A Randomized, Placebo-Controlled, Double-Blind Phase 3 Clinical Study to Investigate the Long-Term Safety of Fezolinetant in Women Suffering From Vasomotor Symptoms (Hot Flashes) Associated with Menopause

Skylight 4

ISN/Protocol 2693-CL-0304

Version 3.2

Incorporating Nonsubstantial Amendment 3 [See Section 13]

19 March 2021

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Sponsor:

Astellas Pharma Global Development, Inc. (APGD)

1 Astellas Way
Northbrook, IL 60062

Protocol History:

Version 1.0, Original [28 Jan 2019]
Version 2.0 Incorporating Substantial Amendment 1 [17 May 2019]
Version 2.1 Incorporating Nonsubstantial Amendment 1 [13 Dec 2019]
Version 3.0 Incorporating Substantial Amendment 2 [15 Jun 2020]
Version 3.1 [UA] Incorporating Country-specific Nonsubstantial Amendment 2 for Ukraine [23 Oct 2020]

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I. SIGNATURES

1. SPONSOR'S SIGNATURES

Required signatures (e.g., protocol authors and contributors, etc.) are located in [Section 14, Sponsor Signatures].

2. INVESTIGATOR'S SIGNATURE

A Randomized, Placebo-Controlled, Double-Blind Phase 3 Clinical Study to Investigate the Long-Term Safety of Fezolinetant in Women Suffering From Vasomotor Symptoms (Hot Flashes) Associated with Menopause

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19 Mar 2021

I have read all pages of this clinical study protocol for which Astellas is the sponsor. I agree to conduct the study as outlined in the protocol and to comply with all the terms and conditions set out therein. I confirm that I will conduct the study in accordance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) guidelines and applicable local regulations. I will also ensure that subinvestigator(s) and other relevant members of my staff have access to copies of this protocol and the ICH GCP guidelines to enable them to work in accordance with the provisions of these documents.

Principal Investigator:

Signature: ----------

Date (DD Mmm YYYY)

Printed Name: ----------
<Insert name and qualification of the Investigator>

Address: ----------

II. CONTACT DETAILS OF KEY SPONSOR'S PERSONNEL

24h-Contact for Serious Adverse Events (SAEs) See [Section 5.8.5 Reporting of Serious Adverse Events (SAEs)] for SAE Fax Number and Email	**Please fax or email the SAE Worksheet to:** **Astellas Pharma Global Development, Inc.** **Pharmacovigilance** **Fax number: +1 888-396-3750** **Alternate fax number: +1 847-317-1241** **Email: safety-US@astellas.com**
CRO Medical Monitor/Study Physician:	PPD ICON Clinical Research PPD ICON Clinical Research PPD PPD Astellas Pharma Global Development, Inc. 1 Astellas Way Northbrook, IL 60062 USA PPD
Clinical Research Contact:	PPD

III. LIST OF ABBREVIATIONS AND DEFINITION OF KEY TERMS

List of Abbreviations

Abbreviations	Description of abbreviations
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
AT	serum aminotransferases
AUC	area under the concentration-time curve
BC	breast cancer
bid	twice daily
BMD	bone mass density
CA	Competent Authorities
CIOMS	Council for International Organizations of Medical Sciences
C_{max}	maximum concentration
CRF	case report form
CRO	contract research organization
C-SSRS	Columbia Suicide Severity Rating Scale
CYP	cytochrome P450
DBL	direct bilirubin
DILI	drug-induced liver injury
DILIsym	drug-induced liver injury modeling software
DMC	Data Monitoring Committee
DXA	dual-energy X-ray absorptiometry
E2	estradiol
ECG	electrocardiogram
eCRF	electronic case report form
ED	early discontinuation
EEA	European Economic Area
EH set	endometrial health analysis set
EOT	end of treatment
EU	European Union
EQ-5D-5L	Euro-Qol 5D-5L
FAS	full analysis set
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice

Abbreviations	Description of abbreviations
GMP	Good Manufacturing Practice
GnRH	gonadotropin releasing hormone
HFs	hot flashes
HRT	hormone replacement therapy
hNK	human neurokinin
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	independent ethics committee
IMP	investigational medicinal product
INR	international normalized ratio
IRB	institutional review board
IRT	interactive response technology
ISN	international study number
KNDy	kisspeptin/neurokinin B/dynorphin
LA-CRF	liver abnormality case report form
LH	luteinizing hormone
MedDRA	Medical Dictionary for Regulatory Activities
MENQoL	Menopause-Specific Quality of Life
MMRM	mixed model for repeated measures
MR-VMS	menopause-related vasomotor symptoms
NK3R	neurokinin-3 receptor
NKB	neurokinin B
NOAEL	no adverse event level
P4	progesterone
Pap	Papanicolaou
PDAS	pharmacodynamic analysis set
PKAS	pharmacokinetic analysis set
PRO	patient-reported outcome
QTLs	quality tolerance limits
RSI	Reference Safety Information
QA	quality assurance
QC	quality control
qd	once daily
SAE	serious adverse event
SAF	Safety Analysis Set

Abbreviations	Description of abbreviations
SAP	Statistical Analysis Plan
SAR	serious adverse reaction
SHBG	sex hormone-binding globulin
SOC	system organ class
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reaction
TBL	total bilirubin
TBS	trabecular bone score
TEAE	treatment-emergent adverse event
TVU	transvaginal ultrasound
ULN	upper limit of normal
USM	Urgent Safety Measure
VAS	visual analog scale
VMS	vasomotor symptoms

Definition of Key Study Terms

Terms	Definition of terms
Baseline	1. Observed values/findings, which are regarded as starting points for comparison. 2. Time when 'Baseline' is observed.
Endpoint	Variable that pertains to the efficacy or safety evaluations of a study. NOTE: Not all endpoints are themselves assessments since certain endpoints might apply to populations or emerge from analysis of results. That is, endpoints might be facts about assessments (e.g., prolongation of survival).
Enroll	To register or enter a subject into a clinical trial. NOTE: Once a subject has received the study drug or placebo, the clinical trial protocol applies to the subject.
Intervention	The investigational product under investigation to evaluate the effect on specified outcomes of interest (e.g., health-related quality of life, efficacy, safety and pharmacoeconomics).
Investigational period	This portion of the study refers to the time that a subject is receiving treatment (investigational product or placebo). This period of time is when major interests of protocol objectives are observed and continues until the last assessment is completed after final administration of the investigational product or placebo.
Follow-up period	Period of time after the last assessment of the protocol. Follow-up observations for sustained adverse events and/or survival are conducted during this period.
Randomization	The process of assigning subjects to treatment or control groups using an element of chance to determine assignments in order to reduce bias.
Rescreen	Subject can rescreen up to 1 time with the approval of the medical monitor, which will result in a new 35-day screening window. The subject will be entered as a new subject in the interactive response technology.
Retest	Subject can retest up to 1 time with approval from the medical monitor within the current 35-day screening window. The subject will retain the same subject identification number.
Screening	A process of active consideration of potential subjects for randomization in a study. NOTE: This is conducted after the subject signs the informed consent and agrees to be evaluated for study participation.
Screen failure	Potential subject who did not meet 1 or more inclusion criteria or met 1 or more exclusion criteria required for participation in a study and was not randomized.
Screening period	Period of time before entering the investigational period, usually from the time when a subject signs the consent until just before the test drug or comparative drug (sometimes without randomization) is given to a subject.
Study period	Period of time from the first site initiation date to the last site completing the last study assessment.
Variable	Any entity that may change as a result of other factors; any attribute, phenomenon or event that can have different qualitative or quantitative values.

