12 October 2023
EMA/528775/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Veoza

International non-proprietary name: Fezolinetant

Procedure No. EMEA/H/C/005851/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Administrative information

Name of the medicinal product:	Veoza
Applicant:	Astellas Pharma Europe B.V. Sylviusweg 62 2333 BE Leiden NETHERLANDS
Active substance:	Fezolinetant
International Non-proprietary Name/Common Name:	fezolinetant
Pharmaco-therapeutic group (ATC Code):	other gynecologicals, other gynecologicals (G02CX06)
Therapeutic indication(s):	Veoza is indicated for the treatment of moderate to severe vasomotor symptoms (VMS) associated with menopause (see section 5.1).
Pharmaceutical form(s):	Film-coated tablet
Strength(s):	45 mg
Route(s) of administration:	Oral use
Packaging:	blister (PA/alu/PVC/alu)
Package size(s):	100 x 1 tablets (unit dose), 28 x 1 tablets (unit dose) and 30 x 1 tablets (unit dose)

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List of abbreviations

ACOG	American College of Obstetricians and Gynaecologists
ADR	adverse drug reaction
AESI	adverse events of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ARC	arcuate nucleus
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUCinf	area under the plasma concentration-time curve from time zero to infinity
AUClast	area under the plasma concentration-time curve from time zero to time of last measurable concentration
BCRP	breast cancer resistance protein
BCS	Biopharmaceutics Classification System
BMI	body mass index
BSAP	bone specific alkaline phosphatase
CDE	Center for Drug Evaluation
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
Cmax	maximal plasma concentration
CMC	chemistry, manufacturing and controls
CNS	central nervous system
COVID-19	coronavirus disease 2019
CQA	critical quality attribute
CTX	carboxy-terminal telopeptide of type I collagen
CYP	cytochrome P450
DSC	differential scanning calorimetry
DXA	dual-energy X-ray absorptiometry
ECG	electrocardiogram
EFD	embryo-foetal development
eGFR	estimated glomerular filtration rate
FAS	full analysis set
FSH	follicle-stimulating hormone
GC	gas chromatography
GD	gestation day
HPLC	high performance liquid chromatography
HT	hormone replacement therapy
ICH	International Council for Harmonisation
IR	infrared
ISE	integrated summary of efficacy
ISS	integrated summary of safety
KF	Karl Fisher
Ki	inhibitory constant
KNDy	kisspeptin/neurokinin B/dynorphin
LD	lactation day
LH	luteinizing hormone
MATE	multidrug and toxin extrusion protein
MENQOL	Menopause-Specific Quality of Life
MMRM	mixed model repeated measures
MnPO	median preoptic nucleus
MO	major objection
MRHD	maximum recommended human dose
MS	mass spectrometry
MV	mass variation
NAMS	North American Menopause Society
NK	neurokinin
NK3R	neurokinin 3 receptor
NKB	neurokinin B
NMT	not more than
NOAEL	no observed adverse effect

NOR	normal operating range
OAT	organic anion transporter
OATP	organic-anion-transporting polypeptides
OCT	organic cation transporter
OVX	ovariectomized
P1NP	procollagen type 1 amino-terminal propeptide
PA	polyamide
PAR	proven acceptable range
PBPK	physiologically-based pharmacokinetic
PCOS	polycystic ovary syndrome
PGI	Patient Global Impression
PGI-C VMS	Patient Global Impression of Change in Vasomotor Symptoms
P-gp	p-glycoprotein
PPND	pre- and postnatal development
PRO	patient-reported outcome
PROMIS SD SF 8b	Patient-reported Outcomes Measurement Information System Sleep Disturbance – Short Form 8b
PVC	polyvinylchloride
QTc	QT interval corrected
QTPP	quality target product profile
SAF	safety analysis set
SHBG	sex hormone-binding globulin
SmPC	Summary of Product Characteristics
SNRIs	serotonin and norepinephrine reuptake inhibitors
SOC	system organ class
SOGC	Society of Obstetricians and Gynaecologists of Canada
SSRI	selective serotonin reuptake inhibitors
TEAE	treatment-emergent adverse event
TG	thermogravimetry
tmax	time to reach maximum concentration
TQT	thorough QT/QTc
TVU	transvaginal ultrasound
UF	uterine fibroids
UHPLC	ultra high performance liquid chromatography
ULN	upper limit of normal
UV	ultraviolet
VMS	vasomotor symptoms
XRPD	X-ray powder diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Astellas Pharma Europe B.V. submitted on 24 August 2022 an application for marketing authorisation to the European Medicines Agency (EMA) for Veoza, through the centralised procedure under Article 3 (2) (a) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 29 January 2021.

The applicant applied for the following indication: Veoza is a non-hormonal selective neurokinin 3 (NK3) antagonist, indicated for the treatment of moderate to severe vasomotor symptoms (VMS) associated with menopause.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

1.3. Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included EMA Decision(s) CW/1/2015 on the granting of a class waiver.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.4.2. New active Substance status

The applicant requested the active substance fezolinetant contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

1.5. Scientific advice

The applicant received the following Scientific advice on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
21 April 2017	EMEA/H/SA/3488/1/2017/SME/III	Prof. Minne Casteels, Dr. Amany N. El-Gazayerly
18 October 2018	EMEA/H/SA/3488/1/FU/1/2018/II	Prof. Minne Casteels, Dr. Peter Mol
29 May 2019	EMEA/H/SA/3488/1/FU/2/2019/III	Dr Ewa Balkowiec-Iskra, Prof. Minne Casteels
25 July 2019	EMEA/H/SA/3488/2/2019/I	Ms. Audrey Sultana, Mr. Christian Gartner
30 January 2020	EMEA/H/SA/3488/1/FU/3/2019/III	Dr Carin Bergquist, Dr Mogens Westergaard
22 July 2021	EMA/SA/0000061311	Hrefna Gudmundsdottir, Audrey Sultana

The Scientific advice pertained to the following quality, non-clinical, and clinical aspects:

- defining the starting materials
- overall nonclinical development plans
- planned investigations to enable environmental risk assessment (ERA)
- plans for cardiac repolarisation interference testing
- clinical pharmacology study plans, including dose finding and drug-drug-interaction studies
- phase 2 study plans
- phase 3 study plans: number of pivotal studies, study designs, efficacy endpoints; study populations, sample size, statistical analysis plan, long-term safety study
- safety measures: liver safety monitoring, need to assess of endometrial health and bone safety
- safety database
- development in women with breast cancer, having moderate to severe VMS symptoms associated with hormone replacement therapy
- investigations of neuropsychological functions and potential for abuse

1.6. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Patrick Vrijlandt Co-Rapporteur: Robert Porszasz

The application was received by the EMA on	24 August 2022
The procedure started on	29 September 2022
The CHMP Rapporteur's first Assessment Report was circulated to all	21 December 2022

CHMP and PRAC members on	
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	2 January 2023
The CHMP Co-Rapporteur's Assessment was circulated to all CHMP and PRAC members on	5 January 2023
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	26 January 2023
The applicant submitted the responses to the CHMP consolidated List of Questions on	19 April 2023
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	30 May 2023
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	8 June 2023
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	22 June 2023
The applicant submitted the responses to the CHMP List of Outstanding Issues on	13 September 2023
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	27 September 2023
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Veoza on	12 October 2023

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Fezolinetant is a non-hormonal, selective neurokinin 3 (NK3) receptor antagonist and is proposed to be indicated for the treatment of moderate to severe vasomotor symptoms (VMS) associated with menopause.

Its development is based on the rationale that VMS associated with menopause are caused by neurological changes in the brain that occur in response to menopause involving kisspeptin/neurokinin B/dynorphin (KNDy) neurons. Fezolinetant inhibits neurokinin B (NKB) binding on the KNDy neuron to help restore the neuronal activity in the thermoregulatory centre of the hypothalamus.

Postmenopause

Postmenopause, also called "menopause" in several guidelines, is defined as the permanent cessation of menstrual periods, determined retrospectively after a woman has experienced 12 months of amenorrhea without any other obvious pathologic or physiologic cause. It occurs at a median age of 51.4 years and is a reflection of complete, or near complete, ovarian follicular depletion, with resulting very low estradiol levels and high follicle-stimulating hormone (FSH) concentrations.

Vasomotor symptoms (VMS)

VMS, also referred to as hot flashes or flushes, involve sudden sensations of heat in the upper body, particularly in the head, neck, chest and upper back. VMS typically begin as the sudden sensation of heat centred on the upper chest and face that rapidly becomes generalized. The sensation of heat lasts from two to four minutes, is often associated with profuse perspiration and occasionally palpitations, and is sometimes followed by chills and shivering, and a feeling of anxiety. VMS usually occur several times per day, although the range may be from only one or two each day to as many as one per hour during the day and night. VMS are particularly common at night. Individuals typically have an average of 17 VMS and 11 night sweats per week. It had been thought that vasomotor symptoms diminish and stop within a few years of onset in most women. However, the duration of VMS from the time of symptom onset is typically 7.4 years [Avis et al, 2015], and vasomotor symptoms can persist for as long as 20 years post-menopause (ACOG Clinical Management Guidelines, 2014, Endocrine Society Clinical Practice Guideline Stuenkel et al, 2015, European Menopause and Andropause Society (EMAS) position statement 2022, UptoDate 2022).

These symptoms are experienced by up to 80% of women during menopause [Gold et al, 2006]. An individual's experience can vary based on a combination of genetic background, psychological factors and other health conditions or treatments (ACOG Clinical Management Guidelines, 2014).

2.1.2. Epidemiology and risk factors

The global prevalence of overall VMS associated with menopause is estimated to be approximately 11% to 47% in women over the age of 40 [Whiteley et al, 2013; Blümel et al, 2011; Freeman & Sherif, 2007]. The prevalence by region of moderate to severe VMS associated with menopause in individuals aged 40 to 65 years is 34% in the US, 40% in Europe and 16% in Japan [Nappi et al, 2021]. Other studies suggest the prevalence of overall VMS ranges from 37% to 46% in China (for post-menopausal individuals) [Wang et al, 2021; Zhang et al, 2021; Lan et al, 2017; Li et al, 2012]. The wide variation of VMS prevalence within regions is largely attributed to differences in study methodologies, including participant selection criteria and method of symptom identification [Miller & Li,2004]. The prevalence of VMS associated with menopause appears to vary by ethnicity, with lowest rates reported among Asian individuals and highest among African or African-American women [Freeman & Sherif, 2007; Gold et al, 2006].

2.1.3. Biologic features, aetiology and pathogenesis

The menopausal transition, also called perimenopause, is marked by fluctuations in sex hormone levels, especially oestradiol levels, as ovarian function is declining. The postmenopause, also called "menopause" in several guidelines, is defined as the permanent cessation of menstrual periods, determined retrospectively after a woman has experienced 12 months of amenorrhea without any other obvious pathologic or physiologic cause. It occurs at a median age of 51.4 years and is a result of complete, or near complete, ovarian follicular depletion, with resulting very low estradiol levels and high follicle-stimulating hormone (FSH) concentrations. This can result in symptoms such as VMS, also referred to as hot flashes or flushes, which are characterized by perspiration, flushing, chills, clamminess, anxiety and on occasion heart palpitations and occur as episodes that usually last 1 to 5

minutes several times per day ([Stuenkel et al, 2015]; ACOG Clinical Management Guidelines, 2014). VMS can severely impact the woman's quality of life (QoL) and are characterized by problems with sleep, mood, concentration, energy and sexual activity (Kagan et al, 2021; Williams et al, 2009; Kravitz et al, 2008) and may significantly interfere with her professional life (Simon & Reape, 2009). Individuals often also report feelings of physical discomfort, depression, anxiety, stress, self-consciousness and embarrassment (Whiteley et al, 2013; Williams et al, 2009; Rendall et al, 2008).

The thermoregulatory centre of the hypothalamus is innervated by KNDy neurons that are normally inhibited by oestrogen and stimulated by the NKB. It has been postulated that an altered thermoregulatory response is due to the drop in ovarian estradiol production, resulting in hypersecretion of gonadotropins FSH and LH, and an increased expression of kisspeptin and neurokinin B (NKB) within the infundibular nucleus of the hypothalamus. Hormonal and neuroendocrine changes associated with menopause are thought to be responsible for the inappropriate activation of heat dissipation effectors and the subsequent hot flush. In recent years, NKB, predominantly acting via the neurokinin 3 receptor (NK3R), has emerged as having an important role in the development of menopausal hot flushes. Neuroendocrine changes in menopause are characterised by reduced production of ovarian oestrogen and progesterone. Due to lack of negative feedback from circulating estrogen, secretion of LH and FSH from the anterior pituitary gland increases. This increase in LH secretion seen is likely mediated by increased secretion of GnRH and altered activity of neurons expressing Kiss1, NKB, and Dynorphin in the infundibular nucleus.

2.1.4. Clinical presentation and diagnosis and stage/prognosis

See section 2.1.1 'Disease or condition'

VMS affects a diverse group of individuals, with adverse health outcomes and burden of disease that have an impact not only on the individual's quality of life but also the wider society (Kagan et al, 2021; Williams et al, 2009). VMS can impact several areas of life and are characterized by problems with sleep, mood, concentration, energy and sexual activity (Kagan et al, 2021; Williams et al, 2009; Kravitz et al, 2008). Individuals often also report feelings of physical discomfort, depression, anxiety, stress, self-consciousness and embarrassment (Whiteley et al, 2013; Williams et al, 2009; Rendall et al, 2008). Individuals with VMS associated with menopause do not always receive adequate and effective care. As a consequence, individuals are required to seek further medical assistance, which significantly increases the use of healthcare resources and incur higher costs than those without VMS (Sarrel et al, 2015). For many women, menopausal symptoms significantly interfere with their professional lives (Simon & Reape, 2009). Effective treatment of VMS has the potential to improve humanistic, economic and societal burden of VMS associated with menopause.

2.1.5. Management

Hormone treatment (HT)

HT (also commonly referred to as hormone replacement therapy (HRT)) with oestradiol is currently the recommended first-line treatment for moderate to severe VMS associated with menopause according to international guidelines ([Baber et al, 2016; de Villiers et al, 2016; Stuenkel et al, 2015]; NAMS Position Statement, 2017; ACOG Clinical Management Guidelines, 2014; SOGC Clinical Practice Guideline: Managing Menopause, 2014, NICE 2015, RCOG 2018).

HT works by supplementing the declined production of estradiol by the ovaries [Martin & Barbieri, 2020]; the key component of HT is oestrogen (estradiol). In women with an uterus, estradiol is combined with a synthetic progestogen or progesterone to protect the endometrium from development

of hyperplasia [Martin & Barbieri, 2022]. Estradiol-only is given to women without a uterus. HT is the gold standard for treatment of the relief of bothersome VMS and vaginal symptoms associated with menopause (NAMS Position Statement, 2017; [Stuenkel et al, 2015]).

However, data from the WHI published in 2002, a hormone therapy (HT) trial (continuous, combined oestrogen-progestogen therapy versus placebo) in older postmenopausal women (mean age 63 years and more than 10 years since menopause), showed a number of adverse outcomes, including an excess risk of CHD, stroke, venous thromboembolism (VTE), and breast cancer. Use of HT decreased significantly in the decade after publication of the WHI results in 2002. The current view is, however, that this study population is not the age group that presents with new onset of menopausal symptoms. The initiation of HT is considered to be a safe option for healthy, symptomatic women who are within 10 years of menopause or younger than age 60 years and who do not have contraindications to HT (NAMS 2017, UptoDate 2022). There are no set time limits for how long women can use HT but is based on the individual benefit risk profile (NICE, RCOG). The EU Core SmPC for HRT does not include a maximum treatment duration, but that HRT should only be continued as long as the benefit outweighs the risk.

Non-hormonal therapies

Non-hormonal medications have been studied for treatment of VMS associated with menopause (Hickey et al, 2017; Drewe et al, 2015). SSRIs, SNRIs, gabapentin and clonidine have been shown to improve VMS associated with menopause in clinical trials, although to a much lesser extent than HT (ACOG Clinical Management Guidelines, 2014; Baber et al, 2016, UptoDate 2022).

Clonidine

Only the centrally acting α2-adrenergic agonist clonidine is approved for the treatment of hot flushes in the EU.

SSRIs/NSRIs (off-label)

In clinical guidelines SSRIs are indicated as first choice in women who cannot take oestrogens, i.e. with a medical history of breast cancer. In the EU, no SSRI is approved for this indication, while in the US paroxetine is approved for the indication of VMS.

Over-the-counter-remedies

Natural over-the-counter remedies, including herbal/non-prescription products, have not been approved for VMS treatment, and their safety and efficacy are not well established. Furthermore, these products do not address the burden of disease considering the very limited evidence to support their use and limited data to support their mechanisms of action (Baber et al, 2016; de Villiers et al, 2016; Stuenkel et al, 2015; NAMS Position Statement, 2017; ACOG Clinical Management Guidelines, 2014; SOGC Clinical Practice Guideline: Managing Menopause, 2014).

As summarized above, there are limits within the available pharmacotherapeutic treatments, which do not fully address the unmet need of VMS associated with menopause in those women who cannot use oestrogens. The availability of safe and efficacious non-hormonal options for the treatment of VMS associated with menopause is important to mitigate the burden of moderate to severe VMS on the individual.

2.2. About the product

Mechanism of action

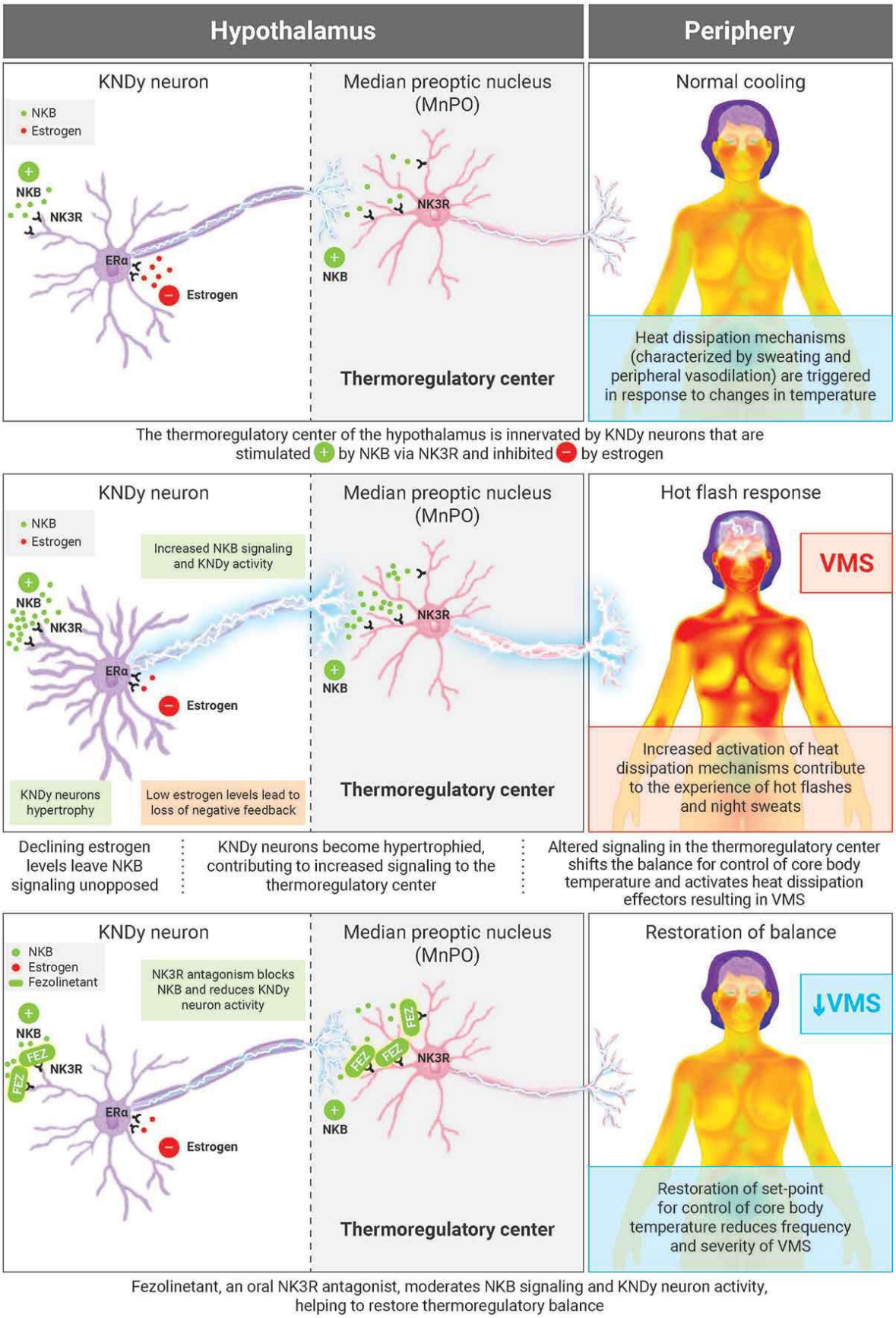
Fezolinetant is a non-hormonal, selective neurokinin 3 (NK3) receptor antagonist that blocks neurokinin B (NKB) binding on the kisspeptin/neurokinin B/dynorphin (KNDy) neuron to modulate neuronal activity in the thermoregulatory centre of the hypothalamus.

It is postulated that VMS associated with menopause are caused by neurological changes in the brain that occur in response to menopause involving KNDy neurons. The development of fezolinetant is based on the rationale that VMS associated with menopause are caused by neurological changes in the brain that occur in response to menopause involving kisspeptin/neurokinin B/dynorphin (KNDy) neurons.

Non-clinical data are claimed to demonstrate that fezolinetant is a non-hormonal selective antagonist that blocks neurokinin B (NKB) binding on the KNDy neuron to moderate neuronal activity in the thermoregulatory centre and improves VMS associated with menopause. Studies show fezolinetant binds competitively, reversibly and with high affinity to the NK3 receptor. *In vitro* studies also demonstrated that fezolinetant is selective for the human NK3 receptor and fully inhibits its activity, compared to the other members of the tachykinin receptor family (human NK1 and human NK2) and other G-protein coupled receptors including the ones known to be implicated in modulation of the gonadotropin-releasing hormone axis. Non-clinical studies also suggest that fezolinetant inhibits the activation of MnPO neurons located in the thermoregulatory centre. The main metabolite of fezolinetant, ES259564, was found to be less potent (approximately 20-fold less potent) at the NK3 receptor than the parent drug. Collectively, these data support the postulated mechanism of action for fezolinetant as a nonhormonal, selective NK3 receptor antagonist that blocks NKB binding on the KNDy neuron to modulate neuronal activity in the thermoregulatory centre [Figure 1].

Furthermore, these data provide the scientific rationale for the potential benefit of fezolinetant in improving VMS associated with menopause through its action in the hypothalamus to calibrate the neuronal activity in the thermoregulatory centre.

Figure 1 Postulated mechanism of action for fezolinetant in moderate to severe VMS associated with menopause



Approved indication

Within this procedure, the Applicant claims the following therapeutic indication:

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

Approved posology

The recommended dose is a 45 mg tablet once daily.

2.3. Type of Application and aspects on development

The fezolinetant clinical program is comprised of 18 completed studies: 11 phase 1 studies, 4 phase 2 studies and 3 phase 3 studies.

Primary evidence for the efficacy of fezolinetant in the treatment of moderate to severe VMS associated with menopause comes from studies 2693-CL-0301 and 2693-CL-0302. These 2 pivotal, phase 3, randomized studies included a 12-week placebo-controlled period followed by a 40-week period of fezolinetant exposure only (52 weeks in total).

Primary evidence for the safety evaluation of fezolinetant comes from the 52-week, placebo-controlled, long-term safety phase 3 study 2693-CL-0304 and from pivotal studies 2693-CL-0301 and 2693-CL-0302.

The Applicant sought regulatory advice from Health Authorities in the EU, US, Canada, Japan and China on the development program of fezolinetant. Information was reviewed to support clinical study applications and provided their advice regarding several aspects of the clinical development program and specific study designs.

2.4. Quality aspects

2.4.1. Introduction

The finished product is presented as film-coated tablets containing 45 mg of fezolinetant.

Other ingredients are:

Core tablet:

Mannitol (E421), hydroxypropyl cellulose (E463), low-substituted hydroxypropyl cellulose (E463a), microcrystalline cellulose (E460), magnesium stearate (E470b)

Film coating:

Hypromellose (E464), talc (E553b), macrogol (E1521), titanium dioxide (E171), iron oxide red (E172)

The product is available in Polyamide (PA)/Aluminium/PVC/Aluminium unit dose blisters in cartons as described in section 6.5 of the SmPC.

2.4.2. Active Substance

2.4.2.1. General information

The chemical name of fezolinetant is 1. Methanone, [(8*R*)-5,6-dihydro-8-methyl-3-(3-methyl-1,2,4-thiadiazol-5-yl)-1,2,4-triazolo[4,3-*a*]pyrazin-7(8*H*)-yl](4-fluorophenyl)-2. (4-Fluorophenyl)[(8*R*)-8-methyl-3-(3-methyl-1,2,4-thiadiazol-5-yl)-5,6-dihydro[1,2,4]triazolo[4,3-*a*]pyrazin-7(8*H*)-yl]methanone corresponding to the molecular formula $C_{16}H_{15}FN_6OS$. It has a relative molecular mass of 358.39 g/mol and the following structure:

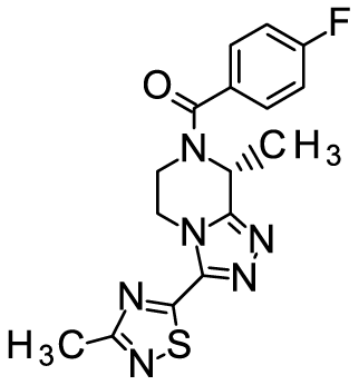


Figure 2 Active substance structure

The chemical structure of fezolinetant was elucidated by a combination of methods. The physicochemical properties were also determined by a combination of methods. Two polymorphic forms (Form I and Form II) have been identified. The drug substance is manufactured as a single polymorphic form (Form I).

The active substance is a white powder, not hygroscopic, very slightly soluble in aqueous solution at 20 ± 5°C between pH 1 and 11, sparingly soluble in ethanol, and highly soluble at 37 ± 1°C in 0.1N hydrochloric acid, in pH 4.5 acetate buffer, and in pH 6.8 phosphate buffer.

Fezolinetant exhibits stereoisomerism (R-configuration) due to the presence of one chiral centre and is formed as a single isomer. The active substance specification includes a test for enantiomer. It was demonstrated that no racemisation occurs during manufacture and storage of the finished product. This justifies absence of further control of stereochemistry in the finished product.

2.4.2.2. Manufacture, characterisation and process controls

Fezolinetant is synthesised by two sources according to the same synthetic route, consisting of four chemical transformation steps with one isolated intermediate and one final crystallisation step, using well defined starting materials with acceptable specifications.

The criticality of quality attributes and process parameters for the manufacturing process of fezolinetant was examined by risk assessment. The critical quality attributes (CQAs) that have an impact on the quality of fezolinetant and critical and non-critical process parameters have been identified. No design space is declared. PARs and NORs have been studied and established for the relevant process parameters and in-process parameters. All operating ranges proposed in the finalised manufacturing process have been sufficiently justified. An adequate control strategy is in place for all critical quality attributes.

Step 1, Step 3 and Step 5 are considered critical steps in the manufacture of fezolinetant. The performed in process controls and the specifications of the intermediates and raw materials used in the manufacturing process are sufficient to ensure the quality of the manufacturing process of the active substance. No recovered solvents and no class I solvents or heavy metal catalysts are used during the manufacture.

Both active substance manufacturers follow the same synthesis process, however, at a different scale. The equivalence of finished product manufactured with two different sources of active substance was demonstrated based on batch data.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances.

Potential and actual impurities were well discussed with regards to their origin and characterised.

The commercial manufacturing process for the active substance was developed in parallel with the clinical development program.

Three process versions (A, B and C) were used during development. Changes introduced have been presented in sufficient detail and have been justified.

The quality of the active substance used in the various phases of the development is considered to be comparable with that produced by the proposed commercial process.

Compliance of the primary packaging material of the active substance with Regulation No 10/2011, as amended, as well as relevant Ph. Eur. monograph, has been confirmed.

2.4.2.3. Specification

The active substance specification includes tests for: description (visual), identification (IR, XRPD), purity (related substances by UHPLC and HPLC), enantiomer by HPLC, residual solvents (GC and GC-MS), residue on ignition (Ph.Eur.), and assay (UHPLC).

Impurities present at higher than the qualification threshold according to ICH Q3A were qualified by toxicological and clinical studies and appropriate specifications have been set.

The evaluation of manufacturing process with regard to mutagenic impurities has been performed in line with ICH M7 and was considered sufficient.

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and related substances testing has been presented.

Batch analysis data for 29 batches of fezolinetant manufactured by three manufacturing processes (Process A, B and C) of the active substance are provided. The presented batch analysis results comply with the active substance specification and confirm batch-to-batch consistency, also between batches of the different manufacturing sites.

2.4.2.4. Stability

Stability data from three pilot scale batches of active substance from both proposed manufacturers stored in the intended commercial package for 24 months (one manufacturer) and 9 months (second

manufacturer) under long term conditions (25 ºC / 60% RH) and for up to 6 months (both manufacturers) under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. Photostability testing following the ICH guideline Q1B demonstrated that the active substance is not photosensitive.

The following parameters were tested: description, Infrared spectroscopy, X-ray powder diffraction, related substances, enantiomer, water content, microbial limits and assay. The analytical methods used were the same as for release (except for procedures of water content via Karl Fisher coulometric titration and microbial limits via Ph.Eur.).

All stability data remained within specifications and generally unchanged within normal analytical variability. The stability trend of fezolinetant between both sites is equivalent.

The stability results indicate that the active substance manufactured by both proposed suppliers is sufficiently stable. The stability results justify the proposed retest period of 36 months without any storage restrictions in the proposed container.

2.4.3. Finished Medicinal Product

2.4.3.1. Description of the product and pharmaceutical development

The finished product is a film-coated tablet that contains 45 mg of the active substance fezolinetant. The tablet is round, light red (approximately 7.1 mm diameter), debossed with the company logo and '645' on the same side.

The composition is summarised in section 2.4.1. (Introduction).

The solubility of active substance at various pH has been properly investigated and discussed.

It has been shown that storage of the active substance and manufacturing / storage of the finished product do not affect the polymorphic form and that there is no relevant change in stereochemistry. Particle size distribution is not controlled in the active substance. It has been adequately demonstrated that active substance particle size is not critical for the finished product performance and manufacturability.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

The aim of the pharmaceutical development was to make an oral immediate release film-coated tablet in a dose strength of 45 mg stable for at least 2 years at room temperature. The choice of the pharmaceutical form and strength adequately addresses the clinical needs.

The applicant has applied QbD principles in the development of the finished product and its manufacturing process. However, no design spaces were claimed for the manufacturing process of the finished product. A QTPP for the finished product was established and CQAs were identified. The development studies were guided by a risk assessment based on prior knowledge from preliminary formulation development trials.

Formulation development studies included optimisation of the component amounts and evaluation of possible impact of material attributes. Changes in component amounts showed no relevant impact on the finished product performance, confirming the robustness of the formulation. No critical material attributes have been identified.

The manufacturing process mainly consists of pulverising the active substance, wet granulation, blending, compression and film-coating. The manufacturing process development was guided by an initial risk assessment. Based on the risk assessment manufacturing process optimisation studies were performed and the manufacturing was confirmed on commercial scale.

No critical process parameters were identified based on the outcome of the manufacturing process development studies. This seems reasonable in view of nature of the active substance and formulation.

The finished product development has been adequately performed.

Dissolution testing is performed according to Ph.Eur. 2.9.3. The dissolution method development is adequate.

The discriminatory power of the dissolution method has been sufficiently demonstrated. The choice of the PA/Aluminium/PVC/Aluminium blisters for the packaging of the finished product is justified. The suitability of the selected packaging configurations is confirmed by the formal stability data. The material complies with Ph.Eur. and EC requirements.

2.4.3.2. Manufacture of the product and process controls

The manufacturing process consists of five main steps: pulverising the active substance, wet granulation, blending, compression and coating. The process is considered a standard manufacturing process.

The manufacturing process parameters, equipment type and capacities and proposed batch size have been laid out in sufficient detail.

No critical steps were identified. This is in line with the development data.

In-process controls have been implemented as requested. This is acceptable.

The proposed bulk holding time and bulk packaging are acceptable.

A process validation scheme has been provided. The applicant committed to validate all relevant manufacturing process steps before commercial launch. This is considered acceptable for a standard process.

2.4.3.3. Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: description (visual), identification (UV, HPLC), related substances (UHPLC), uniformity of dosage units (by MV), dissolution (UHPLC), microbial limits (Ph.Eur.) and assay (UHPLC).

The proposed specifications have been set in accordance with the principles of ICH Q6A and on the manufacturing experience gained during development and they are considered acceptable.

To respond to a Major Objection (MO) during the procedure, the applicant tightened the dissolution limit.

Uniformity of dosage units is performed in accordance with Ph.Eur. 2.9.40 by mass variation, which is acceptable in view of the dose and ratio of active substance (i.e. ≥ 25 mg and ≥ 25% respectively). The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Based on the risk assessment it can be concluded that it is not necessary to include any elemental impurity controls in the finished product specification. The information on the control of elemental impurities is satisfactory.

A risk assessment concerning the potential presence of nitrosamine impurities in the finished product was provided, and further amended to respond to a MO, in order to cover all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on all information provided, and on confirmatory testing, it is accepted that there is no risk of nitrosamine impurities in the active substance or the related finished product. Therefore, no specific control measures are deemed necessary. The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. The stability indicating nature of the UHPLC method for identity, assay and related substances was demonstrated by means of forced degradation studies. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results are provided for several batches of hard capsules used in early development, tablet batches used in the phase 3 clinical trials, and 7 batches of the proposed commercial 45 mg tablet formulation. These confirm the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

2.4.3.4. Stability of the product

Stability data from three pilot scale batches of finished product from one of the two manufacturers stored for up to 24 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The stability data, although from batches manufactured with active substance from one active substance manufacturer, can be considered representative also for the second active substance manufacturer, due to the expected similar stability behaviour of active substance from both sites. The batches of film-coated tablets are identical to those proposed for marketing and were packaged in the primary packaging proposed for marketing. The applicant committed to also generate stability data for three finished product batches manufactured by the second manufacturer, under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines.

Samples were tested for description, related substances (routine method), dissolution, assay, water content (KF), related substances (additional method, covering amongst others the enantiomer impurity) and microbial limits. No clear trends or changes were seen in any of the tested parameters at both storage conditions. All parameters were within the specification limits. Impurity levels remained unchanged during storage. The analytical procedures used are stability indicating.

Photostability testing was performed in accordance with ICH Q1B showing that the finished product is not sensitive to light exposure.

Based on available stability data, the proposed shelf-life of 36 months without any special storage conditions as stated in the SmPC (section 6.3) are acceptable.

2.4.3.5. Adventitious agents

No excipients derived from animal or human origin have been used.

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The two MOs raised during the procedure were adequately resolved, notably by tightening of the dissolution limits for the finished product, and by amending the nitrosamine risk assessment and testing finished product batches. The results of all tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.4.6. Recommendation(s) for future quality development

None.

2.5. Non-clinical aspects

2.5.1. Introduction

Fezolinetant is a small molecule, non-hormonal, selective NK3 receptor antagonist. Fezolinetant blocks NKB binding on the KNDy neuron to modulate neuronal activity in the thermoregulatory center with the outcomes of relief from VMS. It is proposed that fezolinetant be indicated for the treatment of moderate to severe VMS associated with menopause.

2.5.2. Pharmacology

2.5.2.1. Primary pharmacodynamic studies

In vitro studies showed fezolinetant K_i values of ~20 nM for the human NK3 receptor in competitive binding studies using membranes from CHO cells expressing the transfected cloned hNK3 receptor. Studies using monkey and rat NK3 receptors showed similar fezolinetant K_i values for monkey NK3 receptor (K_i ~30 nM) whereas lower affinity was observed for rat NK3 receptor (K_i >180 nM). Fezolinetant showed high selectivity for hNK3 receptor over hNK1- and hNK2 receptors, as K_i values for these two receptors could not be determined in competitive binding studies with fezolinetant concentrations up to 30 µM. Membranes expressing cloned receptors of the GnRH axis showed that for GPR54 (Kisspeptin), NPFF1, NPFF2 or KOP (Kappa Opioid, OP2) receptors, fezolinetant up to 30 µM displaced <50% of radioligand binding. Only GnRH showed >50% displacement (53%) upon 30 µM fezolinetant, indicating fezolinetant' s selectivity for the hNK3 receptor.

Agonist and antagonist activities of fezolinetant on the human NK3 receptor expressed in CHO cells were assessed by a functional aequorin assay using Neurokinin A (NKA) as a reference agonist. Fezolinetant had no agonist activity, but fully antagonized the NKA activity with IC_{50} values of ~15-20 nM.

ES259564 is a major metabolite of fezolinetant. Binding competition assays showed that the affinity for hNK3 receptor was significantly lower than that of fezolinetant, with ES259564 K_i values of ~400 nM. Similar to fezolinetant, the affinity of ES259564 for monkey NK3 receptor was comparable to that of human NK3 receptor, whereas the affinity for rat NK3 receptor was significantly lower (K_i values ~4,000 nM).

An *in vivo* study was performed to investigate fezolinetant's potential to reduce hot flushes in rats. Ovariectomized (OVX) rats are used as a disease model. Compared to the normal rats, these OVX rats showed significantly decreased plasma levels of estradiol, progesterone, and testosterone, and increased plasma levels of LH and FSH. Also, OVX rats showed increased body weight and food intake, together with a decrease in uterine weight.
Fezolinetant at 3 and 10 mg/kg bid significantly decreased plasma LH levels but did not affect other hormone levels. Estradiol at 3 and 10 µg/kg/day sc significantly increased plasma estradiol levels and decreased plasma levels of LH as well as FSH but did not affect plasma levels of progesterone or testosterone. Administration of fezolinetant and estradiol also decreased the weight and food intake in OVX rats, while estradiol also resulted in an increase in uterine weight.
Compared to the normal rats, OVX rats have a significantly increased tail skin temperature without effecting core temperature and a significantly increased heat loss index, i.e. symptoms representing/comparable to hot flushes. Fezolinetant at 3 and 10 mg/kg bid and estradiol at 3 and 10 µg/kg/day sc showed a significant attenuation of these increases in tail skin temperature and heat loss index. These results suggest that fezolinetant attenuates the increase in plasma LH levels and resulting VMS-like symptoms.

Another *in vivo* study showed that fezolinetant (and estradiol) are able to reverse effects observed in OVX rats (increased body weight and food intake and increased LH-concentrations. Lowering of the increased FSH levels was not observed with fezolinetant but was present for estradiol treated rats. Compared to the normal rats, OVX rats showed a significantly increased number of c-fos-positive nuclei in the MnPO area. Fezolinetant 10 mg/kg bid and estradiol 3 µg/kg/day sc resulted in a significant attenuation of this increase to approximately normal level. These results suggest that fezolinetant exerts an inhibitory effect against activation of c-fos expression in MnPO neurons in ovariectomized rats.

The applicant has submitted also secondary PD studies. However, given that these studies focus on (LH) hormone levels, these are considered primary PD studies and therefore discussed below.

Luteinizing hormone (LH) was investigated in castrate male rats following single-dose oral dosing of 0.8, 3, 10 and 20 mg fezolinetant/kg. A significant decrease in LH levels was observed up to 300 min after fezolinetant administration at 10 and 20 mg/kg in comparison to vehicle controls. Following a 3 mg/kg fezolinetant dose, a significant decrease in plasma LH was observed only at the 45 min timepoint. No significant effect of fezolinetant on plasma LH was observed at 0.8 mg/kg for any timepoint.

The effect of 10 mg/kg fezolinetant on pulsatile luteinizing hormone (LH) secretion was tested after single-dose oral administration to ovariectomized (OVX) female rats. LH and follicle-stimulating hormone (FSH) levels were determined subsequently. Fezolinetant induced a significant decrease in LH circulating levels in comparison to vehicle controls. Furthermore, fezolinetant induced no change in FSH circulating levels.

Estradiol levels in intact female rats were studied upon twice daily oral administration of fezolinetant for a period of 10 days. The estrous cycle in a rat is typically 4-5 days, consistent with the estradiol peaks observed in the vehicle rats.

Fezolinetant was administered orally by daily gavage to four groups of female cynomolgus monkeys at doses of 0, 10, 25, and 50 mg/kg for 5 weeks, followed by a recovery phase of 4 weeks.
A fezolinetant related effect on estradiol levels was recorded during the conduct of this study. Estradiol-levels were dose dependently decreased at 25 and 50 mg/kg/day during the dosing phase and recovered again during the recovery phase. In the 10 mg/kg/day group, estradiol levels were decreased in 3/4 females after dosing.
Fezolinetant-related decreases in LH levels were observed, starting at the 10 mg/kg/day level. The decrease in LH was dose-related and most pronounced in the 50 mg/kg/day group and recovered during the 4-week recovery phase. The LH surge, which is coincident with ovulation and is usually observed around day 14 of the cycle, was severely reduced or non-existent in all dosing groups.
Fezolinetant-related decreases in progesterone levels were observed, starting at the 10 mg/kg/day dose level. The decrease in progesterone was dose-related and most pronounced in the 25 and 50 mg/kg/day groups and recovered during the 4-week recovery phase.
No test item-related effects were observed on FSH and testosterone levels.
Male Cynomolgus monkeys were also dosed daily with 0, 10, 25, and 50 mg fezolinetant/kg for 5 weeks, followed by a recovery phase of 4 weeks. Male hormone analysis showed a remarkable individual variation in testosterone, LH and estradiol levels across intervals and treatment groups (including controls) such that no clear treatment-related changes could be determined. However, a small trend towards decreased levels of mean testosterone, LH and estradiol in males of the 25 and 50 mg/kg/day dosing groups in weeks 1 and 2 of the dosing phase was observed, whereas no test item-related effects were seen on male FSH levels.

2.5.2.2. Secondary pharmacodynamic studies

An *in vitro* target selectivity assay on broad target classes demonstrated that fezolinetant (10 µM) is highly selective for hNK3 in comparison to all other target classes tested in the screen: 48 receptors, 6 ion channels, 3 transporters and 48 enzymes. Fezolinetant up to 10 µM showed no inhibition of binding higher than 25% for any of the receptors, ion channels, transporters or enzymes, except for hNK3. Therefore, no effects are expected in humans for any of the receptors, enzymes, ion channels and transporters tested, as the used concentration (10 µM = 3,584 ng/mL) exceeds the C_{max} at MRHD (458 ng/mL, corrected for free fraction ~225 ng/mL) sufficiently.

At 10 µM of fezolinetants' major metabolite, ES259564, inhibition of binding in an *in vitro* target selectivity assay was below 25% for all 45 tested receptors, 7 ion channels and 3 transporters, except for hNK3. Therefore, no effects are expected in humans for any of the receptors, ion channels and transporters tested.

2.5.2.3. Safety pharmacology programme

Oral administration of a single-dose of 25, 125 or 250 mg/kg fezolinetant to rats and observing them for general behavioural, autonomic and motor effects was carried out based on Irwin's method in a GLP compliant study. At a dose level of 25 mg/kg there were no behavioural or physiological changes in male or female rats when compared to controls. At 125 mg/kg, constricted pupils in two male and two female rats were observed between 2.5 and 8 hours post-dose only. At 250 mg/kg, fezolinetant produced signs of mild toxicity in all rats: in both sexes signs were first apparent by 1 hour post-dose, peaked at 5 hours post-dose and had disappeared by 24 hours post-dose. Frequently observed signs were constricted pupils, decreased activity, touch escape response and grip strength. The ratio of C_{max} at 30 mg/kg on day 1 in the 4-week repeated-dose toxicity study (on average 36,600 ng/mL for both sexes) to the human C_{max} at the MRHD (458 ng/mL) was ~80, indicating that no effects on the central nervous system are to be expected in humans.

After a first study where no IC_{50} could be determined, a subsequent GLP compliant study was performed to measure the peak hERG tail current amplitude at near physiological temperature prior to and following exposure to vehicle or fezolinetant using a different solvent for fezolinetant than the previous study. The IC_{50} value in this study was determined at 231.8 µM (83,100 ng/mL), while C_{max} at MRHD was 458 ng/mL (~225 ng/mL when corrected for protein plasma binding). This translates into a 350-fold difference between human free C_{max} at MRHD and IC_{50} value in hERG assay, indicating that no effects on the cardiovascular system with regard to ventricular repolarization and proarrhythmic risk are to be expected in humans.

The cardiotoxic effects of fezolinetant were studied in conscious cynomolgus monkey in a GLP compliant study. Cynomolgus monkeys of Asian origin were dosed orally (gavage) at dose levels of 10, 25, and 50 mg/kg. There were no statistically significant effects of fezolinetant observed in this study. However, a trend was observed suggesting a decrease in the mean $+dP/dt_{max}$ as well as a decreased systolic blood pressure and mean arterial pressure which can be considered a result of fezolinetant treatment. The observed slightly increased heart rates most likely represent a baroreflex compensation in the animals, as a result of the slight decrease in blood pressure. There were no ECG waveform morphologic abnormalities noted on qualitative assessment and no effects in PR, QRS and QTc interval. The ratio of C_{max} at 50 mg/kg on day 1 in the 5-week repeated-dose toxicity study (59,400 nM = 21,300 ng/mL for females) to the human C_{max} at the MRHD (458 ng/mL) was ~46, indicating that no effects on the cardiovascular system are to be expected in humans.

An additional study was performed on the electrophysiological and mechanical parameters of rabbit hearts upon fezolinetant exposure. Three separate isolated hearts excised from adult rabbits were mounted into a retrograde perfusion system and perfused using Tyrode's solution containing 3, 10 or 30 µM fezolinetant. The only statistically significant effect observed was an increase in RR interval at 10 µM fezolinetant (~3.6 µg/mL), but the lack of dose dependency indicates little relevance for this observation. No statistically significant modification of the PR interval, QRS interval, QT interval and QTc interval were observed. In addition, no effects on monophasic action potential (MAP) duration, left ventricular pressure (LVP) or the rate of the contraction (dLVP/dt) of the rabbit hearts were observed for any of the tested concentrations. The highest concentration used in this study was 30 µM (10,800 ng/mL), while C_{max} at MRHD was 458 ng/mL (~225 ng/mL when corrected for protein plasma binding). This translates into a 48-fold difference between human free C_{max} at MRHD and highest concentration tested here, indicating that no effects on the cardiac mechanical and electrophysiological parameters are to be expected in humans.

Respiratory effects of fezolinetant were studied in freely moving conscious rat using whole body plethysmography in a GLP compliant study. Respiratory parameters were measured continuously for a 6-hour post-dose period in rats dosed with 40, 80 or 125 mg fezolinetant/kg. At 40 mg/kg, fezolinetant caused statistically significant decreases in tidal volume at 61 to 90 minutes post-dose for both sexes (31-90 minutes for males). A compensatory, statistically significant increase in respiratory rate was observed at 31 to 90 minutes post-dose in males. Statistically significant increases in respiratory rates were also seen at 91 to 120 and 271 to 300 minutes post-dose. In females, additional decreases in tidal volume were observed from 181 to 240, 271 to 300 and 331 to 360 minutes. A statistically significant increase in respiratory rate and minute volume was observed at 121 to 150 minutes post-dose. At the higher dose levels of 80 and 125 mg/kg, the effects observed at 40 mg/mg were more pronounced. The ratio of C_{max} at 30 mg/kg on day 1 in the 4-week repeated-dose toxicity study (on average 36,600 ng/mL for both sexes) to the human C_{max} at the MRHD (458 ng/mL) was ~80, indicating that no effects on the respiratory system are to be expected in humans.

2.5.2.4. Pharmacodynamic drug interactions

The applicant provided no studies, and this was agreed by the CHMP.

2.5.3. Pharmacokinetics

Validation of methods

LC-MS/MS methods for the detection of fezolinetant and its metabolite ES259564 were developed and validated for mouse, rat, monkey and rabbit (fezolinetant only) plasma.

In rabbits, the validated LC-MS/MS method is suitable for the determination of fezolinetant over the calibration range 1000 to 500000 nmol/L (358 to 179000 ng/mL). For (wild type) mouse plasma, this range was 180-180000 ng/mL.

Regarding the pivotal species, linearity was shown for fezolinetant and ES259564 concentrations measured by LC-MS/MS in rat and cynomolgus monkey plasma between the LLOQ 2.29 nmol/L to 50000 nmol/L, which correlates to 0.821-179000 ng/mL (low-range method and high-range method combined). Another LC-MS/MS method for rat and monkey plasma was suitable for the determination of fezolinetant and ES259564 in over the calibration range of 180 ng/mL to 180,000 ng/mL. For a third LC-MS/MS method, the relationship between peak area ratio of the reference standards to internal standard and the concentration of reference standards in plasma was quadratic over the calibration range of 10.0 to 10000 ng/mL for fezolinetant and linear over the calibration range of 1.00 to 1000 ng/mL for ES259564. Acceptable linearity, precision, accuracy and selectivity were observed over the concentration range 10.0 ng/mL to 10000 ng/mL for fezolinetant and ES259564 using a sample volume of 20 µL.

Radioactive labelled fezolinetant in biological samples were measured by LSC after adding liquid scintillation fluid directly to samples or to those treated by tissue solubilizer, or by quantitative whole-body autoradiography. The methods described above were validated according to GLP (at least the most recent LC-MS/MS validation studies for the pivotal species) and all validation studies were performed at a GLP compliant laboratory.

Single- and repeat-dose pharmacokinetics

The pharmacokinetic characteristics of fezolinetant and the major metabolite ES259564 were evaluated in two singe-dose studies. In both studies rats and cynomolgus monkeys received a single intravenous administration of fezolinetant at 1 mg/kg and oral administration of fezolinetant at 1, 3 or 10 mg/kg. Overall, the pharmacokinetics in rats and monkeys after a single dose were comparable. The increases in fezolinetant and ES259564 C_{max} and AUC_{0-t} were generally dose proportional, although in monkeys, the increase was slightly greater than dose proportional for fezolinetant AUC_{0-t}. Clearance (Cl) of fezolinetant was 132 mL/hr/kg in rats and 262 mL/hr/kg in monkeys, which was less than the liver blood flow in both species, indicating that fezolinetant is not taken up by the liver to a great extent after intravenous bolus administration of fezolinetant. V_{ss} was 1010 mL/kg in rats and 935 mL/kg in monkeys, exceeding total body water and indicating more extensive distribution. T_{max} was approx. 0.5 hours (rats) and 1-2 hours (monkeys) and fezolinetant concentrations declined with $t_{1/2}$ values ranging from 4.46-5.04 hours in rats and 3.36-4.41 hours in monkeys across the dose levels of 1, 3 and 10 mg/kg.

ES259564 concentrations declined in a mono-exponential manner after iv dosing, with a $t_{1/2}$ of 6.34 hours in rats. ES259564 had a T_{max} of 2 hours at all dose levels in rats and monkeys. After reaching C_{max}, ES259564 concentrations declined, with $t_{1/2}$ values ranging 5.09-5.44 hours in rats and 3.11- 5.86 hours in monkeys across dose levels. The increases in ES259564 mean C_{max} and AUC_{0-t} values were generally dose proportional. Following intravenous bolus administration, the mean metabolite to parent ratios were 0.208 and 0.0544 for C_{max} and 0.0900 and 0.362 for AUC_{0-t} in rats and monkeys respectively.

Following oral gavage administration, the mean metabolite to parent ratios ranged from 0.0653 to 0.0713 (rats) and 0.380 to 0.497 (monkeys) for C_{max} and 0.0754 to 0.0810 (rats) 0.474 to 0.623 (monkeys) for AUC_{0-t}.

The bioavailability values of fezolinetant were comparable between rats (91.9-115%) and monkeys (74.6-103%). In humans the bioavailability was also high (>70%).

In mice, three studies were performed with durations of 7, 28 and 182 days. Animals were dosed once daily with doses ranging from 50-600 mg/kg. In the 28- and 182-day studies the maximum dose was decreased to 450 mg/kg per day. Absorption in mice was fast (T_{max} 0.5-3.0 hours) and elimination half-life ranged between 1.0-4.0 hours. Both T_{max} and $t_{1/2}$ were similar across doses and did not differ between day 1 and the end of study. In general, fezolinetant C_{max} increased less than dose proportional with increasing dose. For AUC values the increases were generally greater than dose proportional from 90 to 200 mg/kg/day and less than dose proportional from 200 to 450 mg/kg/day. There was no accumulation in mice in studies up to 182 days (accumulation ratio's 0.663-1.04 for C_{max} and 0.230-0.701 for AUC_{0-24}). ES259564 C_{max} and AUC_{0-24} values were slightly higher (generally less than 2-fold) on Day 182 than on Day 1, indicating no accumulation of ES259564 after multiple doses of fezolinetant in mice. The metabolite to parent ratios ranged from approx. 0.2 to 0.9 for Cmax and from 0.2 to 1.3 for AUC, with higher ratios after repeat dosing. In general, sex differences in fezolinetant and ES259564 C_{max} and AUC_{0-12} values were less than 2-fold in mice.

Five studies were performed to assess toxicokinetics in rats ranging from 28 to 180 days in duration. Animals were dosed once daily with a dose ranging from 10-300 mg/kg. T_{max} ranged from 1.0-8.0 hours, with higher T_{max} observed at the higher doses. Half-lives were between 3.4-6.8 hours irrespective of dose level or sampling occasion. In general, increases C_{max} and AUC were proportional at the mid-dose level and tended towards sub-proportionality at the high-dose level, suggesting there may be some saturation of routes of absorption. Accumulation ratios were similar across studies for both C_{max} (0.570-0.720 in the 5-week, 0.595-0.788 in the 13-week and 0.740-1.21 in the 104-week (measured at 26 weeks) study) and AUC (0.292 to 0.733 in the 5-week, 0.581-0.743 in the 13-week and 0.652-1.22 in the 104-week (measured at 26 weeks) study) and indicated no accumulation of fezolinetant in rats after repeated dosing. Increases in ES259564 maximum concentrations and exposure were generally proportional at all dose levels. The exposure to ES259564 was between 7.4% and 16.4% of the exposure to fezolinetant. Sex differences were minor but were observed in the exposure to the metabolite ES259564 in the 28-day study including both male and female animals. The exposures to ES259564 were higher in males and the increases were greater than dose proportional in males overall (sex difference 1.45-, 4.36- and 2.06-fold for 10, 30 and 100 mg/kg fezolinetant on day 28). In fezolinetant data these sex differences are less pronounced (<2-fold difference).

Three repeat-dose toxicokinetic studies were performed in cynomolgus monkeys (one in male and female animals and two studies in female animals only). The study durations were 5, 13 and 39 weeks. Animals were dosed once daily with 10-50 mg/kg. In the 39-week study the maximum dose was decreased to 40 mg/kg per day. Plasma concentrations of fezolinetant were at a maximum (T_{max}) between 1 and 6 hours on Day 1 and at Week 13, Week 16, Week 26 and Week 39. In one study a T_{max} of 10.4 hours was observed at 25 days. Mean half-lives ($t_{1/2}$) were all between 3.7 and 9.7 hours for fezolinetant, irrespective of dose level or sampling occasion. In general, following multiple oral administrations of fezolinetant, the increase in maximum concentrations and exposures were proportional with respect to dose level. However, the AUC increased in a supra-proportional manner in males, especially at the highest dose level. Overall sex differences remained at <2-fold. In the 39-week study, there appeared to be some minor accumulation of fezolinetant in plasma at all of the dose levels and on all the sampling occasions with repeated administration (1.97-2.64 for C_{max} and 0.84-2.49 for $AUC_{(0-t)}$). ES259564 T_{max} values were 4-6 hours (39-week study) and increases C_{max} and AUC were generally proportional at all

dose levels, suggesting there was no saturation of the routes of elimination or the routes of metabolism from fezolinetant to ES259564.

Pharmacokinetics in pregnant animals were assessed in rats (two studies) and rabbits (one study). In both rat studies, pregnant Wistar Han [Crl:WI(Han)] rats (9 to 11 weeks old at mating) were dosed 10-100 mg/kg fezolinetant between day 6 and day 17 of gestation or from day 6 of gestation to day 21 of lactation. Kinetic parameters were determined at gestation day 17 in the first study and at lactation day 21 in the second study. Pregnant New Zealand White rabbits [Hra:(NZW)SPF] (weight at least 2.7 kg at mating) were dosed 45, 75 and 125 mg/kg per day from day 7 through 19 of gestation. In pregnant rats both the kinetics of fezolinetant and ES259564 were similar to those observed in non-pregnant animals. However, in pregnant rabbits, following a single oral dose of fezolinetant, increases in maximum concentrations and exposure were generally supra-proportional with respect to dose level. At GD19, increases in C_{max} and AUC were generally proportional at the mid-dose level and appeared to be supra-proportional at the high-dose level. On GD 19 accumulation ratios for fezolinetant ranging from 0.941-2.10 for C_{max} and 1.69-6.10 for $AUC_{(0-t)}$ indicating some accumulation at these dose levels.

Overall, the toxicokinetics of fezolinetant were thoroughly studied in a substantial package of repeat-dose studies performed in mice, rats, cynomolgus monkeys and (pregnant) rabbits. The metabolite ES259564 was present and studied in all species except rabbits. Absorption and elimination were fast in all species and values were similar, irrespective of dose level or sampling occasion. Increases in fezolinetant and ES259564 were in general dose-proportional, with some trend toward sub-proportional increase in C_{max} and AUC for fezolinetant in high-doses in rats and supra-proportional AUC increase of fezolinetant in male monkeys especially at the high dose level. No accumulation was seen for fezolinetant in mice and rats, and minor accumulation (approx. 2.5-fold) was observed for C_{max} and AUC in the 39-week monkey study. No substantial sex differences could be identified (but minor sex differences were observed). No substantial differences between the pharmacokinetics in non-pregnant and pregnant animals were observed in rats. Pregnant rabbits could not be compared to non-pregnant animals, since no non-pregnant rabbits were included in the study. In pregnant rabbits some accumulation was observed (approx. 2-fold for C_{max} and 6-fold for AUC).

Distribution

In vitro plasma protein binding of ^{14}C-fezolinetant was investigated by equilibrium dialysis. The plasma protein binding ratios of ^{14C}fezolinetant at concentrations of 0.2, 5 and 100 µg/mL were approx. 31% in mice, 32.5% in rats, 30.5% in rabbits, 29% in cynomolgus monkeys and slightly higher in humans (51%). Plasma protein binding was concentration-independent between 0.2 and 100 µg/mL in all tested species.

Tissue distribution of ^{14}C-fezolinetant was studied in female albino Han Wistar rats and female partially pigmented Lister-Hooded rats, after a single PO dose of 30 mg/kg [^{14}C]fezolinetant. Radioactivity was measured in plasma and by whole-body autoradiography. Tissue: plasma (TP) radioactivity concentration ratios >1.44 (to a maximum of 4.13)) were found in kidney cortex, clitoris, choroid plexus, adrenal (cortex and medulla), bile ducts, liver, large intestine mucosa and urinary bladder wall. Lowest concentrations of radioactivity were determined in the eye (lens body, vitreous humour, aqueous humour), bone surface and white fat. Radioactivity was detected at low levels in the CNS. Exposure (AUC_{0-t}) to the brain was approx. 3-fold lower compared to plasma. No substantial differences in distribution were observed between albino and partially pigmented rats. The concentration in the uveal tract/retina at 1 and 24 h was 2-3-fold higher in partially pigmented than in albino rats but for the skin this large difference was not seen. Quantifiable levels of radioactivity were detected in the uveal tract/retina and pigmented skin at all sampling times. However, levels of radioactivity in these tissues declined over the time course of the study, which suggested that binding was reversible. Only the half-life of the pigmented skin was above that measured in plasma (33.8 hours).

Transfer into blood cells was determined in rats and cynomolgus monkeys. Cb/Cp ratios were 0.580-1.01 in rats and 0.93-1.1 in cynomolgus monkeys during 0.5-24 hours post-dosing.

In pregnant rats, the T/P ratios of the foetus (whole body) were 0.59 to 0.68 against the maternal plasma. In lactating rats, fezolinetant maternal Cmax in plasma was 25.5 µg eq./mL at 1h. In pups, the Cmax reached 1.36 µg eq./mL in plasma at 24 hours. In pups, concentrations in plasma and tissues were similar, except for liver (approx. 3-fold higher than plasma concentrations). Overall, these results indicate that fezolinetant is excreted in milk and absorbed from the intestines in pups.

Metabolism

In vitro metabolic profiles of fezolinetant were investigated in cryopreserved hepatocytes of rats, cynomolgus monkeys and humans (10 µmol/L, for 4 hours). Only 1 metabolite, postulated to be a hydroxylated metabolite (ES259564), was detected in all tested hepatocytes. No human-specific metabolites were formed.

In vivo, metabolic profiles of fezolinetant were investigated in rats (^{14C}fezolinetant at 30 mg/kg), cynomolgus monkeys (^{14}C-fezolinetant at 3 mg/kg) and humans (^{14}C-fezolinetant at 180 mg). In rats, ES259564 (M9) only accounted for 5.0-6.4% of plasma radioactivity, and fezolinetant 90.3-91.8%. In monkeys, ES259564 accounted for 20.7-42.1% and fezolinetant for 45.8-72.1%. Therefore, ES259564 is not considered a major metabolite in rats, but it is in cynomolgus monkeys. For humans, the geometric mean AUC0-inf for fezolinetant was 5463 ng h/mL (29% of total radioactivity in plasma) and 9778 ng h/mL (52% of total radioactivity in plasma) for ES259564.

In rat, monkey and human urine, ES259564 was the most abundant component (44.7%, 67.2% and 55.4% of the dose respectively). Fezolinetant accounted for approx. 5% of the dose in rats and <1% in monkeys and human urine. M3 (a sulfuric acid conjugate) was the primary metabolite in rat faeces (13.8% of dose) but it was detectable neither in monkey nor in human faeces. Only minor amounts of several other metabolites were identified in faeces and bile in rats, monkeys and humans. Postulated metabolic pathways of fezolinetant in humans involve at least 1) oxidation of methyl group in methylthiadiazole moiety (M4, M5, and M9), 2) glucuronidation (M5 and M6), 3) oxidative ring-opening of methylthiadiazole moiety (M1).

Chiral inversion of the unchanged drug did not take place after the oral administration of fezolinetant to rats, cynomolgus monkeys, and humans.

Excretion

Excretion was studied in rats and monkeys using ^{14}C-fezolinetant at 30 mg/kg and 3 mg/kg, respectively. In both species, the main route for excretion was urine, with 52.3% excretion in rats and 81.7% excretion in monkeys through this route. In humans, 76.9% of the dose (180 mg ^{14}C-fezolinetant) was excreted through urine. In rats approx. 36% is excreted in faeces. Excretion in faeces in monkeys and humans is very similar, with 14.6% and 14.7% of radioactivity, respectively. Recoveries were high in all studies, ranging from 91.6-98.5%. The applicant reports a total recovery of 90.9%, but this is lower than the combination of urinary and faecal recovery (91.6%).

2.5.4. Toxicology

2.5.4.1. Single dose toxicity

No separate single dose toxicity studies were conducted with fezolinetant, which is acceptable. Instead, acute toxicity was evaluated in repeated dose toxicity with rats and monkeys following the 1st dosing.

2.5.4.2. Repeat dose toxicity

Pivotal GLP-compliant repeated dose studies were conducted in rats and monkeys and comprised the studies of 4, 13 and 26 weeks duration in rats and 5, 13 and 39 weeks duration in monkeys. Recovery groups were included in the 13- and 39-week monkey studies. Cynomolgus monkey was selected as the relevant nonrodent species as nonhuman primates are anatomically and functionally similar to humans in the reproductive system, which is known to be affected by LH change. In addition, according to the *in vitro* radioligand assay, fezolinetant has a similar affinity for the human and cynomolgus monkey NK3 receptor orthologs.

As the product is intended to be administered for the treatment of hot flushes in menopausal women, sub-chronic and chronic studies were performed in female animals only, which is acceptable.

The highest dose level of 300 mg/kg/day caused mortality in rats (one male, one female) on the 1st day of dosing in the 4-week study (exposure multiple (EM) in males and females on Day 1 of 441 and 675 relative to the anticipated clinical exposure, respectively). Furthermore, lethargy, reduced activity, laboured respiration and staggering were observed on days 1 and 2 following the test substance administration. In monkeys, one animal of the high-dose group of 40 mg/kg/day in the 39-week study died in the course of the study due to severe thrombocytopenia (EM of 102 at the end of the study period).

Effects consistent with the primary pharmacological action of the substance were seen in both species and included oestrous cycle disruptions, the lack of ovarian activity, decreased uterine and/or ovarian weight, uterine stromal atrophy and changes in myometrium and endometrium in monkeys. The achieved plasma exposures at these dose levels were in significant excess of the anticipated clinical exposure (exposure multiples (EM) of 81 and 56 in the 13- and 26-week rat studies and 15 and 26 at the end of the dosing period in the 13- and 39-week monkey studies). The effects were not fully reversible upon 4-week recovery period. Decreases in the LH and progesterone levels were seen in female monkeys in the 5-week study, which included hormone analysis.

In rats, secondary pharmacological effects were exhibited on the liver (increased liver weight accompanied by centrilobular hepatocellular hypertrophy and minor (<50%) increases in plasma levels of alkaline phosphatase, increased cholesterol) and thyroid (increased thyroid weight accompanied by follicular cells hypertrophy). The reported liver findings are normally observed as an adaptive response to the CYP450 induction and in the absence of functional impairment and without any accompanying necrotic changes are considered non-adverse. The thyroid findings are considered secondary to the liver enzyme induction due to the increased thyroid hormone metabolism, resulting in the positive feedback to the pituitary for the stimulation of TSH production and increased thyroid activity.

Signs of neurotoxicity were also seen in rats, in particular in the 13-week study where convulsions were seen in individual animals starting from the lowest tested dose level of 30 mg/kg/day. The incidence of convulsions in this study did not appear to be dose-dependent (2, 3 and 2 females in the low, mid- and high dose groups, respectively), and the frequency of episodes was reduced following the change in the handling procedure. Constricted pupils were also observed in the same study starting from the lowest dose levels; an Irwin Screen carried out after 64 days of fezolinetant administration

found observations that were dose-related in terms of the number of animals affected and duration. At 4 hours post-dose all animals exhibited constricted pupils. At 8 hours post-dose, constricted pupils were seen in 8 females at 100 mg/kg/day and all females at 200 mg/kg/day. Animals in the mid- (100 mg/kg/day) and high dose (200 mg/kg/day) also showed salivation, mouth rubbing, paddling; decreased motor activity and transfer arousal.

None of these effects were observed in the 26-week rat study with the same rat strain in which the same dose levels were tested; however, clonic convulsions/convulsive-like episodes/tremors/twitches were also noted in the rat carcinogenicity study starting from the dose level of 30 mg/kg/day and in the non-GLP mechanistic 13-week EEG study with fezolinetant from 10 mg/kg/day, making the association with treatment probable. The mechanistic EEG study was performed in female rats to further investigate the potential of fezolinetant to induce seizures. EEG and EMG data was collected in rats treated with up to 200 mg/kg fezolinetant per day for up to 3 months. Abnormal clinical signs observed involved changes in muscle tone including twitching, intermittent tremors and rigid stance. However, there were no EEG abnormalities seen which could suggest the potential of fezolinetant to cause seizures.

In monkeys, no signs of neurotoxicity or effects on liver and thyroid were seen. Instead, thrombocytopenia, in some cases severe and resulting in haemorrhagic episodes with regenerative anaemia, was seen in the 13- and 39-week studies at the highest tested dose of 50 and 40 mg/kg/day, respectively, resulting in death of one animal in the 39-week study (EMs of 61.5 and 101.9, respectively, at the end of the study period). Microscopic findings in this animal included marked nephropathy in the kidneys, moderate hypocellularity in the bone marrow of the sternum and minimal to severe haemorrhages in multiple organs. The cause of death was considered to be an acute haemorrhagic anaemia due to severe thrombocytopenia. Furthermore, one animal dosed with 50 mg/kg/day in the 5-week study showed lymphocyte hyperplasia in lymph nodes, spleen and lungs; perivascular inflammation with hyperplasia of the vascular wall in kidneys and hyperplasia of the myometrium and inflammation of the vessels in the myometrium. The mechanism of these effects is not established but can possibly be immune-mediated. However, considering the high exposure multiples relative to the anticipated clinical exposure at the maximum recommended human dose, these findings are not expected to be clinically relevant.

In summary, the risk of adverse effects in patients due to clinical use of fezolinetant is considered low because the adverse effects noted in the repeated-dose toxicity studies occurred at high safety margins.

2.5.4.3. Genotoxicity

The GLP-compliant *in vitro* Ames test and chromosome aberration test in human peripheral blood lymphocytes, conducted according to OECD guidelines 471 and 473, respectively, were clearly negative. The *in vivo* micronucleus test in peripheral blood reticulocytes was conducted as a part of the pivotal GLP-compliant 4-week rat study in which animals were treated at the dose levels of 30, 100 and 300 mg/kg/day, and the blood was sampled on day 4 and day 30 (between 24 and 48 hours after the last dosing). Where possible up to 20000 reticulocytes (CD71+) were analysed per blood sample. The frequency of high CD71 positive reticulocytes (%RET) among total red blood cells (RBC) was assessed as a measure of toxicity. There were no statistically significant increases in the percentage of micronucleated reticulocytes at any dose level in male or female animals sampled on either Day 4 or Day 30. Based on the results of two *in vitro* and one *in vivo* test, fezolinetant is concluded to be not genotoxic.

2.5.4.4. Carcinogenicity

Carcinogenicity of fezolinetant was investigated in the 104-week carcinogenicity study with Wistar rats administered the test substance at the dose levels of 10, 30 and 100 mg/kg/day by oral gavage, and in the 26-week study with transgenic RasH2 mice.

In the rat study, increased incidence of thyroid follicular cell adenomas was observed in the animals treated with 100 mg/kg/day, with a statistically significant trend ($p<0.05$) and dose-responsiveness. This type of tumours in rodents is known to be caused by chronic stimulation of thyroid gland by TSH due to the hepatic enzymes induction and correlates with centrilobular hepatocellular hypertrophy seen in the high dose animals in the same study. Evidence of hepatic enzymes induction leading to hepatocellular hypertrophy and secondary follicular cell hyperplasia in the thyroid was also observed in the repeated dose studies which is consistent with the observations in the 104-week study. It is known that humans are not sensitive to the formation of thyroid tumours by hepatic enzyme induction, thus the observed increased thyroid follicular cell tumour incidence in the rat carcinogenicity study is not considered to be relevant in clinical settings.

Decreased incidences of mammary gland and pituitary neoplastic lesions was seen starting from the mid-dose level in the treated rats which is considered to be related to the pharmacologic action of fezolinetant.

An increased incidence of total brain tumours and thymus tumours was also observed in the study. The brain tumours, however, were different in origin and, when analysed by the tumour type, no increased incidence or dose responsiveness was observed for thymus tumours, however, a dose-dependent increase was seen for B-thymomas (5, 5, 6 and 10 in controls, low, mid- and high-dose groups, respectively). The observed tumours were considered by the Study Director as not related to treatment, as their incidence was stated to be within the historical control incidences (the upper range of 8.2% for benign thymomas in males and females and of 1.9% for malignant thymomas in females) and/or published data (Blankenship et al., 2016 and Tomonari et al., 2018). The historical control data from 5 studies conducted at the same testing facility in the period from 01-01-2015 until 31-12-2019 have been provided by the Applicant upon request. However, analysis of this data indicates that a total incidence of B-thymoma and B- and M-thymomas combined in the high dose group in fact exceeded the historical control range (10.1% vs 8.2% and 11.1% vs 10.1%). The Applicant has also provided an overview of public literature data to justify that thymomas are a common background tumour in Wistar-Han derived rat strains. Overall, although the observed thymoma incidence in the study exceeded the historical control range, high exposure multiples (~75 at mid-dose and ~186 at high-dose based on the total fraction AUC) provide sufficient reassurance for the safety of fezolinetant with regard to carcinogenicity in clinical settings.

The neoplastic lesions observed in the 26-week study with RasH2 mice were reported as being spontaneous background findings observed for the RasH2 mouse mode. While studying data derived from the 37 studies conducted at the testing facility over a period of 4 years, it was concluded that the incidence of B-thymoma was outside the historical control range in the high-dose males (2/23, 8.7%, vs 4% in the historical controls) and in both sexes combined (26.5% vs 25.2%), whereas in females it was within the historical control range (17.8% vs. 20.8%).

