP1A2 inhibitors.

Based on the presented information, the worst-case exposure scenario for fezolinetant and ES259564 it is when co-administered with weak CYP1A2 inhibitors or when taken by patients weighting < 45 Kg.

3.2 Sponsor's position related to the question

Previously, the sponsor submitted a request for waiver of a TQT study based on clinical QT assessments in study ESN364-CPK-102, study Study 2693-CL-0020, and study 2693-CL-0006 (IND130277). At the time, the maximum recommended dosage of fezolinetant was 30 mg QD. The IRT reviewed the sponsor's study reports, including C-QT modeling report and data, and determined based on independent analyses that no significant QTc prolongation was detected at fezolinetant concentrations up to ~2.5-fold higher than the worst-case exposure scenario. At the time of the previous review, the renal and hepatic impairment studies were pending, and worst-case Cmax was calculated from combined effects of strong CYP1A2 inhibition, body weight <

45 Kg, higher Cmax for tablet vs capsule formulation, Asian patients, and an additional 2-fold factor to account for potential impact of organ impairment. Since the review of the sponsor's QT assessments were done under IND, no label language was suggested.

In the current NDA216578 application, the sponsor recommends a higher dosage of 45 mg QD than the previous 30 mg QD, and therefore resubmits a request for TQT study waiver. In the current waiver request, the same QT assessments under the IND130277 are presented (See [TQT study waiver summary](#) and [previous IRT review dated 11/21/2019](#)). In addition, the sponsor has re-calculated the worst-case Cmax based on the projected steady state Cmax of fezolinetant capsule 45 mg QD (375 ng/mL) and the combined effects weak CYP1A2 inhibition (1.4-fold), Asian patient (1.25-fold), low body weight (1.44-fold), tablet formulation (1.225-fold), and organ impairment (1.82-fold). Based on the sponsor's recalculated worst-case Cmax (2250 ng/mL), the highest geometric mean Cmax (5346 ng/mL) in study ESN364-CPK-102 (after a single 900 mg dose) covers > 2-fold of the worst-case exposure and therefore supports waiving the requirement for inclusion of a positive control.

Reviewer's comments:

- 1) *The highest geometric mean Cmax in study ESN364-CPK-102 provides adequate coverage of the new proposed therapeutic and worst-case exposure and supports waiving the requirement for inclusion of a positive control. Therefore, the previous IRT review and conclusions remains applicable to the new recommended dosage of 45 mg QD.*
- 2) *The impact of poor metabolizers on fezolinetant exposure has not yet been characterized. However, given the coverage of the highest geometric mean Cmax in study ESN364-CPK-102 (after a single 900 mg dose) over the projected therapeutic exposure (5346 ng/mL /354 ng/mL = 15-fold), and the absence of concentration-dependent increase in QT interval, subjects with poor metabolism are less likely to be at risk for QT prolongation when taking fezolinetant.*

3.3 Nonclinical Cardiac Safety

Refer to previous QT-IRT review dated 04/02/2019 in DARRTS.

3.4 Clinical Cardiac Safety

Refer to previous QT-IRT review dated 11/21/2019 in DARRTS

3.5 Summary results of prior QTc assessments

Refer to previous QT-IRT review dated 11/21/2019 in DARRTS

3.6 Relevant details of planned Phase 3 study

NA

Thank you for requesting our input into the development of this product. We welcome more discussion with you now and in the future. Please feel free to contact us via email at cderdcrpqt@fda.hhs.gov

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

/s/

ELIFORD N KITABI
10/04/2022 03:30:33 PM

CHRISTINE E GARNETT
10/04/2022 03:33:09 PM

LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	September 16, 2022
Requesting Office or Division:	Division of Urology, Obstetrics, and Gynecology (DUOG)
Application Type and Number:	NDA 216578
Product Name and Strength:	fezolinetant tablets, 45 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Astellas Pharma US, Inc.
FDA Received Date:	June 22, 2022, July 21, 2022, and July 28, 2022
TTT ID #:	2022-707
DMEPA 2 Safety Evaluator:	Justine Kalonia, PharmD
DMEPA 2 Acting Team Leader:	Stephanie DeGraw, PharmD