IV. SYNOPSIS

Date and Version No. of Protocol Synopsis:	19 Mar 2021, Version 3.2
Sponsor: Astellas Pharma Global Development	**Protocol Number:** 2693-CL-0304
Name of Study Drug: Fezolinetant	**Phase of Development:** Phase 3
Title of Study: A Randomized, Placebo-Controlled, Double-Blind Phase 3 Clinical Study to Investigate the Long-Term Safety of Fezolinetant in Women Suffering From Vasomotor Symptoms (Hot Flashes) Associated with Menopause	
Planned Study Period: From 2Q2019 to 3Q2022	
Objectives: Primary objective of the study: • To evaluate the long-term safety and tolerability of fezolinetant in women seeking treatment for relief of Vasomotor Symptoms (VMS) associated with menopause. • To evaluate the effect of fezolinetant on endometrial health after long-term treatment in women seeking treatment for relief of VMS associated with menopause. Secondary objective(s) of the study: • To evaluate the effect of fezolinetant on bone mineral density after long-term treatment in women seeking treatment for relief of VMS associated with menopause. Exploratory objectives of the study: • To evaluate the effect of fezolinetant on subject-reported quality of life measures. • To evaluate the pharmacokinetics of fezolinetant and its metabolite, ESN259564.	
Planned Total Number of Study Centers and Locations: Approximately 250 centers globally.	
Study Population: Women ≥ 40 years and ≤ 65 years of age seeking treatment for VMS associated with menopause.	
Number of Subjects to be Enrolled/Randomized: 1740 total subjects are planned to be randomized at a 1:1:1 ratio of fezolinetant 45 mg once daily: fezolinetant 30 mg once daily: placebo with approximately 580 subjects randomized to each of the treatment groups.	
Study Design Overview: Eligible subjects will complete all screening requirements and randomize into the 52-week placebo-controlled, double-blind, parallel-group, multicenter clinical study to assess the safety and tolerability of fezolinetant and quality-of-life in women seeking treatment for VMS associated with menopause. This study will consist of a screening period (days -35 to -1, including the screening visit [visit 1] assessments), a 52-week treatment period (day 1 [visit 2] to week 52 [visit 15]) and a follow-up visit (week 55 [visit 16]) 3 weeks after the last dose of study drug. An extra 15 screening days are allowed for repeat biopsy, if necessary (days -50 to -1, including the screening visit [visit 1] assessments). NOTE: All study visits will be completed as outpatient visits.	

Study Design Overview *(continued)*:

The screening visit (visit 1) will occur up to 35 days prior to treatment initiation. Eligibility will be assessed via physical examination, clinical laboratory testing, urine pregnancy test, vital signs, electrocardiogram (ECG), Papanicolaou (Pap) test (or equivalent cervical cytology, mammography, transvaginal ultrasound (TVU) and endometrial biopsy. To participate in the study, subjects must be seeking medical treatment for relief of VMS.

Subjects may be retested for assessments up to 1 time upon approval of the medical monitor within the current 35-day screening window and will retain the same subject screening identification number.

Subjects may be rescreened in this study, which will result in a new 35-day screening window and a new subject screening identification number, up to 1 time upon approval of the medical monitor. The following assessments do not need to be repeated at the rescreen provided they fall within the acceptable procedure completed time frame and all results meet inclusion and no exclusion criteria: TVU (acceptable 3 months from date of procedure); dual-energy X-ray absorptiometry (DXA) (acceptable 3 months from date of procedure); endometrial biopsy (acceptable 3 months from date of procedure); subject has documentation of a normal/negative or no clinically significant mammogram findings (obtained at screening or within the prior 12 months of trial enrollment [appropriate documentation includes a written report or an electronic report indicating normal/negative or no clinically significant mammographic findings]), ECG (acceptable 3 months from procedure); and documentation of a normal or not clinically significant Pap test (or equivalent cervical cytology) in the opinion of the investigator within the previous 12 months. Subjects who screen failed due to COVID-19 pandemic study suspension and have a documented evaluable endometrial biopsy from the original screening period do not have to undergo a repeat biopsy should they decide to rescreen.

Subjects who screened for the 2693-CL-0301 or the 2693-CL-0302 study who did not meet the minimum requirement for frequency and severity of VMS prior to randomization may be consented and screened for this study with a new 35-day screening window from the time of consent. For these subjects the following assessments that were completed and/or assessed do not need to be repeated provided they fall within the acceptable procedure completed time frame and all results meet inclusion and no exclusion criteria: TVU (acceptable 3 months from procedure); endometrial biopsy (acceptable 3 months from procedure); subject has documentation of a normal/negative or no clinically significant mammogram findings (obtained at screening or within the prior 12 months of trial enrollment [appropriate documentation includes a written report or an electronic report indicating normal/negative or no clinically significant mammographic findings]); ECG (acceptable 3 months from procedure); and documentation of a normal or not clinically significant Pap test (or equivalent cervical cytology) in the opinion of the investigator within the previous 12 months. These subjects will have to repeat screening labs and complete DXA procedure requirements.

A suction endometrial biopsy will be performed any time during the study in the case of uterine bleeding, in addition to the protocol-required time points.

Study Design Overview *(continued)*:

At the end of treatment (EOT) (or the early discontinuation [ED] visit for subjects who withdraw from the study prior to completion), a TVU and a suction endometrial biopsy will be required. If a subject discontinues from the study, an endometrial biopsy is required at the discontinuation visit along with all other EOT procedures. During the treatment period, any woman with an abnormal endometrial biopsy reported as disordered proliferative endometrium, endometrial hyperplasia or endometrial cancer will be referred to standard of care clinical management and followed to resolution, and the report of any medical or surgical procedures and the resultant pathology will be obtained. The investigator should record any such biopsy, and the associated diagnostic and therapeutic measures, as an AE. A mammogram at week 52/EOT/ED will be conducted if it coincides with the regularly scheduled routine screening mammogram of the patient, in accordance with local medical practice guidelines and the patient's primary care physician. During the treatment period, subjects will return to the study site as indicated in the Schedule of Assessments. Site-based patient-reported outcome (PRO) measures will be self-administered via an electronic device as indicated in the Schedule of Assessments. All assessments must be performed at the site and prior to all other required visit procedures. In the event a subject withdraws from the study prior to completion, all efforts to collect information on the site-based PRO measures should be made before or shortly after withdrawal.

