Summary Report of Benefit-Risk Assessment

VEOZA™ FILM-COATED TABLETS 45 MG

NEW DRUG APPLICATION

Active Ingredient(s)	Fezolinetant
Product Registrant	Astellas Pharma Singapore Pte. Ltd.
Product Registration Number	SIN17196P
Application Route	Abridged evaluation
Date of Approval	05 March 2025

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A INTRODUCTION

Veoza is indicated for the treatment of moderate to severe vasomotor symptoms (VMS) associated with menopause.

The active substance, fezolinetant, is a non-hormonal selective neurokinin 3 (NK3) receptor antagonist that blocks neurokinin B (NKB) binding on the kisspeptin/neurokinin B/dynorphin (KNDy) neuron to modulate neuronal activity in the thermoregulatory centre of the hypothalamus. The KNDy neuron sends signals to the thermoregulatory centre of the brain, which modulates the output to heat dissipating mechanisms in response to input from peripheral warm sensing neurons. By blocking NKB binding on the KNDy neuron, fezolinetant moderates neuronal activity in the thermoregulatory centre and improves VMS associated with menopause.

Veoza is available as a film-coated tablet containing 45 mg of fezolinetant. Other ingredients in the tablet are mannitol, hydroxypropyl cellulose, low-substituted hydroxypropyl cellulose, microcrystalline cellulose, magnesium stearate, hypromellose, talc, macrogol, titanium dioxide and iron oxide red.

B ASSESSMENT OF PRODUCT QUALITY

The drug substance, fezolinetant, is manufactured at [redacted]

The drug product, Veoza™ Film-coated Tablets 45 mg, is manufactured at Astellas Pharma Inc., [redacted] Japan and Bushu Pharmaceuticals Ltd, [redacted] Japan.

Drug substance:

Adequate controls have been presented for the starting materials, intermediates and reagents. The in-process control tests and acceptance criteria applied during the manufacturing of the drug substance are considered appropriate. The drug substance manufacturers are compliant with Good Manufacturing Practice (GMP) standard.

The characterisation of the drug substance and its impurities has been appropriately performed. Potential and actual impurities are adequately controlled in accordance with ICH Q3A and Q3C guidelines.

The drug substance specifications were established in accordance with ICH Q6A guideline, and the impurity limits were appropriately qualified. The analytical methods used were adequately described and non-compendial methods have been validated in accordance with ICH Q2 guideline, with information on the reference standards used for identity, assay and impurities testing presented.

The stability data presented was adequate to support the storage of the drug substance at 25°C with a re-test period of 48 months. The packaging is [redacted]

Drug product:

The tablets are manufactured using wet granulation followed by film-coating which is considered a standard manufacturing process. All drug product manufacturing sites are compliant with GMP standard. Proper development and validation studies were conducted. It has been demonstrated that the manufacturing process is reproducible and consistent. Adequate in-process controls are in place.

The specifications have been established in accordance with ICH Q6A guideline and impurity limits were adequately qualified. The analytical methods used were adequately described and non-compendial methods have been validated in accordance with ICH Q2 guidelines, with information on the reference standards used for identity, assay and impurities testing presented.

The stability data submitted was adequate to support the approved shelf-life of 48 months when stored at or below 30 ºC. The container closure system is an aluminium/aluminium blister containing 10 tablets.

C ASSESSMENT OF CLINICAL EFFICACY

The clinical efficacy of fezolinetant for the treatment of moderate to severe VMS associated with menopause was based on two pivotal Phase 3 studies (2693-CL-0301 [SKYLIGHT 1] and 2693-CL-0302 [SKYLIGHT 2]).

SKYLIGHT 1 and SKYLIGHT 2

SKYLIGHT 1 and SKYLIGHT 2 were two identical Phase 3, randomised, multicentre, placebo-controlled studies to assess the efficacy and safety of fezolinetant at 30 mg and 45 mg doses in women with moderate to severe VMS associated with menopause. Participants were aged 40 to 65 years, had to be seeking treatment or relief for VMS associated with menopause, confirmed as menopausal, and had 7 to 8 moderate to severe VMS per day within the 10 days prior to randomisation.

The studies comprised a 12-week double-blind period, followed by a non-controlled 40-week active treatment extension period. Participants in both studies were randomised in a 1:1:1 ratio to a treatment group (fezolinetant 30 mg, fezolinetant 45 mg or placebo) and stratified by smoking status (current smoker or former/never smoker). After completing 12 weeks of treatment, participants on placebo were re-randomised to either fezolinetant 30 mg or 45 mg treatment groups. Participants who completed treatment with fezolinetant 30 mg or fezolinetant 45 mg in the 12-week double-blind period continued to receive the same fezolinetant dose during the active treatment extension period.

Participants were to record the frequency and severity of VMS on their electronic diary. The co-primary efficacy endpoints in the studies were:

- Mean change in the frequency[1] of moderate to severe VMS from baseline to week 4
- Mean change in the frequency[1] of moderate to severe VMS from baseline to week 12
- Mean change in the severity[2] of moderate to severe VMS from baseline to week 4
- Mean change in the severity[2] of moderate to severe VMS from baseline to week 12

[1] Calculated as the sum of moderate or severe VMS events per day.
[2] Calculated using a weighted average defined as: ([number of mild hot flashes/day × 1] + [number of moderate hot flashes/day × 2] + [number of severe hot flashes/day × 3]) ÷ total number of daily mild/moderate/severe hot flashes.

The key secondary efficacy endpoint was the mean change in the Patient-reported Outcomes Measurement Information System Sleep Disturbance – Short Form 8b (PROMIS SD SF 8b) total score from baseline to week 12.

The secondary endpoints included the following:

- Mean change in the frequency of moderate to severe VMS from baseline to each week up to week 12
- Mean change in the severity of moderate to severe VMS from baseline to each week up to week 12
- Mean percent reduction in the frequency of moderate to severe VMS from baseline to each week up to week 12
- Percent reduction ≥ 50% and at 100% in the frequency of moderate to severe VMS from baseline to each week up to week 12
- Score on the Patient Global Impression of Change in Vasomotor Symptoms (PGI-C VMS) at each visit
- Mean change in the frequency of moderate to severe VMS from baseline to week 24
- Mean change in the severity of moderate to severe VMS from baseline to week 24

The statistical methods employed were appropriate for the endpoints, with adequate control for multiplicity in the analyses. In each study, the family-wise type 1 error rate for the 2 active dose groups compared with placebo for the 4 co-primary endpoints was controlled using a Hochberg approach. If all the co-primary endpoints were statistically significant between fezolinetant and placebo at both doses, then the 5% alpha from the analysis of the co-primary endpoints was passed to the key secondary endpoint as part of the family-wise error rate control.

Supplemental prespecified analyses were conducted to provide further context for interpretation of change in the frequency of moderate to severe VMS. The exploratory analyses were conducted using the thresholds for clinically meaningful within-subject change from an anchor-based analysis, with PGI-C VMS as the anchor measure to establish a clinically meaningful threshold for frequency of moderate to severe VMS.

A total of 1,028 participants were randomised in the 2 pivotal studies: 527 participants in SKYLIGHT 1 and 501 participants in SKYLIGHT 2. The primary analyses were conducted on the full analysis set (FAS), which consisted of 522 randomised participants in SKYLIGHT 1 and 500 randomised participants in SKYLIGHT 2 who received at least 1 dose of study intervention.

The demographics and baseline characteristics were similar between treatment groups in each study. In both pivotal studies, participants had a median age of 54.0 years (range: 40 to 65 years). Most participants were White (~81%). Approximately 20% of participants in each pivotal study received prior treatment with hormone therapy, 22% had a history of oophorectomy and 32% of participants had a history of hysterectomy. The proportion of these baseline characteristics and medical history was similar across treatment groups. The median time since onset of amenorrhea was 61.1 months in SKYLIGHT 1 and 58.6 months in SKYLIGHT 2. The mean of VMS frequency per 24 hours was approximately 11 episodes and the magnitude of severity at baseline was 2.4. The study populations were considered representative of the target population with moderate to severe VMS associated with menopause.

Overview of efficacy results (FAS) (SKYLIGHT 1 and SKYLIGHT 2)