1 REASON FOR REVIEW

As part of the approval process for fezolinetant tablets, the Division of Urology, Obstetrics, and Gynecology (DUOG) requested that we review the proposed fezolinetant prescribing information (PI), patient information (PPI), container (trade and sample) labels, and carton (trade and sample) labeling for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B – N/A
ISMP Newsletters*	C – N/A
FDA Adverse Event Reporting System (FAERS)*	D – N/A
Other	E – N/A
Labels and Labeling	F

N/A=not applicable for this review

*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 CONCLUSION AND RECOMMENDATIONS

The proposed prescribing information (PI), patient information (PPI), container labels, and carton labeling may be improved to promote the safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error in Section 4 for the Division and in Section 5 for Astellas Pharma US, Inc.

4 RECOMMENDATIONS FOR DIVISION OF UROLOGY, OBSTETRICS, AND GYNECOLOGY (DUOG)

Table 2. Identified Issues and Recommendations for Division of Urology, Obstetrics, and Gynecology (DUOG)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Prescribing Information and Patient Information – General Issues			
1.	The proposed proprietary name, (b) (4) is used throughout the prescribing information (PI), patient information (PPI), and container labels and carton labeling.	The proprietary name, (b) (4) was found unacceptable by DMEPA.	We recommend removing the proposed proprietary name, (b) (4) throughout the PI, PPI, and container labels and carton labeling. Until a new name is found to be conditionally acceptable, the placeholder “TRADENAME” may be used. Then replace “TRADENAME” with the proprietary name that is eventually found conditionally acceptable.
Full Prescribing Information – Section 16 How Supplied/Storage and Handling			
2.	We note that the container labels and carton labeling state (b) (4). However, the PI does not include a similar statement.	If this information is necessary (b) (4). As presented, the intention of this statement on the container labels and carton labeling is unclear.	In Table 3 below, we provide a clarifying question for the Sponsor to address regarding the intention of this statement on the container labels and carton labeling. We defer to the Review Team to determine whether a similar “(b) (4)” statement is needed within Section 16 of the PI.

5 RECOMMENDATIONS FOR ASTELLAS PHARMA US, INC.

Table 3. Identified Issues and Recommendations for Astellas Pharma US, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
General Recommendations (All Labels and Labeling)			

1.	The proposed proprietary name, (b) (4) is used throughout the container labels and carton labeling.	The proprietary name, (b) (4) was found unacceptable by DMEPA. Please refer to the advice letter dated September 15, 2022.	Remove the proposed proprietary name, (b) (4) throughout the container labels and carton labeling. Until a new name is found to be conditionally acceptable, the placeholder “TRADENAME” may be used. Then replace “TRADENAME” with the proprietary name that is eventually found conditionally acceptable.
Container Labels and Carton Labeling			
2.	As currently presented, the strength statement is less prominent than the net quantity statements. Additionally, the net quantity is located closer in proximity to the proprietary and established names, such that it may be misinterpreted as the strength.	From post-marketing experience, the risk of numerical confusion between the strength and net quantity increases when the net quantity statement has similar prominence as the product strength.	We recommend you increase the prominence of the strength statement and consider relocating the strength to appear after (under) the established name and dosage form. Additionally, relocate the net quantity statement further away from the product name (e.g., to the bottom of the principal display panel (PDP)).
3.	As currently presented, the professional sample blister label and the carton and tray labeling do not have NDC numbers.	Although the NDC is not required to be on the sample labels and labeling, we recommend including it to allow for product identification. ^a	We recommend you consider adding NDC numbers on the professional sample blister label, carton and tray labeling.
4.	As presented, the container labels and carton labeling contain	Although negative statements should generally be avoided, we find this specific statement	We recommend you revise the negative statement “Do not cut, crush, or chew

^a Guidance for Industry: *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors*. 2022. Available from: <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/safety-considerations-container-labels-and-carton-labeling-design-minimize-medication-errors>.