However, the achieved exposure levels in the mouse study were ca. 50 times higher than the clinical exposure at the MRHD, which provides sufficient reassurance of safety of fezolinetant with regard to carcinogenicity.

2.5.4.5. Reproductive and developmental toxicity

In the GLP-compliant FEED study with Wistar Han rats, in which only females were dosed with 0, 10, 30 and 100 mg/kg/day fezolinetant, the main substance-related toxicological effects were increased oestrous cycle length (7.0 vs 4.0 days in controls and pre-dose) and the decreased number of oestrous cycles (1 vs 3 in controls and pre-dose), with four females in persistent dioestrus. In addition, reduced (-13%) non-gravid uterus/cervix/vagina absolute mean weight adjusted for body weight in the 100 mg/kg/day group compared to controls. These effects were considered to be related to the primary pharmacologic mode of action of the tested substance.

Despite the observed effects, there was no effect on reproductive indices and fertility at any dose tested. Fecundity and fertility indices in the 10 (91%) and 100 mg/kg/day (91%) groups were reduced compared to controls (95%) but were not considered test article-related since there was no dose-related pattern. The NOAEL for fertility was considered to be the highest tested dose of 100 mg/kg/day.

Considering the proposed indication for the treatment of hot flushes associated with menopause, the dosing of only female animals is considered acceptable.

In the EFD study with Wistar Han rats, *in utero* litter loss was seen in 3 females of the high dose group at 100 mg/kg/day in the absence of maternal toxicity. At all dose levels there was an increased number of foetuses with partially fused zygomatic arch ossification bridge (incidences of 0.00%, 2.38%, 1.00% and 2.25% in controls, low, mid- and high-dose groups, respectively, with the background incidence of 0.0-1.7%) and foetuses with thymic remnants (3.86%, 6.83%, 5.60% and 8.48% in controls, low, mid- and high-dose groups, respectively). Both findings are considered to be variations and in the absence of a clear dose response and concomitant associated findings are considered not adverse. The NOAEL for developmental toxicity was thus set at the mid dose of 50 mg/kg/day, which is 62-fold exposure at MRHD. The NOAEL for maternal toxicity was set at the highest tested dose of 100 mg/kg/day.

In the EFD study with NWZ rabbits, adverse effects on embryo-foetal development were observed from the mid-dose of 75 mg/kg/day. Increased numbers of late resorptions and decreased mean foetal weight (M, -8%) were seen at 75 mg/kg/day. At 125 mg/kg/day total embryo loss was seen in 4 females, while 3 more females aborted their litters. Increased mean percentage of post-implantation loss, numbers of early and late resorptions and low gravid uterine weight together with the decreased mean foetal weight (M: -10%, F: -8%) were also seen at this dose level.

In all treated groups there was an increased incidence of foetuses with nodulated ribs, dumbbell ossification of sternebrae and incomplete ossification of thoracic centrum compared to concurrent controls. However, the observed effects are considered to be variations which are not expected to directly affect the foetal survival, and are likely related to the delayed foetal development, consistent with the reduced body weight gain and food consumption observed in maternal animals at all dose levels and lower mean foetal weight seen from 75 mg/kg/day. The NOAEL for developmental toxicity was thus set at the lowest tested dose of 45 mg/kg/day based on increased number of late resorptions and decreased foetal weight at the next dose level, resulting in an exposure margin of 16-fold exposure at MRHD.

In the rat pre- and postnatal developmental toxicity study, increased dose-responsive total litter loss/abortions were observed at the mid dose (n=2) and high dose (n=4). In addition, male pup sexual maturation was slower at the highest dose tested, indicated by an increased time to sexual maturation for males, with some males that did not achieve complete balanopreputial separation at the time of pairing for mating. This resulted in a reduced number of mated and fertile males and a reduced number of pregnant females after mating with males from treated mothers. However, the exposure

margin at the NOAEL and LOAEL for reduced F1 male sexual maturation and fertility was 36- and 204-fold human exposure at MRHD. Therefore, and due to the indication of the product, these findings are considered not clinically relevant. The overall NOAEL was based on total litter loss at the mid and high dose, resulting in an exposure margin of 11-fold exposure at MRHD calculated on lactation day (LD)21.

However, although the adverse effects on embryo-foetal development in the EFD and PPND studies were generally seen at high safety margins, the severity of the effects (embryo- and foetal lethality) and the fact that these effects are considered to be caused by the pharmacodynamics of fezolinetant, raise a concern for the maternal exposure to fezolinetant during pregnancy. As the drug product is indicated for VMS treatment in both peri- and post-menopausal women, the possibility of pregnancy cannot be excluded for the intended patient population. Thus, a contra-indication during pregnancy and suspected pregnancy is considered warranted, as reflected in Sections 4.3 and 4.6 of the SmPC.

2.5.4.6. Toxicokinetic data

Integration of multiple non-clinical toxicokinetic studies demonstrates that fezolinetant reached exposure levels that exceeded the anticipated therapeutic levels in humans.

2.5.4.7. Local Tolerance

No local tolerance studies have been conducted since fezolinetant is administered by the oral route.

2.5.4.8. Other toxicity studies

No antigenicity and immunotoxicity studies have been conducted with fezolinetant since these studies were not considered necessary. This was accepted by the CHMP.

2.5.5. Ecotoxicity/environmental risk assessment

Fezolinetant is considered not to be PBT, nor vPvB.

A risk to the STP, groundwater, sediment and terrestrial compartment is not anticipated based on the prescribed use of fezolinetant. As a risk to the surface water compartment is identified, this is therefore mentioned in the SmPC and package leaflet.

Table 1 Environmental risk assessment studies

Substance (INN/Invented Name): fezolinetant			
CAS-number (if available): 1629229-37-3			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	1.3 (pH 5) 1.4 (pH 7, 9)	Potential PBT (N)
PBT-statement :	The compound is not considered as PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
$PEC_{surface\ water}$, default	0.225	µg/L	> 0.01 threshold (Y)
Other concerns (e.g. chemical class)	potential endocrine disruptor		(Y)
Phase II Physical-chemical properties and fate			

Study type	Test protocol	Results			Remarks
Adsorption-Desorption	OECD 106	K_{oc} = 181 L/kg (sandy loam) 280 L/kg (sandy loam) 788 L/kg (clay) 14.2 L/kg (sludge) 17.2 L/kg (sludge)			geometric mean: 342 L/kg (soil) 15.6 L/kg (sludge)
Ready Biodegradability Test	OECD 301B	not readily biodegradable			
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	not performed			Significant shifting to sediment presumed.
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Raphidoceles subcapitata*	OECD 201	EC10	>10	mg/L	growth rate
Daphnia sp. Reproduction Test	OECD 211	EC10	2.9	mg/L	mortality
Fish, Early Life Stage Toxicity Test/*Danio rerio*	OECD 210	NOEC	0.11	µg/L	fecundity and fertilization rate F0
Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC	≥293	mg/L	respiration, based on water solubility
Phase IIb Studies					
Sediment dwelling organism/*Chironomus riparius*	OECD 218	EC10	2179	mg/kg	development, normalised to 10% o.c.

2.5.6. Discussion on non-clinical aspects

Pharmacodynamics

Pharmacodynamic studies showed that fezolinetant acts as a full NK3R (neurokinin 3 receptor) antagonist, which has two important downstream effects. Most importantly, inhibition of the NK3R, expressed by KNDy neurons present in the arcuate nucleus (Arc), leads to reduced activity in the median preoptic nucleus (MnPO), a brain region associated with temperature regulation that is hypothesized to be dysregulated in menopausal women suffering from vasomotor symptoms. This is shown in a rat model where ovariectomized (OVX) rats showed reduced levels of c-fos expression in the MnPO upon oral dosing of fezolinetant. Secondly, fezolinetant administration is shown to decrease the levels of circulating LH in both (OVX) rats and intact monkeys, whereas FSH levels remained unchanged, indicating an alternative mechanism of action than the traditionally used estrogen replacement therapy for treatment of vasomotor symptoms associated with menopause.

Secondary pharmacology studies revealed no inhibition of binding of any of the receptors, ion channels, transporters and enzymes tested. The Applicant provided a sufficient justification for the target selection in the secondary PD screens for both fezolinetant as well as its major metabolite.

Safety pharmacology studies revealed no risks for fezolinetant administration, since only minor effects were observed at C_{max} values that sufficiently exceed the concentrations of fezolinetant obtained in clinical practice.

Pharmacokinetics

Pharmacokinetics have been thoroughly studied in pre-clinical species. Since fezolinetant was developed for a different (female only) indication there was more non-clinical data available for female

animals than for male animals. In studies that did include male animals, some minor sex differences were observed in exposures to fezolinetant and the metabolite, which were higher in male animals. For mice and monkeys the differences between male and female were <2-fold, for rats, differences in AUC of the metabolite were 1.45-4.36-fold. The differences in fezolinetant AUC were less pronounced between males and females. Therefore, these sex differences are not likely to be of clinical relevance.

In distribution studies, the *in vitro* plasma protein binding was higher in humans (approx. 50%) compared to pre-clinical species (approx. 30%). But since this is <2-fold and means the exposure in humans is lower than in pre-clinical species, this was deemed not relevant for the assessment of toxicology studies. In metabolism studies it became apparent that rats do not produce the major metabolite ES259564 as much as humans (6.4% versus 52%, respectively), but cynomolgus monkeys do (20.7-42.1%). Therefore, and given the high exposure multiples in rats and monkeys, the metabolite is sufficiently qualified in toxicology studies. Excretion was comparable between pre-clinical species and humans, mostly renal excretion (52.3-81.7%) as metabolite ES259564 (44.7-67.2%).

Toxicology

Repeated dose toxicity studies were conducted in rats and cynomolgus monkeys. Cynomolgus monkey was selected as the relevant nonrodent species as nonhuman primates are anatomically and functionally similar to humans in the reproductive system, which is known to be affected by LH change. In addition, according to the *in vitro* radioligand assay fezolinetant has a similar affinity for the human and cynomolgus monkey NK3 receptor orthologs.

Repeated administration of fezolinetant showed the effects consistent with the primary pharmacological action, such as oestrous cycle disruptions, the lack of ovarian activity, decreased uterine and/or ovarian weight, uterine stromal atrophy and changes in myometrium and endometrium in monkeys. These effects were observed at high exposure multiples (>10-fold of MRHD). Furthermore, in rats, secondary pharmacological effects were exhibited on the liver and thyroid which are considered to be an adaptive response to the CYP450 induction and in the absence of functional impairment and accompanying necrotic changes were considered non-adverse. The thyroid findings are considered secondary to the liver enzyme induction due to the increased thyroid hormone metabolism, resulting in the positive feedback to the pituitary for the stimulation of TSH production and increased thyroid activity. It is generally accepted that rodents, and rats in particular, are more sensitive to this type of liver-mediated thyroid toxicity than humans, as the HPT axis in humans is capable of compensating the reduced T3/T4 levels without any clear increase in TSH levels. Thus, these findings are not expected to be clinically relevant.

Unexpected observations of clonic convulsions/convulsion-like episodes were reported in rats across several studies, albeit with no EEG changes which could indicate that fezolinetant would cause the events. The Applicant has classified these occurrences as "atypical" (lasting 10-20 seconds, without any warning sign, occurring during handling, lacking dose-response relationship and reduced in incidence by changes in the handling procedure), and most probably caused by the stress of the animals. There is no clinical evidence from other NK3 receptor antagonists suggesting that this drug class may have an epileptic potential.

In addition, considering that no convulsions were observed in the repeated dose toxicity studies with monkeys (see below), the lack of concomitant EEG findings and the fact that very high exposure multiples to the anticipated clinical exposure were achieved in the rat studies (EM of ca. 80 at a dose level of 30 mg/kg/day in both the 13-week and the carcinogenicity study), it is agreed that the risk to patients appears to be low.

In the carcinogenicity studies with Wistar rats and RasH2 mice, an increased incidence of B-thymoma in both species was noted. At the high dose level in the rat carcinogenicity study the observed

incidences of benign thymoma and benign and malignant thymomas combined were outside the historical control data range of the testing laboratory. In the RasH2 mouse study, the incidence of B-thymoma was outside the historical control range in the high-dose males and in both sexes combined whereas in females it was within the historical control range. However, high safety margins calculated in both species provide sufficient reassurance of the safety of fezolinetant with regard to carcinogenicity in clinical settings.

The observed effects in the reproductive toxicity studies were consistent with the pharmacological action of fezolinetant and included increased oestrous cycle length, decreased number of oestrous cycles and reduced non-gravid uterus/cervix/vagina weight. *In utero* loss was observed at high exposure levels in developmental toxicity studies with rats and rabbits. Furthermore, increased number of early late resorptions, decreased gravid uterine weight and decreased mean foetal weight in combination with nodulated ribs, dumbbell ossification of sternebrae and incomplete ossification of thoracic centrum were seen in rabbits. Although the observed effects were seen only at high safety margins, their severity (embryo-foetal lethality) and the fact that these effects are considered to be caused by the pharmacodynamics of the substance, raise a concern for the maternal exposure to fezolinetant during pregnancy. As the product is indicated for VMS treatment in both peri- and post-menopausal women, the possibility of pregnancy cannot be excluded for the intended patient population. Thus, a contra-indication during pregnancy and suspected pregnancy is considered warranted, as reflected in Sections 4.3 and 4.6 of the SmPC.

Environmental risk assessment

Fezolinetant is considered not to be PBT (persistent, bioaccumulative and toxic), nor vPvB (very persistent, very bioaccumulative).

A risk to the STP, groundwater, sediment and terrestrial compartment is not anticipated based on the prescribed use of fezolinetant. However, as a risk to the surface water compartment is identified, this is therefore mentioned in the SmPC and package leaflet and fezolinetant should be used according to these precautions in order to minimize any potential risks to the environment.

2.5.7. Conclusion on the non-clinical aspects

Pharmacodynamics

The applicant showed proof-of-concept for fezolinetant induced reductions in vasomotor symptoms in a rat OVX model, and provided evidence for a molecular mechanism implicating fezolinetant as a hNK3 receptor antagonist that leads to reduced activity in the median preoptic nucleus, associated with temperature regulation. The secondary PD screens showed that fezolinetant is highly specific, whereas the safety pharmacology studies revealed no cause for concern since the (minor) effects that were present were noted only at exposure multiples sufficiently exceeding the concentrations reached upon MRHD.

Pharmacokinetics

The applicant provided a comprehensive package of non-clinical pharmacokinetic studies. All necessary studies have been provided by the applicant and no major issues nor other concerns with the non-clinical PK package have been identified. Pharmacokinetics of fezolinetant in rats, but especially in cynomolgus monkeys appear to be very similar to pharmacokinetic parameters determined in human volunteers.

Toxicology

Overall, the toxicology programme with fezolinetant is considered adequate and demonstrated the effects which are consistent with primary pharmacological action of fezolinetant. Unexpected toxicological findings (clonic convulsions/convulsion-like episodes) were seen across several rat studies, which were considered unrelated to the pharmacological action of fezolinetant by the Applicant. While this cannot be concluded with certainty, it is agreed that the observed effects do not suggest concern in the clinical settings, taking into account high exposure multiples, the absence of such findings in monkeys and the lack of concomitant EEG changes.

Due to the adverse effects noticed in the EFD and PPND studies (generally at high-exposure margins) and taking into consideration the pharmacodynamic activity of fezolinetant, a contraindication during (suspected) pregnancy was included in the SmPC.

In conclusion, fezolinetant is considered approvable from a non-clinical perspective.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

The Clinical trials were performed in accordance with GCP as claimed by the applicant

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Table 2 Tabular overview of clinical studies

	Region/ Country	Study No.	n	Population	Brief Study Description	Doses Evaluated	Study Description
PK in Healthy Participants	Belgium	ESN364-CPK-101	Part 1: 17 Part 2: 24 Part 3: 24	Part 1: healthy male participants Part 2: healthy male participants Part 3: healthy female participants of childbearing potential	Single center, randomized, double-blind, placebo-controlled, single and MAD escalation in healthy male and female volunteers.	Part 1: Panel A: single dose of 3, 12, 46 and 180 mg Panel B: single dose of 6, 23, 90 and 23 mg Part 2: 20, 60 and 180 mg qd for 10 days Part 3:	SAD and MAD Pharmacokinetics of Hard Gelatin Capsule; Phase 1

	Region/ Country	Study No.	n	Population	Brief Study Description	Doses Evaluated	Study Description
						20, 60 and 180 mg qd for 21 days	
	Belgium	ESN364-CPK-102	Part 1: 16 Part 2: 16 Part 3: 8	Part 1: healthy female participants Part 2: healthy female participants Part 3: healthy male participants	Single center, randomized, double-blind, placebo-controlled, single and MAD escalation in healthy male and female volunteers.	Part 1: Panel A: single dose of 180, 540 and 900 mg Panel B: single dose of 360, 720 and 900 mg Part 2: 540 and 720 mg qd for 7 days Part 3: Single dose of 720 and 900 mg	SAD and MAD Pharmacokinetics of Hard Gelatin Capsule; Phase 1
	The Netherlands	ESN364-CPK-103	5	Healthy menopausal female participants	Single center, open-label, absorption, metabolism, and excretion in healthy postmenopausal women.	180 mg	Pharmacokinetics/ Mass balance of Hard Gelatin Capsule; Phase 1
	Japan	2693-CL-0020	Part 1: 16 Part 2: 28	Part 1: healthy male participants Part 2: healthy male participants; healthy premenopausal and postmenopausal female participants	Placebo-controlled, randomized, double-blind, 2-part in healthy Japanese men (part 1) and healthy premenopausal or postmenopausal Japanese women (part 2).	Part 1: Single dose of 15 or 60 mg Part 2: Single and multiple doses of 180 mg qd for 10 days	Single and Multiple dose Pharmacokinetics of Hard Gelatin Capsule in Japanese Participants; Phase 1
PK in Healthy Participants	China	2693-CL-0030	16	Healthy female participants	Open-label, single and multiple dose study in healthy Chinese female participants.	15, 30 (single and multiple doses) and 60 mg	Single and Multiple dose Pharmacokinetics of Phase 3 Tablet in Chinese Participants; Phase 1
Drug-drug Interactions	Germany	2693-CL-0006	18	Healthy postmenopausal female participants	Open-label, single sequence in	30 mg (single dose)	Fluvoxamine (strong CYP1A2 inhibitor) Drug-drug Interaction of

	Region/ Country	Study No.	n	Population	Brief Study Description	Doses Evaluated	Study Description
					postmenopausal female smokers and nonsmokers.		Hard Gelatin Capsule; Phase 1
Intrinsic Factors	US	2693-CL-0007	26	Female participants with mild (n = 8) or moderate (n = 8) hepatic impairment; healthy female participants with normal (n = 10) hepatic function	Multicenter, open-label, single oral dose study in female participants comprising 3 groups based on hepatic function.	30 mg (single dose)	Mild and Moderate Hepatic Impairment; Single dose with Phase 3 Tablet; Phase 1
	US	2693-CL-0008	27	Female participants with mild (n = 6), moderate (n = 6) or severe (n = 5) renal function; healthy female participants with normal (n = 10) renal function	Multicenter, open-label, single oral dose study comprising 4 groups based on renal function.	30 mg (single dose)	Mild to Severe Renal Impairment; Single dose with Phase 3 Tablet; Phase 1
Biopharmaceutics	US	2693-CL-0009	16	Healthy postmenopausal female participants	Randomized, open-label, single dose crossover in postmenopausal women.	120 mg (single dose); 2-period crossover, 120 mg single dose in each period	RBA of Phase 3 Tablets vs Capsules Used in Phase 1/2 Studies; Phase 1
	US	2693-CL-0010	22	Healthy female participants	Randomized, open-label, 2 period, 2 sequence, single dose crossover study in healthy female participants.	45 mg (single dose)	BE of Single To-be-marketed Tablet vs Phase 3 Tablets; Phase 1
	US	2693-CL-0012	16	Healthy female participants	Randomized, open-label, 2 period, 2 sequence, single dose crossover study in healthy female participants.	45 mg (single dose)	Food Effect of Single-To-be-Marketed Tablet; Phase 1

BE: bioequivalence; CYP: cytochrome P450; HF: hot flashes; MAD: multiple ascending dose; n: number of participants dosed; PCOS: polycystic ovarian syndrome; RBA: relative bioavailability; SAD: single ascending dose; UF: uterine fibroids; VMS: vasomotor symptoms.

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

Methods and bioanalysis

The bioanalytical methods for measuring fezolinetant and metabolite ES259564 in human plasma and urine were validated in studies **B1132137-1**, **2693-ME-0004**, **2693-ME-0005**, **2693-ME-0001** and **2693-ME-0016**.

Non-compartmental analysis

Pharmacokinetic parameters were determined using a non-compartmental approach in the dedicated clinical pharmacology studies.

Modelling and Simulation studies

Population PK analysis was performed using non-linear mixed effect models to characterize the fezolinetant concentration-time profile, to assess the impact of covariates on the PK of fezolinetant and to estimate PK parameters for subsequent exposure-response analyses. The model was based on PK data from female participants in 14 studies (8 Phase 1 studies, 4 Phase 2 studies and 2 Phase 3 studies); Studies **ESN364-CPK-101, ESN364-CPK-102, 2693-CL-0006, 2693-CL-0009, 2693-CL-0010, 2693-CL-0012, 2693-CL-0020, 2693-CL-0030, ESN364_HF_204, ESN364_HF_205, ESN364-UF-02, ESN364_PCO_201, 2693-CL-0301** and **2693-CL-0302**. The final population pharmacokinetic model was developed in NONMEM version 7.4 and was a two-compartment model with first-order elimination and the absorption part of the model was best described using an Erlang distribution with 6 transit compartments. Food effect, formulation, smoking status, bodyweight, race and dose were considered significant covariate effects. Inter-individual variability was estimated on the apparent clearance (CL/F), the apparent central volume of distribution (Vc/F), the apparent peripheral volume of distribution (Vp/F) and the transit rate constant (ktr). The residual error was described using a proportional error stratified by time (>3.5h or not) and study phase (phase 1 and 2 versus phase 3).

PK/PD modelling was performed to characterise the relationship between fezolinetant exposure ($AUC_{0\text{-}tau}$) and both the frequency and severity (mild, moderate or severe) of VMS during the Phase 2b study **ESN364_HF_205** and during the first 12 weeks of treatment in the Phase 3 studies (**2693-CL-0301** and **2693-CL-0302**). Models were constructed using non-linear mixed-effects models with NONMEM software. $AUC_{0\text{-}tau}$ estimated to achieve a 50% reduction (corrected for placebo) in VMS frequency was 42.911 ng.h/mL and the $AUC_{0\text{-}tau}$ estimated to achieve 50% reduction (corrected for placebo) in maximum severity reduction was 746 ng.h/mL.

PBPK modelling was used to predict the effect of moderate and weak CYP1A2 inhibitors on the PK of fezolinetant. A PBPK model was first constructed for fezolinetant based on study **ESN-364-CPK-102** in healthy female participants. Model parameters for CYP1A2 intrinsic clearance and absorption parameters were manually adjusted to describe the plasma concentration-time profile. A clinical study was performed with a strong CYP1A2 inhibitor, fluvoxamine, which formed the basis of the simulated influence of CYP1A2 inhibition of the PBPK model. A PBPK model of fluvoxamine was used, without modifications, as implemented in Simcyp (version 17.1). Cimetidine and mexiletine were selected as

weak and moderate CYP1A2 inhibitors, respectively. A PBPK model was constructed for mexiletine based on available literature data. For cimetidine, the PBPK model as implemented in Simcyp was used, but modified as this model did not include a CYP1A2 inhibition parameter as default. The model of fezolinetant was verified by predicting the pharmacokinetic data obtained in healthy volunteers of study **ESN364-CPK-101**. Secondly, the effect of fluvoxamine on fezolinetant pharmacokinetics was verified by simulating PK data observed in study **2693-CL-0006**.

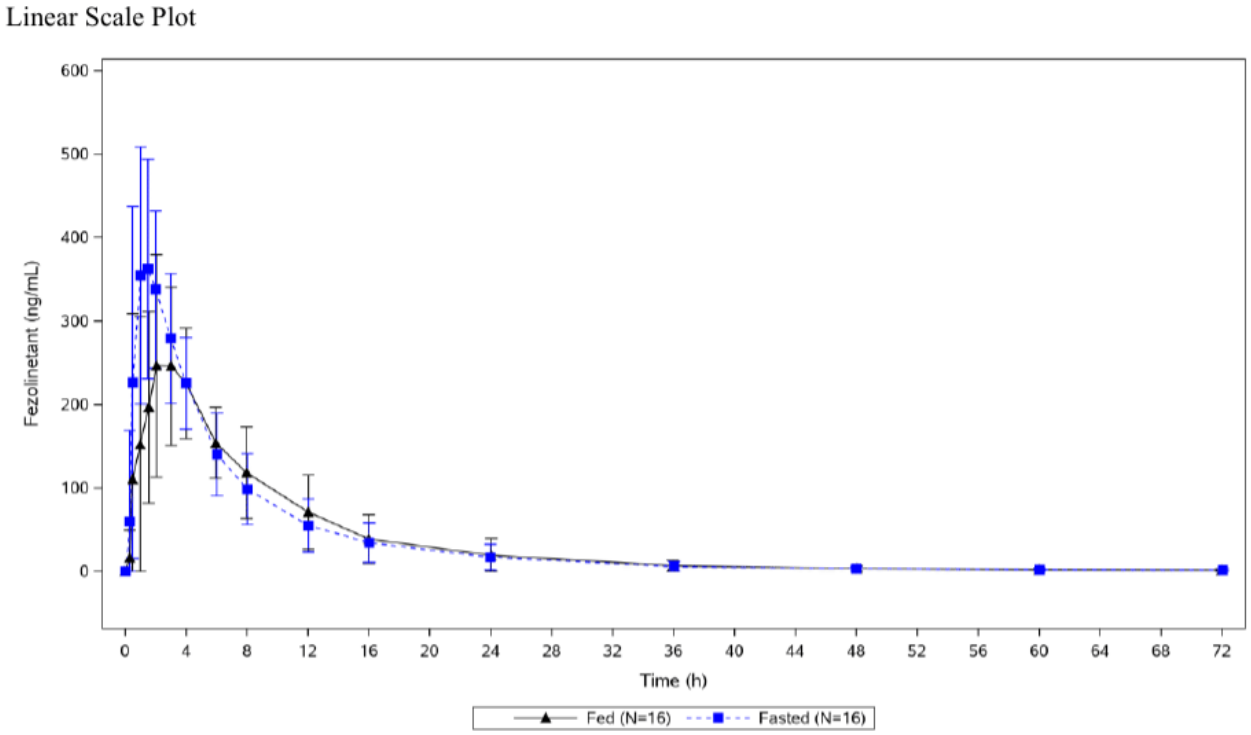
PBPK modelling was also used to predict the effect of fezolinetant on the PK of OAT1 and OAT3 substrates. PBPK models for the OAT1 substrates cefuroxime and cidofovir were used as provide by the FDA. PBPK models for the OAT3 substrates methotrexate and oseltamivir carboxylate were used as implemented in Simcyp (version 15) and the FDA, respectively. Probenecid, using the model as implemented in Simcyp, was used as perpetrator drug for these OAT1 and OAT3 substrates.

A PBPK study was performed to predict the risk of hepatotoxicity. The model was based on exposure data from studies **ESN364-CPK-101** and **ESN364-CPK-102** and on results from in vitro studies regarding bile acid toxicity (inhibition of transporters NTCP, MRP3, MRP4 and BSEP), mitochondrial toxicity and oxidative stress caused by fezolinetant or its metabolite ES259564).

Absorption

A typical concentration-time profile of fezolinetant is shown in the figure below following administration of a 45 mg dose in study **2693-CL-0012**.

Figure 3 Mean (SD) fezolinetant plasma concentration-time profiles by food condition in healthy female subjects (study **2693-CL-0012**)



The absolute bioavailability of fezolinetant has not been determined. Absolute bioavailability based on the mass balance study (study **ESN364-CPK-103**) was estimated to be at least 77%, which was based on renal excretion of the radiolabelled dose.

Following a single dose of 45 mg of the to-be-marketed formulation under both fasting and fed conditions, C_{max} of fezolinetant was 328 – 506 ng/mL and t_{max} was 1.5 – 2.0 h.

Steady state Cmax and $AUC_{0\text{-}tau}$ were predicted to be 458 ng/mL and 3855 ng.h/mL, respectively (at a dose of 45 mg QD) based on the population pharmacokinetic analysis.

Two bioequivalence studies (studies **2693-CL-0009** and **2693-CL-0010**) were performed to compare the hard gelatin capsules used in the phase 1 and 2 studies with the tablets used in the phase 3 studies (using a dose of 120 mg) and to compare the tablets used in the phase 3 studies (at a dose of 30 + 15 mg) with the to-be-marketed tablets (45 mg). The tablet formulation used in the phase 3 studies can be considered bioequivalent with the capsule formulation regarding AUC. Cmax was 23% higher with the phase 3 tablet formulation compared to the capsule formulation used in phase 1 and 2.

A relative bioavailability study (study **2693-CL-0012**) was performed to investigate the effect of a high-fat meal on the PK of fezolinetant. No food effect was observed on $AUC_{0\text{-}inf}$ after administration of a single dose of 45 mg fezolinetant (to-be-marketed formulation) to healthy female subjects. Cmax was 23% lower under fed conditions compared to fasted conditions.

Distribution

Fezolinetant has protein binding ratios (determined by equilibrium dialysis) from 50.2% to 52.4% at concentrations of 200 – 100,000 ng/mL in human plasma (study **2693-ME-0012**). Blood-to-plasma ratio was estimated to be 0.9 (study **ESN364-CPK-103**).

The apparent steady-state volume of distribution for the typical female participant predicted from the population PK model was 189 L. In healthy female participants including postmenopausal women from phase 1 studies, the apparent volume of distribution ranged from 104 to 392 L.

Excretion

In the mass balance study (**ESN364-CPK-103**)**,** a total of 90.9% of the total radioactivity was recovered after a single oral administration of 180 mg ^{14}C-fezolinetant. The single dose pharmacokinetics of fezolinetant is dose proportional until 180 mg, so the results of the mass-balance study with a dose of 180 mg can be extrapolated to the proposed therapeutic dose of 45 mg.

Fezolinetant was mainly excreted in urine (77% of the administered dose) and faeces (14%). The majority (78%) of the administered dose is excreted in the first 24 hours. Only 1.1% of the fezolinetant dose was excreted unchanged after a single oral dose of 180 mg (**ESN364-CPK-103**) and 1.5-2.2% after multiple doses of 60-180 mg qd (**ESN364-CPK-101** and **ESN364-CPK-102**).

Fezolinetant has a relatively short half-life (t1/2) of 4.3-6.4 hours after a single dose of 180 – 900 mg in healthy female subjects and is comparable to the t1/2 after multiple doses of 20 – 720 mg qd. The CL/F after a single dose of 180-900 mg in healthy female subjects is 14.5-33.9 L/h and also comparable with the CL/F after multiple doses of 20-720 mg qd.

Furthermore, the t1/2 of 4.72 hours of the total radioactivity in plasma was shorter or at least comparable to the t1/2 of fezolinetant determined in plasma, suggesting that there is limited slow release of fezolinetant from tissues and/or formation of metabolites with significantly slower elimination relative to fezolinetant.

Population PK modelling predicted CL/F of fezolinetant to be 10.8 L/h in a non-smoking 70 kg female subject. Elimination half-life was predicted to be 9.6 h.

Metabolism

In Vitro metabolism

One main metabolite, ES259564, was detected when 10 µM fezolinetant was incubated for 4 hours with cryopreserved hepatocytes (10 donors) in study **CYP0720-R1**. The major metabolite ES259564 has approximately 20-fold less potency against the human NK3 receptor compared with the parent drug. ES259564 is not expected to have significant off-target activities with biological activity only observed for human NK3.

The CYP-enzymes involved in the formation of the metabolite ES259564 were further investigated in study **2693-ME-0009** using recombinant human CYPs, human liver microsomes and inhibitors. Data from the recombinant human CYPs experiment showed that metabolite ES259564 was formed by CYP1A2, CYP2C9, CYP2C19 and CYP2D6. Further investigation in human liver microsomes with selective inhibitors of the identified CYP-enzymes demonstrated that the formation of metabolite ES259564 was strongly inhibited by a selective CYP1A2 inhibitor (83.3%) and weakly by the selective CYP2C19 (22.0%) and CYP2C9 (17.5%) inhibitors. No inhibition of the formation of metabolite ES259564 was observed with the selective CYP2D6 inhibitor. The activity of ES259564 formation in human liver microsomes was strongly correlated with the activity of CYP1A2 ($p<0.001$, $r = 0.8076$) and weakly correlated with the activities of CYP2C9 ($p<0.05$, $r =0.5412$) and CYP4A11 ($p<0.05$, $r = 0.5279$), respectively. The contribution ratios of CYP1A2, CYP2C9, CYP2C19, and CYP2D6 to the formation of ES259564 were estimated to be 38.4%, 56.4%, 3.5%, and 1.6%, respectively.

In Vivo metabolism

In vivo data from study **ESN364-CPK-103** showed that fezolinetant is extensively metabolised. Five metabolites (M1, M4, M5, M6 and M9 (ES259564)) were identified in human plasma, urine and faeces. Additionally, 2 unidentified metabolites in urine and 4 unidentified metabolites in faeces were detected.

In human plasma from 0-8 hours post-dose, only unchanged fezolinetant and ES259564 were detected contributing 29% and 52% to the total radioactivity in plasma, respectively. The exposure to ES259564 was 1.8-fold higher than to fezolinetant in study **ESN364-CPK-103**. Other metabolites could be present in human plasma, since 19% of the total radioactivity could not be identified.

In urine from 0–48 hours post-dose, ES259564 was the major metabolite accounting for 55.4% of the administered dose. Other metabolites M1, M4, M5 and M6 individually contributed to 1.5–6.1% of the dose. The two unidentified metabolites contributed <1% of the dose.

In faeces from 0–144 hours post-dose, M4 was the major metabolite accounting for 7.4% of the dose. Metabolites M1 and ES259564 were also found in faeces and accounted for 1.0-1.9% to the dose. The four unidentified metabolites all contributed <1%.

Transporters

Fezolinetant was found to be not a substrate for P-gp (at 1 -200 µM), BCRP (at 1-10 µM), OAT1B1 (at 1-10 µM), OAT1B3 (at 1-10 µM), OATP1A2 (at 3-30 µM), OATP2B1 (at 3-30 µM), PEPT1 (at 3-30 µM), MRP2 (at 3-30 µM) and MRP3 (at 3-30 µM) in studies **2693-ME-0008**, **ESN364-DDI-004**, **ESN364-DDI-005** and **Tebu-03-25Feb2015.**

Metabolite ES259564 was found to be a substrate for P-gp (at 2-200 µM), but not for BCRP (at 5 µM), OATP1B1 (at 3-30 µM), OATP1B3 (at 3-30 µM), OAT1 (at 3-30 µM), OAT3 (at 3-30 µM), OCT2 (at 3-30 µM), MATE1 (at 3-30 µM) and MATE2-K (at 3-30 µM) in studies **ESN364-DDI-004**, **ESN364-DDI-005**, **Tebu-03-25Feb2015** and **2693-ME-0024**.

Inter-conversion

The enantiomer of fezolinetant (AS3472948) was not detected in human plasma samples (1-3 hours post-dose) in study **2693-ME-0015**, showing that chiral inversion of the unchanged drug does not take place after oral administration.

Pharmacokinetics of metabolites

The pharmacokinetics of the major inactive metabolite ES259564 was investigated in most pharmacokinetic studies. Other metabolites contributed to <10% of the administered dose and were therefore not determined.

C_{max} of ES259564 is 217 – 263 ng/mL, t_{max} is 2.0 – 3.0 h (studies **2693-CL-0010** and **2693-CL-0012**). Metabolite ES259564 has a t1/2 of 5.4-7.9 hours after a single dose of 30-180 mg fezolinetant in healthy female subjects. The pharmacokinetics of metabolite ES259564 seem dose proportional in terms of $AUC_{0\text{-}inf}$ after a single dose in a dose range of 30 – 900 mg. The $AUC_{0\text{-}tau}$ at steady state is dose proportional between 20-60 mg and 540 mg, but increases slightly more than dose proportional for 180 mg and 720 mg. The ratio of metabolite ES259564 to the parent drug fezolinetant in healthy female subjects ranged between 0.66-1.84 after a single oral dose of 20-900 mg fezolinetant.

The metabolite/parent ratio in plasma decreased with the grade of hepatic impairment and increased with the grade of renal impairment. The t1/2 of metabolite ES259564 slightly increased in these groups to 11-14 hours. These findings are in line with the metabolism of fezolinetant, which is primarily metabolised to ES259564 and excreted with the urine afterwards.

Dose proportionality and time dependencies

Dose Proportionality

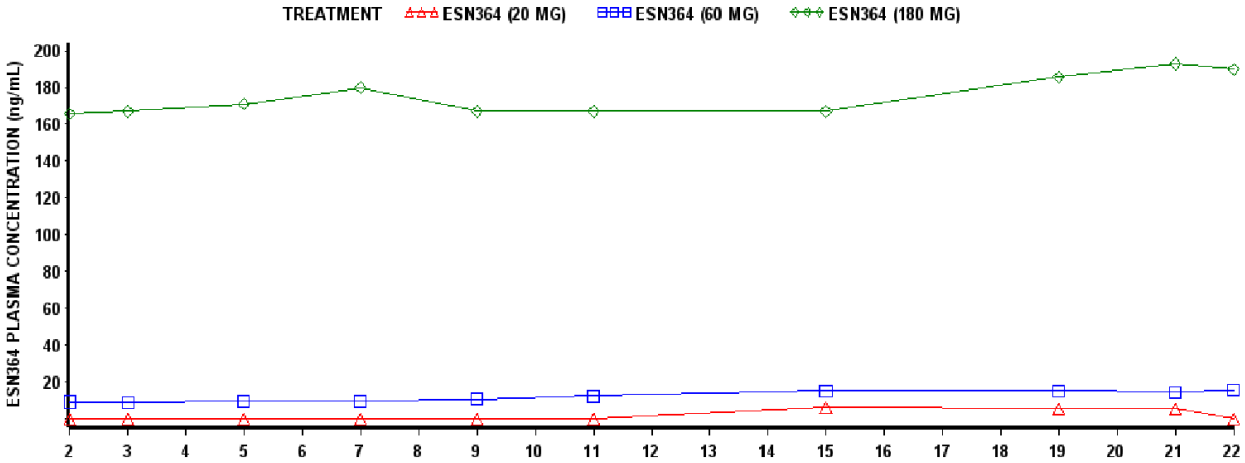
After multiple dose administration, dose proportionality over the entire dose range studied, 20 to 720 mg qd was assessed by combining data in female cohorts between Studies ESN364-CPK-101 and ESN364-CPK-102. The increase in fezolinetant Cmax was dose proportional, however $AUC_{0\text{-}tau}$ was slightly greater than dose proportional at dosages higher than 60 mg. Male data of **study ESN364-CPK-102** indicated dose proportional pharmacokinetics after single dose administration in the dose range of 20-60 mg.

Time dependency

In Study **ESN364-CPK-101**, after multiple ascending doses of 20 mg, 60 mg or 180 mg qd of fezolinetant in healthy women of childbearing potential, minimal accumulation of fezolinetant was observed after 10 days of 60 or 180 mg qd administration. The mean accumulation index values for 60 and 180 mg qd fezolinetant in healthy women of childbearing potential were 1.23 and 1.18, respectively. In Study **ESN364-CPK-102**, after multiple doses of 540 mg or 720 mg qd of fezolinetant in healthy female participants, accumulation ratios slightly increased to values of 1.47 to 1.74, respectively.

Based on data from Study **ESN364-CPK-101**, PK of fezolinetant does not change over time (Figure 4).

Figure 4 Trough plasma concentrations of fezolinetant in women of child-bearing potential in study ESN364-CPK-101



Pharmacokinetics in target population

Menopausal status was not identified as a significant covariate affecting the pharmacokinetics of fezolinetant in the population PK modelling study **2693-PK-0010**. Simulations with 45 mg qd predicted a $C_{max,ss}$ of 458 ng/mL and $AUC_{0\text{-}tau,ss}$ of 3855 ng*h/mL which are 2.9% and 12.2% lower when compared to the exposure in premenopausal women.

Special populations

Impaired renal function

Mean $AUC_{0\text{-}last}$ of fezolinetant was 1.1 to 1.5-fold lower in the mild, moderate and severe renal impairment groups compare to respective normal renal function groups (Study **2693-CL-0008**).

In the population PK analysis, mild renal impairment did not have a significant effect on $AUC_{0\text{-}tau}$ and C_{max} of fezolinetant.

The C_{max} and AUC of metabolite ES259564 in moderate and severe renal impairment patients increased significantly with 1.8 to 2.3-fold and 1.8 to 4.8-fold, respectively.

Impaired hepatic function

In comparison to healthy subjects, the $AUC_{0\text{-}t/0\text{-}inf}$ of fezolinetant increased 1.6-fold and 1.9-fold in patients with mild and moderate hepatic impairment, respectively. The C_{max} showed a slight increase of 1.2-fold for patients with mild hepatic impairment and a slight decrease of 1.2-fold for patients with moderate hepatic impairment.

The $AUC_{0\text{-}t/0\text{-}inf}$ of metabolite ES259564 was comparable between healthy subjects and patients with mild and moderate hepatic impairment. The C_{max} of metabolite ES259564 was reduced with 1.3-fold and 1.9-fold in patients with mild and moderate hepatic impairment, respectively.

Gender

According to the results of the population PK model, males have a 2-fold higher CL/F, consequently 2-fold reduction in $AUC_{0\text{-}inf}$ and 1.2-fold reduction in C_{max} relative to females.

Race

Population PK modelling predicted that African American participants have an increase in central volume of distribution resulting in a 6.6% reduction in C_{max} compared to non-African American participants. No differences in $AUC_{0\text{-}tau}$ were predicted. This is considered not clinically relevant. Asian race was initially estimated to have 22.5% higher $AUC_{0\text{-}tau}$ and 10% higher C_{max} compared to the western population. However, Asian race was not identified as a statistically significant covariate in the final model.

In the analysis based on the Phase 2b study (study ESN364_HF_205), African Americans had smaller maximum reductions in the probability of severe VMS due to fezolinetant compared to non-African American subjects. In addition, in African American subjects, the concentration to achieve a 50% reduction in VMS frequency (EC50) was increased compared to non-African American subjects (428 vs 134 ng/mL) in the population PK/PD analysis. This was however not found in the analysis based on the Phase 3 studies, where covariates had no significant effect.

Bodyweight

In the population PK analysis (**2693-PK-0010**), bodyweight had no statistically significant impact on $AUC_{0\text{-}inf}$. Subjects weighing 100 kg were predicted to have a 17.2% lower C_{max} and subjects weighing 55 kg were predicted to have a 25.6% higher C_{max}.

Elderly

Approximately 90% of the population PK database consisted of post-menopausal women. The dataset included women with ages ranging from 19 to 65 years. In pre-menopausal women, predicted $AUC_{0\text{-}tau}$ was 12% lower compared to post-menopausal women.

Table 3 Age groups included in the PK database

	Age < 65	**Age 65-74 (Older subjects number /total number)**	**Age 75-84 (Older subjects number /total number)**	**Age 85+ (Older subjects number /total number)**
PK Trials	1488	0	0	0

No clear age effects are apparent from the PK data. No specific dose recommendation for elderly is therefore considered necessary.

Paediatrics

No pharmacokinetic studies in children were performed since fezolinetant is indicated for postmenopausal female subjects.

Smoking

For smokers compared to non-smokers, steady-state $AUC_{0\text{-}inf}$ was predicted to be 33.9% lower and in a DDI study, smoking decreased $AUC_{0\text{-}inf}$ by 50%.

In the PK/PD models, smoking had smaller maximum reductions in the probability of severe VMS due to fezolinetant compared to non-smoking subjects.

Pharmacokinetic interaction studies

In silico

PBPK modelling predicted a weak CYP1A2 inhibitor to increase $AUC_{0\text{-}inf}$ and C_{max} of fezolinetant by 75% and 42%, respectively. A moderate inhibitor was predicted to increase $AUC_{0\text{-}inf}$ and C_{max} of fezolinetant by 4-fold and 20%, respectively.

PBPK modelling predicted that fezolinetant is not a clinically relevant inhibitor of OAT1 and OAT3.

In vitro

Based on in vitro data the Applicant concluded that fezolinetant and metabolite ES259564 are no direct or time-dependent inhibitors of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4 at a concentration of 0.1-25 µM.

Fezolinetant and metabolite ES259564 are no inhibitors of the transporters P-gp, BCRP, BSEP, OATP1B1, OATP1B3, OCT2, MATE1, MATE2-K and MRP2, as the IC50-values were found to be >70 µM, which is above the estimated maximal systemic concentration (fezolinetant 31.44 µM, ES259564 34.53 µM) and maximal intestinal concentration (fezolinetant 50.22 µM).

The IC_{50}-values for fezolinetant for OAT1 and OAT3 were 18.9 and 27.5, respectively. These values are below the systemic maximal concentration 31.44 µM, indicating that fezolinetant is a potential inhibitor of these transporters.

Fezolinetant was not an inducer of CYP1A2 at the maximal systemic and maximal intestinal concentration.

Metabolite ES259564 was not an inducer of CYP1A2, CYP2B6 and CYP3A4 at maximal systemic concentrations.

In vivo

In study **2693-CL-0006**, co-administration of a single dose of 30 mg fezolinetant with fluvoxamine (strong CYP1A2/CYP2C19 inhibitor and weak CYP2C9/CYP2D6 inhibitor) increased the C_{max} and $AUC_{0\text{-}inf}$ of fezolinetant with 1.8-fold and 9.4-fold, respectively. The increase of C_{max} and $AUC_{0\text{-}inf}$ after co-administration with fluvoxamine was slightly higher among smokers (2.0-fold and 9.9-fold, respectively) when compared to non-smokers (1.6-fold and 8.9-fold, respectively).

Smoking, a CYP1A2 inducer, decreased the C_{max} and $AUC_{0\text{-}inf}$ of fezolinetant with 1.4-fold and 2.1-fold, respectively.

2.6.2.2. Pharmacodynamics

Mechanism of action

The thermoregulatory centre of the hypothalamus is innervated by KNDy neurons that are normally inhibited by oestrogen and stimulated by the NKB. Through the menopausal transition, declining oestrogen disrupts the balance with NKB. KNDy neurons become hypertrophied, contributing to increased signalling to the thermoregulatory centre. This shifts the balance for control of core body temperature, resulting in VMS.

Fezolinetant is claimed to be the first-in-class, non-hormonal, selective neurokinin 3 (NK3) receptor antagonist. It blocks neurokinin B (NKB) binding on the kisspeptin/neurokinin B/dynorphin (KNDy) neuron to help restore the neuronal activity in the thermoregulatory centre of the hypothalamus.

It is postulated that fezolinetant improves VMS, and thus their QoL, through its antagonistic action in the hypothalamus, as it calibrates the neuronal activity in the thermoregulatory centre.

Primary and Secondary pharmacology

Primary Pharmacodynamics

Human Studies with Pharmacodynamic Endpoints included 3 phase 1 studies ESN364 CPK 101, ESN364-CPK-102, and 2693 CL 0020 (Japanese study), in healthy volunteers:

- Study ESN364 CPK 101 - A Phase I, double-Blind, placebo-controlled (6:2 ratio), single and multiple dose escalation study of ESN364 to evaluate PK, PD, safety and tolerability in healthy male and female volunteers of childbearing potential aged 18-45 years. Study ESN364-CPK-101 investigated fezolinetant in SAD (3 to 180 mg) and MAD (20 to 180 mg qd) in 65 healthy male and female participants.
- Study ESN364-CPK-102 - Phase I, double-blind, placebo-controlled (6:2 ratio), SAD and MAD study of fezolinetant to evaluate PK, safety, tolerability and Maximum Tolerated Dose (MTD) in healthy female and male volunteers in 3 study periods. Study performed in Belgium. Study ESN364-CPK-102 had similar design as Study ESN364-CPK-101 but investigated higher doses in SAD (180 to 900 mg) and MAD (540 to 720 mg qd) in 40 healthy male and female participants.
- Study 2693 CL 0020 (Japanese study) - Phase 1 placebo-controlled, randomized (ratio 3:1), single and multiple oral dose study (15 and 60 mg) in healthy Japanese male and pre- and post-menopausal female Subjects.
- Phase 2 Study ESN364_HF_204 – 12-week double-blind, placebo-controlled, parallel-group, proof-of-concept study to assess the effect of 12-week administration of fezolinetant in postmenopausal women with hot flushes (HF), who received either placebo or 90 mg fezolinetant bid. PD parameters included FSH and LH.
- Phase 2 Study ESN364_HF_205 - 12-week, randomized, double-blind, placebo-controlled, dose-ranging, parallel-group study in postmenopausal women with HF, randomized to 1 of 8 treatment groups: 15 mg bid, 30 mg bid, 60 mg bid, 90 mg bid, 30 mg qd, 60 mg qd, 120 mg qd, or placebo bid. PD parameters included LH, E2, FSH or SHBG levels.
- Phase 3 studies 2693-CL-0301, 2693-CL-0302, 2693-CL-0304, sparse PD data (i.e. baseline, week 4, week 12, week 24, week 16 [only for 2693-CL-0301 and -0302] and week 52) were collected on LH, androstenedione, E2, estrone, FSH, testosterone, dehydroepiandrosterone, FT or SHBG.

PD Phase 1 studies

Phase 1 study **ESN364-CPK-101** investigated fezolinetant in SAD (3 to 180 mg) and MAD (20 to 180 mg qd) in 65 healthy male and female participants.

Male volunteers

After SD of ESN354 from 3 mg to up to 180 mg, a dose-dependent decrease in total testosterone (T) and free testosterone (FT), FSH and LH plasma concentrations was observed compared to placebo. No clear effect was noted on SHBG plasma concentrations. Between-subject variability was very high.

After MAD of ESN354 of 20, 60, and 180 mg over 10 days, a dose dependent decrease in total (T) and free testosterone (FT), FSH and LH plasma concentrations was observed. After multiple administration (Day 10), total T plasma concentrations <5.2 nmol/L (level associated with testosterone deficiency)

were found for 50% of the subjects at the dose of 20 mg (median 1.77h), for 50% of the subjects at a dose of 60 mg (median 4.21h) and for 66.7% of the subjects at a dose of 180 mg (median 7.5h).

Female volunteers of reproductive age

After SD of ESN354 of 20, 60, and 180 mg in healthy women of reproductive age, admitted in the study when they were between day 2 - 5 of their menstrual cycle (day 1 = first day of bleeding), total testosterone (T), Free T, FSH, SHBG, LH, estradiol (E2), Free E2 and progesterone (P4) plasma concentrations over 24 hours post-dose were not clearly impacted.

After MAD of ESN354 of 20, 60, and 180 mg:

- *MAD PD parameter concentrations* monitored over 24h after the last administration (Day 21):

  A decrease in FSH and LH plasma concentrations was observed with the treatments 20 and 180 mg, while an increase was observed with 60 mg; total E2 and free E2, and P4 plasma concentrations were increased with 20, 60 and 180 mg; total T was increased, but no clear change in free T was noted.

- *MAD PD parameter concentrations over the menstrual cycle (including Day 22 sample):*

  Based on plasma concentrations monitored from Day 1 to 24h after the last administration (Day 22) (i.e., over the time extent of the menstrual cycle during presence of study drug in the body):

  - the time to reach the peak concentration in LH (LH surge) was lengthened with 60 and 180 mg (median ≈17 days) compared to placebo (median ≈ 8 days);
  - No clear difference of FSH plasma concentration was noted between treatments and placebo.
  - A decrease in total E2 plasma concentration was observed with 60 mg; the time to reach the peak concentration in total and free E2l was lengthened with 60 and 180 mg (18 and 19 days) compared to placebo (≈ 9 days).
  - A dose-dependent decrease in P4 plasma concentration was observed with 60 and 180 mg compared with placebo and 20 mg dose; median time to reach the peak concentration was around 18 days for the doses 60 and 180 mg, compared to 14 days for placebo and the 20 mg dose. For the majority of subjects in the dose groups 60 and 180 mg, the premenstrual peak in P4 was not yet reached at Day 22. The higher levels for E2 and P4 measured on Day 21 for the treatment groups are explained by a shift in the menstrual cycle because of the action of the study drug. This delay in menstrual cycle shifts the natural cyclic increase of these hormones towards the end-of-treatment (and even beyond).

  The *exploratory analyses* showed a drop in E2 concentrations below 110 pmol/L for 2 days in the placebo and the 20 mg dose group; for the 60 and 180 mg dose this drop lasted for 5.4 and 8.2 days respectively. However, the exposure to E2 as measured by AUClast indicated that exposures to E2 did not fall below the exposures associated with undesirable side effects (bone mineral density loss), which is set at average E2 plasma concentrations of 110 pmol/L (55440 h.pmol/L). A dose-dependent decrease in P4 was noted for the 60 and 180 mg dose respectively (for 504h and 503h, 22 days), whereas a normal P4 production was maintained with 15 days of P4 levels below 5 ng/mL for both placebo and 20 mg.

  An increase in mean *menstrual cycle duration* for the first cycle were noted for the 60 mg and 180 mg dose, with a mean change from baseline of 8.8 and 8.0 days respectively. Once withdrawn from the study drug, the normal menstrual cycle resumed immediately with cycle lengths comparable to the pre-dose menstrual cycle.

The difference in mean changes in mean *endometrium thickness* was minor, although there was a trend towards a decreased rate of endometrium build-up between early follicular phase and midcycle.

No relevant differences were observed in the number of *dominant follicles* visualized via vaginal ultrasound between placebo, 20 mg, 60 mg, and 180 mg ESN364 treatment groups.

Phase 1 Study **ESN364-CPK-102** had similar design as Study ESN364-CPK-101 but investigated higher doses in SAD (180 to 900 mg) and MAD (540 to 720 mg qd) in 40 healthy male and female participants. As this study was mainly aimed at investigating safety, tolerability and PK of ESN364, the results for female hormone parameters in Parts 1 and 2 should be interpreted with caution as there was no standardization for their menstrual or hormonal cycle nor for the use of oral contraceptives and the possibility of being (peri)menopausal.

Female volunteers

After SD in Healthy Female Volunteers (180 mg - 900 mg), a slight decrease in absolute LH and FSH values was observed and a sustained decrease at 24 hours was noted after a dose of 540 mg, 720 mg and 900 mg.

After MAD, a decrease in absolute FSH and LH values was observed. No clear impact was observed on leptin or ghrelin, compared to placebo.

Male volunteers

After SD of 720 and 900 mg in healthy men, a decrease in total T, free T (FT), and LH concentrations was observed. The effect seemed maximal, as no dose effect was observed. No impact was observed on SHBG. No effect was observed for leptin or ghrelin.

Study 2693 CL 0020 was a placebo-controlled, randomized, SD and MAD study of 15 and 60 mg in healthy Japanese male and pre- and post-menopausal female Subjects.

SD in healthy male volunteers (15 mg and 60 mg or placebo)

After SAD of 15 and 60 mg in healthy male subjects, mean LH, FSH, total and free T serum concentrations decreased compared to placebo and the decrease was greater in 60 mg group than 15 mg group. Maximum decrease was observed between 6 to 12 hours post-dose. All concentrations returned to baseline by 24 hours post-dose. No notable change of mean SHBG serum concentration.

SD and MAD in healthy men, premenopausal- and postmenopausal women (180 mg or placebo)

After SAD and MAD of 180 mg for 10 days of 180 mg in healthy men, a decrease in mean LH, FSH, total and free T serum concentrations was observed. Maximum decrease was observed between 6 to 12 hours post-dose. These concentrations returned to baseline by 48 hours post-dose. There were no changes of SHBG serum concentration.

After SD and MD in healthy pre- and postmenopausal females, a similar pattern was noted for LH, FSH, and SHBG, but no tendency was observed in total and free T. As individual E2 and P4 serum concentrations showed high variability, the impact of SAD and MAD was difficult to interpret.

PD parameters in Phase 2 studies

Phase 2 Study ESN364_HF_204 was a double-blind, placebo-controlled, parallel-group, proof-of-concept study to assess the effect of 12-week administration of fezolinetant in early postmenopausal women with hot flushes (HF), who received either placebo (n = 44) or 90 mg fezolinetant (n = 43) bid. As to PD parameters, a decrease in median FSH and LH concentrations was noted in the fezolinetant group over time, which decrease was most pronounced at week 12 at the 3-hours post-dose sampling

time point. During follow-up, a normalization in FSH and LH levels compared to baseline levels was observed.

Phase 2 Study ESN364_HF_205 was a 12-week, randomized, double-blind, placebo-controlled, dose-ranging, parallel-group study in postmenopausal women with HF, randomized to 1 of 8 treatment groups: 15 mg bid, 30 mg bid, 60 mg bid, 90 mg bid, 30 mg qd, 60 mg qd, 120 mg qd, or placebo bid. In the fezolinetant groups, there was a mean and median decrease in LH levels from baseline at all postbaseline time points, particularly at 3 hours post-dose at week 4, which was dose-related and persisted through week 12. There were no clinically meaningful changes in E2, FSH or SHBG levels compared to placebo.

PD parameters in Phase 3 studies

In phase 3 studies **2693-CL-0301**, and **2693-CL-0302** and **2693-CL-0304**, only sparse PD data (i.e. baseline, week 4, week 12, week 24, week 16 [only for 2693-CL-0301 and -0302] and week 52) were collected from phase 3 studies. In postmenopausal women with VMS, administration of fezolinetant at 30 or 45 mg qd a transient decrease in LH was detected at 3 hours post-dose but no long-term effect on LH was observed, but no clear trend or clinically relevant changes in sex hormones including androstenedione, E2, estrone, FSH, testosterone, dehydroepiandrosterone, FT or SHBG.

2.6.3. Discussion on clinical pharmacology

Bioanalytical methods

The bioanalytical validation reports are in line with the ICH M10 on bioanalytical method validation / Guideline on bioanalytical method validation of the EMA (EMEA/CHMP/EWP/192217/2009 Rev. 1 Corr. 2**).

The results of the population PK model suggest that the different assays perform similarly across the different studies.

Population PK analysis

Regarding the population PK analysis, the final model is based on the Erlang distribution model described by Rousseau et al (2004) and seems overly complex for the amount of data collected in the absorption phase. Nonetheless, simulated AUC and Cmax values were sufficiently comparable to observed values. The population PK model can be considered acceptable for this purpose.

In the population PK model, the coefficient of variation of the estimation of the interindividual variability of Vp was very high (600%) and this could be a clear sign of over parameterization. However, as the impact of the model in this procedure is rather limited, this issue is no longer pursued.

PBPK models regarding interactions

The PBPK model for CYP1A2 inhibition was verified using data from study ESN364-CPK-101. A model was constructed for mexiletine. Verification was performed based on published studies. Predicted/observed ratios were within 1.5-fold and acceptable. For cimetidine, the Simcyp simulator provided PBPK model for cimetidine was used, with adjusted Ki for CYP1A2 (as found in the literature or calculated based on IC50 values found in the literature). Predicted/observed ratios were however within 1.5-fold and therefore acceptable. The model for fezolinetant was also verified using the study regarding the interaction of fezolinetant with fluvoxamine. Simulated plasma concentration profile was compared to the results obtained in the clinical drug interaction study (study 2693-CL-0006). The exposure for this study was overpredicted. This is accepted here because no overprediction of AUC was

observed in the verification based on study ESN364-CPK-101 and predicted/observed ratios for AUCinf and Cmax were acceptable.

A publication has been provided in which the verification of the Simcyp Simulator regarding inhibition of CYP enzymes has been described (Kilford et al, 2022). The study by Kilford et al is limited regarding CYP1A2, with 3 substrates and 2 inhibitors. This verification does not include moderate inhibitors of CYP1A2. However, the Applicant has performed a verification with mexiletine and cimetidine, a moderate and a weak inhibitor. Overall, the estimation of the effect of moderate and weak CYP1A2 inhibitors can be considered acceptable. Since the maximum effect (inhibition by strong inhibitor fluvoxamine) has been investigated clinically and considering the 9-fold increase that was observed in AUCinf in the presence of the strong inhibitor fluvoxamine, the estimated increase of 3.2 – 4.5-fold in the presence of a moderate inhibitor is plausible. Contraindication of co-administration of fezolinetant with strong or moderate CYP1A2 inhibitors is agreed. When co-administered with a weak CYP1A2 inhibitor, the increase in AUC will generally be within 2-fold and Cmax within 1.5-fold, and therefore it is agreed that no specific dosing advice is given for co-administration with a weak CYP1A2 inhibitor.

The PBPK model regarding OAT1/OAT3 inhibition was verified based on published studies, with cefuroxime and cidofovir as OAT1 substrates, methotrexate and oseltamivir carboxylate as OAT3 substrates and probenecid as inhibitor. Predicted/observed ratios for AUC and Cmax were acceptable. Sensitivity analysis regarding Ki values for OAT1 and OAT3 (up to 100-fold higher and lower) indicated no relevant effect of variation in Ki on the effect of fezolinetant on AUC and Cmax of the substrates. The Applicant could not verify the model with other OAT1/OAT3 inhibitors than probenecid. The only other clinical inhibitor of OAT1/OAT3 that could be evaluated is teriflunomide, however this substance is not very specific. Verification of the model was performed with only 1 inhibitor (probenecid), which is not a very broad basis to support that OAT1/OAT3 inhibition is not expected. It is acknowledged that there are no other suitable OAT1/OAT3 inhibitors and it is considered that the risk of fezolinetant being a relevant inhibitor in vivo is considered low. A statement that fezolinetant inhibited OAT1 and OAT3 in vitro was added to the SmPC.

Absorption

In the first bioequivalence study (study **2693-CL-0009**), Cmax was 23% higher with the phase 3 tablet formulation compared to the capsule formulation used in phase 1 and 2. A majority of the efficacy and safety data is however obtained with the phase 3 tablet formulation. Therefore, the higher Cmax does not affect the B/R discussion. In the second bioequivalence study, the phase 3 tablet and the to-be-marketed tablet formulation were bioequivalent in healthy female subjects.

The formulation used in the phase 3 studies and the to-be-marketed formulation were shown to be bioequivalent. No clinically relevant food effect was observed. Fezolinetant can therefore be used with or without food.

Fezolinetant was highly permeable in Caco-2 cells. pH-dependent absorption is not expected to be relevant because in the dissolution studies, dissolution was > 85% within 15 minutes for all investigated pH values.

Distribution

Fezolinetant has an apparent volume of distribution of around 190 L. This indicates quite extensive distribution to the tissues. The blood-to-plasma ratio was approximately 1, indicating distribution to red blood cells. Protein-binding is estimated to be approximately 50%, independent of the fezolinetant concentration.

Metabolism

In vitro data demonstrate an important contribution of CYP1A2 in the formation of metabolite ES259564. Some contradicting results were generated in study **2693-ME-0009** regarding the estimated relative contribution of CYP1A2 (38.4%) and CYP2C9 (56.4%), when these results were compared to the results of the experiments with selective inhibitors of these enzymes and the correlation experiments. However, given the nearly complete absorption of fezolinetant after oral administration (>77%) from the mass balance study and considering the 9.4-fold increase in fezolinetant exposure when given with fluvoxamine (strong CYP1A2 and CYP2C19 inhibitor and weak CYP2C9 and CYP2D6 inhibitor) and the 2.1-fold decrease of fezolinetant exposure in smokers (CYP1A2 inducer, without known effect on CYP2C9/2C19) in the *in vivo* DDI-study **2693-CL-0006**, it can be reasoned that CYP1A2 is the main enzyme involved in the metabolism of fezolinetant. Reference is also made to the effect of smoking on the sensitive CYP1A2 substrate caffeine, which shows a comparable decrease in AUC as fezolinetant.

Excretion

The major elimination route of fezolinetant is as metabolite in the urine. As indicated above, fezolinetant is primarily extensively metabolised to the metabolite ES259564 by CYP1A2, which is mainly excreted in urine. Other metabolites in urine and faeces contribute to <10% of the dose.

The CL_R of metabolite ES259564 is 13.1 L/h (or 218 mL/min) in subjects with normal renal function (Study **2693-CL-0008**), which is higher than the glomerular filtration rate, indicating active transport to the urine of the metabolite. Additionally, it was shown that metabolite ES259564 is a substrate for P-gp, which might contribute to the active transport to the urine. Observed trough, 1h and 2h post-dose concentrations of metabolite ES259564 from clinical studies 2693-CL-0301, 2693-CL-0302, and 2693-CL-0304 in participants receiving fezolinetant with and without co-administrations of a P-gp inhibitors were assessed. There is overlap in the boxplots, indicating comparable concentrations in participants with and without co-administration of P-gp inhibitors. Thus, it is not expected that there is a difference in safety due to accumulation of the metabolite by co-administration of P-gp inhibitors.

Inter-conversion

The enantiomer of fezolinetant (AS3472948) was not detected in human plasma samples (1-3 hours post-dose) in study **2693-ME-0015**, showing that chiral inversion of the unchanged drug does not take place after oral administration.

Consequences of possible genetic polymorphism

No conclusive data on the consequences of CYP1A2, the primary route of fezolinetant metabolism, polymorphisms on CYP1A2 activity are currently known (Koonrungsesomboon et al., 2018). Minimal contribution of CYP2C9 and CYP2C19 to the metabolism of fezolinetant is expected. Therefore, no relevant effects of genetic polymorphisms are to be expected.

Dose proportionality

The pharmacokinetics of fezolinetant are dose proportional in the range of 20 to 60 mg. Above 60 mg, $AUC_{0\text{-}tau}$ increases slightly more than proportional.

Time dependency

The PK of fezolinetant is time independent with only marginal accumulation at therapeutic dose levels.

Intra- and inter-subject variability

The intra-subject variability was larger in the absorption phase than in the elimination phase of the pharmacokinetic profile of fezolinetant. Additionally, intra-subject variability was larger in the phase 3 studies compared to the phase 1 and 2 studies.

The inter-subject variability was in general modest, but especially the distribution phase of the pharmacokinetic profile shows large inter-subject variability, but it is acknowledged that the clinical relevance of the high between-subject variability in Vp is limited.

Pharmacokinetics in the target population

No distinction between healthy postmenopausal women and postmenopausal women with VMS is made in the population PK modelling **study 2693-PK-0010**. However, the vast majority (90%) of the postmenopausal women included in the dataset represent postmenopausal women with VMS and therefore analyses for postmenopausal women can also be interpreted as for postmenopausal women with VMS. The estimated difference in pharmacokinetics between healthy female premenopausal subjects and postmenopausal female subjects with VMS is not considered clinically relevant.

Special populations

Impaired renal function: Study **2693-CL-0008** was conducted with 30 mg fezolinetant instead of the to-be-marketed 45 mg dose, but this is not expected to result in a different outcome as dose proportionality can be concluded in the dose range of 20-60 mg. The decrease in exposure to fezolinetant in renal impairment patients is likely a result of the small sample size and variation, as 100% is included in the 90%-CIs of the ratios. Renal function is not a significant factor influencing the pharmacokinetics of fezolinetant. The C_{max} of fezolinetant was comparable with subjects with normal renal function in all grades of renal impairment patients. The results of the population pharmacokinetic analysis should be interpreted with caution as only limited (n=19) or no subjects with moderate or severe renal impairment were present in the population PK dataset. Furthermore, less than 2% of the fezolinetant was excreted unchanged in the urine across all grades of renal impairment, which is consistent with the amount found in healthy volunteers of the mass-balance study. This is as expected from fezolinetant, since it is extensively metabolised. It can be concluded that renal impairment (mild, moderate and severe) does not have an impact on the C_{max} and AUC of fezolinetant after a single dose of 30 mg.

Severe renal impairment patients are excluded from use of fezolinetant in the SmPC, which is supported from a pharmacokinetic point of view due to the possible accumulation of the metabolite. In an in vitro study which was performed as part of the DILISYM study, the metabolite ES259564 was found to inhibit the mitochondrial electron transport chain. Due to the accumulation of ES259564 in case of severe renal impairment and its potential for mitochondrial toxicity in hepatocytes, the exclusion of the use of fezolinetant in patients with severe renal impairment is endorsed from this point of view. Patients with severe renal impairment have almost 4.8 x higher exposure to metabolite ES259564 compared to healthy subjects. There is no sufficient long-term clinical data to support the safety of the higher metabolite/parent-ratio in the severe renal impairment patient population. Monitoring on toxicity of is not deemed sufficient to mitigate this omission, and this group should be excluded from the use of fezolinetant.

Impaired hepatic function: The results of study **2693-CL-0007** with a 30 mg dose can be extrapolated to a single dose of 45 mg, as the pharmacokinetics of fezolinetant is dose-proportional within a range of 20-60 mg. No dose recommendation is necessary for patients with mild hepatic impairment. Fezolinetant is not recommended by the Applicant for patients with moderate or severe hepatic impairment, because of the approximately 2-fold increase in $AUC_{0\text{-}inf}$ in subjects with moderate hepatic impairment and the lack of subjects with severe hepatic impairment.

It is acknowledged that there is limited safety/efficacy data in the severe and moderate hepatic impairment patient population for fezolinetant. However, the concentration of the metabolite (which is associated with safety) is expected to be lower in patients with moderate hepatic impairment, and a dose modification is plausible since there is a 2-fold increase in exposure for fezolinetant and no difference in exposure for metabolite ES259564.A dose modification for patients with moderate hepatic impairment was however not acceptable for the Applicant.

Section 4.2 of the SmPC states that Veoza is not recommended for individuals with moderate or severe hepatic impairment and monitoring of liver function in women with known or suspected hepatic disorder is advised during treatment in section 4.4. of the SmPC.

In the absence of knowledge on the influence of severe hepatic impairment on the pharmacokinetics of fezolinetant and metabolite, and the likely reduced clinical relevancy of treatment of these patients, it is agreed to not further pursue to study the influence of severe hepatic impairment.

Sex: According to the results of the population PK model in study 2693-PK-0003, males have 2-fold higher CL/F, consequently 2-fold reduction in AUC and 1.2-fold reduction in Cmax relative to females. This difference (if true and with clinical consequences) is not relevant for the current indication.

Race: No clinically relevant race effects were identified in the population pharmacokinetic analysis.

Bodyweight: The effect of bodyweight on the pharmacokinetics of fezolinetant (investigated up to 126 kg) is considered not clinically relevant. However, it should be noted that only a limited bodyweight range (42 – 126 kg) was investigated in the clinical pharmacology program.

Elderly: Age was not investigated as covariate in the population pharmacokinetic analysis, due to the strong correlation with post- versus pre-menopausal stratification of the population. No clear age effects are apparent from the PK data, but a relatively narrow age range was investigated. This is acceptable for the currently requested indication.

Paediatrics: No studies in paediatrics were conducted as the intended indication is absent in the paediatric population.

Smoking: For smokers compared to non-smokers, steady-state AUC was predicted to be 33.9% lower and in a DDI study smoking decreased AUC by 50%. Smoking was not included as a covariate in the final PopPK-model because it failed the pre-specified statistical criteria. However, no significant difference in efficacy between smokers and non-smokers was observed the phase 3 studies despite the lower exposure, supporting that dose modification is not needed for both populations. See Clinical efficacy/safety for further assessment.

Drug-drug interactions

Regarding the in vitro studies to assess DDI-potential of fezolinetant and metabolite ES259564, based on in vitro data, it is concluded that fezolinetant and metabolite ES259564 are no direct or time-dependent inhibitors of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4.

In study CYP0720, R2F Donor 1 showed positive CYP2B6 induction for fezolinetant in the range 4-100 µM, as the results indicate a concentration dependent increase in CYP2B6 mRNA of 1.19 to 1.94-fold, which are >20% when compared to the maximum increase in CYP2B6 mRNA of the positive control phenobarbital of 5.62-fold. The 1.94-fold increase in Donor 1 which exceeds 20% of the response of the positive control was observed at the concentration of 100 µmol/L. Lower concentrations and other donors were within the negative cut-off value. Since 100 µmol/L exceeds the 50x Cmax,u value of 31.4 µmol/L (EMA guideline) and even the 15x $C_{max,u}$ value of 9.4 µmol/L (according to the more recent ICH M12 guideline), no induction effect is expected at clinical concentrations of fezolinetant. Thus, in vivo DDI studies with fezolinetant as inducer of CYP2B6 are not required. Furthermore, all donors show a

concentration dependent increase in CYP3A4 mRNA for fezolinetant. CYP3A4 mRNA increased 1.97 to 3.63-fold in the concentration range of 40-100 µM, which is below the maximal intestinal concentration cut-off value of 50.22 µM. However, this is based on 50x $C_{max,u}$ from the EMA guideline. At 15x $C_{max,u}$ of 9.4 µmol/L (according to the more recent ICH M12 guideline) no inducibility was observed in all donors. Thus, no in vivo study is necessary for fezolinetant as CYP3A4 inducer.