	SKYLIGHT 1			SKYLIGHT 2		
	Fezolinetant 30 mg (N=173)	**Fezolinetant 45 mg (N=174)**	**Placebo (N=175)**	**Fezolinetant 30 mg (N=166)**	**Fezolinetant 45 mg (N=167)**	**Placebo (N=167)**
Co-primary Endpoints						
Change from Baseline in Mean Frequency of Moderate to Severe VMS per 24 h						
Baseline mean (SD)	10.65 (4.73)	10.44 (3.92)	10.51 (3.79)	11.23 (4.88)	11.79 (8.26)	11.59 (5.02)
LS mean (SE) change from baseline to week 4	-5.19 (0.30)	-5.39 (0.30)	-3.32 (0.29)	-5.53 (0.33)	-6.26 (0.33)	-3.72 (0.33)
LS mean (SE) difference vs placebo p-value	**-1.87 (0.42)** p < 0.001	**-2.07 (0.42)** p < 0.001	-	**-1.82 (0.46)** p < 0.001	**-2.55 (0.46)** p < 0.001	-
LS mean (SE) change from baseline to week 12	-6.28 (0.32)	-6.44 (0.31)	-3.90 (0.31)	-6.83 (0.39)	-7.50 (0.39)	-4.97 (0.39)
LS mean (SE) difference vs placebo p-value	**-2.39 (0.44)** p < 0.001	**-2.55 (0.43)** p < 0.001	-	**-1.86 (0.55)** p < 0.001	**-2.53 (0.55)** p < 0.001	-
Change from Baseline in Mean Severity of Moderate to Severe VMS per 24 h						
Baseline mean (SD)	2.39 (0.34)	2.40 (0.35)	2.43 (0.35)	2.44 (0.33)	2.41 (0.34)	2.41 (0.32)
LS mean (SE) change from baseline to week 4	-0.42 (0.04)	-0.46 (0.04)	-0.27 (0.04)	-0.47 (0.05)	-0.61 (0.05)	-0.32 (0.05)
LS mean (SE) difference vs placebo p-value	**-0.15 (0.06)** p = 0.012	**-0.19 (0.06)** p = 0.002	-	**-0.15 (0.06)** p = 0.021	**-0.29 (0.06)** p < 0.001	-
LS mean (SE) change from baseline to week 12	-0.60 (0.05)	-0.57 (0.05)	-0.37 (0.05)	-0.64 (0.06)	-0.77 (0.06)	-0.48 (0.06)
LS mean (SE) difference vs placebo p-value	**-0.24 (0.08)** p = 0.002	**-0.20 (0.08)** p = 0.007	-	**-0.16 (0.08)** p = 0.049	**-0.29 (0.08)** p < 0.001	-
Key Secondary Endpoint						
Change from Baseline in PROMIS Sleep Disturbance - Short Form 8b Total Score						
Baseline mean (SD)	26.4 (6.6)	27.1 (7.0)	26.4 (6.6)	27.3 (6.6)	26.2 (6.6)	27.4 (7.0)
LS mean (SE) change from baseline to week 12	-3.7 (0.6)	-4.2 (0.5)	-3.2 (0.5)	-4.1 (0.5)	-5.5 (0.5)	-3.4 (0.5)
LS mean (SE) difference vs placebo p-value	-0.5 (0.8) p = 0.489	-1.1 (0.7) p = 0.155	-	-0.7 (0.7) p = 0.381	-2.0 (0.7) p = 0.007	-
Secondary Endpoints						
Responder Analysis: Proportion of Participants with ≥ 50% Reduction in Frequency of Moderate to Severe VMS from Baseline						
Week 4 responders	77 (44.5%)	94 (54.0%)	49 (28.0%)	84 (50.6%)	88 (52.7%)	44 (26.3%)
Odds ratio (95% CI) p-value	2.061 (1.323, 3.233) p = 0.001	3.025 (1.947, 4.746) p < 0.001	-	2.902 (1.829, 4.657) p < 0.001	3.218 (2.025, 5.172) p < 0.001	-
Week 12 responders	77 (44.5%)	99 (56.9%)	52 (29.7%)	84 (50.6%)	101 (60.5%)	71 (42.5%)
Odds ratio (95% CI) p-value	1.894 (1.220, 2.961) p = 0.005	3.156 (2.035, 4.944) p < 0.001	-	1.373 (0.891, 2.122) p = 0.152	2.090 (1.351, 3.252) p < 0.001	-
Responder Analysis: Proportion of Participants with 100% Reduction in Frequency of Moderate to Severe VMS from Baseline						
Week 4 responders	6 (3.5%)	8 (4.6%)	5 (2.9%)	10 (6.0%)	17 (10.2%)	3 (1.8%)
Odds ratio (95% CI) p-value	1.257 (0.370, 4.468) p = 0.711	1.570 (0.508, 5.328) p = 0.441	-	3.474 (1.039,15.712) p = 0.062	6.184 (2.025, 26.875) p = 0.004	-
Week 12 responders	12 (6.9%)	18 (10.3%)	6 (3.4%)	15 (9.0%)	25 (15.0%)	9 (5.4%)
Odds ratio (95% CI) p-value	2.100 (0.795, 6.157) p = 0.148	3.262 (1.329, 9.194) p = 0.015		1.701 (0.733, 4.169) p = 0.225	3.049 (1.420, 7.125) p = 0.006	-

CI: confidence interval; SD: standard deviation; SE: standard error; LS: least squares; PROMIS: Patient-Reported Outcome Measurement Information System; VMS: vasomotor symptoms.

In both studies, both fezolinetant 30 mg and 45 mg treatment groups met all 4 co-primary endpoints. Participants treated with fezolinetant 30 mg and 45 mg had a statistically significant reduction in the frequency of moderate to severe VMS from baseline to week 4 (least squares [LS] mean difference: -1.82 to -1.87 for 30 mg; -2.07 to -2.55 for 45 mg) and week 12 (LS mean difference: -1.86 to -2.39 for 30 mg; -2.53 to -2.55 for 45 mg) relative to placebo. Both doses of fezolinetant also resulted in a statistically significant reduction in the severity of moderate to severe VMS from baseline to week 4 (LS mean difference: -0.15 for 30 mg; -0.19 to -0.29 for 45 mg) and week 12 (LS mean difference: -0.16 to -0.24 for 30 mg; -0.20 to -0.29 for 45 mg) compared to placebo. The 45 mg dose of fezolinetant demonstrated slightly greater reductions in VMS frequency and severity compared to the 30 mg dose. Only the 45 mg dose group consistently met the threshold of clinically meaningful reduction in VMS frequency, defined as a reduction of ≥ 2 VMS per day compared to placebo, at weeks 4 and 12. Efficacy was generally consistent across subgroup analyses by age, race, body mass index and smoking status.

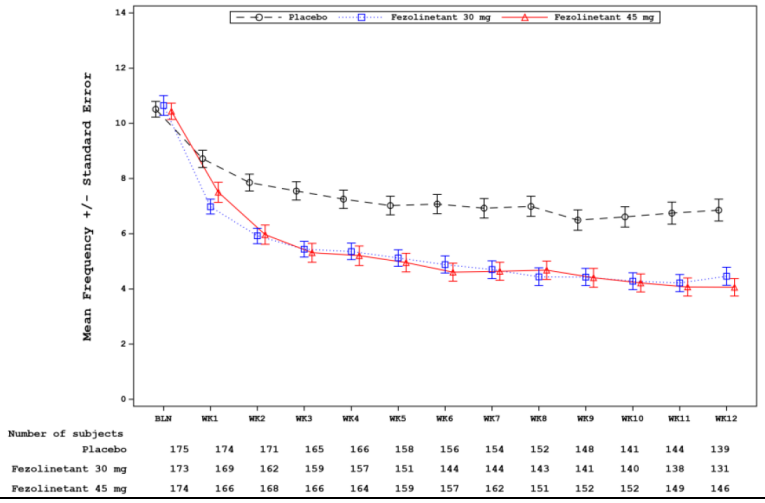
Based on the supplemental prespecified analyses, the identified clinically meaningful within-subject change thresholds in the frequency of moderate to severe VMS across both studies were -5.37 to -6.11 at week 4 and -5.70 to -6.66 at week 12. A higher proportion of participants in the fezolinetant 30 mg and 45 mg groups than those in the placebo group achieved a clinically meaningful within-subject change from baseline in the frequency of moderate to severe VMS at weeks 4 and 12. At week 4, the proportion of responders were 42.8% to 43.4% in the fezolinetant 30 mg group and 44.8% to 47.9% in the 45 mg group, compared to 19.2% to 25.1% for placebo. At week 12, the proportion of responders were 38.6% to 38.7% in the fezolinetant 30 mg group and 46.1% to 47.7% in the 45 mg group, compared to 24.0% to 27.5% for placebo.

For the key secondary endpoint, fezolinetant 45 mg showed a statistically significant reduction in PROMIS SD SF 8b total score from baseline to week 12 compared to placebo (LS mean difference: -2.0) in SKYLIGHT 2. The 30 mg dose in SKYLIGHT 2 and both doses (30 mg and 45 mg) in SKYLIGHT 1 demonstrated numerical reductions in PROMIS SD SF 8b scores from baseline to week 12, but the differences relative to placebo were not statistically significant (LS mean difference: -0.5 to -1.1).

In terms of the secondary endpoints, participants treated with fezolinetant 30 mg and 45 mg had larger reductions from baseline in mean frequency of moderate to severe VMS relative to placebo at each week up to week 12. The reduction in the frequency of moderate to severe VMS started at the first post-baseline assessment (week 1) and continued to decrease until week 4 after which it remained relatively stable through week 12, which was similar to placebo. The same trend was observed for the mean severity of moderate to severe VMS.

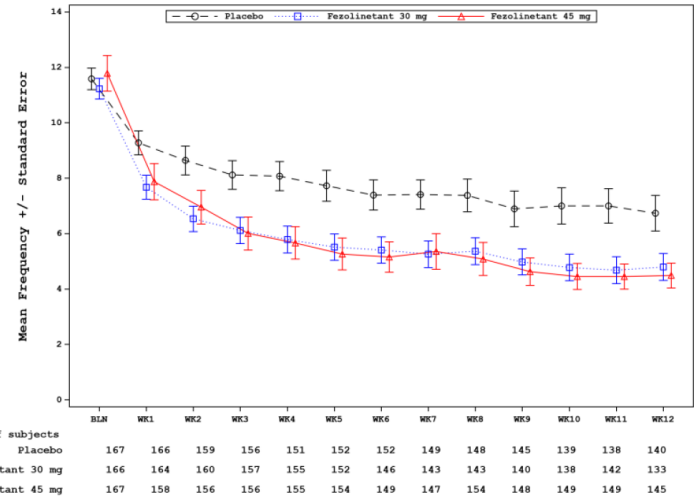
Mean frequency of moderate to severe VMS per 24 h up to 12 weeks

SKYLIGHT 1



Number of subjects	BLN	WK1	WK2	WK3	WK4	WK5	WK6	WK7	WK8	WK9	WK10	WK11	WK12
Placebo	175	174	171	165	166	158	156	154	152	148	141	144	139
Fezolinetant 30 mg	173	169	162	159	157	151	144	144	143	141	140	138	131
Fezolinetant 45 mg	174	166	168	166	164	159	157	162	151	152	152	149	146