Following the completion of the treatment period (week 52 or ED), subjects will complete an EOT (or ED) visit and final safety follow-up visit 3 weeks after the last dose of study drug is administered (week 55 or 3 weeks following ED).

A Data Monitoring Committee (DMC) will oversee the safety of fezolinetant for the duration of the study.

COVID-19 Consideration:

All attempts should be made to conduct the protocol-defined scheduled visits. In cases where a subject is unable to visit the clinic due to site closure related to the COVID-19 pandemic, the following alternative measures may be implemented to ensure subject safety and continuity of care while participating in the study:

- Telemedicine Conferences (telephone visits) to evaluate changes in a subject's medical condition or medications and completion of electronic patient-reported outcome questionnaires following the process defined in the COVID-19 *Notification of Pause and Screening Enrollment* memo released on 27 March 2020 provided to the site by the sponsor.
- Safety laboratory tests collected at a local lab to include biochemistry, hematology, liver biochemistry and coagulation panel testing.
- Home healthcare services may be available in cases where arrangements are made in advance by the site upon request from the subject(s)

Due to the nature of the Screening (visit 1), Randomization, week 0 (visit 2) and EOT/ED week 52 (visit 15) visits, which include important study procedures, these visits must be conducted in the clinic. All other visits during the COVID-19 pandemic may be conducted utilizing all or some of the following services: home healthcare, telemedicine conferences (telephone visits) or safety laboratory tests collected at a local laboratory.

Subjects who screen failed due to COVID-19 pandemic study suspension and have a documented evaluable endometrial biopsy from the original screening period do not have to undergo a repeat biopsy should they decide to rescreen.

Inclusion/Exclusion Criteria:

Inclusion:

Subjects who meet all of the following criteria will be eligible to participate in the study:

1. 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.
2. Subject is born female, aged ≥ 40 years and ≤ 65 years of age at the screening visit.
3. Subject has a body mass index ≥ 18 kg/m^2 and ≤ 38 kg/m^2.
4. 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 (follicle stimulating hormone > 40 IU/L), or
   - Having had bilateral oophorectomy ≥ 6 weeks prior to the screening visit
5. Subject is seeking treatment for relief for VMS associated with menopause.
6. 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; hematology and biochemistry parameters; pulse rate and/or blood pressure; and ECG within the reference range for the population studied, or showing no clinically relevant deviations, as judged by the investigator.
7. Subject has documentation of a normal/negative or no clinically significant mammogram findings (obtained at screening or within the prior 12 months of trial enrollment). Appropriate documentation includes a written report or an electronic report indicating normal/negative or no clinically significant mammographic findings.
8. Subject is willing to undergo a TVU to evaluate the uterus and ovaries at screening and at week 52 (EOT). For subjects who are withdrawn from the study prior to completion, a TVU should be collected at the ED visit.
9. Subject is willing to undergo an endometrial biopsy at screening and at week 52 (EOT) or the ED visit for subjects who are withdrawn from the study prior to completion, and any time during the study in the case of uterine bleeding. The endometrial biopsy obtained at screening must be considered evaluable.
10. 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 12 months or at screening.
11. Subject has a negative urine pregnancy test at screening.
12. Subject has a negative serology panel (i.e., negative hepatitis B surface antigen, negative hepatitis C virus antibody and negative human immunodeficiency virus antibody screens) at screening.
13. Subject agrees not to participate in another interventional study while participating in the present study.

Exclusion:

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

1. Subject uses a prohibited therapy (strong or moderate cytochrome P450 [CYP] 1A2 inhibitors, hormone replacement therapy [HRT], hormonal contraceptive, any treatment for VMS [prescription, over the counter or herbal]) or is not willing to wash out and discontinue such drugs for the full extent of the study.
2. Subject has a known substance abuse or alcohol addiction within 6 months of screening, as assessed by investigator.
3. Subject has previous or current history of a malignant tumor, except for basal cell carcinoma.
4. Subject's systolic blood pressure is ≥ 130 mmHg or diastolic blood pressure is ≥ 80 mmHg based on the average of 2 to 3 readings on at least 2 different occasions within the screening period.
   - Subjects who do not meet the criteria may, at the discretion of the investigator, be re-assessed after initiation or review of antihypertensive measures.
   - Subjects with a medical history of hypertension can be enrolled at the discretion of the investigator once they are medically cleared (stable and compliant).
5. Subject has a history of severe allergy, hypersensitivity or intolerance to drugs in general, including the study drug and any of its excipients.
6. 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.
7. Subject has an endometrial biopsy confirming presence of disordered proliferative endometrium, endometrial hyperplasia, endometrial cancer, or other clinically significant findings in the opinion of the investigator at screening.
8. Subject has a history within the last 6 months of undiagnosed uterine bleeding.
9. Subject has a history of seizures or other convulsive disorders.
10. Subject has a medical condition or chronic disease (including history of neurological [including cognitive], hepatic, renal, cardiovascular, gastrointestinal, pulmonary [e.g., moderate asthma], endocrine or gynecological disease) or malignancy that could confound interpretation of the study outcome in the opinion of the investigator.
11. Subject has active liver disease, jaundice, elevated liver aminotransferases (ALT or AST), elevated or total bilirubin, elevated International Normalized Ratio (INR), or elevated, alkaline phosphatase (ALP). Patients with mildly elevated ALT or AST up to 1.5 times the upper limit of normal (ULN) can be enrolled if total and direct bilirubin (DBL) are normal. Patients with mildly elevated ALP (up to 1.5 × ULN) can be enrolled if cholestatic liver disease is excluded and no cause other than fatty liver is diagnosed. Patients with Gilbert's syndrome with elevated total bilirubin (TBL) may be enrolled as long as DBL, hemoglobin, and reticulocytes are normal.
12. Subject has creatinine > 1.5 × ULN; or estimated glomerular filtration rate using the Modification of Diet in Renal Disease formula ≤ 59 mL/min per 1.73 m^2 at the screening visit.
13. Subject has a history of suicide attempt or suicidal behavior within the last 12 months or has suicidal ideation within the last 12 months (a response of "yes" to questions 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 the time of visit 2 (randomization).
14. Subject has previously been enrolled in a clinical trial with fezolinetant.

Exclusion continued:

15. 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.
16. Subject is unable or unwilling to complete the study procedures.
17. Subject has any condition which, in the investigator's opinion, makes the subject unsuitable for study participation.
18. This criterion has been removed.
19. This criterion has been removed.
20. Subject has had a partial or full hysterectomy.

Waivers to the inclusion and exclusion criteria will **NOT** be allowed.