Exposure-response relationship regarding efficacy

Regarding the PK/PD (exposure-response relationship regarding efficacy), overall, the model appears fit-for-purpose. Based on the prediction of this model, on a population level, more effect is expected of fezolinetant on severity than on frequency of VMS, at clinically relevant exposures. Interindividual variation is however expected to be large.

Exposure-response relationship regarding safety

In the PBPK study to predict hepatotoxicity (DILIsym study), no clear in vitro/in vivo relationship has been described and no simulations were shown with independent datasets. Thus, the model cannot be used to predict ALT increases at certain doses. The results of this analysis should therefore be considered supportive only.

The in vitro test regarding mitochondrial toxicity indicates that the metabolite ES259564 can cause mitochondrial toxicity in hepatocytes. No exposure-safety analysis of ES259564 was conducted. It is acknowledged that the safety database of fezolinetant covers the safety of both fezolinetant and the metabolite ES259564 and that the impact of fezolinetant versus ES259564 cannot be differentiated. No liver toxicity was observed in rats and monkeys. Clinically, increases in liver enzymes ALT and AST were observed, which is sufficiently addressed in the SmPC.

Discussion on primary pharmacodynamics

Mechanism of action

Fezolinetant is a first-in-class orally active product with a new mechanism of action. The product is a nonhormonal selective neurokinin 3 (NK3) receptor antagonist. It blocks neurokinin B (NKB) binding on the kisspeptin/neurokinin B/dynorphin (KNDy) neuron, which is postulated to restore the disbalance in-KNDy neuronal activity in the thermoregulatory centre of the hypothalamus.

Single and multiple rising dose

Single and multiple rising dose up to 900 mg in healthy male volunteers resulted in a dose dependent decrease in total (T) and free testosterone (FT), FSH and LH plasma concentrations. After multiple administration up to 180 mg over 10 days, dose dependent decrease total T plasma concentrations <5.2 nmol/L (level associated with testosterone deficiency) were found.

Single dose up to 180 mg in women of reproductive age which started during day 2-5 of their menstrual cycle, did not have a clear impact on hormonal PD parameters. Based on plasma concentrations monitored from Day 1 to 24h after the last administration (Day 22) (i.e., over the time extent of the menstrual cycle during presence of study drug in the body), multiple dose of 60 and 180 mg resulted in a decrease in LH and the time to reach the peak concentration in LH (LH surge) was lengthened with 60 and 180 mg. A decrease in total E2 plasma concentration and the time to reach the peak concentration in total and free E2l was lengthened. A dose-dependent decrease in P4 plasma concentration was observed and median time to reach the peak concentration was delayed and for the majority of subjects, the premenstrual peak in P4 was not yet reached at Day 22. This delay in menstrual cycle shifts the natural cyclic increase of these hormones towards the end-of-treatment (and even beyond). This resulted in an increase in menstrual cycle duration of approximately 8 days. After discontinuation, the normal menstrual cycle resumed. Changes in mean endometrium thickness was

minor, with a trend towards a decreased rate of endometrium build-up between early follicular phase and midcycle. No relevant differences were observed in the number of dominant follicles visualized via vaginal ultrasound.

In **phase 2 studies** (12-weeks) in postmenopausal women with VMS treated with higher doses up to 180 mg, a dose-related decrease in LH levels from baseline which persisted through week 12, but no clinically meaningful changes in E2, FSH or SHBG levels compared to placebo.

In **phase 3 studies** (52 weeks) in postmenopausal women with VMS treated with 30 or 45 mg qd resulted in a transient decrease in LH at 3 hours postdose but no long-term effect on LH was observed, and no clear trend or clinically relevant changes in sex hormones including androstenedione, E2, estrone, FSH, testosterone, dehydroepiandrosterone, FT or SHBG.

Conclusion primary PD

In ***healthy male volunteers***, fezolinetant resulted in a dose-dependent decrease total testosterone plasma concentrations, without evidence of effect on free testosterone.

In ***healthy female volunteers of reproductive age***, MAD of 60 and 180 mg resulted in a decrease in LH and a delay in time to reach the peak concentration in LH (LH surge), a decrease in total E2 plasma concentration and delay in the time to reach the peak concentration in total and free E2, and a decrease in progesterone plasma concentration was observed and median time to reach the premenstrual peak in progesterone. This delay in menstrual cycle shifts resulted in an increase in menstrual cycle duration of about 8 days. No changes in endometrium thickness, or in the number of dominant follicles were observed.

In ***postmenopausal women***, a dose-related decrease in LH levels from baseline was noted with higher doses up to 180 mg. in phase 3 studies, which applied 30 mg and 45 mg, a transient decrease in LH at 3 hours post-dose but no long-term effect on LH was observed, and no clear trend or clinically relevant changes in sex hormones including androstenedione, E2, estrone, FSH, testosterone, dehydroepiandrosterone, FT or SHBG.

Secondary pharmacology

No dedicated clinical TQT study was conducted. Instead, in line with ICH E14 recommendations and Scientific White Paper on Concentration QTc Modeling [Garnett et al, 2018], a model based TQT study waiver package is included in the submission. The Applicant utilized the model-based approach to assess the QT prolongation risk of fezolinetant. An analysis of the concentration-QTc relationship using data from single- and multiple-ascending dose Study ESN364-CPK-102 was conducted to evaluate the QT prolongation potential of fezolinetant.

Two different models were considered including one model that evaluated only fezolinetant concentrations and a separate model that evaluated the effect of fezolinetant and the primary metabolite, ES259564. From both models, ddQTcF values were predicted at clinically relevant concentrations: therapeutic exposure (the approximate steady-state mean Cmax for a 45 mg qd dose of fezolinetant), supratherapeutic exposure (6-times multiplier), higher-than-supratherapeutic exposure (10-times multiplier). Results of the two models were consistent. No clinically relevant prolongation of ddQTcF was predicted at the concentrations of interest. This was corroborated by the results from an analysis on data from the single and multiple dose PK study in Japanese participants [Study 2693-CL-0020].

No significant QTcF prolongation was detected in the model-based QT assessment performed using data from the single- and multiple- ascending dose Study ESN364-CPK-102, and therefore no clinical TQT study was conducted.

Thus, the model predicted upper 90% CI for Fridericia-corrected QT interval did not exceed 10 msec at the therapeutic concentration, supratherapeutic concentration or 10-times the therapeutic concentration indicating a lack of QT prolongation potential for fezolinetant at the clinical dosage regimen.

Of note, clinical ECG information are discussed under the safety section.

2.6.4. Conclusions on clinical pharmacology

The pharmacokinetics and pharmacodynamics of fezolinetant and the main metabolite, ES259564, have been appropriately characterized in the target population.

2.6.5. Clinical efficacy

The clinical development programme for fezolinetant in the treatment of VMS associated with menopause consists of 4 global, randomized, double-blind, placebo-controlled phase 2 and phase 3 studies (ESN364_HF_204, ESN364_HF_205, 2693-CL-0301 (SKYLIGHT 1) and 2693-CL-0302 (SKYLIGHT 2)).

The two phase 3 studies were conducted in the US, Canada and Europe: 2693-CL-0301 (SKYLIGHT 1) and 2693-CL-0302 (SKYLIGHT 2) are considered pivotal (see Table 4). The efficacy data of these studies are discussed under section 'main studies'.

The two phase 2 studies, ESN364_HF_204 and ESN364_HF_205, provide supportive data and are considered the dose response studies for this application. The efficacy data of these studies are discussed under section 'dose-response studies'.

Study 2693-CL-0304 (SKYLIGHT 4) is a 12-month, double-blind, placebo-controlled study concerned a long-term safety study and is further discussed under section 'supportive studies' and the safety section.

Table 4 Overview of fezolinetant studies relevant to efficacy evaluation

Study Number CTD location	Status	Region(s)	Study Design	Treatment Period	Formulation, Dosing Regimens Evaluated (FAS Participants†)
Pivotal Phase 3 Studies					
2693-CL-0301 [Module 5.3.5.1, 2693-CL-0301 CSR]	Completed	US, Canada and Europe	Randomized, multicenter, placebo-controlled 12-week double-blind, followed by an active treatment extension period	52 weeks: 12-week placebo-controlled period and 40-week extension period	Fezolinetant 30 mg (173) or fezolinetant 45 mg (174) or placebo (175) Once daily, tablet, oral
2693-CL-0302 [Module 5.3.5.1, 2693-CL-0302 CSR]					Fezolinetant 30 mg (166) or fezolinetant 45 mg (167) or placebo (167) Once daily, tablet, oral
Supportive Phase 2 Studies					
ESN364_HF_204 [Module 5.3.5.1, ESN364_HF_204 CSR]	Completed	EU (Belgium)	Proof-of-concept, randomized, multicenter, double-blind, placebo-controlled	12 weeks	Capsule Fezolinetant 90 mg bid (43) Placebo bid (44)
ESN364_HF_205 [Module 5.3.5.1, ESN364_HF_205 CSR]	Completed	US	Randomized, multicenter, double-blind, placebo-controlled, dose-ranging	12 weeks	Capsule Fezolinetant 15 mg bid (45) Fezolinetant 30 mg bid (43) Fezolinetant 60 mg bid (45) Fezolinetant 90 mg bid (42) Fezolinetant 30 mg qd (43) Fezolinetant 60 mg qd (44) Fezolinetant 120 mg qd (44) Placebo (43)

FAS: full analysis set.

† Analyses were performed on the intent-to-treat analysis set for study ESN364_HF_204.

2.6.5.1. Dose response studies

Study ESN364_HF_204 (phase 2a/proof-of-concept study)

Phase 2a Study ESN-HF-204 was 12-week double-blind, placebo-controlled, parallel-group, multicenter, proof-of-concept study to assess the efficacy and safety/tolerability of 12-week administration of fezolinetant 180 mg administered as 90 mg bid in early postmenopausal women suffering from HF (VMS). A total of 80 subjects were planned to be included in the study, i.e., 40 subjects in the active treatment arm and 40 subjects in the placebo arm.

The 180mg dose was selected since in the first-in-human Phase I study (study ESN364 CPK 101), the mid-range dose of ESN364, 60 mg/day, was demonstrated to be associated with a submaximal LH suppression, and thus a submaximal suppression of the KNDy neuron. At the same time, when ESN364 given as a dose of 180 mg/day was also tested in the first-in-human Phase I study, it was demonstrated to be safe and well tolerated. LH suppression was maximal with this dose level, and this was correlated with maximal suppression of the KNDy neuron.

During menopause, the negative feedback by E2 is un-existing, due to the cessation of estrogen production in the ovaries. The lacking negative E2 feedback will cause the KNDy neuron to become hyperactive in an attempt to restore the needed E2 levels via the increased release of LH/FSH. When dealing with a hyperactive state of the KNDy neuron, as assumedly is the case in the post-menopause period, a once-daily morning dose of ESN364 probably was not expected to yield the desired suppression of KNDy at night, preventing night sweats. For this reason, a high dose of ESN364 (total daily dose of 180 mg) given as 90 mg b.i.d. had to be tested to investigate the possibility to completely suppress LH secretion.

The study participants were postmenopausal women, between 40 and 65 years old, defined as spontaneous amenorrhea for at least 12 months or 6 months with FSH >40 IU/L, or having had bilateral oophorectomy having at least 49 moderate or severe HF or night sweats, recorded over a period of 7 consecutive days.

The primary objective was to evaluate the effect of ESN364 on the severity and frequency of hot flashes in early postmenopausal women suffering from hot flashes, in terms of changes in weekly Hot Flash Score (HFS) (including mild, moderate and severe) from baseline to Week 12.

The primary efficacy endpoint was the change from baseline in weekly HFS.

A mean score of 28.76 and 25.76 for the fezolinetant group and placebo group, respectively, was observed. The mean HFS score decreased over time to 2.69 and 14.36 at Week 12 for the fezolinetant and placebo group, respectively, corresponding to a mean decrease of 26.51 and 12.19, respectively, as shown in Table 5 below. A statistically significant difference ($p<0.001$) in general HFS between the fezolinetant group and placebo group was observed at Week 12.

Table 5 Changes in Weekly General Hot Flash Score From Baseline to Week 12 (ITT Population)

	Placebo	ESN364
Baseline		
N	44	43
Mean	25.76	28.76
95% CI for Mean	(22.64;28.88)	(24.64;32.88)
Week 12		
N	40	40
Mean	14.36	2.69
95% CI for Mean	(9.78;18.95)	(1.39;3.99)
Change from Baseline to Week 12		
N	40	40
Mean	-12.19	-26.51
95% CI for Mean	(-16.55;-7.83)	(-30.83;-22.18)
ANCOVA result Week 12		
LS mean difference	-	-12.34
95% CI for LS Mean	-	(-16.89;-7.79)
p-value		<0.001

N = Number of observations L.S.: Least square mean difference vs placebo, obtained from an ANCOVA Model with treatment group as fixed effect and baseline weekly general HFS as covariate

Secondary efficacy endpoints

- *Hot Flash Severity Scores*

This was calculated using two different methods. No differences in outcome were observed in HF severity scores calculated by method 1 as compared to method 2.

Using the first method, a statistically significant difference ($p<0.001$) in weekly HF severity score between the ESN364 group and placebo group was observed at all time points.

- *Number of Subjects With at Least 70%, 80%, and 90% Reduction from Baseline in Weekly HFS*

A statistically significant difference ($p<0.001$) in response between the ESN364 and placebo group was observed from Week 1 onwards, for response in terms of at least 70 or 80% reduction from baseline in the weekly number of moderate and severe HFS.

- *Number of Subjects With at Least 50%, 70%, and 90% Reduction in the Weekly Frequency of Moderate and Severe Hot Flashes*

A statistically significant difference ($p\leqslant0.037$) in response between the ESN364 and placebo group was observed from Week 1 onwards, for response in terms of at least 50, 70, or 90% reduction from baseline in the weekly frequency of moderate and severe HF. At Week 12, 72.5% of the subjects administered ESN364 had a reduction from baseline in the weekly frequency of moderate and severe HF of at least 90%, compared to 20.0% of the subjects administered placebo.

Safety summary

Most frequent AEs in the fezolinetant group (>2 patients)) included headache, nasopharyngitis, palpitations, diarrhoea, influenza, while these were headache, nasopharyngitis, and arthritis. Most

treatment-related TEAEs were gastrointestinal disorders (SOC), reported for 6 subjects in the ESN364 group and for none of the subjects administered placebo.

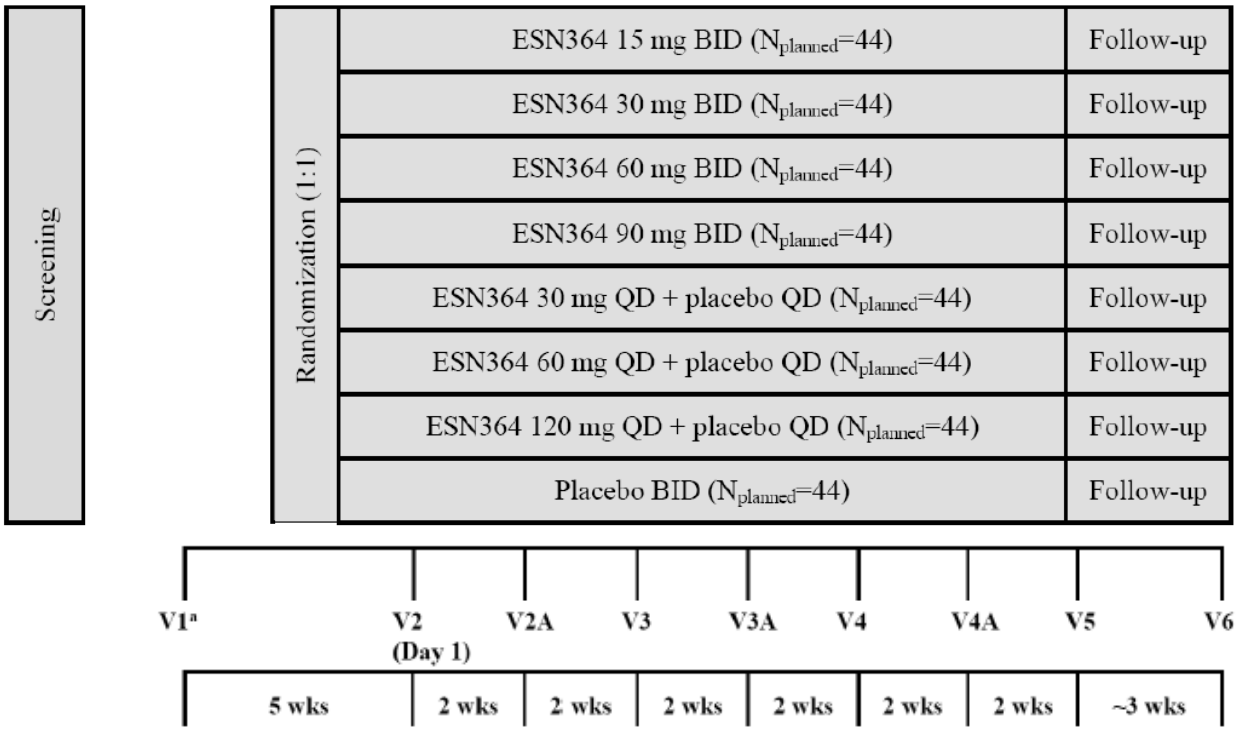
Study ESN364_HF_205 (dose-ranging study)

Study ESN364_HF_205 was a 12-week randomized, placebo-controlled, double-blind, dose-ranging, Phase 2b study to investigate the efficacy of ESN364 in postmenopausal women suffering from VMS. The study was performed in the US in 2018.

A total of 352 patients were planned to be enrolled. Patients were randomized to 1 of 8 treatment groups (i.e., 44 patients in each arm). Patients and study personnel were blinded to the treatment (placebo or fezolinetant), dosage and dose-regimen (15 mg, 30 mg, 60 mg, 90 mg twice daily or 30 mg, 60 mg, 120 mg once daily).

This study consisted of a screening period (days -35 to -1), a minimum 7-day collection of baseline vasomotor symptom frequency and severity assessments), a 12-week treatment period, and a follow-up visit 3 weeks after the last dose of study drug, see Figure 5.

Figure 5 Overview of study design



a. Screening was to be performed up to 35 days prior to randomization, with a minimum of 7 days to allow for baseline data collection of vasomotor symptom frequency and severity. V = visit.

The rationale for the study was to refine both the dose level and dosing regimen in order to define the minimal effective dose level of fezolinetant to treat moderate and severe VMS. The aim is to demonstrate a fezolinetant dose response using twice daily (BID) dosing as well as once daily (QD) dosing in the morning and to select the optimal dose for phase 3.

The study participants had the following characteristics:

- Women > 40 years and ⩽ 65 years of age at the screening visit;
- A body mass index between 18 kg/m2 to 38 kg/m2 (extremes included);
- Spontaneous amenorrhea for ⩾ 12 consecutive months; or spontaneous amenorrhea for ⩾ 6 months with biochemical criteria of menopause FSH > 40 IU/L); or having had bilateral oophorectomy ⩾ 6 weeks prior to the screening visit (with or without hysterectomy);
- At least 50 moderate to severe VMS per week (i.e., 7 consecutive days), as recorded in the daily diary during the screening period;
- a normal/negative or no clinically significant findings mammogram (obtained at screening or within the prior 9 months of study enrolment).
- Willing to undergo a transvaginal ultrasound to assess endometrial thickness at screening and at week 12 (end-of-treatment)
- Willing to undergo an endometrial biopsy at screening when patient's transvaginal ultrasound showed endometrial thickness ⩾ 4 mm) and at week 12 (end-of-treatment – all patients), for patients with uterine bleeding, and for patients withdrawn.

The primary objective was to evaluate the effect of different doses and dosing regimens of ESN364 on frequency and severity of VMS (hot flashes).

The following outcomes were observed for the 15 mg, 30 mg, 60 mg, 90 mg twice daily or 30 mg, 60 mg, 120 mg once daily.

The primary efficacy objectives required the evaluation of the effect of ESN364 on the 4 co-primary endpoints:

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

All 4 of these co-primary endpoints were significantly different from placebo for the 60 mg QD, 60 mg BID, and the 90 mg BID dose groups.

Effect of Different Doses and Dosing Regimens of ESN364 on Frequency and Severity of VMS

- Frequency of Moderate to Severe VMS in FAS, Change from Baseline to Week 4 and to Week 12

For the primary analysis of the *mean change in frequency of moderate to severe VMS*, all active groups were significantly different from placebo at both weeks 4 and 12.

Table 6 Primary analysis of change in the mean frequency of moderate and severe VMS per 24 h from Baseline to Week 4 and Week 12: FAS

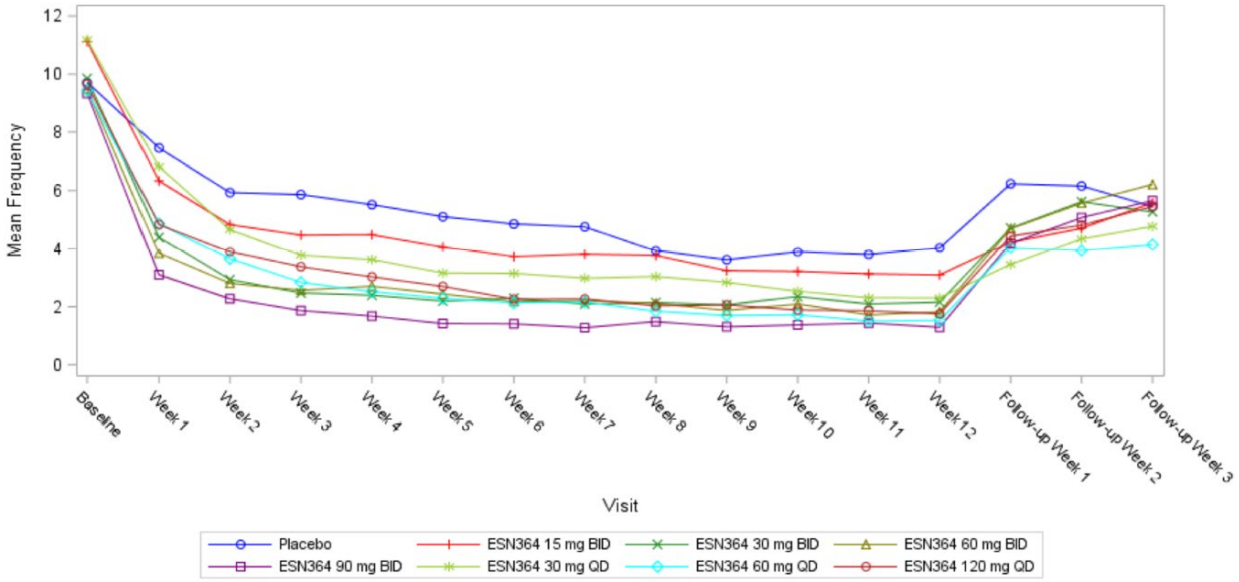
Analysis Visit	Treatment Group	n	Change from Baseline	Difference from Placebo		
			LS Mean (SE)	LS Mean (SE)	95% CI	P-value
Week 4	Placebo (n = 43)	42	-4.2 (0.65)	NA	NA	NA
	ESN364 15 mg BID (n = 45)	40	-6.1 (0.61)	-1.9 (0.84)	(-3.56, -0.25)	0.0240 *
	ESN364 30 mg BID (n = 43)	41	-7.2 (0.64)	-3.0 (0.84)	(-4.68, -1.38)	0.0004 *
	ESN364 60 mg BID (n = 45)	40	-7.0 (0.62)	-2.8 (0.84)	(-4.44, -1.14)	0.0010 *
	ESN364 90 mg BID (n = 42)	37	-7.7 (0.65)	-3.5 (0.84)	(-5.20, -1.89)	< 0.0001 *
	ESN364 30 mg QD (n = 43)	40	-6.5 (0.65)	-2.3 (0.84)	(-4.00, -0.68)	0.0058 *
	ESN364 60 mg QD (n = 44)	43	-7.2 (0.61)	-3.0 (0.82)	(-4.65, -1.41)	0.0003 *
	ESN364 120 mg QD (n = 44)	42	-6.6 (0.63)	-2.4 (0.84)	(-4.06, -0.76)	0.0042 *
Week 12	Placebo (n = 43)	37	-5.3 (0.58)	NA	NA	NA
	ESN364 15 mg BID (n = 45)	38	-7.2 (0.54)	-1.8 (0.75)	(-3.30, -0.35)	0.0154 *
	ESN364 30 mg BID (n = 43)	37	-7.5 (0.56)	-2.1 (0.74)	(-3.60, -0.67)	0.0043 *
	ESN364 60 mg BID (n = 45)	31	-7.6 (0.55)	-2.3 (0.75)	(-3.76, -0.83)	0.0023 *
	ESN364 90 mg BID (n = 42)	31	-8.0 (0.58)	-2.6 (0.75)	(-4.09, -1.16)	0.0005 *
	ESN364 30 mg QD (n = 43)	33	-7.4 (0.58)	-2.1 (0.75)	(-3.52, -0.58)	0.0064 *
	ESN364 60 mg QD (n = 44)	36	-7.9 (0.54)	-2.6 (0.74)	(-4.04, -1.15)	0.0005 *
	ESN364 120 mg QD (n = 44)	36	-7.4 (0.57)	-2.1 (0.75)	(-3.52, -0.59)	0.0063 *

Subset of the safety analysis set who had a baseline and at least one postbaseline efficacy evaluation (Full Analysis Set). Note: Baseline was the average frequency of 24 h vasomotor symptom from 7 non-missing days prior to day 1. The LS means, standard errors, confidence intervals, and P-values come from an ANCOVA model with change from baseline as the dependent variable and treatment group, pooled center, smoking status as factors and baseline measurement, baseline weight as covariates. For subjects in the efficacy analysis populations with missing primary efficacy endpoints, multiple imputation by fully conditional specification methods were used. NA: not applicable; VMS: vasomotor symptoms. * P-values from the model < 0.05.

All active doses reduced the mean frequency of symptoms compared to placebo, not only at week 4 and week 12, but also from week 1, onwards through 12 weeks of active treatment, see figure below. The VMS diary was also completed on a daily basis throughout the follow-up period and week-specific averages were calculated from the daily scores during this time.

After discontinuation of ESN364 treatment after week 12, the frequency of moderate and severe VMS started to increase.

Figure 6 Plot of weekly mean frequency of moderate and severe VMS per 24h: FAS



Subset of the safety analysis set who had a baseline and at least one postbaseline efficacy evaluation (Full Analysis Set). Note: Baseline was the average frequency of 24 h vasomotor symptom from 7 non-missing days prior to day 1. VMS: vasomotor symptoms

– *Primary Analysis: Severity of Moderate to Severe VMS in FAS, Change from Baseline to Week 4 and to Week 12*

Compared to baseline, both active and placebo groups had decreases in severity of moderate and severe VMS LS means (Table 7). Compared to placebo, all active groups had decreases in severity of moderate and severe VMS LS means. For the primary analysis of the mean change in severity of moderate to severe VMS, all groups were significantly different from placebo from baseline to week 4, but only 60 mg BID, 90 mg BID and 60 mg QD doses demonstrated a statistically significant difference from placebo at week 12.

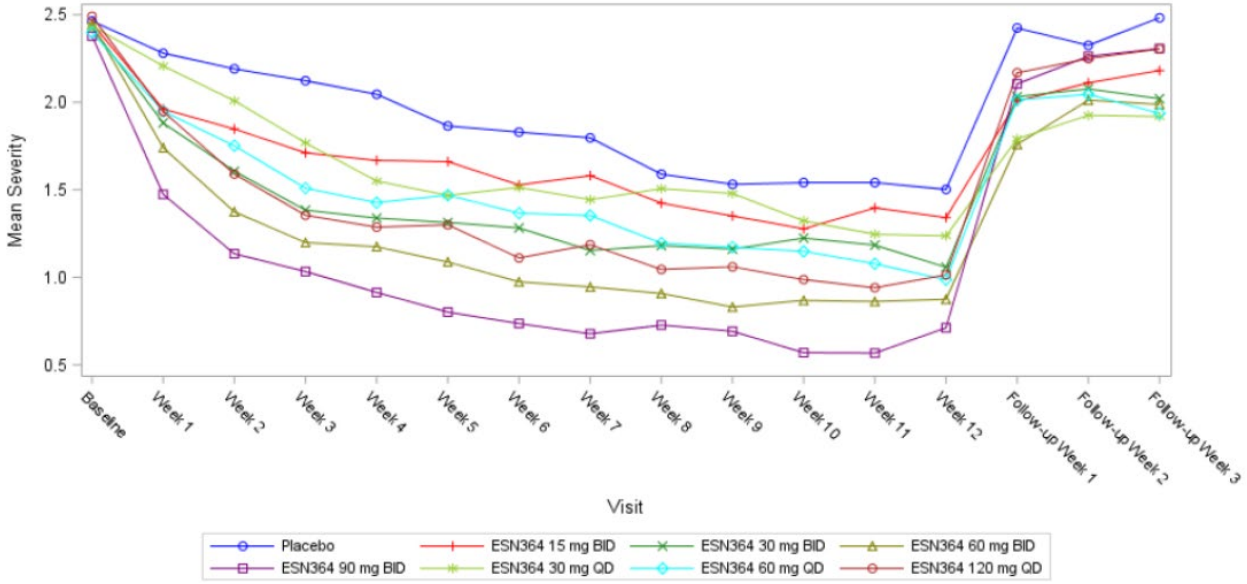
Table 7 Primary analysis of change in the mean severity of moderate and severe VMS per 24 h from Baseline to Week 4 and Week 12: FAS

Analysis Visit	Treatment Group	n	Change from Baseline	Difference from Placebo		
			LS Mean (SE)	LS Mean (SE)	95% CI	P-value
Week 4	Placebo (n = 43)	42	-0.3 (0.15)	NA	NA	NA
	ESN364 15 mg BID (n = 45)	40	-0.8 (0.14)	-0.5 (0.20)	(-0.84, -0.07)	0.0215 *
	ESN364 30 mg BID (n = 43)	41	-0.9 (0.15)	-0.6 (0.20)	(-1.01, -0.24)	0.0017 *
	ESN364 60 mg BID (n = 45)	40	-1.2 (0.14)	-0.8 (0.20)	(-1.21, -0.44)	< 0.0001 *
	ESN364 90 mg BID (n = 42)	37	-1.3 (0.15)	-1.0 (0.20)	(-1.37, -0.59)	< 0.0001 *
	ESN364 30 mg QD (n = 43)	40	-0.7 (0.15)	-0.4 (0.20)	(-0.81, -0.04)	0.0322 *
	ESN364 60 mg QD (n = 44)	43	-0.9 (0.14)	-0.6 (0.19)	(-0.99, -0.23)	0.0017 *
	ESN364 120 mg QD (n = 44)	42	-1.0 (0.15)	-0.7 (0.20)	(-1.08, -0.31)	0.0004 *
Week 12	Placebo (n = 43)	37	-0.8 (0.16)	NA	NA	NA
	ESN364 15 mg BID (n = 45)	38	-1.0 (0.15)	-0.3 (0.21)	(-0.67, 0.16)	0.2324
	ESN364 30 mg BID (n = 43)	37	-1.1 (0.16)	-0.4 (0.21)	(-0.80, 0.04)	0.0736
	ESN364 60 mg BID (n = 45)	31	-1.3 (0.16)	-0.6 (0.21)	(-0.98, -0.15)	0.0080 *
	ESN364 90 mg BID (n = 42)	31	-1.4 (0.17)	-0.6 (0.21)	(-1.07, -0.22)	0.0028 *
	ESN364 30 mg QD (n = 43)	33	-0.9 (0.16)	-0.2 (0.21)	(-0.58, 0.26)	0.4647
	ESN364 60 mg QD (n = 44)	36	-1.3 (0.15)	-0.5 (0.21)	(-0.92, -0.10)	0.0160 *
	ESN364 120 mg QD (n = 44)	36	-1.1 (0.16)	-0.4 (0.21)	(-0.78, 0.06)	0.0901

Subset of the safety analysis set who had a baseline and at least one postbaseline efficacy evaluation (FAS). Note: Baseline was the average severity of 24h vasomotor symptom from 7 non-missing days prior to day 1. The LS means, standard errors, confidence intervals, and P-values come from an ANCOVA model with change from baseline as the dependent variable and treatment group, pooled center, smoking status as factors and baseline measurement, baseline weight as covariates. For subjects in the efficacy analysis populations with missing primary efficacy endpoints, multiple imputation by fully conditional specification methods were used. VMS: vasomotor symptoms. NA: not applicable. * P-values from the model < 0.05.

All active doses reduced the mean severity of symptoms compared to placebo during all 12 weeks of active treatment (Figure 7). During follow-up weeks, when treatment was not administered, the severity of symptoms returned to near baseline levels.

Figure 7 Plot of weekly Mean Severity of Moderate and Severe VMS per 24 h: FAS



Secondary endpoints

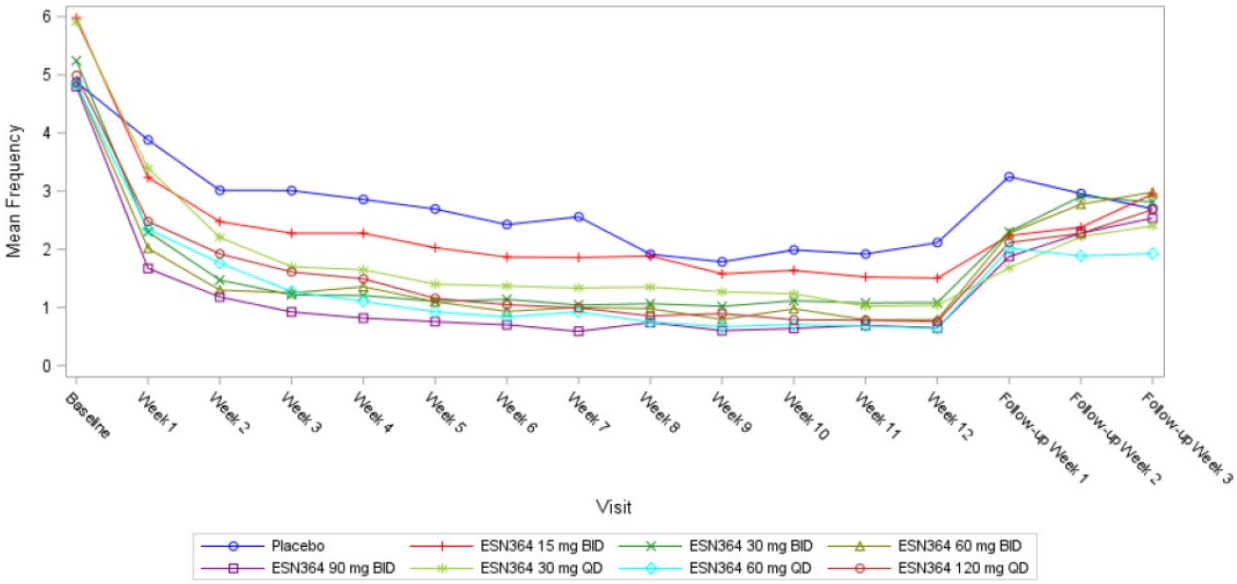
Secondary Analysis: Frequency of moderate to severe VMS change from baseline to week 4 and 12

All additional analyses (including examining the frequency and severity of symptoms at all weeks) broadly supported the primary analysis and demonstrated the reduction of VMS symptoms in patients treated with ESN364. Like the primary analysis, all doses were statistically significantly different from placebo at week 4 and week 12 for the change in the mean frequency of moderate and severe VMS. As with the primary analysis, the change was greater than placebo by at least 2 points, for all dose groups except 15 mg BID.

– *Frequency and severity of VMS by Diurnal Variation*

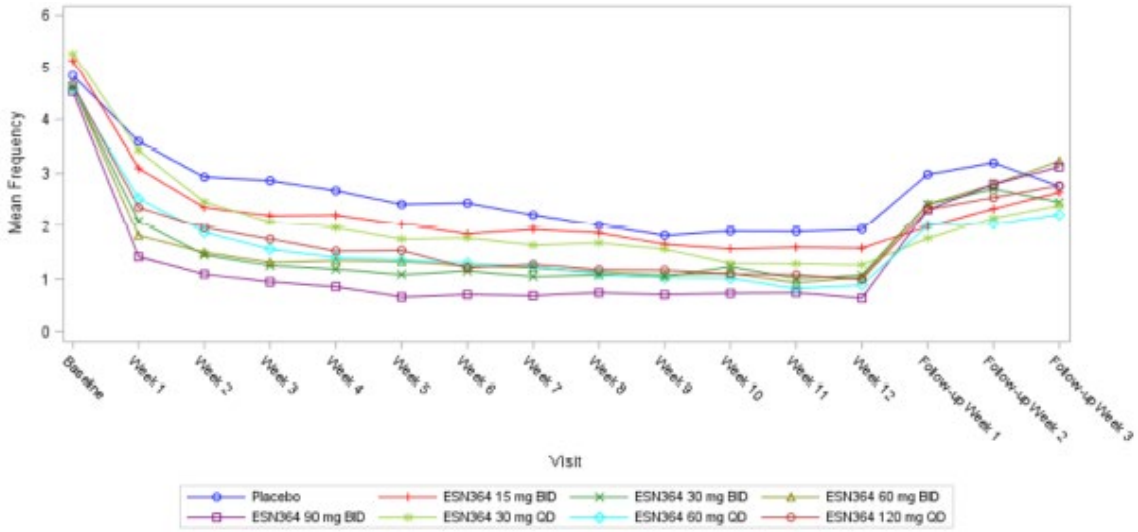
The plots of weekly mean frequency of moderate and severe VMS for daytime (Figure 8) and night time (Figure 9) support the primary analysis, as well as the plots of weekly mean severity. No dose-related or treatment-related diurnal trends are seen.

Figure 8 Plot of weekly mean frequency of moderate and severe VMS per 12h Day Time: FAS



Subset of the safety analysis set who had a baseline and at least one postbaseline efficacy evaluation (FAS). Note: The 12-hour day time VMS was between 08:00 and 19:59. Baseline was the average frequency of 12 h day-time vasomotor symptom from 7 non-missing days prior to prior to day 1. VMS: vasomotor symptoms.

Figure 9 Plot of weekly mean frequency of moderate and severe VMS per 12h night time: FAS



Subset of the safety analysis set who had a baseline and at least one postbaseline efficacy evaluation (FAS). Note: The 12 hour night time VMS was between 20:00 and 07:59 (next day). Baseline was the average frequency of 12 h night-time vasomotor symptom from 7 non-missing days prior to day 1. VMS: vasomotor symptoms.

Effect of Different Doses and Dosing Regimens of ESN364 on Responder Rates Using Variation of Responder Definitions

The number (and percentage) of patients with reductions in VMS per 24 hours by week showed a greater percentage of patients with relative and absolute decreases in the ESN364 groups than in the placebo group for mild, moderate and severe VMS as well as moderate and severe VMS.

– *Percent Reduction of VMS from Baseline to Each Study Week*

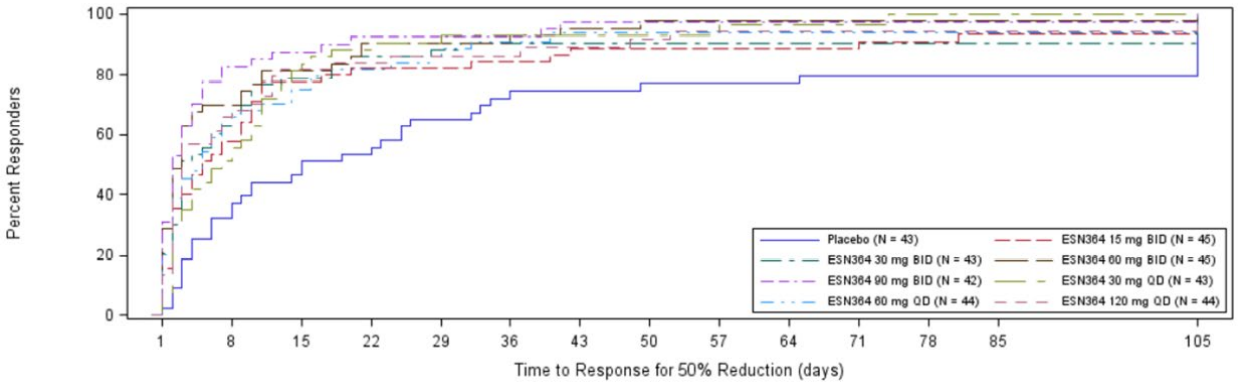
<u>50% reduction</u>

For patients with mild, moderate, or severe VMS, the odds of experiencing at least a 50% reduction in VMS frequency were significantly greater following treatment with ESN364 than placebo across all active treatment groups at week 4, except the 15 mg BID and 30 mg QD groups.

At week 12, the higher dose groups (60 mg BID, 90 mg BID, 60 mg QD, and 120 mg QD) performed better but there were no significant differences from placebo at the lower dose groups.

The mean time to achieve a 50% reduction in moderate and severe VMS symptoms was 15.1 days in the placebo group, and 2.2 to 8.4 days in the ESN364 groups. The Kaplan-Meier plot of time to 50% reduction is shown in Figure 10, which clearly demonstrates the rapid onset of effect in the ESN364 groups.

Figure 10 Kaplan-Meier Plot of Time to 50% Reduction Responders of Moderate and Severe VMS: FAS



Subset of the safety analysis set who had a baseline and at least one postbaseline efficacy evaluation (Full Analysis Set).
The time to response was the first day with at least 50% response. The censoring time was the number of days from first dosing date up to the last dosing date. For the non-responders it was censored at the end of treatment. The numbers at risk for each time point are presented in the source figure. VMS: vasomotor symptoms.

100% reduction

The odds of experiencing a 100% reduction in VMS frequency were significantly greater following treatment with ESN364 90 mg BID and 120 mg QD than placebo at week 4. At week 12, only the 90 mg BID treatment group showed a statistically significant difference from placebo in the odds of achieving a 100% reduction in VMS frequency. During the follow-up period there were no differences between placebo and the ESN364 treatment groups in the odds of achieving a 50%, 70%, or 90% reduction in VMS symptoms.

– *Absolute Reduction in moderate to severe VMS from Baseline to Each Study Week*

For patients with moderate, or severe VMS, the odds of experiencing an absolute reduction of at least 2 at week 4, was significantly higher in the ESN364 90 mg BID, 60 mg QD, and 120 mg QD groups than placebo. There was no statistically significant difference between the ESN364 treatment groups and placebo at week 12, or last week on treatment for the odds of experiencing a decrease of 2 in moderate or severe VMS.

– *Patient reported outcomes*

No consistent result was observed, however, for the GCS, the VMS domain scores were statistically significantly different from placebo ($P < 0.05$) for all doses at weeks 4, 8, and 12, with the exception of the ESN364 15 mg BID and 30 mg QD groups. With MENQoL the VMS domain score for ESN364 showed the greatest LS mean difference from placebo of all the domains. Statistically significant and clinically meaningful reductions in VMS domain scores were observed with ESN364 30, 60, and 90 mg BID as well as 120 mg QD versus placebo at weeks 4 and 12. Specifically, 60 mg QD showed a

statistically significant and clinically meaningful reduction vs placebo at week 12. For the HFRDIS, most active treatment groups were statistically different from placebo at week 4 and the highest dose groups (60 mg BID, 90 mg BID, and 120 mg QD) retained this significant difference at week 12.

Safety

– *Adverse Events*

The overall incidence of TEAEs was comparable between placebo and each ESN364 treatment groups.

The most common TEAEs (≥ 10%) by MedDRA SOC were: gastrointestinal disorders, infections and infestations, general disorders and administration site conditions, investigations, nervous system disorders, respiratory, thoracic and mediastinal disorders, and skin and subcutaneous tissue disorders.

The most common TEAEs (≥ 5%) drug-related in any treatment group were diarrhoea (3 patients [6.7%] in the ESN364 60 mg QD group) and headache (3 patients [6.7%] in the ESN364 60 mg QD group; 3 patients [6.8%] in the 120 mg QD group).

Five patients reported severe TEAEs: liver function test increased, adjustment disorder with depressed mood, cholelithiasis and drug-induced liver injury, and retinal detachment [see Table below]. The events of drug-induced liver injury, and liver function test increased were considered by the investigator to be drug-related.

There was 1 serious TEAE of squamous cell carcinoma of the skin, but this was not considered related to the study drug.

No PT was the cause for discontinuation in more than 1 patient in any treatment group. However, 5 patients, in the 60 and 90 mg BID, and 60 and 120 mg QD dose groups discontinued due to changes in liver enzymes. The majority of TEAEs leading to discontinuation were considered to be related to the study drug by the investigator.

Potential DILI

Data is based on the investigator's assessment as recorded in the eCRF, see Table 8 below. The 5 patients who had TEAEs associated with elevated liver enzymes were in the ESN364 groups.

Table 8 Treatment-Emergent Adverse Events of Drug-Induced Liver Injury: SAF

System Organ Class Preferred Term	Placebo (n = 43)	ESN364 BID				ESN364 QD		
		15 mg (n = 45)	30 mg (n = 43)	60 mg (n = 45)	90 mg (n = 44)	30 mg (n = 43)	60 mg (n = 45)	120 mg (n = 44)
Overall	0	0	0	2 (4.4%)	1 (2.3%)	0	1 (2.2%)	1 (2.3 %)
Hepatobiliary disorders	0	0	0	0	0	0	1 (2.2%)	0
Drug-induced liver injury	0	0	0	0	0	0	1 (2.2%)	0
Investigations	0	0	0	2 (4.4%)	1 (2.3%)	0	0	1 (2.3 %)
Hepatic enzyme increased	0	0	0	1 (2.2%)	0	0	0	1 (2.3 %)
Alanine aminotransferase increased	0	0	0	1 (2.2%)	0	0	0	0
Aspartate aminotransferase increased	0	0	0	1 (2.2%)	0	0	0	0
Liver function test increased	0	0	0	0	1 (2.3%)	0	0	0

All enrolled subjects who received the study drug (Safety Analysis Set, SAF). Number of subjects and percentage of subjects (%) are shown. Sorting order: ascending order by System Organ Class Code and descending by the total number of subjects by Preferred Term. In case of ties, ascending order by Preferred Term Code is applied.

Adverse Events of Special Interest

A total of 8 patients had TEAEs of special interest, one patient with oral paraesthesia (in the 30 mg BID group) and a few isolated cases of uterine bleeding with no reports of endometrial hyperplasia.

Increase transaminase ALT or AST > 3 × ULN

There were 9 patients with ALT or AST > 3 × ULN. Of these, 3 patients had ALT or AST > 8 × ULN (60 mg BID, 90 mg BID, and 60 mg QD). There were no cases of total bilirubin > 2 × ULN, and consequently no Hy's law cases. A total of 5 patients discontinued due to changes in liver enzymes following ESN364. Elevated aminotransferase levels > 3 × ULN of brief duration without a corresponding elevation in total bilirubin have been seen in association with studies of ESN364. None of these elevations have been associated with evidence of liver functional impairment or liver associated symptoms. Elevations seen in this study were transient irrespective whether the study drug was stopped or not and generally occurred within a window of 4 to 8 weeks of treatment. For 2 unblinded cases, the investigator and liver experts considered the elevated aminotransferases to be probably related to study drug, although there was evidence of underlying hepatic conditions in both patients that could potentially confound the interpretation of these enzyme changes.

Other safety related observations

There were small, non-dose-related, clinically insignificant changes in bone turnover marker concentrations during the study, with no differences from placebo.

There was no increase in endometrial thickness compared with placebo. There were no shifts to abnormal, clinically significant in endometrial biopsy results.

Endometrial biopsies were performed and assessed centrally by a blinded pathologist, with assessment by 2 additional pathologists in the event that hyperplasia was indicated. No patients had a clinically significant endometrial biopsy finding.

For further safety aspects please see section on 'Clinical Safety'.

Rationale for dose selection for the phase 3 clinical trials

Based on results from the above-described phase 2b dose-ranging study (Study ESN364_HF_205), fezolinetant demonstrated clinically relevant and significant improvement in VMS frequency and severity and remained safe and tolerable from doses of 15 mg bid to 120 mg qd.

Dose- and concentration-response models were developed to further support selection of doses for future phase 3 clinical trials. Both the dose-response [MCP-MOD] and concentration-response (nonlinear mixed-effects models) analyses demonstrated increased improvements in VMS frequency and VMS severity with increasing fezolinetant exposure. Consistent with the observed data from Study ESN364_HF_205, no clinically relevant difference was noted between predicted efficacy (frequency or severity) for the qd and bid treatment groups given the same total daily dose. Model predictions indicated a mean placebo-corrected change from baseline reduction in VMS frequency of -1.74 and -1.95 for the 30 mg qd and 45 mg qd doses, respectively, at week 12 with a mean baseline of 9.5 VMS per day. At a higher mean baseline of 11.5 VMS per day, the historical mean baseline observed in moderate/severe VMS patients, the mean predicted placebo-corrected change from baseline reduction in VMS frequency for 30 mg and 45 mg qd doses is -2.11 and -2.37, respectively, at week 12. For VMS severity based on the moderate to severe VMS, the model predicted placebo-corrected change from baseline for 30 mg and 45 mg qd doses was -0.34 and -0.41, respectively, at week 12.

In addition to the dose- and exposure-response analyses, a mechanistic, mathematical model of drug-induced liver injury was used to better characterize and understand the increase in transaminases noted for 9 participants in Study ESN364_HF_205. A PBPK model was established to simulate fezolinetant and ES259564 concentrations in plasma and in the liver. The in vitro assay results were incorporated into a representation of fezolinetant and ES259564 effects in the software. Fezolinetant was simulated at clinically relevant doses in a human simulated population sample representing variability in exposure and toxicity pathway parameters. ALT elevations were predicted to be dose-dependent. The phase 3 doses, 30 mg qd and 45 mg qd, were selected with minimal risk of ALT elevation. Reduced hepatotoxicity was predicted with clinical monitoring (i.e. dosing stopped if ALT > 8 x ULN, with weekly monitoring). The model predicted that both parent and metabolite contributed to the simulated hepatotoxicity with the parent being slightly more potent than the metabolite.

Based on the phase 2 clinical efficacy and safety results and modelling and simulation analyses, the 30 mg qd dosing regimen was considered the lowest effective dose. In addition, a 45 mg qd dose, while not previously studied, was predicted to increase the probability of achieving efficacy endpoints while limiting the risk of potential exposure related transaminase elevations.

2.6.5.2. Main studies

Two pivotal phase 3 studies 2693-CL-0301 (SKYLIGHT 1) and 2693-CL-0302 (SKYLIGHT 2) were submitted. Of note, these studies are identical.

Study 2693-CL-0301 (SKYLIGHT 1)

Study design

Study 2693-CL-0301 (SKYLIGHT 1) was a phase 3, randomized, placebo-controlled, 12-week double-blind study, followed by a non-controlled extension treatment period of 40 weeks, to assess the efficacy and safety of fezolinetant in women suffering from moderate to severe vasomotor symptoms associated with menopause. The study was conducted in the US, Canada and Europe from July 2019 to August 2021. The study design is presented below [Figure].

Approximately 450 participants were planned to be enrolled into this study, with 150 participants per treatment arm:

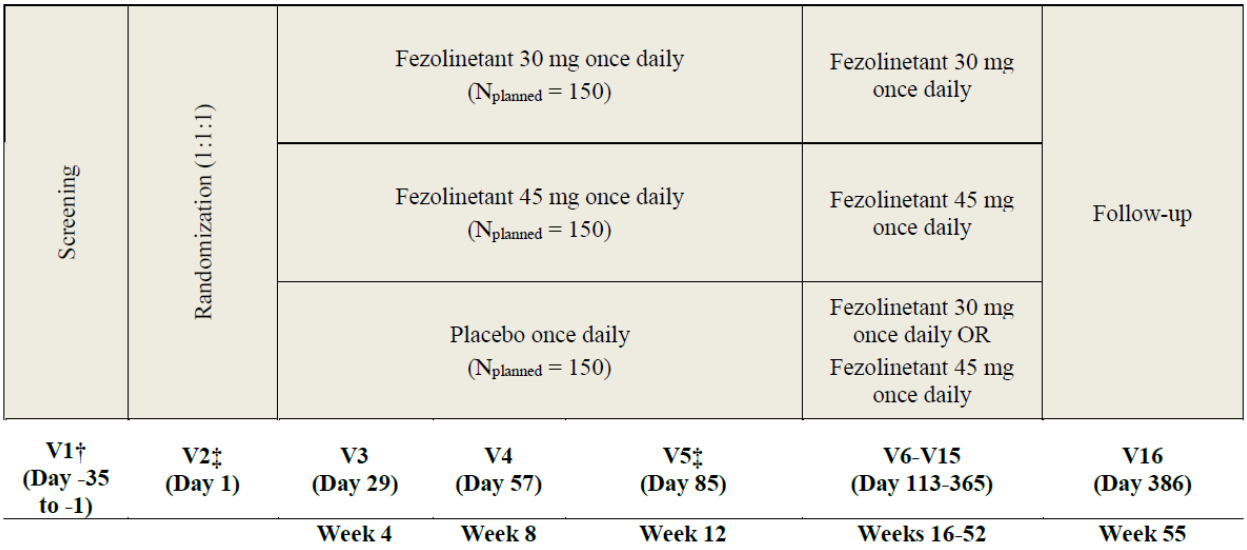
- Fezolinetant 30 mg tablets once daily
- Fezolinetant 45 mg tablets once daily
- Placebo tablets once daily

The first 12 weeks of the study were randomized, double-blinded and placebo-controlled and participants were randomized to placebo, fezolinetant 30 mg or fezolinetant 45 mg. Participants were randomized in a 1:1:1 ratio to a treatment group according to the randomization schedules and stratified by smoking status (active smoker or non-smoker). After completing 12 weeks of treatment, participants on placebo were re-randomized in a 1:1 ratio to 30 mg or 45 mg of fezolinetant in the active treatment extension period (i.e., extension period without placebo control) through end of study. Participants who were already randomized on an active group continued on their assigned dose for the remaining 40 weeks of treatment. Following the completion (or ED) of the treatment period

(week 52), participants were to complete an EOT (or ED) visit and final safety follow-up visit 3 weeks after the last dose of study intervention was administered (week 55).

The study consisted of a screening period (days -35 to -1, including the screening visit (i.e. visit 1) and collection of VMS frequency and severity assessments) and a 52-week treatment period (day 1 (i.e. visit 2) to week 52 (visit 15)) (Figure 11). The study was performed on an outpatient basis.

Figure 11 Study scheme



N: number; V: visit. † Screening was to be performed up to 35 days prior to randomization, with a minimum of 10 days to allow for baseline data collection of VMS frequency and severity.

Methods

- **Study Participants**

The patient population for this study is women ≥ 40 years and ≤ 65 years of age with moderate to severe VMS (⩾ 50/week) associated with menopause.

Inclusion criteria

Subject who meets all of the following criteria will be eligible to participate in the study:

- Institutional Review Board (IRB)/Independent Ethics Committee (IEC)-approved written informed consent and privacy language as per national regulations must be obtained from the subject or legally authorized representative prior to any study-related procedures (including withdrawal of prohibited medication, if applicable).
- Subject is born female, aged ≥ 40 years and ≤ 65 years of age at the screening visit.
- Subject has a body mass index between 18 kg/m^2 to 38 kg/m^2 (extremes included).
- Subject must be seeking treatment or relief for VMS associated with menopause and confirmed as menopausal per 1 of the following criteria at the screening visit:
    - Spontaneous amenorrhea for ≥ 12 consecutive months
    - Spontaneous amenorrhea for ≥ 6 months with biochemical criteria of menopause (FSH > 40 IU/L); or

    - Having had bilateral oophorectomy ≥ 6 weeks prior to the screening visit (with or without hysterectomy).

- Within the 10 days prior to randomization, subject must have a minimum average of 7 to 8 moderate to severe HFs (VMS) per day, or 50 to 60 per week.
- Subject is in good general health as determined on the basis of medical history and general physical examination, including a bimanual clinical pelvic examination and clinical breast examination devoid of relevant clinical findings, performed at the screening visit; haematology and biochemistry parameters, pulse rate and/or blood pressure and ECG within the reference range for the population studied, or showing no clinically relevant deviations, as judged by the investigator.
- Subject has documentation of a normal/negative or no clinically significant findings mammogram (obtained at screening or within the prior 9 months of study enrolment).
- Subject is willing to undergo a TVU to evaluate the uterus and ovaries at screening and at week 52 (EOT), and for subjects who are withdrawn from the study prior to completion, a TVU at the ET visit. This is not required for subjects who have had a partial (supracervical) or full hysterectomy.
- Subject is willing to undergo an endometrial biopsy at screening and at week 52 (EOT), for subjects with uterine bleeding, and for subjects who are withdrawn from the study prior to completion. This is not required for subjects who have had a partial (supracervical) or full hysterectomy.
- Subject has documentation of a normal or not clinically significant Pap test (or equivalent cervical cytology) in the opinion of the investigator within the previous 9 months or at screening.
- Subject has a negative urine pregnancy test at screening.
- Subject has a negative serology panel (including hepatitis B surface antigen, hepatitis C virus antibody and human immunodeficiency virus antibody screens).
- Subject agrees not to participate in another interventional study while participating in the present study.

Exclusion criteria

Subject who meets any of the following criteria will be excluded from participation in the study:

- Subject uses a prohibited therapy (strong or moderate CYP1A2 inhibitors, HRT, hormonal contraceptive or any treatment for VMS [prescription, over the counter or herbal]) or is not willing to wash out and discontinue use of such drugs for the full duration of study conduct.
- Subject has known substance abuse or alcohol addiction within 6 months of screening, as assessed by the investigator.
- Subject has previous or current history of a malignant tumour, except for basal cell carcinoma.
- Subject has uncontrolled hypertension as assessed by the investigator.
- Subject has history of severe allergy, hypersensitivity or intolerance to drugs in general, including the study drug and any of its excipients.
- For subjects with a uterus: Subject has an unacceptable result from the TVU assessment at screening (i.e., full length of endometrial cavity cannot be visualized or presence of a clinically significant finding).
- For subjects with a uterus: Subject has an endometrial biopsy confirming presence of endometrial hyperplasia, endometrial cancer or other clinically significant findings in the opinion of the

investigator at screening. A biopsy with insufficient material for evaluation is acceptable provided the endometrial thickness is no greater than 4 mm.

- Subject has a history within the last 6 months of undiagnosed uterine bleeding.
- Subject has a history of seizures or other convulsive disorders.
- Subject has a medical condition or chronic disease (including history of neurological [including cognitive], hepatic, renal, cardiovascular, gastrointestinal, pulmonary [e.g., moderate asthma], endocrine or gynaecological disease) or malignancy that could confound interpretation of the study outcome in the opinion of the investigator.
- Subject has active liver disease, jaundice or elevated liver function tests > 1.5 times the ULN including ALT, AST, TBL, alkaline phosphatase or lactate dehydrogenase (LDH).
- Subject has creatinine > 1.5 × ULN; or estimated glomerular filtration rate (eGFR) using the Modification of Diet in Renal Disease formula ≤ 59 mL/min per 1.73 m^2 at screening.
- Subject has a history of suicide attempt or suicidal behaviour within the last 12 months or has suicidal ideation within the last 12 months (a response of "yes" to question 4 or 5 on the suicidal ideation portion of the Columbia Suicide Severity Rating Scale [C-SSRS]), or who is at significant risk to commit suicide, as assessed by the investigator at screening and at visit 2 (randomization).
- Subject has had previous exposure with fezolinetant.
- Subject is participating concurrently in another interventional study or participated in an interventional study within 28 days prior to screening or received any investigational drug within 28 days or within 5 half-lives prior to screening, whichever is longer.
- Subject is unable or unwilling to complete the study procedures.
- Subject or relative is the investigator or other site staff directly involved in the conduct of the study.
- Subject is an employee of Astellas.
- Subject has any condition, which in the investigator's opinion, makes the subject unsuitable for study participation.

- **Treatments**

Study drug

Fezolinetant study drug was supplied in a blinded form by the applicant as fezolinetant 30 mg and 15 mg once daily tablets.

Comparative drug

Placebo was supplied by the applicant in a blinded form to match the active fezolinetant drug tablets.

- **Objectives**

The study objectives pertaining to the 12-week double-blind treatment period assessed efficacy and safety of fezolinetant vs placebo. In addition, the effect of fezolinetant was described up to 24 weeks for the active treatment extension period without a placebo control. The safety of fezolinetant was assessed throughout the 52-week period.

Primary objective

- To evaluate the efficacy of fezolinetant vs placebo on the frequency and severity of moderate to severe VMS.
    - The estimand of the primary objective used a hypothetical strategy and compared participants as though they had continued on the assigned treatment.

Key secondary objective

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

Secondary objectives

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

Exploratory objectives

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

- **Outcomes/endpoints**

Co-primary endpoints

The primary efficacy objective required the evaluation of 4 co-primary endpoints:

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

Key secondary endpoint

The key secondary efficacy objective examined the effect of fezolinetant vs placebo on the following:

- Mean change in the PROMIS SD SF 8b total score from baseline to week 12

Secondary endpoints

The secondary efficacy objectives examined the effect of fezolinetant vs placebo on the following:

- Mean change in the frequency of moderate to severe VMS from baseline to each week up to week 12
- Mean change in the severity of moderate to severe VMS from baseline to each week up to week 12

- Mean percent reduction in the frequency of moderate to severe VMS from baseline to each week up to week 12
- Percent reduction ⩾ 50% and at 100% in the frequency of moderate to severe VMS from baseline to each week up to week 12
- Score on the PGI-C VMS at each visit

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

- Mean change in the frequency of moderate to severe VMS from baseline to week 24 (descriptive)
- Mean change in the severity of moderate to severe VMS from baseline to week 24 (descriptive)

Exploratory endpoints

- Mean change in the frequency of mild, moderate to severe VMS from baseline to each week up to week 12
- Mean change in the severity of mild, moderate to severe VMS from baseline to each week up to week 12
- Mean percent reduction in the frequency of mild, moderate to severe VMS from baseline to each week up to week 12
- Percent reduction ⩾ 75% and ⩾ 90% in the frequency of moderate to severe VMS from baseline to each week up to week 12 (VMS responder)
- Percent reduction ⩾ 50%, ⩾ 75%, ⩾ 90% and at 100% in the frequency of mild, moderate to severe VMS from baseline to each week up to week 12 (VMS responder)
- Mean change in the frequency and severity of moderate to severe VMS from baseline to each visit in the active treatment extension period and the follow-up visit
- Change in serum concentrations of sex hormones and SHBG from baseline to each visit
- Mean change in serum concentrations of BSAP, P1NP and CTX from baseline to each visit
- Plasma concentrations of fezolinetant and metabolite ES259564 at prespecified time points
- Mean change on the PROMIS SD SF 8b total score from baseline to each visit
- Mean change on the PROMIS SRI SF 8a total score from baseline to each visit
- Score on PGI-S SD at each visit
- Score on PGI-C SD at each visit
- Mean change on the MENQOL total score from baseline to each visit
- Mean change on the MENQOL domain scores from baseline to each visit
- Mean change on the EQ-5D-5L total score and VAS from baseline to each visit
- Mean change on the WPAI-VMS domain scores from baseline to each visit
- Mean change in the severity of moderate to severe VMS from baseline to each week up to week 12 (excluding mild events postbaseline)
- Mean and mean change from baseline in the daily frequency of moderate to severe VMS for the first week

NOTE: Assessments after the 12-week placebo-controlled period were descriptive only because there was no placebo control.

Safety endpoints

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

- Frequency and severity of AEs
- TVUs and endometrial biopsy findings
- Change from baseline to each time point in vital signs: sitting systolic and diastolic BP and pulse rate
- Change from baseline to each time point in ECG parameters
- Change from baseline to each time point in laboratory tests: haematology, biochemistry and urinalysis

Clearly defined primary and secondary outcome measures and, when applicable, any methods used to enhance the quality of measurements (e.g., multiple observations, training of assessors, central/independent reviews).

- **Sample size**

A total of 450 subjects were planned to be randomized; 150 subjects in each treatment arm. In the phase 2b dose-ranging study, the observed least-squares mean difference between fezolinetant and placebo in change from baseline to week 12 (and week 4) in mean daily frequency of moderate to severe VMS ranged from -1.8 to -3.0 and for change in mean severity of moderate to severe VMS, the observed mean treatment differences ranged from -0.2 and -1.0. For a pairwise comparison using a 2-sample t-test at a 2-sided 2.5% alpha (adjusting for 2 active doses), 120 subjects per arm would provide 79% or more power to detect an effect size of -2.0 in mean daily frequency or more assuming a SD of 5 and -0.40 in mean severity or more. Assuming approximately 20% of subjects discontinue prematurely, the number of subjects will be increased from 120 to 150 subjects per arm.

- **Randomisation and Blinding (masking)**

Subjects were randomized in a 1:1:1 ratio to a double-blind treatment arm according to the randomization schedules and stratified by smoking status (active smoker or non-smoker) through IRT. The first 12 weeks of the study were double blind. Subjects were randomized to receive fezolinetant or placebo in a blinded fashion such that the investigator, sponsor's study management team, clinical staff, nor the subject will know which agent is being administered. Subjects who completed the 12-week treatment period and received placebo were randomized to either fezolinetant 30 mg or 45 mg. The extension period remained blinded to the site personnel and participating subjects.

- **Statistical methods**

The full analysis set (FAS) consisted of all subjects who were randomized and received at least 1 dose of study drug, regardless of the treatment received. This was the primary analysis set for efficacy analyses. The per protocol set (PPS) consisted of the subset of the FAS who did not meet criteria for PPS exclusion. The safety analysis set (SAF) consisted of all randomized subjects who took at least 1 dose of study drug, a subject was assigned to the treatment group received as first dose.

All statistical comparisons were conducted using 2-sided tests at the α = 0.05 significance level unless specifically stated otherwise. All null hypotheses were of no treatment difference.

For each of the 4 co-primary efficacy endpoints, a mixed models repeated measures analysis of covariance (MMRM) was used with treatment group, week and smoking status (current vs former/never) as factors, with baseline weight and baseline measurement as covariates, as well as an interaction of treatment by week and an interaction of baseline measurement by week. An unstructured covariance structure was used to model the within-patient errors. MMRM used all available on-treatment data to inform mean treatment effect estimates without requiring explicit imputation for missing data (i.e., for discontinued subjects). This approach is consistent with the hypothetical strategy used for the estimand, which is to compare patients as though they had continued on the assigned treatment. Comparisons between the fezolinetant and placebo were calculated based on least-squares mean contrasts using a 2-tailed 95% confidence interval (CI).

Frequency of moderate or severe VMS events were calculated as the sum of moderate or severe VMS events per day. Severity of post-baseline co-primary severity endpoints were calculated using a weighted average defined as shown below:

> *([number of mild hot flashes/day × 1] + [number of moderate hot flashes/day × 2] + [number of severe hot flashes/day × 3])/total number of daily (or weekly) mild/moderate/severe hot flashes*

The family-wise type I error rate for the 2 active dose groups compared to placebo for the 4 co-primary efficacy endpoints was controlled using a Hochberg approach. All 4 co-primary endpoints had to be statistically significant for a given dose to be considered successful. The trial was to be considered successful if at least one dose is statistically significant. If all the co-primary endpoints were statistically significant at both doses, then the 5% alpha was passed to the key secondary endpoint as part of the family-wise error rate.

Sensitivity analyses were carried out for the co-primary efficacy endpoints based on the PPS populations. The analysis for each of the co-primary endpoints also was conducted using a simplified MMRM model with treatment group and week as factors, with baseline measurement as a covariate, as well as an interaction of treatment by week and baseline by week. Furthermore, discontinuation-reason based multiple imputation (MI) will be used to examine the sensitivity of the primary analysis results to departures from the missing at random assumption by using "Jump to Reference" MI, assuming data is missing not at random for subjects who discontinue early.

The PROMIS SD SF 8b scale was analysed using MMRM, similar to the primary analysis of the co-primary endpoints. For each of the binary secondary responder endpoints, logistic regression was used for the analysis. A missing value was imputed as a non-responder. PGI-C was analysed using Cochran Mantel Haenszel test.

No formal interim analysis was planned for this study.

Results

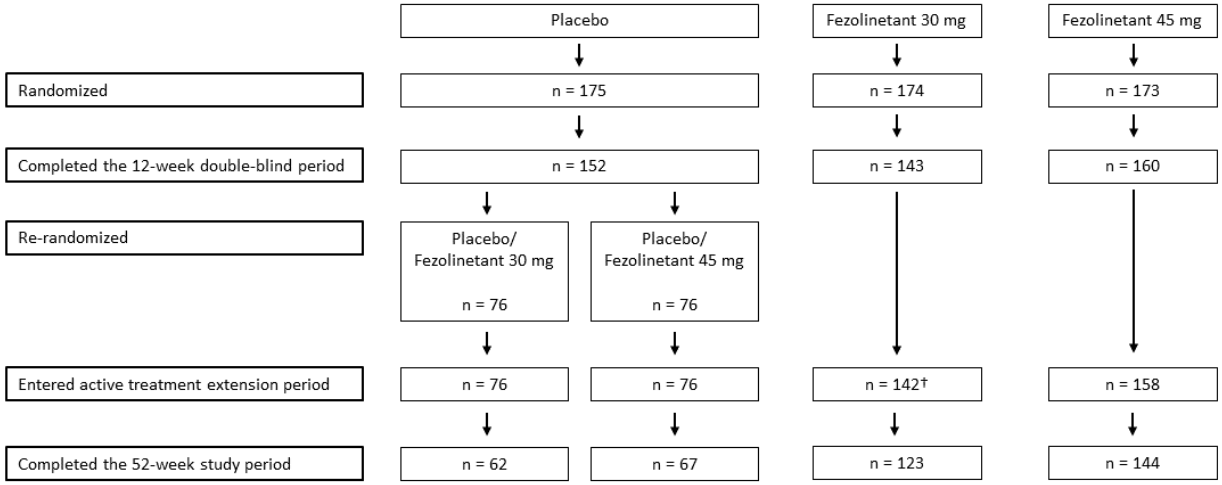
- **Participant flow**

A total of 527 participants were randomized: 175 participants in the placebo group, 176 in the fezolinetant 30 mg group and 176 in the fezolinetant 45 mg group. Of those, 522 took the study intervention: 175 participants in the placebo group, 173 in the fezolinetant 30 mg group and 174 in the fezolinetant 45 mg group. A total of 455 participants completed the 12-week double-blind period

[Figure 12 and Table 9]. Of these participants, 452 participants entered the active treatment extension period; 396 participants completed the 52-week period.

The most common reason for withdrawal of treatment was "withdrawal by subject" (4.8%) during the 12-week double-blind period and the 52-week period (10.2%). Overall, there were no important differences in frequencies of reason for withdrawal between treatment groups.

Figure 12 Treatment disposition (safety analysis set)



All randomized participants who took at least 1 dose of study intervention (Safety Analysis Set). † One participant who was randomized to fezolinetant 45 mg received fezolinetant 30 mg during the 12-week study period. Therefore, this participant is included in the fezolinetant 30 mg group for the Safety Analysis Set and in the fezolinetant 45 mg group for the Full Analysis Set per the prespecified analysis set definition.

- **Recruitment**

A total of 2205 unique participants signed informed consent and were screened, of which 1678 participants failed screening. The main reasons for screening failure were related to the following entry criteria: participant must have had 7 to 8 moderate to severe VMS, participant unable or unwilling to complete the study procedures and participant with BP levels above protocol-specified. A total of 21 participants failed screening due to endometrial abnormalities detected by TVU or biopsy.