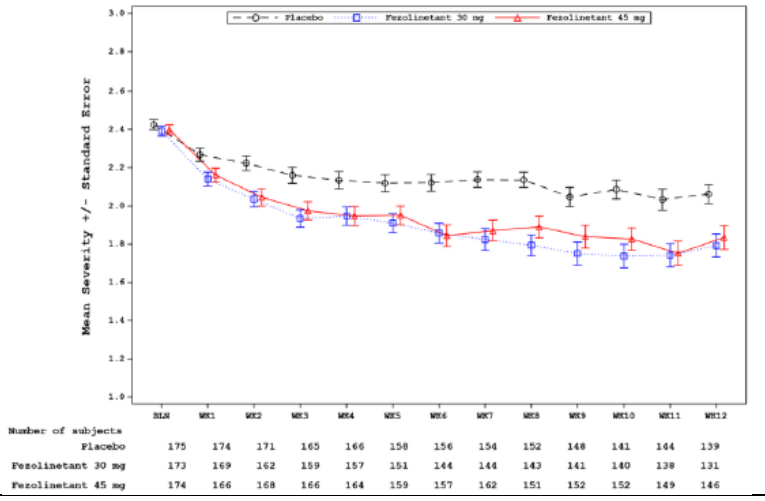
SKYLIGHT 2



Number of subjects	BLN	WK1	WK2	WK3	WK4	WK5	WK6	WK7	WK8	WK9	WK10	WK11	WK12
Placebo	167	166	159	156	151	152	152	149	148	145	139	138	140
Fezolinetant 30 mg	166	164	160	157	155	152	146	143	143	140	138	142	133
Fezolinetant 45 mg	167	158	156	156	155	154	149	147	154	148	149	149	145

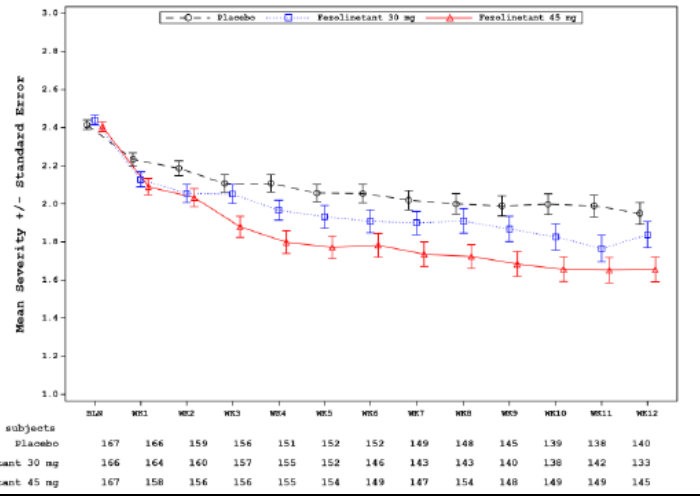
Mean severity of moderate to severe VMS per 24 h up to 12 weeks

SKYLIGHT 1



Number of subjects	BLN	WK1	WK2	WK3	WK4	WK5	WK6	WK7	WK8	WK9	WK10	WK11	WK12
Placebo	175	174	171	165	166	158	156	154	152	148	141	144	139
Fezolinetant 30 mg	173	169	162	159	157	151	144	144	143	141	140	138	131
Fezolinetant 45 mg	174	166	168	166	164	159	157	162	151	152	152	149	146

SKYLIGHT 2



Number of subjects	BLN	WK1	WK2	WK3	WK4	WK5	WK6	WK7	WK8	WK9	WK10	WK11	WK12
Placebo	167	166	159	156	151	152	152	149	148	145	139	138	140
Fezolinetant 30 mg	166	164	160	157	155	152	146	143	143	140	138	142	133
Fezolinetant 45 mg	167	158	156	156	155	154	149	147	154	148	149	149	145

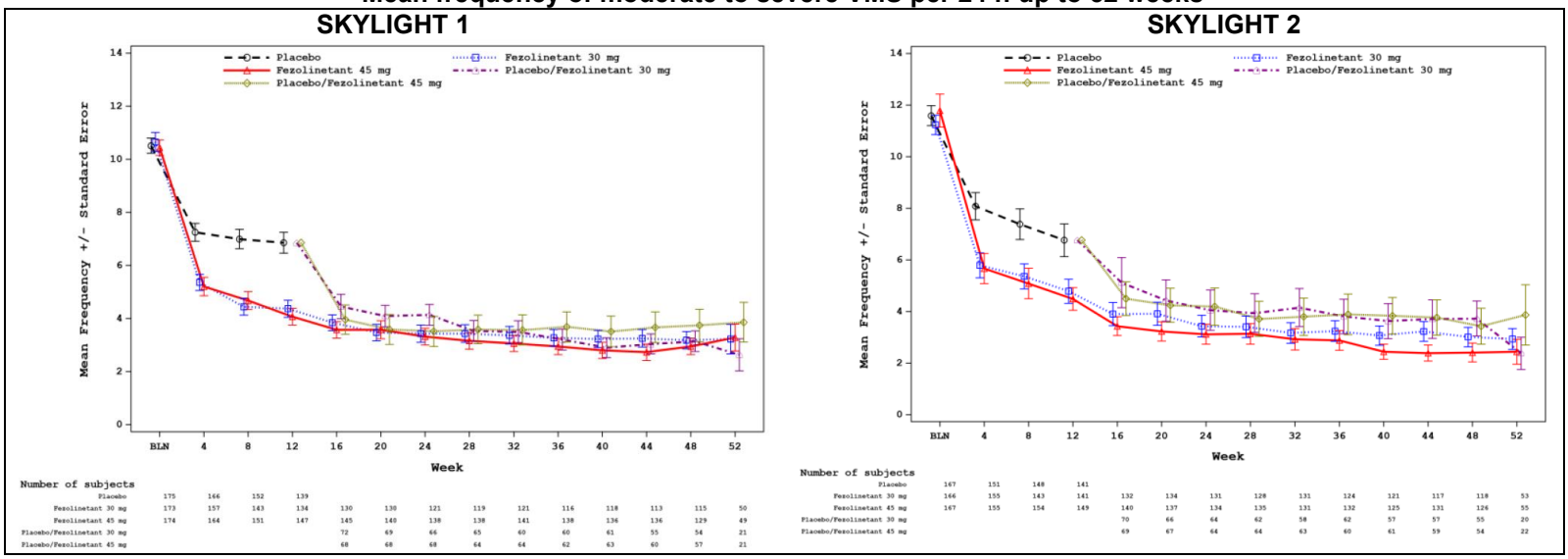
Participants treated with fezolinetant 30 mg and 45 mg had greater percent reductions from baseline in the frequency of moderate to severe VMS relative to placebo; these differences were observed after week 1 of treatment with fezolinetant with continued improvement until week 4 and sustained benefit throughout the 12-week double-blind period. In the responder analysis, there were also higher proportions of participants with ≥ 50% and 100% reductions in frequency in the fezolinetant 30 mg and 45 mg groups compared with placebo from baseline to each week up to week 12. The proportions of participants who had ≥ 50% reductions in the frequency of moderate to severe VMS at week 12 were 29.7% to 42.5% in the placebo group, 44.5% to 50.6% in the fezolinetant 30 mg group and 56.9% to 60.5% in the fezolinetant 45 mg group. The proportions of participants who had ≥ 100% reductions in the frequency of moderate to severe VMS at week 12 were 3.4% to 5.4% in the placebo group, 6.9% to 9.0% in the fezolinetant 30 mg group and 10.3% to 15.0% in the fezolinetant 45 mg group.

A higher proportion of participants in the fezolinetant groups reported a positive change in the patient-reported outcomes (PRO) PGI-C VMS (“moderately better” and “much better”) compared with placebo at weeks 4 and 12. At week 4, positive changes were reported by

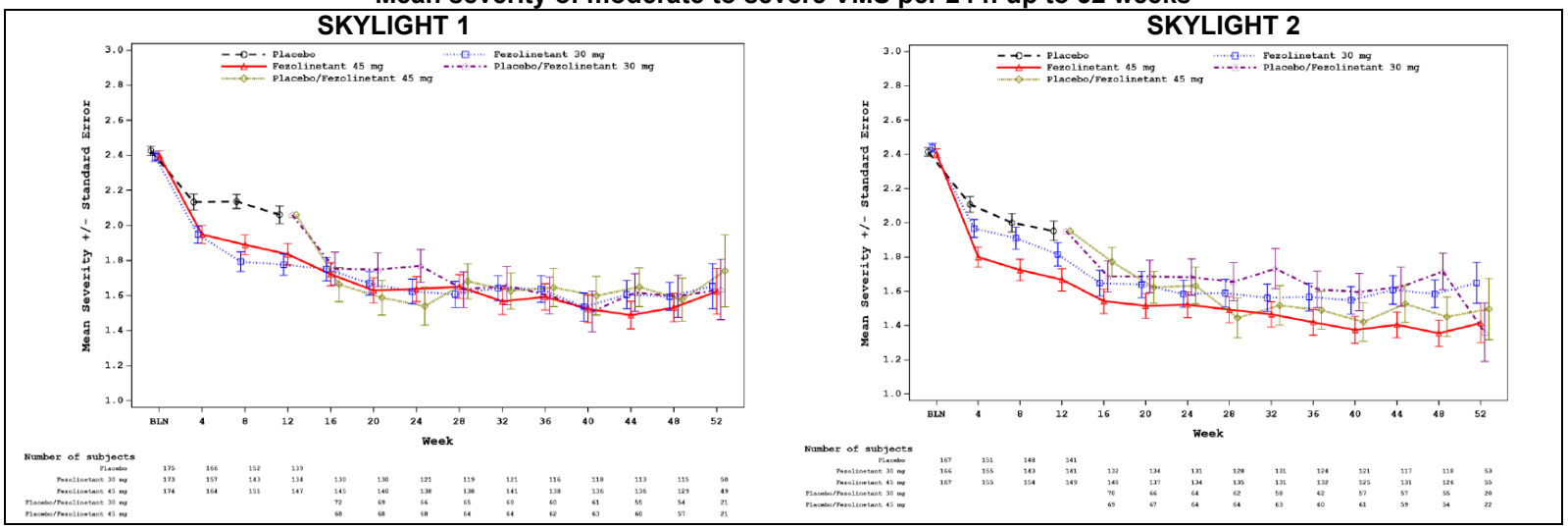
52.9% to 55.3% in the fezolinetant 30 mg group and 60.0% to 62.9% in the 45 mg group, versus 31.8% to 33.1% for placebo. At week 12, the proportions were 54.1% to 66.4% in the fezolinetant 30 mg group and 66.2% to 71.9% in the 45 mg group, compared to 39.6% to 41.0% for placebo.