Investigational Product(s):

Fezolinetant 15 mg tablet

Fezolinetant 30 mg tablet

Dose(s):

30 mg (One 30 mg tablet and one placebo tablet) once daily

45 mg (One 15 mg tablet and one 30 mg tablet) once daily

Mode of Administration:

Oral

Comparative Drug(s):

Placebo, 2 tablets to match once daily

Dose(s):

Not applicable

Mode of Administration:

Oral

Concomitant Medication Restrictions or Requirements:

Medications for the treatment of VMS (including prescription medications, over the counter and herbal) taken during the 12 months prior to screening and other medication taken 90 days prior to the screening visit and up to the first dose of study medication (treatment period) will be documented in the appropriate electronic case report form (eCRF) as prior medication.

Medications taken after the first dose of study medication and through the last study-related activity will be documented on the appropriate CRF as concomitant medication. Prior and concomitant medications to be documented include but are not limited to: vitamins, herbal remedies (e.g., St. John's wort, valerian), over the counter and prescription medications.

Subjects will be instructed not to take any concomitant medication without first consulting the investigator or study coordinator throughout the duration of the study.

Prohibited Concomitant Medications:

The following medications and therapies are prohibited throughout the study (from signing of informed consent form [ICF] through the last study-related activity):

- Use of hormonal medications such as hormone therapy, HRT or hormonal contraception or any treatment for menopausal symptoms (prescription, over the counter or herbal).
- Investigational research products that have not been approved for any indication in the country where the subject is enrolled.
- Strong or moderate CYP1A2 inhibitors are prohibited.

Duration of Treatment:

Subject will take study drug daily from day 1 (randomization) for a duration of 52 weeks.

Formal Stopping Rules

Subject Discontinuation:

A subject **must** be withdrawn from the study treatment for any of the following reasons:

- Withdrawal of informed consent.
- Lost to follow-up.
- If for safety reasons it is in the best interest of the subject that she be withdrawn, in the investigator's opinion.
- Development of a medical condition that requires concomitant treatment with a prohibited therapy.
- Development of seizures or other convulsive disorders.
- Breaking of the randomization code during administration of the study drug by the investigator or by a member of the site staff. If the code is broken by the sponsor for safety reporting purposes or early time point analysis, the subject may remain in the study.
- Confirmed (within 72 hours from the notification of test result) decrease in platelets below 75,000 mm^3, which does not normalize after 7 days or immediate withdrawal in case of platelets below 50,000 mm^3.
- Development of severe hepatic abnormality defines as ALT or AST > 8 × ULN.
- Confirmed (within 72 hours from the notification of test result) severe hepatic abnormality defined as any of the following:
    - ALT or AST > 5 × ULN for more than 2 weeks;
    - ALT or AST > 3 × ULN **AND** TBL > 2 × ULN or INR > 1.5; or
    - ALT or AST > 3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (> 5% increase from baseline).
- The subject becomes pregnant.
- Category 2 results of secondary or tertiary screening endometrial biopsy diagnosis.

Study Discontinuation:

The sponsor may terminate this study prematurely, or treatment arm, either in its entirety or at any study site, for reasonable cause provided that written notice is submitted in advance of the intended termination. Advance notice is not required if the study is stopped due to safety concerns. If the sponsor terminates the study for safety reasons, the sponsor will immediately notify the investigator and subsequently provide written instructions for study termination.

Endpoints for Evaluation:

Primary Endpoint:

The primary variable will require the evaluation of the safety of fezolinetant on the following:

- Frequency and severity of adverse events.
- Percentage of subjects with endometrial hyperplasia.
- Percentage of subjects with endometrial cancer.

Secondary Endpoints:

- Change from baseline in endometrial thickness at 12 months.
- Percentage of subjects with disordered proliferative endometrium.
- Change from baseline in bone mass density and trabecular bone score at hip and spine at 12 months.
- Vital signs: sitting systolic and diastolic blood pressure and pulse rate.
- Laboratory tests: hematology, biochemistry and urinalysis
- C-SSRS.
- ECG parameters.

Exploratory Endpoints:

The exploratory variables include the effect of fezolinetant on the following:

- Mean change on the Menopause-Specific Quality of Life (MENQOL) Total Score from baseline to specified time points (week 4, 12, 24 and 52).
- Mean change on the MENQOL 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) Total Score from baseline to specified time points (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:

Sample Size Justification:

The sample size is not calculated based on the statistical power for efficacy evaluation to detect treatment difference, as the primary objective of this study is to assess long-term safety.

The total sample size will be 1740 subjects who will be randomly assigned 1:1:1 to fezolinetant 45 mg once daily group (580); fezolinetant 30 mg once daily group (580) and placebo group (580). This sample size would provide high probability to observe events of special interest that has with a fairly low background event rate that is less than 1%. If an assumed background rate of 0.26% such as for endometrial hyperplasia, this sample size would be able to demonstrate that the point estimate is less than or equal to 1% and upper bound of one-sided 95% CI to be $\leq$ 4% with at least 95% probability, assuming up to 60% (including baseline, ED and subject refusal of endometrial biopsy at EOT) of subjects may not have evaluable biopsy data.

Safety:

Safety analyses will be performed on the safety analysis set (SAF), which is defined as all subjects who received at least 1 dose of study medication.

Endometrial health-related endpoints such as hyperplasia, cancer and proliferative endometrium will be analyzed on the endometrial health analysis set (EH set). The EH set is defined as subjects having 1 year evaluable biopsy results.

The number and percentage of treatment-emergent adverse events (TEAEs) reported during the study period will be summarized by system organ class, preferred term, seriousness, severity and relationship to treatment, overall and by treatment group. The rate of endometrial hyperplasia, cancer and disordered proliferative endometrium will be evaluated separately.

Changes from baseline for vital signs, ECGs and laboratory assessments will be summarized in tables by treatment group and visit.

Descriptive summary statistics and listing of events will be provided for the C-SSRS by timepoint and for the entire study.

Efficacy:

No efficacy data will be collected.

Exploratory Endpoints:

The exploratory endpoints include the MENQOL and EQ-5D-5L which will be assessed at baseline and weeks 4, 12, 24 and 52. The exploratory endpoints will be analyzed for the full analysis set (FAS). Summary statistics will be provided by treatment group.

Pharmacokinetics:

Descriptive statistics on the actual values will be summarized by visit and treatment arm. Pharmacokinetics may be evaluated by a population pharmacokinetic approach. All details of population analyses will be described in a separate analysis plan and a separate report will be written. When deemed necessary, data from this study may be combined with data from other studies.