- **Baseline data**

Demographics and Baseline Characteristics

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

Table 9 Demographic and Selected Baseline Characteristics (Safety Analysis Set)

Parameter	Category/Statistic	Placebo (n = 175)	Fezolinetant 30 mg (n = 174)	Fezolinetant 45 mg (n = 173)	Total (n = 522)
Age (years)	N	175	174	173	522
	Mean (SD)	54.7 (4.8)	54.2 (4.9)	54.2 (5.1)	54.4 (4.9)
	Median	54.0	53.5	54.0	54.0
	Min, Max	41, 65	42, 65	40, 65	40, 65
Age category	< 55 years	91 (52.0%)	93 (53.4%)	97 (56.1%)	281 (53.8%)
	≥ 55 years	84 (48.0%)	81 (46.6%)	76 (43.9%)	241 (46.2%)
Race	White	142 (81.1%)	148 (85.5%)	141 (81.5%)	431 (82.7%)
	Black or African American	28 (16.0%)	21 (12.1%)	26 (15.0%)	75 (14.4%)
	American Indian or Alaska Native	2 (1.1%)	0	1 (0.6%)	3 (0.6%)
	Asian	3 (1.7%)	3 (1.7%)	3 (1.7%)	9 (1.7%)
	More Than One Race	0	1 (0.6%)	1 (0.6%)	2 (0.4%)
	Missing	0	1	0	1
Ethnicity	Hispanic or Latino	46 (26.4%)	43 (24.7%)	47 (27.2%)	136 (26.1%)
	Not Hispanic or Latino	128 (73.6%)	131 (75.3%)	126 (72.8%)	385 (73.9%)
	Missing	1	0	0	1

Parameter	Category/Statistic	Placebo (n = 175)	Fezolinetant 30 mg (n = 174)	Fezolinetant 45 mg (n = 173)	Total (n = 522)
Weight (kg)	n	175	174	173	522
	Mean (SD)	74.41 (12.14)	75.24 (14.07)	75.50 (12.66)	75.05 (12.97)
	Median	73.60	74.20	74.30	73.85
	Min, Max				
BMI (kg/m^2)	n	175	174	172	521
	Mean (SD)	28.19 (4.28)	28.14 (4.83)	28.28 (4.35)	28.20 (4.49)
	Median	28.23	27.90	27.87	27.96
	Min, Max	18.8, 37.7	18.0, 37.8	18.4, 37.9	18.0, 37.9
BMI category (kg/m^2)	< 18.5	0	1 (0.6%)	1 (0.6%)	2 (0.4%)
	≥ 18.5 to < 25	44 (25.1%)	50 (28.7%)	40 (23.3%)	134 (25.7%)
	≥ 25 to < 30	71 (40.6%)	60 (34.5%)	79 (45.9%)	210 (40.3%)
	≥ 30	60 (34.3%)	63 (36.2%)	52 (30.2%)	175 (33.6%)
	Missing	0	0	1	1
Smoking status stratification factor†	Current	22 (12.6%)	22 (12.6%)	22 (12.7%)	66 (12.6%)
	Former/never	153 (87.4%)	152 (87.4%)	151 (87.3%)	456 (87.4%)
Prior hormone replacement therapy	Yes	33 (19.4%)	31 (18.0%)	30 (17.9%)	94 (18.4%)
	No	137 (80.6%)	141 (82.0%)	138 (82.1%)	416 (81.6%)
	Missing	5	2	5	12

All randomized participants who took at least 1 dose of study intervention (Safety Analysis Set). The participant population for this study consisted of female individuals as per inclusion criteria. BMI: body mass index (weight [kg]/height [m2]); Max: maximum; Min: minimum; NC: not calculated. † Current vs former or never smoking status was a stratification factor for randomization.

Medical history

The frequency of medical history items was balanced across treatment groups. Frequently reported medical history included hypertension (21.8%), seasonal allergy (12.1%), GERD (11.9%), uterine leiomyoma (11.9%), caesarean section (11.9%), hyperthyroidism (10.5%) and female sterilization (10.2%). A total of 32.2% participants with hysterectomy and 21.5% with oophorectomy enrolled into this study; the proportion of participants with hysterectomy or oophorectomy was similar across treatment groups.

- **Numbers analysed**

Of the 527 participants randomized in this study, 522 took at least 1 dose of study intervention and were included in the Safety Analysis Set (SAF) and Full Analysis Set (FAS), and 5 participants did not take the study intervention (Table 10). A total of 499 participants took at least 1 dose of fezolinetant during either the 12-week double-blind or active treatment extension periods and were included in the SAF, Fezolinetant and FAS, Fezolinetant.

Table 10 Participant classification (all randomized participants)

Analysis Set	Placebo (n = 175)	Fezolinetant 30 mg (n = 176)	Fezolinetant 45 mg (n = 176)	Total (n = 527)
12-week Double-blind Period				
Safety analysis set†	175 (100.0%)	174 (98.9%)	173 (98.3%)	522 (99.1%)
Full analysis set‡	175 (100.0%)	173 (98.3%)	174 (98.9%)	522 (99.1%)

Analysis Set	Placebo/ Fezolinetant 30 mg (n = 76)	Placebo/ Fezolinetant 45 mg (n = 76)	Fezolinetant 30 mg (n = 176)	Fezolinetant 45 mg (n = 176)	Total (n = 504)
52-week Period					
Safety analysis set§	76 (100.0%)	76 (100.0%)	174 (98.9%)	173 (98.3%)	499 (99.0%)
Full analysis set§	76 (100.0%)	76 (100.0%)	173 (98.3%)	174 (98.9%)	499 (99.0%)

Participants on placebo were re-randomized to 30 mg or 45 mg of fezolinetant in the active treatment extension period. FAS: full analysis set. † All randomized participants who took at least 1 dose of study intervention. A participant erroneously receiving a treatment different from their randomized treatment was assigned to the treatment group that the participant received as first dose. ‡ All participants who were randomized and received at least 1 dose of study intervention. The randomized treatment for each participant was used for summaries by treatment group based on the FAS, even if a participant erroneously received a different treatment. § All participants who were randomized and received at least 1 dose of fezolinetant during either the 12-week double-blind period or the active treatment extension periods. ¶All randomized participants from the FAS who were treated according to the protocol without any major deviations at week 12 endpoint. Reasons for exclusion from PPS12 included: no measurement of the primary efficacy endpoint available at week 12; < 85% interactive diary compliance during the 12-week treatment period; treatment compliance less than or equal to 85% between randomization and week 12. ††All participants who were randomized and received at least 1 dose of fezolinetant during either the 12-week double-blind or the active treatment extension periods.

- **Outcomes and estimation**

Co-primary efficacy endpoints

Primary analysis: frequency and severity of moderate to severe vasomotor symptoms, change from baseline to weeks 4 and 12

All 4 co-primary endpoints were met in both fezolinetant groups (30 mg and 45 mg). Participants treated with fezolinetant 30 mg and 45 mg had statistically significant reductions in the frequency of moderate to severe VMS from baseline to weeks 4 and 12, relative to placebo (Table 11).

Table 11 Primary analysis of co-primary endpoints: change from baseline in mean frequency of moderate to severe vasomotor symptoms per 24 h (full analysis set); 12-week double-blind period

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

All participants who were randomized and received at least 1 dose of study intervention (Full Analysis Set). The LS means, SE, CI, and P values come from a MMRM analysis of covariance model with change from baseline as the dependent variable and treatment group, week and smoking status (current vs former/never) as factors, with baseline measurement and baseline weight as covariates, as well as an interaction of treatment by week and an interaction of baseline measurement by week. CI: confidence interval; LS: least squares; Max: maximum; Min: minimum; MMRM: mixed model repeated measurements; NA: not applicable. † A negative change indicated a reduction/improvement from baseline (i.e., a favourable outcome). ‡ Differences were calculated by subtracting the LS mean of placebo group from the LS mean of fezolinetant group. § P value is for comparison of fezolinetant with placebo from the above described MMRM model. ¶ Largest p-value within each dose compared to placebo. †† Statistically significant adjusting for multiplicity using the Hochberg procedure at the 5% significance level (statistical significance of the 4 co-primary endpoints).

Participants treated with fezolinetant 30 mg and 45 mg had statistically significant reductions from baseline in the severity of moderate to severe VMS relative to placebo at weeks 4 and 12 (Table 12).

Table 12 Primary Analysis of Co-primary Endpoints: Change from Baseline in Mean Severity of Moderate to Severe Vasomotor Symptoms per 24 h (Full Analysis Set); 12-week Double-blind Period

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

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

Sensitivity Analysis

Per Protocol Set

Participants in the PPS treated with fezolinetant 30 mg and 45 mg had statistically significant reductions in the frequency and severity of moderate to severe VMS from baseline to weeks 4 and 12 relative to placebo. Sensitivity analyses performed for the PPS support the primary analysis for the co-primary endpoints.

Discontinuation-reason based multiple imputation

In order to evaluate the impact of a MAR assumption in the primary analysis model MMRM, a sensitivity analysis was conducted. In the discontinuation-reason based multiple imputation sensitivity analyses, participants treated with fezolinetant 30 mg and 45 mg had statistically significant reductions from baseline to weeks 4 and 12 in the frequency and severity of moderate to severe VMS relative to placebo. The multiple imputation sensitivity analyses support the primary analysis conclusions.

Subgroup Analysis

Subgroup analyses of smoking, race, BMI and age were also performed for the co-primary endpoints. The interpretation of the results is limited due to the small number of participants in each subgroup; nonetheless, none of these subgroups had an impact on the efficacy of fezolinetant.

Key Secondary Analysis: PROMIS SD SF 8b Total Score, change from baseline to week 12

The applicant has selected the mean change in the PROMIS SD SF 8b total score from baseline to week 12 as key secondary endpoint in order to assess self-reported sleep disturbance over the past 7 days and includes perceptions of restless sleep; satisfaction with sleep; refreshing sleep; difficulties sleeping, getting to sleep or staying asleep; amount of sleep; and sleep quality.

Participants treated with fezolinetant 30 mg and 45 mg had a numerical decrease (improvement) from baseline to week 12 in PROMIS SD SF 8b. The difference relative to placebo was not statistically significant.

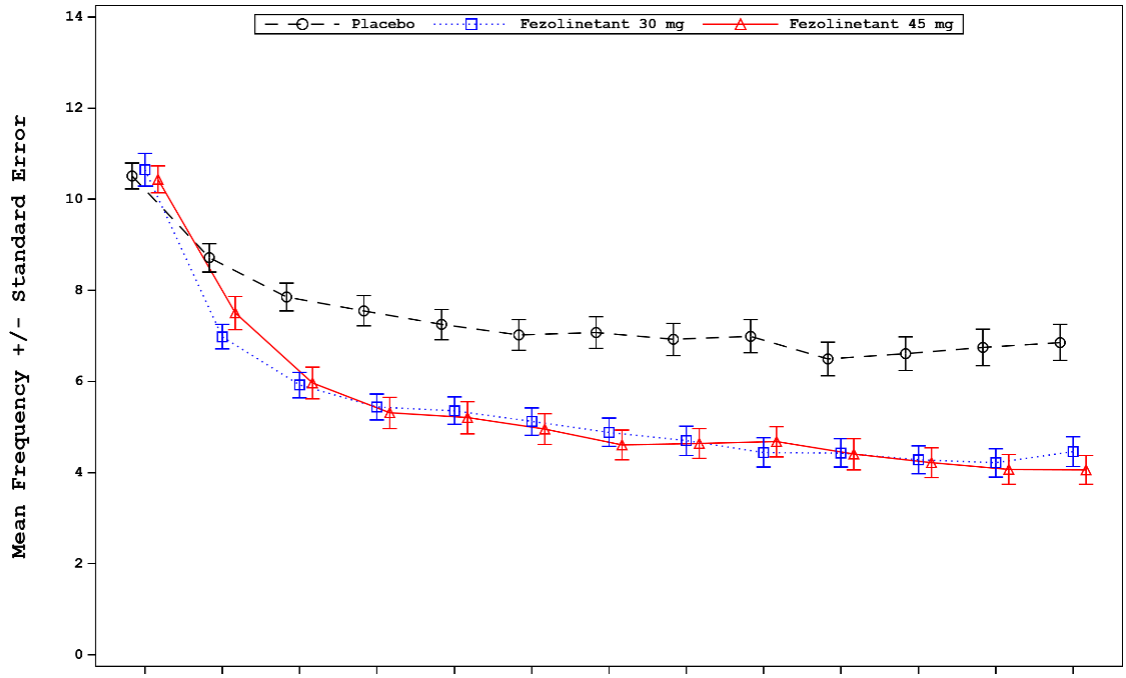
An analysis of PROMIS SD SF 8b excluding question 4 (i.e., "I had difficulty falling asleep") showed consistent results in the reduction from baseline to week 12 in mean total score for both fezolinetant groups (30 mg and 45 mg) relative to placebo.

Other Secondary Efficacy Endpoints

- *Frequency of Moderate to Severe VMS, Change from Baseline to Each Week up to Week 12*

Participants treated with fezolinetant 30 mg and 45 mg had greater reductions from baseline in mean frequency of moderate to severe VMS compared with placebo after week 1 of treatment with fezolinetant, with continued improvement until week 4; these greater reductions were maintained during the 12-week double-blind period.

Figure 13 Mean frequency of moderate to severe vasomotor symptoms per 24 h (full analysis set); 12-week double-blind period



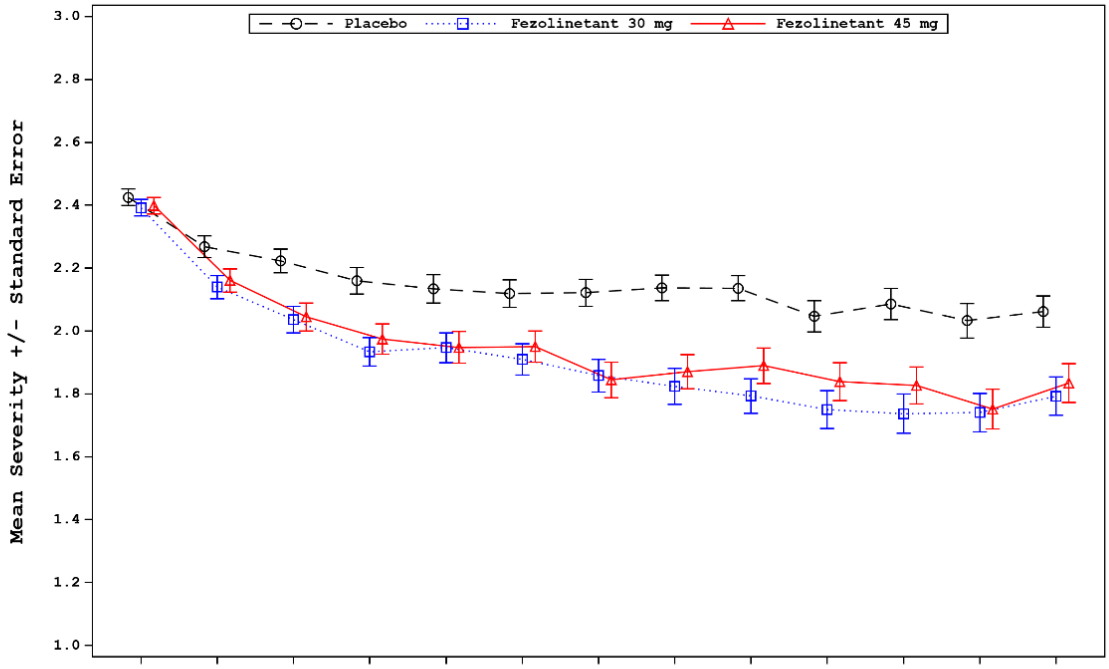
Number of subjects													
Placebo	175	174	171	165	166	158	156	154	152	148	141	144	139
Fezolinetant 30 mg	173	169	162	159	157	151	144	144	143	141	140	138	131
Fezolinetant 45 mg	174	166	168	166	164	159	157	162	151	152	152	149	146

All participants who were randomized and received at least 1 dose of study intervention (Full Analysis Set). Summary statistics are based on non-missing observed data. BLN: baseline.

- *Severity of Moderate to Severe VMS, Change from Baseline to Each Week up to Week 12*

Participants treated with fezolinetant 30 mg and 45 mg had greater reductions from baseline in mean severity of moderate to severe VMS compared with placebo after week 1 of treatment with fezolinetant; these greater reductions were maintained during the 12-week double-blind period.

Figure 14 Mean Severity of Moderate to Severe Vasomotor Symptoms per 24 h (Full Analysis Set); 12-Week Double-blind Period



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

All participants who were randomized and received at least 1 dose of study intervention (Full Analysis Set). Summary statistics are based on non-missing observed data. BLN: baseline.

- *Frequency of Moderate to Severe VMS, Percent Reduction from Baseline to Each Week up to Week 12*

Participants treated with fezolinetant 30 mg and 45 mg had a statistically significant percent reduction from baseline in the frequency of moderate to severe VMS relative to placebo (Table 13); 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.

Table 13 Percent change from baseline in mean frequency of moderate to severe vasomotor symptoms per 24 h at selected visits (full analysis set); 12-week double-blind period

Analysis Visit	Statistic	Placebo (n = 175)	Fezolinetant 30 mg (n = 173)	Fezolinetant 45 mg (n = 174)
Baseline	n	175	173	174
	Mean (SD)	10.51 (3.79)	10.65 (4.73)	10.44 (3.92)
	Median	9.40	9.60	9.28
	Min, Max	7.0, 31.2	3.4, 54.4	7.0, 37.0
Week 4	n	166	157	164
	Mean (SD)	7.25 (4.29)	5.36 (3.76)	5.20 (4.48)
	Median	7.50	5.00	4.27
	Min, Max	0.0, 27.2	0.0, 14.9	0.0, 31.6
	Percentage Change from Baseline†			
	n	166	157	164
	Mean (SD)	-30.46 (35.30)	-47.80 (34.96)	-50.63 (35.44)
	Median	-27.73	-48.98	-56.08
	Min, Max	-100.0, 71.7	-100.0, 49.6	-100.0, 84.1
	LS mean (SE)	-30.59 (2.67)	-47.34 (2.72)	-51.65 (2.69)
	95% CI (2-sided)	-35.83, -25.35	-52.69, -41.99	-56.94, -46.35
	Difference in LS Means‡: Fezolinetant vs Placebo			
	LS mean (SE)	NA	-16.75 (3.81)	-21.05 (3.79)
	95% CI (2-sided)		-24.24, -9.26	-28.50, -13.61
	P value§ (2-sided)		< 0.001	< 0.001
Week 12	n	139	131	146
	Mean (SD)	6.85 (4.66)	4.46 (3.72)	4.06 (3.85)
	Median	6.43	3.80	3.29
	Min, Max	0.0, 29.3	0.0, 17.1	0.0, 23.7
	Percentage Change from Baseline†			
	n	139	131	146
	Mean (SD)	-34.97 (39.65)	-56.26 (35.87)	-61.35 (32.71)
	Median	-35.06	-63.83	-66.66
	Min, Max	-100.0, 113.2	-100.0, 41.7	-100.0, 52.2
	LS mean (SE)	-37.06 (2.89)	-57.13 (2.95)	-61.24 (2.86)
	95% CI (2-sided)	-42.73, -31.38	-62.93, -51.33	-66.85, -55.62
	Difference in LS Means‡: Fezolinetant vs Placebo			
	LS mean (SE)	NA	-20.08 (4.13)	-24.18 (4.06)
	95% CI (2-sided)		-28.19, -11.96	-32.16, -16.20
	P value§ (2-sided)		< 0.001	< 0.001

All participants who were randomized and received at least 1 dose of study intervention (Full Analysis Set). The LS means, SE, CI, and P values come from a MMRM analysis of covariance model with percent change from baseline as the dependent variable and treatment group, week and smoking status (current vs former/never) as factors, with baseline measurement and baseline weight as covariates, as well as an interaction of treatment by week and an interaction of baseline measurement by week. CI: confidence interval; LS: least squares; Max: maximum; Min: minimum; MMRM: mixed model repeated measurements; NA: not applicable. † A negative percent change indicated a reduction/improvement from baseline (i.e., a favourable outcome). ‡ Differences were calculated by subtracting the LS mean of placebo group from the LS mean of fezolinetant group. § P value is for comparison of fezolinetant with placebo from the above described MMRM model.

- *Responder Analysis: Percent Reduction ⩾ 50% and at 100% in the Frequency of Moderate to Severe VMS per 24 h, from Baseline to Each Week up to Week 12*

A higher proportion of participants had a ⩾ 50% reduction in the frequency of moderate to severe VMS in the fezolinetant 30 mg and 45 mg groups than in the placebo group at all visits during the 12-week double-blind period; these differences were statistically significant (Table 14). The proportion of participants who had ⩾ 50% reductions in the frequency of moderate to severe VMS increased in each

visit, from 10.3% (placebo), 27.2% (30 mg) and 25.3% (45 mg) at week 1 to 29.7% (placebo), 44.5% (30 mg) and 56.9% (45 mg) at week 12.

During the 12-week double-blind period, the proportion of participants in the fezolinetant 45 mg groups with a 100% reduction in the frequency of moderate and severe VMS was higher compared with placebo at all visits [Table]. A similar trend was observed in the fezolinetant 30 mg group at all visits. The proportion of participants who had 100% reductions in the frequency of moderate to severe VMS increased in each visit, from 0.6% (placebo), 1.7% (30 mg) and 2.3% (45 mg) at week 2 to 3.4% (placebo), 6.9% (30 mg) and 10.3% (45 mg) at week 12. There were no responders at week 1 in any of the treatment groups, thus the proportion of participants with a 100% reduction in the frequency of moderate and severe VMS was not calculated.

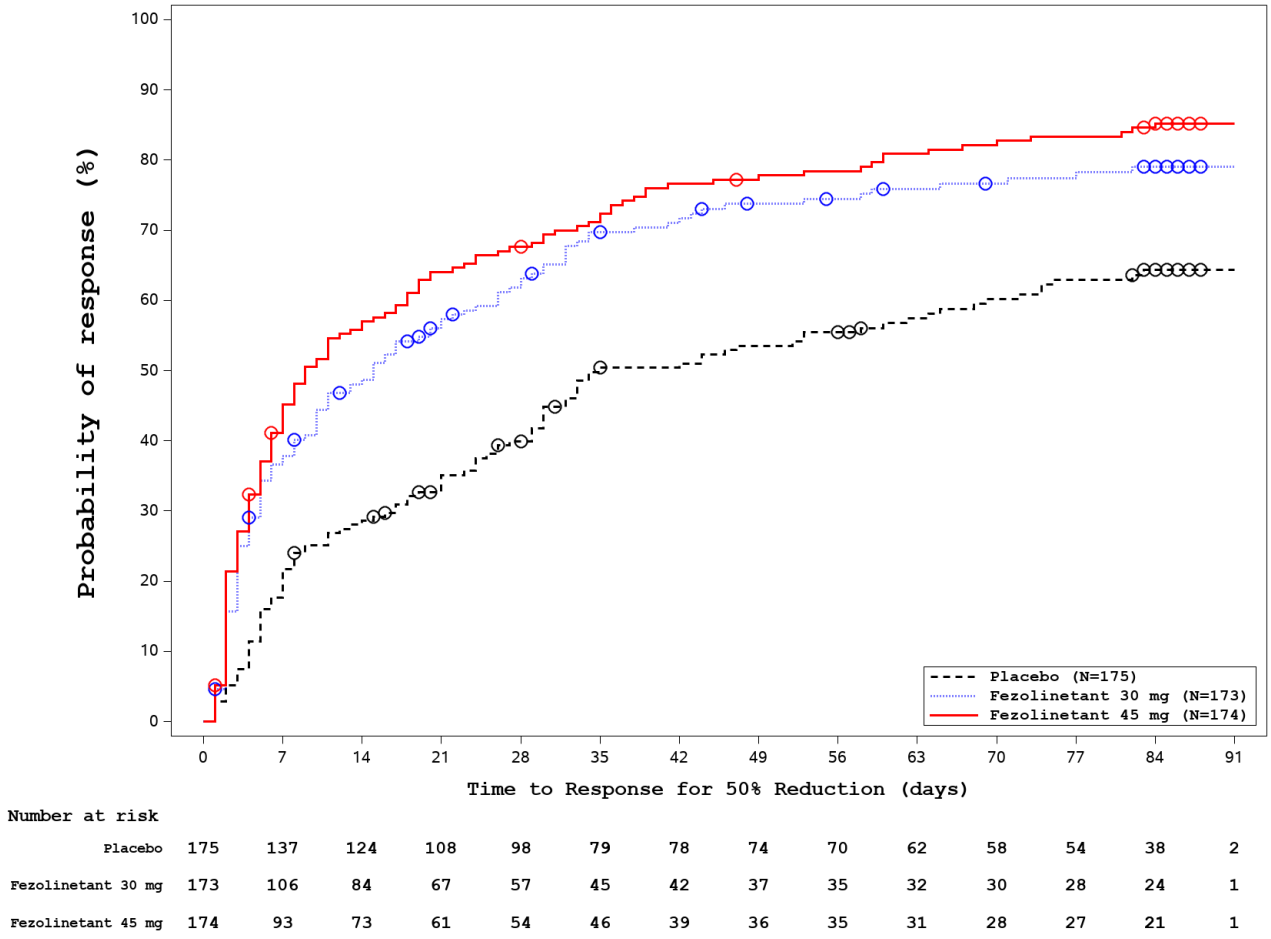
Table 14 Responder analysis of change from baseline in frequency of moderate to severe vasomotor symptoms at selected visits (Full Analysis Set); 12-week double-blind period

Analysis Visit	Responder Criteria	Statistic	Placebo (n = 175)	Fezolinetant 30 mg (n = 173)	Fezolinetant 45 mg (n = 174)
Week 4	≥ 50% Reduction from Baseline	Responders	49 (28.0%)	77 (44.5%)	94 (54.0%)
		Odds ratio: Fezolinetant vs Placebo	NA	2.061	3.025
		95% CI (2-sided)		1.323, 3.233	1.947, 4.746
		P value (2-sided) †		0.001	< 0.001
	≥ 100% Reduction from Baseline	Responders	5 (2.9%)	6 (3.5%)	8 (4.6%)
		Odds ratio: Fezolinetant vs Placebo	NA	1.257	1.570
		95% CI (2-sided)		0.370, 4.468	0.508, 5.328
		P value (2-sided) †		0.711	0.441
Week 12	≥ 50% Reduction from Baseline	Responders	52 (29.7%)	77 (44.5%)	99 (56.9%)
		Odds ratio: Fezolinetant vs Placebo	NA	1.894	3.156
		95% CI (2-sided)		1.220, 2.961	2.035, 4.944
		P value (2-sided) †		0.005	< 0.001
	≥ 100% Reduction from Baseline	Responders	6 (3.4%)	12 (6.9%)	18 (10.3%)
		Odds ratio: Fezolinetant vs Placebo	NA	2.100	3.262
		95% CI (2-sided)		0.795, 6.157	1.329, 9.194
		P value (2-sided) †		0.148	0.015

All participants who were randomized and received at least 1 dose of study intervention (Full Analysis Set). Participants with missing vasomotor symptoms at an analysis visit were considered non-responders. †Based on logistic regression with treatment group and smoking status (current vs former/never) as factors and mean frequency of vasomotor symptoms as a covariate. An odds ratio of > 1 indicated a favourable response in the fezolinetant group. CI: Confidence interval; NA: not applicable.

Median time to a ⩾ 50% reduction response (95% CI) was 15 days (10,22) and 9 days (7, 15) in the fezolinetant 30 mg and 45 mg groups respectively, compared with 35 days (30, 62) in the placebo group (Figure 15). Median times to 100% reduction response were not estimable.

Figure 15 Kaplan-Meier plot of time to ⩾ 50% reduction responders of moderate to severe vasomotor symptoms (Full Analysis Set); 12-week double-blind period



Number at risk

Placebo	175	137	124	108	98	79	78	74	70	62	58	54	38	2
Fezolinetant 30 mg	173	106	84	67	57	45	42	37	35	32	30	28	24	1
Fezolinetant 45 mg	174	93	73	61	54	46	39	36	35	31	28	27	21	1

All participants who were randomized and received at least 1 dose of study intervention (Full Analysis Set). Based on Kaplan-Meier estimates stratified by treatment group. The time to response was the first day with ⩾ 50% response. The censoring time was the number of days from first dosing date up to the last dosing date. For the non-responders, it was censored at the end of treatment. An open circle indicated censoring.

Efficacy in VMS over 24 weeks

After completing 12 weeks of treatment, participants on placebo were re-randomized in a 1:1 ratio to 30 mg or 45 mg of fezolinetant in the active treatment extension period (i.e., extension period without placebo control) for 40 weeks through end of study (week 52).

- *Frequency of Moderate to Severe VMS, Change from Baseline to Week 24.*

Participants treated with fezolinetant 30 mg and 45 mg for the entire study had greater reductions in the frequency of moderate to severe VMS compared with placebo during the 12-week double-blind period. This improvement in VMS frequency was sustained through week 24 [Table].

In participants who received placebo for the 12-week double-blind period, there was an improvement in VMS frequency from baseline to week 24 of fezolinetant exposure (study week 36) once these participants were re-randomized from placebo to fezolinetant treatment (30 mg or 45 mg) for the active treatment extension period (Table 15). This improvement included the placebo effect during the 12-week double-blind period and the effect from the re-randomization from placebo to fezolinetant treatment (30 mg or 45 mg).

Overall, this improvement in VMS frequency was sustained through week 24 of fezolinetant exposure, with no evidence of reduced effect size suggestive of tachyphylaxis.

Table 15 Change from baseline to week 24 (24 weeks of fezolinetant exposure) in mean frequency of moderate to severe vasomotor symptoms per 24 h (Full Analysis Set, Fezolinetant); 52-week period

Analysis Visit	Statistic	Placebo/ Fezolinetant 30 mg (n = 76)	Placebo/ Fezolinetant 45 mg (n = 76)	Fezolinetant 30 mg (n = 173)	Fezolinetant 45 mg (n = 174)
Baseline ‡	n	76	76	173	174
	Mean (SD)	10.26 (3.05)	10.57 (4.12)	10.65 (4.73)	10.44 (3.92)
	Median	9.40	9.10	9.60	9.28
	Min, Max	7.0, 25.9	7.1, 31.2	3.4, 54.4	7.0, 37.0
24 weeks of Fezolinetant Exposure §	n	60	62	121	138
	Mean (SD)	3.20 (3.03)	3.68 (4.48)	3.43 (3.58)	3.32 (3.70)
	Median	2.24	2.71	2.43	2.07
	Min, Max	0.0, 10.6	0.0, 27.4	0.0, 20.0	0.0, 23.9
	Change from Baseline†				
	n	60	62	121	138
	Mean (SD)	-6.89 (3.67)	-7.32 (4.53)	-7.15 (6.02)	-7.32 (4.58)
	Median	-7.64	-7.46	-7.00	-7.10
	Min, Max	-19.4, 1.8	-21.7, 4.6	-54.4, 7.9	-35.1, 7.1

All participants who were randomized and received at least 1 dose of fezolinetant during either the 12-week double-blind or the active treatment extension periods (Full Analysis Set, Fezolinetant). Results in this table include only data from 24 weeks of fezolinetant exposure. For the placebo/fezolinetant groups, data from the 12-week placebo-controlled period (placebo data) are not included. These participants were re-randomized in a 1:1 ratio to 30 mg or 45 mg of fezolinetant after 12 weeks of placebo and only data from the active treatment extension period (while they were receiving fezolinetant) are analysed for these participants. For the fezolinetant groups, data from the 12-week period are included as these participants were on fezolinetant for the entire duration of the study. Max: maximum; Min: minimum. † A negative change indicated a reduction/improvement from baseline (i.e., a favourable outcome). ‡ Baseline for all treatment groups is the value taken at the start of the study, on or prior to first dose of placebo or fezolinetant. § Week 24 from study start for participants in the fezolinetant 30 mg and 45 mg groups; Week 36 from study start for participants in the placebo/fezolinetant groups.

- *Severity of Moderate to Severe VMS, Change from Baseline to Week 24*

Participants treated with fezolinetant 30 mg and 45 mg for the study had reductions in the severity of moderate to severe VMS compared with placebo during the 12-week double-blind period. This improvement in VMS severity was sustained through week 24 (Table 16).

In participants who received placebo for the 12-week double-blind period, there was an improvement in VMS severity once these participants were re-randomized from placebo to fezolinetant treatment (30 mg or 45 mg) for the active treatment extension period. This improvement included the placebo effect during the 12-week double-blind period and the effect from the re-randomization from placebo to fezolinetant treatment (30 mg or 45 mg). Overall, this improvement in VMS severity was sustained through week 24 of fezolinetant exposure, with no evidence of reduced effect size suggestive of tachyphylaxis.

Table 16 Change from Baseline to Week 24 (24 Weeks of Fezolinetant Exposure) in Mean Severity of Moderate to Severe Vasomotor Symptoms per 24 h (Full Analysis Set, Fezolinetant); 52-week Period

Analysis Visit	Statistic	Placebo/ Fezolinetant 30 mg (n = 76)	Placebo/ Fezolinetant 45 mg (n = 76)	Fezolinetant 30 mg (n = 173)	Fezolinetant 45 mg (n = 174)
Baseline ‡	n	76	76	173	174
	Mean (SD)	2.38 (0.34)	2.42 (0.36)	2.39 (0.34)	2.40 (0.35)
	Median	2.32	2.34	2.33	2.36
	Min, Max	1.8, 3.0	1.9, 3.0	1.8, 3.0	1.8, 3.0
24 weeks of Fezolinetant Exposure §	n	60	62	121	138
	Mean (SD)	1.60 (0.81)	1.65 (0.84)	1.62 (0.77)	1.64 (0.84)
	Median	1.84	1.92	1.94	1.94
	Min, Max	0.0, 3.0	0.0, 3.0	0.0, 3.0	0.0, 3.0
	Change from Baseline†				
	n	60	62	121	138
	Mean (SD)	-0.78 (0.80)	-0.76 (0.89)	-0.75 (0.82)	-0.77 (0.90)
	Median	-0.70	-0.36	-0.43	-0.56
	Min, Max	-3.0, 0.3	-2.6, 0.7	-3.0, 0.4	-3.0, 0.9

Baseline includes moderate to severe incidences. Postbaseline includes mild, moderate and severe incidences. All participants who were randomized and received at least 1 dose of fezolinetant during either the 12-week double-blind or the active treatment extension periods (Full Analysis Set, Fezolinetant). Results in this table include only data from 24 weeks of fezolinetant exposure. For the placebo/fezolinetant groups, data from the 12-week placebo-controlled period (placebo data) are not included. These participants were re-randomized in a 1:1 ratio to 30 mg or 45 mg of fezolinetant after 12 weeks of placebo and only data from the active treatment extension period (while they were receiving fezolinetant) are analysed for these participants. For the fezolinetant groups, data from the 12-week period are included as these participants were on fezolinetant for the entire duration of the study. Max: maximum; Min: minimum. † A negative change indicated a reduction/improvement from baseline (i.e., a favourable outcome). ‡ Baseline for all treatment groups is the value taken at the start of the study, on or prior to first dose of placebo or fezolinetant. § Week 24 from study start for participants in the fezolinetant 30 mg and 45 mg groups; Week 36 from study start for participants in the placebo/fezolinetant groups.

- *PGI-C VMS Score*

The PGI assesses patient-perceived global impressions of severity in sleep disturbance and change in VMS and sleep disturbance. It is comprised of 2 companion 1-item PRO measures analogous to the Clinical Global Impression (CGI) scales [Busner J & Targum SD, 2007]. These measures provide brief, stand-alone global assessments prior to and after initiating a study medication. The Patient Global Impression evaluates the following: (a) patient-perceived severity of a condition (PGI-S) and (2) patient-perceived change from the initiation of treatment (PGI-C). In this study, PGI scales will be used to evaluate meaningful within-person changes over time in VMS (PGI-C) and sleep disturbance (PGI-S and PGI-C).

A higher proportion of participants in the fezolinetant 30 mg and 45 mg groups compared with placebo reported a positive change in PGI-C VMS at weeks 4 and 12. Overall, participants in both the fezolinetant 30 mg and 45 mg groups had a statistically significant difference relative to placebo. The trend observed in the fezolinetant 30 mg and 45 mg groups in the first 12 weeks of treatment was maintained throughout the active treatment extension period. In the placebo/fezolinetant groups, more than 60% of the participants reported a 'much better' response in either group during the 52-week period compared to 23.5% of the participants at week 12 during the 12-week double-blind period.

Exploratory Efficacy Endpoints

Moderate to Severe VMS

- *Responder Analysis: Percent Reduction ⩾ 75% and ⩾ 90% in the Frequency of Moderate to Severe VMS from Baseline to Each Week up to Week 12*

A higher proportion of responders had a ⩾ 75% reduction in the frequency of moderate to severe VMS in the fezolinetant 30 mg and 45 mg groups than in the placebo group at all visits during the 12-week double-blind period. The proportion of participants who had ⩾ 75% reductions in the frequency of moderate to severe VMS increased in each visit, from 3.4% (placebo), 10.4% (30 mg) and 8.0% (45 mg) in the fezolinetant groups at week 1 to 13.1% (placebo), 30.1% (30 mg) and 34.5% (45 mg) at week 12.

The same trend was also observed for responders with a ⩾ 90% reduction in the frequency of moderate to severe VMS. The proportion of participants who had ⩾ 90% reductions in the frequency of moderate to severe VMS per 24 hours increased in each visit, from 1.7% in the placebo group and 7.5% in the fezolinetant groups at week 2 to 6.9% (placebo), 16.8% (30 mg) and 20.1% (45 mg) at week 12.

- *Clinically Meaningful Within-Subject Change Thresholds, Frequency of Moderate to Severe Vasomotor Symptoms*

Supplemental prespecified analyses on the clinically meaningful within-subject change thresholds in the frequency of moderate to severe VMS were conducted according to the prespecified Psychometric Analysis Plan

The anchor-based method was the primary approach, and the PGI-C VMS was proposed as the primary anchor measure. Analyses identified clinically meaningful thresholds for frequency of VMS reduction: at week 4, the threshold was -5.37 and at week 12, the threshold was -5.70.

A higher proportion of participants in the fezolinetant 30 mg and 45 mg groups than those in the placebo group (significant at 5% without multiplicity adjustment) achieved a clinically meaningful within-subject change from baseline to weeks 4 and 12 in the frequency of moderate to severe VMS; this was observed for the different missing data imputation analysis: last observation carried forward, missing as a non-responder, and including observed cases only.

- *Severity of Moderate to Severe VMS, Change from Baseline to Each Week up to Week 12 Excluding Mild Events Postbaseline*

Participants treated with fezolinetant 30 mg and 45 mg had greater reductions in the mean change from baseline to weeks 4 and 12 in the severity of moderate to severe VMS excluding mild events postbaseline compared with placebo. These reductions were similar to those observed in the analysis that did include these mild events.

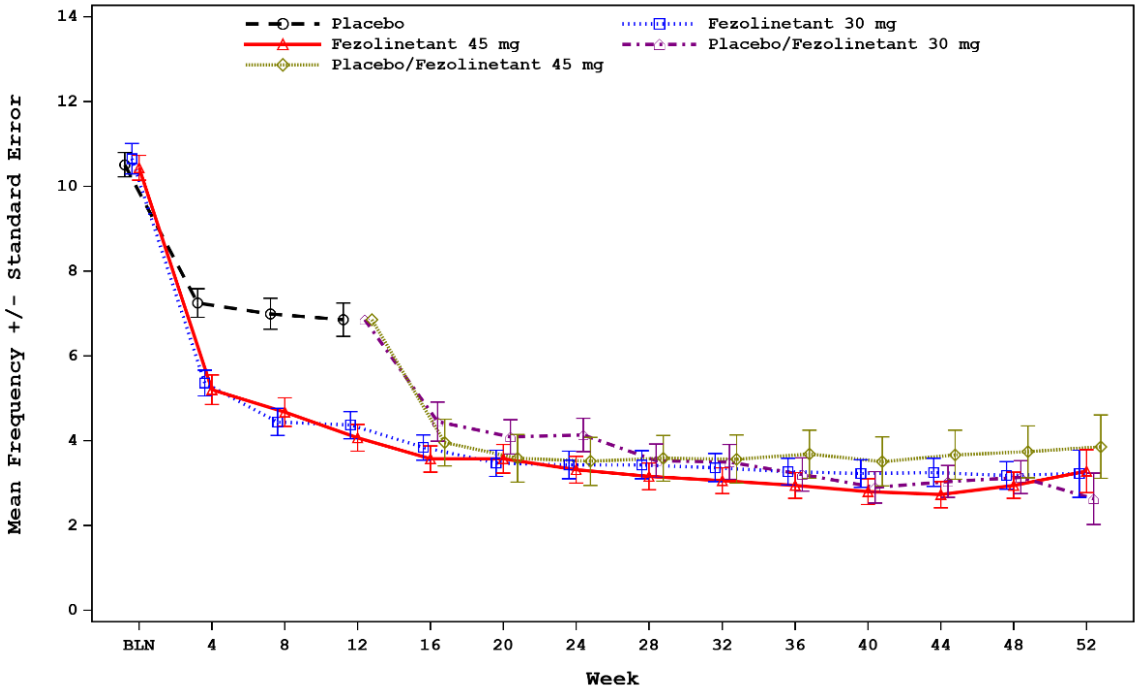
- *Mean Change from Baseline in the Daily Frequency of Moderate to Severe VMS for the First Week*

During the first week of treatment, the reductions from baseline in the frequency of moderate to severe VMS were greater in the fezolinetant groups compared with placebo for each daily score evaluation.

- *Frequency and Severity of Moderate to Severe VMS, Change from Baseline to Each Visit in the Active Treatment Extension Period and the Follow-up Visit*

In an analysis of change from baseline to each visit, fezolinetant demonstrated a reduction in VMS frequency and severity as early as week 1 with improvement sustained over time up to 52 weeks [Figure 16, Figure 17].

Figure 16 Mean Frequency of Moderate to Severe Vasomotor Symptoms per 24 h by Visit (Full Analysis Set, Fezolinetant); 52-week Period

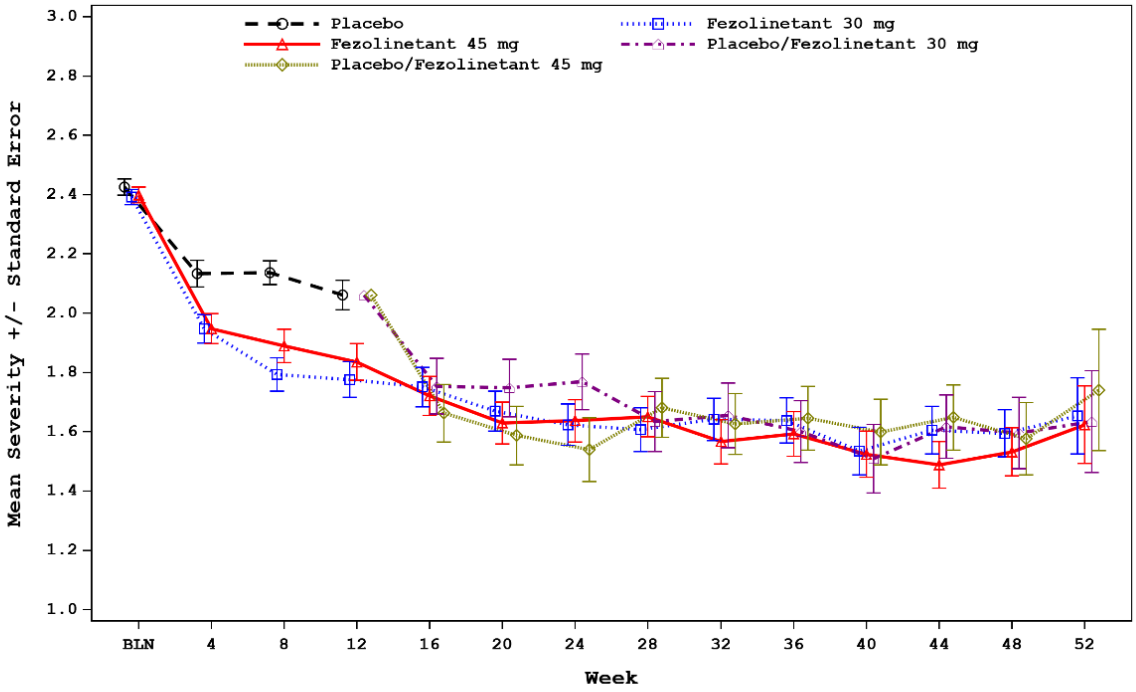


Number of subjects

	BLN	4	8	12	16	20	24	28	32	36	40	44	48	52
Placebo	175	166	152	139										
Fezolinetant 30 mg	173	157	143	134	130	130	121	119	121	116	118	113	115	50
Fezolinetant 45 mg	174	164	151	147	145	140	138	138	141	138	136	136	129	49
Placebo/Fezolinetant 30 mg					72	69	66	65	60	60	61	55	54	21
Placebo/Fezolinetant 45 mg					68	68	68	64	64	62	63	60	57	21

All participants who were randomized and received at least 1 dose of fezolinetant during either the 12-week double-blind or the active treatment extension periods (Full Analysis Set, Fezolinetant). Baseline for all treatment groups is the value taken at the start of the study, on or prior to first dose of placebo or fezolinetant. At week 12, participants in the placebo group were re-randomized in a 1:1 ratio to 30 mg or 45 mg of fezolinetant for the active treatment extension period. For the fezolinetant groups, participants were on fezolinetant for the entire duration of the study. Weeks shown indicate weeks relative to initial randomization. BLN: baseline. Participants on placebo when re-randomized to active fezolinetant demonstrated benefit from fezolinetant treatment on VMS frequency and severity throughout the remainder of the 52-week study

Figure 17 Mean severity of moderate to severe vasomotor symptoms per 24 h by visit (Full Analysis Set, Fezolinetant); 52-week period



Number of subjects														
Placebo	175	166	152	139										
Fezolinetant 30 mg	173	157	143	134	130	130	121	119	121	116	118	113	115	50
Fezolinetant 45 mg	174	164	151	147	145	140	138	138	141	138	136	136	129	49
Placebo/Fezolinetant 30 mg					72	69	66	65	60	60	61	55	54	21
Placebo/Fezolinetant 45 mg					68	68	68	64	64	62	63	60	57	21

All participants who were randomized and received at least 1 dose of fezolinetant during either the 12-week double-blind or the active treatment extension periods (Full Analysis Set, Fezolinetant) Baseline for all treatment groups is the value taken at the start of the study, on or prior to first dose on placebo or fezolinetant. At week 12, participants in the placebo group were re-randomized in a 1:1 ratio to 30 mg or 45 mg of fezolinetant for the active treatment extension period. For the fezolinetant groups, participants were on fezolinetant for the entire duration of the study. Weeks shown indicate weeks relative to initial randomization. BLN: baseline.

Exploratory outcomes - Mild, Moderate and Severe VMS (inclusion of mild VMS in the analyses)

- *Frequency of Mild, Moderate and Severe VMS, Change from Baseline to Each Week up to Week 12*

Participants treated with fezolinetant 30 mg and 45 mg had greater reductions from baseline in the mean change in frequency of mild, moderate and severe VMS compared with placebo during the 12-week double-blind period. These reductions were similar to those observed for moderate and severe VMS.

- *Frequency of Mild, Moderate and Severe VMS, Percent Reduction from Baseline to Each Week up to Week 12*

Participants treated with fezolinetant 30 mg and 45 mg had reductions from baseline in the percent change in frequency of mild, moderate and severe VMS relative to placebo during the 12-week double-blind period. The decreases were similar to those observed for moderate and severe VMS.

- *Responder Analysis: Percent Reduction ⩾ 50%, ⩾ 75%, ⩾ 90% and at 100% in the Frequency of Mild, Moderate and Severe VMS from Baseline to Each Week up to Week 12*

A higher proportion of responders had a ⩾ 50% reduction in the frequency of mild, moderate and severe VMS in the fezolinetant groups than in the placebo group at all visits during the 12-week double-blind period. A similar trend was observed for responders with a ⩾ 75%, ⩾ 90% and 100% reduction in mean frequency of mild, moderate to severe VMS, except for responders with a ⩾ 90% and 100% reduction in the fezolinetant 30 mg group at week 3, responders with a ⩾ 90% reduction in the fezolinetant 45 mg group and responders with a 100% reduction in both fezolinetant treatment groups at week 4. The proportion of participants with a ⩾ 90% and 100% reduction in the frequency of mild, moderate to severe VMS was not calculated since there were no responders at week 1 in any of treatment groups.

- *Severity of Mild, Moderate and Severe VMS, Change from Baseline to Each Week up to Week 12*

Participants treated with fezolinetant 30 mg and 45 mg had greater reductions from baseline in mean severity of mild, moderate and severe VMS compared with placebo during the 12-week double-blind period; these greater reductions were statistically significant relative to placebo.

Exploratory outcomes - Patient-reported Outcomes

- *PROMIS SD SF 8b Total Score, Change from Baseline to Week 4*

There was a numerical reduction (improvement) from baseline in PROMIS SD SF 8b (sleep disturbance) relative to placebo at week 4 in participants treated with fezolinetant 30 mg (P = 0.156) and a statistically significant reduction with fezolinetant 45 mg (P = 0.008).

- *PROMIS SRI SF 8a Change from baseline to week 4 and week 12*

PROMIS SRI SF 8a assesses sleep-related impairment. It is an 8-item PRO measure that evaluates self-reported perceptions of alertness, sleepiness and tiredness during usual waking hours and the perceived functional impairments during wakefulness associated with sleep problems or impaired alertness.

There was a numerical reduction (improvement) from baseline in PROMIS SRI SF 8a relative to placebo at weeks 4 and 12 in participants treated with fezolinetant 30 mg (P = 0.047 at week 4 and P = 0.044 at week 12); in participants treated with fezolinetant 45 mg, there was a statistically significant reduction at week 4 (P < 0.001) and week 12 (P = 0.013).

- *PGI Scales*

There was a difference in the proportions of participants reporting sleep disturbance severity problems (PGI-S SD) in the fezolinetant 30 mg and 45 mg groups compared with placebo at weeks 4 (30 mg: P = 0.224, 45 mg: P = 0.032) and 12 (30 mg: P = 0.548, 45 mg: P = 0.066).

The proportion of participants with severe problems in PGI-S SD was lower in the fezolinetant 30 mg and 45 mg groups relative to placebo at weeks 4 and 12. The proportion of participants with severe problems decreased from baseline to weeks 4 and 12 in both fezolinetant 30 mg and 45 mg groups.

The proportion of participants with moderate problems in PGI-S SD was lower in the fezolinetant 30 mg group relative to placebo at week 4. The proportion of participants with severe problems was lower in the fezolinetant 30 mg and 45 mg groups relative to placebo at week 12. The proportion of participants with moderate problems decreased from baseline to weeks 4 and 12 in all treatment groups.

By week 4, the proportions of participants with mild problems in PGI-S SD increased from baseline in the fezolinetant 30 mg and 45 mg groups and were higher than in the placebo group.

A higher proportion of participants in the fezolinetant 30 mg and 45 mg groups compared with placebo reported a positive change in PGI-C SD at weeks 4 and 12. The proportion of participants who reported a little better, moderately better and much better PGI-C SD combined scores was numerically higher in the fezolinetant 30 mg group (week 4: P = 0.078, week 12: P = 0.365) and statistically significantly higher with fezolinetant 45 mg group (weeks 4 and 12: P < 0.001) compared with placebo.

- *MENQOL*

The MENQOL assesses quality of life as it relates to menopausal symptoms. It is a 29-item PRO measure that assesses the impact of 4 domains of menopausal symptoms, as experienced over the last week: vasomotor (items 1 to 3), psychosocial (items 4 to 10), physical (items 11 to 26) and sexual (items 27 to 29).

In participants treated with fezolinetant 30 mg and 45 mg, there was reduction (improvement) from baseline in the menopause quality of life (MENQOL) total score relative to placebo at weeks 4 and 12. Reductions (improvements) relative to placebo were also observed in all MENQOL domains at weeks 4 and 12, including in the physical (45 mg/week 4: P = 0.004, 45 mg/week 12: P = 0.036), psychosocial (30 mg/week 4: P = 0.027, 30 mg/week 12: P = 0.041, 45 mg/week 12: P = 0.007), sexual (30 mg/week 4: P = 0.032, 45 mg/week 4: P = 0.002) and vasomotor (30 mg/week 4: P < 0.001, 45 mg/week 4: P < 0.001, 30 mg/week 12: P < 0.001, 45 mg/week 12: P < 0.001) domains.

- *EQ-5D-5L*

The EQ-5D-5L assesses general health-related quality of life. It is a 5-item standardized measure of health status that provides a simple, generic measure of health for clinical and economic appraisal [EuroQol Research Foundation, 2018; van Reenen & Janssen, 2015]. This PRO measure comprises 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression.

In participants treated with fezolinetant 30 mg, there was an increase (improvement) from baseline in EQ-5D-5L VAS score relative to placebo at weeks 4 and 12; this difference was not statistically significant. In participants treated with fezolinetant 45 mg, there was an increase from baseline in EQ-5D-5L VAS score relative to placebo at week 4; this difference was statistically significant (P = 0.025).

- *WPAI-VMS*

The WPAI-VMS assesses VMS-related work productivity and activity impairment. It is a 6-item PRO measure that examines VMS-related work productivity and activity in the preceding 7 days [Reilly Associates, 2013; Reily et al, 1993].

In participants treated with fezolinetant 30 mg and 45 mg, there was a numerical reduction (improvement) from baseline in WPAI-VMS domain scores relative to placebo at weeks 4 and 12, including in the activity impairment (30 mg/week 4: P < 0.001, 45 mg/week 4: P < 0.001, 30 mg/week 12: P = 0.033, 45 mg/week 12: P = 0.001), overall work productivity loss (45 mg/week 4: P = 0.006, 45 mg/week 12: P < 0.001), and presenteeism (45 mg/week 4: P = 0.003, 30 mg/week 12: P = 0.029, 45 mg/week 12: P < 0.001) domains.

The effect of fezolinetant treatment on WPAI-VMS domain scores was sustained throughout the active treatment extension period, with the exception of the absenteeism domain.

Study 2693-CL-0302 (SKYLIGHT 2)

Study 2693-CL-0302 (SKYLIGHT 2) was a phase 3, randomized, placebo-controlled, 12-week double-blind study, followed by a non-controlled extension treatment period of 40 weeks, to assess the efficacy and safety of fezolinetant in women suffering from moderate to severe vasomotor symptoms associated with menopause. The study is conducted in the US, Canada and Europe from July 2019 to April 2021.

The study design, treatments, objectives, outcomes/endpoints, sample size, the randomisation and blinding, as well as the statistical methos are identical to that of the SKYLIGHT 1 study. The only difference to note was related to the inclusion and exclusion criteria of the SKYLIGHT 2 study. These were identical to those of the SKYLIGHT 1 study, apart from the following criteria:

- Subject has documentation of a normal/negative or no clinically significant findings mammogram and Pap test (obtained at screening or within the prior 12 months of study enrolment), instead of 9 months in the previous study.
- The exclusion criterion of uncontrolled hypertension is more clearly specified in SKYLIGHT 2 as compared to the previous study.

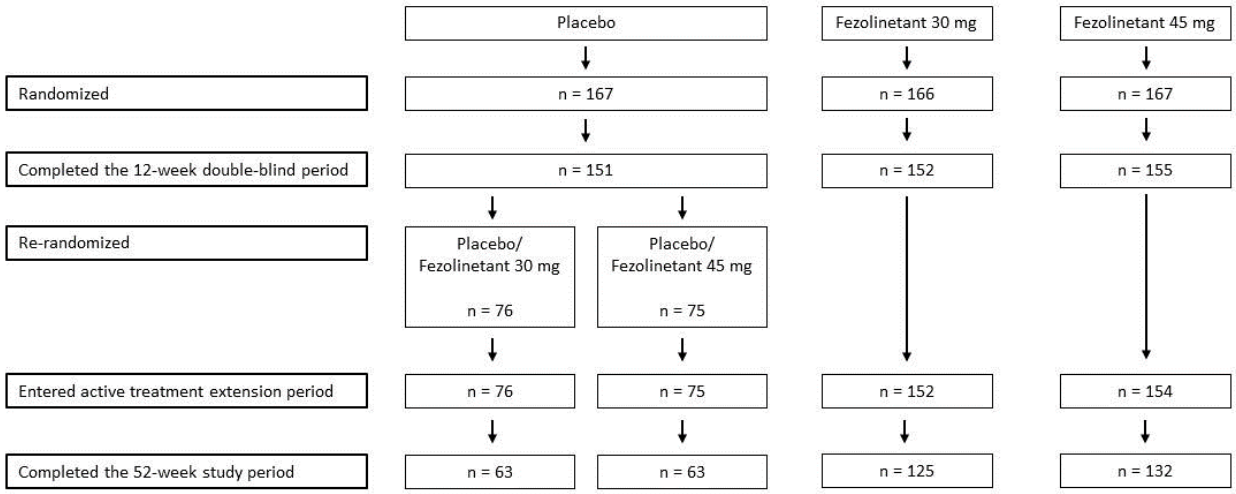
Results

- **Participant flow**

A total of 501 participants were randomized: 168 participants in the placebo group, 166 in the fezolinetant 30 mg group and 167 in the fezolinetant 45 mg group. Of those, 500 took the study intervention: 167 participants in the placebo group, 166 in the fezolinetant 30 mg group and 167 in the fezolinetant 45 mg group. A total of 458 participants completed the 12-week double-blind period (Figure 18 and Table 17). Of these participants, 457 participants entered the 40-week active treatment extension period; 383 participants completed the 52-week period.

The most common reason for treatment discontinuation was "withdrawal by subject" during the 12-week double-blind period (4.6%) and the 52-week period (11.8%) (Table 17). Overall, there was no difference in frequencies of reason for withdrawal between treatment groups. One participant in the placebo/fezolinetant 45 mg group discontinued due to death from multiple injuries and was considered by the investigator as not related to study intervention.

Figure 18 Treatment disposition (safety analysis set)



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

Table 17 Treatment disposition

Category	Placebo (n = 167)	Fezolinetant 30 mg (n = 166)	Fezolinetant 45 mg (n = 167)	Total (n = 500)
12-week Double-blind Period (Safety Analysis Set)				
Completed	151 (90.4%)	152 (91.6%)	155 (92.8%)	458 (91.6%)
Treatment discontinuation †	16 (9.6%)	14 (8.4%)	12 (7.2%)	42 (8.4%)
Primary reason for study intervention discontinuation ‡				
Adverse event	1 (0.6%)	1 (0.6%)	2 (1.2%)	4 (0.8%)
Death	0	0	0	0
Lost to follow-up	2 (1.2%)	1 (0.6%)	2 (1.2%)	5 (1.0%)
Protocol deviation	1 (0.6%)	5 (3.0%)	0	6 (1.2%)
Withdrawal by subject	11 (6.6%)	6 (3.6%)	6 (3.6%)	23 (4.6%)
Other §	1 (0.6)	1 (0.6)	2 (1.2)	4 (0.8)

Category	Placebo/ Fezolinetant 30 mg (n = 76)	Placebo/ Fezolinetant 45 mg (n = 75)	Fezolinetant 30 mg (n = 166)	Fezolinetant 45 mg (n = 167)	Total (n = 484)
52-week Period (Safety Analysis Set, Fezolinetant)					
Completed	63 (82.9%)	63 (84.0%)	125 (75.3%)	132 (79.0%)	383 (79.1%)
Treatment discontinuation	13 (17.1%)	12 (16.0%)	41 (24.7%)	35 (21.0%)	101 (20.9%)
Primary reason for study intervention discontinuation					
Adverse event	2 (2.6%)	3 (4.0%)	5 (3.0%)	7 (4.2%)	17 (3.5%)
Death	0	1 (1.3%)	0	0	1 (0.2%)
Lost to follow-up	2 (2.6%)	1 (1.3%)	3 (1.8%)	3 (1.8%)	9 (1.9%)
Protocol deviation	0	0	5 (3.0%)	2 (1.2%)	7 (1.4%)
Withdrawal by subject	9 (11.8%)	5 (6.7%)	23 (13.9%)	20 (12.0%)	57 (11.8%)
Other¶	0	2 (2.7%)	5 (3.0%)	3 (1.8%)	10 (2.1%)

All randomized participants who took at least 1 dose of study intervention (Safety Analysis Set). All participants who were randomized and received at least 1 dose of fezolinetant during either the 12-week double-blind or the active treatment extension periods (Safety Analysis Set, Fezolinetant). Participants in the placebo/fezolinetant groups were re-randomized in a 1:1 ratio to 30 mg or 45 mg of fezolinetant after 12 weeks of placebo and only data from the active treatment extension period are shown in the placebo/fezolinetant columns (fezolinetant exposure). Data from the 12-week placebo-controlled period (placebo data) are not included in the placebo/fezolinetant columns but are shown in the placebo column in the 12-week double-blind period rows. Four participants (0.8%) discontinued treatment due to COVID-19 during the 12-week double-blind period and 11 (2.3%) discontinued due to COVID-19 during the 52-week period. † Prior to week 12/visit 5. ‡ Primary study intervention treatment status up to and including the week 12/visit 5 timepoint.

- **Recruitment**

A total of 1662 unique participants signed informed consent and were screened, of which 1161 participants failed screening. The main reasons for screening failure were related to the following entry criteria: participant must have had 7 to 8 moderate to severe VMS, participant unable or unwilling to complete the study procedures and participant with BP levels above protocol-specified. A total of 10 participants failed screening due to endometrial abnormalities detected by TVU or biopsy.

- **Baseline data**

Demographics and Baseline Characteristics

Demographics and baseline characteristics were similar between treatment groups (Table 18). Slightly more than half of participants were aged < 55 years (52.8%), with a median age of 54.0 years. Most participants were White (79.4%), not Hispanic or Latino (78.6%) and were either former smokers or had never smoked (79.4%). In addition, 21.5% of participants received prior treatment with HRT.

Table 18 Demographic and Selected Baseline Characteristics (Safety Analysis Set)

Parameter	Category/Statistic	Placebo (n = 167)	Fezolinetant 30 mg (n = 166)	Fezolinetant 45 mg (n = 167)	Total (n = 500)
Age (years)	n	167	166	167	500
	Mean (SD)	54.7 (4.6)	53.9 (4.9)	54.3 (5.4)	54.3 (5.0)
	Median	54.0	54.0	55.0	54.0
	Min, Max	44, 65	42, 65	40, 65	40, 65
Age category	< 55 years	89 (53.3%)	93 (56.0%)	82 (49.1%)	264 (52.8%)
	≥ 55 years	78 (46.7%)	73 (44.0%)	85 (50.9%)	236 (47.2%)
Race	White	134 (80.2%)	131 (78.9%)	132 (79.0%)	397 (79.4%)
	Black or African American	31 (18.6%)	35 (21.1%)	33 (19.8%)	99 (19.8%)
	American Indian or Alaska Native	0	0	1 (0.6%)	1 (0.2%)
	Asian	1 (0.6%)	0	0	1 (0.2%)
	More Than One Race	1 (0.6%)	0	1 (0.6%)	2 (0.4%)
Ethnicity	Hispanic or Latino	32 (19.3%)	34 (20.5%)	41 (24.6%)	107 (21.4%)
	Not Hispanic or Latino	134 (80.7%)	132 (79.5%)	126 (75.4%)	392 (78.6%)
	Missing	1	0	0	1
Weight (kg)	n	167	166	167	500
	Mean (SD)	74.57 (14.68)	75.33 (14.09)	74.62 (12.45)	74.84 (13.75)
	Median	71.70	74.05	73.00	73.00
	Min, Max	46.2, 125.0	48.0, 108.4	45.0, 107.4	45.0, 125.0
BMI (kg/m^2)	n	167	166	167	500
	Mean (SD)	28.16 (4.99)	27.94 (4.69)	27.91 (4.35)	28.00 (4.68)
	Median	27.78	27.76	27.28	27.58
	Min, Max	18.6, 38.0	18.1, 37.6	18.0, 37.5	18.0, 38.0
BMI category (kg/m^2)	< 18.5	0	1 (0.6%)	1 (0.6%)	2 (0.4%)
	≥ 18.5 to < 25	53 (31.7%)	54 (32.5%)	45 (26.9%)	152 (30.4%)
	≥ 25 to < 30	62 (37.1%)	58 (34.9%)	73 (43.7%)	193 (38.6%)
	≥ 30	52 (31.1%)	53 (31.9%)	48 (28.7%)	153 (30.6%)
Smoking status stratification factor†	Current	35 (21.0%)	34 (20.5%)	34 (20.4%)	103 (20.6%)
	Former/never	132 (79.0%)	132 (79.5%)	133 (79.6%)	397 (79.4%)
Prior hormone replacement therapy	Yes	31 (18.6%)	37 (22.6%)	38 (23.3%)	106 (21.5%)
	No	136 (81.4%)	127 (77.4%)	125 (76.7%)	388 (78.5%)
	Missing	0	2	4	6

All randomized participants who took at least 1 dose of study intervention (Safety Analysis Set). The participant population for this study consisted of female individuals as per inclusion criteria. BMI: body mass index (weight [kg]/height [m2]); Max: maximum; Min: minimum. † Current vs former or never smoking status was a stratification factor for randomization.

Medical history

The frequency of medical history items was balanced across treatment groups. Frequently reported medical history included hypertension (21.2%), uterine leiomyoma (14.6%), seasonal allergy (14.2%), gastroesophageal reflux disease (12.0%) and drug hypersensitivity (12.0%). A total of 32.0%

participants with hysterectomy and 21.8% with oophorectomy enrolled in this study; the proportion of participants with hysterectomy or oophorectomy was similar across treatment groups.

The median time since onset of HFs (VMS) was 56.3 months (range: 2 to 396 months).

- **Numbers analysed**

Of the 501 participants randomized in this study, 500 took at least 1 dose of study intervention and were included in the SAF and FAS and 1 participant did not take the study intervention [Table]. Of these, 81 participants were excluded from the PPS at week 4 and 139 at week 12. The main reasons for exclusion from the PPS included low interactive diary compliance and no measurement of the primary efficacy endpoints; the proportion of participants with reason for exclusion from PPS was similar across treatment groups.

A total of 484 participants took at least 1 dose of fezolinetant during either the 12-week double-blind or active treatment extension periods and were included in the SAF, Fezolinetant and FAS, Fezolinetant (Table 19).

Table 19 Participant classification (all randomized participants)

Analysis Set	Placebo (n = 168)	Fezolinetant 30 mg (n = 166)	Fezolinetant 45 mg (n = 167)	Total (n = 501)
12-week Double-blind Period				
Safety analysis set †	167 (99.4%)	166 (100%)	167 (100%)	500 (99.8%)
Full analysis set †	167 (99.4%)	166 (100%)	167 (100%)	500 (99.8%)
Per protocol set - week 4‡	145 (86.3%)	138 (83.1%)	136 (81.4%)	419 (83.6%)
Per protocol set - week 12 §	126 (75.0%)	112 (67.5%)	123 (73.7%)	361 (72.1%)

Analysis Set	Placebo/ Fezolinetant 30 mg (n = 76)	Placebo/ Fezolinetant 45 mg (n = 75)	Fezolinetant 30 mg (n = 166)	Fezolinetant 45 mg (n = 167)	Total (n = 484)
52-week Period					
Safety analysis set ¶	76 (100.0%)	75 (100.0%)	166 (100.0%)	167 (100.0%)	484 (100.0%)
Full analysis set ¶	76 (100.0%)	75 (100.0%)	166 (100.0%)	167 (100.0%)	484 (100.0%)

Participants on placebo were re-randomized in a 1:1 ratio to 30 mg or 45 mg of fezolinetant in the active treatment extension period. FAS: full analysis set; PPS: per protocol set. † All randomized participants who took at least 1 dose of study intervention. A participant erroneously receiving a treatment different from their randomized treatment was assigned to the treatment group that the participant received as first dose. ‡ All randomized participants from the FAS who were treated according to the protocol without any major deviations at week 4 endpoint. Reasons for exclusion from PPS4 included: no measurement of the primary efficacy endpoint available at week 4; <85% interactive diary compliance during the 4-week treatment period; treatment compliance less than or equal to 85% between randomization and week 4. § All randomized participants from the FAS who were treated according to the protocol without any major deviations at week 12 endpoint. Reasons for exclusion from PPS12 included: no measurement of the primary efficacy endpoint available at week 12; < 85% interactive diary compliance during the 12-week treatment period; treatment compliance less than or equal to 85% between randomization and week 12. ¶ All participants who were randomized and received at least 1 dose of fezolinetant during either the 12-week double-blind or the active treatment extension periods.

- **Outcomes and estimation**

Co-primary Efficacy Endpoints

Primary Analysis: Frequency and Severity of Moderate to Severe Vasomotor Symptoms, Change from Baseline to Weeks 4 and 12

All 4 co-primary endpoints were met in both fezolinetant groups (30 mg and 45 mg). Participants treated with fezolinetant 30 mg and 45 mg had statistically significant reductions in the frequency of moderate to severe VMS from baseline to weeks 4 and 12, relative to placebo (Table 20).

Table 10 Primary analysis of co-primary endpoints: change from baseline in mean frequency of moderate to severe vasomotor symptoms per 24 h (full analysis set); 12-week double-blind period

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

All participants who were randomized and received at least 1 dose of study intervention (Full Analysis Set). The LS means, SE, CI and P values come from a MMRM analysis of covariance model with change from baseline as the dependent variable and treatment group, week and smoking status (current vs former/never) as factors, with baseline measurement and baseline weight as covariates, as well as an interaction of treatment by week and an interaction of baseline measurement by week. CI: confidence interval; LS: least squares; Max: maximum; Min: minimum; MMRM: mixed model repeated measurements; NA: not applicable. † A negative change indicated a reduction/improvement from baseline (i.e., a favourable outcome). ‡ Differences were calculated by subtracting the LS mean of placebo group from the LS mean of fezolinetant group. § P value is for comparison of fezolinetant with placebo from the above described MMRM model. ¶ Largest p value within each dose compared to placebo. †† Statistically significant

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

Participants treated with fezolinetant 30 mg and 45 mg had statistically significant reductions in the severity of moderate to severe VMS from baseline to weeks 4 and 12 relative to placebo (Table 21).

Table 21 Primary analysis of co-primary endpoints: change from baseline in mean severity of moderate to severe vasomotor symptoms per 24 h (full analysis set); 12-week double-blind period

Analysis Visit	Statistic	Placebo (n = 167)	Fezolinetant 30 mg (n = 166)	Fezolinetant 45 mg (n = 167)
Baseline	n	167	166	167
	Mean (SD)	2.41 (0.32)	2.44 (0.33)	2.41 (0.34)
	Median	2.37	2.44	2.34
	Min, Max	2.0, 3.0	2.0, 3.0	1.9, 3.0
Week 4	n	151	155	155
	Mean (SD)	2.11 (0.56)	1.97 (0.65)	1.80 (0.74)
	Median	2.04	2.00	1.97
	Min, Max	0.0, 3.0	0.0, 3.0	0.0, 3.0
	Change from Baseline†			
	n	151	155	155
	Mean (SD)	-0.31 (0.48)	-0.47 (0.58)	-0.61 (0.63)
	Median	-0.14	-0.27	-0.42
	Min, Max	-2.1, 0.4	-3.0, 0.5	-2.7, 0.3
	LS mean (SE)	-0.32 (0.05)	-0.47 (0.05)	-0.61 (0.05)
	95% CI (2-sided)	-0.41, -0.23	-0.56, -0.38	-0.70, -0.52
	Difference in LS Means‡: Fezolinetant vs Placebo			
	LS mean (SE)	NA	-0.15 (0.06)	-0.29 (0.06)
	95% CI (2-sided)		-0.27, -0.02	-0.41, -0.16
	P value (2-sided unadjusted) §		0.021	< 0.001
	P value (2-sided adjusted) ¶		0.049 ††	< 0.001 ††
Week 12	n	140	133	145
	Mean (SD)	1.95 (0.68)	1.84 (0.79)	1.66 (0.79)
	Median	2.00	2.00	1.74
	Min, Max	0.0, 3.0	0.0, 3.0	0.0, 3.0
	Change from Baseline†			
	n	140	133	145
	Mean (SD)	-0.46 (0.65)	-0.60 (0.75)	-0.74 (0.71)
	Median	-0.28	-0.25	-0.61
	Min, Max	-3.0, 0.6	-3.0, 0.4	-2.8, 0.5
	LS mean (SE)	-0.48 (0.06)	-0.64 (0.06)	-0.77 (0.06)
Week 12	95% CI (2-sided)	-0.59, -0.36	-0.76, -0.53	-0.88, -0.65
	Difference in LS Means‡: Fezolinetant vs Placebo			
	LS mean (SE)	NA	-0.16 (0.08)	-0.29 (0.08)
	95% CI (2-sided)		-0.33, 0.00	-0.45, -0.13
	P value (2-sided unadjusted) §		0.049	< 0.001
	P value (2-sided adjusted) ¶		0.049 ††	< 0.001 ††

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

Sensitivity Analysis

Per Protocol Set

Participants in the PPS treated with fezolinetant 30 mg and 45 mg had statistically significant reductions in the frequency and severity of moderate to severe VMS from baseline to weeks 4 and 12 relative to placebo. Sensitivity analyses performed for the PPS support the primary analysis for the co-primary endpoints.