Efficacy analyses during the active treatment extension period showed that the effect of fezolinetant on VMS frequency and severity observed during the first 12 weeks was sustained through week 52 in participants treated with fezolinetant 30 mg and 45 mg for the entire study. Participants on placebo when re-randomised to active fezolinetant demonstrated additional and sustained benefit from fezolinetant treatment on VMS frequency and severity from baseline throughout the 52-week study.

Mean frequency of moderate to severe VMS per 24 h up to 52 weeks



Mean severity of moderate to severe VMS per 24 h up to 52 weeks



In conclusion, both fezolinetant 30 mg and 45 mg doses met all 4 co-primary endpoints in terms of reductions in VMS frequency and severity in both pivotal studies, with a trend for a slightly larger effect in the 45 mg group. The primary efficacy results were supported by improvements in the key secondary endpoint of PROMIS SD SF 8b and positive trends in other

secondary endpoints. Comparing the two dose groups, fezolinetant 45 mg had a more robust and more consistent reduction in VMS associated with menopause compared with fezolinetant 30 mg across the efficacy endpoints. Notably, only the 45 mg dose consistently demonstrated a clinically meaningful reduction in VMS frequency, defined as a reduction of ≥ 2 VMS per day compared to placebo, at weeks 4 and 12. Overall, the data adequately supported the proposed dose of fezolinetant 45 mg for the treatment of moderate to severe VMS associated with menopause.

D ASSESSMENT OF CLINICAL SAFETY

The safety evaluation of fezolinetant was based primarily on the following pooled safety populations, POP1 and POP4.

- POP1 consisted of the 12-week placebo-controlled Phase 3 studies SKYLIGHT 1 and 2 to assess the short-term safety profile of fezolinetant.
- POP4 consisted of a 52-week safety study SKYLIGHT 4[3] to assess the long-term safety profile of fezolinetant.

POP1 included 1,022 participants: 340 in the fezolinetant 30 mg group, 340 in the fezolinetant 45 mg group and 342 in the placebo group. The median duration of exposure to study drug was 84 days in each treatment group.

POP4 included 1,830 participants: 611 in the fezolinetant 30 mg group, 609 in the fezolinetant 45 mg group and 610 in the placebo group. The median duration of exposure to study drug was 364 days in each treatment group. The majority of participants (75.4%) had exposure to study drug of at least 252 days. The safety exposure is considered adequate for assessment of the safety profile of fezolinetant 45 mg dose.

Overview of safety profile in POP1 (12-week safety population)

AE	Fezolinetant 30 mg (N=340)	Fezolinetant 45 mg (N=340)	Placebo (N=342)
TEAE	132 (38.8%)	135 (39.7%)	132 (38.6%)
Drug-related TEAE	41 (12.1%)	38 (11.2%)	33 (9.6%)
Serious TEAE	5 (1.5%)	4 (1.2%)	1 (0.3%)
Drug-related serious TEAE	2 (0.6%)	0	0
TEAE leading to withdrawal of treatment	12 (3.5%)	9 (2.6%)	10 (2.9%)
Deaths	0	0	0

Overview of safety profile in POP4 (52-week safety population)

AE	Fezolinetant 30 mg (N=611)	Fezolinetant 45 mg (N=609)	Placebo (N=610)
TEAE	415 (67.9%)	389 (63.9%)	391 (64.1%)
Drug-related TEAE	94 (15.4%)	110 (18.1%)	106 (17.4%)
Serious TEAE	20 (3.3%)	23 (3.8%)	14 (2.3%)
Drug-related serious TEAE	0	3 (0.5%)	1 (0.2%)
TEAE leading to withdrawal of treatment	34 (5.6%)	28 (4.6%)	26 (4.3%)
Deaths	1 (0.2%)	0	0

In both POP1 and POP4, the incidences of treatment-emergent adverse events (TEAEs) were similar across all treatment groups. In POP1, the most frequently reported TEAEs (fezolinetant

[3] SKYLIGHT 4 was a Phase 3, randomised, placebo-controlled, double-blind, 52-week study evaluating long-term safety, tolerability, and endometrial health effects of fezolinetant 30 mg and 45 mg.

30 mg vs 45 mg vs placebo) were headache (4.1% vs 5.0% vs 5.0%), upper respiratory tract infection (2.4% vs 2.1% vs 2.9%) and blood glucose increased (2.1% vs 1.8% vs 0.3%). In POP4, the most frequently reported TEAEs (fezolinetant 30 mg vs 45 mg vs placebo) were headache (8.5% vs 9.0% vs 9.2%) and COVID-19 (6.2% vs 5.3% vs 6.2%). The majority of TEAEs (> 94%) in all treatment groups were mild or moderate in severity.

In POP1, the most frequent TEAEs related to study intervention in the combined fezolinetant group were headache (1.3%), dry mouth (1.2%) and nausea (1.0%). In POP4, the most frequent TEAEs related to study intervention in the combined fezolinetant group were headache (3.1% in the combined fezolinetant group vs 3.3% in placebo group), nausea (1.1% vs 1.5%), diarrhoea (1.0% vs 0.8%) and vaginal haemorrhage (1.0% vs 1.8%). TEAEs related to study intervention were generally similar in the fezolinetant and placebo groups, except for alanine aminotransferase (ALT) increased (0.5% in fezolinetant 30 mg group vs 0.8% in fezolinetant 45 mg group vs 0.2% in placebo group) and somnolence (0.7% vs 0.2% vs 0%).

The overall incidence of serious TEAEs was low but were slightly higher in the fezolinetant groups versus the placebo group in POP1 and POP4. In POP1, 9 serious TEAEs were reported in the combined fezolinetant group compared with 1 serious TEAE in the placebo group. The serious TEAEs were assessed as unrelated except for 2 events in the fezolinetant 30 mg group: 1 event of liver function test increased and 1 event of transaminases increased. In POP4, the most frequent serious TEAEs were abdominal pain [1 (0.2%) in fezolinetant 30 mg group vs 2 (0.3%) in fezolinetant 45 mg group vs 0 in placebo group] and endometrial adenocarcinoma [1 (0.2%) vs 2 (0.3%) vs 0]. No other serious TEAEs occurred in ≥ 3 participants across all groups.

The frequencies of TEAEs leading to withdrawal of treatment were generally low and similar across treatment groups in POP1 and POP4. In POP1, no specific TEAE led to withdrawal for more than 2 participants in any treatment group, except nausea and headache (3 each in placebo group). In POP4, TEAE led to withdrawal for > 2 participants in any treatment group were fatigue [3 (0.5%) in fezolinetant 45 mg group], headache [3 (0.5%) in placebo group and 4 (0.7%) in fezolinetant 45 mg group], and nausea [4 (0.7%) in fezolinetant 30 mg group].

There were two deaths reported in the clinical studies. In SKYLIGHT 2, one participant in the placebo/fezolinetant 45 mg group died due to multiple injuries from a motorcycle passenger accident. In SKYLIGHT 4, one participant in the fezolinetant 30 mg group died due to cardiac arrest with anoxic brain injury. This participant had multiple risk factors, including obesity, chronic obstructive pulmonary disease, hypertension, and type 2 diabetes mellitus. Both events were considered not related to the study intervention by the investigator.

The incidences of treatment-emergent adverse events of special interest (AESIs) were generally similar across the treatment groups in POP4.

TEAEs of special interest in POP4 (52-week safety population)

TEAEs of special interest	Fezolinetant 30 mg (N=611)	Fezolinetant 45 mg (N=609)	Placebo (N=610)
Endometrial hyperplasia/ cancer or disordered proliferative endometrium	2 (0.3%)	6 (1.0%)	2 (0.3%)
Uterine bleeding	20 (3.3%)	19 (3.1%)	30 (4.9%)
Liver test elevations	35 (5.7%)	32 (5.3%)	30 (4.9%)
Thrombocytopenia	3 (0.5%)	1 (0.2%)	1 (0.2%)
Bone fractures	9 (1.5%)	10 (1.6%)	10 (1.6%)
Potential abuse liability	3 (0.5%)	1 (0.2%)	0

Depression	19 (3.1%)	11 (1.8%)	13 (2.1%)
Wakefulness	7 (1.1%)	4 (0.7%)	4 (0.7%)
Effect on memory	0	1 (0.2%)	1 (0.2%)

With regard to endometrial safety, the frequency of endometrial hyperplasia or malignancy in the fezolinetant group in SKYLIGHT 4 met the prespecified criterion of ≤ 1%, with an upper bound of the one-sided 95% CI not exceeding 4%. There was no clinically relevant impact on endometrial thickness from baseline to week 52. The incidences of the AESIs of endometrial hyperplasia, cancer or disordered proliferative endometrium as well as uterine bleeding were low, with a higher incidence of uterine bleeding in the placebo group. The results did not suggest significant concerns regarding endometrial safety for fezolinetant.

The incidence of liver test elevations was greater in the fezolinetant 30 mg and 45 mg groups than in the placebo group. The most frequently reported preferred terms for the AESI of liver test elevations were ALT increased, gamma-glutamyltransferase increased, blood alkaline phosphatase increased and aspartate aminotransferase increased. Most events were mild or moderate in severity. Transaminase elevations were generally transient and resolved while on study intervention or shortly after drug discontinuation. No cases of Hy's law were identified. The package insert has included warnings on hepatotoxicity, with recommendations for baseline hepatic function evaluation followed by monthly monitoring for the first three months, patient education on symptoms to report, and discontinuation criteria based on transaminase and bilirubin elevations.