Pharmacodynamics:

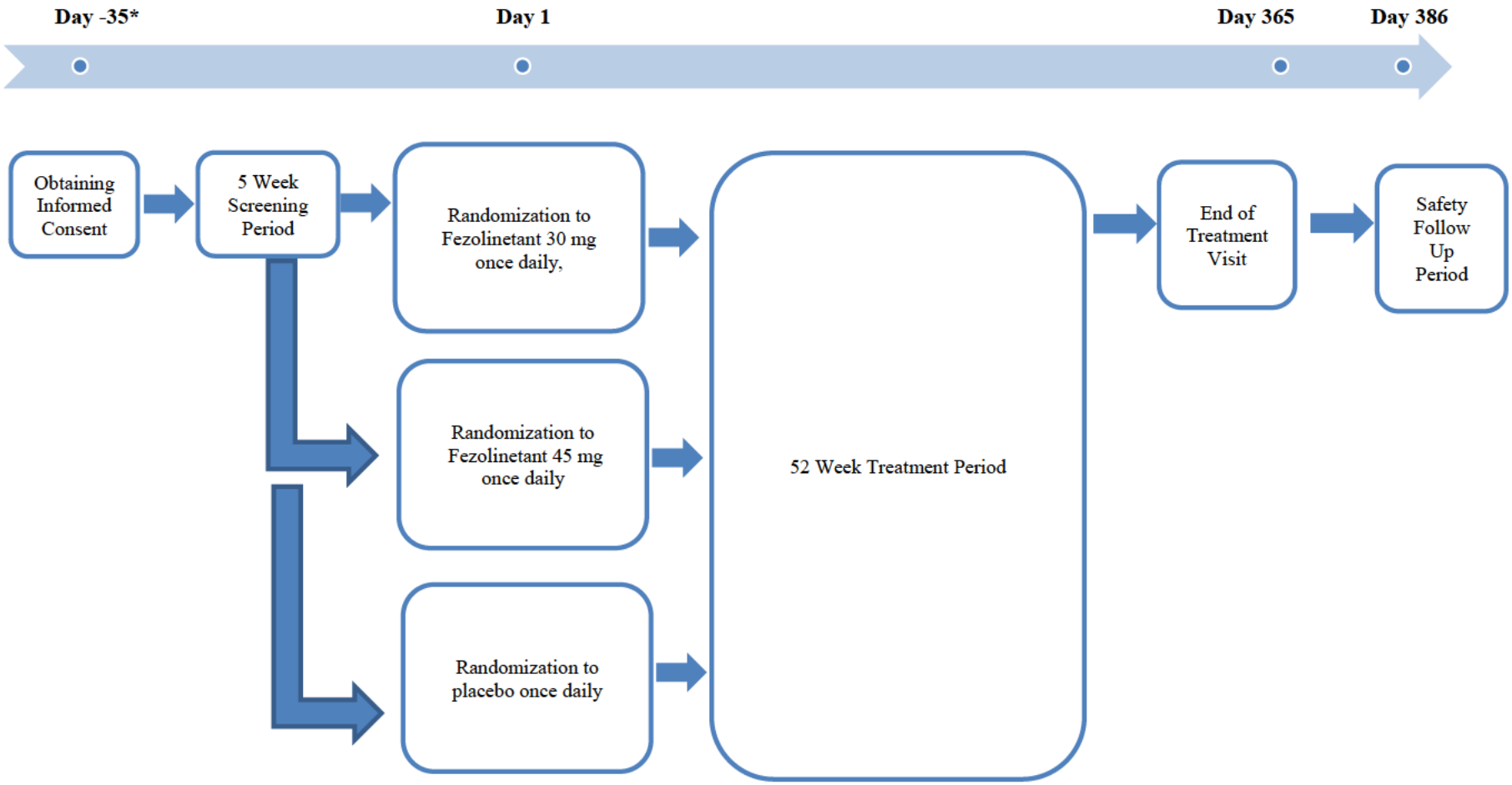
Individual plasma hormone concentration values and actual sampling times relative to study drug intake will be listed. Descriptive statistics on the actual values and changes from baseline values will be summarized by assessment timepoint and by treatment arm. Pharmacodynamic data and efficacy data may be evaluated by a population pharmacodynamics or population pharmacokinetic/pharmacodynamic approach. All details of population analyses will be described in a separate analysis plan and a separate report will be written. When deemed necessary, data from this study may be combined with data from other studies.

Interim analyses:

Not applicable.

V. FLOW CHART AND SCHEDULE OF ASSESSMENTS

Flow Chart:



* An extra 15 screening days are allowed for repeat biopsy, if necessary (days -50 to -1, including the screening visit [visit 1] assessments).

Table 1 Schedule of Assessments

Assessments	Screening Visit[a,x]	Randomi-zation[x]	Treatment Period									Follow-Up Visit[b]
Study Visit	**Visit 1**	**Visit 2**	**Visit 2b**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visits 9, 10, 11, 12, 13 and 14**	**Visit 15/ EOT/ED[y]**	**Visit 16**
Time of Visit	**Week -5 to -1**	**Week 0**	**Week 2**	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24**	**Weeks 28, 32, 36, 40, 44 and 48**	**Week 52**	**Week 55**
Visit days	**Days -35 to -1**	**Day 1**	**Day 15**	**Day 29**	**Day 57**	**Day 85**	**Day 113**	**Day 141**	**Day 169**	**Day 197, 225, 253, 281, 309 and 337**	**Day 365**	**Day 386**
Visit Window (days)[c]	**-35 to -1**	**-**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**-14 /+ 6**	**± 3**
Informed consent[d]	X											
Inclusion/exclusion criteria	X	X										
Medical history/ concomitant diseases	X											
Mammogram[e]	X										X	
Demographic data[f]	X											
Physical examination[g]	X	X[h]		X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X	X
Urine pregnancy test	X											
Clinical laboratory[i] and urinalysis	X	X	X[i]	X	X	X	X	X	X	X	X	X
Vital signs[j]	X	X		X	X	X	X	X	X	X	X	X
12-lead ECG[k]	X										X	
Pap test[l]	X											
Transvaginal ultrasound (TVU)[m]	X										X	
Endometrial biopsy[n]	X[n]										X[o]	
DXA[p]	X										X	
Serology[q]	X											

Table continued on next page

Footnotes

Assessments	Screening Visit[a,x]	Randomi-zation[x]	Treatment Period									Follow-Up Visit[b]
Study Visit	**Visit 1**	**Visit 2**	**Visit 2b**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visits 9, 10, 11, 12, 13 and 14**	**Visit 15/ EOT/ED[y]**	**Visit 16**
Time of Visit	**Week -5 to -1**	**Week 0**	**Week 2**	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24**	**Weeks 28, 32, 36, 40, 44 and 48**	**Week 52**	**Week 55**
Visit days	**Days -35 to -1**	**Day 1**	**Day 15**	**Day 29**	**Day 57**	**Day 85**	**Day 113**	**Day 141**	**Day 169**	**Day 197, 225, 253, 281, 309 and 337**	**Day 365**	**Day 386**
Visit Window (days)[c]	**-35 to -1**	**-**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**-14 /+ 6**	**± 3**
Blood pharmacodynamic sample[r]		X		X		X			X		X	X
Blood pharmacokinetic sample[s]				X[r]		X			X		X	
C-SSRS[t]	X	X				X			X		X	X
EQ-5D-5L[u]		X		X		X			X		X	
MENQoL[u]		X		X		X			X		X	
ePRO training		X										
Randomization		X										
Dispense study drug[v]		X		X	X	X	X	X	X	X		
Study drug compliance and accountability[w]		X		X	X	X	X	X	X	X	X	
Concomitant medications and AEs[x]	X	X	X	X	X	X	X	X	X	X	X	X