Discontinuation-reason based multiple imputation

In order to evaluate the impact of a MAR assumption in the primary analysis model MMRM, a sensitivity analysis was conducted. In the discontinuation-reason based multiple imputation sensitivity analyses, participants treated with fezolinetant 30 mg and 45 mg had statistically significant reductions from baseline to weeks 4 and 12 in the frequency and severity of moderate to severe VMS relative to placebo. The multiple imputation sensitivity analyses support the primary analysis conclusions.

Subgroup Analysis

Subgroup analyses of smoking status, age, race and BMI were also performed for the co-primary endpoints. The interpretation of the results is limited due to the small number of participants in each subgroup; nonetheless, none of these subgroups had an impact on the efficacy of fezolinetant.

Key Secondary Analysis: PROMIS SD SF 8b Total Score, Change from Baseline to Week 12

Participants treated with fezolinetant 45 mg had a statistically significant reduction (improvement) from baseline in PROMIS SD SF 8b relative to placebo at week 12. There was a numerical decrease from baseline to week 12 in PROMIS SD SF 8b in participants treated with fezolinetant 30 mg; the difference relative to placebo was not statistically significant.

Table 22 Key secondary analysis: change from baseline in PROMIS Sleep Disturbance – Short Form 8b (full analysis set); 12-week double-blind period

Analysis Visit	Statistic	Placebo (n = 167)	Fezolinetant 30 mg (n = 166)	Fezolinetant 45 mg (n = 167)
Baseline	n	166	165	167
	Mean (SD)	27.4 (7.0)	27.3 (6.6)	26.2 (6.6)
	Median	28.0	28.0	26.0
	Min, Max	8, 40	11, 40	8, 40
Week 12	n	144	139	145
	Mean (SD)	23.8 (7.0)	23.0 (7.7)	21.2 (5.7)
	Median	24.0	23.0	22.0
	Min, Max	8, 40	8, 40	8, 35
	Change from Baseline†			
	n	143	139	145
	Mean (SD)	-3.6 (7.3)	-4.6 (8.1)	-4.8 (6.8)
	Median	-2.0	-5.0	-5.0
	Min, Max	-23, 13	-27, 19	-23, 14
	LS mean (SE)	-3.4 (0.5)	-4.1 (0.5)	-5.5 (0.5)
	95% CI (2-sided)	-4.5, -2.4	-5.1, -3.1	-6.5, -4.4
	Difference in LS Means‡: Fezolinetant vs Placebo			
	LS mean (SE)	NA	-0.7 (0.7)	-2.0 (0.7)
	95% CI (2-sided)		-2.1, 0.8	-3.5, -0.6
	P value (2-sided unadjusted) §		0.381	0.007 ¶

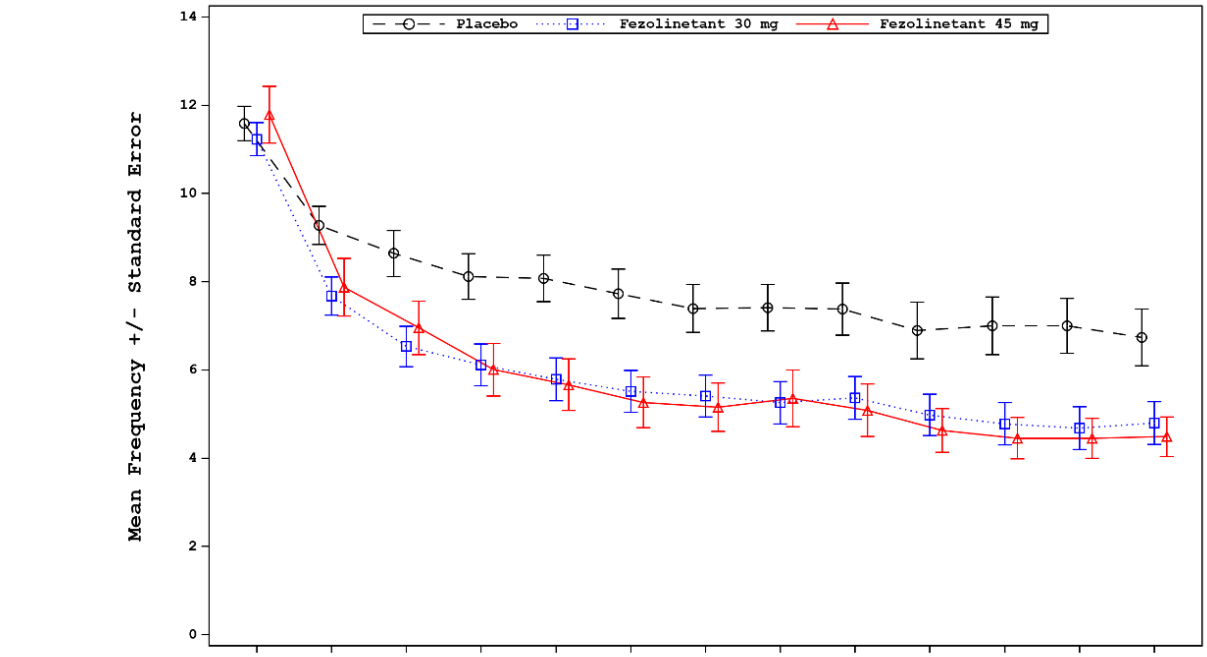
All participants who were randomized and received at least 1 dose of study intervention (Full Analysis Set). The LS means, SE, CI and P values come from a MMRM analysis of covariance model with change from baseline as the dependent variable and treatment group, week and smoking status (current vs former/never) as factors, with baseline measurement and baseline weight as covariates, as well as an interaction of treatment by week and an interaction of baseline measurement by week. CI: confidence interval; LS: least squares; MMRM: mixed model repeated measurements; NA: not applicable; PROMIS SD SF 8b: Patient-Reported Outcome Measurement Information System Sleep Disturbance – Short Form 8b. † A negative change indicated a reduction/improvement from baseline (i.e., a favorable outcome). ‡ Differences were calculated by subtracting the LS mean of placebo group from the LS mean of fezolinetant group. § P value is for comparison of fezolinetant with placebo from the above described MMRM model. ¶ Statistically significant adjusting for the multiplicity using the Hochberg procedure.An analysis of PROMIS SD SF 8b excluding question 4 (i.e., "I had difficulty falling asleep") showed consistent results with those from the primary PROMIS SD SF8b analysis [Table] in the reduction from baseline to week 12 in mean total score for both fezolinetant groups (30 mg and 45 mg) relative to placebo.

Secondary Efficacy Endpoints

Frequency of Moderate to Severe VMS, Change from Baseline to Each Week up to Week 12

Participants treated with fezolinetant 30 mg and 45 mg had greater reductions from baseline in mean frequency of moderate to severe VMS compared with placebo after week 1 of treatment with fezolinetant, with continued improvement until week 4; these greater reductions were maintained during the 12-week double-blind period (Figure 19).

Figure 19 Mean frequency of moderate to severe vasomotor symptoms per 24 h (full analysis set); 12-week double-blind period



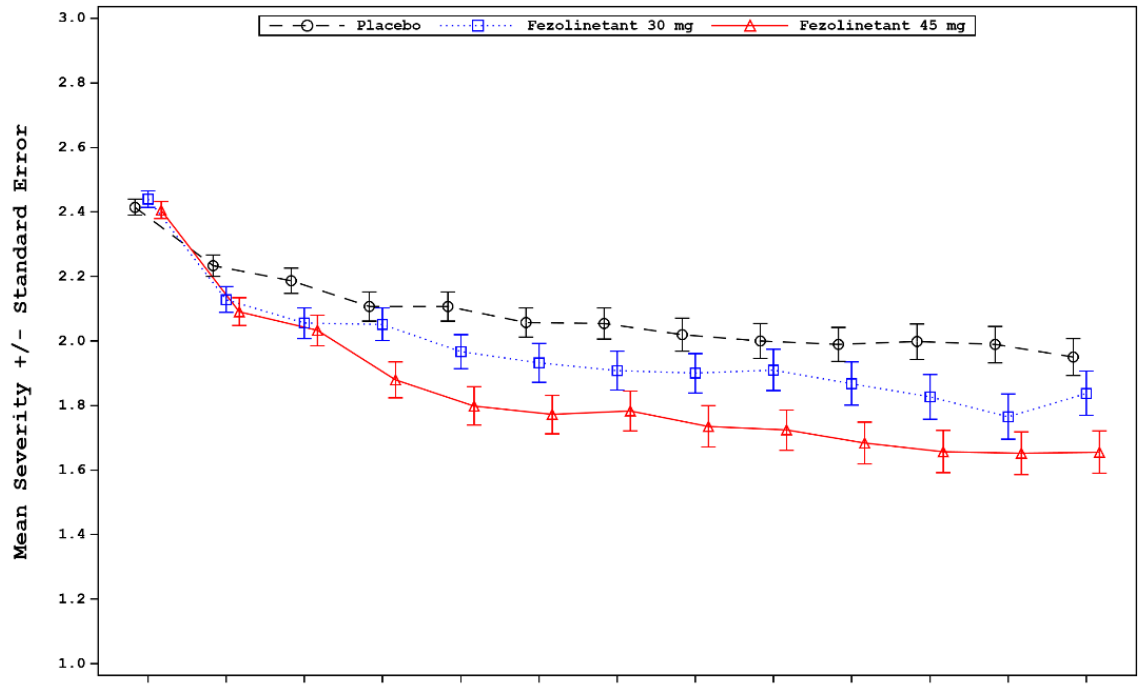
Number of subjects	BLN	WK1	WK2	WK3	WK4	WK5	WK6	WK7	WK8	WK9	WK10	WK11	WK12
Placebo	167	166	159	156	151	152	152	149	148	145	139	138	140
Fezolinetant 30 mg	166	164	160	157	155	152	146	143	143	140	138	142	133
Fezolinetant 45 mg	167	158	156	156	155	154	149	147	154	148	149	149	145

All participants who were randomized and received at least 1 dose of study intervention (Full Analysis Set). Summary statistics are based on non-missing observed data. BLN: baseline.

Severity of Moderate to Severe VMS, Change from Baseline to Each Week up to Week 12

Participants treated with fezolinetant 30 mg and 45 mg had greater reductions from baseline in mean severity of moderate to severe VMS compared with placebo after week 1 of treatment with fezolinetant; these greater reductions were maintained during the 12-week double-blind period (Figure 20).

Figure 20 Mean severity of moderate to severe vasomotor symptoms per 24 h (full analysis set); 12-week double-blind period



Number of subjects													
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

All participants who were randomized and received at least 1 dose of study intervention (Full Analysis Set). Summary statistics are based on non-missing observed data. BLN: baseline.

Frequency of Moderate to Severe VMS, Percent Reduction from Baseline to Each Week up to Week 12

Participants treated with fezolinetant 30 mg and 45 mg had a statistically significant percent reduction from baseline in the frequency of moderate to severe VMS relative to placebo (Table 23); these differences were observed after week 1 of treatment with fezolinetant with continued improvement until week 4 and sustained benefit through the 12-week double-blind period.

Table 23 Percent change from baseline in mean frequency of moderate to severe vasomotor symptoms per 24 h at selected visits (full analysis set)

Analysis Visit	Statistic	Placebo (n = 167)	Fezolinetant 30 mg (n = 166)	Fezolinetant 45 mg (n = 167)
Baseline	n	167	166	167
	Mean (SD)	11.59 (5.02)	11.23 (4.88)	11.79 (8.26)
	Median	10.10	10.15	9.90
	Min, Max	5.6, 40.7	2.5, 54.1	7.0, 91.1
Week 4	n	151	155	155
	Mean (SD)	8.08 (6.50)	5.79 (6.02)	5.67 (7.29)
	Median	7.29	4.17	4.14
	Min, Max	0.0, 48.7	0.0, 49.1	0.0, 68.7
	Percentage Change from Baseline†			
	n	151	155	155
	Mean (SD)	-33.60 (34.14)	-51.60 (36.48)	-55.16 (36.25)
	Median	-29.82	-56.66	-61.11
	Min, Max	-100.0, 77.4	-100.0, 65.7	-100.0, 106.1
	LS mean (SE)	-34.72 (2.78)	-51.06 (2.77)	-56.37 (2.77)
	95% CI (2-sided)	-40.18, -29.26	-56.49, -45.62	-61.82, -50.92
	Difference in LS Means‡: Fezolinetant vs Placebo			
	LS mean (SE)	NA	-16.34 (3.92)	-21.65 (3.92)
	95% CI (2-sided)		-24.04, -8.63	-29.36, -13.94
	P value§ (2-sided)		< 0.001	< 0.001
Week 12	n	140	133	145
	Mean (SD)	6.73 (7.58)	4.80 (5.59)	4.49 (5.39)
	Median	5.00	3.29	2.83
	Min, Max	0.0, 64.0	0.0, 44.0	0.0, 33.3
	Percentage Change from Baseline†			
	n	140	133	145
	Mean (SD)	-45.35 (39.79)	-58.64 (35.44)	-64.27 (34.92)
	Median	-50.56	-64.84	-72.27
	Min, Max	-100.0, 103.8	-100.0, 36.1	-100.0, 120.4
	LS mean (SE)	-46.91 (2.87)	-60.55 (2.87)	-65.85 (2.85)
	95% CI (2-sided)	-52.56, -41.26	-66.20, -54.90	-71.45, -60.25
	Difference in LS Means‡: Fezolinetant vs Placebo			
	LS mean (SE)	NA	-13.64 (4.07)	-18.94 (4.05)
	95% CI (2-sided)		-21.62, -5.65	-26.89, -10.98
	P value§ (2-sided)		< 0.001	< 0.001

All participants who were randomized and received at least 1 dose of study intervention (Full Analysis Set). The LS means, SE, CI and P values come from a MMRM analysis of covariance model with percent change from baseline as the dependent variable and treatment group, week and smoking status (current vs former/never) as factors, with baseline measurement and baseline weight as covariates, as well as an interaction of treatment by week and an interaction of baseline measurement by week. CI: confidence interval; LS: least squares; Max: maximum; Min: minimum; MMRM: mixed model repeated measurements; NA: not applicable. † A negative percent change indicated a reduction/improvement from baseline (i.e., a favourable outcome). ‡ Differences were calculated by subtracting the LS mean of placebo group from the LS mean of fezolinetant group. § P value is for comparison of fezolinetant with placebo from the above described MMRM model.

Responder Analysis: Percent Reduction ⩾ 50% and at 100% in the Frequency of Moderate to Severe VMS per 24 h, from Baseline to Each Week up to Week 12

A higher proportion of participants had a ⩾ 50% reduction in the frequency of moderate to severe VMS in the fezolinetant 30 mg and 45 mg groups than in the placebo group at all visits during the 12-week double-blind period; these differences were statistically significant, with the exception of week 12 for participants in the fezolinetant 30 mg group (Table 24). The proportion of participants who had ⩾ 50%

reductions in the frequency of moderate to severe VMS increased in each visit, from 16.8% (placebo), 27.7% (30 mg) and 34.7% (45 mg) at week 1 to 42.5% (placebo), 50.6% (30 mg) and 60.5% (45 mg) at week 12.

During the 12-week double-blind period, the proportion of participants in the fezolinetant 45 mg group with a 100% reduction in the frequency of moderate to severe VMS was higher compared with placebo at all visits (Table 24). A similar trend was observed in the fezolinetant 30 mg group at all visits, with the exception of weeks 1 and 3 at which the proportion was similar to that noted in the placebo group. The proportion of participants who had 100% reductions in the frequency of moderate to severe VMS increased in each visit, from 0.6% (placebo), 0.6% (30 mg) and 1.8% (45 mg) at week 1 to 5.4% (placebo), 9.0% (30 mg) and 15.0% (45 mg) at week 12.

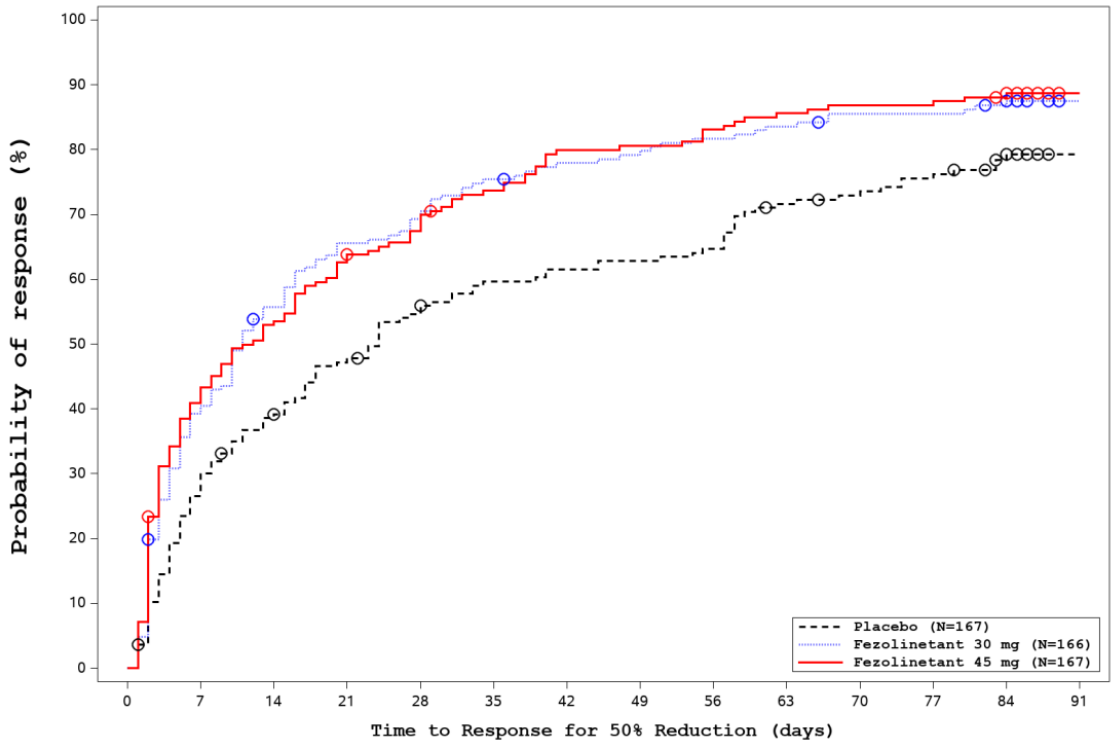
Table 24 Responder analysis of change from baseline in frequency of moderate to severe vasomotor symptoms at selected visits (full analysis set); 12-week double-blind period

Analysis Visit	Responder Criteria	Statistic	Placebo (n = 167)	Fezolinetant 30 mg (n = 166)	Fezolinetant 45 mg (n = 167)
Week 4	≥ 50% Reduction from Baseline	Responders	44 (26.3%)	84 (50.6%)	88 (52.7%)
		Odds ratio: Fezolinetant vs Placebo	NA	2.902	3.218
		95% CI (2-sided)		1.829, 4.657	2.025, 5.172
		P value (2-sided) †		< 0.001	< 0.001
	≥ 100% Reduction from Baseline	Responders	3 (1.8%)	10 (6.0%)	17 (10.2%)
		Odds ratio: Fezolinetant vs Placebo	NA	3.474	6.184
		95% CI (2-sided)		1.039, 15.712	2.025, 26.875
		P value (2-sided) †		0.062	0.004
Week 12	≥ 50% Reduction from Baseline	Responders	71 (42.5%)	84 (50.6%)	101 (60.5%)
		Odds ratio: Fezolinetant vs Placebo	NA	1.373	2.090
		95% CI (2-sided)		0.891, 2.122	1.351, 3.252
		P value (2-sided) †		0.152	< 0.001
	≥ 100% Reduction from Baseline	Responders	9 (5.4%)	15 (9.0%)	25 (15.0%)
		Odds ratio: Fezolinetant vs Placebo	NA	1.701	3.049
		95% CI (2-sided)		0.733, 4.169	1.420, 7.125
		P value (2-sided) †		0.225	0.006

All participants who were randomized and received at least 1 dose of study intervention (Full Analysis Set). Participants with missing vasomotor symptoms at an analysis visit were considered non-responders. † Based on logistic regression with treatment group and smoking status (current vs former/never) as factors and mean frequency of vasomotor symptoms as a covariate. An odds ratio of > 1 indicated a favourable response in the fezolinetant group. CI: Confidence interval; NA: not applicable.

Median time to a ⩾ 50% reduction response (95% CI) was 11 days (8, 15) and 12 days (7, 16) in the fezolinetant 30 mg and 45 mg groups respectively, compared with 24 days (17, 31) in the placebo group (Figure 21). Median times to 100% reduction response were not estimable.

Figure 21 Kaplan-Meier Plot of time to ⩾ 50% reduction responders of moderate to severe vasomotor symptoms (full analysis set); 12-week double-blind period



Number at risk

Placebo	167	116	99	85	70	64	61	59	56	44	40	36	24	0
Fezolinetant 30 mg	166	98	72	56	48	40	35	32	29	26	22	22	10	1
Fezolinetant 45 mg	167	94	77	59	49	42	32	31	27	23	21	20	14	0

All participants who were randomized and received at least 1 dose of study intervention (Full Analysis Set). Based on Kaplan-Meier estimates stratified by treatment group. The time to response was the first day with ⩾ 50% response. The censoring time was the number of days from first dosing date up to the last dosing date. For the non-responders, it was censored at the end of treatment. An open circle indicated censoring.

Frequency of Moderate to Severe VMS, Change from Baseline to Week 24

Participants treated with fezolinetant 30 mg and 45 mg for the entire study had greater reductions in the frequency of moderate to severe VMS compared with placebo during the 12-week double-blind period. This improvement in VMS frequency was sustained through week 24 (Table 25).

In participants who received placebo for the 12-week double-blind period, there was an improvement in VMS frequency from baseline to week 24 of fezolinetant exposure (study week 36) once these participants were re-randomized from placebo to fezolinetant treatment (30 mg or 45 mg) for the active treatment extension period [Table]. This improvement included the placebo effect during the 12-week double-blind period and the effect from the re-randomization from placebo to fezolinetant treatment (30 mg or 45 mg). Overall, this improvement in VMS frequency was sustained through week 24 of fezolinetant exposure, with no evidence of reduced effect size suggestive of tachyphylaxis.

Table 25 Change from baseline to week 24 (24 weeks of fezolinetant exposure) in mean frequency of moderate to severe vasomotor symptoms per 24 h (full analysis set, fezolinetant); 52-week period

Analysis Visit	Statistic	Placebo/ Fezolinetant 30 mg (n = 76)	Placebo/ Fezolinetant 45 mg (n = 75)	Fezolinetant 30 mg (n = 166)	Fezolinetant 45 mg (n = 167)
Baseline ‡	n	76	75	166	167
	Mean (SD)	12.44 (6.60)	10.91 (2.95)	11.23 (4.88)	11.79 (8.26)
	Median	10.15	10.33	10.15	9.90
	Min, Max	7.2, 40.7	5.6, 19.9	2.5, 54.1	7.0, 91.1
24 weeks of Fezolinetant Exposure §	n	62	60	131	134
	Mean (SD)	3.81 (5.24)	3.89 (6.07)	3.43 (4.83)	3.12 (4.50)
	Median	2.57	1.93	2.17	1.33
	Min, Max	0.0, 33.1	0.0, 29.3	0.0, 38.0	0.0, 28.9
	Change from Baseline†				
	n	62	60	131	134
	Mean (SD)	-9.01 (5.80)	-7.08 (5.40)	-7.86 (4.21)	-7.96 (4.53)
	Median	-7.74	-7.66	-7.60	-7.60
	Min, Max	-39.0, 5.0	-19.9, 13.6	-25.6, 5.6	-26.4, 12.3

All participants who were randomized and received at least 1 dose of fezolinetant during either the 12-week double-blind or the active treatment extension periods (Full Analysis Set, Fezolinetant). Results in this table include only data from 24 weeks of fezolinetant exposure. For the placebo/fezolinetant groups, data from the 12-week placebo-controlled period (placebo data) are not included. These participants were re-randomized in a 1:1 ratio to 30 mg or 45 mg of fezolinetant after 12 weeks of placebo and only data from the active treatment extension period (while they were receiving fezolinetant) are analysed for these participants. For the fezolinetant groups, data from the 12-week period are included as these participants were on fezolinetant for the entire duration of the study. Max: maximum; Min: minimum. † A negative change indicated a reduction/improvement from baseline (i.e., a favourable outcome). ‡ Baseline for all treatment groups is the value taken at the start of the study, on or prior to first dose of placebo or fezolinetant. § Week 24 from study start for participants in the fezolinetant 30 mg and 45 mg groups; Week 36 from study start for participants in the placebo/fezolinetant groups.

Severity of Moderate to Severe VMS, Change from Baseline to Week 24

Participants treated with fezolinetant 30 mg and 45 mg for the entire study had reductions in the severity of moderate to severe VMS compared with placebo during the 12-week double-blind period. This improvement in VMS severity was sustained through week 24 (Table 26).

In participants who received placebo for the 12-week double-blind period, there was an improvement in VMS severity once these participants were re-randomized from placebo to fezolinetant treatment (30 mg or 45 mg) for the active treatment extension period (Table 26). This improvement included the placebo effect during the 12-week double-blind period and the effect from the re-randomization from placebo to fezolinetant treatment (30 mg or 45 mg). Overall, this improvement in VMS severity was sustained through week 24, with no evidence of reduced effect size suggestive of tachyphylaxis.

Table 26 Change from Baseline to Week 24 (24 Weeks of Fezolinetant Exposure) in Mean Severity of Moderate to Severe Vasomotor Symptoms per 24 h (Full Analysis Set, Fezolinetant); 52-week Period

Analysis Visit	Statistic	Placebo/ Fezolinetant 30 mg (n = 76)	Placebo/ Fezolinetant 45 mg (n = 75)	Fezolinetant 30 mg (n = 166)	Fezolinetant 45 mg (n = 167)
Baseline ‡	n	76	75	166	167
	Mean (SD)	2.38 (0.33)	2.44 (0.31)	2.44 (0.33)	2.41 (0.34)
	Median	2.34	2.43	2.44	2.34
	Min, Max	2.0, 3.0	2.0, 3.0	2.0, 3.0	1.9, 3.0
24 weeks of Fezolinetant Exposure §	n	62	60	131	134
	Mean (SD)	1.61 (0.84)	1.49 (0.86)	1.58 (0.91)	1.52 (0.87)
	Median	1.67	1.69	1.79	1.54
	Min, Max	0.0, 3.0	0.0, 3.0	0.0, 3.0	0.0, 3.0
	Change from Baseline†				
	n	62	60	131	134
	Mean (SD)	-0.78 (0.85)	-0.95 (0.88)	-0.85 (0.88)	-0.90 (0.80)
	Median	-0.61	-0.79	-0.59	-0.90
	Min, Max	-3.0, 0.6	-3.0, 0.5	-3.0, 0.4	-2.8, 0.7

Baseline includes moderate to severe incidences. Postbaseline includes mild, moderate and severe incidences. All participants who were randomized and received at least 1 dose of fezolinetant during either the 12-week double-blind or the active treatment extension periods (Full Analysis Set, Fezolinetant). Results in this table include only data from 24 weeks of fezolinetant exposure. For the placebo/fezolinetant groups, data from the 12-week placebo-controlled period (placebo data) are not included. These participants were re-randomized in a 1:1 ratio to 30 mg or 45 mg of fezolinetant after 12 weeks of placebo and only data from the active treatment extension period (while they were receiving fezolinetant) are analysed for these participants. For the fezolinetant groups, data from the 12-week period are included as these participants were on fezolinetant for the entire duration of the study. Max: maximum; Min: minimum. † A negative change indicated a reduction/improvement from baseline (i.e., a favourable outcome). ‡ Baseline for all treatment groups is the value taken at the start of the study, on or prior to first dose of placebo or fezolinetant. § Week 24 from study start for participants in the fezolinetant 30 mg and 45 mg groups; Week 36 from study start for participants in the placebo/fezolinetant groups.

PGI-C VMS Score

A higher proportion of participants in the fezolinetant 30 mg and 45 mg groups compared with placebo reported a positive change in PGI-C VMS at weeks 4 and 12. Overall, participants in both the fezolinetant 30 mg and 45 mg groups had a statistically significant difference relative to placebo. The trend observed in the fezolinetant 30 mg and 45 mg groups in the first 12 weeks of treatment was maintained throughout the active treatment extension period.

In the placebo/fezolinetant groups, a higher proportion of participants reported a positive change in PGI-C VMS during the active treatment extension period compared with the 12-week double-blind period. In the placebo/fezolinetant groups, approximately 60% of the participants reported a 'much better' response in either group during the 52-week period compared with 24.3% of the participants at week 12 during the 12-week double-blind period.

Exploratory Efficacy Endpoints

Moderate to Severe VMS

- *Responder Analysis: Percent Reduction ⩾ 75% and ⩾ 90% in the Frequency of Moderate to Severe VMS from Baseline to Each Week up to Week 12*

A higher proportion of responders had a ⩾ 75% reduction in the frequency of moderate to severe VMS in the fezolinetant 30 mg and 45 mg groups than in the placebo group at all visits during the 12-week

double-blind period. The proportion of participants who had ⩾ 75% reductions in the frequency of moderate to severe VMS increased in each visit, from 3.6% in the placebo and 11.4% in each fezolinetant groups at week 1 to 21.0% (placebo), 33.7% (30 mg) and 39.5% (45 mg) at week 12.

The same trend was also observed for responders with a ⩾ 90% reduction in the frequency of moderate to severe VMS. The proportion of participants who had ⩾ 90% reductions in the frequency of moderate to severe VMS increased in each visit, from 1.2% in the placebo group, 3.6% (30 mg) and 3.0% (45 mg) in the fezolinetant groups at week 1 to 12.0% (placebo), 18.1% (30 mg) and 26.3% (45 mg) at week 12.

- *Clinically Meaningful Within-Subject Change Thresholds, Frequency of Moderate to Severe Vasomotor Symptoms*

Supplemental prespecified analyses on the clinically meaningful within-subject change thresholds in the frequency of moderate to severe VMS were conducted according to the prespecified Psychometric Analysis Plan.

The anchor-based method was the primary approach, and the PGI-C VMS was proposed as the primary anchor measure. Analyses identified clinically meaningful thresholds for frequency of VMS reduction: at week 4, the threshold was -6.11 and at week 12, the threshold was -6.66.

A higher proportion of participants in the fezolinetant 30 mg and 45 mg groups than those in the placebo group (significant at 5% without multiplicity adjustment) achieved a clinically meaningful within-subject change from baseline to weeks 4 and 12 in the frequency of moderate to severe VMS; this was observed for the different missing data imputation analysis: last observation carried forward, missing as a non-responder and including observed cases only.

- *Severity of Moderate to Severe VMS, Change from Baseline to Each Week up to Week 12 Excluding Mild Events Postbaseline*

Participants treated with fezolinetant 30 mg and 45 mg had greater reductions in the mean change from baseline to weeks 4 and 12 in the severity of moderate to severe VMS excluding mild events postbaseline compared with placebo. These reductions were similar to those observed in the analysis that did include these mild events.

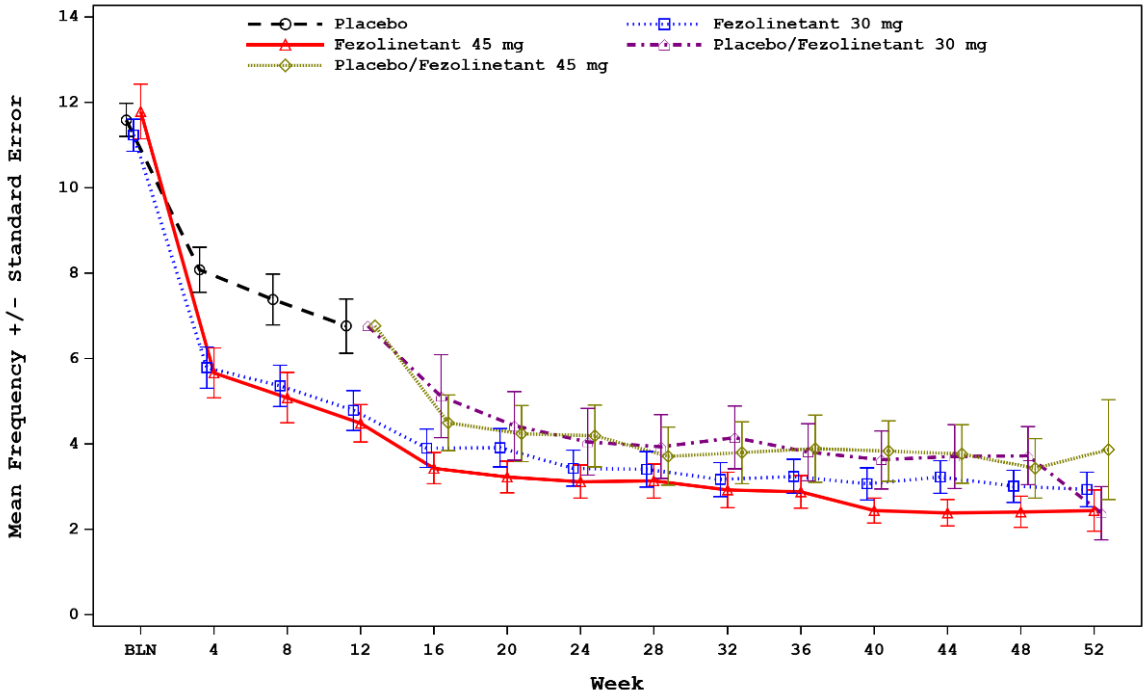
- *Mean Change from Baseline in the Daily Frequency of Moderate to Severe VMS for the First Week*

During the first week of treatment, the reductions from baseline in the frequency of moderate to severe VMS were greater in the fezolinetant groups compared with placebo for each daily score evaluation.

- *Frequency and Severity of Moderate to Severe VMS, Change from Baseline to Each Visit in the Active Treatment Extension Period and the Follow-up Visit*

In an analysis of change from baseline to each visit, fezolinetant demonstrated a reduction in VMS frequency and severity as early as week 1 with improvement sustained over time up to 52 weeks. Participants on placebo when re-randomized to active fezolinetant demonstrated benefit from fezolinetant treatment on VMS frequency and severity throughout the remainder of the 52-week study (Figure 22).

Figure 22 Mean Frequency of Moderate to Severe Vasomotor Symptoms per 24 h by Visit (Full Analysis Set, Fezolinetant); 52-week Period



Number of subjects														
Placebo	167	151	148	141										
Fezolinetant 30 mg	166	155	143	141	132	134	131	128	131	124	121	117	118	53
Fezolinetant 45 mg	167	155	154	149	140	137	134	135	131	132	125	131	126	55
Placebo/Fezolinetant 30 mg					70	66	64	62	58	62	57	57	55	20
Placebo/Fezolinetant 45 mg					69	67	64	64	63	60	61	59	54	22

All participants who were randomized and received at least 1 dose of fezolinetant during either the 12-week double-blind or the active treatment extension periods (Full Analysis Set, Fezolinetant) Baseline for all treatment groups is the value taken at the start of the study, on or prior to first dose of placebo or fezolinetant. At week 12, participants in the placebo group were re-randomized in a 1:1 ratio to 30 mg or 45 mg of fezolinetant for the active treatment extension period. For the fezolinetant groups, participants were on fezolinetant for the entire duration of the study. Weeks shown indicate weeks relative to initial randomization. BLN: baseline.

Mild, Moderate and Severe VMS

- *Frequency of Mild, Moderate and Severe VMS, Change from Baseline to Each Week up to Week 12*

Participants treated with fezolinetant 30 mg and 45 mg had greater reductions from baseline in the mean change in frequency of mild, moderate and severe VMS compared with placebo at each week during the 12-week double-blind period. These reductions were similar to those observed for moderate and severe VMS.

- *Frequency of Mild, Moderate and Severe VMS, Percent Reduction from Baseline to Each Week up to Week 12*

Participants treated with fezolinetant 30 mg and 45 mg had reductions from baseline in the percent change in frequency of mild, moderate and severe VMS relative to placebo during the 12-week double-blind period. The decreases were similar to those observed for moderate and severe VMS.

- *Responder Analysis: Percent Reduction ⩾ 50%, ⩾ 75%, ⩾ 90% and at 100% in the Frequency of Mild, Moderate and Severe VMS from Baseline to Each Week up to Week 12*

A higher proportion of responders had a ⩾ 50% reduction in the frequency of mild, moderate and severe VMS in the fezolinetant groups than in the placebo group at all visits during the 12-week

double-blind period. The same trend was observed for responders with a ⩾ 75%, ⩾ 90% and 100% reduction in mean frequency of mild, moderate and severe VMS.

- *Severity of Mild, Moderate and Severe VMS, Change from Baseline to Each Week up to Week 12*

Participants treated with fezolinetant 30 mg and 45 mg had greater reductions from baseline in mean severity of mild, moderate and severe VMS compared with placebo during the 12-week double-blind period.

Patient-reported Outcomes

- *PROMIS SD SF 8b Total Score*

There was a numerical reduction (improvement) from baseline in PROMIS SD SF 8b (sleep disturbance) relative to placebo at week 4 in participants treated with fezolinetant 30 mg (P = 0.082) and a statistically significant reduction with fezolinetant 45 mg (P < 0.001). The reductions at week 4 and week 12 in the fezolinetant 30 mg and 45 mg groups were maintained throughout the active treatment extension period.

Participants who received placebo for the 12-week double-blind period had an improvement from baseline in PROMIS SD SF 8b once these participants were re-randomized from placebo to fezolinetant treatment (30 mg or 45 mg) for the active treatment extension period. This improvement in sleep in these participants after re-randomization to fezolinetant was similar to that achieved by the participants in the fezolinetant groups from the study start.

- *PROMIS SRI SF 8a*

There was a numerical reduction (improvement) from baseline in PROMIS SRI SF 8a relative to placebo at weeks 4 and 12 in participants treated with fezolinetant 30 mg (week 4: P =0.976, week 12: P = 0.293) or 45 mg (week 4: P =0.054, week 12: P = 0.164). These reductions in the fezolinetant 30 mg and 45 mg groups were maintained throughout the active treatment extension period. Participants who received placebo for the 12-week double-blind period had an improvement from baseline in PROMIS SRI SF 8a once these participants were re-randomized from placebo to fezolinetant treatment (30 mg or 45 mg) for the active treatment extension period.

- *PGI Scales*

There was a difference in the proportions of participants reporting sleep disturbance severity problems (PGI-S SD) in the fezolinetant 30 mg and 45 mg groups compared with placebo at weeks 4 (30 mg: P= 0.060, 45 mg: P < 0.001) and 12 (30 mg: P= 0.104, 45 mg: P =0.028). The proportion of participants with severe problems in PGI-S SD was lower in the fezolinetant 30 mg and 45 mg groups relative to placebo at weeks 4 and 12. The proportion of participants with severe problems decreased from baseline to weeks 4 and 12 in both fezolinetant 30 mg and 45 mg groups.

The proportion of participants with moderate problems in PGI-S SD was lower in the fezolinetant 30 mg and 45 mg groups relative to placebo at week 4. A lower proportion relative to placebo was also observed at week 12 in the fezolinetant 45 mg group. The proportion of participants with moderate problems decreased from baseline to weeks 4 and 12 in both fezolinetant 30 mg and 45 mg groups.

By week 4, the proportions of participants with mild problems in PGI-S SD increased from baseline in the fezolinetant 30 mg and 45 mg groups and were higher than in the placebo group.

The effect of fezolinetant treatment on the improvement of PGI-S SD was observed throughout the active treatment extension period, indicating a sustained benefit in sleep disturbance, a symptom linked with VMS associated with menopause.

A higher proportion of participants in the fezolinetant 30 mg and 45 mg groups compared with placebo reported a positive change in PGI-C SD at weeks 4 and 12. The proportion of participants who reported a little better, moderately better and much better PGI-C SD combined scores was higher in the fezolinetant 30 mg (week 4: P = 0.003, week 12: P = 0.038) and 45 mg groups (weeks 4 and 12: P < 0.001) compared with placebo.

The trend observed in the fezolinetant 30 mg and 45 mg groups was maintained throughout the active treatment extension period, as reported until week 36 (week 24 of fezolinetant exposure). In the placebo/fezolinetant groups, a higher proportion of participants reported a positive change in PGI-C SD during the active treatment extension period (reported until week 24 [week 12 of fezolinetant exposure]) compared with the 12-week double-blind period. These results from the active treatment extension period in the placebo/fezolinetant groups followed the trend observed in the participants who received fezolinetant for the entire study.

- *MENQOL*

In participants treated with fezolinetant 30 mg and 45 mg, there was reduction (improvement) from baseline in MENQOL total score relative to placebo at weeks 4 and 12. Reductions (improvement) relative to placebo were also observed in all MENQOL domains at weeks 4 and 12, including in the physical (30 mg/week 4: P = 0.048; 45 mg/week 4: P = 0.001, 45 mg/week 12: P = 0.004), psychosocial (45 mg/week 4: P = 0.006, 45 mg/week 12 = 0.012), sexual (45 mg/week 4: P = 0.040) and vasomotor (30 mg/week 4: P < 0.001, 45 mg/week 4: P < 0.001, 30 mg/ week 12: P = 0.006, 45 mg/week 12: P < 0.001) domains.

These improvements in MENQOL total score and domains in the fezolinetant 30 mg and 45 mg groups were maintained throughout the active treatment extension period.

Participants who received placebo for the 12-week double-blind period had an improvement from baseline in MENQOL total score and domains once these participants were re-randomized from placebo to fezolinetant treatment (30 mg or 45 mg) for the active treatment extension period, with the exception of the sexual and physical domains which remained similar compared with the 12-week double-blind period.

- *EQ-5D-5L*

In participants treated with fezolinetant 30 mg and 45 mg, there was an increase (improvement) from baseline in EQ-5D-5L VAS score relative to placebo at weeks 4 and 12. There was no difference from placebo in EQ-5D-5L dimension scores at weeks 4 or 12.

The treatment effect on EQ-5D-5L VAS score in the fezolinetant 30 mg and 45 mg groups was sustained throughout the active treatment extension period. Participants who received placebo for the 12-week double-blind period had an increase from baseline in EQ-5D-5L VAS score once these participants were re-randomized from placebo to fezolinetant treatment (30 mg or 45 mg) for the active treatment extension period.

The magnitude of effect of fezolinetant on EQ-5D-5L dimension scores observed during the active treatment extension period was similar to that of the 12-week double-blind period.

- *WPAI-VMS*

In participants treated with fezolinetant 30 mg and 45 mg, there was a numerical reduction (improvement) from baseline in WPAI-VMS domain scores relative to placebo at weeks 4 and 12, including in the absenteeism (45 mg/week 12: P = 0.043), activity impairment (30 mg/week 4: P = 0.018, 45 mg/week 4: P = 0.020, 45 mg/week 12: P = 0.004), overall work productivity loss (45 mg/week 4: P = 0.012, 30 mg/week 12: P = 0.006, 45 mg/week 12: P < 0.001) and presenteeism (45

mg/week 4: P = 0.010, 30 mg/week 12: P = 0.045, 45 mg/week 12: P = 0.004) domains. The effect of fezolinetant treatment on WPAI-VMS domain scores was sustained throughout the active treatment extension period, with the exception of the absenteeism domain.

- **Summary of main efficacy results**

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 27 Summary of efficacy for trial 693-CL-0301 (SKYLIGHT 1)

Title: A Phase 3, Randomized, Placebo-controlled, 12-week Double-blind Study, followed by a Non-Controlled Extension Treatment Period, to Assess the Efficacy and Safety of Fezolinetant in Women Suffering from Moderate to Severe Vasomotor Symptoms (Hot Flashes) Associated with Menopause		
Study identifier	2693-CL-0301 (short title: Skylight 1), EudraCT 2018-003528-35	
Design	randomized, 12-week double-blind, placebo-controlled, parallel group, multicentre clinical study	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	12 weeks 35 days screening period 40 weeks
Hypothesis	Superiority	
Treatments groups	Fezolinetant 30 mg	Women aged ⩾ 40 years and ⩽ 65 years suffering from moderate to severe VMS associated with menopause. Treatment: 30 mg (one 30 mg tablet and one 15 mg placebo tablet) once daily Duration: 52 weeks Number randomized: 176 patients
	Fezolinetant 45 mg	Women aged ⩾ 40 years and ⩽ 65 years suffering from moderate to severe VMS associated with menopause. Treatment: 45 mg (one 30 mg tablet and one 15 mg tablet) once daily Duration: 52 weeks Number randomized: 176 patients
	Placebo	Women aged ⩾ 40 years and ⩽ 65 years suffering from moderate to severe VMS associated with menopause.

			Treatment: Placebo (one 30 mg placebo tablet and one 15 mg placebo tablet) once daily Duration: 12 weeks* Number randomized: 175 patients * After completing 12 weeks of treatment, subjects on placebo were reassigned to 30 mg or 45 mg of active treatment in a non-controlled extension treatment period through end of study. Subjects who were already randomized on an active arm continued on their assigned dose for the remaining 40 weeks of treatment
Endpoints and definitions	Co- primary endpoints		• Mean change in the frequency of moderate to severe VMS from baseline to week 4 • Mean change in the frequency of moderate to severe VMS from baseline to week 12 • Mean change in the severity of moderate to severe VMS from baseline to week 4 • Mean change in the severity of moderate to severe VMS from baseline to week 12
	Key secondary endpoint		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
Database lock	5 Feb 2021 (12 week DBL)		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	Full Analysis Set (all participants who were randomized and received at least 1 dose of study drug) 4 and 12 weeks			
Effect estimate per comparison (co-primary endpoints)	Treatment group	Placebo	Fezolinetant 30 mg	Fezolinetant 45 mg
	Number of subject	175	176	176
	Mean change in the frequency of moderate to severe VMS from baseline to week **4** LS mean (SE) (95% CI)	-3.32 (0.29) (-3.89, -2.74)	-5.19 (0.30) (-5.78, -4.60)	-5.39 (0.30) (-5.97, -4.81)

	Difference in LS means (fezolinetant vs placebo) in the frequency of moderate to severe VMS from baseline to week **4** LS mean (SE) (95% CI) (p-value)	-	-1.87 (0.42) (-2.69, -1.05) (p<0.001)	-2.07 (0.42) (-2.89, -1.25) (p<0.001)
	Mean change in the frequency of moderate to severe VMS from baseline to week **12** LS mean (SE) (95% CI)	-3.90 (0.31) (-4.50, -3.29)	-6.28 (0.32) (-6.90, -5.66)	-6.44 (0.31) (-7.04, -5.84)
	Difference in LS means (fezolinetant vs placebo) in the frequency of moderate to severe VMS from baseline to week **12** LS mean (SE) (95% CI) (p-value)	-	-2.39 (0.44) (-3.25, -1.52) (p<0.001)	-2.55 (0.43) (-3.40, -1.70) (p<0.001)
	Mean change in the severity of moderate to severe VMS from baseline to week **4** LS mean (SE) (95% CI)	-0.27 (0.04) (-0.35, -0.19)	0.42 (0.04) (-0.50, -0.34)	-0.46 (0.04) (-0.54, -0.37)
	Difference in LS means (fezolinetant vs placebo) in the severity of moderate to severe VMS from baseline to week **4** LS mean (SE) (95% CI) (p-value)	-	-0.15 (0.06) (-0.27, -0.03) (p=0.012)	-0.19 (0.06) (-0.30, -0.07) (p=0.002)
	Mean change in the severity of moderate to severe VMS from baseline to week **12** LS mean (SE) (95% CI)	-0.37 (0.05) (-0.47, -0.26)	0.60 (0.05) (-0.71, -0.50)	-0.57 (0.05) (-0.67, -0.47)
	Difference in LS means (fezolinetant vs placebo) in the severity of moderate to severe VMS from baseline to week **12** LS mean (SE) (95% CI) (p-value)	-	-0.24 (0.08) (-0.39, -0.09) (p=0.001)	-0.20 (0.08) (-0.35, -0.06) (p=0.007)

Effect estimate per comparison (key secondary endpoint)	**Mean change in the PROMIS SD SF 8b total score** from baseline to week 12 (LS mean (SE) (95% CI)	-3.2 (0.5) (-4.2, -2.1)	-3.7 (0.6) (-4.8, -2.6)	-4.2 (0.5) (-5.3, -3.2)
	Difference in LS means (fezolinetant vs placebo) in the PROMIS SD SF 8b total score from baseline to week 12 (LS mean (SE) (95% CI) (p-value)		-0.5 (0.8) (-2.0, 1.0) (p=0.489)	1.1 (0.7) (-2.5, 0.4) (p=0.155)
Notes	None.			

Table 28 Summary of efficacy for trial 2693-CL-0302 (short title: Skylight 2)

Title: A Phase 3, Randomized, Placebo-controlled, 12-week Double-blind Study, followed by a Non-Controlled Extension Treatment Period, to Assess the Efficacy and Safety of Fezolinetant in Women Suffering from Moderate to Severe Vasomotor Symptoms (Hot Flashes) Associated with Menopause		
Study identifier	2693-CL-0302 (short title: Skylight 2)	
Design	randomized, 12-week double-blind, placebo-controlled, parallel group, multicentre clinical study	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	12 weeks 35 days screening period 40 weeks
Hypothesis	Superiority	
Treatments groups	Fezolinetant 30 mg	Women aged ⩾ 40 years and ⩽ 65 years suffering from moderate to severe VMS associated with menopause. Treatment: 30 mg (one 30 mg tablet and one 15 mg placebo tablet) once daily Duration: 52 weeks Number randomized: 166 patients
	Fezolinetant 45 mg	Women aged ⩾ 40 years and ⩽ 65 years suffering from moderate to severe VMS associated with menopause.

			Treatment: 45 mg (one 30 mg tablet and one 15 mg tablet) once daily Duration: 52 weeks Number randomized: 167 patients
	Placebo		Women aged ⩾ 40 years and ⩽ 65 years suffering from moderate to severe VMS associated with menopause. Treatment: Placebo (one 30 mg placebo tablet and one 15 mg placebo tablet) once daily Duration: 12 weeks* Number randomized: 167 patients * After completing 12 weeks of treatment, subjects on placebo were reassigned to 30 mg or 45 mg of active treatment in a non-controlled extension treatment period through end of study. Subjects who were already randomized on an active arm continued on their assigned dose for the remaining 40 weeks of treatment
Endpoints and definitions	Co- primary endpoints		• Mean change in the frequency of moderate to severe VMS from baseline to week 4 • Mean change in the frequency of moderate to severe VMS from baseline to week 12 • Mean change in the severity of moderate to severe VMS from baseline to week 4 • Mean change in the severity of moderate to severe VMS from baseline to week 12
	Key secondary endpoint		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
Database lock	23 April 2021		
Results and Analysis			

Analysis description	**Primary Analysis**			
Analysis population and time point description	Full Analysis Set (all participants who were randomized and received at least 1 dose of study drug) 4 and 12 weeks			
Effect estimate per comparison (co-primary endpoints)	Treatment group	Placebo	Fezolinetant 30 mg	Fezolinetant 45 mg
	Number of subject	167	166	167
	Mean change in the frequency of moderate to severe VMS from baseline to week **4** LS mean (SE) (95% CI)	-3.72 (0.33) (-4.36, -3.07)	-5.53 (0.33) (-6.17, -4.90)	-6.26 (0.30) (-5.97, -4.81)
	Difference in LS means (fezolinetant vs placebo) in the frequency of moderate to severe VMS from baseline to week **4** LS mean (SE) (95% CI) (p-value)	-	-1.82 (0.46) (-2.73, -0.91) (p<0.001)	-2.55 (0.46) (-3.45, -1.64) (p<0.001)
	Mean change in the frequency of moderate to severe VMS from baseline to week **12** LS mean (SE) (95% CI)	-4.97 (0.39) (-5.73, -4.20)	-6.63 (0.39) (-7.59, -6.06)	7.50 (0.39) (-8.25, -6.74)
	Difference in LS means (fezolinetant vs placebo) in the frequency of moderate to severe VMS from baseline to week **12** LS mean (SE) (95% CI) (p-value)	-	-1.86 (0.55) (-2.94, -0.78) (p<0.001)	-2.53 (0.55) (-3.60, -1.46) (p<0.001)
	Mean change in the severity of moderate to severe VMS from baseline to week **4** LS mean (SE)	-0.32 (0.05) (-0.41, -0.23)	-0.47 (0.05) (-0.56, -0.38)	-0.61 (0.05) (-0.70, -0.52)

	(95% CI)			
	Difference in LS means (fezolinetant vs placebo) in the severity of moderate to severe VMS from baseline to week **4** LS mean (SE) (95% CI) (p-value)	-	-0.15 (0.06) (-0.27, -0.02) (p=0.021)	-0.29 (0.06) (-0.41, -0.16) (p=0.001)
	Mean change in the severity of moderate to severe VMS from baseline to week **12** LS mean (SE) (95% CI)	-0.48 (0.06) (-0.59, -0.36)	-0.64 (0.06) (-0.76, -0.53)	-0.77 (0.06) (-0.88, -0.65)
	Difference in LS means (fezolinetant vs placebo) in the severity of moderate to severe VMS from baseline to week **12** LS mean (SE) (95% CI) (p-value)	-	-0.16 (0.08) (-0.33, -0.00) (p=0.049)	-0.29 (0.08) (-0.45, -0.13) (p<0.001)
Effect estimate per comparison (key secondary endpoint)	**Mean change in the PROMIS SD SF 8b total score** from baseline to week 12 (LS mean (SE) (95% CI)	-3.4 (0.5) (-4.5, -2.4)	-4.1 (0.5) (-5.1, -3.1)	-5.5 (0.5) (-6.5, -4.4)
	Difference in LS means (fezolinetant vs placebo) in the PROMIS SD SF 8b total score from baseline to week 12 (LS mean (SE) (95% CI) (p-value)	-	-0.7 (0.7) (-2.1, 0.8) (p=0.381)	-2.0 (0.7) (-3.5, -0.6) (p=0.007)
Notes	None.			

2.6.5.3. Clinical studies in special populations

Not applicable

2.6.5.4. In vitro biomarker test for patient selection for efficacy

Not applicable

2.6.5.5. Analysis performed across trials (pooled analyses and meta-analysis)

Not applicable

2.6.5.6. Supportive study

Study 2693-CL-0304 – SKYLIGHT 4 – long term safety study

Methods

Study design

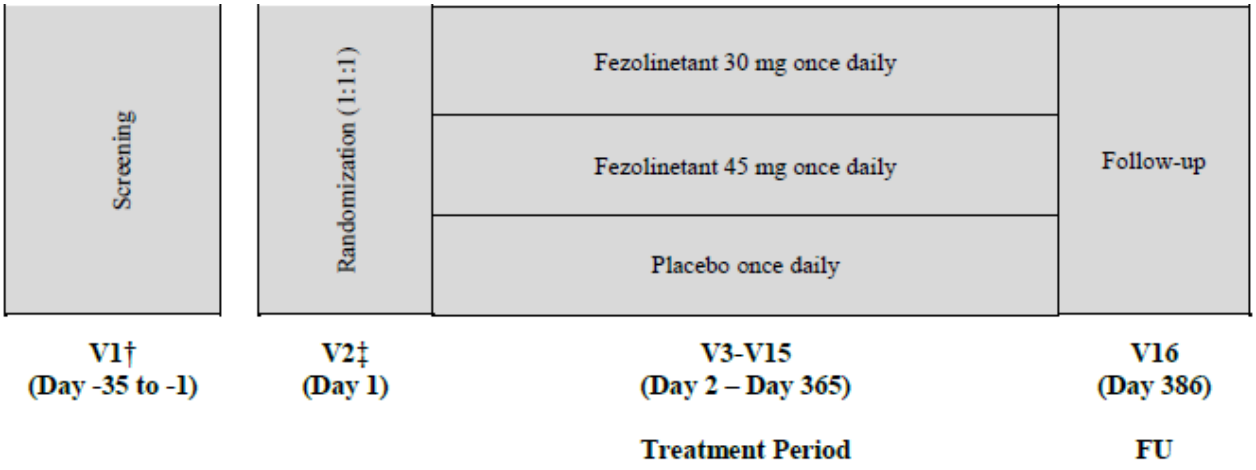
Study 2693-CL-0304 (SKYLIGHT 4) was a 52-week, randomized, placebo-controlled, double-blind, parallel-group, multicentre, phase 3 clinical study to investigate the **long-term safety** and **endometrial health** of fezolinetant in women suffering from VMS associated with menopause.

Approximately 1150 participants were originally planned to be enrolled into this study, which was increased to 1740, with 580 participants per treatment arm in protocol version 3.0 (15 Jun 2020). Participants were randomized 1:1:1 to receive placebo once daily, fezolinetant 30 mg once daily or fezolinetant 45 mg once daily. Approximately 1150 participants were originally planned to be enrolled into this study, which was increased to 1740, with 580 participants per treatment arm in protocol version 3.0 (15 Jun 2020):

- Fezolinetant 30 mg once daily
- Fezolinetant 45 mg once daily
- Placebo once daily

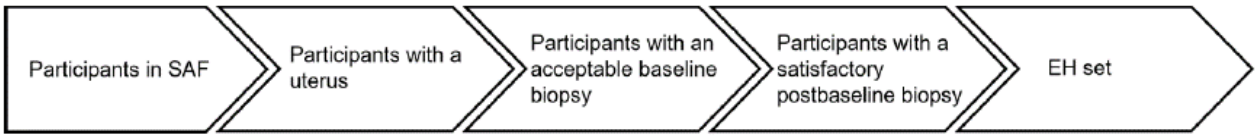
The study consisted of a screening period (days -35 to -1, including the screening visit [visit 1]), and a 52-week treatment period (day 1 [visit 2] to week 52 [visit 15]) and a follow-up visit (Figure 23). The study was performed on an outpatient basis.

Figure 23 Study scheme



FU: follow-up; V: visit. † Screening was to be performed up to 35 days prior to randomization. ‡ Refer to the schedule of assessments for visit 2b.

Figure 24 Flowchart for Inclusion in Endometrial Health Set



The satisfactory endometrial biopsy results were summarized for the EH set. The EH set consisted of all participants who were randomized and received at least 1 dose of study drug, had the postbaseline biopsy done within 30 days after the last dose of study drug and who 1) had an acceptable baseline biopsy at baseline (at least 1 endometrial biopsy with satisfactory tissue and no read of hyperplasia, disordered proliferative pattern or malignancy), where baseline was the last non missing value on or prior to first dose of study drug. When more than 1 biopsy result was present at postbaseline, if there was no final diagnosis of hyperplasia, disordered proliferative pattern or malignancy, the last non-missing satisfactory result within the window was counted; otherwise, the more severe result was counted. 2) had a satisfactory endometrial biopsy result after or on day 326 or a postbaseline final diagnosis of hyperplasia, disordered proliferative pattern or malignancy prior to day 326. EH: endometrial health.

Study participants

The patient population for this study is women ⩾ 40 years and ⩽ 65 years of age with moderate to severe VMS (⩾ 50/week) associated with menopause.

The participant population for this study consisted of individuals born female aged ⩾ 40 and ⩽ 65 years seeking treatment for VMS associated with menopause.

Inclusion criteria

Participants had to be seeking treatment for relief for VMS associated with menopause, confirmed as menopausal per 1 of the following criteria at the screening visit:

- Spontaneous amenorrhea for ≥ 12 consecutive months
- Spontaneous amenorrhea for ≥ 6 months with biochemical criteria of menopause (FSH > 40 IU/L)
- Having had bilateral oophorectomy ≥ 6 weeks prior to the screening visit.

And their screening endometrial biopsy had to be considered evaluable for participants with a uterus.

Exclusion criteria

Participants were excluded if they used a prohibited therapy (and were not willing to wash out and discontinue such drugs for the full extent of the study);

- had an unacceptable result from the TVU assessment at screening;

- had an endometrial biopsy confirming presence of disordered proliferative endometrium, endometrial hyperplasia, endometrial cancer or other clinically significant finding;
- had history within the last 6 months of undiagnosed uterine bleeding;
- had a partial (supracervical) or full hysterectomy (protocol v3.0 and above);
- or had active liver disease, jaundice or elevated liver alanine aminotransferase (ALT) or aspartate aminotransferase (AST), total or direct bilirubin, international normalized ratio or alkaline phosphatase (ALP).
- Participants enrolled on protocol versions 1.0 and 2.0 were not required to have an intact uterus;
- Protocol version 3.0 incorporating substantial amendment 2 [15 June 2020] included exclusion criterion 20 which excluded participants who had partial or full hysterectomies.

Treatments

Study drug

Fezolinetant study drug was supplied in a blinded form by the applicant as fezolinetant 30 mg and 15 mg once daily tablets.

Comparative drug

Placebo was supplied by the applicant in a blinded form to match the active fezolinetant drug tablets.

Objectives

Primary objectives

- to evaluate the **long-term safety** and tolerability of fezolinetant in female individuals seeking treatment for relief of VMS associated with menopause,
- to evaluate the effect of fezolinetant on **endometrial health** after long-term treatment in female individuals seeking treatment for relief of VMS associated with menopause.

Secondary objective

- to evaluate the effect of fezolinetant on **bone mineral density** after long-term treatment in female individuals seeking treatment for relief of VMS associated with menopause.

Exploratory objectives

- to evaluate the effect of fezolinetant on subject-reported quality of life measures and
- to evaluate the pharmacokinetics of fezolinetant and its metabolite, ESN259564.

Outcomes/endpoints

Primary endpoints

The primary variable required the evaluation of the safety of fezolinetant on the following:

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

Secondary endpoints

The secondary objectives examined the effect of fezolinetant on:

- Change from baseline in endometrial thickness at 12 months
- Percentage of subjects with disordered proliferative endometrium
- Change from baseline in bone mineral density (BMD) and trabecular bone score (TBS) at hip and spine at 12 months
- Vital signs: sitting systolic and diastolic blood pressure and pulse rate
- Laboratory tests: haematology, biochemistry and urinalysis
- Columbia-Suicide Severity Rating Scale (C-SSRS)
- ECG parameters

Exploratory endpoints

Exploratory Endpoints were also evaluated in this study:

- mean change on the Menopause-Specific Quality of Life (MENQOL) Total Score and Domain Scores from baseline to specified time points (week 4, 12, 24 and 52),
- mean change on the Euro-Qol-5D-5L (EQ-5D-5L) visual analog scale (VAS) from baseline to specified time points (week 4, 12, 24 and 52), EQ-5D-5L domain scores at specified timepoints (week 4, 12, 24 and 52),
- change from baseline to specified time points in serum concentrations of sex hormones and sex hormone-binding globulin (SHBG) (week 4, 12, 24, 52 and 55),
- plasma concentrations of fezolinetant and the fezolinetant metabolite ESN259564 at specified time points (week 4, 12, 24 and 52).

Statistical methods

In general, summary statistics were provided for all the safety parameters. For AESIs, the rate, odds ratio and their corresponding 95% exact confidence intervals (CI) were presented, which were constructed based on Santner-Snell approach.

Endometrial safety

For the percentage of participants with a final diagnosis of endometrial hyperplasia, endometrial cancer and disordered proliferative endometrium, the exact (Clopper-Pearson) upper one-sided 95% CI was provided. The analysis was based on the final diagnosis evaluated from the 3 pathologists. The final diagnosis was the concordance of the 3 pathologists' diagnoses: if at least 2 pathologists agreed, the result was included, if none of them agreed, then the worst result was used.

Liver safety was analysed by the descriptive summary of change from baseline to each visit, and percentages of participants with post-baseline ALT or AST > 3 x ULN and/or total bilirubin > 2 x ULN.

Endometrial thickness and bone density

Treatment comparisons were performed for endometrial thickness and bone density related endpoints. Changes from baseline in endometrial thickness and bone densities were analysed and each fezolinetant group was compared to placebo using an analysis of covariance (ANCOVA) model, with treatment and strata smoking status (current vs former/never) as factors, with baseline weight and baseline as covariates.

Liver safety

Liver safety was analysed by the descriptive summary of change from baseline to each visit, and percentages of participants with post-baseline ALT or AST > 3 x ULN and/or total bilirubin > 2 x ULN.

Results

Participant flow

A total of 4344 unique participants signed informed consent and were screened. Of those, 2513 failed screening.

A total of 1831 participants were randomized: 611 participants in the placebo group, 611 in the fezolinetant 30 mg group and 609 in the fezolinetant 45 mg group. 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.

The most common reason for discontinuation of treatment was "withdrawal by subject", with a greater percentage of participants in the placebo group discontinuing for this reason than in the fezolinetant groups. No participants discontinued study intervention due to death.

Table 29 Treatment Disposition (Safety Analysis Set)

Category	Placebo (n = 610)	Fezolinetant 30 mg (n = 611)	Fezolinetant 45 mg (n = 609)	Total (n = 1830)
Completed	410 (67.2%)	451 (73.8%)	444 (72.9%)	1305 (71.3%)
Treatment discontinuation †	200 (32.8%)	160 (26.2%)	165 (27.1%)	525 (28.7%)
Primary reason for study intervention discontinuation				
Adverse event	27 (4.4%)	34 (5.6%)	28 (4.6%)	89 (4.9%)
Death	0	0	0	0
Lost to follow-up	39 (6.4%)	30 (4.9%)	33 (5.4%)	102 (5.6%)
Protocol deviation	1 (0.2%)	6 (1.0%)	5 (0.8%)	12 (0.7%)
Withdrawal by subject	119 (19.5%)	79 (12.9%)	85 (14.0%)	283 (15.5%)
Other	14 (2.3%)	11 (1.8%)	14 (2.3%)	39 (2.1%)

All randomized participants who took at least 1 dose of study intervention (Safety Analysis Set). A total of 46 participants (2.5%) discontinued treatment due to COVID-19 during the 52-week study period.

Protocol Deviations

A total of 321 participants (17.5%) had a major protocol deviation. The most common major protocol deviation in all treatment groups was that participants who entered the study did not satisfy the entry criteria [230 participants]).

Conduct of the study

Number of study centres and countries

This study was conducted at 181 centres that enrolled participants in 8 countries (United States [141 sites], Canada [10 sites], Spain [2 sites], Latvia [2 sites], Ukraine [2 sites], Czech Republic [6 sites], United Kingdom [7 sites] and Poland [11 sites]).

Study period

11 Jul 2019 (date of first evaluation) to 21 Jan 2022 (date of last evaluation).

Number of participants (planned and analysed)

Of the 1831 participants randomized in this study, 1830 participants received at least 1 dose of study intervention and were included in the Safety Analysis Set (SAF) and Full Analysis Set (FAS) and 1 participant (placebo group) did not take the study intervention (Table 30). The endometrial health set (the population used to assess biopsy data) consisted of 599 participants.

Table 30 Participant classification (all randomized participants)

Analysis Set	Placebo (n = 611)	Fezolinetant 30 mg (n = 611)	Fezolinetant 45 mg (n = 609)	Total (n = 1831)
Safety analysis set †	610 (99.8%)	611 (100%)	609 (100%)	1830 (99.9%)
Full analysis set ‡	610 (99.8%)	611 (100%)	609 (100%)	1830 (99.9%)
Endometrial health set §	186 (30.4%)	210 (34.4%)	203 (33.3%)	599 (32.7%)

† All randomized participants who took at least 1 dose of study intervention. Any participant erroneously receiving a treatment that was different from the randomized treatment was assigned to the treatment group that the patient received as first dose. ‡ All randomized participants who took at least 1 dose of study intervention. The randomized treatment for each participant was used for summaries by treatment group based on the full analysis set, even if a participant erroneously received a different treatment. § All randomized participants who received at least 1 dose of study intervention, had the postbaseline biopsy done within 30 days after the last dose of study intervention, and had an acceptable biopsy at baseline (at least 1 endometrial biopsy with satisfactory tissue and no read of hyperplasia, disordered proliferative pattern or malignant) and had a satisfactory endometrial biopsy result after or on day 326 or had a postbaseline final diagnosis of hyperplasia, disordered proliferative pattern or malignant prior to day 326

Baseline data

Demographics and Baseline Characteristics

The SAF included White (79.9%) and Black (17.2%) participants, with 20.1% of participants self-identifying as Hispanic or Latino. Most (80.9%) participants were either former smokers or had never smoked. A total of 18.6% of participants had undergone a hysterectomy and 13.5% had undergone an oophorectomy. In addition, 17.0% of participants had received prior treatment with HRT.

Table 31 Demographic and selected baseline characteristics (safety analysis set)

Parameter	Category/Statistic	Placebo (n = 610)	Fezolinetant 30 mg (n = 611)	Fezolinetant 45 mg (n = 609)	Total (n = 1830)
Age (years)	n	610	611	609	1830
	Mean (SD)	54.9 (4.8)	54.7 (4.7)	54.7 (4.8)	54.7 (4.8)
	Median	55.0	55.0	55.0	55.0
	Min, Max	41, 65	40, 65	41, 65	40, 65
Age category	< 55 years	284 (46.6%)	303 (49.6%)	292 (47.9%)	879 (48.0%)
	≥ 55 years	326 (53.4%)	308 (50.4%)	317 (52.1%)	951 (52.0%)
Race	White	502 (82.3%)	479 (78.5%)	479 (78.8%)	1460 (79.9%)
	Black or African American	91 (14.9%)	114 (18.7%)	110 (18.1%)	315 (17.2%)
	American Indian or Alaska Native	3 (0.5%)	3 (0.5%)	2 (0.3%)	8 (0.4%)
	Asian	8 (1.3%)	8 (1.3%)	13 (2.1%)	29 (1.6%)
	More Than One Race	6 (1.0%)	6 (1.0%)	4 (0.7%)	16 (0.9%)
	Missing	0	1	1	2
Ethnicity	Hispanic or Latino	133 (21.8%)	118 (19.3%)	116 (19.1%)	367 (20.1%)
	Not Hispanic or Latino	477 (78.2%)	493 (80.7%)	491 (80.9%)	1461 (79.9%)
	Missing	0	0	2	2
Weight (kg)	n	610	611	609	1830
	Mean (SD)	75.38 (13.14)	75.82 (13.22)	75.86 (13.88)	75.69 (13.41)
	Median	74.38	74.50	74.90	74.80
	Min, Max	39.0, 115.0	45.1, 123.8	45.8, 123.4	39.0, 123.8
BMI (kg/m^2)	n	609	610	608	1827
	Mean (SD)	28.24 (4.56)	28.41 (4.53)	28.42 (4.72)	28.36 (4.60)
	Median	27.89	28.13	28.28	28.12
	Min, Max	18.3, 38.0	18.7, 38.0	18.5, 38.0	18.3, 38.0
BMI category	< 18.5 kg/m^2	2 (0.3%)	0	0	2 (0.1%)
	≥ 18.5 to < 25 kg/m^2	151 (24.8%)	148 (24.3%)	163 (26.8%)	462 (25.3%)
	≥ 25 to < 30 kg/m^2	256 (42.0%)	245 (40.2%)	216 (35.5%)	717 (39.2%)
	≥ 30 kg/m^2	200 (32.8%)	217 (35.6%)	229 (37.7%)	646 (35.4%)
	Missing	1	1	1	3
Smoking status stratification factor †	Current	117 (19.2%)	116 (19.0%)	116 (19.0%)	349 (19.1%)
	Former/never	493 (80.8%)	495 (81.0%)	493 (81.0%)	1481 (80.9%)
Prior hormone replacement therapy	Yes	115 (19.4%)	98 (16.4%)	91 (15.3%)	304 (17.0%)
	No	479 (80.6%)	501 (83.6%)	503 (84.7%)	1483 (83.0%)
	Missing	16	12	15	43
Oophorectomy	No	524 (85.9%)	536 (87.7%)	523 (85.9%)	1583 (86.5%)
	Yes	86 (14.1%)	75 (12.3%)	86 (14.1%)	247 (13.5%)
Hysterectomy	No	483 (79.2%)	511 (83.6%)	495 (81.3%)	1489 (81.4%)
	Yes	127 (20.8%)	100 (16.4%)	114 (18.7%)	341 (18.6%)

All randomized participants who took at least 1 dose of study intervention (Safety Analysis Set). The participant population for this study consisted of female individuals as per inclusion criteria. BMI: body mass index (weight [kg]/height [m2]); Max: maximum; Min: minimum. † Current versus former or never smoking status was a stratification factor for randomization.

Efficacy results

No primary efficacy data were collected for this study. The primary and secondary objectives of this study were safety. Efficacy endpoints in the form of health-related quality of life assessments are described under exploratory efficacy endpoints.

Exploratory Endpoint - Menopause-Specific Quality of Life

In participants treated with fezolinetant 30 mg and 45 mg, there was reduction from baseline (improvement) in MENQOL total score at weeks 4, 12, 24 and 52, with greater reductions in the fezolinetant groups than in the placebo group. The reduction versus placebo was statistically significant at weeks 4, 12 and 52 for both fezolinetant doses. Fezolinetant demonstrated a statistically significant

difference in the MENQOL VMS domain at all timepoints for the fezolinetant 30 mg and 45 mg groups. No significant differences were observed in the MENQOL psychosocial, physical and sexual domains for either fezolinetant dose group when compared to placebo.