A numeric imbalance was observed in the incidence of serious TEAEs in the system organ class of neoplasms benign, malignant and unspecified (including cysts and polyps) between fezolinetant [5 (0.8%) in fezolinetant 30 mg group, 7 (1.1%) in fezolinetant 45 mg group] and placebo groups [2 (0.3%)] in SKYLIGHT 4. However, the type of events in the fezolinetant groups were diverse and not clustered. There was no evidence of genotoxicity or carcinogenicity in the non-clinical studies. The literature does not suggest a plausible mechanistic hypothesis for the role of NK3 receptor antagonism in the development of neoplasms. Taken together, the observed imbalance in serious neoplasm events was likely a chance occurrence and did not appear to be clinically relevant.

For other AESIs, there were no notable differences between fezolinetant and placebo in the incidences of the bone fractures, potential abuse liability, depression, wakefulness, effect on memory or thrombocytopenia.

Overall, the safety profile of fezolinetant was mainly characterised by gastrointestinal disorders and hepatotoxicity. Adequate warnings and recommendations for management of hepatotoxicity, including laboratory monitoring and treatment discontinuation, have been included in the package insert to mitigate the risks. No relevant differences were observed between fezolinetant 30 mg and 45 mg doses. The safety data were supportive of the proposed dose of fezolinetant 45 mg for the intended population.

E ASSESSMENT OF BENEFIT-RISK PROFILE

VMS affect a significant proportion of menopausal women, often persisting for several years and impacting quality of life. Hormone therapy is the current first-line treatment for moderate to severe VMS, but it is associated with certain risks and is contraindicated in women with certain medical conditions, such as breast cancer and thromboembolic disorders. Therefore,

there is a need for non-hormonal therapies for women who cannot or choose not to use hormone therapy due to contraindications or concerns about potential adverse effects.

Fezolinetant 30 mg and 45 mg demonstrated statistically significant reductions in the co-primary endpoints of frequency and severity of moderate to severe VMS from baseline to weeks 4 and 12 compared to placebo. The 45 mg dose consistently achieved clinically meaningful reduction in VMS frequency, defined as a decrease of ≥ 2 VMS per day compared to placebo, at both weeks 4 and 12. Compared to placebo, the 45 mg dose showed LS mean differences of -2.07 to -2.55 at week 4 and -2.53 to -2.55 at week 12 for reduction in the frequency of moderate to severe VMS, and -0.19 to -0.29 at week 4 and -0.20 to -0.29 at week 12 for reduction in the severity of moderate to severe VMS. The reduction in frequency and severity of VMS was accompanied by improvements in sleep disturbance and quality of life, as demonstrated by the PROMIS SD SF 8b and PGI-C VMS endpoints. The treatment effect of 45 mg was numerically larger compared to 30 mg.

In terms of safety, the most common drug-related TEAEs reported with fezolinetant were headache, dry mouth and nausea. The majority of the AEs were mild to moderate in severity, and the discontinuations due to TEAEs were low. The most notable safety concern with fezolinetant was hepatotoxicity. Appropriate warnings have been included in the package insert, including recommendations for hepatic function monitoring and criteria for treatment discontinuation.

Given that 45 mg dose demonstrated more consistent efficacy compared to the 30 mg dose with a similar safety profile, the proposed 45 mg dose was considered appropriate. Overall, the benefits of fezolinetant in reducing frequency and severity of moderate to severe VMS associated with menopause outweighed the identified safety risks and the benefit-risk profile was considered positive.

F CONCLUSION

Based on the review of quality, safety and efficacy data, the benefit-risk balance of Veoza for the treatment of moderate to severe VMS associated with menopause was deemed favourable and approval of the product registration was granted on 05 March 2025.

APPROVED PACKAGE INSERT AT REGISTRATION

1. NAME OF THE MEDICINAL PRODUCT

VEOZA™ FILM-COATED TABLETS 45 MG

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient: fezolinetant

Each film-coated tablet contains 45 mg of fezolinetant and is formulated for oral administration.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Fezolinetant 45 mg tablets are round, light red, film-coated tablets debossed with the Astellas logo and '645' on the same side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

VEOZA is indicated for the treatment of moderate to severe vasomotor symptoms (VMS) associated with menopause (see section 5.1).

4.2 Posology and method of administration

Posology
The recommended dose is 45 mg once daily.

Benefit of long-term treatment should be periodically assessed since the duration of VMS can vary by individual.

Missed dose
If a dose of VEOZA is missed or not taken at the usual time, the missed dose should be taken as soon as possible, unless there is less than 12 hours before the next scheduled dose. Individuals should return to the regular schedule the following day.

Elderly
Fezolinetant has not been studied for safety and efficacy in women initiating VEOZA treatment over 65 years of age. No dose recommendation can be made for this population.

Hepatic impairment
No dose modification is recommended for individuals with Child-Pugh Class A (mild) chronic hepatic impairment (see section 5.2).

VEOZA is not recommended for use in individuals with Child-Pugh Class B (moderate) or C (severe) chronic hepatic impairment. Fezolinetant has not been studied in individuals with Child-Pugh Class C (severe) chronic hepatic impairment (see section 5.2).

Renal impairment
No dose modification is recommended for individuals with mild (eGFR 60 to less than 90 mL/min/1.73 m^2) or moderate (eGFR 30 to less than 60 mL/min/1.73 m^2) renal impairment (see section 5.2).

VEOZA is not recommended for use in individuals with severe (eGFR less than 30 mL/min/1.73 m^2) renal impairment. Fezolinetant has not been studied in individuals with end-stage renal disease (eGFR less than 15 mL/min/1.73 m^2) and is not recommended for use in this population (see section 5.2).

Paediatric population
There is no relevant use of VEOZA in the paediatric population for the indication of moderate to severe VMS associated with menopause.

Method of administration
VEOZA should be administered orally once daily at about the same time each day with or without food and taken with liquids. Tablets are to be swallowed whole and not broken, crushed, or chewed due to the absence of clinical data under these conditions.

4.3 Contraindications

Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1.
Concomitant use of moderate or strong CYP1A2 inhibitors (see section 4.5).

4.4 Special warnings and precautions for use

Hepatotoxicity
Across the three phase 3 studies, elevations in serum alanine aminotransferase (ALT) levels at least 3 times the upper limit of normal (ULN) occurred in 2.1% of women receiving fezolinetant compared to 0.8% of women receiving placebo. Elevations in serum aspartate aminotransferase (AST) levels at least 3 times the ULN occurred in 1.0% of women receiving fezolinetant compared to 0.4% of women receiving placebo (see section 4.8). ALT and/or AST elevations were not accompanied by an increase in bilirubin greater than 2 times the ULN with fezolinetant. Women with ALT or AST elevations were generally asymptomatic. Transaminase levels returned to pre-treatment levels or close to these without sequelae with dose continuation, and upon dose interruption, or discontinuation.

In the post-marketing setting, cases of serious but reversible hepatotoxicity have been reported within the first few weeks of treatment. Patients have experienced transaminase elevations (greater than 10 times the ULN) with concurrent elevations in bilirubin and/or alkaline phosphatase (ALP), sometimes associated with signs or symptoms such as fatigue, pruritus, jaundice, dark urine, or abdominal pain.

Evaluate hepatic function (ALT, AST, ALP, and bilirubin) before initiating therapy. Do not initiate fezolinetant if ALT or AST is equal to or exceeds 2 times the ULN or if the total bilirubin is elevated (e.g., equal to or exceeds 2 times the ULN).

Patients should discontinue fezolinetant immediately and seek medical attention, including hepatic laboratory tests, if they experience signs or symptoms that may suggest hepatotoxicity such as new onset fatigue, decreased appetite, nausea, vomiting, pruritus, jaundice, pale feces, dark urine, or abdominal pain.

Follow-up evaluation of hepatic function is recommended monthly for the first three months of initiating fezolinetant and thereafter periodically based on clinical judgement.
Discontinue fezolinetant if:

- transaminase elevations are greater than 5 times the ULN.
- transaminase elevations are greater than 3 times the ULN and the total bilirubin level is greater than 2 times the ULN.

Exclude alternative causes of hepatic laboratory test elevations.

Patients with existing liver disease
Patients with active liver disease, or Child-Pugh Class B (moderate) or C (severe) chronic hepatic impairment have not been included in the clinical efficacy and safety studies with fezolinetant.

The pharmacokinetics of fezolinetant have been studied in women with Child-Pugh Class A (mild) and B (moderate) chronic hepatic impairment (see section 5.2). Monitoring of liver function in women with known or suspected hepatic disorder is advised during treatment.

4.5 Interaction with other medicinal products and other forms of interaction

Effect of other drugs on fezolinetant

CYP1A2 inhibitors

Fezolinetant is a substrate of CYP1A2. Concomitant use of fezolinetant with drugs that are moderate or strong inhibitors of CYP1A2 increase the plasma C_{max} and AUC of fezolinetant (see section 5.2). Concomitant use of moderate or strong CYP1A2 inhibitors with fezolinetant is contraindicated (see section 4.3).

4.6 Fertility, pregnancy and lactation

Pregnancy

The use of fezolinetant in pregnant women is not indicated. There is no data on the use of fezolinetant in pregnant women. It is recommended that perimenopausal women of childbearing potential use an effective non-hormonal contraceptive method.

In embryo-fetal toxicity animal studies with fezolinetant, embryo-lethality occurred at high doses above the human therapeutic dose in rats and rabbits, but no teratogenicity was observed (see section 5.3).

Breast-feeding

The use of fezolinetant in breast-feeding women is not recommended. There is no data to assess the effects of fezolinetant on the breastfed child or the effects on milk production. It is not known if fezolinetant is present in human milk.

Following administration of radiolabeled fezolinetant to lactating rats, the radioactivity concentration in milk was higher than that in the plasma at all time points, indicating that fezolinetant-derived components transferred to the tissues in infant rats via breast milk.