AE: adverse event; anti-HBc: antibody to hepatitis B core antigen; anti-HBs: hepatitis B surface antibody; C-SSRS: Columbia Suicide Severity Rating Scale; E2: estradiol; ECG: electrocardiogram; eCRF: electronic Case Report Form; DXA: dual-energy X-ray absorptiometry; ED: early discontinuation; EOT: end of treatment; ePRO: electronic patient-reported outcome; EQ-5D-5L: Euro-Qol 5D-5L; FSH: follicle-stimulating hormone; HBsAG: hepatitis B virus surface antigen; HCV: hepatitis C virus; HIV: human immunodeficiency virus; INR: International Normalized Ratio; LH: luteinizing hormone; MENQoL: Menopause-Specific Quality of Life; Pap test: Papanicolaou test; PD: pharmacodynamic; PK: pharmacokinetic; SHBG: sex hormone-binding globulin; TVU: transvaginal ultrasound; VMS: vasomotor symptoms.

Footnotes continued on next page

a. The screening visit is to occur on or within 35 days of randomization (day 1 [visit 2]). Subjects may be retested 1 time for assessments upon approval of the medical monitor. An extra 15 screening days are allowed for repeat biopsy, if necessary (days -50 to -1, including the screening visit [visit 1] assessments). The following assessments do not need to be repeated at the rescreen provided they still fall within the acceptable screening time window: TVU, DXA, endometrial biopsy, mammogram, ECG and Pap test (or equivalent cervical cytology). Subjects who screened for the 2693-CL-0301 or the 2693-CL-0302 study that did not meet the minimum requirement for frequency and severity of VMS prior to randomization may be re-screened for this study. The following assessments do not need to be repeated at the rescreen provided they still fall within the acceptable screening time window: TVU, endometrial biopsy, mammogram, ECG and Pap test (or equivalent cervical cytology). History of average caffeinated beverage intake will be collected at baseline. At each clinic visit, the caffeinated beverage intake within the past 24 hours will be recorded.

b. The follow-up visit (visit 16) will occur approximately 3 weeks following the last dose of study drug.

c. Subjects will return to the study site for visits and procedures to occur within ±3 days of the scheduled day. Unscheduled visits can be planned outside the scheduled visits.

d. Signed informed consent will be collected for all subjects before any study-related procedures are conducted.

e. At screening, in the event that the subject does not have a documented normal/negative or no clinically significant findings mammogram from the previous 12 months on record. A mammogram at week 52/EOT/ED will be conducted if it coincides with the regularly scheduled routine screening mammogram of the patient, in accordance with local medical practice guidelines and the patient's primary care physician.

f. Includes age, race, sex and smoking status (smoker/non-smoker), etc. Demographic information may vary based on country requirements.

g. Includes height (at the screening visit only), weight and waist circumference. A bimanual clinical pelvic and clinical breast examination will be performed at the screening visit. A bimanual clinical pelvic examination can be performed at any time in the study where clinically indicated.

h. At day 1 (visit 2) thru week 48 (visit 14), excluding visit 2b, a symptom directed physical exam will be conducted which includes weight and waist circumference.

i. Includes biochemistry, coagulation and hematology panel. Visit 2b will only include liver biochemistry and INR testing.

j. Includes oral/tympanic temperature, sitting blood pressure and pulse rate (sitting).

k. The subject should rest in supine position for at least 10 minutes prior to the ECG.

l. Only in the event the subject does not have a normal/negative or no clinically significant findings Pap test (or equivalent cervical cytology) from previous 12 months on record.

m. TVU will be performed at screening and at week 52/EOT and in case of uterine bleeding during treatment.

n. Endometrial biopsy will be performed at screening and in case of uterine bleeding during treatment. Subject may schedule the endometrial biopsy on a separate day, within the screening period. Subjects that require a retest biopsy due to insufficient or unevaluable result, will have an extended screening period and will be allowed an additional 15 days of screening (i.e., days -50 to -1). Screening biopsy results are valid for study entry up to 3 months from date of procedures for applicable subjects. Subjects who screen failed due to the COVID-19 pandemic study suspension and have a documented evaluable endometrial biopsy from the original screening period do not have to undergo a repeat biopsy should they decide to rescreen.

o. Endometrial biopsy will be required at EOT or ED. For EOT/ED week 52 (visit 15) biopsies that are evaluated as insufficient material or unevaluable, a retest biopsy will be required. Any of the three pathologists can determine if a EOT/ED biopsy is insufficient or unevaluable. However, if two pathologists read the EOT/ED endometrial biopsy as evaluable and issue the same diagnosis, and the 3rd pathologist reads the biopsy as insufficient or unevaluable, the biopsy does not need to be repeated.

Footnotes continued on next page

p. For practical reasons, the timing of DXA may vary from the actual time of the visit, depending on the DXA availability (DXA appointment). The screening visit (days -35 to -1 [visit 1]) DXA can be performed once the subject has been deemed eligible based on screening laboratory tests, or at visit 2 but must be performed before randomization. The week 52 (visit 15) DXA should be performed between week 50 and week 52, inclusive. For subjects who are withdrawn from the study prior to completion, a DXA will be completed as soon as possible after study drug discontinuation (preferably within 2 weeks).

q. For HBsAG, anti-HCV antibodies, anti-HBs antibodies, anti-HBc antibodies and anti-HIV antibodies.

r. Pharmacodynamic samples will be taken predose (1 hour) at day 1 (visit 2), week 4 (visit 3), week 12 (visit 5), week 24 (visit 8), at week 52 (visit 15) and week 55 (visit 16). Markers include LH, FSH, E2, SHBG, androstenedione, dehydroepiandrosterone, estrone and testosterone.

s. Pharmacokinetic samples to be taken predose at week 4 (visit 3), week 12 (visit 5), week 24 (visit 8), and at EOT/ED week 52 (visit 15) and at 1 to 3 hour postdose at week 4 (visit 3). A predose sample will be collected for any subject with a signal of elevated (> 3 × ULN) transaminases. For the week 52 (visit 15) PK/PD samples, the last dose of study drug should be administered the day prior to the week 52 (visit 15) visit. Sites should collect week 52 (visit 15) PK/PD samples approximately at the same time when study drug would typically be given on site.

t. A clinician will administer the C-SSRS measure electronically at the clinic visit, prior to any invasive procedures. This will be administered electronically via the site tablet at screening, (visit 1), week 0 (visit 2), week 12 (visit 5), week 24 (visit 8), EOT/ED week 52 (visit 15) and the follow-up visit (week 55 [visit 16]).