	the following negative statement: “Do not cut, crush, or chew tablets.” This can be improved for clarity.	is necessary as this is a film-coated tablet that should be swallowed whole. However, it can be improved by adding an affirmative statement prior to the negative statement. ^b	tablets” to read “Swallow tablet whole. Do not cut, crush, or chew tablets.”
5.	The “(b) (4)” statement can be improved.	To ensure consistency with the Physician Labeling Rule (PLR) formatted Prescribing Information Labeling.	We recommend you revise the statement from: “(b) (4): Take one tablet daily by mouth. Do not cut, crush, or chew tablets. Each tablet contains 45 mg of fezolinetant. (b) (4)” to read: “Recommended Dosage: Take one tablet daily by mouth. Swallow tablet whole. Do not cut, crush, or chew tablets. Each tablet contains 45 mg of fezolinetant. See Prescribing Information.”
6.	We note that the container labels and carton labeling include the following statement: (b) (4)	The intent of this statement is unclear. If this information is necessary (b) (4)	Please provide the rationale for this statement and revise the labels and labeling accordingly.
Carton Labeling			
7.	As currently presented, there is no machine-readable (2D data matrix barcode) product	In June 2021, FDA finalized guidance on product identifiers required under the Drug Supply Chain Security Act (DSCSA).* The Act requires manufacturers	We recommend that you review the draft guidance. If you determine that the product identifier requirements apply to your

	identifier on the carton labeling.	and re-packagers, respectively, to affix or imprint a product identifier to each package and homogenous case of a product intended to be introduced in a transaction in(to) commerce beginning November 27, 2017, and November 27, 2018, respectively. * The guidance is available from: https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm621044.pdf	product's labeling, we request you add a placeholder for the machine-readable (2-D data matrix barcode) product identifier to the carton labeling.
8.	For the professional sample carton and tray labeling, we note the strength statement is presented as "45 mg"; therefore, it may not be immediately clear that the designated strength is per single unit (i.e., tablet).	Failure to clearly express the product strength per single unit may lead to wrong dose errors. In fact, we are aware of reports where confusion occurred because it was not clear that the designated strength was per unit (e.g. XX mg per tablet).^b	On the professional sample carton and tray labeling, consider adding "per tablet" to the strength statement, such that it reads "45 mg per tablet".

^b Institute for Safe Medication Practices. 2006 May 04. Guessing not appropriate. ISMP Med Saf Alert Acute Care. 11(9):1-4.

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for fezolinetant tablets that Astellas Pharma US, Inc. submitted on July 21, 2022.

Table 4. Relevant Product Information for fezolinetant tablets	
Initial Approval Date	N/A
Active Ingredient	fezolinetant
Indication	for the treatment of moderate to severe vasomotor symptoms (VMS) associated with menopause
Route of Administration	oral
Dosage Form	tablets
Strength	45 mg
Dose and Frequency	45 mg (1 tablet) once daily with or without food
How Supplied	Trade Product: - Bottles of 30 tablets with child resistant closure and desiccant - Bottles of 90 tablets with child resistant closure and desiccant Sample product: Tray carton contains 4 cartons that each contain one blister card of 7 tablets.
Storage	Store at 20°C to 25°C (68°F to 77°F) with excursions permitted from 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].
Container Closure	- Trade product: High density polyethylene (HDPE) bottles with child resistant (CR) (b) (4) closures lined with induction seals and desiccant. - Sample Product: Aluminum/aluminum blisters

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^c along with postmarket medication error data, we reviewed the following fezolinetant tablets labels and labeling submitted by Astellas Pharma US, Inc.

- Container labels received on July 28, 2022 (bottle container labels)
- Carton labeling received on June 22, 2022 (bottle carton labeling)
- Professional Sample Blister cards received on July 28, 2022 (sample blister container labels)
- Professional Sample Carton Labeling received on July 28, 2022 (sample blister tray and carton labeling)
- Patient Information received on July 21, 2022, available from <\\CDSESUB1\evsprod\nda216578\0002\m1\us\114-labeling\draft\labeling\fezolinetant-tab-plr4-usppi-en-clean.docx>
- Prescribing Information (Image not shown) received on July 21, 2022, available from <\\CDSESUB1\evsprod\nda216578\0002\m1\us\114-labeling\draft\labeling\fezolinetant-tab-plr4-uspi-en-clean.docx>

F.2 Label and Labeling Images

Container Labels



5 Pages of Draft Labeling have been Withheld in Full as
B4(CCI/TS) Immediately Following this Page

^c Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

JUSTINE H KALONIA
09/16/2022 10:01:34 AM

STEPHANIE L DEGRAW
09/16/2022 11:07:45 AM