Exploratory Endpoint - EuroQoL-5D-5L

Participants in the fezolinetant 30 mg and fezolinetant 45 mg treatment groups had improvements in EQ-5D-5L VAS score throughout the study, however differences were not statistically significantly different from the placebo group. There was no difference from placebo in EQ-5D-5L dimension scores at weeks 4, 12, 24 and 52.

Safety results

The long-term safety results of SKYLIGHT 4 are discussed in the safety section.

2.6.6. Discussion on clinical efficacy

Design and conduct of clinical studies

The efficacy results in the clinical development programme of fezolinetant in this indication are based on the efficacy data from two pivotal phase 3 studies, study 2693-CL-0301 and study 2693-CL-0303 (SKYLIGHT 1 and 2). Importantly, the study design of the current SKYLIGHT 2 study was stated, by the applicant, to be identical to study SKYLIGHT 1. Further, long-term, double-blind, placebo-controlled data from safety study 2693-CL-0304 (SKYLIGHT 4) are provided to support durability of fezolinetant efficacy.

Rationale for the dosing used in the phase 3 clinical trials

The dose-response and concentration-response (nonlinear mixed-effects models) analyses demonstrated clinically relevant increased improvements in VMS frequency and VMS severity with increasing fezolinetant exposure with no difference in once or twice daily dosing. Model predictions indicated a clear reduction in VMS frequency and severity with 30 mg and was therefore considered the lowest effective dose, with the 45 mg showing slightly better results.

In addition, a physiologically-based pharmacokinetic (PBPK) study predicted no ALT elevations for 30 mg and 60 mg for 12 weeks.

This dose was, however, not earlier studied and was therefore proposed to be included as an additional study arm in the phase 3 trials. The current application only only refers to the 45mg qd.

Design and conduct of the main clinical studies

Pivotal studies 2693-CL-0301 and 2693-CL-0302 - SKYLIGHT 1 and 2

As earlier noted, the study designs of the studies SKYLIGHT 1 and 2 were identical. The design of the studies took into consideration the CHMPScientific Advices.

The **pivotal trials SKYLIGHT 1 and 2** were two 12-week, randomized, placebo-controlled, double-blind phase 3 studies to assess the efficacy and safety of fezolinetant in postmenopausal women suffering from moderate to severe vasomotor symptoms (VMS). The 12-week randomized, double-blind and placebo-controlled period, was followed by a 40-week open-label, non-controlled extension treatment period in which former placebo patients were re-randomised to receive fezolinetant 35 mg or 45 mg.

A duration of the double-blind placebo-controlled treatment period of 12 weeks (3 months) is agreed for evaluation of efficacy in patients with VMS symptoms due to postmenopause, as it is in line with the CHMP guideline on clinical investigation of medicinal products for hormone replacement therapy of oestrogen deficiency symptoms in postmenopausal women (EMEA/CHMP/021/97 Rev. 1).

Patient population. The study population selected can be considered reflective of the target population indicated for treatment of VMS in the post menopause, although it is noted that the number of patients with ovariectomy and hysterectomy is rather high. Key eligibility criteria were women, aged 40 – 65 years, inclusive, with moderate to severe VMS (average ⩾ 7 moderate to severe VMS per day or ⩾ 50 per week)) and confirmed as postmenopausal (defined as having amenorrhea for ⩾ 12 consecutive months, or amenorrhea for ⩾ 6 months with FSH >40 IU/L or having had bilateral oophorectomy), who seek treatment for relief for VMS. Key exclusion criteria were use of treatments for VMS, undiagnosed uterine bleeding within 6 months, active liver disease or elevated liver aminotransferases (ALT or AST) and renal impairment as eGFR ⩽ 59 mL/min per 1.73 m^2. However, it is noted that a history of seizures or other convulsive disorders was an exclusion criterion. Since it cannot be concluded with certainty that the convulsions in non-clinical studies are not related to the pharmacological action of fezolinetant, this exclusion criterion was added as a warning in section 4.4 of the SmPC.

Eligible patients were randomly assigned 1:1:1 to receive **study treatment** of fezolinetant 30 mg qd tablets, fezolinetant 45 mg qd tablets and placebo qd tablets. The dose regimen and once daily dose regimen is considered adequately supported by phase 1 and 2 studies and safety analyses (see also discussion on rationale of dose selection above) and in line with the recommendations on dosing in section 4.2 of the SmPC of fezolinetant, and therefore acceptable. The choice to select placebo as comparator is considered acceptable, as for this indication of VMS an active comparator, i.e. hormone replacement therapy, is not generally requested for efficacy purposes. Efficacy can be adequately assessed compared to placebo, as was also agreed during the earlier SAs. In terms of prior and concomitant therapy, treatment with hormone replacement therapy (HRT) and the concomitant use of CYP1A2 inhibitors was not allowed, which is considered acceptable.

The primary analysis in the 12-week double-blind period consisted of meeting **4 co-primary efficacy endpoints**, defined as the mean change in the frequency from baseline to weeks 4 and 12 and mean change in the severity from baseline to weeks 4 and 12 for either the 30 mg and the 45 mg fezolinetant versus placebo. The studies were not powered to compare efficacy between dose groups. These endpoints are similar to those in the Phase 2b dose-finding trial 2693-CL-0205, and in line with the CHMP guideline on clinical investigation of medicinal products for hormone replacement therapy of oestrogen deficiency symptoms in postmenopausal women (EMEA/CHMP/021/97 Rev. 1) and can be considered adequate. In addition, the applicant has selected the PRO of the mean change in the PROMIS SD SF 8b total score from baseline to week 12 as **key secondary efficacy endpoint** in order to assess self-reported sleep disturbance over the past 7 days and includes 8 questions on the perceptions of restless sleep, satisfaction with sleep, refreshing sleep, difficulties sleeping, getting to sleep or staying asleep, amount of sleep and sleep quality. Sleep disturbance and related complaints are an important reason why women seek treatment for VMS. This evaluation can be considered supportive for the primary analysis, pending results.

Regarding **other secondary and exploratory endpoints** included to further evaluate efficacy on the frequency and severity of VMS, the responder analyses, i.e. patients with ≥50 and 100 percent reduction in baseline VMS frequency is considered an important endpoint to assess individual improvement in VMS baseline frequency. Additionally, QoL assessments including patient reported outcomes (PROs) specific symptoms such as productivity and VMS impact. The secondary and exploratory endpoints are considered to further support the evaluation of the efficacy of the treatment on VMS by individual perception of VMS, pending results. Finally, PD parameters, which included

oestradiol, progesterone and SHBG, will provide further information on hormonal effects of fezolinetant noted in phase 1 and phase 2 studies.

Randomisation and blinding procedures are considered acceptable. The **sample size** was estimated to be approximately 450 subjects, 150 subjects in each treatment arm, and was based on the treatment effect observed in the phase 2 dose-ranging study. The sample size is acceptable.

The definitions of the analysis populations are standard and acceptable. Regarding the **statistical methods** of the study, the analysis of the co-primary endpoints was performed using a mixed model for repeated measures (MMRM), including treatment group, week and smoking status as factors, baseline weight and baseline measurement as covariate and treatment by week and baseline by week interactions. The additional covariate baseline weight was added to the model because weight or obesity impact VMS, which is acceptable. The primary analysis model does not use missing data imputation but relies on the implicit missing at random imputation of the MMRM model, consistent with a hypothetical estimand strategy. As mentioned in scientific advice this was considered problematic and it was advised to consider using a treatment policy strategy. However, considering the data the impact of the estimand choice is not likely to influence final results and sensitivity analyses of the co-primary endpoint confirm the robustness of the primary analysis. Continuous secondary endpoints used the same analysis as the primary endpoints and Cochran Mantel Haenszel for responder endpoints and logistic regression for PGI-C, which is appropriate. Multiplicity will be controlled by a combination of a Hochberg procedure (for the 2 doses), co-primary endpoints (for the four primary endpoints within a dose arm) and a hierarchical testing (key secondary PRO endpoint PROMIS SD SF). This will preserve the overall type I error rate and is acceptable.

Efficacy data and additional analyses

Study 2693-CL-0301 (SKYLIGHT 1) – pivotal 12-week, double-blind, placebo-controlled, phase 3

Generally, the recruited patients reflect a postmenopausal population with VMS regarding **demographics**. The participants had a median age of 54.0 years. Most participants were white (82.7%) and were either former smokers or had never smoked (87.4%), 12.6% were current smokers. In addition, 18.4% of participants received prior treatment with HRT. It is noted that patients with VMS with known or previous breast cancer or other oestrogen-dependent malignant tumours have not been included in the clinical trials and this information should be added to section 4.4 of the SmPC (see also SmPC). These **baseline characteristics** were well-balanced in the three study arms of post-menopausal women with VMS. It was, however, noted that a remarkable number of participants with a hysterectomy (i.e. 32.2%) and with ovariectomy (i.e. 21.5%) were enrolled into this study. The majority (70%) of the patients was included with spontaneous amenorrhea for ≥ 12 consecutive months, 4% with spontaneous amenorrhea for ⩾ 6 months with biochemical criteria of menopause (FSH > 40 IU/L), and 15% were having bilateral oophorectomy ⩾ 6 weeks prior to the screening visit (with or without hysterectomy), based on the pre-defined inclusion criteria.

Although it is acknowledged that many guidelines use the term '*menopause*' to define women who are amenorrhoeic for at least 12 months (RCOG/NICE 2015, ACOG 2018, UptoDate 2022), for clarity and to be in line with the inclusion criteria of the pivotal studies, the patients were defined as '*postmenopausal*'. . Of note, the limited data currently available in premenopausal women showed that fezolinetant relevantly interfered in the hormonal balance of the menstrual cycle, with lengthening of the duration of the menstrual cycle. During the perimenopausal transitional years oestradiol levels fluctuate with a significant inter- and intra-individual variability, which may be expected for both perimenopausal women with and without VMS (Stuenkel et al, 2015; ACOG Clinical Management Guidelines, 2014; Burger et al 1995; Santoro et al 1996; Shideler et al 1989). On the contrary, postmenopause is the period of complete, or near complete, ovarian follicular depletion, resulting in low to very low oestradiol levels.

In the current MAA, efficacy and safety of fezolinetant was only established in postmenopausal women with VMS, i.e. in a background of low to very low oestrogen levels, in line with its MoA of restoring disrupted balance in thermoregulation due to very low circulating oestradiol levels in postmenopause. As the thermoregulatory centre of the hypothalamus in the brain is innervated by KNDy neurons that are normally inhibited by oestrogen and stimulated by NKB, the background situation in postmenopausal women is considered different, compared to perimenopausal women who have up to large variations in oestrogen levels. In the context of the MoA, it is difficult to predict the efficacy (and safety) of fezolinetant, which concerns a first-in-class nonhormonal selective neurokinin 3 (NK3) receptor antagonist acting beyond the blood-brain-barrier, in perimenopausal women with moderate to severe VMS.
However, since there have no major safety concerns been observed with the use of fezolinetant in postmenopausal women within the current MAA, the CHMP has agreed on the proposed wording for the indication, including the terminology "VMS associated with menopause" and section 5.1 of the SmPC clearly reflects that the study population investigated was restricted to postmenopausal women alone.

Regarding the **primary analysis, 4 co-primary efficacy endpoints** on the frequency of moderate to severe VMS from baseline to weeks 4 and 12 have been evaluated. Regarding the first co-primary endpoint, treatment with fezolinetant resulted in a higher reduction in the **frequency** of moderate to severe VMS from baseline to **week 4** compared to placebo.

The differences in frequency in LS means of fezolinetant vs placebo were statistically significant for both the 30 mg fezolinetant (LS mean (SE) of -1.87 (0.42; 95% CI: -2.69 to -1.05; p<0.001)) and the 45 mg fezolinetant (LS mean (SE) of -2.07 (0.42; 95% CI: -2.89 to -1.25; p<0.001)). Based on these outcomes, it can be concluded that the first co-primary endpoint on the mean change in the frequency of moderate to severe VMS from baseline to week 4 was met.

Regarding the second co-primary endpoint, treatment with fezolinetant resulted also in a higher reduction in the **frequency** of moderate to severe VMS from baseline to **week 12** compared to placebo.

The differences in frequency in LS means of fezolinetant vs placebo were also statistically significant for both the 30 mg fezolinetant (LS mean (SE) of -2.39 (0.44; 95% CI: -3.25 to -1.52; p<0.001)) and the 45 mg fezolinetant (LS mean (SE) of -2.55 (0.43; 95% CI: -3.40 to -1.70; p<0.001)). Therefore, it can be concluded that the second co-primary endpoint on the mean change in the frequency of moderate to severe VMS from baseline to week 12 was also met.

Also regarding the third co-primary endpoint, a reduction in the change from baseline in mean **severity** of moderate to severe VMS has been observed in **week 4**, compared to placebo.

With a difference in severity of the LS means, that was statistically significant (LS mean (SE) of -0.15 (0.06 95% CI: -0.27 to -0.03; p=0.012)) for the 30 mg fezolinetant and for the 45 mg fezolinetant (LS mean (SE) of -0.19 (0.06; 95% CI: -0.30 to -0.07; p=0.002)) as compared to placebo, the third co-primary endpoints was met.

Finally, regarding the fourth co-primary endpoint, a reduction in the change from baseline in mean **severity** of moderate to severe VMS has been observed in **week 12**, compared to placebo.

The differences in severity in LS means for fezolinetant vs placebo were similar to the week 4 data and were statistically significant for both the 30 mg fezolinetant (LS mean (SE) of -0.24 (0.08 95% CI: -0.39 to -0.09; p=0.001)) and the 45 mg fezolinetant (LS mean (SE) of -0.20 (0.08; 95% CI: -0.35 to -0.06; p=0.007)), as compared to placebo. Thus, the fourth co-primary endpoint on the mean change in the severity of moderate to severe VMS from baseline to week 12 was also met.

Based on these data, it can be concluded that participants treated with fezolinetant 30 mg or 45 mg had statistically significant reductions in the frequency and severity of moderate to severe VMS from baseline to weeks 4 and 12, as compared to and despite of the notable placebo effect. All 4 co-primary endpoints were met in both fezolinetant groups. The improvement in VMS frequency in participants in both treatment arms can be interpreted as clinically meaningful as they consistently reduced the number of VMS with ≥ 2 per day relative to placebo. Further, although the study was not powered to demonstrate a difference between the two dosing arms, it should be noted that for these co-primary efficacy endpoints of frequency at weeks 4 and 12 and severity at week 4, the fezolinetant 45 mg group had numerically slightly larger LS mean changes from baseline, as compared to the fezolinetant 30 mg. This was, however, not observed for the fourth endpoint on VMS severity at week 12. Consistent with the primary analysis, the outcome of the 2 **sensitivity analyses** (PPS and discontinuation-reason based multiple imputation) supports the outcome of the primary efficacy analysis on the co-primary efficacy endpoints, as these also demonstrated an statistically significant beneficial treatment effect (reduction in frequency and severity of VMS) with the use of fezolinetant. The subgroup analyses, performed for the primary analysis with respect to age, race, BMI or smoking status, suggested that none of these subgroups had an impact on the efficacy of fezolinetant. Results obtained were consistent between groups, although a large variability was observed, which could be due to low patient numbers. Findings should therefore be interpreted with caution.

Regarding the **key secondary analysis**, the applicant has selected the mean change in the **PROMIS SD SF 8b total score** from baseline to week 12 as key secondary endpoint in order to assess 8 questions on self-reported sleep disturbance over the past 7 days. A negative change indicated an improvement from baseline (i.e., a favourable outcome). A numerical reduction (mean (SD)) from baseline to week 12 in sleep disturbances has been observed with -3.7 for the 30 mg fezolinetant, and -4.2 for the 45 mg fezolinetant versus -3.2 for placebo. The difference in LS means for the 30 mg fezolinetant vs placebo was (LS mean (SE)) -0.5 (0.8) CI 95% -2.0, 1.0; p=0.489) and, a slightly larger effect was seen with the 45 mg fezolinetant vs placebo (LS mean (SE) -1.1 (0.7) CI 95% -2.5, 0.4; p=0.155), but differences were not statistical different versus placebo.

Other secondary outcomes suggested similar beneficial effects, in line with the findings in the primary analyses. Regarding the frequency of moderate to severe VMS, change from baseline to each week up to week 12, treatment with fezolinetant 30 mg and 45 mg resulted in a larger decrease from baseline in mean frequency of moderate to severe VMS, compared with placebo. The decrease in the fezolinetant groups 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 the placebo arm. A similar trend was observed on the mean severity of moderate to severe VMS. Regarding the percent reduction of frequency in VMS from baseline to each week up to week 12: participants treated with fezolinetant 30 mg and 45 mg had a greater percent reduction from baseline in the frequency of moderate to severe VMS relative to placebo. The beneficial effect was also seen in the responder analysis on frequency (percent reduction $\geqslant$ 50% and at 100%), where a nominal statistical significant higher proportion of participants had a $\geqslant$ 50% reduction in the frequency of moderate to severe VMS in the fezolinetant 30 mg (44.5% (77/173); with an Odds ratio (95% CI) of 2.061 (1.323, 3.233; p=0.001)) and 45 mg (54% (94/174 with an Odds ratio (95% CI) of 3.025 (1.947, 4.746; p<0.001)) groups than in the placebo group (28.0% (49/175) at week 4. Similar findings were seen at week 12, i.e. 44.5%, and 56.9%, for the 30 and 45 mg respectively, vs 29.7% with placebo. Similar findings were seen in participants with a 100% reduction in the frequency of moderate to severe VMS, but these differences were not statistically significant. Regarding the PROs on PGI-C VMS scores, which assesses patient-perceived global impressions of severity in sleep disturbance and change in VMS and sleep disturbance, positive trends were seen in favour of fezolinetant.

Several **exploratory efficacy endpoints** were assessed during the study and the results suggest a comparable beneficial effect, when taking also into account mild VMS together with moderate and severe VMS. Further, exploratory PRO evaluations (PROMIS SRI SF 8a, MENQOL, EQ-5D-5L, WPAI-VMS and PGIS) showed improvements with the use of fezolinetant as compared to placebo.

Regarding the open-label, uncontrolled long-term efficacy data, assessed from week 13 to week 24, when participants on placebo were re-randomized in a 1:1 ratio to 30 mg or 45 mg of fezolinetant in the open-label extension period, the frequency and severity of moderate to severe VMS, change from baseline to week 24 was measured. The improvement in efficacy of fezolinetant in VMS frequency and VMS severity, as noted in the first 12 weeks for both initial fezolinetant groups, was sustained through week 24. The reduction in frequency and severity of VMS on the former placebo groups is comparable with the degree of reduction noted in the patient groups who used fezolinetant for the entire 24 weeks.

Study 2693-CL-0302 (SKYLIGHT 2) – pivotal 12-week, double-blind, placebo-controlled, phase 3

As earlier noted, the study designs of the studies SKYLIGHT 1 and 2 was stated, by the applicant, to be identical. In the SKYLIGHT 2 study, the **participant flow** is considered comparable to the SKYLIGHT 1 study, as 1662 participants were screened, of which eventually 501 participants were randomized (n=168 placebo group, n=166 fezolinetant 30 mg group, n=167 fezolinetant 45 mg group) and 383 participants completed the 52-week period. The main reasons for screening failure were related to the same entry criteria, as in SKYLIGHT 1. Further, the number of subjects who completed the study was considered high with 79% at week 52. Treatment completion rates were generally similar across study arms. Among 12% discontinued due to withdrawal by subject and 4% because of adverse events. The degree and type of protocol deviations are comparable to the previous SKYLIGHT 1 study.

The **baseline characteristics** and gynaecological history appear to be well-balanced across the three study arms and are similar to those in the previous SKYLIGHT 1 study. The participants had a median age of 54.0 years. Most participants were white (79.4%) and were either former smokers or had never smoked (79.4%) and >20% were current smokers. In addition, 21.5% of participants received prior treatment with HRT. A total of 32.0% participants with hysterectomy and 21.8% with oophorectomy enrolled into this study.

Similarly to the **primary analyses** findings in the SKYLIGHT 1 study, the data of the SKYLIGHT 2 study showed that all 4 co-primary endpoints were met in both fezolinetant dosing groups. Regarding the first co-primary endpoint, treatment with fezolinetant resulted in a higher reduction in the **frequency** of moderate to severe VMS from baseline to **week 4** compared to placebo.

The differences of frequencies in LS means of fezolinetant and placebo were statistically significant for both the 30 mg fezolinetant (LS mean (SE) of -1.82 (0.46; 95% CI: -2.73 to -0.91; p<0.001)) and the 45 mg fezolinetant (LS mean (SE) of -2.55 (0.46; 95% CI: -3.45 to -1.64; p<0.001)), on which outcome it can be concluded that the first co-primary endpoint on the mean change in the frequency of moderate to severe VMS from baseline to week 4 was met.

Further, regarding the second co-primary endpoint, treatment with fezolinetant resulted also in a higher reduction in the **frequency** of moderate to severe VMS from baseline to **week 12** compared to placebo.

The differences of frequencies in LS means were statistically significant for both the 30 mg fezolinetant (LS mean (SE) of -1.86 (0.55; 95% CI: -2.94 to -0.78; p<0.001)) and the 45 mg fezolinetant (LS mean (SE) of -2.53 (0.55; 95% CI: -3.60 to -1.46; p<0.001)) as compared to placebo. Therefore, it can be concluded that the second co-primary endpoint on the mean change in the frequency of moderate to severe VMS from baseline to week 12 was also met.

Also, regarding the third co-primary endpoint, a reduction in the change from baseline in mean **severity** of moderate to severe VMS has been observed in **week 4**, compared to placebo.

With a difference in severity of fezolinetant, that was statistically significant (LS mean (SE) of -0.15 (0.06 95% CI: -0.27 to -0.02; p=0.021)) for the 30 mg fezolinetant and for the 45 mg fezolinetant (LS mean (SE) of -0.29 (0.06; 95% CI: -0.41 to -0.16; p=0.001)), as compared to placebo, the third co-primary endpoints was met.

For the fourth co-primary endpoint, a reduction in the change from baseline in mean **severity** of moderate to severe VMS has been observed in **week 12**, compared to placebo.

The differences in severity were similar to the week 4 data and were statistically significant for both the 30 mg fezolinetant (LS mean (SE) of -0.16 (0.08 95% CI: -0.33 to -0.00; p=0.049)) and the 45 mg fezolinetant (LS mean (SE) of -0.29 (0.08; 95% CI: -0.45 to -0.13; p<0.001)) as compared to placebo. Thus, the fourth co-primary endpoint on the mean change in the severity of moderate to severe VMS from baseline to week 12 was also met.

Importantly, as seen in the SKYLIGHT 1 study, the improvement in VMS frequency in participants in the treatment arm of 45 mg can be interpreted as clinically meaningful as they consistently reduced the number of VMS frequency with $\geqslant$ 2 per day relative to placebo. Further, although the study was not powered to show a difference between the two dosing arms, for these co-primary efficacy endpoints of frequency and severity at weeks 4 and 12 in the current study SKYLIGHT 2, the fezolinetant 45 mg group had somewhat greater LS mean changes from baseline compared to the fezolinetant 30 mg. The findings of the 2 **sensitivity analyses** provide a similar outcome as of the primary efficacy analysis on the co-primary efficacy endpoints. The subgroup analyses performed for the primary analysis with respect age, race, BMI or smoking status suggested that none of these subgroups had an impact on the efficacy of fezolinetant, in line with the SKYLIGHT 1 subgroup analyses.

The **key secondary efficacy endpoint** PRO of the mean change in the PROMIS SD SF 8b change from baseline to week 12, evaluating the change in sleep disturbances, was only met for the highest dose of 45 mg fezolinetant. A trend towards a reduction in sleep disturbances has been observed, as seen in the difference in LS means of 30 mg fezolinetant vs placebo (LS mean (SE) was -0.7 (0.7) CI 95% -2.1, 0.8; p=0.381). The beneficial effect on sleep disturbances was larger, than the 30 mg group, and statistically significant for the difference in LS means of 45 mg fezolinetant vs placebo with -2.0 (0.7) (CI 95% -3.5, -0.6; p=0.007).

Consistent with the primary efficacy analyses, the **other secondary efficacy endpoints** suggested similar beneficial effects of fezolinetant. The data on mean change in VMS frequency and severity from baseline to each week up to week 12 were in line with the findings in the SKYLGHT 1 study, which is reassuring. Also, a responder analysis was performed by percent reduction $\geqslant$ 50% and at 100% in the frequency of moderate to severe VMS per 24 h, from baseline to each week up to week 12. A beneficial effect has been found, where a nominal statistical significant higher proportion of participants had a $\geqslant$ 50% reduction in the frequency of moderate to severe VMS in the fezolinetant 30 mg (50.6% (84/166); with an Odds ratio (95% CI) of 2.902 (1.829, 4.657; p<0.001)) and 45 mg (52.7% (88/167 with an slightly larger Odds ratio (95% CI) of 3.218 (2.025, 5.172; p<0.001)) groups than in the placebo group (26.3% (44/167) at week 4 during the 12-week double-blind period. Similar findings were seen at week 12; although not statistically significant for the lower dose of 30 mg. Also, a higher proportion of participants with a 100% reduction was found for the treatment arms over time, and as compared to the placebo arm at weeks 4 and 12, but these differences were not nominal statistically significant for the 30 mg. A trend in favour of fezolinetant was also suggested with PRO data from the PGI-C VMS scores.

No deviations have been found in the results of the **exploratory efficacy analyses**, as compared to the earlier findings and the findings in SKYLIGHT 1. Long-term efficacy data in open-label long-term extension. Further, the beneficial treatment effect remained over a longer-term, as the effect of fezolinetant, as compared to placebo, in VMS frequency and VMS severity was sustained through week 24 of fezolinetant exposure.

Study 2693-CL-0304 (SKYLIGHT 4) – supportive long-term placebo-controlled **safety** study with explorative efficacy data

Study 2693-CL-0304 (SKYLIGHT 4) was a 52-week, randomized, placebo-controlled, double-blind, parallel-group, multicentre, phase 3 clinical study to investigate the long-term safety and endometrial health of fezolinetant in women suffering from VMS associated with menopause. Participants were randomized 1:1:1 to receive placebo once daily, fezolinetant 30 mg once daily or fezolinetant 45 mg once daily. Approximately 1150 participants were originally planned to be enrolled into this study, which was increased to 1740, with 580 participants per treatment arm. The study is in accordance with earlier SAs and can therefore be considered appropriate. A duration of 52 weeks of treatment is adequate, as it is in line with the 1-year duration recommended for assessment of endometrial safety in the EMA guideline on HRT. This guideline also recommends including at least 300 patients in whom endometrial biopsies are taken at study entry and at the end of week 52. Inclusion key criteria are participants had to be seeking treatment for relief for VMS associated with menopause, confirmed as menopausal, and an evaluable endometrial biopsy at screening for participants with a uterus. The **eligibility criteria** are acceptable for adequate assessment of endometrial safety during use of fezolinetant versus placebo. The study population can be considered representative for the target population.
The **primary objectives** of the study were to evaluate the long-term safety and tolerability of fezolinetant in female individuals seeking treatment for relief of VMS associated with menopause, and to evaluate the effect of fezolinetant on endometrial health after long-term treatment in female individuals seeking treatment for relief of VMS associated with menopause.
The **secondary objective** was to evaluate the effect of fezolinetant on bone mineral density after long-term treatment in female individuals seeking treatment for relief of VMS associated with menopause. The primary and secondary objectives are considered acceptable for assessment of the long-term safety and endometrial health of fezolinetant. The endometrial safety analysis was based on the final diagnosis evaluated from the 3 pathologists. The final diagnosis was the concordance of the 3 pathologists' diagnoses: if at least 2 pathologists agreed, the result was included, if none of them agreed, then the worst result was used. The assessment protocol applied for the final diagnosis of endometrial hyperplasia, endometrial cancer and disordered proliferative endometrium is considered in line with the recommendations of the EMA guideline for HRT regarding the diagnostic approach of adverse effects on the endometrium.
Exploratory efficacy objective was to evaluate the effect of fezolinetant on subject-reported quality of life measures. The **exploratory efficacy endpoints** were the mean change on the MENQOL Total Score and Domain Scores from baseline to specified time points (week 4, 12, 24 and 52), and the mean change on the EQ-5D-5L visual analog scale (VAS) from baseline to specified time points (week 4, 12, 24 and 52), EQ-5D-5L domain scores at specified timepoints (week 4, 12, 24 and 52).

Results SKYLIGHT 4. Of the 4344 subjects who were screened, 1831 participants were randomized: 611 participants in the placebo group, 611 in the fezolinetant 30 mg group and 609 in the fezolinetant 45 mg group. A total of 1305 (71%) completed the 52-week period, which is moderately high. The number of completers is, furthermore, generally similar between the three study arms. No large differences have been observed as compared to the pivotal studies. The safety analysis population is the primary analysis population, which is supported for a long-term safety study. The proportion of participants included in the analyses is high with 99.9%. The number of patients in the fezolinetant

groups is less than recommended in the CHMP's 'guideline on clinical investigation of medicinal products for hormone replacement therapy of oestrogen deficiency symptoms in postmenopausal women' with regard to precision of the point estimate of incidence of endometrial hyperplasia/cancer, which is set at approximately 300 patients with biopsy treated for one year.
The **baseline demographic characteristics** are mostly well-balanced across the 3 study arms and are largely comparable to those in the phase 3 pivotal studies SKYLIGHT 1 and 2.

Efficacy results suggested that participants treated with fezolinetant 30 mg and 45 mg had greater improvements in MENQOL total score, MENQOL domain scores and EQ-5D-5L VAS score throughout the 52-week study than noted in the placebo group.
The **safety results** of this pivotal safety study is further **discussed in detail under the 'safety' section**.

2.6.7. Conclusions on the clinical efficacy

Based on the current available data, with a complete efficacy data set, a statistical significant and clinically relevant beneficial treatment effect of fezolinetant 30 mg and 45 mg has been demonstrated as compared to placebo in terms of the frequency and severity of VMS in postmenopausal women at weeks 4 and 12, with a trend for a slightly larger effect in the 45 mg fezolinetant group. Also, a relevant improvement in the key secondary endpoint on the PRO of sleep disturbance was observed. The primary efficacy outcomes were supported with positive trends in favour of fezolinetant in a number of other secondary endpoints on VMS frequency and severity and QoL of the patients in several PRO evaluations, such as on sleep, work productivity and VMS impact. The study data supports the benefit in the studied population, i.e. postmenopausal women. No data or comprehensive extrapolation exercise are available to support efficacy and safety of fezolinetant in perimenopausal women having fluctuating oestradiol levels. The proposed wording for the indication, including the terminology '*VMS associated with menopause'* has, therefore, been supported with reference to SmPC section 5.1.

2.6.8. Clinical safety

Introduction

In the fezolinetant clinical development program, safety was evaluated based on the assessment of:

- Adverse events (AEs),
- AEs of clinical interest (alanine aminotransferase (ALT) or aspartate aminotransferase (AST) $\geqslant 3 \times$ upper limit of normal (ULN)) clinical laboratory tests,
- Endometrial safety (biopsies, TVU) (SKYLIGHT 4),
- Bone mineral density (BMD) measurements by dual-energy X-ray absorptiometry (DXA),
- Evaluation of areas of medical focus, i.e. endometrial safety, hepatic safety, bone safety, CNS safety, thrombocytopenia, elevated glucose and elevated CK

Clinical safety data supporting the application are presented as integrated analyses of pooled safety data from five clinical studies. These are the completed two phase 2 and three phase 3 studies. The 3 phase 3 studies 2693-CL-0301 (SKYLIGHT 1), 2693-CL-0302 (SKYLIGHT 2) and 2693-CL-0304 (SKYLIGHT 4) are comprising the majority of the safety populations.

SKYLIGHT 1 and 2 were 12-week randomized, placebo-controlled, double-blind, parallel-group studies with an open-label extension period of 40 weeks. The placebo-controlled 12-week data are used for the short-term comparative safety results.

SKYLIGHT 4 was a 52-week, randomized, placebo-controlled, double-blind, parallel-group, multicentre, phase 3 clinical study specifically conducted to investigate the long-term safety (including bone health) and endometrial health of fezolinetant. This study is further discussed under the separate section on endometrial health, which is an adverse event (AE) of special interest.

The completed phase 1 VMS studies and completed phase 2 studies are not included in the pooling strategy but are supportive for analyses of hepatic safety signals.

Integrated safety populations

The analysis populations, POP1 POP2 POP3 POP4 and POP5, used to describe safety for 12 and 52 weeks in study participants with VMS associated with menopause are summarized in Table 32 below.

The Safety Analysis Set for each population consisted of all randomized participants who took at least 1 dose of study intervention. This definition is consistent with the analysis of safety data conducted according to each individual study SAP.

Of note, the safety-related inclusion criteria were similar for all phase 2 and 3 studies in participants with VMS associated with menopause. Safety-related exclusion criteria were also similar across these studies, with the exception of the phase 2, proof-of-concept study ESN364_HF_204. This study did not include criteria for a normal mammogram or Papanicolaou result prior to entry, nor did it exclude those with hypertension or abnormal TVU or endometrial biopsy results. However, these differences between the phase 2 study and the phase 3 studies do not preclude pooling of these data in the selected populations for analyses.

Table 32 Studies contributing to pooled safety populations

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

AE: adverse event; TVU: transvaginal ultrasound; VMS: vasomotor symptoms. † In addition, POP2 was evaluated at 12 weeks (12-week POP2) to assess the placebo-controlled safety profile from the 3 phase 3 Studies 2693-CL-0301, 2693-CL-0302 and 2693-CL-0304, specifically for AEs and categorical increases in liver parameters. ‡ Placebo/fezolinetant 30/45 mg represents treatment for

participants who received placebo initially and completed 12 weeks of treatment and were re-randomized to fezolinetant 30/45 mg for the remaining 40 weeks of treatment (i.e., active treatment extension period) in the two confirmatory phase 3 Studies 2693-CL-0301 and 2693-CL-0302. Thus, for the two treatment groups, the treatment duration was up to 40 weeks. § Includes fezolinetant 30 mg (tablet) and placebo/fezolinetant 30 mg (tablet) in Studies 2693-CL-0301 and 2693-CL-0302 fezolinetant 30 mg (tablet) in 2693-CL-0304, and fezolinetant 30 mg qd (capsule) in ESN364_HF_205. ¶ Includes fezolinetant 45 mg (tablet) and placebo/fezolinetant 45 mg (tablet) in Studies 2693-CL-0301 and 2693-CL-0302 and fezolinetant 45 mg (tablet) in 2693-CL-0304. Note that this treatment group is the same as POP2 fezolinetant 45 mg total group. ††Includes doses from the 2 phase 2 Studies ESN364_HF_204 and ESN364_HF_205, which used the capsule formulation.

2.6.8.1. Patient exposure

Overall extent of exposure

12-week safety population, placebo-controlled (POP1)

For POP1 (Studies 2693-CL-0301 and 2693-CL-0302), 1028 participants were randomized, 1022 took study drug and were included in the Safety Analysis Set, and 913 (89.3%) completed the 12-week, double-blind treatment period. The median duration of exposure to study drug was 84 days in each treatment group. The majority of participants in POP1 had an exposure to study drug of at least 84 days.

The median compliance with study drug in POP1 was 100.0% across all treatment groups.

Supportive 12-week safety populations (POP2, POP3 and POP5)

In POP2, exposure to study drug of at least 84 days (12 weeks) was reported for 78.5% participants in the placebo group and > 88% of participants in the fezolinetant treatment groups.

In POP3 and POP5, exposure to study drug of at least 84 days was reported for > 68% participants across treatment groups. Overall median compliance with study drug in POP3 and POP5 was > 98.0% and consistent across treatment groups. Results were consistent with POP1.

52-week safety population, placebo controlled (POP4)

Median duration of exposure to study intervention was 364 days in each treatment group, with an overall mean treatment duration of 296.0 days (Table 33). The majority of participants (1380, 75.4%) had study intervention exposure of $\geqslant$ 252 days and 763 (41.7%) had a study intervention exposure of $\geqslant$ 365 days.

Table 33 Study Intervention Exposure (Safety Analysis Set)

Category	Category/ Statistic	Placebo (n = 610)	Fezolinetant 30 mg (n = 611)	Fezolinetant 45 mg (n = 609)	Fezolinetant Total (n = 1220)	Total (n = 1830)
Duration (days) †	n	610	611	609	1220	1830
	Mean (SD)	284.4 (130.8)	301.2 (119.8)	302.4 (117.9)	301.8 (118.8)	296.0 (123.2)
	Median	364.0	364.0	364.0	364.0	364.0
	Min, Max	1, 401	1, 399	1, 446	1, 446	1, 446
Duration category †	≥ 7 days	602 (98.7%)	601 (98.4%)	598 (98.2%)	119 (98.3%)	1801 (98.4%)
	≥ 14 days	592 (97.0%)	595 (97.4%)	596 (97.9%)	1191 (97.6%)	1783 (97.4%)
	≥ 21 days	581 (95.2%)	590 (96.6%)	586 (96.2%)	1176 (96.4%)	1757 (96.0%)
	≥ 28 days	573 (93.9%)	581 (95.1%)	578 (94.9%)	1159 (95.0%)	1732 (94.6%)
	≥ 42 days	546 (89.5%)	565 (92.5%)	561 (92.1%)	1126 (92.3%)	1672 (91.4%)
	≥ 56 days	539 (88.4%)	559 (91.5%)	560 (92.0%)	1119 (91.7%)	1658 (90.6%)
	≥ 84 days	515 (84.4%)	546 (89.4%)	542 (89.0%)	1088 (89.2%)	1603 (87.6%)
	≥ 168 days	467 (76.6%)	494 (80.9%)	501 (82.3%)	995 (81.6%)	1462 (79.9%)
	≥ 252 days	441 (72.3%)	471 (77.1%)	468 (76.8%)	939 (77.0%)	1380 (75.4%)
	≥ 365 days	235 (38.5%)	259 (42.4%)	269 (44.2%)	528 (43.3%)	763 (41.7%)

All randomized participants who took at least 1 dose of study intervention (Safety Analysis Set). Max: maximum; Min: minimum. † Duration was defined as (the date of last dosing) — (the date of first dosing) + 1.

Supportive 52-week safety population (POP2)

It should be noted that in POP2, an imbalance in the duration of exposure between placebo and fezolinetant groups exists due to the 2693-CL-0301 and 2693-CL-0302 study designs.

The placebo group contains data up to week 12 for Studies 2693-CL-0301 and 2693-CL-0302 and week 52 for Study 2693-CL-0304, while the fezolinetant groups include data up to 40 weeks for Studies 2693-CL-0301 and 2693-CL-0302 and 52 weeks for Study 2693-CL-0304. Therefore, qualitative comparisons across treatment groups in POP2 may be confounded by the differential exposure to study drug across the treatment groups.

For POP2 (Studies 2693-CL-0301, 2693-CL-0302 and 2693-CL-0304), 2859 participants were randomized; the Safety Analysis Set consisted of 952 participants in the placebo group, 951 participants in the fezolinetant 30 mg group, 949 participants in the fezolinetant 45 mg group, 152 participants in the placebo/fezolinetant 30 mg group and 151 participants in the placebo/fezolinetant 45 mg group.

Over 70% of participants completed study drug treatment, with the primary reasons for withdrawal of treatment being "Withdrawal by subject" and "adverse event".

The median duration of exposure was lower in the placebo and placebo/fezolinetant groups than in the fezolinetant groups. The median duration of exposure was 138 days in the placebo group, 364 days in the fezolinetant 30 mg, fezolinetant 45 mg, fezolinetant 30 mg total and fezolinetant 45 mg total groups and 280 days in the placebo/fezolinetant 30 mg and placebo/fezolinetant 45 mg groups.

The majority (⩾ 75%) of participants in the fezolinetant groups in POP2 had exposure to study drug of at least 252 days [Table 38]. Interpretation of the placebo exposure is limited given the two pivotal studies, 2693-CL-0301 and 2693-CL-0302, re-randomized the placebo participants to active fezolinetant treatment after week 12.

The median compliance with study intervention was 99.6 to 100.0% in all treatment groups.

Table 34 Study drug exposure (safety analysis set); POP2: Phase 3 52-week

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

All randomized participants who took at least 1 dose of study intervention (Safety Analysis Set). POP2 is comprised of Studies 2693-CL-0301, 2693-CL-0302 and 2693-CL-0304. Duration was defined as (the date of last dosing of study drug) - (the date of first dosing of study) + 1. Duration for crossover participants receiving fezolinetant in extension period was defined as (the date of last dosing of fezolinetant) - (the date of first dosing of fezolinetant) + 1. Overall Compliance (%) = Total number of tablets actually taken over duration of treatment x 100 /(duration(days) x 2). Overall compliance was calculated for participants whose total number of tablets taken and the complete date of the first dose and the last dose of study drug during the treatment duration were known. ISS: integrated summary of safety. † Includes fezolinetant 30 mg (tablet) and placebo/fezolinetant 30 mg (tablet) in Studies 2693-CL-0301 and 2693-CL-0302 and fezolinetant 30 mg (tablet) in 2693-CL-0304. ‡ Includes fezolinetant 45 mg (tablet) and placebo/fezolinetant 45 mg (tablet) in Studies 2693-CL-0301 and 2693-CL-0302 and fezolinetant 45 mg (tablet) in 2693-CL-0304.

2.6.8.2. Adverse events

Overview of Adverse Events

12-week safety population, placebo-controlled (POP1)

In POP1, the percentages of TEAEs were generally balanced across treatment groups (Table 35). A greater number of TEAEs related to study intervention, serious TEAEs, and serious TEAEs related to study intervention were observed in the fezolinetant groups versus the placebo group. The percentage of TEAEs leading to withdrawal was low with no increase in withdrawals in the higher dose group. No deaths occurred during the 12-week period.

Table 35 Overview of treatment-emergent adverse events and death (safety analysis set); POP1

Category	Placebo (n = 342)	Fezolinetant 30 mg (n = 340)	Fezolinetant 45 mg (n = 340)	Fezolinetant Total (n = 680)
TEAEs	132 (38.6%)	132 (38.8%)	135 (39.7%)	267 (39.3%)
Drug-related† TEAE	33 (9.6%)	41 (12.1%)	38 (11.2%)	79 (11.6%)
Serious TEAE‡	1 (0.3%)	5 (1.5%)	4 (1.2%)	9 (1.3%)
Drug-related† serious TEAE‡	0	2 (0.6%)	0	2 (0.3%)
TEAE leading to withdrawal of treatment	10 (2.9%)	12 (3.5%)	9 (2.6%)	21 (3.1%)
Drug-related† TEAE leading to withdrawal of treatment	7 (2.0%)	7 (2.1%)	8 (2.4%)	15 (2.2%)
Death§	0	0	0	0

All randomized participants who took at least 1 dose of study intervention (Safety Analysis Set). POP1 is comprised of Studies 2693-CL-0301 and 2693-CL-0302. A TEAE was defined as an adverse event observed after starting administration of study drug and either up to 21 days after the last dose of study drug, or first dose of study drug during the extension period, whichever occurred first. ISS: integrated summary of safety; TEAE: treatment-emergent adverse event. † A reasonable possibility that the event may have been caused by the study drug as assessed by the investigator. If relationship was missing, then it was considered as drug-related. ‡ Includes serious adverse events upgraded by the sponsor based on review of the sponsor's list of Always Serious Terms, if any upgrade was done. § All reported deaths after the first study drug administration.

Supportive 12-week safety populations (POP2, POP3 and POP5)

Results for the 12-week POP2 were consistent with those of POP1, and no new safety signals were observed. The incidence of TEAEs, TEAEs resulting in withdrawal of study treatment and death were similar across the treatment groups. The incidence of serious TEAEs was slightly greater in the fezolinetant 45 mg group than in the placebo and fezolinetant 30 mg groups.

Results for POP3 and POP5 were consistent with those in POP1. The incidence of TEAEs, serious TEAEs, TEAEs resulting in withdrawal of study treatment and death were similar across the placebo, fezolinetant 30 mg and fezolinetant 45 mg treatment groups.

52-week safety population, placebo controlled (POP4)

POP 4 population (SKYLIGHT 4)

Overall, in POP4, the incidences of TEAEs and TEAEs related to study intervention were similar across all treatment groups [Table 40]. The incidence of serious TEAEs was slightly higher in the fezolinetant groups than in the placebo group. A total of 4 participants (1 in the placebo group and 3 in the fezolinetant 45 mg group) experienced a serious TEAE which was considered by the investigator as related to study intervention. The frequency of TEAEs leading to withdrawal of treatment was similar across the treatment groups (4.3% in the placebo group, 5.6% in the fezolinetant 30 mg group and 4.6% in the fezolinetant 45 mg group).

Table 36 Overview of treatment-emergent adverse events and death (safety analysis set); POP4: Study 2693-CL-0304

Category	Placebo (n = 610)	Fezolinetant 30 mg (n = 611)	Fezolinetant 45 mg (n = 609)	Fezolinetant Total (n = 1220)
TEAE	391 (64.1%)	415 (67.9%)	389 (63.9%)	804 (65.9%)
Drug-related TEAE†	106 (17.4%)	94 (15.4%)	110 (18.1%)	204 (16.7%)
Serious TEAE‡	14 (2.3%)	20 (3.3%)¶	23 (3.8%)	43 (3.5%)¶
Drug-related† serious TEAE‡	1 (0.2%)	0	3 (0.5%)	3 (0.2%)
TEAE leading to withdrawal of treatment	26 (4.3%)	34 (5.6%)	28 (4.6%)	62 (5.1%)
Drug-related† TEAE leading to withdrawal of treatment	16 (2.6%)	16 (2.6%)	17 (2.8%)	33 (2.7%)
Death§	0	1 (0.2%)	0	1 (0.1%)

All randomized participants who took at least 1 dose of study intervention (Safety Analysis Set). A TEAE was defined as an adverse event observed after starting administration of study drug and up to 21 days after the last dose of study drug. TEAE: treatment-emergent adverse event. † A reasonable possibility that the event may have been caused by the study drug as assessed by the investigator. If relationship was missing, then it was considered as drug-related. ‡ Includes serious adverse events upgraded by the sponsor based on review of the sponsor's list of Always Serious Terms, if any upgrade was done. § All reported deaths after the first study drug administration. ¶ A serious TEAE of benign breast neoplasm, a serious TEAE of hepatitis and a serious TEAE of hypercholesterolaemia, all in the fezolinetant 30 mg group, were incorrectly upgraded by the sponsor to Always Serious term in the clinical database.

Supportive 52-week safety population (POP2)

Overall, in POP2 there was a slightly higher proportion of participants with TEAEs, serious TEAEs and TEAEs leading to withdrawal of treatment in the fezolinetant 30 mg total and fezolinetant 45 mg total groups than in the placebo group . However, the proportion of participants with events related to study intervention was similar across the treatment groups.

There were 2 deaths (fezolinetant 30 mg group and placebo/fezolinetant 45 mg group) and neither event was considered by the investigator to be related to the study intervention; see section 'serious adverse events and deaths' for further details.

The exposure-adjusted incidence rate (number of participants with an event per 100 participant years) for the main TEAE categories was similar across the treatment groups for POP2 with the exception of serious TEAEs, which had a higher rate in the fezolinetant groups than in the placebo group . Serious TEAEs related to the study intervention showed a similar exposure-adjusted incidence rate across treatment groups. Both the percentage of participants, and the exposure-adjusted incidence rate of participants with TEAEs of all categories, serious TEAEs, and TEAEs leading to withdrawal of study treatment, were similar for the fezolinetant 30 mg total and fezolinetant 45 mg total treatment groups.

Common Adverse Events

12-week safety population, placebo-controlled (POP1)

In POP1, the 3 most frequently reported TEAEs in the fezolinetant total group by preferred term were headache, upper respiratory tract infection, and blood glucose increased. For the placebo group the 3 most frequently reported TEAEs by preferred term were headache, upper respiratory tract infection and diarrhoea. Incidences of TEAEs were similar across the treatment groups [Table 41]. No TEAE by preferred term was reported for > 5% of participants in any treatment group during the 12-week double-blind period. Blood creatine phosphokinase increased was reported as a TEAE for 2 participants

(0.6%) in the fezolinetant 30 mg group, 4 participants (1.2%) in the fezolinetant 45 mg group and no participants in the placebo group.

Table 37 Treatment-emergent adverse events by preferred term ⩾ 1% in the fezolinetant total group (safety analysis set); POP1

MedDRA (v23.0) Preferred Term	Placebo (n = 342)	Fezolinetant 30 mg (n = 340)	Fezolinetant 45 mg (n = 340)	Fezolinetant Total (n = 680)
Overall	132 (38.6%)	132 (38.8%)	135 (39.7%)	267 (39.3%)
Headache	17 (5.0%)	14 (4.1%)	17 (5.0%)	31 (4.6%)
Upper respiratory tract infection	10 (2.9%)	8 (2.4%)	7 (2.1%)	15 (2.2%)
Blood glucose increased	1 (0.3%)	7 (2.1%)	6 (1.8%)	13 (1.9%)
Arthralgia	2 (0.6%)	9 (2.6%)	3 (0.9%)	12 (1.8%)
Dry mouth	1 (0.3%)	6 (1.8%)	6 (1.8%)	12 (1.8%)
Abdominal pain upper	4 (1.2%)	5 (1.5%)	4 (1.2%)	9 (1.3%)
Dizziness	2 (0.6%)	5 (1.5%)	4 (1.2%)	9 (1.3%)
Nausea	4 (1.2%)	3 (0.9%)	6 (1.8%)	9 (1.3%)
Weight increased	3 (0.9%)	8 (2.4%)	1 (0.3%)	9 (1.3%)
Fatigue	5 (1.5%)	4 (1.2%)	4 (1.2%)	8 (1.2%)
Nasopharyngitis	6 (1.8%)	7 (2.1%)	1 (0.3%)	8 (1.2%)
Alanine aminotransferase increased	4 (1.2%)	1 (0.3%)	6 (1.8%)	7 (1.0%)
Hypertension	4 (1.2%)	5 (1.5%)	2 (0.6%)	7 (1.0%)

All randomized participants who took at least 1 dose of study intervention (Safety Analysis Set). POP1 is comprised of Studies 2693-CL-0301 and 2693-CL-0302. Number of participants and percentage of participants (%) are shown. Sorting order: descending by the number of participants of fezolinetant total group by Preferred Term. In case of ties, ascending order by Preferred Term is applied. ISS: integrated summary of safety; TEAE: treatment-emergent adverse event.

Supportive 12-week safety populations (POP2, POP3 and POP5)

Results for the 12-week POP2 were consistent with those from POP1. The 3 most frequently reported TEAEs by preferred term for the placebo group were headache, upper respiratory tract infection and diarrhoea. The 3 most frequently reported TEAEs by preferred term for the fezolinetant total group were headache, nasopharyngitis and nausea. Incidences for each preferred term were similar across the treatment groups. The incidence of TEAEs in POP3 and POP5 was consistent with those from POP1.

The incidence of TEAEs by time interval in the 12-week POP2, POP3 and POP5 showed that the events occurred throughout the 12-week period and were not clustered at a specific time period, with the exception of headache, which was reported more frequently in the first 14 days of the studies in all treatment groups.

52-week safety population, placebo controlled (POP4)

In POP4, the most frequently reported TEAEs (⩾ 5%) in the fezolinetant total group were headache and COVID-19, consistent with the placebo group (Table 38). No TEAE by preferred term was reported for > 10% of participants in any treatment group during the 52-week period. Overall, incidences of TEAEs were balanced across the treatment groups.

The onset of TEAEs by time interval in POP4, in general, showed that no specific pattern was evident based on the time course of the reported adverse events, and no difference was observed between treatment groups.

Table 38 Most Frequently (> 2%) Reported (Any Treatment Group) Treatment-emergent Adverse Events by Preferred Term (Safety Analysis Set)

MedDRA (v23.0) Preferred Term	Placebo (n = 610)	Fezolinetant 30 mg (n = 611)	Fezolinetant 45 mg (n = 609)	Fezolinetant Total (n = 1220)
Overall	391 (64.1%)	415 (67.9%)	389 (63.9%)	804 (65.9%)
Headache	56 (9.2%)	52 (8.5%)	55 (9.0%)	107 (8.8%)
COVID-19	38 (6.2%)	38 (6.2%)	32 (5.3%)	70 (5.7%)
Urinary tract infection	18 (3.0%)	29 (4.7%)	18 (3.0%)	47 (3.9%)
Back pain	13 (2.1%)	27 (4.4%)	18 (3.0%)	45 (3.7%)
Diarrhoea	16 (2.6%)	21 (3.4%)	24 (3.9%)	45 (3.7%)
Arthralgia	23 (3.8%)	15 (2.5%)	25 (4.1%)	40 (3.3%)
Nausea	15 (2.5%)	18 (2.9%)	19 (3.1%)	37 (3.0%)
Insomnia	11 (1.8%)	12 (2.0%)	24 (3.9%)	36 (3.0%)
Upper respiratory tract infection	20 (3.3%)	15 (2.5%)	18 (3.0%)	33 (2.7%)
Hypertension	18 (3.0%)	13 (2.1%)	18 (3.0%)	31 (2.5%)
Nasopharyngitis	18 (3.0%)	15 (2.5%)	15 (2.5%)	30 (2.5%)
Fatigue	16 (2.6%)	10 (1.6%)	17 (2.8%)	27 (2.2%)
Anxiety	8 (1.3%)	13 (2.1%)	11 (1.8%)	24 (2.0%)
Sinusitis	14 (2.3%)	13 (2.1%)	11 (1.8%)	24 (2.0%)
Abdominal pain	5 (0.8%)	10 (1.6%)	13 (2.1%)	23 (1.9%)
Hot flush	10 (1.6%)	8 (1.3%)	15 (2.5%)	23 (1.9%)
Gamma-glutamyltransferase increased	8 (1.3%)	14 (2.3%)	8 (1.3%)	22 (1.8%)
Blood alkaline phosphatase increased	15 (2.5%)	11 (1.8%)	10 (1.6%)	21 (1.7%)
Constipation	13 (2.1%)	7 (1.1%)	12 (2.0%)	19 (1.6%)
Vaginal haemorrhage	16 (2.6%)	10 (1.6%)	8 (1.3%)	18 (1.5%)
Dyspepsia	13 (2.1%)	6 (1.0%)	9 (1.5%)	15 (1.2%)

All randomized participants who took at least 1 dose of study intervention (Safety Analysis Set). Number of participants and percentage of participants (%) are shown. Treatment-emergent adverse events are reported at the discretion of the investigator. Sorting order: descending by the number of participants of total fezolinetant group by preferred term. In case of ties, ascending order by preferred term code was applied. COVID-19: coronavirus disease 2019.

Supportive 52-week safety population (POP2)

The most frequently reported TEAEs (≥ 5%) in the fezolinetant total group for POP2 were headache and COVID-19, consistent with the placebo group. No TEAE by preferred term was reported for > 10% of participants in any treatment group during the 52-week period. The onset of TEAEs by time interval in POP2, in general, showed that no specific pattern was evident based on the time course of the reported TEAEs. The observed percentage of participants with TEAEs overall increased in all treatment groups after 84 days may be due to wider analysis windows in subsequent intervals. In addition, this coincides with the end of the double-blind treatment period in Studies 2693-CL-0301 and 2693-CL-0302, and results should be interpreted with caution given the absence of a placebo control in studies 2693-CL-0301 and 2693-CL-0302.

Adverse Drug Reactions

Potential ADRs were identified methodically using POP4 (Study 2693 CL 0304, SKYLIGHT 4), followed by medical review for plausibility of a causal relationship between fezolinetant treatment and the event. This population was identified as it has a robust, placebo-controlled design. The evaluation is supported by POP2, although the duration of placebo treatment in this population varied as Studies 2693 CL 301 and 2693 CL 302 included placebo only up to 12 weeks while Study 2693 CL 0304 included placebo for 52 weeks.

Diarrhoea

The incidence of the TEAE of diarrhoea was higher in the fezolinetant 30 mg (3.4%) and fezolinetant 45 mg (3.9%) groups than in the placebo group (2.6%), with a larger difference versus placebo for the fezolinetant 45 mg group than the 30 mg group in POP4 [Table]. The majority of events were mild or moderate in severity and self-limiting. None of the events were reported as a serious TEAE and 2 participants (1 [0.2%] in the placebo group and 1 [0.2%] in the fezolinetant 30 mg group) had TEAEs which led to treatment withdrawal. Of the events reported, 5 of the 16 participants in the placebo group, 5 of the 21 in the fezolinetant 30 mg group and 7 of the 24 in the fezolinetant 45 mg group reported TEAEs of diarrhoea that were considered by the investigator to be related to study intervention. An evaluation of time to onset of the reported events of diarrhoea relative to first dose of treatment demonstrated no discernible pattern or differences across treatment groups. The percentage of participants with TEAEs of diarrhoea was greater in participants receiving fezolinetant $\geqslant$ 60 mg than those receiving lower doses in POP3.

In the supportive POP2 assessment, diarrhoea was not identified by the criteria. The incidence of the TEAE of diarrhoea in POP2 was 2.4% in the placebo group, 2.3% in the fezolinetant 30 mg total group and 3.2% in the fezolinetant 45 mg total group (2.7% in the fezolinetant total group).

Based on the increased incidence of diarrhoea in the fezolinetant 45 mg group in POP4, the sponsor considers diarrhoea to be an ADR for fezolinetant. This was agreed by the CHMP.

Insomnia

The incidence of the TEAE of insomnia was higher in the fezolinetant 30 mg (2.0%) and fezolinetant 45 mg (3.9%) groups than in the placebo group (1.8%), with a larger difference versus placebo for the fezolinetant 45 mg group than the 30 mg group in POP4 (Table 39). None of the events were reported as a serious TEAE and 2 participants (both in the fezolinetant 45 mg group [0.3%]) had events which led to treatment withdrawal. Of the events reported, 2 of the 11 participants in the placebo group, 2 of the 12 in the fezolinetant 30 mg group and 4 of the 24 in the fezolinetant 45 mg group reported TEAEs of insomnia that were considered by the investigator to be related to study intervention.

Across the fezolinetant treatment groups in POP4, there were 36 participants with TEAEs of insomnia all of which were mild to moderate in severity and 11 participants with TEAEs of insomnia in the placebo group which were mild to moderate in severity. Of the 36 participants with TEAEs in the fezolinetant groups, 28 participants had new onset of events and 8 participants had a medical history of insomnia. From the 12 participants with TEAEs of insomnia in the placebo group, 8 were new and 4 participants had a medical history of insomnia. Onset of insomnia in relationship to first dose did not demonstrate a consistent pattern across the fezolinetant and placebo groups.

In the supportive POP2 assessment, the incidence of the TEAE of insomnia was 1.6% in the placebo group, 2.0% in the fezolinetant 30 mg total group and 3.0% in the fezolinetant 45 mg total group, with a larger difference versus placebo for the fezolinetant 45 mg total group than the 30 mg total group (2.5% in the fezolinetant total group). All events were mild or moderate in severity. None of the events were reported as a serious TEAE and 2 participants (in the fezolinetant 45 mg total group

[0.2%]) had TEAEs which led to treatment withdrawal. Of the events reported, 3 of the 15 participants in the placebo group, 3 of the 22 in the fezolinetant 30 mg total group and 6 of the 33 in the fezolinetant 45 mg total group reported TEAEs of insomnia that were considered by the investigator to be related to study intervention. An evaluation of time to onset of the reported events of insomnia relative to first dose of treatment demonstrated no discernible pattern or differences across treatment groups.

Sleep disturbance was assessed as an efficacy endpoint (quality of life) in Studies 2693 CL 0301 and 2693 CL 0302 and results showed a benefit in the fezolinetant 30 mg and 45 mg groups compared with placebo after 12 weeks of treatment.

Based on the increased incidence of insomnia in the fezolinetant 45 mg group in POP4, and supported by data from POP2, the sponsor considers insomnia to be an ADR for fezolinetant. This was agreed by the CHMP.

Abdominal pain

The incidence of the TEAE of abdominal pain was higher in the fezolinetant 30 mg (1.6%) and fezolinetant 45 mg (2.1%) groups than in the placebo group (0.8%), with a larger difference versus placebo for the fezolinetant 45 mg group than the 30 mg group in POP4. The majority of events were mild or moderate in severity and self-limiting. Three serious TEAEs of abdominal pain were reported in the fezolinetant groups (1 in the fezolinetant 30 mg group, 2 in the fezolinetant 45 mg group). Five participants had events which led to treatment withdrawal (2 in the placebo group [0.3%], 2 in fezolinetant 30 mg group [0.3%] and 1 in fezolinetant 45 mg group [0.2%]). Of the events reported, 1 of the 5 participants in the placebo group, 2 of the 10 in the fezolinetant 30 mg group and 2 of the 13 in the fezolinetant 45 mg group reported TEAEs of abdominal pain that were considered by the investigator to be related to study intervention. An evaluation of time to onset of the reported events of abdominal pain relative to first dose of treatment demonstrated no discernible pattern or differences across treatment groups.

In the supportive POP2 assessment, abdominal pain was not identified by the criteria. The incidence of the TEAE of abdominal pain in POP2 was 0.6% in the placebo group, 1.6% in the fezolinetant 30 mg total group and 1.8% in the fezolinetant 45 mg total group (1.7% in the fezolinetant total group).

Based on the increased incidence of abdominal pain in the fezolinetant 45 mg group in POP4, the sponsor considers abdominal pain to be an ADR for fezolinetant. This was agreed by the CHMP.

Table 39 Treatment-emergent Adverse Events of Diarrhoea, Insomnia and Abdominal Pain (Safety Analysis Set); POP4 52-week: Study 2693 CL 0304

Preferred Term	Placebo (n = 610)	Fezolinetant 30 mg (n = 611)	Fezolinetant 45 mg (n = 609)
Diarrhoea	16 (2.6%)	21 (3.4%)	24 (3.9%)
Insomnia	11 (1.8%)	12 (2.0%)	24 (3.9%)
Abdominal pain	5 (0.8%)	10 (1.6%)	13 (2.1%)

All randomized participants who took at least 1 dose of study intervention (Safety Analysis Set). A TEAE was defined as an adverse event observed after starting administration of study intervention and up to 21 days after the last dose of study intervention. ISS: integrated summary of safety; TEAE: treatment emergent adverse event.

ALT increased

In the supportive POP2 assessment, the incidence of the TEAE of ALT increased was 0.9% in the placebo group, 1.9% in the fezolinetant 30 mg total group and 2.8% in the fezolinetant 45 mg total group (2.4% in the fezolinetant total group). One serious TEAE of ALT increased was reported for 1 participant (0.1%) in the fezolinetant 45 mg total group and 7 participants withdrew treatment due to events of ALT increased (2 [0.2%] in the placebo group, 2 [0.2%] in the fezolinetant 30 mg total group and 3 [0.3%] in the fezolinetant 45 mg total group). Of the events reported, 2 of the 9 participants in the placebo group, 3 of the 21 in the fezolinetant 30 mg total group and 12 of the 31 in the fezolinetant 45 mg total group reported TEAEs of ALT increased that were considered by the investigator to be related to study intervention. Onset of transaminase elevations occurred at various timepoints throughout the study, with no overt cluster of time to onset across the treatment groups, and there was no dominant pattern of rise and fall of the transaminase values.

ALT elevations (as determined by laboratory data) of > 3 x ULN were observed with fezolinetant treatment in 1.2% of participants treated with fezolinetant 30 mg and 1.9% of participants treated with fezolinetant 45 mg, compared with 0.9% on placebo in the 52-week, placebo-controlled safety study (Study 2693 CL 0304, POP4). The general pattern was also observed across the phase 3 program. ALT or AST elevations > 5 x ULN were infrequent and balanced across treatment groups. There were no Hy's law cases. Across the program, these ALT elevations > 3 x ULN were occasionally accompanied by AST elevations. ALT or AST elevations were generally transient and typically resolved on continued therapy or shortly after drug discontinuation. Onset of transaminase elevations occurred at various timepoints throughout the study duration, with no overt cluster of time to onset across the treatment groups, and there was no dominant pattern of rise and fall of the transaminase values. None of the transaminase elevations were accompanied by concomitant changes in elevated total bilirubin. These elevations were rarely associated with clinical symptoms.

Based on a review of the data the sponsor considers ALT increased to be an ADR for fezolinetant. This was agreed by the CHMP.

Urinary tract infection

The incidence of the TEAE of urinary tract infection was higher in the fezolinetant 30 mg group (4.7%) than in the placebo (3.0%) and fezolinetant 45 mg (3.0%) groups in POP4. The incidence of this TEAE was the same in the fezolinetant 45 mg and placebo groups. None of the events led to treatment withdrawal and none were reported as serious TEAEs; 1 serious TEAE for the related preferred term of urinary tract infection bacterial was reported for 1 (0.2%) participant in the fezolinetant 30 mg group. Of the events reported, 1 of the 18 participants in the placebo group reported a TEAE of urinary tract infection that was considered by the investigator to be related to study intervention. An evaluation of time to onset of the reported events of urinary tract infection relative to first dose of treatment demonstrated no discernible pattern or differences across treatment groups.

In the supportive POP2 assessment, the incidence of the TEAE of urinary tract infection was 2.3% in the placebo group, 3.4% in the fezolinetant 30 mg total group and 2.9% in the fezolinetant 45 mg total group. None of the events led to treatment withdrawal, and there were no serious TEAEs of urinary tract infection; 1 serious TEAE for the related preferred term of urinary tract infection bacterial was reported for 1 (0.1%) participant in the fezolinetant 30 mg total group. Of the events reported, 1 of the 22 participants in the placebo group reported a TEAE of urinary tract infection that was considered by the investigator to be related to study intervention. An evaluation of time to onset of the reported events of urinary tract infection relative to first dose of treatment demonstrated no discernible pattern or differences across treatment groups.

Given the inverse dose response and the limited biological plausibility, urinary tract infection was not considered an ADR. This was agreed by the CHMP.

Back pain

Incidence of the TEAE of back pain was higher in the fezolinetant 30 mg (4.4%) and fezolinetant 45 mg (3.0%) groups than in the placebo group (2.1%), with a larger difference for fezolinetant 30 mg group than the 45 mg group in POP4. None of the events were reported as a serious TEAE and 1 participant (placebo group [0.2%]) had a TEAE which led to treatment withdrawal. Of the events reported, 1 of the 13 participants in the placebo group and 2 of the 27 participants in the fezolinetant 30 mg group reported TEAEs of back pain that were considered by the investigator to be related to study intervention. An evaluation of time to onset of the reported events of back pain relative to first dose of treatment demonstrated no discernible pattern or differences across treatment groups.

In the supportive POP2 assessment, the incidence of the TEAE of back pain was 1.7% in the placebo group, 3.7% in the fezolinetant 30 mg total group and 3.1% in the fezolinetant 45 mg total group (3.4% in the fezolinetant total group). None of the events were reported as a serious TEAE and 1 participant (in the placebo group [0.1%]) had a TEAE which led to treatment withdrawal. Of the events reported, 1 of the 16 participants in the placebo group, 2 of the 41 in the fezolinetant 30 mg total group and 1 of the 34 in the fezolinetant 45 mg total group reported TEAEs of back pain that were considered by the investigator to be related to study intervention. An evaluation of time to onset of the reported events of back pain relative to first dose of treatment demonstrated no discernible pattern or differences across treatment groups.

Given the inverse dose response and the limited biological plausibility, back pain was not considered an ADR. This was agreed by the CHMP.

COVID-19

In the supportive POP2 assessment, the incidence of the TEAE of COVID-19 was 4.1% in the placebo group, 5.8% in the fezolinetant 30 mg total group and 6.1% in the fezolinetant 45 mg total group (5.9% in the fezolinetant total group). Serious TEAEs of COVID 19 were reported for 1 (0.1%) participant in the placebo group, 2 (0.2%) participants each in the fezolinetant 30 mg total group and 45 mg total group, and serious TEAEs of the related event of COVID 19 pneumonia were reported for 1 participant each (0.1% each) in the placebo, fezolinetant 30 mg total and 45 mg total groups. Two participants (0.2%) in the placebo group and 1 each in the fezolinetant 30 mg total and 45 mg total groups (0.1% each) withdrew treatment due to TEAEs of COVID-19. No TEAEs of COVID-19 were considered by the investigator to be related to study intervention. An evaluation of time to onset of the reported events of COVID 19 relative to first dose of treatment demonstrated no discernible pattern or differences across treatment groups.

Given the lack of biological plausibility of an increase in viral infection rates with fezolinetant and due to the program being conducted during a global pandemic, COVID-19 was not considered an ADR. This was agreed by the CHMP.

Gamma-glutamyl transferase increased

In the supportive POP2 assessment, the incidence of the TEAE of gamma glutamyltransferase increased was 1.3% in the placebo group, 2.4% in the fezolinetant 30 mg total group and 1.5% in the fezolinetant 45 mg total group (1.9% in the fezolinetant total group). One participant in the placebo group (0.1%), and no participants in the fezolinetant 30 mg total group or 45 mg total group had events which were reported as a serious TEAE and 2 participants (both in the placebo group [0.2%]) had events which led to treatment withdrawal. Of the events reported, 3 of the 12 participants in the placebo group, 3 of the 26 in the fezolinetant 30 mg total group and 2 of the 16 in the fezolinetant 45

mg total group reported TEAEs of gamma glutamyltransferase increased that were considered by the investigator to be related to study intervention. An evaluation of time to onset of the reported events of gamma glutamyltransferase increased relative to first dose of treatment demonstrated no discernable pattern or differences across treatment groups.

Objective laboratory data for GGT showed no clinically relevant changes from baseline.

Given the inverse dose response and the limited biological plausibility, gamma glutamyltransferase increased was not considered an ADR. This was agreed by the CHMP.

Blood creatine phosphokinase increased

In the supportive POP2 assessment, the incidence of the TEAE of blood creatine phosphokinase increased was 0.3% in the placebo group, 1.4% in the fezolinetant 30 mg total group and 2.1% in the fezolinetant 45 mg total group (1.7% in the fezolinetant total group). None of the participants had events which were reported as a serious TEAE and 1 participant (in the fezolinetant 45 mg group [0.1%]) had an event which led to treatment withdrawal. Of the events reported, 1 of the 3 participants in the placebo group and 2 of the 23 in the fezolinetant 45 mg total group reported TEAEs of blood creatine phosphokinase increased that were considered by the investigator to be related to study intervention. An evaluation of time to onset of the reported events of blood creatine phosphokinase increased relative to first dose of treatment demonstrated no discernable pattern or differences across treatment groups.

Objective laboratory data for CK showed no clinically relevant changes from baseline.

Based on the totality of the data, although there is a higher incidence of TEAEs of blood creatine phosphokinase increased in the fezolinetant 45 mg group than in the fezolinetant 30 mg group, the sponsor does not consider it to be an ADR. This was agreed by the CHMP.

Treatment-emergent Adverse Events of Special Interest

The following treatment-emergent AESIs were defined:

- AE of liver test elevations
- AE of uterine bleeding
- AE of endometrial hyperplasia or cancer or disordered proliferative endometrium
- AE of thrombocytopenia
- AE of bone fractures
- AE of potential abuse liability
- AE of depression
- AE of wakefulness
- AE of effect on memory

These AESIs are discussed below, but it should be noted that endometrial safety is further discussed under section ‘endometrial health’, and that hepatic safety, bone safety, CNS safety and thrombocytopenia are further discussed under ‘evaluation of areas of medical focus’:

12-week safety population, placebo-controlled (POP1)

In POP1, the number of treatment-emergent AESIs was generally balanced across treatment groups (Table 40). No treatment-emergent AESIs were reported for more than 5 participants in any treatment group with the exception of liver test elevations, which were reported in 8 participants in the fezolinetant 30 mg group and 10 participants in the fezolinetant 45 mg group and depression which was reported in 6 participants in the placebo group.