u. ePRO assessments are self-administered electronically via the site tablet at the study site at week 0 (visit 2), week 4 (visit 3), week 12 (visit 5), week 24 (visit 8) and week 52 (visit 15). The ePRO assessments are administered before any other study assessments/procedures are performed; assessments at visit 2 must occur prior to randomization/first dosing; assessments at week 4 (visit 3), week 12 (visit 5), week 24 (visit 8) must occur prior to dosing; in the event a subject withdraws from the study, efforts to collect information on the site-based subject-reported outcome measures should be made before or shortly after discontinuation.

v. Subjects will be assigned study drug as a kit containing either fezolinetant or placebo. Study drug intake will be done with a glass of room temperature tap water. The first intake of study drug will take place at the study site on day 1 (visit 2) under the supervision of the study staff. On study visit days (except for EOT/ED week 52 [visit 15]), the daily dose of study drug will be taken at the study site, under the supervision of the study staff, after collection of predose blood samples. On all other days throughout the treatment period, subjects will be instructed to take their study drug at home, in the morning with water.

w. Subjects will be asked to return all unused study drug. Compliance of study drug intake will be assessed by counting returned study drug and recorded in the source documents and the IRT.

x. AEs and intake of concomitant medication(s) will be monitored continuously from informed consent until the last study-related activity.

y. Screening (visit 1), Randomization, week 0 (visit 2) and EOT/ED week 52 (visit 15) visits, must be conducted in the clinic and not home healthcare, telemedicine conferences or a local laboratory.

1 INTRODUCTION

1.1 Introduction to Fezolinetant

Fezolinetant is a small-molecule, selective neurokinin-3 receptor (NK3R) antagonist currently being developed as an innovative non-hormonal treatment specifically targeting the cause of vasomotor symptoms (VMS) in postmenopausal women (menopause-related vasomotor symptoms [MR-VMS]).

For more information, refer to the Investigator's Brochure (IB) for fezolinetant.

1.2 Background

1.2.1 Vasomotor Symptoms (Hot Flashes): Epidemiology and Etiology

VMS, commonly known as hot flashes (HFs), are the most common complaint among women entering menopause and for many women, may continue to occur for up to 5 years (although around 20% of women will continue to experience them for up to 15 years) [Stearns et al, 2003; Rossouw et al, 2002; Kronenberg, 1994]. The large prospective cohort Study of Women's Health Across the Nation found that overall prevalence of VMS was approximately 70% [Thurston & Joffe, 2011].

VMS can have a significant negative impact on quality of life and are therefore a major reason for menopausal women to seek medical attention. Despite the vast numbers of individuals affected, the physiology of VMS is not fully understood, although a disturbance in normal thermoregulatory function is thought to be the main underlying cause. The primary presentation of VMS is a subjective and transient sensation of heat, flushing and sweating that usually last 4 to 10 min and may be followed by a feeling of being chilled. VMS may be accompanied by palpitations, feelings of anxiety and sleep disruption leading to fatigue or irritability; in rare occurrence, panic may occur [Kronenberg et al, 1994; Kronenberg et al, 1990].

The most effective and commonly used treatment for VMS is hormone replacement therapy (HRT), but a Women's Health Initiative study raised questions about the long-term safety of this treatment [Rossouw et al, 2002]. Thus, current guidelines recommend a limited duration of HRT due to associated risks of breast cancer (BC), coronary artery disease, stroke and thromboembolism [de Villiers et al, 2016; Rossouw et al, 2002]. Furthermore, the current safety data do not support the use of HRT in several groups of patients (e.g., those with BC/endometrial cancer, liver disease). The perceived limitations of HRT, coupled with the limited efficacy and adverse effects observed with nonhormonal therapies (e.g., selective serotonin reuptake inhibitors) have led clinicians to search for other treatment options for VMS. One selective serotonin reuptake inhibitor is approved in the US for the treatment of MR-VMS (Brisdelle®, low dose paroxetine). Studies of venlafaxine and fluoxetine in women with a prior history of BC have suggested that certain antidepressants with the ability to inhibit serotonin reuptake may significantly reduce MR-VMS [Loprinzi et al, 2002; Loprinzi et al, 2000; Stearns et al, 2000].

Over the past 20 years, a growing body of evidence has implicated neurokinin B (NKB) NK3R signaling in the etiology of menopausal VMS. Recent advances in the field have

demonstrated that the gonadotropin-releasing hormone (GnRH) pulse frequency is modulated by the kisspeptin/neurokinin B/dynorphin (KNDy) neurons (also known as 'KiSS Neuron') in the arcuate nucleus of the hypothalamus [Millar & Newton, 2013]. Neuroanatomical studies have shown that these neurons are sensitive to NKB/NK3R signaling [Hrabovszky, 2014]. By studying brain specimens at post mortem, [Rance & Young, 1991] initially showed that in postmenopausal women, hypothalamic neurons are hypertrophied and have increased NKB gene expression and neuronal activity compared with premenopausal women. This was also found to be true in ovariectomized monkeys but moreover, this change could be reversed by treatment with sex steroid replacement thus suggesting this was a dynamic change in response to reduced circulating concentrations of estradiol (E2) as occurs in the menopause [Rance, 2009]. Subsequent work in rats highlighted the importance of the hypothalamic median pre-optic nucleus in the propagation of the NKB-mediated signal that results in VMS [Rance et al, 2013]. The median pre-optic nucleus is a neural area that receives input from, and projects to, the autonomic thermoregulatory pathway, expresses NK3R and hence results in activation of heat dissipation effectors that characterize VMS. Importantly, estrogen also acts directly on the estrogen receptor alpha expressed on KNDy neurons to decrease similarly KNDy neuron activity [Ruka et al, 2016; Lehman et al, 2010]. Additionally, Crandall et al. recently found that genetic variation in tachykinin receptor 3, which is the gene that encodes NK3R, may account for the variability in experience of VMS reported among women [Crandall et al, 2017].

1.3 Fezolinetant Nonclinical and Clinical Data

1.3.1 Summary of Nonclinical Studies

In vitro studies demonstrated that fezolinetant is a potent full inhibitor of human neurokinin 3 (hNK3) receptor and is highly selective for hNK3 in comparison to the other members of tachykinin receptor family (hNK 1 and hNK) and other G-protein coupled receptors including the ones known to be implicated in modulation of GnRH axis.

In vivo animal pharmacology studies have been focused on the effects of fezolinetant on reproductive hormones. These studies demonstrated that fezolinetant significantly reduces plasma luteinizing hormone (LH) levels in castrate male rats at a dose range of 3 to 20 mg/kg.

In ovariectomized female rats, fezolinetant significantly reduced the mean plasma levels and pulsatile LH secretion frequency and amplitude at 10 mg/kg dosage. Fezolinetant significantly reduced circulating LH levels in castrate male monkeys following single and 5-day repeated oral dosing at 5 mg/kg per day. After 5 consecutive days of dosing, fezolinetant had no effect on plasma follicle-stimulating hormone (FSH) levels, demonstrating that antagonism of the neurokinin 3 receptor is a means to selectively inhibit LH, but not FSH.