Fertility

There is no data on the effect of fezolinetant on human fertility. In the fertility study in female rats, fezolinetant did not affect fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

No formal studies on the effects of the ability to drive and use machines have been performed; however, fezolinetant is considered to have a negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

The safety of fezolinetant was evaluated in three phase 3 studies (SKYLIGHT 1, 2, and 4). SKYLIGHT 1 and 2 were 12-week, randomized, placebo-controlled, double-blind studies, followed by a 40-week extension treatment period in women with moderate to severe VMS associated with menopause. SKYLIGHT 4 was a 52-week, randomized, placebo-controlled, double-blind long-term safety study in women with VMS associated with menopause. A total of 2203 women were administered fezolinetant once daily.

Across the phase 3 studies, the most frequent adverse reactions (≥ 3%) with fezolinetant 45 mg were diarrhea and insomnia.

There were no serious adverse reactions reported at an incidence greater than 1% across the total study population.

The most frequent adverse reactions leading to discontinuation with fezolinetant 45 mg were alanine aminotransferase (ALT) increased (0.3%) and insomnia (0.2%).

Tabulated summary of adverse reactions
Adverse reactions observed during clinical studies and from spontaneous reporting are listed below by frequency category in each system organ class. Frequency categories are defined as follows: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000); and not known (cannot be estimated from the available data).

Table 1. Adverse reactions for fezolinetant 45 mg

MedDRA system organ class (SOC)	Adverse reaction (preferred term)	Frequency category	Frequency %
Gastrointestinal disorders	Diarrhea	Common	3.2%
	Abdominal pain	Common	1.8%
Psychiatric disorders	Insomnia	Common	3.0%
Hepatobiliary disorders	Alanine aminotransferase (ALT) increased	Common	2.8%
	Aspartate aminotransferase (AST) increased	Common	1.5%
	Hepatotoxicity[1]	Not known[2]	Not known[2]

Preferred term in MedDRA (v.23.0).
[1] See Description of selected adverse reactions section.
[2] Adverse reactions of an unknown frequency have been identified during post-approval use of fezolinetant. Because these reactions were reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate the frequency or establish a causal relationship to drug exposure.

Description of selected adverse reactions

Hepatotoxicity
Serious cases of hepatotoxicity in which ALT and/or AST elevations were accompanied by an increase in total bilirubin including symptoms have been reported post-marketing (see section 4.4).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

4.9 Overdose

Doses of fezolinetant up to 900 mg have been tested in clinical studies in healthy women. At 900 mg, headache, nausea, and paresthesia were observed.

In the case of overdose, the individual should be closely monitored, and supportive treatment should be considered based on signs and symptoms.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other gynecologicals, other gynecologicals, ATC code: G02CX06.

Mechanism of action
Fezolinetant is a nonhormonal selective neurokinin 3 (NK3) receptor antagonist that blocks neurokinin B (NKB) binding on the kisspeptin/neurokinin B/dynorphin (KNDy) neuron to modulate neuronal activity in the thermoregulatory center.

The thermoregulatory center in the hypothalamus is innervated by KNDy neurons, which are inhibited by estrogen and stimulated by the neuropeptide NKB. Through the menopausal transition, declining estrogen disrupts the balance with NKB. Unopposed, NKB signaling increases KNDy neuronal activity leading to hypertrophy of the KNDy neuron and altered activity on the thermoregulatory center, resulting in VMS, also known as hot flashes and night sweats.

Pharmacodynamic effects
Fezolinetant treatment provided relief from VMS over 24 hours. Fezolinetant is not a hormone and treatment with fezolinetant did not show any clear trends or clinically relevant changes in sex hormones measured (follicle-stimulating hormone, testosterone, estrogen, and dehydroepiandrosterone sulfate) in menopausal women. Transient decrease of luteinizing hormone (LH) levels was observed at peak concentrations of fezolinetant.

Cardiac electrophysiology
A model-based approach was conducted to assess the QT prolongation risk of fezolinetant. No clinically relevant prolongation of QTc interval was predicted by the model at the therapeutic or supratherapeutic concentrations.

Clinical efficacy and safety
SKYLIGHT 1 (2693-CL-0301) and SKYLIGHT 2 (2693-CL-0302) studies
Efficacy: Effects on VMS
The efficacy of fezolinetant was evaluated in 1022 women with moderate to severe VMS associated with menopause in two 12-week, randomized, placebo-controlled, double-blind phase 3 studies, followed by a 40-week extension treatment period. The mean age was 54 years (range: 40 to 65 years) and women were Caucasian (81%), Black (17%), Asian (1%), and Hispanic/Latina (24%) ethnicity. Women who had a minimum average of 7 moderate to severe VMS per day were enrolled in the studies.

The study population included postmenopausal women with one of more of the following: prior hormone replacement therapy (HRT) use (19.9%), prior oophorectomy (21.6%), or prior hysterectomy (32.1%). The median time interval since amenorrhoea/menopause was 63.8 months with a high variability (range: 5 to 495 months).

The co-primary efficacy endpoints for both studies were the change from baseline in moderate to severe VMS frequency and severity to weeks 4 and 12. Data from the studies showed a statistically significant and clinically meaningful (≥ 2 hot flashes per 24 hours) reduction from baseline in the frequency of moderate to severe VMS to weeks 4 and 12 for fezolinetant 45 mg compared to placebo. Data from the studies showed a statistically significant reduction from baseline in the severity of moderate to severe VMS to weeks 4 and 12 for fezolinetant 45 mg compared to placebo.

Fezolinetant is efficacious across a wide range of women, irrespective of age, race, ethnicity, body mass index (BMI), and smoking status. Furthermore, the efficacy of fezolinetant is observed regardless of VMS frequency, severity, duration at baseline or time since amenorrhea, prior medical history of sleep disturbance, or prior medical history of hypertension. In addition, fezolinetant is efficacious in women with or without hysterectomy or oophorectomy, with or without prior HRT, and with or without concurrent use of serotonin reuptake inhibitor (SSRI).

Fezolinetant 45 mg reduced the frequency and severity of VMS within week one. Improvement in VMS frequency and severity was sustained throughout the 52-week studies.

Women initially on placebo and subsequently re-randomized to fezolinetant during the extension period experienced a reduction in frequency and severity of VMS consistent with that in women receiving fezolinetant throughout the studies.

Results of the co-primary endpoint for change from baseline to weeks 4 and 12 in mean frequency of moderate to severe VMS per 24 hours from SKYLIGHT 1 and 2 and from pooled studies are shown in Table 2.

Table 2. SKYLIGHT 1 and 2: Mean baseline and change from baseline in mean frequency of moderate to severe VMS per 24 hours to weeks 4 and 12

Parameter	SKYLIGHT 1		SKYLIGHT 2		Pooled studies (SKYLIGHT 1 and 2)	
	Fezolinetant 45 mg (n=174)	Placebo (n=175)	Fezolinetant 45 mg (n=167)	Placebo (n=167)	Fezolinetant 45 mg (n=341)	Placebo (n=342)
Baseline						
Mean (SD)	10.44 (3.92)	10.51 (3.79)	11.79 (8.26)	11.59 (5.02)	11.10 (6.45)	11.04 (4.46)
Change from baseline to week 4						
LS Mean (SE)	-5.39 (0.30)	-3.32 (0.29)	-6.26 (0.33)	-3.72 (0.33)	-5.79 (0.23)	-3.51 (0.22)
Mean % Reduction[2]	50.63%	30.46%	55.16%	33.60%	52.84%	31.96%
Difference vs Placebo (SE)	-2.07 (0.42)	--	-2.55 (0.46)	--	-2.28 (0.32)	--
P-value	< 0.001[1]	--	< 0.001[1]	--	< 0.001	--
Change from baseline to week 12						
LS Mean (SE)	-6.44 (0.31)	-3.90 (0.31)	-7.50 (0.39)	-4.97 (0.39)	-6.94 (0.25)	-4.43 (0.25)
Mean % Reduction[2]	61.35%	34.97%	64.27%	45.35%	62.80%	40.18%
Difference vs Placebo (SE)	-2.55 (0.43)	--	-2.53 (0.55)	--	-2.51 (0.35)	--
P-value	< 0.001[1]	--	< 0.001[1]	--	< 0.001	--

[1] Statistically significantly superior compared to placebo at the 0.05 level with multiplicity adjustment.
LS Mean: Least Squares Mean estimated from a mixed model for repeated measures analysis of covariance;
SD: Standard Deviation; SE: Standard Error.

[2] Mean % Reduction is a descriptive statistic and not from the mixed model.

Figures 1 and 2 show the mean frequency of moderate to severe VMS per 24 hours in SKYLIGHT 1 and 2.

Figure 1. SKYLIGHT 1: Mean (SE) frequency of moderate to severe VMS per 24 hours by week