Table 40 Treatment-emergent Adverse Events of Special Interest (Safety Analysis Set); POP1

MedDRA (v23.0) TEAE of Special Interest (Overall)	Placebo (n = 342)	Fezolinetant 30 mg (n = 340)	Fezolinetant 45 mg (n = 340)	Fezolinetant Total (n = 680)
Endometrial Hyperplasia/Cancer or Disordered Proliferative Endometrium	0	0	0	0
Uterine Bleeding	3 (0.9%)	4 (1.2%)	3 (0.9%)	7 (1.0%)
Liver Test Elevations	5 (1.5%)	8 (2.4%)	10 (2.9%)	18 (2.6%)
Thrombocytopenia	1 (0.3%)	2 (0.6%)	1 (0.3%)	3 (0.4%)
Bone Fractures	1 (0.3%)	2 (0.6%)	1 (0.3%)	3 (0.4%)
Potential Abuse Liability	1 (0.3%)	0	0	0
Depression	6 (1.8%)	5 (1.5%)	4 (1.2%)	9 (1.3%)
Wakefulness	2 (0.6%)	3 (0.9%)	2 (0.6%)	5 (0.7%)
Effect on Memory	0	1 (0.3%)	0	1 (0.1%)

All randomized participants who took at least 1 dose of study intervention (Safety Analysis Set). POP1 is comprised of Studies 2693-CL-0301 and 2693-CL-0302. Number of participants and percentage of participants (%) are shown. Includes events as defined by predefined Adverse Events of Interest search strategy. In Study 2693-CL-301, the term of 'endometrial disorder' was not included in the list of AESI search terms. AESI: adverse event of special interest; ISS: integrated summary of safety; TEAE: treatment-emergent adverse event.

Supportive 12-week safety populations (POP2, POP3 and POP5)

In the 12-week POP2, the number of treatment-emergent AESIs was similar across treatment groups. No treatment emergent AESIs were reported for more than 12 participants (1.3%) in any treatment group.

In POP3, the number of treatment-emergent AESIs was higher in the fezolinetant ⩾ 60 mg group (33 participants, 12.5%), than in the 15 mg, 30 mg, 45 mg and placebo groups (4.4%, 7.2%, 5.1% and 6.8% of participants, respectively). This was primarily due to a higher incidence of liver test elevations (4.9% of participants in the fezolinetant ⩾ 60 mg group compared to 0, 2.5%, 2.1% and 2.1% of participants in the 15 mg, 30 mg, 45 mg and placebo groups, respectively). No treatment-emergent AESIs were reported for more than 5% of participants in any treatment group.

In POP5, the number of treatment-emergent AESIs was similar across treatment groups. No treatment-emergent AESIs were reported for more than 5% of participants in any fezolinetant treatment group.

52-week safety population, placebo controlled (POP4)

In POP4, the frequency of treatment-emergent AESIs was generally similar across the treatment groups (Table 41). Analysis of the incidence of treatment-emergent AESIs using the Santner-Snell approach showed that the 95% CI for the odds ratio included 1 for all calculable comparisons versus placebo, indicating no difference between fezolinetant 30 mg or fezolinetant 45 mg and placebo.

Table 41 Treatment-emergent adverse events of special interest (safety analysis set); POP4: Study 2693-CL-0304

MedDRA (v23.0) TEAE of Special Interest (Overall)	Placebo (n = 610)	Fezolinetant 30 mg (n = 611)	Fezolinetant 45 mg (n = 609)	Fezolinetant Total (n = 1220)
Endometrial Hyperplasia/Cancer or Disordered Proliferative Endometrium	2 (0.3%)	2 (0.3%)	6 (1.0%)	8 (0.7%)
Uterine Bleeding	30 (4.9%)	20 (3.3%)	19 (3.1%)	39 (3.2%)
Liver Test Elevations	30 (4.9%)	35 (5.7%)	32 (5.3%)	67 (5.5%)
Thrombocytopenia	1 (0.2%)	3 (0.5%)	1 (0.2%)	4 (0.3%)
Bone Fractures	10 (1.6%)	9 (1.5%)	10 (1.6%)	19 (1.6%)
Potential Abuse Liability	0	3 (0.5%)	1 (0.2%)	4 (0.3%)
Depression	13 (2.1%)	19 (3.1%)	11 (1.8%)	30 (2.5%)
Wakefulness	4 (0.7%)	7 (1.1%)	4 (0.7%)	11 (0.9%)
Effect on Memory	1 (0.2%)	0	1 (0.2%)	1 (0.1%)

All randomized participants who took at least 1 dose of study intervention (Safety Analysis Set). Includes events as defined by predefined Adverse Events of Interest search strategy. A TEAE was defined as an adverse event observed after starting administration of study drug and up to 21 days after the last dose of study drug. ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI: confidence interval; TBL: total bilirubin; TEAE: treatment-emergent adverse event.

Supportive 52-week safety population (POP2)

In POP2, the incidence of treatment-emergent AESIs was generally similar across the treatment groups.

The exposure-adjusted incidence rate (number of participants with an event per 100 participant-years) showed an overall incidence of treatment-emergent AESIs of 19.1 participants per 100 participant years in the placebo group, and 16.3 participants per 100 participant years in the total fezolinetant group. The exposure-adjusted incidence rate for liver test elevations, thrombocytopenia, bone fractures, potential abuse liability, wakefulness and effect on memory was similar across the treatment groups. The exposure-adjusted incidence of endometrial hyperplasia/cancer or disordered proliferative endometrium was < 1 participant per 100 participant-years in the placebo, fezolinetant 30 mg total and fezolinetant 45 mg total groups. The exposure adjusted incidence of uterine bleeding showed a higher rate in the placebo group than in the fezolinetant groups.

Evaluation of areas of medical focus

Following results of nonclinical studies, early clinical studies, phase 3 clinical studies and discussions with health authorities, areas of medical focus requiring analysis across multiple safety variables (i.e., laboratory data, imaging data and reported TEAE data) have been identified. These topics include endometrial safety, hepatic safety, bone safety, CNS safety, thrombocytopenia, elevated glucose and elevated CK and are discussed below.

Hepatic safety

A comprehensive evaluation was conducted for hepatic safety of fezolinetant in the treatment of moderate to severe VMS associated with menopause. This included oversight by an independent LSMP throughout the clinical program. The totality of data supports the hepatic safety of fezolinetant in the treatment of VMS associated with menopause at the proposed therapeutic dose.

Asymptomatic, transient, dose-related transaminase elevations without associated increases in bilirubin were observed in the phase 2 fezolinetant program. As a result, hepatic safety was designated an AESI and the sponsor worked closely with independent, external hepatic experts to develop a thorough process to monitor hepatic safety during the phase 3 fezolinetant program.

Hepatic safety assessments were performed at the integrated program level, the study level and the individual participant level to inform the hepatic safety profile for fezolinetant. Liver biochemistry parameters (ALT, AST, total bilirubin, ALP and their combination) were assessed throughout all study visits in the phase 2 and phase 3 program. An LSMP consisting of 3 independent hepatologists experienced in the assessment of DILI monitored the program and studies. Additional evaluations include assessment of time course and pattern of hepatic safety findings relative to first dose of study drug as well as subgroup analyses across a series of intrinsic and extrinsic factors to potentially identify population segments who may be more vulnerable to hepatic safety sequelae. Relevant liver clinical laboratory results, TEAEs, liver panel assessments and the reported events of special interest relative to hepatic safety were assimilated into a comprehensive assessment of hepatic safety to inform the safety profile of fezolinetant.

Laboratory Investigations of transaminase elevations

12-week safety population, placebo-controlled (POP1)

There were 9 participants with ALT or AST levels > 3 x ULN in POP1 ; 2 participants in the placebo group, 4 participants in the fezolinetant 30 mg group and 3 in the fezolinetant 45 mg group. ALT or AST levels > 5 x ULN, > 8 x ULN and > 10 x ULN were reported only for participants in the fezolinetant 30 mg treatment group.

In POP1, 1 participant had an AST level > 20 x ULN (fezolinetant 30 mg group); this participant had an ALT level > 10 x ULN at the same time point. The participant had a serious, severe TEAE of liver function test increased. The serious TEAE was considered by the investigator as related to the study intervention. The study intervention was withdrawn, and the event resolved at the time of the cut-off for the 12 week double-blind period.

None of the participants in POP1 had bilirubin levels > 2 x ULN.

Supportive 12-week safety populations (POP2, POP3 and POP5)

The incidence of liver test elevations in the 12-week POP2 was low. There were no Hy's law cases.

In the 12-week POP2, ALT elevations > 3 x ULN were reported for 2 participants (0.2%) in the placebo group, 5 participants (0.5%) in the fezolinetant 30 mg group and 9 participants (1.0%) in the fezolinetant 45 mg group. ALT or AST values > 5 x ULN were infrequent (⩽ 0.3% participants) in all treatment groups and showed no dose dependency. Results were consistent with those in POP1.

The incidence of liver test elevations in POP3 was low across the treatment groups and results were consistent with those in POP1. There were no cases of Hy's law.

In POP3, the proportion of participants with an ALT or AST elevation > 3 x ULN showed a dose dependency across the fezolinetant 30 mg, fezolinetant 40 mg and fezolinetant 60 mg groups. However, ALT or AST values > 5 x ULN were infrequent (⩽ 2.0% participants) in all treatment groups. Of note, there was a higher incidence in the fezolinetant ⩾ 60 mg group. No cases of Hy' s law were identified.

The incidence of liver test elevations in POP5 was low, there were no ALT or AST elevations in the 15 mg twice daily or 30 mg once daily dose groups and results were consistent with those in POP1.

52-week safety population, placebo controlled (POP4)

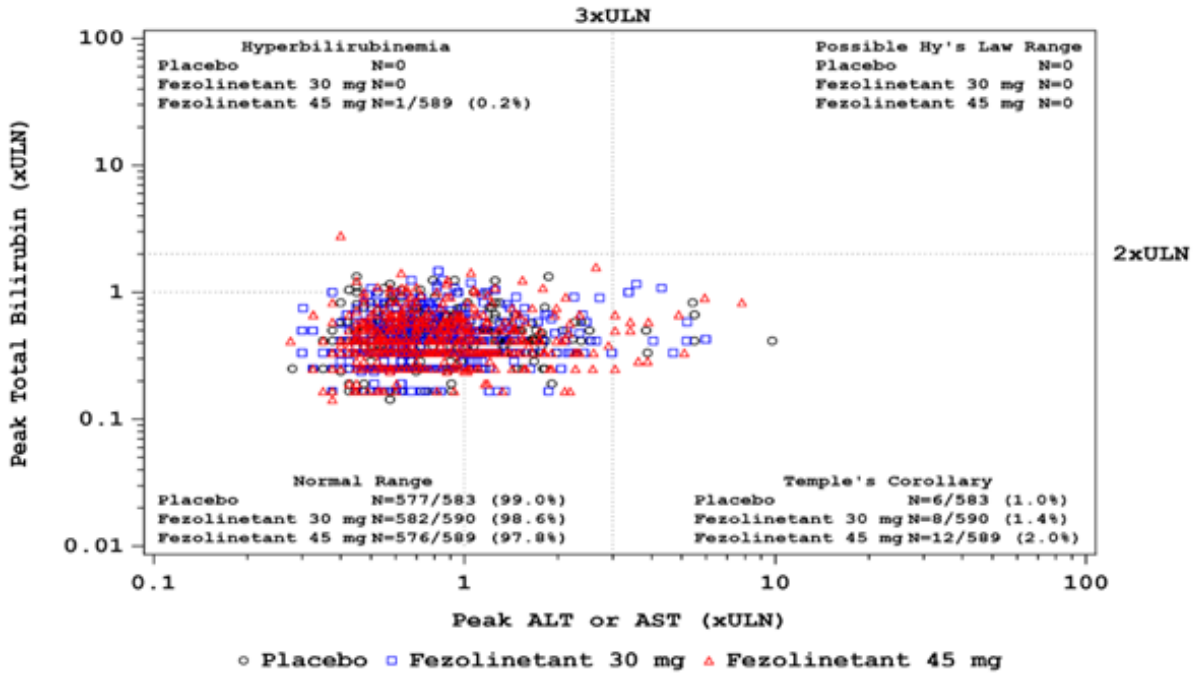
In POP4, there was no trend towards an increase in ALT or AST values over time in any treatment group. There were 26 participants with ALT or AST levels > 3 x ULN during the treatment period. ALT elevations of > 3 x ULN were reported for 5 participants (0.9%) in the placebo group, 7 participants (1.2%) in the fezolinetant 30 mg group and 11 participants (1.9%) in the fezolinetant 45 mg group . There was a low and similar incidence of AST or ALT values > 5 x ULN across the treatment groups. One participant had bilirubin level > 2 x ULN (fezolinetant 45 mg group). This participant had a medical history of Gilbert's syndrome, and no ALT or AST elevations > 3 x ULN.

There were no Hy's law cases (Figure 25).

The exposure-adjusted results (number of participants with an event per 100 participant years) were consistent with the unadjusted incidence data; a higher rate of ALT elevations > 3 x ULN was observed in the fezolinetant groups, but the rate for elevations > 5 x ULN was similar across treatment groups.

Time to onset for elevations in liver chemistry for ALT, AST or bilirubin occurred at various timepoints throughout the study duration, with no overt cluster of time to onset across the treatment groups, and there was no dominant pattern of rise and fall of the transaminase values. Time to onset for ALT or AST elevations varied from week 2 through to week 52, with no difference between placebo and fezolinetant groups.

Figure 25 Drug-induced Serious Hepatotoxicity (eDISH) Plot: Maximum of (AST or ALT) vs Maximum Total Bilirubin Values (Safety Analysis Set); POP4: Study 2693-CL-0304



All randomized participants who took at least 1 dose of study intervention (Safety Analysis Set). Peak ALT or AST (x ULN) = maximum of (maximum x ULN postbaseline value for ALT, maximum x ULN postbaseline value for AST). Potential Hy's Law: (ALT or AST > 3 x ULN) and Total Bilirubin > 2 x ULN. ALT: alanine transferase; AST: aspartate transferase; eDISH: drug-induced serious hepatotoxicity; ULN: upper limit of the normal range.

Supportive 52-week safety population (POP2)

In POP2, the incidence of liver test elevations was low. There were no Hy's law cases across the phase 3 program (POP2).

There were 41 participants in the fezolinetant total group with ALT or AST levels > 3 x ULN during the treatment period. There was a greater percentage of participants with an ALT or AST value > 3 x ULN in the fezolinetant groups than in the placebo group, with evidence of dose dependency, in particular for ALT. ALT elevations of > 3 x ULN were reported for 7 participants (0.8%) in the placebo group, 14 participants (1.3%) in the fezolinetant 30 mg total group and 23 participants (2.1%) in the fezolinetant 45 mg group. However, there was no apparent dose dependency for AST or ALT values > 5 x ULN.

The exposure-adjusted results (number of participants with an event per 100 participant years) were consistent with the overall incidence. The rate of events of ALT or AST > 3 x ULN was 1.5 per 100 participant-years in the placebo group, 1.8 per 100 participant-years in the fezolinetant 30 mg total group, 2.7 per 100 participant years in the fezolinetant 45 mg total group and 2.3 in the fezolinetant total group.

Onset of elevations in liver chemistry for ALT, AST or bilirubin occurred at various timepoints throughout the study duration, with no overt cluster of time to onset across the treatment groups, and there was no dominant pattern of rise and fall of the transaminase values. Time to onset for ALT or AST elevations varied from week 2 through to week 52, with no difference between placebo and fezolinetant groups.

Subgroup analyses regarding hepatic safety

Subgroup analyses by various intrinsic and extrinsic factors did not identify a specific population with increased hepatic safety risk associated with fezolinetant treatment. No increased risk of transaminase elevations was identified based upon race, smoking status or baseline BMI. There were also no meaningful differences in the number of participants with categorical findings of liver biochemistry across the treatment groups by age, diabetic status or geographic region. There was a slightly higher incidence of treatment-emergent AESIs of liver test elevations in North American participants than in European participants; however, there were no meaningful differences in the number of participants with categorical findings of liver biochemistry when grouped by geographical region. The number of participants with a history of NAFLD or NASH was too small to draw meaningful conclusions.

Treatment-emergent AESIs regarding hepatic safety

Treatment-emergent AESIs related to hepatic safety were reported more frequently for the fezolinetant 30 mg and 45 mg groups as compared with the placebo group (POP2 and POP4). However, after adjustment for exposure, similar incidence rates for treatment-emergent AESIs relating to liver test elevations were comparable between placebo and fezolinetant-treated participants and between the 2 fezolinetant doses. These events predominantly reflected non-serious and asymptomatic liver test abnormalities captured through protocol-specified routine testing. Most treatment-emergent AESIs were mild or moderate. The most frequently reported preferred terms for the treatment-emergent AESIs of liver test elevations were ALT increased, GGT increased, blood ALP increased and AST increased.

Across the phase 3 program (POP2), 7 SAEs related to hepatic safety were reported in 6 participants (1 participant in the placebo group, 3 in the fezolinetant 30 mg total group and 2 in the fezolinetant 45 mg total group). None of the events were fatal, life-threatening nor resulted in inpatient or prolonged hospitalization.

Liver Safety Monitoring Panel (LSMP)

The phase 3 clinical development program has been monitored by an LSMP on an ongoing and regular basis. The LSMP conducted a blinded review of individual participant cases that met the criteria pertaining to elevated transaminases or other liver health markers, as well as urgent individual case review and an aggregate unblinded review across the fezolinetant phase 3 programme. At all

timepoints during ongoing study conduct, the LSMP supported continuation of the fezolinetant clinical development program.

Of the participants with ALT or AST levels > 3 x ULN:

- Study 2693-CL-0301: Of the 10 participants with ALT or AST levels > 3 x ULN, 4 participants were assessed by the LSMP as having possible causality (1 in the placebo group, 1 in the placebo/fezolinetant 30 mg group and 2 in the fezolinetant 45 mg group) and 2 as probable causality (both in the fezolinetant 30 mg group); the causality for the other 4 events was assessed as unlikely.
- Study 2693-CL-0302: Of the 12 participants with ALT or AST levels > 3 x ULN, 5 were assessed by the LSMP as having possible causality (3 participants in the fezolinetant 45 mg group and 2 in the placebo/fezolinetant 45 mg group) and 2 as probable causality (1 participant in the fezolinetant 30 mg group and 1 in the fezolinetant 45 mg group); the causality for the other 5 events was assessed as unlikely.
- Study 2693-CL-0304: Of the 26 participants with ALT or AST levels > 3 x ULN, 12 were assessed by the LSMP as having possible causality (3 participants in the placebo group, 4 participants in the fezolinetant 30 mg group and 5 in the fezolinetant 45 mg group) and 5 as probable causality (0 participants in the placebo group, 1 in the fezolinetant 30 mg group and 4 in the fezolinetant 45 mg group); the causality for the other 9 events was assessed as unlikely (3 participants in each treatment group).

Epidemiologic Context

In individuals receiving placebo in clinical studies investigating statins, the prevalence of hypertransaminasemia was 0.6% to 0.9% [Villani et al, 2019], consistent with the incidence of ALT or AST > 3 x ULN in the placebo arm in the fezolinetant clinical studies. Common risk factors for elevated transaminase levels include NAFLD, NASH, heavy alcohol intake, use of some medications, illegal drug use, metabolic syndrome, obesity, diabetes and dyslipidemia [Sheka et al, 2020; Pratt & Kaplan, 2000]. The global increased incidence of NAFLD has increased with increasing prevalence of obesity, type 2 diabetes and metabolic syndrome [Sheka et al, 2020; Thandra et al, 2020; Perumpail et al, 2017; Rinella, 2015; Vernon et al, 2011].

Non-clinical

No adverse effects were observed in rats and cynomolgus monkeys. In rats, centrilobular hepatocellular hypertrophy without biomarker changes (ALT or bilirubin) was observed and was considered an adaptive change associated with the induction of hepatic metabolic enzymes.

Bone Safety

A comprehensive evaluation of bone safety was conducted in the clinical program for fezolinetant. Overall, the data support the bone safety of fezolinetant in the treatment of VMS associated with menopause.

Bone safety was assessed in the phase 3 studies using objective laboratory imaging (DXA to assess BMD and TBS), bone markers and through collection of AESIs.

Data for the DXA endpoints, were collected only in Study 2693-CL-0304, and therefore **POP4** is the most appropriate population. All studies collected TEAE data, and the phase 3 studies collected information on bone fractures as part of treatment-emergent AESI reporting.

In Studies 2693-CL-0301 and 2693-CL-0302, bone markers were collected, and therefore POP2 presents an integrated analysis of the results for this endpoint.

Dual-energy X-ray Absorptiometry (DXA) on Bone Mineral Density (BMD) and Trabecular Bone Score (TBS)

52-week safety population, placebo controlled (POP4) on DXA

BMD and TBS at hip and spine were assessed by DXA in Study 2693-CL-0304 only, therefore only results for POP4 are presented.

There were no clinically relevant changes from baseline to week 52 in BMD and TBS results (IQC and XCAL corrected) in POP4 (Table 42 and Table 43). For the T-scores of femoral neck, however, there was a consistent drop in mean score, not unexpected in this population, that was less pronounced for fezolinetant than placebo. The sensitivity analyses supported the primary analysis conclusions for these bone assessments. It should be noted that the clinical studies did not control for vitamin or mineral intake.

Table 42 Change from Baseline to Week 52: IQC and XCAL corrected bone mineral density (safety analysis set); POP4: Study 2693-CL-0304

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

All randomized participants who took at least 1 dose of study intervention (Safety Analysis Set). The LS Means, SE, CI, and P values come from an ANCOVA model with change from baseline at the week 52 timepoint as response, treatment and smoking status

(current vs former/never) as fixed effects with baseline weight and baseline as covariates. Records marked as poor image quality will be excluded from this analysis. † Differences are calculated by subtracting the LS mean of placebo group from the LS mean of fezolinetant group. ‡ P value is for comparison of fezolinetant with placebo from the above described ANCOVA model. ANCOVA: analysis of covariance; BMD: bone mineral density; CI: confidence interval; IQC: internal quality control; LS: least squares; XCAL: factor of uncertainty measurement for calibration.

Table 43 Change from baseline to week 52: IQC and XCAL corrected trabecular bone score (safety analysis set); POP4: Study 2693-CL-0304

Reading	Placebo (n = 610)	Fezolinetant 30 mg (n = 611)	Fezolinetant 45 mg (n = 609)
TBS Parameter: Bone Mineral Density T-Score			
Hip (Femoral Neck)			
n	246	221	234
LS mean change from baseline (SE)	-0.087 (0.021)	-0.049 (0.023)	-0.081 (0.022)
Difference in LS means (SE) †	-	0.038 (0.028)	0.006 (0.028)
95% CI	-	-0.018, 0.093	-0.049, 0.060
2-sided P value ‡	-	0.182	0.838
Hip (Femur)			
n	246	221	234
LS mean change from baseline (SE)	-0.089 (0.019)	-0.051 (0.020)	-0.063 (0.020)
Difference in LS means (SE) †	-	0.038 (0.025)	0.025 (0.025)
95% CI	-	-0.012, 0.087	-0.023, 0.074
2-sided P value ‡	-	0.136	0.308
Hip (Trochanter)			
n	246	221	234
LS mean change from baseline (SE)	-0.076 (0.023)	-0.044 (0.025)	-0.041 (0.024)
Difference in LS means (SE) †	-	0.032 (0.031)	0.035 (0.030)
95% CI	-	-0.029, 0.092	-0.024, 0.094
2-sided P value ‡	-	0.300	0.242
Spine			
n	253	225	242
LS mean change from baseline (SE)	-0.110 (0.028)	-0.101 (0.030)	-0.088 (0.030)
Difference in LS means (SE) †	-	0.010 (0.037)	0.022 (0.037)
95% CI	-	-0.064, 0.083	-0.050, 0.094
2-sided P value ‡	-	0.799	0.547

All randomized participants who took at least 1 dose of study intervention (Safety Analysis Set). The LS Means, SE, CI, and P values come from an ANCOVA model with change from baseline at the week 52 timepoint as response, treatment and smoking status (current vs former/never) as fixed effects with baseline weight and baseline as covariates. Footnotes continued on next page. Records marked as poor image quality were excluded from this analysis. † Differences are calculated by subtracting the LS mean of placebo group from the LS mean of fezolinetant group. ‡ P value is for comparison of fezolinetant with placebo from the above described ANCOVA model. ANCOVA: analysis of covariance; CI: confidence interval; IQC: internal quality control; LS: least squares; TBS: trabecular bone score; XCAL: factor of uncertainty measurement for calibration.

Bone Fractures (POP4)

The most commonly reported preferred term was foot fracture (7 participants), and there were 4 participants with wrist fractures and no reported hip fractures in this study. There were no differences between the treatment groups with regards to the percentage of participants with bone fracture events or the fracture location: 1.6% of participants in the placebo group, 1.5% of participants in the fezolinetant 30 mg group and 1.6% of participants in the fezolinetant 45 mg group had treatment-emergent AESIs of bone fracture. Medical history of fractures was similar across the treatment groups.

Treatment-emergent AESIs

For the reported treatment-emergent AESI of bone fractures, there was no evidence for an increase in the incidence of fracture events in the fezolinetant groups compared with placebo for POP1, POP2, POP3, POP4 or POP5.

Bone markers in supportive 52-week safety populations (POP2)

Study 2693-CL-0304 did not collect bone marker data, and therefore results for POP2 are representative of Studies 2693-CL-0301 and 2693-CL-0302 only.

In POP2, there were no clinically relevant changes from baseline to week 52 in BSAP, P1NP or CTX results . Of note, there is a potential limitation of some bone marker assessments, as the studies did not control for vitamin or mineral intake.

Epidemiologic Context

Decreases in BMD are associated with decreased estrogen levels and menopause [Cheng et al, 2007]. The prevalence of osteoporosis in the US, EU and Asia increases progressively with age from 50-59 years to 60-69 years [Choi et al, 2021; Hernlund et al, 2013; Yoshimura et al, 2009; Cheng et al, 2007]. A similar pattern is seen for the incidence rates for postmenopausal osteoporotic fractures [Amin et al, 2014; Hernlund et al, 2013; Ettinger et al, 2010].

Nonclinical

DXA scans showed no impact of fezolinetant on bone mass in 2 repeat-dose toxicity studies in cynomolgus monkeys.

<u>CNS Safety</u>

A comprehensive evaluation of CNS safety was conducted in the clinical program for fezolinetant. Overall, the data support the CNS safety of fezolinetant in the treatment of VMS associated with menopause.

Given that fezolinetant crosses the blood brain barrier, a thorough review of CNS effects was performed through the collection of TEAEs, through the collection of treatment-emergent AESIs and through the assessment of suicide risk with the C-SSRS. Pre-specified CNS AESIs included potential abuse liability, depression, wakefulness, and effect on memory.

Treatment-emergent AESI in supportive 52-week safety populations (POP2)

The CNS AESIs in POP2 showed a low incidence and similar results across the treatment groups for events of:

- potential abuse liability (0.1% in the placebo group, 0.3% in the fezolinetant 30 mg total and 0.1% in the fezolinetant 45 mg total groups)
- depression (2.0% in the placebo group, 2.4% in the fezolinetant 30 mg total and 1.9% in the fezolinetant 45 mg total groups)
- wakefulness (0.6% in the placebo group, 1.0% in the fezolinetant 30 mg total and 0.6% in the fezolinetant 45 mg total groups)
- effect on memory (0.1% in the placebo group, 0.2% in the fezolinetant 30 mg total and 0.2% in the fezolinetant 45 mg total groups).

Treatment-emergent AESIs relating to potential abuse liability were infrequently reported in POP1, POP2 and POP4. The events reported in this category described feelings of brain fogginess, calm, and "bad mood", that were generally mild, resolved while on therapy and did not connote a psychological

effect that would be desirable or lend itself to intentional non-therapeutic use (abuse). The phase 3 program shows no evidence of abuse liability potential using a broad, sensitive strategy for potential events of interest.

The incidence of treatment-emergent AESIs relating to depression, wakefulness and effect on memory were low and similar between placebo and fezolinetant groups for POP1, POP2 and POP4 with no dose relationship observed.

TEAEs

With regards to TEAEs, events from the nervous system SOC were commonly reported in the phase 3 studies across all treatment groups, with the most common events being mild to moderate headache and dizziness that infrequently led to study drug withdrawal (POP2). The results were generally similar across treatment groups with the exception of a small number which are discussed further below.

Migraine

Reported adverse events of migraine and migraine with aura from the HLT migraine headaches were assessed across the phase 3 program. In the 12-week populations the incidence in the fezolinetant 30 mg and fezolinetant 45 mg groups was the same as or less than in the placebo group.

In the 52-week data from POP2, TEAEs within the HLT migraine headaches were reported for 0.6% of participants in the placebo group and 0.8% of participants in the total fezolinetant group with no evidence of a dose-relationship. The majority of these events were reported as mild or moderate in severity and the majority were reported as not related to study intervention by the investigator. There was no discernible pattern across the 52-week treatment period with regard to time to onset and no evidence of clustering after the first dose administration in any treatment group. TEAEs of migraine leading to withdrawal of study intervention were reported for 1 participant in the placebo group, 1 participant in the fezolinetant 30 mg total group and 1 participant in the fezolinetant 45 mg total group. None of the TEAEs of migraine headaches were reported as serious.

From an epidemiologic context, migraine is a highly prevalent medical condition, affecting approximately 1 in 7 US adults aged 18 years or older, with a higher prevalence in women than in men [Burch et al, 2015; Sacco et al, 2012]. It is more common in women of reproductive age and during the menopausal transition, while prevalence in the postmenopausal period tends to decrease, characterized by stable low estrogen levels [Ornello et al, 2021; Ripa et al, 2015]. CDC reported that the prevalence of severe headache or migraine in the past 3 months was 24.2% and 17.6% among U.S. women aged 45-54 and 55-64, respectively [CDC NCHS, 2016]. Similarly, another study reported a 1-year migraine prevalence of 25.5% and 18.2% among women in their 40’s and 50’s [Lipton et al, 2007]. Results from other countries have been consistent with these data [GBD collaborators, 2018]. Studies are not conclusive on whether there is an association between menopausal symptoms and migraine [Mattsson, 2003, Wang et al, 2003].

Syncope

Reported adverse events of syncope were assessed across the phase 3 program for fezolinetant in POP2. TEAEs of syncope were reported for 0.1% of participants in the placebo group and 0.5% of participants in the total fezolinetant group with no evidence of a dose-relationship. Most of these events were reported as mild or moderate in severity and the majority were reported as not related to the study intervention by the investigator. There was no discernible pattern across the 52-week treatment period with regard to time to onset and no evidence of clustering after first dose administration in any treatment group. None of the reported TEAEs of syncope lead to withdrawal of study intervention. None of the TEAEs of syncope was reported as serious.

Insomnia

Reported adverse events of insomnia were assessed across the phase 3 program for fezolinetant in POP2. TEAEs of insomnia were reported for 1.6% of participants in the placebo group and 2.5% of participants in the total fezolinetant group. All of these events were reported as mild or moderate in severity. The majority of the events were reported as not related to treatment. There was no discernible pattern across the 52-week treatment period with regard to time to onset and no evidence of clustering after first dose administration in any treatment group. Two participants in the fezolinetant 45 mg total group had events of insomnia which led to withdrawal of study intervention. None of the TEAEs of insomnia was reported as serious.

Risk for Suicide

The Columbia Suicide Severity Rating Scale (C-SSRS) was used in the phase 3 Studies 2693-CL-0301, 2693-CL-0302 and 2693 CL 0304. Data were analysed per ISS/SCS. C-SSRS data from the phase 2 studies is presented in the individual CSRs. Evaluation of the C-SSRS conducted across the clinical program showed that treatment with fezolinetant had no impact on suicide risk.

In POP2 at baseline, the investigator-reported suicidal ideation or behaviour was similar across the treatment groups: 3 participants (0.3%) in the placebo group, 3 participants (0.3%) in the fezolinetant 30 mg total group and 5 participants (0.5%) in the fezolinetant 45 mg total group. In POP2 at week 12, suicidal ideation or behaviour was reported for 1 participant (0.1%) in the placebo group and 3 participants (0.3%) in the fezolinetant 45 mg total group, and self-injurious behaviour without suicidal intent was reported for 1 participant (0.1%) in the placebo group. In POP2 at week 52, the reporting of suicidal ideation or behaviour was similar across the treatment groups: the investigator reported suicidal ideation for 1 participant (0.3%) in the placebo group, 0 participants in the fezolinetant 30 mg total group and 1 participant (0.1%) in the fezolinetant 45 mg total group.

Results for POP4 were consistent with those from POP2.

Nonclinical

Specific nonclinical studies were performed to evaluate physical dependency and reinforcing effects.

Oral administration of 10, 30 or 100 mg/kg per day fezolinetant for 28 days did not produce a withdrawal syndrome in male or female rats upon cessation of dosing. Fezolinetant did not have the potential of causing physical dependency in rats under the conditions of this study. Intravenous self-administration of 0.25, 0.50, or 0.75 mg/kg per 0.2 mL fezolinetant did not result in a statistically significant difference in response patterns compared to the vehicle. Fezolinetant did not produce reinforcing effects in male or female Lister Hooded rats.

No CNS adverse effects were observed in cynomolgus monkey (in 5-, 13- and 39-week studies). In rats, sedative-like CNS findings (decreased activity, touch escape response, and grip strength) were noted at a dose of 250 mg/kg after single dose in the safety pharmacology study, at 300 mg/kg per day in the 4 week repeat dose toxicity study and at 100 mg/kg per day in the 13-week repeat dose toxicity study. These clinical signs were not apparent 24 hours post-dose. The ratio of C max (27400 ng/mL) at 30 mg/kg (NOAEL) on day 1 in the 13-week rat study to the human C max (458 ng/mL) at 45 mg was 60.

Selected Laboratory Safety

Thrombocytopenia

Thrombocytopenia was observed in the nonclinical program in monkeys at the highest tested doses and was associated with bleeding. As a result, thrombocytopenia was considered a medical event of interest, and the potential for a signal was monitored in the phase 3 clinical studies by evaluating the

treatment-emergent AESI of thrombocytopenia and examining the clinical laboratory data for platelet counts < 150 x 109/L.

Laboratory Investigations - 52-week safety populations, placebo controlled (POP4)

POP4, the incidence of clinically relevant hematology and coagulation parameter values was similar across the treatment groups. In POP4, the incidence of platelet count abnormalities (< 150 x 109/L) was low and similar across the treatment groups (Table 44); only 1 participant (placebo group) had an incidence of platelet values ⩽ 50 x 109/L.

Table 44 Number (%) of Participants with Platelet Counts < 150 x 109/L (Safety Analysis Set); POP4: Study 2693-CL-0304

Criteria	Placebo (n = 610)	Fezolinetant 30 mg (n = 611)	Fezolinetant 45 mg (n = 609)	Fezolinetant Total (n = 1220)
<150 x 10^9/L	23/559 (4.1%)	23/575 (4.0%)	22/571 (3.9%)	45/1146 (3.9%)

Laboratory Investigations - Supportive 52-week safety populations (POP2)

Laboratory assessments of thrombocytopenia (platelet counts < 150 x 109/L) were similar across treatment groups over 12 weeks for POP3, or over 52 weeks for POP2 and POP4 (differences ⩽ 1.1% between placebo and fezolinetant 30 mg or fezolinetant 45 mg).

In POP2, platelet count abnormalities (< 150 x 109/L) were infrequent and showed no clinically relevant difference between treatment groups.

Treatment-emergent AESIs of thrombocytopenia

Treatment-emergent AESIs of thrombocytopenia also showed no meaningful differences across treatment groups over 12 weeks for POP1, 12-week POP2, POP3 or POP5, or over 52 weeks for POP2 and POP4 (incidence of < 1.0% for all placebo and fezolinetant 30 mg and fezolinetant 45 mg groups). TEAEs of thrombocytopenia also showed no meaningful differences between treatment groups. There was no apparent dose-dependency with the incidence of events, with general similarity between fezolinetant 30 mg and fezolinetant 45 mg groups.

Epidemiology

Studies in European populations have estimated the prevalence of thrombocytopenia to be 1.6% to 3.9% (all ages and sexes) [van Zeventer et al, 2021; Biino et al, 2012; Biino et al, 2011; Santimone et al, 2011]. In POP2, the incidence of thrombocytopenia (platelet count < 150 x 109/L) during treatment was 2.9% to 4.0%, and in POP4 it was 3.9% to 4.1%, consistent with the published literature.

Nonclinical

At the highest doses tested in repeated-dose toxicity studies, thrombocytopenia was observed in cynomolgus monkeys, which also showed anemia or hypocellular bone marrow, however, thrombocytopenia was reversible with a 4-week withdrawal period.

Elevated Glucose

A comprehensive evaluation of safety with regard to clinically relevant elevations in glucose levels was conducted in the clinical program for fezolinetant. The totality of data suggests that glucose elevations were not associated with fezolinetant treatment.

The potential for a signal was assessed by evaluating the TEAEs of carbohydrate tolerance analyses (including diabetes), diabetes mellitus (including subtypes) and hyperglycemic conditions (NEC) and examining the clinical laboratory data for mean and median changes from baseline and categorical shifts in values. Samples may have been collected under fasted or non-fasted conditions and may not have been collected at consistent times of the day. Additional confounders included past medical history of diabetes, glucose intolerance or overweight/obesity at study entry. Post hoc analysis for POP2 examined shifts in glucose levels and associated TEAEs according to diabetic status at baseline.

Laboratory Investigations - 12-week safety population, placebo controlled (POP1)

The upper limit of the normal range for glucose for the phase 3 studies as defined by the central laboratory was > 5.6 mmol/L (100.9 mg/dL). Elevations in glucose that were considered clinically meaningful were based upon the non-fasting criteria for the diagnosis of diabetes and were equal to having a measurement of glucose ⩾ 11.1 mmol/L (200 mg/dL).

Laboratory Investigations – supportive 12-week safety population (POP3)

In POP3, there were no clinically relevant changes from baseline in glucose values during the 12-week period in the fezolinetant or placebo groups. Results for POP3 showed a slightly greater percentage of participants in the fezolinetant 30 mg and 45 mg total groups with categorized increases in glucose values at weeks 4 and 12 than in the placebo group.

Laboratory Investigations - 52-week Safety Population, placebo-controlled (POP4)

For POP4, mean change from baseline in glucose levels showed no clinically significant changes in any of the treatment groups.

Shifts in glucose levels from low to high, normal to high or missing at baseline to high at the week 52 visit during the study were reported for 40/256 participants (15.6%) in the placebo group, 43/272 (15.8%) in the fezolinetant 30 mg group and 55/262 participants (21.0%) in the fezolinetant 45 mg group. There were variations across the treatment groups with regard to the proportion of participants with shifts to high postbaseline glucose values, however there were no meaningful differences between the fezolinetant and placebo groups.

Laboratory Investigations – supportive 52-week Safety Population (POP2)

For POP2, mean change from baseline in glucose levels showed no clinically significant changes in any of the treatment groups.

Shifts in glucose levels from low to high, normal to high or missing at baseline to high at the week 52 visit during the study were reported for 40/256 participants (15.6%) in the placebo group, 71/442 (16.1%) in the fezolinetant 30 mg total group and 93/449 participants (20.7%) in the fezolinetant 45 mg total group.

In POP2, shifts in glucose values (< 200 mg/dL at baseline to ⩾ 200 mg/dL postbaseline) for non-diabetic participants were infrequent with a similar incidence across treatment groups (⩽ 1.0% participants in the placebo, fezolinetant 30 mg total or fezolinetant 45 mg total groups at any timepoint). For diabetic participants (where the denominator was smaller), shifts from < 200 mg/dL at baseline to ⩾ 200 mg/dL postbaseline were more frequent, but there were no meaningful differences between treatment groups (< 20% of participants in the placebo and fezolinetant total groups).

TEAEs of blood glucose elevations

In POP2, TEAEs of blood glucose elevations were reported for 1.2% of participants in the placebo group, 3.2% of participants in the fezolinetant 30 mg total group and 2.7% of participants in the

fezolinetant 45 mg total group. In the fezolinetant groups, the TEAEs were predominantly the preferred term of blood glucose increased. All events were mild or moderate in severity.

When assessed by diabetic status (at study entry), the percentage of participants with TEAEs of blood glucose elevations was greater in those participants with diabetes than those without, suggesting that the events were associated with the underlying comorbidity of diabetes.

In a post hoc analysis of POP2 by history of diabetes at baseline, more participants in the fezolinetant groups than in the placebo group had a TEAE within the category of blood glucose elevations, regardless of diabetes status at baseline. The most commonly reported term was blood glucose increased. Overall, AEs of blood glucose elevations were reported for 11 participants (1.2%) in the placebo group, 35 participants (3.2%) in the fezolinetant 30 mg total group and 30 participants (2.7%) in the fezolinetant 45 mg total group. Very few participants were reported as having a TEAE of type 2 diabetes mellitus and the incidence in the placebo group (0.4% of participants) was similar to that in the fezolinetant total group (0.5% of participants).

In POP2, a post hoc analysis demonstrated that few participants had a shift in glucose from a baseline value < 200 mg/dL to a value $\geqslant$ 200 mg/dL at any timepoint, and regardless of history of diabetes at baseline. The number of participants with a shift to a higher glucose level was small in all treatment groups, and there was no appreciable difference between placebo and the fezolinetant treatment groups.

Nonclinical

In toxicology studies in rats and cynomolgus monkeys, serum glucose level was normal after fezolinetant administration.

Elevated Creatine Kinase

A comprehensive evaluation of safety with regard to elevations in CK was conducted in the clinical program for fezolinetant. The totality of the data supports the safety of fezolinetant regarding CK elevations.

The potential for a signal was assessed by evaluating the clinical laboratory data for mean and median changes from baseline and categorical shifts in values and reported TEAEs of blood creatine phosphokinase increased.

Laboratory Investigations

Laboratory assessments of CK showed no meaningful differences across treatment groups over 12 weeks for POP3 or over 52 weeks for POP2 or POP4.

TEAEs

The incidences of TEAEs associated with elevated CK also showed no meaningful differences across treatment groups over 12 weeks for POP1, 12-week POP2, POP3 or POP5, or over 52 weeks for POP2 and POP4. In addition, there was no dose-dependency as evidenced by no consistent difference in incidence of events between fezolinetant 30 mg or 45 mg groups.

A serious TEAE associated with elevated CK (rhabdomyolysis) was reported for 1 participant, who received fezolinetant 30 mg. This event was not considered related to study intervention; the alternative aetiology of history of rhabdomyolysis and attribution to cross-fit workout temporally aligned to the onset of the reported event are noted.

Nonclinical

There was no assessment of CK in the nonclinical program. A literature search did not reveal an association between CK and NK3 receptor antagonism.

Neoplasms benign, malignant and unspecified (including cysts and polyps)

Overall, the 52-week long term 2693-CL-0304 safety data supports the safety of fezolinetant in the treatment of VMS associated with menopause. However, due to a numeric imbalance observed in the incidence of serious TEAEs in the SOC of neoplasms benign, malignant and unspecified (incl cysts and polyps) between fezolinetant and placebo groups reported in the long-term safety study (POP4), the sponsor performed a thorough post hoc review of these events for the phase 2 and 3 studies.

Treatment-emergent neoplasm events were defined by the MedDRA (v 23.0) SOC neoplasms benign, malignant and unspecified (incl cysts and polyps). Events were investigated at the serious level in Study 2693-CL-0304 (serious TEAEs in POP4), at the pooled phase 3 population level (serious TEAEs in POP2), at the all TEAE level (all TEAEs in POP2) and also in the phase 2 studies, with the focus of the current discussion being that of the malignant neoplasms. The sponsor used a conservative approach for the detection of potential signals of malignancy. Per sponsor procedures, all TEAEs in the SOC of neoplasms, benign, malignant and unspecified (incl cysts and polyps) are upgraded to serious, excluding benign neoplasms and cancers in remission, regardless of the status reported by the investigator. Reported serious TEAEs include malignant (solid, hematologic, skin) and benign neoplasms. These data were also evaluated by exposure adjusted incidence rates across the treatment groups.

Of note, there was no previous potential concern for malignant neoplasms identified in the nonclinical carcinogenicity or genotoxicity studies nor in phase 2 or pivotal phase 3 studies. Based on the observed imbalance in the 2693-CL-0304 study, the sponsor performed a thorough post hoc review across phase 2 and 3 studies.

Phase 2a and 2b studies

No potential concern for malignant neoplasms was recognized for the phase 2a and 2b studies in the target population of VMS associated with menopause (ESN364_HF_204 and ESN364_HF_205) with a total of 1 TEAE of squamous cell carcinoma of the skin at fezolinetant 60 mg once daily in the latter study.

Phase 3 studies

While the focus of this discussion is the malignant TEAEs of the neoplasm SOC, specifically in POP4, incremental data for POP2 includes the following:

Study 2693-CL-0301: 1 participant each with

- Squamous cell carcinoma of skin; onset day 63 (placebo/fezolinetant 30 mg)
- Apocrine breast carcinoma; onset day 11 (placebo/fezolinetant 45 mg)

Study 2693-CL-0302: 1 participant each with

- Invasive breast carcinoma; onset day 151 (placebo/fezolinetant 30 mg)
- Squamous cell carcinoma of skin; onset day 104 (fezolinetant 45 mg)

Serious TEAEs in POP4

Reported serious TEAEs included malignant (solid, hematologic, skin) and benign neoplasms. In POP4, 2 participants (0.3%) in the placebo group had serious TEAEs within the SOC of neoplasms benign,

malignant and unspecified (incl cysts and polyps): neurilemmoma benign and squamous cell carcinoma of skin. No change was made to study treatment in either instance and the events were assessed unrelated to the study intervention by the investigator.

In POP4, 5 participants (0.8%) in the fezolinetant 30 mg group and 7 participants (1.1%) in the fezolinetant 45 mg group had serious TEAEs within the SOC of neoplasms benign, malignant and unspecified (incl cysts and polyps). These included:

- 3 participants with endometrial adenocarcinoma
- 2 participants with colon cancer
- 1 participant with chronic lymphocytic leukemia
- 1 participant with squamous cell carcinoma of the oral cavity
- 1 participant with non-small cell lung cancer with hepatic metastases
- 3 participants with skin malignancies: 1 participant with basal cell carcinoma, 1 participant with squamous cell carcinoma and 1 participant with malignant melanoma in situ
- 1 participant with a benign breast neoplasm

TEAEs in POP2

All TEAEs: All TEAEs in POP2 (serious and non-serious) within the SOC of neoplasms benign, malignant and unspecified (incl cysts and polyps) were reported for 11 participants (1.2%) in placebo group, 19 participants (1.7%) in the fezolinetant 30 mg total group, 25 participants (2.3%) in the fezolinetant 45 mg total group and 44 participants (2.0%) in the fezolinetant total group. Exposure-adjusted incidence rates in POP2 for non-benign neoplasms (high level group term) were 0.2, 0.7 and 1.2 per 100 participant-years in the placebo, fezolinetant 30 mg total group and fezolinetant 45 mg total group, respectively. This broader analysis of neoplastic events was less informative as the majority of events were benign, a large proportion were of uterine leiomyoma, with a similar incidence of these across treatment groups and are not a focus of this discussion.

A similar analysis was conducted across the entire phase 2 and phase 3 program (POP2 and POP5) which was aligned with the POP2 analysis.

Literature on Biologic Mechanisms

A review of the biological mechanisms from published literature on the effects of NK3 receptor antagonism on neoplasms is summarized by [Mehboob et al, 2021; Yoshida et al, 2021; Muñoz & Coveñas, 2020; Nizam et al, 2020; Dickmen et al, 2019; Nizam & Erin, 2018; Xu et al, 2018; Gao & Wang, 2017; Obata et al, 2017; Ma et al, 2016; Obata et al, 2016; Cejudo Roman et al, 2012; Muñoz & Rosso 2010; Hennig et al, 1995]. The preponderance of available literature does not suggest a plausible mechanistic hypothesis for the role of NK3 receptor antagonism in the development of neoplasms. On the contrary, most literature point to tachykinin agonism as playing a role in neoplastic development, whilst antagonism is a plausible therapeutic antineoplastic target [Coveñas & Muñoz, 2014].

Endometrial safety

A comprehensive evaluation of endometrial safety was conducted across the program for fezolinetant.

Most important are considered the long-term double-blind placebo-controlled data from **study 2693-CL-0304 (SKYLIGHT 4)** are provided to support long-term safety, especially on endometrial health. Therefore, this endometrial health results of the study are discussed in the safety section here below:

Outcomes and estimation

Endometrial Biopsy

The endometrial health set consisted of all randomized participants who received at least one dose of study intervention, had the postbaseline biopsy done within 30 days after the last dose of study intervention, had an acceptable biopsy at baseline (at least one endometrial biopsy with satisfactory tissue and no read of hyperplasia, malignant or disordered proliferative pattern) and had an satisfactory endometrial biopsy result after or on day 326 or had a postbaseline final diagnosis of hyperplasia, malignant or disordered proliferative pattern prior to day 326.

A total of 127 participants (20.8%) in the placebo group, 100 participants (16.4%) in the fezolinetant 30 mg group and 114 participants (18.7%) in the fezolinetant 45 mg group had undergone a hysterectomy and were therefore ineligible for entry into the endometrial health set. For those participants with a uterus, the disposition is summarized in [Table 49]. The endometrial health set consisted of 599 participants: 186 in the placebo group, 210 in the fezolinetant 30 mg group and 203 in the fezolinetant 45 mg group (Table 45).

Table 45 Disposition of Endometrial Biopsy Results (Randomized Participants)

Reason	Placebo (n = 611)	Fezolinetant 30 mg (n = 611)	Fezolinetant 45 mg (n = 609)
Randomized	611	611	609
Safety Analysis Set	610	611	609
Had a hysterectomy	127	100	114
Post-baseline final diagnosis of hyperplasia, malignancy or disordered proliferative pattern before day 326 †	2	2	2
Acceptable biopsy at baseline AND satisfactory sample at postbaseline	214	239	228
< 326 days	20	18	20
> last dose + 30 days	8	11	5
Endometrial health set	186	210	203

† These participants had an acceptable biopsy at baseline except for the 2 participants from the fezolinetant 45 mg group: participant 4800442605 had disordered proliferative pattern and participant 4801641915 had hyperplasia at baseline, therefore these 2 participants were not included in the endometrial health set.

Endometrial hyperplasia

No participants in the fezolinetant 30 mg group were classified with a final diagnosis of hyperplasia; the one-sided upper limit of the 95% CI was 1.4%. From the fezolinetant 45 mg group, 1 participant (0.5%) was classified with a final diagnosis of hyperplasia; the one-sided upper limit of the 95% CI was 2.3%.

Endometrial carcinoma

One participant, from the fezolinetant 30 mg group, had a final diagnosis of malignancy with a rate of 0.5% and the upper limit of the one-sided 95% CI was 2.2%.

Disordered proliferative pattern

The percentage of participants with a final biopsy diagnosis of disordered proliferative pattern was higher in the placebo group than in the fezolinetant groups.

There were 3 participants with treatment-emergent AESIs of endometrial adenocarcinoma.

Transvaginal Ultrasound

All participants with a uterus were required to have a TVU to assess endometrial thickness at screening and week 52 or discontinuation visit. TVUs were performed locally and read centrally. Changes from baseline in endometrial thickness are described in (Table 46).

As only participants with a uterus were eligible for TVU assessment, the number of eligible participants for TVU assessment is lower than the number of participants in the SAF. Approximately 70% of participants with a baseline TVU assessment had a post-baseline TVU.

In all treatment groups, there was a small mean and median decrease from baseline to week 52 in endometrial thickness, consistent with the clinical setting in postmenopausal participants. There was no statistically significant difference between fezolinetant and placebo in change from baseline to week 52 in endometrial thickness (P > 0.05). Based on the TVU data, fezolinetant has no impact on endometrial thickness after 1 year of treatment.

Table 46 Endometrial Thickness Measured by Transvaginal Ultrasound: Change From Baseline to Week 52 (Safety Analysis Set)

Statistic	Placebo (n = 610)	Fezolinetant 30 mg (n = 611)	Fezolinetant 45 mg (n = 609)
Endometrial thickness at baseline (mm)			
n	464	489	483
Mean (SD)	3.59 (2.19)	3.52 (2.15)	3.51 (2.59)
Median	3.03	3.06	2.72
Min, Max	0.7, 13.8	0.4, 16.6	0.6, 23.8
Endometrial thickness at week 52 (mm)			
n	320	339	347
Mean (SD)	3.52 (2.59)	3.26 (2.03)	3.21 (2.01)
Median	2.96	2.84	2.74
Min, Max	0.7, 22.5	0.7, 19.7	0.6, 13.7
Change from baseline			
n	316	334	346
Mean (SD)	-0.17 (2.35)	-0.15 (1.97)	-0.28 (2.30)
Median	-0.16	-0.10	-0.11
Min, Max	-9.1, 10.5	-12.7, 7.1	-16.5, 9.1
LS mean change from baseline			
LS mean (SE)	-0.09 (0.11)	-0.17 (0.11)	-0.26 (0.11)
95% 2-sided CI	-0.31, 0.13	-0.39, 0.05	-0.48, -0.05
Difference in LS means: fezolinetant vs placebo			
LS mean (SE)	-	-0.08 (0.14)	-0.17 (0.14)
95% 2-sided CI	-	-0.36, 0.21	-0.45, 0.11
2-sided P value	-	0.604	0.239

All randomized participants who took at least 1 dose of study intervention (Safety Analysis Set). The LS Means, SE, CI, and P values come from an ANCOVA model with change from baseline at the week 52 timepoint as response, treatment and smoking status (current vs former/never) as fixed effects with baseline weight and baseline covariates. Differences were calculated by subtracting the LS mean of the placebo group from the LS mean of the fezolinetant group. P value is for comparison of fezolinetant with placebo from the above described ANCOVA model. ANCOVA: analysis of covariance; CI: confidence interval; LS: least squares; Max: maximum; Min: minimum.

Supplemental data on endometrial health

Endometrial biopsy data of SKYLIGHT 1, 2 and 4 (POP2)

For Studies 2693-CL-0301 and 2693-CL-0302, participants' screening endometrial biopsy had to be considered evaluable (only from v 3.0 of the protocol), and approximately 32% of participants from these studies had a medical history of hysterectomy and were therefore not included in the EH set for POP2.

In POP2, a total 302 participants were included in the fezolinetant 30 mg group, and 304 participants in the fezolinetant 45 mg group .

In POP2 for the events of endometrial hyperplasia and malignancy, the rate of events in the fezolinetant groups was $\leqslant$ 1% with the upper bound of the one-sided 95% CI being $\leqslant$ 4%, consistent with the results for POP4 .

The incidence of hyperplasia or malignancy was similar in the fezolinetant 30 mg and fezolinetant 45 mg groups in the EH set. All of the endometrial malignancy cases were identified during the 2693-CL-0304 study; there were no participants with endometrial malignancy in Studies 2693 Cl 0301 or 2693 CL 0302.

In POP2, the incidence of disordered proliferative pattern was similar in the fezolinetant 30 mg and fezolinetant 45 mg groups in the EH set.

Former placebo-patients in SKYLIGHT 1 and 2

Participants who were initially on placebo and re-randomized to fezolinetant in Studies 2693 CL-0301 and 2693 CL 0302 were not included in the primary EH set. However, supportive analyses were conducted which included these re-randomized participants plus the EH set. Additional supportive analyses were conducted for the re-randomized participants only.

The combined supportive analysis of biopsy results for participants in the EH set plus those in the EH set for re-randomized participants showed the rate of events of both hyperplasia and malignancy in the fezolinetant groups was $\leqslant$ 1% with the upper bound of the one-sided 95% CI being $\leqslant$ 4%. The results of this supportive analysis of EH set plus re-randomized participants was concordant with and supportive of the primary analysis for the EH set (POP4) .

The additional supportive analysis of the re-randomized participants only had a small number of participants (n $\leqslant$ 51), and upper limit of the one-sided 95% CI exceeded the 4% threshold, as expected given the small number of participants.

TVU results of SKYLIGHT 1, 2 and 4

In POP2, change from baseline to week 52 in endometrial thickness as assessed by TVU showed no clinically relevant changes in any of the treatment groups. The POP2 data are concordant with, and support the conclusions from, the assessment of TVU in POP4.

Treatment-emergent AESIs - endometrial hyperplasia, cancer, or disordered proliferative endometrium

In POP4, the frequency of treatment-emergent endometrial hyperplasia, cancer, or disordered proliferative endometrium was low across all treatment groups, with a higher incidence of uterine

bleeding in the placebo group. Analysis of the incidence of treatment-emergent AESIs in POP4 using the Santner-Snell approach showed that the 95% CI for the odds ratio for each category included 1 for all calculable comparisons versus placebo, indicating no difference between placebo and either fezolinetant 30 mg or fezolinetant 45 mg.

The frequencies of treatment-emergent endometrial hyperplasia, cancer, disordered proliferative endometrium, or uterine bleeding in POP2 were also low.

Three participants had a TEAE of endometrial adenocarcinoma: 1 of whom was included in the EH set.

Phase 2 studies endometrial safety

There were no notable findings in the phase 2 program in VMS studies for endometrial safety. In Study ESN364_HF_205 in postmenopausal females, there was no increase in endometrial thickness, as measured by TVU, compared with placebo, and a few isolated cases of uterine bleeding, which were not associated with clinically significant endometrial biopsy findings. Study ESN364_HF_204 did not include TVUs or endometrial biopsies; and the 1 event of uterine bleeding was in the placebo group.

Epidemiologic context of endometrial alterations

Both disordered proliferative endometrium and endometrial hyperplasia are on a continuum of morphological endometrial alterations resulting from unopposed estrogenic stimulation, and these conditions can be precursors to endometrial carcinoma [Damle et al, 2013]. Studies in the US indicate that the incidence of endometrial hyperplasia increases with age from 40-44 years to 50-54 years, and then starts to decrease [Reed et al, 2009; Lacey et al, 2012]. In addition, data from the Surveillance, Epidemiology and End Results (SEER) registry database in the US shows increasing incidence rates of endometrial cancer with age from 40-44 years to 65-69 years [SEER*Explorer, 2015-2019]. There is a similar trend in incidence by age for endometrial hyperplasia and endometrial cancer both globally and in the EU [Yuk, 2016; Ferlay et al, 2020].

Currently, the available standard of care of HT for VMS associated with menopause carries a risk of hyperplasia. Randomized controlled trials in individuals receiving HT demonstrate an increased incidence rate of hyperplasia in individuals taking estrogens than in those taking placebo; however, differences between studies show wide variations [Sriprasert et al, 2021; Simon et al, 2010; Johnson et al, 2005; Portman et al, 2003].

Data from the US show that the use of HT employing estrogen only appears to result in an increased risk of disordered proliferative endometrium and endometrial cancer and that the addition of a progestin appears to mitigate the risks of unopposed E2 [Mørch et al, 2016; Trabert et al, 2013; Karageorgi et al, 2010; Beral et al, 2005; Lacey et al, 2005; Kurman et al, 2000].

Risk factors of endometrial carcinoma include obesity, changes in balance of female hormones, more years of menstruation, never having been pregnant, hormone therapy for breast cancer (e.g., tamoxifen), simple atypical hyperplasia and complex atypical hyperplasia. Obese and overweight individuals are approximately 2 to 4 times as likely as normal-weight individuals to develop endometrial cancer [American Cancer Society, 2019]. Simple atypical hyperplasia develops into cancer in about 8% of cases if it is not treated. Complex atypical hyperplasia has a risk of becoming cancer in up to 29% of cases if it is not treated, and the risk of having an undetected endometrial cancer is even higher [American Cancer Society, 2019].

Biologic Plausibility

The nonhormonal mechanism of action of fezolinetant via NK3 receptor antagonism and blocking of KNDy neuron activity is not mechanistically expected to alter the estrogen balance for postmenopausal individuals. In individuals suffering from VMS (HF), long term administration of fezolinetant did not

show a clear trend or clinically relevant change in sex hormones including androstenedione, E2, estrone, FSH, testosterone, dehydroepiandriosterone, free testosterone, or SHBG. In addition to affecting the thermoregulatory center in the hypothalamus, KNDy neurons control the release of GnRH. Therefore, fezolinetant activity decreases GnRH pulse frequency, leading to transient lowering effects on LH. In individuals suffering from VMS (HF), a transient decrease in LH was detected at peak levels of drug but no long-term effect on LH was observed.

Nonclinical

There were no abnormal thickenings of the endometrium in the sexually matured cynomolgus monkey in repeated-dose toxicity studies.

Conclusion

Based on the totality of data across the fezolinetant phase 3 studies, the evidence supports no association of fezolinetant exposure with a risk of endometrial hyperplasia, malignancy or disordered proliferative endometrium. Importantly, in the 52-week long-term safety study 2693-CL-0304, the primary endpoints of endometrial hyperplasia and malignancy each met the prespecified criterion of $\leqslant$ 1% with upper bound of one-sided 95% CI not exceeding 4%. The additional analyses including the biopsy data from studies 2693-CL-0301 and 2693-CL-0302 are concordant with the primary analysis conclusions. Furthermore, fezolinetant has no impact on endometrial thickness after 1 year of treatment. The incidences of the treatment-emergent AESIs of uterine bleeding and of endometrial hyperplasia, cancer or disordered proliferative endometrium were low, with a higher incidence of uterine bleeding in the placebo group. Fezolinetant is not associated with hyperplasia or malignancy. The epidemiology information on endometrial safety and risk factors is only available for the standard of care, which is distinct from the nonhormonal option of fezolinetant. The characterization of fezolinetant supports the endometrial safety of fezolinetant in the treatment of moderate to severe VMS associated with menopause at the proposed therapeutic dose.

Other observations related to safety

Safety observations reported in non-clinical or early clinical studies were examined in the context of the overall phase 3 program to assess for potential safety signals.

Hyperthyroidism

Thyroid follicular cell hypertrophy was observed in the nonclinical studies in rats, therefore an evaluation of hyperthyroidism was conducted. Overall, the data support the safety of fezolinetant with respect to hyperthyroidism risk in the treatment of VMS associated with menopause at the proposed therapeutic dose.

In POP2, TEAEs of hyperthyroidism were reported for 3 participants: 1 participant (0.1%) in the placebo group and 2 participants (0.2%) in the fezolinetant 45 mg total group.

In POP4, hyperthyroidism was reported as a TEAE for 2 participants: 1 (0.2%) in the placebo group and 1 (0.2%) in the fezolinetant 45 mg group.

The overall incidence of TEAEs of hyperthyroidism was low and similar across the treatment groups in both 52-week populations.

Oral Paraesthesia

As oral paraesthesia was a dose limiting side effect in the phase 1 program, an evaluation of oral paraesthesia was conducted in the clinical program for fezolinetant. Overall, the data support the

safety of fezolinetant with respect to oral paraesthesia risk in the treatment of VMS associated with menopause at the proposed therapeutic dose.

In POP2, there were 6 events of paraesthesia oral: 3 participants (0.3%) in the placebo group, 2 participants (0.2%) in the fezolinetant 30 mg total group and 1 participant (0.1%) in the fezolinetant 45 mg total group.

In POP4, there were 5 events of paraesthesia oral: 2 participants (0.3%) in the placebo group, 2 participants (0.3%) in the fezolinetant 30 mg group and 1 participant (0.2%) in the fezolinetant 45 mg group.

The overall incidence of TEAEs of oral paraesthesia was low and similar across the treatment groups in both 52-week populations.

2.6.8.3. Serious adverse event/deaths/other significant events

Deaths

In total, there were 2 deaths reported in the fezolinetant program (one in Study 2693-CL-0302, and one cardiac arrest with anoxic brain injury in Study 2693-CL-0304). Both events were considered not related to the study intervention by the investigator.

Serious Adverse Events

12-week safety population, placebo-controlled (POP1)

In POP1, the number of serious TEAEs was low (⩽ 1.5% in any treatment group) . Individual preferred terms were not reported in more than 1 participant. Overall, 1 serious TEAE was reported in the placebo group compared with 9 serious TEAEs in the fezolinetant total 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 (verbatim preferred term of elevated liver function test) and 1 event of transaminases increased (verbatim preferred term of transaminitis), which was reported as serious as it met the protocol-specified discontinuation criteria.

For the event of biliary dyskinesia, symptoms were observed prior to study start, and for atrial fibrillation this was reported as an ongoing medical history. The event of paraesthesia concerned facial paraesthesia, which was reported as due to use of a continuous positive airway pressure mask.

Results for the 12-week POP2, were consistent with those from POP1, with ⩽ 1.5% of participants in any treatment group experiencing a serious TEAE. Serious TEAEs related to study intervention were transaminases increased in the fezolinetant 30 mg group and liver function test abnormal in the fezolinetant 45 mg group.

For POP3 and POP5, the overall incidence of serious TEAEs was low, with ⩽ 1.5% of participants in any treatment group experiencing a serious TEAE. There were no serious TEAEs related to study intervention in POP5. Serious TEAEs by time interval for 12-week POP2, POP3 and POP5 showed that no specific pattern was evident based on the time course of the reported serious TEAEs.

52-week safety population, placebo-controlled (POP4)

In POP4, the overall incidence of serious TEAEs was low. The most frequent serious TEAEs were abdominal pain (0 participants in the placebo group, 1 participant [0.2%] in the fezolinetant 30 mg group, and 2 participants [0.3%] in the fezolinetant 45 mg group) and endometrial adenocarcinoma (0 participants in the placebo group, 1 participant [0.2%] in the fezolinetant 30 mg group and 2

participants [0.3%] in the fezolinetant 45 mg group). No other serious TEAEs by preferred term occurred in ⩾ 3 participants across all treatment groups.

There were a greater percentage of participants with serious TEAEs within the SOC of neoplasms benign, malignant and unspecified (incl. cysts and polyps) in the fezolinetant groups than in the placebo group (difference of ⩾ 0.5%).

Supportive 52-week safety population (POP2)

In POP2, the overall incidence of serious TEAEs was low, although there was a higher incidence in the fezolinetant groups than in the placebo group. Differences were partly driven by serious TEAEs within the SOC of neoplasms benign, malignant and unspecified (including cysts and polyps) (0.2% in the placebo group and 0.9% in the fezolinetant total group). The short latency period (from study initiation to event onset) and the differences in exposure between placebo and fezolinetant groups may confound these results.

The most frequent serious TEAEs by preferred term (> 2 participants) in the fezolinetant total group were: COVID 19 (4 participants, 0.2%), abdominal pain (3 participants, 0.1%), chest pain (3 participants, 0.1%), endometrial adenocarcinoma (3 participants, 0.1%) and squamous cell carcinoma of the skin (3 participants, 0.1%). Serious TEAEs by preferred term were reported for ⩽ 2 participants in the placebo, fezolinetant 30 mg total or fezolinetant 45 mg total treatment groups with the exception of chest pain (3 participants, 0.3% in the fezolinetant 45 mg total group). Differences between the fezolinetant 30 mg total and fezolinetant 45 mg total treatment groups at the SOC and preferred term level were < 1%.

Serious TEAEs related to study intervention in POP2 were reported for 1 participant (0.1%) in the placebo group, 2 participants (0.2%) in the fezolinetant 30 mg total group and 5 participants (0.5%) in the fezolinetant 45 mg total group. Serious TEAEs related to study intervention at the preferred term level were reported for ⩽ 0.1% participants in each treatment group with the exception of hepatotoxicity (1 participant [0.7%] in the placebo/fezolinetant 45 mg group).

The onset of serious TEAEs by time interval in POP2, in general, showed that no specific pattern was evident based on the time course of the reported TEAEs. The observed percentage of participants with serious TEAEs overall increased in all treatment groups after 84 days may be due to wider analysis windows in subsequent intervals. In addition, this coincides with the end of the double-blind treatment period in Studies 2693 CL 0301 and 2693 CL 0302, and results should be interpreted with caution given the absence of a placebo control in studies 2693 CL 0301 and 2693 CL 302.

2.6.8.4. Laboratory findings

Haematology Laboratory Parameters

12-week Safety Populations

Central Tendency

There were no clinically relevant changes from baseline in any of the haematology parameters during the 12-week periods covered by POP3.

Abnormal Values

Results for POP3 showed no clinically relevant differences between the treatment groups with regard to the incidence of haematology abnormalities based on shift tables.

In POP3, platelet count abnormalities (< 150 x 109/L) were infrequent and showed no clinically relevant differences between treatment groups.

52-week Safety Populations

Central Tendency

There were no clinically relevant changes from baseline in any of the haematology parameters during the 52-week period covered by POP2 in the fezolinetant or placebo groups. There were no clinically relevant changes in any of the haematology parameters during the 52-week period covered by POP4 in the fezolinetant or placebo groups.

Abnormal Values

In POP4, the incidence of clinically relevant haematology and coagulation parameter values was similar across the treatment groups.

In POP4, the incidence of platelet count abnormalities (< 150 x 109/L) was low and similar across the treatment groups ; only 1 participant (placebo group) had an incidence of platelet values ⩽ 50 x 109/L.

There was no clinically relevant difference between treatment groups with regard to the incidence of haematology abnormalities based on shift tables in POP2.

In POP2, platelet count abnormalities (<150 x 109/L) were infrequent and showed no clinically relevant difference between treatment groups .

Biochemistry Laboratory Parameters

12-week Safety Populations

Central Tendency

In POP3, there were no clinically relevant changes from baseline in clinical chemistry parameters during the 12-week period in the fezolinetant or placebo groups.

Abnormal Values

Results for POP3 showed no clinically relevant differences between the treatment groups with regard to the incidence of clinical chemistry abnormalities.

52-week Safety Populations

Central Tendency

There were no clinically relevant changes clinical chemistry parameters during the 52-week period covered by POP4 in the fezolinetant or placebo groups.

There were no clinically relevant changes in clinical chemistry parameters during the 52-week period covered by POP2 in the fezolinetant or placebo groups.

Abnormal Values

There were no clinically relevant differences between treatment groups with regard to the incidence of clinical chemistry abnormalities in POP4.

There were no clinically relevant differences between the treatment groups with regard to the incidence of clinical chemistry abnormalities in POP2.

Creatine Kinase

12-week Safety Populations

In POP3, there were no clinically relevant changes from baseline in CK values during the 12-week period in the fezolinetant or placebo groups.

Results for POP3 showed no clinically relevant differences between the treatment groups with regard to the incidence of CK abnormalities.

52-week Safety Populations

In POP4, there were generally small, clinically unremarkable changes from baseline in the mean CK values over the study duration across treatment groups.

In POP4, mild to moderate CK elevations were observed at baseline and throughout the study at an individual participant level across treatment groups. Isolated elevations during the study showed no specific pattern.

For the majority of these participants the elevated CK level was not reported as a TEAE. There were 16 participants with blood creatine phosphokinase increased TEAEs: 3 participants (0.5%) in the placebo group, 7 participants (1.1%) in the fezolinetant 30 mg group and 6 participants (1.0%) in the fezolinetant 45 mg group. All events were mild or moderate in severity; one was considered by the investigator to be related to study intervention (in the placebo group). No events led to the withdrawal of study treatment.

Overall, an association between CK elevations and fezolinetant treatment was not observed.

In POP2, there were generally small, clinically unremarkable, changes from baseline in the mean CK values over the study duration across treatment groups.

In POP2, mild to moderate CK elevations were observed at baseline and throughout the study at an individual participant level across treatment groups. Categorized increases during the study showed no specific pattern or timing and were as common as decreases.

In POP2 for participants with a CK value $\leqslant$ ULN at baseline, categorical findings of CK > ULN were reported for a similar proportion of participants across all treatment groups at all timepoints. There was no apparent association between elevations and duration in the study. Values > 2.5 x ULN were reported for < 1.5% of participants in any treatment group at any timepoint.

In POP2 for participants with a baseline CK value > ULN, categorical findings of CK > 2.5 x ULN were low with a similar incidence across the treatment groups.

Elevated CK levels were reported as TEAEs in more participants receiving fezolinetant than placebo. There were 41 participants with blood creatine phosphokinase increased TEAEs: 3 participants (0.3%) in the placebo group, 15 participants (1.4%) in the fezolinetant 30 mg total group and 23 participants (2.1%) in the fezolinetant 45 mg total group. All events were mild or moderate in severity; 3 events were considered by the investigator to be related to study intervention (2 in the fezolinetant 45 mg total group and 1 in the placebo group). One participant in the fezolinetant 45 mg total group had an event that led to the withdrawal of study treatment.

A CK elevation associated with a relevant TEAE was reported for 1 participant (fezolinetant 30 mg group) who had a serious TEAE of rhabdomyolysis. The event was considered not related to study intervention; the alternative aetiology of history of rhabdomyolysis and concurrent cross-fit workout was reported at the time of the TEAE.

Glucose

It should be noted that the study protocols did not require glucose assessments to be fasting, nor were they required to be obtained consistently at a particular time of day.

12-week Safety Populations

In POP3, there were no clinically relevant changes from baseline in glucose values during the 12-week period in the fezolinetant or placebo groups.

Results for POP3 showed a slightly greater percentage of participants in the fezolinetant 30 mg and 45 mg total groups with categorized increases in glucose values at weeks 4 and 12 than in the placebo group.

52-week Safety Populations

For POP4, mean change from baseline in glucose levels showed no clinically significant changes in any of the treatment groups.