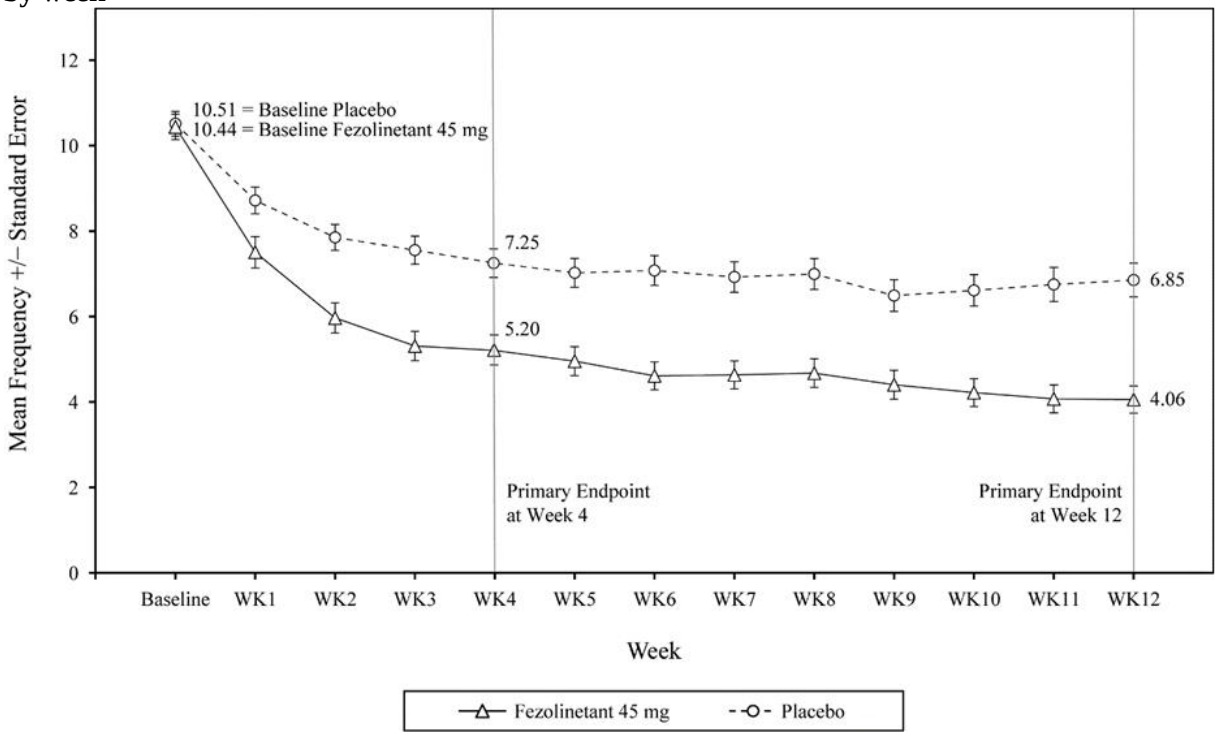
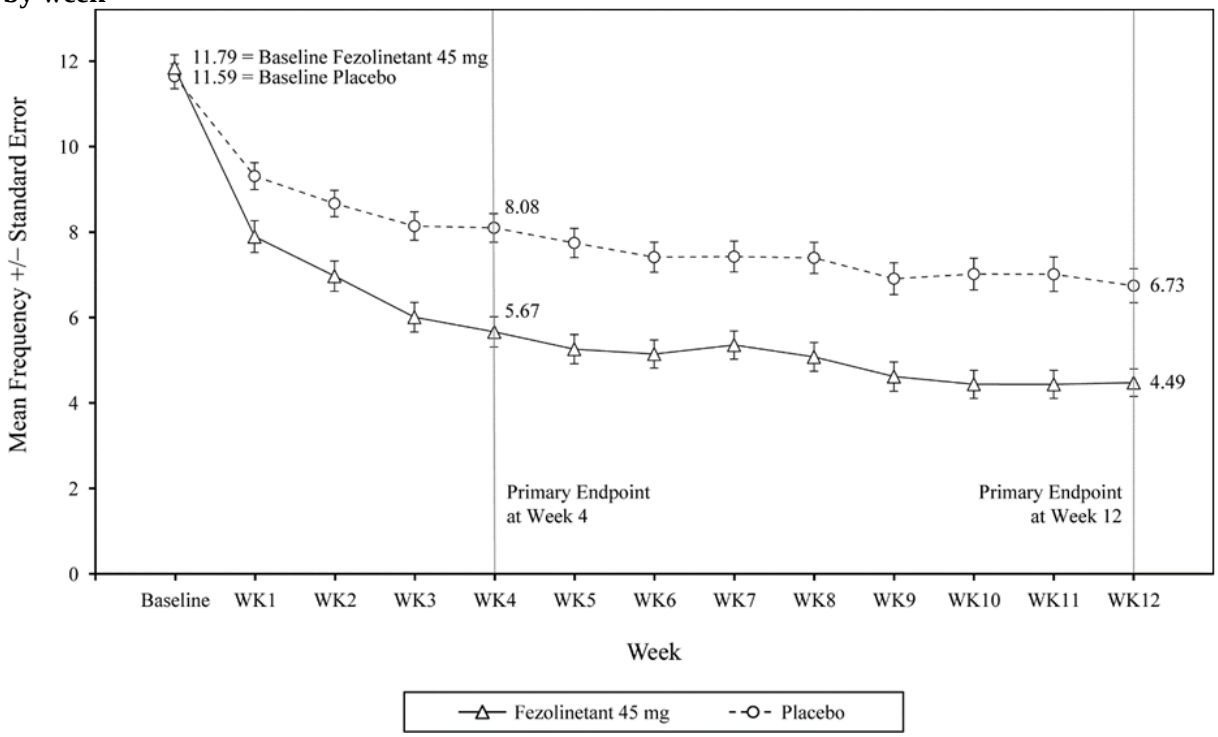


Figure 2. SKYLIGHT 2: Mean (SE) frequency of moderate to severe VMS per 24 hours by week



Results of the co-primary endpoint for change from baseline to weeks 4 and 12 in mean severity of moderate to severe VMS per 24 hours from SKYLIGHT 1 and 2 and from pooled studies are shown in Table 3.

Table 3. SKYLIGHT 1 and 2: Mean baseline and change from baseline in mean severity of moderate to severe VMS per 24 hours to weeks 4 and 12

Parameter	SKYLIGHT 1		SKYLIGHT 2		Pooled studies (SKYLIGHT 1 and 2)	
	Fezolinetant 45 mg (n=174)	Placebo (n=175)	Fezolinetant 45 mg (n=167)	Placebo (n=167)	Fezolinetant 45 mg (n=341)	Placebo (n=342)
Baseline						
Mean (SD)	2.40 (0.35)	2.43 (0.35)	2.41 (0.34)	2.41 (0.32)	2.40 (0.35)	2.42 (0.34)
Change from baseline to week 4						
LS Mean (SE)	-0.46 (0.04)	-0.27 (0.04)	-0.61 (0.05)	-0.32 (0.05)	-0.53 (0.03)	-0.30 (0.03)
Difference vs Placebo (SE)	-0.19 (0.06)	--	-0.29 (0.06)	--	-0.24 (0.04)	--
P-value	0.002[1]	--	< 0.001[1]	--	< 0.001	--
Change from baseline to week 12						
LS Mean (SE)	-0.57 (0.05)	-0.37 (0.05)	-0.77 (0.06)	-0.48 (0.06)	-0.67 (0.04)	-0.42 (0.04)
Difference vs Placebo (SE)	-0.20 (0.08)	--	-0.29 (0.08)	--	-0.24 (0.06)	--
P-value	0.007[1]	--	< 0.001[1]	--	< 0.001	--

[1] Statistically significantly superior compared to placebo at the 0.05 level with multiplicity adjustment.
LS Mean: Least Squares Mean estimated from a mixed model for repeated measures analysis of covariance;
SD: Standard Deviation; SE: Standard Error.

Other efficacy: Patient-reported outcomes

Sleep disturbance (PROMIS SD SF 8b)

Pooled efficacy analysis (SKYLIGHT 1 and 2) of the key secondary endpoint resulted in fezolinetant 45 mg demonstrating an improvement from baseline to week 12 (LS mean difference (SE): -1.5 (0.5), 95% CI: (-2.5, -0.5), nominal P-value: 0.004) in sleep disturbance compared to placebo, measured by the patient-reported outcomes measurement information system (PROMIS) Sleep Disturbance Short Form 8b Total Score. A reduction in PROMIS SD 8b was maintained through 52 weeks.

Menopause-specific quality-of-life (MENQoL)
Fezolinetant 45 mg resulted in an improvement from baseline to week 12 in health-related quality-of-life (HRQoL) compared to placebo, measured by the MENQoL total score and the VMS domain score of MENQoL. Reductions in MENQoL were maintained through 52 weeks. Results are shown in Table 4.

Table 4. SKYLIGHT 1 and 2: Mean baseline and change from baseline in total score and VMS domain score of MENQoL to week 12

Parameter	Pooled studies (SKYLIGHT 1 and 2)	
	Fezolinetant 45 mg (n=341)	**Placebo (n=342)**
Total score		
Baseline mean (SD)	4.3 (1.4)	4.3 (1.4)
Mean (SD) change from baseline to week 12[1]	-1.3 (1.4)	-0.9 (1.4)
LS mean difference (SE) at week 12[2]	-0.5 (0.1)	--
95% CI	-0.7, -0.3	--
P-value[3]	< 0.001	--
VMS domain score		
Baseline mean (SD)	6.5 (1.6)	6.5 (1.4)
Mean (SD) change from baseline to week 12[1]	-2.4 (2.1)	-1.6 (2.0)
LS mean difference (SE) at week 12[2]	-0.9 (0.2)	--
95% CI	-1.2, -0.6	--
P-value[3]	< 0.001	--

[1] A negative change indicates a reduction/improvement from baseline.
[2] Differences are calculated by subtracting the LS mean of the placebo group from the LS mean of the fezolinetant group. LS Mean: Least Squares Mean estimated from a mixed model for repeated measures analysis of covariance; SD: Standard Deviation; SE: Standard Error; CI: Confidence Interval.
[3] Multiplicity unadjusted p-value.

Safety: Endometrial safety
In the long-term safety data (SKYLIGHT 1, 2, and 4), endometrial safety of fezolinetant 45 mg was assessed by transvaginal ultrasound and endometrial biopsies (304 women had baseline and post-baseline endometrial biopsies during 52 weeks of treatment).

Endometrial biopsy assessments did not identify an increased risk of endometrial hyperplasia or malignancy according to pre-specified criteria for endometrial safety. Transvaginal ultrasound did not reveal increased endometrial thickness.

5.2 Pharmacokinetic properties

In healthy women, fezolinetant C_{max} and AUC increased proportionally with doses between 20 and 60 mg once daily.

After once-a-day dosing, steady-state plasma concentrations of fezolinetant were generally reached by day 2, with minimal fezolinetant accumulation. The pharmacokinetics of fezolinetant do not change over time.

Absorption
Fezolinetant C_{max} is usually achieved at 1 to 4 hours post-dose.

Effect of food
Fezolinetant may be administered with or without food. No clinically significant differences in fezolinetant pharmacokinetics were observed following administration with a high-calorie, high-fat meal.

Distribution
The mean apparent volume of distribution (Vz/F) of fezolinetant is 189 L. The plasma protein binding of fezolinetant is low (51%). The distribution of fezolinetant into red blood cells is almost equal to plasma.

Biotransformation
Fezolinetant is primarily metabolized by CYP1A2 in humans to yield oxidized major metabolite ES259564. ES259564 is approximately 20-fold less potent against human NK3 receptor with no significant off-target activities. The metabolite-to-parent ratio ranges from 0.7 to 1.8.

Elimination
The apparent clearance at steady-state of fezolinetant is 10.8 L/h. Following oral administration, fezolinetant is mainly eliminated in urine (76.9%) and to a lesser extent in feces (14.7%). In urine, a mean of 1.1% of the administered fezolinetant dose was excreted unchanged and 61.7% of the administered dose was excreted as ES259564. The effective half-life ($t_{1/2}$) of fezolinetant is 9.6 hours in women with VMS.

Special populations
Effects of age, race, and body weight
There are no clinically relevant effects of age (18 to 65 years), race (Black, Asian, Other), body weight (42 to 126 kg), or menopause status on the pharmacokinetics of fezolinetant.

Renal impairment
Following single-dose administration of 30 mg fezolinetant, there was no clinically relevant effect on fezolinetant exposure (C_{max} and AUC) in women with mild (eGFR 60 to less than 90 mL/min/1.73 m^2) to severe (eGFR less than 30 mL/min/1.73 m^2) renal impairment. The AUC of ES259564 was not changed in women with mild renal impairment but increased approximately 1.7- to 4.8-fold in moderate (eGFR 30 to less than 60 mL/min/1.73 m^2) and severe renal impairment. Fezolinetant has not been studied in individuals with end-stage renal disease (eGFR less than 15 mL/min/1.73 m^2).

Hepatic impairment
Following single-dose administration of 30 mg fezolinetant in women with Child-Pugh Class A (mild) chronic hepatic impairment, mean fezolinetant C_{max} increased by 23% and AUC_{inf} increased by 56%, relative to women with normal hepatic function. In women with Child-Pugh Class B (moderate) chronic hepatic impairment, mean fezolinetant C_{max} decreased by 15% and AUC_{inf} increased by 96%. The C_{max} of ES259564 decreased in both mild and moderate chronic hepatic impairment groups while AUC_{inf} and AUC_{last} slightly increased less than 15%. Fezolinetant has not been studied in individuals with Child-Pugh Class C (severe) chronic hepatic impairment.

Pharmacologically induced menopause
Fezolinetant has not been studied in individuals with VMS induced by pharmacologic treatment of malignancy (e.g., breast cancer).

Drug-drug interactions
Clinical studies
Strong CYP1A2 inhibitors
Co-administration with fluvoxamine, a strong CYP1A2 inhibitor, resulted in an overall 1.8-fold increase in fezolinetant C_{max} and 9.4-fold increase in AUC; no change in t_{max} was observed.

Moderate CYP1A2 inducers
Smoking (moderate inducer of CYP1A2) decreased fezolinetant C_{max} to a geometric LS mean ratio of 71.74%, while AUC decreased to a geometric LS mean ratio of 48.29%. Smoking does not cause any clinically significant differences in fezolinetant efficacy.

Physiologically-based pharmacokinetic modeling predictions
Weak and moderate CYP1A2 inhibitors
Based on physiologically-based pharmacokinetic modeling, a typical weak CYP1A2 inhibitor (cimetidine; 300 mg every 6 hours) is predicted to increase the fezolinetant C_{max} by 1.3-fold and the AUC by 2-fold. A typical moderate CYP1A2 inhibitor (mexiletine; 400 mg every 8 hours) is predicted to increase the fezolinetant C_{max} by 1.4-fold and the AUC by 4.6-fold.

In vitro studies

Cytochrome P450 (CYP) enzymes

Fezolinetant is primarily metabolized by CYP1A2 and to a lesser extent by CYP2C9 and CYP2C19. Fezolinetant and ES259564 are not inhibitors of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. Fezolinetant and ES259564 are not inducers of CYP1A2, CYP2B6, and CYP3A4.

Transporters

Fezolinetant is not a substrate nor an inhibitor of P-glycoprotein (P-gp). ES259564 is a substrate of P-gp, but not an inhibitor of P-gp.

Both fezolinetant and ES259564 are not a substrate of BCRP, OATP1B1, and OATP1B3. In addition, ES259564 is not a substrate of OAT1, OAT3, OCT2, MATE1, and MATE2-K.

5.3 Preclinical safety data

Carcinogenesis, mutagenesis, impairment of fertility

An increase in the incidence of thyroid follicular cell adenoma was noted in the 2-year rat carcinogenicity study (186-fold the AUC_{24} at the human therapeutic dose of 45 mg). The increase is considered to be a rat specific effect secondary to the induction of hepatocyte metabolic enzymes and, therefore, does not constitute a clinical carcinogenic risk. In the 26-week carcinogenicity study in rasH2 transgenic mice, neoplasms were not induced (47-fold the AUC_{24} at the human therapeutic dose).

Fezolinetant and ES259564 showed no genotoxic potential in the bacterial reverse mutation test, chromosomal aberration test, or *in vivo* micronucleus test.

Fezolinetant had no effect on female fertility or early embryonic development up to 100 mg/kg/day in rats (143-fold the AUC_{24} at the human therapeutic dose).

In embryo-fetal development toxicity studies, embryo-lethality was noted at the AUC_{24} 128- and 174-fold higher than the AUC_{24} at the human therapeutic dose in rats and rabbits, respectively. Rabbits also showed increased late resorption and reduced fetal weight at 75 mg/kg/day (28-fold the AUC_{24} at the human therapeutic dose). The no observed adverse effect level (NOAEL) for embryo-fetal development was 50 mg/kg/day in rats and 45 mg/kg/day in rabbits (62- and 16-fold the AUC_{24} at the human therapeutic dose in rats and rabbits, respectively). Fezolinetant did not show teratogenic potential in either rats or rabbits.

In the pre- and post-natal development study in rats, the NOAEL for maternal and fetal toxicity was 30 mg/kg/day (36-fold the AUC_{24} at the human therapeutic dose) based on delayed parturition and embryo-lethality at 100 mg/kg/day. The NOAEL for F1 generation development was determined to be 100 mg/kg/day for females (204-fold the AUC_{24} at the human therapeutic dose) and 10 mg/kg/day for males (11-fold the AUC_{24} at the human therapeutic dose). The F1 male showed incomplete balanopreputial separation which may delay male reproductive maturation or affect fertility.

Animal toxicology and/or pharmacology

Mortality was observed at 300 mg/kg/day (197-fold the AUC_{24} at the human therapeutic dose of 45 mg) in the rat 4-week repeat dose toxicity study. Moribund animals showed lethargy, reduced activity, labored respiration and staggering gait, and body weight loss. No mortality was noted in 13- or 26-week repeat dose toxicity studies at doses up to 200 mg/kg/day (148-fold the AUC_{24} at the human therapeutic dose). In female rats, daily administration of fezolinetant for 26 weeks at doses equal to or greater than 30 mg/kg/day (56-fold the AUC_{24} at the human therapeutic dose) showed uterine atrophy and epithelial mucification of the vagina and cervix.

In cynomolgus monkeys, fezolinetant administration at a dose of 40 mg/kg/day for 39 weeks was associated with mortality in one animal (102-fold the AUC_{24} at the human therapeutic dose). The moribund animal showed acute hemorrhagic anemia and severe thrombocytopenia. Thrombocytopenia

was also observed in one surviving animal at a dose of 40 mg/kg/day, but not in other animals. In female cynomolgus monkeys, daily administration of fezolinetant for 39 weeks at doses equal to or greater than 10 mg/kg/day (26-fold the AUC_{24} at the human therapeutic dose) showed reduced ovarian activity.

In the rat safety pharmacology study, constricted pupils were noted at doses equal to or greater than 125 mg/kg. Decreased activity, touch escape response, and grip strength, which were thought to be indicative of sedation, were noted at 250 mg/kg. These clinical signs were not apparent at 24 hours post-dose. These sedation-like effects were also confirmed in the 4- and 13-week repeated dose toxicity studies in rats. The NOAEL for sedation-like effects was 30 mg/kg/day and 60-fold the C_{max} at the human therapeutic dose. Conversely, no CNS findings, including sedation, were observed in cynomolgus monkeys (5-, 13-, and 39-week repeated dose studies) up to the highest dose (40 or 50 mg/kg/day, 67-fold the C_{max} at the human therapeutic dose).

Fezolinetant inhibited hERG current density with an IC_{50} value of 231.8 µmol/L (83074.8 ng/mL, 371-fold the C_{max} at the human therapeutic dose). The telemetry study in cynomolgus monkeys and the Langendorff study showed no effects on the cardiovascular system. These results indicate that fezolinetant has little or no cardiovascular effects.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol, hydroxypropyl cellulose, low-substituted hydroxypropyl cellulose, microcrystalline cellulose, magnesium stearate, hypromellose, talc, polyethylene glycol (macrogol), titanium dioxide, and ferric oxide (iron oxide red).

6.2 Incompatibilities

None.

6.3 Shelf life

The expiry date can be found on the packaging.

6.4 Special precautions for storage

Store in the original package until dispensed in order to protect from moisture and humidity.

Package type	Recommended storage conditions
Aluminum/aluminum blisters	Store at or below 30°C.

6.5 Nature and contents of container

Aluminum/aluminum blisters containing 10 film-coated tablets per blister.
Pack size:
10 film-coated tablets.
30 film-coated tablets.
Not all pack sizes may be marketed.

6.6 Instructions for use and handling

Swallow the tablet whole with liquids. Do not cut, crush, or chew the tablet before swallowing.
Fezolinetant can be taken with or without food.
Keep this and all medications out of the reach of children.

7. PRODUCT REGISTRANT

Astellas Pharma Singapore Pte. Ltd.
6 Temasek Boulevard
#26-03/05 Suntec Tower Four
Singapore 038986

For any enquiry, please write to pv@sg.astellas.com.

8. DATE OF REVISION OF PACKAGE INSERT

Feb2025 (CCDSv4)