Shifts in glucose levels from low to high, normal to high or missing at baseline to high at the week 52 visit during the study were reported for 40/256 participants (15.6%) in the placebo group, 43/272 (15.8%) in the fezolinetant 30 mg group and 55/262 participants (21.0%) in the fezolinetant 45 mg group. There were variations across the treatment groups with regard to the proportion of participants with shifts to high postbaseline glucose values, however there were no meaningful differences between the fezolinetant and placebo groups.

TEAEs associated with blood glucose increase showed a similar incidence between placebo and fezolinetant treatment groups in POP4.

For POP2, mean change from baseline in glucose levels showed no clinically significant changes in any of the treatment groups.

Shifts in glucose levels from low to high, normal to high or missing at baseline to high at the week 52 visit during the study were reported for 40/256 participants (15.6%) in the placebo group, 71/442 (16.1%) in the fezolinetant 30 mg total group and 93/449 participants (20.7%) in the fezolinetant 45 mg total group.

In POP2, shifts in glucose values (< 200 mg/dL at baseline to $\geqslant$ 200 mg/dL postbaseline) for non-diabetic participants were infrequent with a similar incidence across treatment groups ($\leqslant$ 1.0% participants in the placebo, fezolinetant 30 mg total or fezolinetant 45 mg total groups at any timepoint). For diabetic participants (where the denominator was smaller), shifts from < 200 mg/dL at baseline to $\geqslant$ 200 mg/dL postbaseline were more frequent, but there were no meaningful differences between treatment groups (< 20% of participants in the placebo and fezolinetant total groups).

In POP2, TEAEs of blood glucose elevations were reported for 1.2% of participants in the placebo group, 3.2% of participants in the fezolinetant 30 mg total group and 2.7% of participants in the fezolinetant 45 mg total group]. In the fezolinetant groups, the TEAEs were predominantly the preferred term of blood glucose increased. All events were mild or moderate in severity.

When assessed by diabetic status (at study entry), the percentage of participants with TEAEs of blood glucose elevations was greater in those participants with diabetes than those without, suggesting that the events were associated with the underlying comorbidity of diabetes.

Overall, an association between glucose elevations and fezolinetant treatment was not observed.

Vital Signs

12-week Safety Populations

Mean and median change from baseline in systolic blood pressure, diastolic blood pressure and pulse rate showed no clinically relevant changes from baseline in any of the treatment groups during the initial 12-week period for POP2.

52-week Safety Populations

In POP4, there was no clinically relevant mean or median change from baseline in systolic blood pressure, diastolic blood pressure and pulse rate for any treatment groups.

In POP2, there were no clinically relevant mean or median changes from baseline in systolic blood pressure, diastolic blood pressure and pulse rate for any of the treatment groups.

Physical findings - Electrocardiograms

No significant QTc prolongation was detected in the QT assessment performed using data from the single- / multiple-ascending dose study and therefore no clinical thorough QT study was conducted. Phase 3 studies collected 12 lead ECG data.

12-week Safety Populations

There were no clinically relevant changes in the quantitative interval measures of the ECG parameters in any of the treatment groups throughout the initial 12-week double-blind period for POP2. The majority of participants (> 97%) in all treatment groups had a QTcF $\leqslant$ 450 msec at baseline and at week 12 for POP2. No participants had a QTcF > 480 msec at week 12.

52-week Safety Populations

In POP2, there were no clinically relevant changes in the quantitative interval measures of the ECG parameters in any of the treatment groups. The majority of participants (> 97%) in all treatment groups had a QTcF $\leqslant$ 450 msec at baseline and at week 52. One participant had a QTcF > 480 but $\leqslant$ 500 msec at week 52 (fezolinetant 45 mg group) and 1 participant in the fezolinetant 30 mg group had a QTcF > 500 msec at week 52.

In POP4, there was no clinically relevant changes in the quantitative interval measures of the ECG parameters in any treatment groups. The majority of participants (> 95%) in any treatment group had QTcF $\leqslant$ 450 msec during the study. Two participants (1 in the fezolinetant 30 mg group and 1 in the fezolinetant 45 mg group) had a QTcF > 480 msec and $\leqslant$ 500 msec at baseline. At week 52, 1 participant (fezolinetant 45 mg group) had a QTcF > 480 msec and $\leqslant$ 500 msec (481 msec) and 1 participant (fezolinetant 30 mg group) had a QTcF > 500 msec (510 msec).

Across the entire phase 3 program, there were no reported cases of ventricular tachycardia, ventricular fibrillation, electrocardiogram T wave abnormal, QT prolongation or Torsades de pointes.

2.6.8.5. In vitro biomarker test for patient selection for safety

Not applicable.

2.6.8.6. Safety in special populations

Subgroup analyses were performed for the intrinsic factors of age, race, ethnicity, BMI, isolated NAFLD and NASH and diabetic status, and the extrinsic factors of smoking status and geographical Region. For the 12-week safety analyses, the 12-week POP2 population was used, with POP2 and POP4 providing information for 52-week safety. For some subgroup analyses, the interpretation was limited due to the small number of participants with selected characteristics. Overall, subgroup analyses did not reveal any populations at increased risk with fezolinetant.

2.6.8.7. Immunological events

Not applicable.

2.6.8.8. Safety related to drug-drug interactions and other interactions

Not applicable.

2.6.8.9. Discontinuation due to adverse events

12-week Safety Populations

In POP1, the number of TEAEs leading to withdrawal of treatment was low and balanced across treatment groups. No specific TEAE leading to withdrawal of study treatment (by preferred term) was reported for more than 2 participants in the placebo or fezolinetant 30 mg or 45 mg treatment groups, with the exception of nausea and headache; both were reported for 3 participants in the placebo group. There was no apparent dose response.

TEAEs related to study intervention leading to withdrawal of study treatment in POP1 were reported for 7 participants (2.0%) in the placebo group, 7 participants (2.1%) in the fezolinetant 30 mg group and 8 participants (2.4%) in the 45 mg fezolinetant group. Of those, in the placebo group, there was 1 participant with an event of ALT increased; in the fezolinetant 30 mg group there was 1 participant with an event of liver function test increased and 1 participant with transaminases increased; in the fezolinetant 45 mg group there was 1 participant with an event of ALT increased and 1 participant with INR increased. TEAEs related to study intervention leading to withdrawal of study treatment reported for $\geqslant$ 2 participants by preferred term in any treatment group were abdominal pain upper (2 participants [0.6%] in the placebo group and 2 participants [0.6%] in the fezolinetant 45 mg group), nausea (2 participants [0.6%] in the placebo group and 2 participants [0.6%] in the fezolinetant 45 mg group) and headache (2 participants [0.6%] in the placebo group).

The events of liver function test increased and transaminases increased (both in the fezolinetant 30 mg group) were serious.

Results for the 12-week POP2, as well as the ones for POP3 and POP5 were consistent with those for POP1; there were few TEAEs leading to withdrawal of study treatment, and results were similar across treatment groups. The incidence of TEAEs related to study intervention leading to withdrawal of treatment was similar across the treatment groups.

52-week Safety Populations

In POP2, the number of TEAEs leading to withdrawal of study treatment was low . The percentage of participants with TEAEs leading to withdrawal of study treatment showed differences of < 2% between placebo and fezolinetant treatment groups.

No TEAE leading to withdrawal of study treatment (by preferred term) was reported for more than 3 participants in the placebo, fezolinetant 30 mg total or fezolinetant 45 mg total treatment groups, with the exception of fatigue, dizziness, nausea and headache . There was no apparent dose-response.

TEAEs related to study intervention leading to withdrawal of study treatment in POP2 were similar across the treatment groups: 24 participants (2.5%) in the placebo group, 25 participants (2.3%) in the fezolinetant 30 mg total group, 31 participants (2.8%) in the fezolinetant 45 mg total group and 56 participants (2.5%) in the fezolinetant total group. No TEAE leading to withdrawal of study treatment by preferred term was reported as being related to study intervention for > 4 participants in the placebo, fezolinetant 30 mg total or fezolinetant 45 mg total groups.

In POP4, the number of TEAEs leading to withdrawal of study treatment was low and similar across groups. No specific TEAE leading to withdrawal of study treatment (by preferred term) was reported for more than 2 participants in any treatment group, with the exception of fatigue (3 participants [0.5%] in the fezolinetant 45 mg group), headache (3 participants [0.5%] in the placebo group and 4 participants [0.7%] in the fezolinetant 45 mg group) and nausea (4 participants [0.7%] in the fezolinetant 30 mg group). At the preferred term level results were similar across treatment groups. There was no apparent dose response.

TEAEs related to study intervention leading to withdrawal of study treatment in POP4 were similar across the treatment groups: 16 participants (2.6%) in the placebo group, 16 participants (2.6%) in the fezolinetant 30 mg group and 17 participants (2.8%) in the fezolinetant 45 mg. No TEAE leading to withdrawal of study treatment was reported as being related to the study intervention for more than 3 participants in any treatment group.

2.6.8.10. Post marketing experience

Fezolinetant is not currently marketed in any region and no post marketing data are available.

2.6.9. Discussion on clinical safety

In the fezolinetant clinical development program, safety was evaluated based on the assessment of:

- Adverse events (AEs);
- AEs of clinical interest (AECI) (alanine aminotransferase (ALT) or aspartate aminotransferase (AST) $\geqslant 3 \times$ upper limit of normal (ULN)) clinical laboratory tests;
- Endometrial safety (endometrial biopsies, TVU) (SKYLIGHT 4);
- Bone mineral density (BMD) measurements by dual-energy X-ray absorptiometry (DXA);
- Evaluation of areas of medical focus, i.e. endometrial safety, hepatic safety, bone safety, CNS safety, thrombocytopenia, elevated glucose and elevated CK.

The **safety database** is primarily based on the integrated analyses of pooled safety data from five clinical studies. These are the completed two phase 2 and three phase 3 studies. The 3 phase 3 studies 2693-CL-0301 (SKYLIGHT 1), 2693-CL-0302 (SKYLIGHT 2) and 2693-CL-0304 (SKYLIGHT 4) are comprising the majority of the safety populations. Of note, the study conduct and explorative efficacy results of SKYLIGHT 4 are separately discussed under the efficacy section, the study safety results are discussed below.

The **safety analysis populations** are divided in 5 subpopulations and consists of (pooled) data of five studies (i.e. ESN364_HF_204, ESN364_HF_205, SKYLIGHT 1, 2 and 4). The safety analysis populations, POP1 POP2 POP3 POP4 and POP5, are used to describe safety for 12 and 52 weeks in the study participants with VMS associated with menopause.

- POP1 consists of the 12-week placebo-controlled phase 3 studies SKYLIGHT 1 and 2 for assessment of the short-term safety profile for 12 weeks.
- POP2 consists of phase 3 studies SKYLIGHT 1, 2 (1 -week placebo-controlled phase + 40 week open label uncontrolled extension) and 52-week placebo-controlled SKYLIGHT 4 for assessment of the safety profile up to 52 weeks.,
- POP3 consists of phase 2 dose-response studies ESN364_HF_204, ESN364_HF_205, and phase 3 studies SKYLIGHT 1, 2 and 4 for assessment of the 12-week safety in doses lower than 30 mg and higher than 45 mg.

- POP4 consists of long-term placebo-controlled phase 3 study SKYLIGHT 4 to assess long-term safety of 52 weeks, and
- POP5 consists of phase 2 dose-response studies ESN364_HF_204, ESN364_HF_205 for assessment of the 12-week safety in doses lower than 30 mg and higher than 45 mg (i.e. a subset of POP3).

The placebo-controlled 12-week data of SKYLIGHT 1 and 2, known as POP1, are primarily used for the short-term comparative safety results. The 12-week data from POP2, POP3 and POP5 are considered supportive data to POP1.

The placebo-controlled 52-week data of SKYLIGHT 4, known as POP4, are primarily used for the long-term comparative safety results. The 52-week data of POP2 are considered supportive data to POP4.

Regarding the **exposure** in the placebo-controlled 12-week safety data (POP1), a total of 1022 patients have been exposed to fezolinetant. The median duration of exposure to fezolinetant was 84 days in each treatment group. In the placebo-controlled 52-week data of SKYLIGHT 4 (POP 4), a total of 1220 patients were having fezolinetant, of which 609 on 45 mg fezolinetant. The median duration of exposure to study intervention was 364 days in each treatment group. The current safety database for fezolinetant fulfils the requirements of ICH-E1, as according to the guideline ICH-E1 on 'Population Exposure' 100 patients exposed for a minimum of one-year (i.e. 609 patients on 45 mg fezolinetant for 364 days) is considered to be acceptable to include as part of the safety data base at dosage levels intended for clinical use.

In the placebo controlled 12-week period (POP1), the overall percentage of patients reporting **adverse events** (AEs) ranged from 38.8 and 39.7% (n=132 and n=135), in 30 and 45 mg fezolinetant arms, respectively, and was similar, as compared to placebo (38.6% (n=132)). Results of POP2, POP3 and POP5 for the 12-week safety analysis were generally similar with those in POP1.
In the placebo-controlled 52-week period (POP4), the number of participants who reported AEs was 67.9% (n=415) and 63.9% (n=389) in the fezolinetant 30 and 45 mg arms, as compared to placebo with 64.1% (n=391). This was considered comparable across groups. There was a slightly higher number of participants with serious AEs in the fezolinetant 30 mg (3.3%, n=20) and fezolinetant 45 mg (3.8%, n=23) groups, than in the placebo group (2.3%, n=14). Similar findings were seen in the POP2 safety set.

In the 12-week placebo-controlled safety analysis (POP1), the **most frequent reported AEs** by preferred term in the fezolinetant total group were headache (n=14 (4.1%) for 30 mg and n=17 (5.0%) for 45 mg vs. n=17 (5.0%) for placebo), upper respiratory tract infection (n=8 (2.4%) for 30 mg and n=7 (2.1%) for 45 mg vs. n=10 (2.9%) for placebo), and blood glucose increased (n=7 (2.1%) for 30 mg and n=6 (1.8%) for 45 mg vs. n=1 (0.3%) for placebo). No AE was reported for > 5% of participants in any treatment group during the 12-week double-blind period. Incidences of AEs were generally similar across the treatment groups. Imbalances are further discussed below. Findings were similar for POP2, POP3 and POP5.
In the 52-week placebo-controlled safety analysis (POP4), the most frequently reported AEs by preferred term in the fezolinetant total group were headache (n=52 (8.5%) for 30 mg and n=55 (9.0%) for 45 mg vs. n=56 (9.2%) for placebo) and COVID-19 (n=38 (6.2%) for 30 mg and n=32 (5.1%) for 45 mg vs. n=38 (6.2%) for placebo). Incidences of AEs were generally similar across the treatment groups. No large difference was seen with POP2 data.

The **most frequently reported treatment-related AEs** were headache and nausea. This was reported in the placebo-controlled 12-week (POP1) and in the placebo-controlled 52-week (POP4) analyses.

In the 52-week placebo-controlled safety analysis (POP4), the most frequent AEs related to study intervention were headache (3.3% in the placebo group and 3.1% in the fezolinetant total group), nausea (1.5% in the placebo group and 1.1% in the fezolinetant total group) and diarrhoea (0.8% in the placebo group and 1.0% in the fezolinetant total group). No imbalances have been observed.

Adverse drug reactions (ADRs). Potential ADRs were identified methodically using placebo-controlled data of SKYLIGHT 4 (POP4), followed by medical review for plausibility of a causal relationship between fezolinetant treatment and the event. Use of POP4 in the analyses of ADRs is appropriate.
The AEs on diarrhoea were reported more commonly in the fezolinetant groups (3.4-3.9%) compared to the placebo group (2.6%). The supportive POP2 data supported this finding. Therefore, diarrhoea was included as an ADR in section 4.8 of the SmPC. Also, for the event of insomnia, an imbalance was found of 2.0-3.9% in the fezolinetant groups versus the placebo group with 1.8%. A similar difference was observed with patients experiencing insomnia for the first time. These findings were supported with the POP2 population. This was also included as an ADR in section 4.8 of the SmPC. Similarly for the event of abdominal pain the comparative frequencies showed an imbalance between groups (n=5 (0.8%) placebo versus n=10 (1.6%) 30 mg and n=13 (2.1%) 45 mg fezolinetant). The POP2 data showed a comparable effect. Abdominal pain is considered an ADR and was added to section 4.8 of the SmPC. The event of ALT increased (as determined by laboratory data) of > 3 x ULN was found in 0.9% placebo, 1.9% in 30 mg and 2.8% in 45 mg fezolinetant. Of these, 2 of the 9 participants in the placebo group, 3 of the 21 in the fezolinetant 30 mg total group and 12 of the 31 in the fezolinetant 45 mg total group were considered by the investigator to be related to study intervention. ALT increase is considered to be an ADR for fezolinetant and the Product Information reflects this finding. Of note, the event of increases in ALT has been further assessed in this report, see section 'AEs of special interest'. The AEs of urinary tract infection, back pain and gamma glutamyltransferase (GGT) were not considered related to the study drug. Therefore, it is agreed that these AEs are not considered ADRs.

Treatment-emergent Adverse Events of Special Interest (AESIs). The following treatment-emergent AESIs were defined: liver test elevations, uterine bleeding, endometrial hyperplasia or cancer or disordered proliferative endometrium, thrombocytopenia, bone fractures, potential abuse liability, depression, wakefulness, effect on memory. Of these, liver test evaluations, endometrial hyperplasia/cancer and proliferative endometrium and bone have also been separately investigated in POP 4 (SKYLIGHT 4 study). No new significant safety concerns could be revealed from the safety reviews on these AESIs.

Evaluation of areas of medical focus. Following results of nonclinical studies, early clinical studies, phase 3 clinical studies and discussions with health authorities, areas of medical focus requiring analysis across multiple safety variables (i.e., laboratory data, imaging data and reported TEAE data) have been identified and are discussed below:

- Following the 12-week placebo-controlled evaluations (POP1) on **hepatic safety**, there was a slight imbalance seen in ALT elevations (n=2 (0.6%) placebo, n=4 (1.2%) fezolinetant 30 mg and n=3 (0.9%) fezolinetant 45 mg) and AST elevations > 3 x ULN between groups (n=1 (0.3%) placebo, n=3 (0.9%) fezolinetant 30 mg and n=0 (0%) fezolinetant 45 mg). Importantly, ALT or AST levels > 5 x ULN, > 8 x ULN and > 10 x ULN were reported only for participants in the fezolinetant 30 mg treatment group. The one participant with an ALT > 10 x ULN had also an AST level > 20 x ULN and was reported as an SAE of 'liver function test increased', which was considered as related to the study intervention. There were no Hy's law cases (an ALT of >3× ULN and concomitant jaundice (bilirubin > 2.5 mg/dL). Findings for POP2, POP5 and POP3 were consistent with POP1.
  In the placebo-controlled 52 week data (POP4), also a disbalance was found for both the ALT

elevations (n=5 (0.9%) placebo, n=7 (1.2%) fezolinetant 30 mg and n=11 (1.9%) fezolinetant 45 mg) and the AST elevations > 3 x ULN between groups (n=3 (0.5%) placebo, n=5 (0.8%) fezolinetant 30 mg and n=5 (0.8%) fezolinetant 45 mg). No clear pattern or trend for the time to onset could be observed from the data, as this occurrence varied from week 2 to week 52 with no difference between placebo or fezolinetant. Similar findings were seen in POP2, for which the exposure-adjusted results demonstrated the highest incidence in the highest dosing group of ALT or AST elevations: 1.5/100 PY in the placebo group, 1.8/100 PY in the fezolinetant 30 mg total group, and 2.7/100 PY in the fezolinetant 45 mg total group.
Reported AE data for hepatic safety related terms are concordant with the laboratory hepatic safety findings and it should be noted that most of them are non-serious. Across the phase 3 program (POP2), no clear trend could be identified from the serious cases, as 7 SAEs related to hepatic safety were reported in 6 participants (1 participant in the placebo group, 3 in the fezolinetant 30 mg total group and 2 in the fezolinetant 45 mg total group). None of the events were fatal, life-threatening nor resulted in inpatient or prolonged hospitalization. Of the 41 participants on fezolinetant with elevated liver enzymes, 3 participants (7%) had clinical symptoms of liver injury. Two participants had nausea (30 mg), of whom one discontinued. One had abdominal pain (45 mg), who discontinued, but recovered without sequelae. None of the patients on placebo were reported with clinical symptoms of liver injury. Further, 0.7% of patients on placebo versus 0.6% of patients on fezolinetant 30 mg and 45 mg discontinued related to the AEs on hepatic safety. No new relevant safety concerns could be revealed from these data.
Importantly, these ALT/AST increases were also observed in earlier dose-response studies and led to a dose reduction of the dose selected for phase 3 studies.
Based on a review of the available data, the sponsor considers 'ALT increased' to be an ADR for fezolinetant, which is agreed. However, 'AST increased' was also be considered an ADR, and was added to the ADR in section 4.8 of the SmPC of fezolinetant. Further, since patients with any hepatic medical condition or hepatic chronic disease were excluded from the pivotal studies, and since hepatic safety could be an issue with higher doses (the hepatic safety effect is dose-dependent), and in line with other non-hormonal products that have AST and ALT elevations stated as ADRs in section 4.8 of the SmPC (i.e relugolyx), patients with such conditions known or suspected hepatic disorder should be warned and should be monitored with hepatic function test evaluations, which was mentioned in section 4.4. of the SmPC.

- For the assessment of **bone safety**, effects of fezolinetant on bone mineral density (BMD) and trabecular bone score (TBS) at hip and spine were assessed by dual-energy X-ray absorptiometry (DXA) in the 52 week placebo-controlled SKYLIGHT 4 study (POP4). From the placebo-controlled 52-week data (POP4), as compared to baseline data, no clinically relevant changes in BMD and TBS results have been observed in the 3 study arms. Further, there were no imbalances in bone fracture AEs reported in POP4 between the fezolinetant arms (n=9 (1.5%) 30 mg fezolinetant, n=10 (1.6%) 45 mg fezolinetant) and the placebo arm (n=10 (1.6%)). This was also not seen in the POP1, POP2, POP3 and POP5. Bone markers and preclinical data showed no impact of fezolinetant. Based on these data, it can be concluded that the use of fezolinetant has no adverse effect on bone health.

- Regarding **CNS safety**, the applicant has provided a thorough review, since fezolinetant crosses the blood brain barrier. The incidence of pre-specified AEs concerning CNS effects of potential abuse liability, depression, wakefulness and effect on memory were low and similar between placebo and fezolinetant groups for POP1, POP2 and POP4 with no dose relationship observed with fezolinetant.
  Further, the low incidence of AEs related to migraine did not show an imbalance between placebo and the fezolinetant groups at the 12 and 52 week (0.8% in fezolinetant and 0.6% in placebo) analyses. Epidemiologically, migraine is a highly prevalent in the target population. Also, the risk

for suicide was measured by the Columbia Suicide Severity Rating Scale (C-SSRS). There were no relevant differences seen between the fezolinetant and placebo groups on suicidal ideation or behaviour in POP2 or POP4 at week 12 and 52. Also the events on syncope were very low with 0.1% placebo vs 0.5% total fezolinetant.
However, the incidence of insomnia (1.6% placebo vs 2.5% total fezolinetant group) showed an imbalance in the POP2 data and insomnia was included as an ADR in the SmPC of fezolinetant.
In 3 animal (rat) studies an effect on convulsions and seizures was observed. Although plasma levels in the rats were considerably higher than the human clinical exposure, in 2 of the 3 studies these AEs were seen from the lowest dose and were therefore not of clinical relevance.

- In preclinical data, reversible **thrombocytopenia** was observed in cynomolgus monkeys at the highest doses tested in repeated-dose toxicity studies and was therefore a medical event of interest. In the clinical studies thrombocytopenia was defined as platelet counts < 150 x 109/L. In the placebo-controlled 52-week POP4 data, incidence of thrombocytopenia was similar between treatment groups (4.0% (n=23), and 3.9% (n=22) the 30 mg and 45 mg fezolinetant groups respectively versus 4.1% (n=23) patients in the placebo group. Therefore, no further information on this concern is needed.
- For the evaluation of **elevated glucose**, there were no clinically relevant changes from baseline in mean or median glucose levels in laboratory evaluations.
- **Elevated creatine kinase** (CK). In the laboratory data no increases in AEs related to CK elevation was observed across treatment groups in any population.
- Regarding the **neoplasms**, benign, malignant and unspecified (including cysts and polyps), the review of the 52-week safety population, placebo controlled (POP4), although numbers were low, a slight imbalance is seen in the SAEs within the SOC of neoplasms benign, malignant and unspecified (including cysts and polyps). Two participants (0.3%) in the placebo group vs 5 participants (0.8%) in the fezolinetant 30 mg group and 7 participants (1.1%) in the fezolinetant 45 mg group. However, the type of events in the fezolinetant groups were diverse and not clustered.

  No evidence was found of genotoxicity or carcinogenicity in the fezolinetant non-clinical program
  In conclusion, in the absence of a of genotoxicity or carcinogenicity signal in the non-clinical program, and no plausible MOA indicating a role of fezolinetant in the development of neoplasms, the noted imbalance of serious events of malignancy cases of diverse origin in the fezolinetant groups as compared to the placebo groups are considered a chance finding. Therefore, an association of the use with fezolinetant and the occurrence of malignancies could not be established. Inclusion in the SmPC of fezolinetant is not needed.

Endometrial health. A comprehensive evaluation of endometrial safety was conducted across the program for fezolinetant. Long-term data from study 2693-CL-0304 (SKYLIGHT) 4 are provided to support durability of fezolinetant efficacy, especially on endometrial health. The endometrial study results of SKYLIGHT 4 are discussed below:

For the analysis of **endometrial safety**, data from endometrial biopsies and TVUs were available for the 52-week populations. POP4 was considered the primary population, as endometrial health was a primary study objective of the SKYLIGHT 4 study, which is acceptable.
Endometrial health set population. In the endometrial health set (EH set), n=186 for placebo, n=210 for 30 mg fezolinetant and n=203 for 45 mg fezolinetant were included. The endometrial health set consisted of all randomized participants who received at least one dose of study intervention, had the postbaseline biopsy done within 30 days after the last dose of study intervention, had an acceptable biopsy at baseline (at least one endometrial biopsy with satisfactory tissue and no read of hyperplasia, malignant or disordered proliferative pattern) and had an satisfactory endometrial biopsy

result after or on day 326 or had a postbaseline final diagnosis of hyperplasia, malignant or disordered proliferative pattern prior to day 326. Based on this definition it is assumed that all patients in this endometrial health set have taken fezolinetant for at least 12 months, which is in line with the recommendation of the EMA guideline on HRT.

Diagnostic work-up. The analysis was based on the final diagnosis evaluated from the 3 pathologists. The final diagnosis was the concordance of the 3 pathologists' diagnoses: if at least 2 pathologists agreed, the result was included, if none of them agreed, then the worst result was used. This diagnostic approach is in line with the EMA guideline for HRT.
The third analysis of the fezolinetant 30 mg and fezolinetant 45 mg groups in POP2, each containing over 300 participants with biopsy data, showed that the upper limit of the analysis on endometrial hyperplasia plus carcinoma (i.e. third analysis) did not exceed 2 and does not exceed the threshold for concern as described in the EMA guideline (Guideline on clinical investigation of medicinal products for hormone replacement therapy of oestrogen deficiency symptoms in postmenopausal women' (EMEA/CHMP/021/97 Rev. 1)). Regarding disordered proliferative pattern, the results with regard to the incidence in the EH set did not show a difference between fezolinetant treatment groups and placebo.
Treatment-emergent AESIs of endometrial adenocarcinoma**.** In the data set, 3 participants with treatment-emergent AESIs of endometrial adenocarcinoma were identified. Of these, the first case was taken into account in the EH analysis and the exclusions were considered acceptable.
Regarding the transvaginal ultrasonography (TVU) data, in the EH set, there was no statistically significant difference in change from baseline to week 52 in endometrial thickness as measured by TVU between fezolinetant-treated and placebo-treated participants. The TVU data support that fezolinetant has no impact on endometrial thickness after 1 year of treatment.

Supplemental data on endometrial health. In POP2 (which also includes long-term data of POP4), a similar analysis on incidence of hyperplasia/carcinoma based on endometrial biopsies taken after 52 weeks of treatment was performed with data from the SKYLIGHT 1, 2 and 4 studies, as was done in the SKYLIGHT 4 study (POP4). Participants who were initially on placebo and re-randomized to fezolinetant in SKYLIGHT 1 and 2 were not included in the primary EH set. The incidences of endometrial hyperplasia and endometrial carcinoma were similar, i.e. no additional cases were observed in the other studies, but the upper limit of the 95% CI is lower as more patients are included in this safety analysis.
A supportive analysis was also performed in the POP2 dataset to additionally include participants re-randomized to fezolinetant 30 mg or 45 mg after 12-weeks of placebo treatment and provided similar results.
The findings regarding endometrial thickness (change from baseline to week 52) collected in POP2 were comparable to the POP4 data, as no clinically relevant changes have been identified.
Therefore, the totality of data suggests that the use of fezolinetant has no adverse effects on the endometrium.

Other observations related to safety. Regarding other observations related to safety, thyroid follicular cell hypertrophy was observed in the non-clinical studies in rats. In the human safety population only a very low number of cases have been reported with no imbalances between study arms: 1 (0.2%) in the placebo group and 1 (0.2%) in the fezolinetant 45 mg group, and thus no imbalance could be found in the long-term data (POP4). No further information is needed. The concern of oral paraesthesia was an important side effect in the phase 1 programme but noted with much higher doses than applied in the phase 3 program. In the safety data sets a low number of patients reported this event, with no difference in comparison to placebo. No further information is needed.

In total, two **deaths** have been reported. One was not considered related to the study drug and the second fatal AE occurred in a patient (on 30 mg fezolinetant) who also presented major confounding factors. The patient did not receive any form of QT-prolonging drug.

Regarding the **serious adverse events** (SAEs), In the 52-week safety analysis on SAEs, the overall incidence was low with a higher incidence in the fezolinetant groups (n=36 (3.8%) and n=39 (4.1%) in 30 and 45 mg, respectively) compared to placebo (n=15 (1.6%)). Results from the 12-week analysis showed the same pattern. The most frequent SAEs in the fezolinetant total group were: COVID-19 (4 participants, 0.2%), abdominal pain (3 participants, 0.1%), chest pain (3 participants, 0.1%), endometrial adenocarcinoma (3 participants, 0.1%) and squamous cell carcinoma of the skin (3 participants, 0.1%). No clear pattern or further trend can be found from these data, as most SAEs were reported as isolated cases.

Laboratory findings. Regarding **haematology**, based on the data provided from safety population POP2, POP3 and POP4, no large differences between the study treatment and placebo in potentially clinically significant laboratory abnormalities have been observed. Of note, the events of thrombocytopenia and the incidence of platelet counts abnormalities are further discussed under section 'AEs of special interest'. No safety signals in the abnormalities of **clinical chemistry** were identified.

Regarding the **vital signs** no clinically meaningful changes have been observed in the blood pressure and pulse measurements over the duration of treatment. Based on the non-clinical and phase 1 study findings, no **QT prolongation** was detected. Therefore, no QT prolongation potential was anticipated to be expected during the confirmatory clinical phase in a target population generally not at increased risk for arrhythmias. Accordingly, only standard ECG monitoring has been performed in the confirmatory study phase, which is considered appropriate. No clinically relevant changes in the ECG parameters or clinically meaningful differences between study arms have been found in the safety populations data sets, which is reassuring.

No trends or patterns have been observed In **special populations**. Subgroup analyses were performed for the intrinsic factors of age, race, ethnicity, BMI, isolated NAFLD (non-alcoholic fatty liver disease) and NASH (non-alcoholic steatohepatitis) and diabetic status, and the extrinsic factors of smoking status and geographical region. No trends or patterns have been observed in special populations (age, race, ethnicity, BMI, diabetic status, smoking status, geographical region). Also, by grouping the patients on status with isolated non-alcoholic fatty liver disease and non-alcoholic steatohepatitis no trends or patterns have been found, but the number was too small to draw meaningful conclusions.

The incidence of **AEs leading to discontinuations** (POP1) at the 12-week analysis was overall low and was the same in the fezolinetant groups (n=12 (3.5%) 30 mg and n=9 (2.6%) 45 mg), as compared to the placebo group (n=10 (2.9%), which is reassuring. The most frequent AEs leading to discontinuations were nausea and headache; both were reported for 3 participants in the placebo group. Most AEs have been reported as isolated cases. No pattern with respect to type of AE leading to discontinuation of study drug could be observed.
The incidence of AEs leading to discontinuations (POP2) at the 52-week analysis remained overall low and was generally similar in the fezolinetant groups (n=51 (5.4%) 30 mg and n=43 (4.5%) 45 mg), as compared to the placebo group (n=37 (3.9%). The most frequent AEs leading to discontinuations were fatigue, dizziness, nausea and headache. AEs related to study intervention leading to withdrawal of study treatment in POP2 were similar across the treatment groups with n=24 (2.5%) placebo, n=25 (2.3%) fezolinetant 30 mg, n=31 (2.8%) fezolinetant 45 mg, which is reassuring. Apart from the 6 cases of fatigue in the fezolinetant groups compared to none in the placebo group, no other pattern

with respect to type of AE leading to discontinuation of study drug could be observed in the 52 weeks data.

The proposed broader target population also includes perimenopausal women, which introduces new safety issues. These women were not investigated in the clinical trials, but more importantly these women could still be fertile, whereas fezolinetant should not be used during pregnancy because of the observed foetal toxicity in animal studies. The issue was addressed through appropriate wording for the SmPC (i.e., contra-indication for pregnant women).

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

2.6.10. Conclusions on the clinical safety

Based on the currently available data, fezolinetant appears to be generally well tolerated with only 51 (5.4%) and 43 (4.5%) in the 30 mg and 45 mg study arms, respectively, as compared to the placebo group with 37 (3.9%) patients, who discontinued due to adverse events during a 52-weeks treatment-period in the pivotal studies. The most common treatment-related AEs were headache and nausea and were of mild or moderate nature. Further, based on extensive assessment, no significant adverse effects on the endometrial, hepatic and bone safety could be revealed with the use of fezolinetant. In conclusion, the current safety profile of fezolinetant does not suggest any major safety concerns, with no relevant differences between the 30 mg and 45 mg dose.

2.7. Risk Management Plan

2.7.1. Safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	Use in individuals with Child-Pugh Class B or C (moderate or severe) chronic hepatic impairment

2.7.2. Pharmacovigilance plan

No additional pharmacovigilance activities.

2.7.3. Risk minimisation measures

Safety concern	Routine risk minimisation activities
Missing information: Use in individuals with Child-Pugh Class B or C (moderate or severe) chronic hepatic impairment	Routine risk communication: *SmPC section 4.2* *SmPC* section *4.4* *PL section 2* Routine risk minimization activities recommending specific clinical measures to address the risk: • Specific recommendation not to use fezolinetant in patients with Child-Pugh Class B (moderate) or C (severe) chronic hepatic impairment is provided in SmPC sections 4.2 and 4.4 as well as in PL section 2.

2.7.4. Conclusion

The CHMP considers that the risk management plan version 3.0 is acceptable.

2.7.5. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.7.6. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 12 May 2023. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.8. Product information

2.8.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.8.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Veoza (fezolinetant) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Vasomotor symptoms (VMS), also referred to as hot flashes or flushes, are characterized by perspiration, flushing, chills, clamminess, anxiety and on occasion heart palpitations and occur as episodes that usually last 1 to 5 minutes several times per day (Stuenkel et al, 2015), ranging from only 1 per day to 1 per hour, and are also common at night. The symptoms of VMS are experienced by up to 80% of women during menopause (Gold et al, 2006). Although menopause is a natural and inevitable physiological process marking the decline of the reproductive capacity, symptoms, such as VMS, commonly persist for nearly a decade.

VMS can severely impact the woman's quality of life (QoL) and are characterized by problems with sleep, mood, concentration, energy and sexual activity (Kagan et al, 2021; Williams et al, 2009; Kravitz et al, 2008) and may significantly interfere with her professional life (Simon & Reape, 2009). Individuals often also report feelings of physical discomfort, depression, anxiety, stress, self-consciousness and embarrassment (Whiteley et al, 2013; Williams et al, 2009; Rendall et al, 2008).

The thermoregulatory centre of the hypothalamus is innervated by KNDy neurons that are normally inhibited by oestrogen and stimulated by the NKB. Through the menopausal transition, declining oestrogen disrupts the balance with NKB. KNDy neurons become hypertrophied, contributing to increased signalling to the thermoregulatory centre. This shifts the balance for control of core body temperature, resulting in VMS.

Fezolinetant is claimed to be the first-in-class, non-hormonal, selective neurokinin 3 (NK3) receptor antagonist. It blocks neurokinin B (NKB) binding on the kisspeptin/neurokinin B/dynorphin (KNDy) neuron to help restore the neuronal activity in the thermoregulatory centre of the hypothalamus.

It is postulated that fezolinetant improves VMS, and thus their QoL, through its antagonistic action in the hypothalamus, as it calibrates the neuronal activity in the thermoregulatory centre. It can especially be used in women in need for treatment of VMS, but who cannot use oestrogens, since for these patients alternative therapy remain limited.

3.1.2. Available therapies and unmet medical need

HT (also commonly referred to as hormone replacement therapy (HRT)) with oestrogen is currently the recommended first-line treatment for moderate to severe VMS associated with menopause according

to international guidelines (Baber et al, 2016; de Villiers et al, 2016; Stuenkel et al, 2015; NAMS Position Statement, 2017; ACOG Clinical Management Guidelines, 2014; SOGC Clinical Practice Guideline: Managing Menopause, 2014). In women with an uterus, oestrogen is combined with a synthetic progestogen or progesterone to protect the endometrium from development of hyperplasia and endometrial cancer (Martin & Barbieri, 2022). Oestrogen-only is given to postmenopausal women without a uterus. HT is the gold standard for treatment of the relief of bothersome VMS and vaginal symptoms associated with menopause (NAMS Position Statement, 2017; Stuenkel et al, 2015). Efficacy of HT in reduction of VMS frequency is 77% relative to placebo (Cochrane Data Base Syst. Rev. 2001).

However, data from the Women's Health Initiative (WHI) published in 2002, a trial on HT (continuous, combined oestrogen-progestin therapy vs placebo) in older post-menopausal women (mean age 63 years and over 10 years since menopause), showed a number of adverse outcomes, including an excess risk of CHD, stroke, venous thromboembolism (VTE), and breast cancer. Use HT decreased significantly in the decade after this publication. The current view is, however, that this study population is not the age group that presents with new onset of menopausal symptoms. The initiation of menopausal hormone therapy (MHT) is considered to be a safe option for healthy, symptomatic women who are within 10 years of menopause or younger than age 60 years and who do not have contraindications to HT (NAMS 2017, UptoDate 2022). There are no set time limits for how long women can use HT, but is based on the individual benefit risk profile (NICE, RCOG). The EU Core SmPC for HRT does not include a maximum treatment duration, but that HRT should only be continued as long as the benefit outweighs the risk.

Non-hormonal therapies

Non-hormonal medications have been studied for treatment of VMS associated with menopause (Hickey et al, 2017; Drewe et al, 2015). SSRIs, SNRIs, gabapentin and clonidine have been shown to improve VMS associated with menopause in clinical trials, although to a much lesser extent than HT (ACOG Clinical Management Guidelines, 2014; Baber et al, 2016, UptoDate 2022).

Clonidine

The centrally acting α2-adrenergic agonist clonidine is approved for the treatment of hot flushes in the EU.

SSRIs/NSRIs (off-label)

In clinical guidelines SSRIs are indicated as first choice in women who cannot take oestrogens, i.e. with a medical history of breast cancer. In the EU, no SSRI is approved for this indication, while in the US paroxetine is approved for the indication of VMS.

Over-the-counter-remedies

Natural over-the-counter remedies, including herbal/non-prescription products, have not been approved for VMS treatment, and their safety and efficacy are not well established. Furthermore, these products do not address the burden of disease considering the very limited evidence to support their use and limited data to support their mechanisms of action (Baber et al, 2016; de Villiers et al, 2016; Stuenkel et al, 2015; NAMS Position Statement, 2017; ACOG Clinical Management Guidelines, 2014; SOGC Clinical Practice Guideline: Managing Menopause, 2014).

Unmet medical need

As summarized above, there are limits within the available pharmacotherapeutic treatments, which do not fully address the unmet need of VMS associated with menopause in those women who cannot use oestrogens. The availability of safe and efficacious non-hormonal options for the treatment of VMS

associated with menopause is important to mitigate the burden of moderate to severe VMS on the individual.

3.1.3. Main clinical studies

Dose finding was performed in two phase 2 studies (ESN364_HF_204 and ESN364_HF_205). The dose regimens to be tested in the 2 pivotal phase 3 studies SKYLIGHT 1 and 2 - 30 and 45 mg fezolinetant once daily (qd) - were chosen based on the phase 2 clinical efficacy and safety results and the dose- and concentration-response models and the dose- and exposure-response analysis, with 30 mg as the lowest effective dose. In addition, a 45 mg qd dose was predicted to increase the probability of achieving efficacy endpoints with limited risk of potential exposure related transaminase elevations noted in the phase 2 study with doses of 60 mg and higher. This dose was, however, not earlier studied and was, therefore, proposed to be included as an additional study arm in the phase 3 trials. The registration dose, i.e. 45 mg fezolinetant, similar to one of the tested dose regimens, was chosen based on the efficacy and safety results of the two pivotal phase 3 studies.

Three phase 3 trials have been submitted within the dossier; two **pivotal identical studies (SKYLIGHT 1 and 2)**, and a **supportive long-term safety study (SKYLIGHT 4)**.

The 2 pivotal phase 3 trials SKYLIGHT 1 and 2 of identical design, were randomized, placebo-controlled, double-blind studies with a duration of 12 weeks. The 12-week period was followed by a 40-week, non-controlled, open-label extension treatment period. In total 527 women (n=176 on 30 mg, n=176 on 45 mg vs n=175 on placebo) in SKYLIGHT 1 and 500 women (n=166 on 30 mg, n=167 on 45 mg vs n=167 placebo) in SKYLIGHT 2, were included. Key eligibility criteria were women, aged 40 – 65 years, inclusive, with moderate to severe VMS (average $\geqslant$ 7 moderate to severe VMS per day or $\geqslant$ 50 per week)) and confirmed as menopausal (defined as having amenorrhea for $\geqslant$ 12 consecutive months, or amenorrhea for $\geqslant$ 6 months with FSH >40 IU/L or having had bilateral oophorectomy), who seek treatment for relief for VMS. Key exclusion criteria were use of treatments for VMS, undiagnosed uterine bleeding within 6 months, active liver disease or elevated liver aminotransferases (ALT or AST) and renal impairment as eGFR $\leqslant$ 59 mL/min per 1.73 m^2. The primary analysis consisted of meeting **4 co-primary endpoints**, defined as mean change in the **frequency** from baseline to weeks 4 and 12 and mean change in the **severity** from baseline to weeks 4 and 12. The **key secondary endpoint** evaluated 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. Other relevant secondary endpoints included percent responders with 50% percent reduction in number of VMS, changes from baseline to week 24 and QoL evaluations.

Additionally, a phase 3, randomized, placebo-controlled, double-blind, parallel-group, multicentre, clinical long-term safety study with a duration of 52 weeks was performed to investigate the **long-term safety (including bone health) and endometrial safety** of fezolinetant in 1830 (n=611 on 30 mg, n=609 on 45 mg and n=610 on placebo) postmenopausal women suffering from VMS.

3.2. Favourable effects

Regarding the **primary analysis of SKYLIGHT 1,** the **4 co-primary efficacy endpoints** have been met, as the treatment with fezolinetant 30 and 45 mg resulted in a higher reduction in frequency and severity of moderate to severe VMS from baseline to weeks 4 and 12, compared to placebo.

- The LS mean change (SE) of **frequency at week 12** was -6.28 (0.32) for 30 mg fezolinetant, and -6.44 (0.31) for 45 mg fezolinetant vs -3.90 (0.31) for placebo. The differences in LS mean (SE) were statistically significant of fezolinetant vs placebo for both the 30 mg fezolinetant (LS mean

(SE) of -2.39 (0.44; 95% CI: -3.25 to -1.52; p<0.001)) and the 45 mg fezolinetant (LS mean (SE) of -2.55 (0.43; 95% CI: -3.40 to -1.70; p<0.001)), with a numerically slightly larger change in the 45 mg study arm. Similar findings were seen at week 4.

- The LS mean change (SE) of **severity at week 12** was -0.60 (0.05) for 30 mg fezolinetant, and -0.57 (0.05) for 45 mg fezolinetant vs -0.37 (0.05) for placebo. The differences in LS mean (SE) were statistically significant of fezolinetant vs placebo for both the 30 mg fezolinetant LS mean (SE) of -0.24 (0.08 95% CI: -0.39 to -0.09; p=0.001)) and the 45 mg fezolinetant (LS mean (SE) of -0.20 (0.08; 95% CI: -0.35 to -0.06; p=0.007). Similar findings were seen at week 4.

The observed reduction in VMS relative to placebo at weeks 4 and 12 was generally greater, than 2 hot flushes, indicative of a clinically relevant improvement, which level of clinical relevance is also applied in phase 3 placebo-controlled HRT studies.

The outcome of the 2 **sensitivity analyses** (PPS and discontinuation-reason based multiple imputation) were consistent with the co-primary efficacy endpoints. In a number of subgroup analyses on the co-primary endpoints for age, race, BMI, and smoking status fezolinetant treatment effects were similar, suggesting that none of these subgroups had an impact on the efficacy of fezolinetant. However, the interpretation of the results is limited due to the small number of participants in each subgroup.

Looking at the **key secondary endpoint**, i.e. PROMIS SD SF 8b from baseline to week 12, in order to assess 8 questions on self-reported sleep disturbance over the past 7 days, treatment with fezolinetant 30 mg resulted in a numerical reduction (mean (SD)) from baseline to week 12 in sleep disturbances with a difference in LS mean versus placebo of -0.5 (SE 0.8) CI 95% -2.0, 1.0; p=0.489) and a slightly larger effect was seen with the 45 mg fezolinetant vs placebo (LS mean (SE) -1.1 (0.7) CI 95% -2.5, 0.4; p=0.155).
This effect is in line with the outcome of another PRO secondary endpoint of PGI-C VMS scores, which assessed patient-perceived global impressions of severity in sleep disturbance and change in VMS and sleep disturbance. Greater improvements were observed in both the fezolinetant groups in PGI-C VMS scores over the 12 week treatment period, as compared to the placebo group. Further, exploratory PRO analyses (PROMIS SRI SF 8a, MENQOL, EQ-5D-5L, WPAI-VMS and PGIS) showed also improvements with the use of fezolinetant as compared to placebo.

Other secondary outcomes showed similar beneficial effects on VMS frequency and severity, in line with the findings in the primary analyses. Regarding the frequency and severity of moderate to severe VMS, change from baseline to each week up to week 12, treatment with fezolinetant 30 mg and 45 mg resulted in a larger decrease from baseline in mean frequency of moderate to severe VMS, compared with placebo, which 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. This effect was also observed by the percent reduction from baseline to each week up to week 12 on frequency of moderate to severe VMS. The beneficial effect was also seen in the responder analysis on frequency (percent reduction $\geqslant$ 50% and at 100%), where a statistically significant higher proportion of participants had a $\geqslant$ 50% reduction in the frequency of moderate to severe VMS in the fezolinetant 30 mg (44.5% (77/173); with an Odds ratio (95% CI) of 2.061 (1.323, 3.233; p=0.001)) and 45 mg (54% (94/174 with an Odds ratio (95% CI) of 3.025 (1.947, 4.746; p<0.001)) groups, than in the placebo group (28.0% (49/175) at week 4. Similar findings were seen at week 12, i.e. 44.5%, and 56.9%, for the 30 and 45 mg respectively, vs 29.7% with placebo. Also a higher proportion of participants with a 100% reduction in the frequency of moderate to severe VMS was found for the treatment arms as compared to the placebo arm at weeks 4 and 12, but these differences were not statistically significant.

The findings on the **primary analyses**, demonstrated in the **SKYLIGHT 2** study, were in line with the abovementioned findings in the SKYLIGHT 1 study.

The **4 co-primary efficacy endpoints** have been met, as the treatment with fezolinetant 30 and 45 mg resulted in a higher reduction in frequency and severity of moderate to severe VMS from baseline to weeks 4 and 12, compared to placebo. The differences in LS means of the **frequency at week 12** of fezolinetant and placebo were statistically significant for both the 30 mg fezolinetant (LS mean (SE) of -1.86 (0.55; 95% CI: -2.94 to -0.78; p<0.001)) and the 45 mg fezolinetant (LS mean (SE) of -2.53 (0.55; 95% CI: -3.60 to -1.46; p<0.001), and were comparable to the week 4 results. The differences in LS means of the **severity at week 12** were similar to the week 4 data and were statistically significant for both the 30 mg fezolinetant (LS mean (SE) of -0.16 (0.08 95% CI: -0.33 to -0.00; p=0.049)) and the 45 mg fezolinetant (LS mean (SE) of -0.29 (0.08; 95% CI: -0.45 to -0.13; p<0.001)) as compared to placebo. Sensitivity analyses were consistent with the primary outcomes.

Effects of fezolinetant treatment on the **key secondary PRO endpoint** in the SKYLIGHT 2 trial were similar to those observed in SKYLIGHT 1 trial. For the PROMIS SD SF 8b, a trend towards a greater reduction in sleep disturbances has been observed, as seen in the difference in LS means of 30 mg fezolinetant vs placebo (LS mean (SE) was -0.7 (0.7) CI 95% -2.1, 0.8; p=0.381). The beneficial effect on sleep disturbances was larger and statistically significant for the difference in LS means of 45 mg fezolinetant vs placebo with -2.0 (0.7) (CI 95% -3.5, -0.6; p=0.007). This was also seen in other exploratory PRO evaluations (PROMIS SRI SF 8a, MENQOL, EQ-5D-5L, WPAI-VMS and PGIS) and were also broadly similar with that noted in the SKYLIGHT 1 study.

Regarding **other secondary endpoints** on VMS, the reduction in VMS frequency and severity, the mean change decrease was larger for the two fezolinetant arms, as compared to the placebo group, but started for all 3 study arms at the first post-baseline assessment (week 1) and continued to decrease until week 4 after, which it remained relatively stable through week 12 and week 24. The reduction in VMS relative to placebo at week 12 was greater than 2 hot flushes, indicative of a clinically relevant improvement (which level of clinical relevance is also applied in phase 3 placebo-controlled HRT studies). Further, a responder analysis was performed by percent reduction $\geqslant$ 50% and at 100% in the frequency of moderate to severe VMS per 24 h, from baseline to each week up to week 12. A beneficial effect has been found, where a statistical significant higher proportion of participants had a $\geqslant$ 50% reduction in the frequency of moderate to severe VMS in the fezolinetant 30 mg (50.6% (84/166); with an Odds ratio (95% CI) of 2.902 (1.829, 4.657; p<0.001)) and 45 mg (52.7% (88/167 with an slightly larger Odds ratio (95% CI) of 3.218 (2.025, 5.172; p<0.001)) groups than in the placebo group (26.3% (44/167) at week 4 during the 12-week double-blind period, with similar findings at week 12.

Regarding the uncontrolled long-term efficacy data obtained in SKYLIGHT 1 and 2 over 24 weeks, including participants on placebo who were re-randomized in a 1:1 ratio to 30 mg or 45 mg of fezolinetant in the open-label extension period, the frequency and severity of moderate to severe VMS, change from baseline to week 24 was sustained, as noted in the first 12 weeks for both initial fezolinetant groups. The reduction in frequency and severity of VMS on the former placebo groups is comparable with the degree of reduction noted in the patient groups who used fezolinetant for the entire 24 weeks. From the data provided on week 24, no relevant differences between the two dosing arms of 30 mg and 45 mg could be observed.

As the overall efficacy data in the target population demonstrated a beneficial effect on VMS, with overall a somewhat larger effect with the 45 mg fezolinetant, as compared to the 30 mg fezolinetant, the applicant proposes the 45 mg dose for treatment in the requested indication.

3.3. Uncertainties and limitations about favourable effects

The efficacy in perimenopausal women having fluctuating oestrogen levels is not clinically evaluated and is not substantiated by an extrapolation approach or a separate study.

3.4. Unfavourable effects

In general, the safety database is sufficient. The **exposure**, in the placebo-controlled 12-week safety data, a total of 1022 have been exposed to fezolinetant, with a median duration of 84 days in each treatment group. In the placebo-controlled 52-week data, a total of 1220 patients were having fezolinetant, of which 609 on 45 mg fezolinetant with a median duration of 364 days in each treatment group.

The overall percentage of patients reporting **adverse events** (AEs) in the first 12 weeks of the placebo-controlled data ranged from 38.8 and 39.7% (n=132 and n=135), in the 30 mg and 45 mg groups, respectively, and was similar relative to placebo (38.6% (n=132)). Also, in the 52-week safety analysis of the placebo-controlled data, the number of participants reporting AEs was 67.9% (n=415) and 63.9% (n=389) in the fezolinetant 30 and 45 mg arms, as compared to placebo with 64.1% (n=391), and was considered comparable across groups. The **most frequently reported AEs** (in 12-week data) were headache (4.1%) for 30 mg and (5.0%) for 45 mg versus (5.0%) for placebo, upper respiratory tract infection (2.4%) for 30 mg and (2.1%) for 45 mg versus (2.9%) for placebo), and blood glucose increased (2.1%) for 30 mg and (1.8%) for 45 mg versus (0.3%) for placebo). In 52-week data, this was headache (8.5%) for 30 mg and (9.0%) for 45 mg versus (9.2%) for placebo and COVID-19 (6.2%) for 30 mg and (5.1%) for 45 mg versus (6.2%) for placebo. Incidences of AEs were generally similar across the treatment groups.

AE of special interest or areas of medical focus.

- **Endometrial safety.** In a separate placebo-controlled study of 52 weeks (SKYLIGHT 4), endometrial safety was assessed.
  - The primary endpoint of the study, based on the requirements of the FDA was met. The separately presented incidence of endometrial hyperplasia and endometrial carcinoma in fezolinetant-treated participants, was within the pre-specified limits of $\leqslant$ 1% with an upper bound of the one-sided 95% CI $\leqslant$ 4%, according to the FDA Draft Guidance. The incidence rate (IR) of endometrial hyperplasia was 0% (upper limit 1-sided 95%CI: 1.4%) for 30 mg and 0.5% (upper limit 1-sided 95%CI: 2.3%) for fezolinetant 45 mg. The IR of endometrial carcinoma was 0.5% (upper limit 1-sided 95%CI: 2.2%) for 30 mg and 0% (upper limit 1-sided 95% CI:1.5%). Similar findings were seen in other study populations (POP2) which included POP4, and long-term data of SKYLIGHT 1 and 2.
  - Incidence in pooled data from POP2 (containing >300 participants with biopsy data meeting the prespecified EH set criteria, in-line with the EMA's guidance on sample size): One patient in the fezolinetant 30 mg group had a diagnosis of endometrial hyperplasia/carcinoma (incidence rate (IR) 0.3%; upper limit two-sided 95% CI: 1.83%). One patient in the fezolinetant 45 mg group had hyperplasia (IR 0.3%; upper limit two-sided 95% CI: 1.82%). The upper limits did not exceed 2 and is therefore in line with and does not exceed the threshold for concern as described in the recommendations for endometrial safety included in the EMA guideline on HRT.
  - Regarding disordered proliferative pattern, the results with regard to the incidence did not show a difference between fezolinetant treatment and placebo groups.

- Regarding the transvaginal ultrasonography (TVU) data, there was no statistically significant difference in change from baseline to week 52 in endometrial thickness between fezolinetant versus placebo (30 mg versus placebo: LS means -0.17 (0.14); CI 95%:-0.45, 0.11; p>0.6, and 45 mg versus placebo: LS means -0.08 (0.14); CI 95%:-0.36, 0.21; p>0.2).

- Regarding **hepatic safety**, in the placebo-controlled 52-week data a disbalance was found for both the ALT and AST elevations (defined as > 3 x ULN) with fezolinetant, relative to placebo. ALT elevations were seen in n=7 (1.2%) fezolinetant 30 mg and n=11 (1.9%) fezolinetant 45 mg versus in n=5 (0.9%) placebo. The AST elevations were n=5 (0.8%) in fezolinetant 30 mg and n=5 (0.8%) in fezolinetant 45 mg versus n=3 (0.5%) in placebo. There were no Hy's law cases (an ALT of >3× ULN and concomitant jaundice (bilirubin > 2.5 mg/dL)). Further, no clear pattern or trend for the time to onset could be observed from the data, as this occurrence varied from week 2 to week 52 with no difference between placebo or fezolinetant. Similar findings were seen in 12-week data, for which the exposure-adjusted results demonstrated with the highest incidence in the highest dosing group of ALT or AST elevations: 1.5/100 PY in the placebo group, 1.8/100 PY in the fezolinetant 30 mg total group, and 2.7/100 PY in the fezolinetant 45 mg total group. This was also seen in the other study safety populations.

- For the assessment of **bone safety**, in the placebo-controlled 52-week data, as compared to baseline data, no clinically relevant changes in bone mineral density (BMD) and trabecular bone score (TBS) results based on DXA scans have been observed between the 3 study arms. Further, there was no imbalance in number of bone fracture AEs reported in the 52-week data between the fezolinetant arms (n=9 (1.5%) 30 mg fezolinetant, n=10 (1.6%) 45 mg fezolinetant) versus the placebo arm (n=10 (1.6%)). This was also not seen in the other study safety populations. Bone markers and preclinical data showed no impact of fezolinetant.

- In preclinical data, reversible **thrombocytopenia** was observed, in cynomolgus monkeys at the highest doses tested in repeated-dose toxicity studies and was therefore a medical event of interest. In the clinical studies thrombocytopenia was defined as platelet counts < 150 x 10^9/L. In the placebo-controlled 52-week data, incidence of thrombocytopenia was similar between treatment groups (4.0% (n=23), and 3.9% (n=22) the 30 mg and 45 mg fezolinetant groups respectively versus 4.1% (n=23) patients in the placebo group. Similar findings were observed with the 12-week data.

- Regarding the **neoplasms**, benign, malignant and unspecified (including cysts and polyps), the MAH performed a thorough post hoc review of these events for the phase 2 and 3 studies. No evidence was found of genotoxicity or carcinogenicity in the fezolinetant non-clinical program.

- **CNS safety** was thoroughly reviewed, since fezolinetant crosses the blood brain barrier. The incidence of pre-specified AEs concerning CNS effects of potential abuse liability, depression, wakefulness and effect on memory were low and similar between placebo and fezolinetant dose groups for the different safety populations. Further, the low incidence of AEs related to migraine, risk for suicide and syncope did not show an imbalance between placebo and the fezolinetant groups at the 12 and 52 week. However, the incidence of insomnia (1.6% placebo vs 2.5% total fezolinetant group) showed an imbalance in the POP2 data. As stated earlier, the applicant proposes to include insomnia as an ADR in the SmPC of fezolinetant.

Two **deaths** have been reported in the safety population of fezolinetant. Events leading to death were not considered related to the study intervention by the investigator.

Overall, the incidence of subjects with **serious adverse events** (SAEs) relatively low in the placebo-controlled 12-week analysis, as only 10 SAEs were reported, one (0.3%) in the placebo group and 5 (1.5%) in the 30 mg and 4 (1.2%) in the 45 mg fezolinetant group. All reported SAEs were isolated

cases. In the placebo-controlled 52-week safety analysis, the overall incidence was also low with a higher incidence in the fezolinetant groups (n=36 (3.8%) and n=39 (4.1%) in 30 and 45 mg, respectively) compared to placebo (n=15 (1.6%)).

The overall incidence of **AEs leading to discontinuations** at the 52-week analysis remained overall low and was generally similar in the fezolinetant groups (n=51 (5.4%) 30 mg and n=43 (4.5%) 45 mg), as compared to the placebo group (n=37 (3.9%).

No trends or patterns have been observed in **special populations**, i.e. the intrinsic factors of age, race, ethnicity, BMI, isolated NAFLD (non-alcoholic fatty liver disease) and NASH (non-alcoholic steatohepatitis) and diabetic status, and the extrinsic factors of smoking status and geographical region.

3.5. Uncertainties and limitations about unfavourable effects

The proposed broader target population also includes perimenopausal women, which introduces new safety issues. These women were not investigated in the clinical trials, but more importantly these women could still be fertile, whereas fezolinetant should not be used during pregnancy because of the observed foetal toxicity in animal studies. The issue was addressed through appropriate wording for the SmPC (i.e., contra-indication for pregnant women).

3.6. Effects Table

Table 47 Effects Table for fezolinetant for treatment of VMS associated with menopause (data cut-off: June 2022)

Effect	Short Description	Unit	Fezolinetant 45 mg	Uncertainties (Unc)/ Strength of evidence (SoE)	References
Favourable Effects					
Co-Primary endpoints	Difference in LS means (fezolinetant vs placebo) in the frequency of moderate to severe VMS from baseline to week 4	LS mean (SE) (95% CI) (p-value)	-2.07 (0.42) (-2.89, -1.25) (p<0.001)	**SoE:** • Consistent with SKYLIGHT 2: 30 mg (LS mean (SE) of -1.82 (0.46; 95% CI: -2.73 to -0.91; p<0.001)) and 45 mg (LS mean (SE) of -2.55 (0.46; 95% CI: -3.45 to -1.64; p<0.001)) • Consistent in 2 sensitivity analyses. • No differences in subgroups **Unc:** • -	SKYLIGHT 1 and 2

Effect	Short Description	Unit	Fezolinetant 45 mg	Uncertainties (Unc)/ Strength of evidence (SoE)	References
	Difference in LS means (fezolinetant vs placebo) in the frequency of moderate to severe VMS from baseline to week 12	LS mean (SE) (95% CI) (p-value)	-2.55 (0.43) (-3.40, -1.70) (p<0.001)	**SoE:** • Consistent with SKYLIGHT 2: 30 mg (LS mean (SE) of -1.86 (0.55; 95% CI: -2.94 to -0.78; p<0.001)) and 45 mg (LS mean (SE) of -2.53 (0.55; 95% CI: -3.60 to -1.46; p<0.001)) • Consistent in 2 sensitivity analyses. • No differences in subgroups • Clinically meaningful with reduction of ≥ 2 VMS **Unc:** • -	SKYLIGHT 1 and 2
	Difference in LS means (fezolinetant vs placebo) in the severity of moderate to severe VMS from baseline to week 4	LS mean (SE) (95% CI) (p-value)	-0.19 (0.06) (-0.30, -0.07) (p=0.002)	**SoE:** • Consistent with SKYLIGHT 2: 30 (LS mean (SE) of -0.15 (0.06 95% CI: -0.27 to -0.02; p=0.021)) and 45 mg (LS mean (SE) of -0.29 (0.06; 95% CI: -0.41 to -0.16; p=0.001)) • Consistent in 2 sensitivity analyses. • No differences in subgroups **Unc:** • -	SKYLIGHT 1 and 2
	Difference in LS means (fezolinetant vs placebo) in the severity of moderate to severe VMS from baseline to week 12	LS mean (SE) (95% CI) (p-value)	-0.20 (0.08) (-0.35, -0.06) (p=0.007)	**SoE:** • Consistent with SKYLIGHT 2: 30 mg (LS mean (SE) of -0.16 (0.08 95% CI: -0.33 to -0.00; p=0.049)) and 45 mg (LS mean (SE) of -0.29 (0.08; 95% CI: -0.45 to -0.13; p<0.001)) • Consistent in 2 sensitivity analyses. • No differences in subgroups **Unc:** • -	SKYLIGHT 1 and 2
Key secondary endpoint	Difference in LS means (fezolinetant vs placebo) in the PROMIS SD SF 8b total score from baseline to week 12	LS mean (SE) (95% CI) (p-value)	1.1 (0.7) (-2.5, 0.4) (p=0.155)	**SoE:** • Consistent with SKYLIGHT 2: 30 mg (LS mean (SE) -0.7 (0.7) CI 95% -2.1, 0.8; p=0.381) and 45 mg (LS mean (SE) of -2.0 (0.7) CI 95% -3.5, -0.6; p=0.007)), which latter was statistically significant. **Unc:** • Data are not statistically significant	SKYLIGHT 1 and 2
Unfavourable Effects					

Effect	Short Description	Unit	Fezolinetant 45 mg	Uncertainties (Unc)/ Strength of evidence (SoE)	References
Key safety concern	Endometrial safety: Incidence rate (IR) of hyperplasia	IR (upper limit 1-sided 95%CI)	0.5% (2.3%)	**SoE:** • primary endpoint met, in line with FDA guideline (≤ 1%, upper limit 1-sided 95%CI ≤4%) • Analysis of POP2 (SKYLIGHT 1, 2 and 4) showed similar findings • Also no impact on endometrial thickness at 1yr **Unc:** • Stats not in line with EMA guideline • Low numbers • Maintenance of effect over >1 year	SKYLIGHT 4
	Endometrial safety: Incidence rate (IR) of malignancy	IR (upper limit 1-sided 95%CI)	0% (1.5%)	**SoE:** • primary endpoint met, in line with FDA guideline (≤ 1%, upper limit 1-sided 95%CI ≤4%) • Analysis of POP2 (SKYLIGHT 1, 2 and 4) showed similar findings • Also no impact on endometrial thickness at 1yr **Unc:** • Stats not in line with EMA guideline • Low numbers • Maintenance of effect over >1 year	SKYLIGHT 4
	Hepatic safety: frequency of ALT increases > 3 x ULN in POP4	N (%)	n=11 (1.9%)	**SoE:** • Higher than in placebo with n=5 (0.9%) (imbalance) • Similar findings in POP1, 2, 3, and 5 • Also seen in phase 2 dose-response studies **Unc:** • Low numbers • Discontinuations not mentioned • Maintenance of effect over >1 year	SKYLIGHT 4
	Bone safety: frequency of bone fracture AEs in POP4	N (%)	n=10 (1.6%)	**SoE:** • Similar to placebo: n=10 (1.6%) • Similar findings in POP1, 2, 3, and 5 • No clinically relevant changes in BMD and TBS results and bone markers • No impact in DXA scans in 2 repeat-dose toxicity studies in cynomolgus monkeys **Unc:** • Low numbers • Maintenance of effect over >1 year	SKYLIGHT 4

Abbreviations: Unc: Uncertainties, SoE: Strength of evidence.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Fezolinetant is claimed to be the first-in-class, non-hormonal, selective neurokinin 3 (NK3) receptor antagonist. It blocks neurokinin B (NKB) binding on the kisspeptin/neurokinin B/dynorphin (KNDy) neuron to help restore the neuronal activity in the thermoregulatory centre of the hypothalamus. This is expected to result in the reduction of severe vasomotor symptoms (VMS) in postmenopausal women. In line with its proposed mechanism of action, the proposed indication of fezolinetant is, therefore, the "treatment of moderate to severe vasomotor symptoms (VMS) associated with menopause (see section 5.1)".

The current application is mainly based on the results of two identical, 12-week, pivotal, placebo-controlled studies (SKYLIGHT 1 and 2) in women, aged 40 – 65 years, with moderate to severe VMS (i.e. average ⩾ 7 moderate to severe VMS per day or ⩾ 50 per week) and confirmed as postmenopausal (defined as having amenorrhea for ⩾ 12 consecutive months, or amenorrhea for ⩾ 6 months with FSH >40 IU/L or having had bilateral oophorectomy). This patient population is considered to be representative for the target population. However, the initially proposed wording in section 5.1 of the SmPC did not completely reflect the studied population, as it may also be interpreted that perimenopausal women (having fluctuating oestrogen levels) were included, while a treatment effect in this population has not been substantiated by clinical data. Therefore, the term "postmenopausal" was introduced in section 5.1. With this modification, and since no major efficacy and safety issues has been observed in the studied population, i.e. postmenopausal women, the CHMP decided that the proposed wording for the indication, including the terminology "VMS associated with menopause", is approvable.

The study was, in general, well-conducted. The choice to select placebo as comparator is considered acceptable, as for this indication an active comparator, i.e. hormone replacement therapy, is not generally requested for efficacy purposes. The investigated endpoints are relevant to postmenopausal women with moderate to severe VMS.

Results of the SKYLIGHT 1 study show a significant and considerable effect on the most important effects of severity and frequency (-2.39 for 30 mg and -2.55 for 45 mg) in patients receiving fezolinetant, compared to placebo, despite the high placebo response. The improvement in VMS frequency in participants in both treatment arms of fezolinetant can be interpreted as clinically meaningful, since they consistently reduced the number of VMS with ⩾ 2 per day, relative to placebo. Treatment with fezolinetant resulted in a fast (at the first post-baseline assessment at week 1) reduction in VMS which continued to decrease until week 4 and sustained over 12 weeks with over 50% having a ⩾ 50% reduction in the frequency of VMS (i.e. responder rate), compared to 26% in the placebo group. Sensitivity analyses were supportive of the primary outcome. Fezolinetant treatment effects were consistent across the investigated subgroups age, race, BMI or smoking status, though it is noted that the number of patients in these subgroups are low. Further, the effect on frequency and severity was sustained over time through 24 weeks of use with the study drug. Of note, the effect with 45 mg is suggested to be slightly larger, than with 30 mg fezolinetant.

In line with the reductions in frequency and severity of VMS, also a beneficial effect on sleep disturbance was demonstrated in the SKYLIGHT 1 study, by the key secondary endpoint analysis of the PROMIS SD SF 8b score. Similarly, better improvements were observed in the fezolinetant groups for other PRO evaluations on sleep, on general quality of life (QoL) and on work productivity, as compared to the placebo group, suggesting less frequent and less severe VMS positively impacting the QoL of postmenopausal women suffering from moderate to severe VMS. There is good concordance among

efficacy endpoints. Therefore, it can be agreed that the reduction in frequency, by approximately 2 VMS per day, and severity, relative to placebo, can be considered to be clinical relevant in the target population.

The reduction on frequency and severity in the identical SKYLIGHT 2 study were, in general, similar to those observed in the SKYLIGHT 1 study and the evidence of efficacy was considered statistically convincing. The reduction in VMS frequency was -1.86 for 30 mg and -2.53 for 45 mg) in patients receiving fezolinetant, compared to placebo, for which the 45 mg showed to be clinically meaningful as the relative number of VMS was reduced with $\geqslant$ 2 per day. The effect of 45 mg is suggested to be slightly larger than with 30 mg fezolinetant. Importantly, the responder rates of $\geqslant$ 50% reduction in the VMS frequency, the course, the durability over 24 weeks and changes in QoL from baseline in postmenopausal women with severe and frequent VMS in the SKYLIGHT 2 were generally similar to those patients the SKYLIGHT 1 trial, which support the effect of fezolinetant in the target population and can support the general indication in the treatment of moderate to VMS.

The clinical safety database is, in general, sufficient, as the duration of exposure for the 52-week analysis was 364 days in 609 postmenopausal women with moderate to severe VMS on 45 mg fezolinetant. The patients were dosed according to the registration dose in the SmPC. The presented clinical data do not raise major particular concerns, with headache and nausea being the most common treatment-related adverse events (AEs). Fezolinetant is well-tolerated, since the majority of the adverse events are mild to moderate in severity, and the discontinuations due to drug-related adverse events are low (5%), which is re-assuring. Based on extensive assessment, no significant effect on the risk of endometrial, hepatic and bone safety could be revealed with the use of fezolinetant.

3.7.2. Balance of benefits and risks

In terms of benefit, fezolinetant provides a significant and clinically meaningful beneficial treatment effect on moderate to severe VMS in postmenopausal women, as measured by reductions in the frequency and severity of moderate to severe VMS from baseline to weeks 4 and 12, as compared to placebo, with a somewhat greater effect seen with the higher dose of 45 mg. Although based on indirect comparison (Cochrane Data Base Syst. Rev. 2001), the reduction in frequency and severity of VMS achieved is less than noted with oestrogen replacement therapy, the obtained efficacy is considered of clinical relevance, especially for patients in whom oestrogen use is contra-indicated. The reduction in frequency and severity of VMS was accompanied by improvement in sleep disturbance and QoL. The use of fezolinetant (both 30 and 45 mg) appeared to be well tolerated with an acceptable safety profile, especially on endometrial health, hepatic and bone safety, and without major safety signals. Therefore, there is no objection against the choice of the applicant to only apply for the 45 mg for clinical use. The benefit/risk balance is positive.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable.

3.8. Conclusions

The overall benefit/risk balance of Veoza is positive, subject to the conditions stated in section ‘Recommendations’.

4. Recommendations

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that fezolinetant is to be qualified as a new active substance in itself as it is not a constituent of a medicinal product previously authorised within the European Union.