More information including details on the toxicological studies can be found in the IB.

1.3.2 Summary of Clinical Studies

To date, 10 clinical studies have been completed with fezolinetant; 6 phase 1 studies (ESN364-CPK-101, ESN364-CPK-102, ESN364-CPK-103, 2693-CL-0020, 2693-CL-0006 and 2693-CL-009) and 4 phase 2 studies (ESN364-HF-204, ESN364-UF-02, ESN364-PCO-201 and ESN364_HF_205). Two of the 4 phase 2 studies were performed in women with MR-VMS (Studies ESN364_HF_204 and ESN364_HF_205). The 10 completed studies with fezolinetant are shown in Table 2.

The pharmacokinetics of fezolinetant were characterized in studies in healthy subjects and in patients with VMS. After oral intake, fezolinetant showed generally dose proportional pharmacokinetics at doses between 20 and 60 mg once daily in female subjects. Maximum concentration (C_{max}) was generally reached within 1 to 4 hours postdose with terminal half-life ranging between 4-6 hours in healthy subjects and patients. With a once daily dose regimen, steady state plasma concentrations were achieved by approximately day 2 with minimal accumulation. Low plasma protein binding of fezolinetant (50%) was observed with almost equal distribution of fezolinetant into red blood cells and plasma, with a blood-to-plasma ratio of 0.9.

Fezolinetant undergoes extensive metabolism, primarily by cytochrome P450 (CYP) 1A2 enzyme, to form the major metabolite ES259564. A strong CYP1A2 inhibitor (fluvoxamine) increased fezolinetant area under the concentration-time curve (AUC) and C_{max} approximately 9-fold and 1.8-fold, respectively, while smoking was shown to decrease AUC and C_{max} to a geometric least squares mean ratio of 48.3% and 71.7%, respectively (2693-CL-0006).

In a recently completed mass balance study (ESN364_CPK_103), the routes of excretion of fezolinetant were found to be via urine (76.9%) and feces (14.7%). In urine, a mean of 1.1% of the administered fezolinetant dose was excreted unchanged and 61.7% of the administered dose was excreted as metabolite ES259564.

Fezolinetant did not show clinically significant food effects on its pharmacokinetic exposure parameters (ESN364_CPK_101). Based on population pharmacokinetic modeling analyses, body weight was not identified as an important predictor of AUC. However, male subjects are predicted to have 53.2% reduction AUC and 14.9% reduction in C_{max}, compared to females. Asian population was predicted to have a 25% increase in steady-state C_{max} and AUC, which is consistent with clinical observations (Study 2693-CL-0020)

Based on a recently completed relative bioavailability study (2693-CL-0009), the tablet formulation showed slightly higher pharmacokinetic exposure (approximately 8% higher for $AUC_{0\text{-}inf}$ and 23% higher for C_{max}) than capsule formulation.

Table 2 Completed Studies with Fezolinetant

Study Number	Development Phase	Description	Location	Number of Subjects/Patients Randomized
ESN364-CPK-101	1	First-in-human study. Single and multiple ascending doses from 3 to 180 mg tested in 65 healthy males and females	Belgium	SAD: Fezolinetant = 12 Placebo = 4 MAD: Fezolinetant = 36 Placebo = 12
ESN364-CPK-102	1	180 to 900 mg single doses and up to 720 mg per day for 7 days in healthy males and females	Belgium	SAD: Fezolinetant = 18 Placebo = 6 MAD: Fezolinetant = 12 Placebo = 4
ESN364-CPK-103	1	^{14}C-ESN-364 (270 µg) ADME study in healthy postmenopausal females	Netherlands	Fezolinetant = 5
2693-CL-0020	1	Placebo-controlled, single and multiple oral dose study in healthy Japanese male and healthy Japanese pre- and postmenopausal female subjects	Japan	(Blinded) Fezolinetant = 33 Placebo = 11
2693-CL-0009	1	A randomized crossover study to assess the relative bioavailability of ESN364 following a single dose of tablet formulation compared to a single dose of capsule formulation in healthy postmenopausal female subjects	US	Fezolinetant = 16
2693-CL-0006	1	"A Phase 1 Study to Assess the Effect of Multiple Doses of Fluvoxamine and Smoking on the Single Dose Pharmacokinetics of ESN364 in Healthy Postmenopausal Female Subjects"	Germany	(Open-label) Fezolinetant = 18
ESN364_HF_204	2a	Proof of concept study in MR-VMS	Belgium	Fezolinetant 90 mg twice daily = 43 Placebo = 44

Table continued on next page

Study Number	Development Phase	Description	Location	Number of Subjects/Patients Randomized
ESN364-UF-02	2a	Proof of concept study in heavy menstrual bleeding due to uterine fibroids	EU	Fezolinetant 60 mg once daily = 10 Fezolinetant 180 mg once daily = 6 Placebo = 7
ESN364-PCO-201	2a	Proof of concept study in polycystic ovary syndrome	EU	Fezolinetant 60 mg once daily = 23 Fezolinetant 180 mg once daily = 23 Placebo = 27
ESN364_HF_205	2b	Dose ranging study in menopausal VMS	US	Fezolinetant 15 mg twice daily = 45 Fezolinetant 30 mg twice daily = 44 Fezolinetant 60 mg twice daily = 45 Fezolinetant 90 mg twice daily = 44 Fezolinetant 30 mg once daily = 45 Fezolinetant 60 mg once daily = 45 Fezolinetant 120 mg once daily = 44 Placebo = 44

ADME: absorption, distribution, metabolism and excretion; MAD: multiple ascending dose; MR-VMS: Menopause-Related Vasomotor Symptoms; SAD: single ascending dose; VMS: vasomotor symptoms.
Source: Fezolinetant (ESN-364) Investigator's Brochure.

Study ESN364_HF_204 was a 12-week double-blind, placebo-controlled, parallel-group, multicenter, proof of concept study to assess the effect of 12-week administration of fezolinetant in early postmenopausal women suffering from HFs. A total of 80 patients, 40 in each treatment group, completed the entire study. In this study, the mean HF frequency for the moderate and severe VMS at weeks 4 and 12 reduced by approximately 88% and 93% from baseline compared to a placebo decrease of 38% and 46%, respectively ($P < 0.001$). The mean HF score for the moderate and severe VMS at weeks 4 and 12 dropped approximately 89% and 94% from baseline compared to a placebo decrease of 38% and 46%, respectively ($P < 0.001$). Most often a statistically significant difference between the fezolinetant and placebo group was observed after only 1 week of treatment, demonstrating a very rapid onset.

Study ESN364_HF_205 was a 12-week double-blind, placebo-controlled, parallel-group, multicenter, dose-ranging study to assess the effect of 12-week administration of once daily and twice daily doses of fezolinetant in early postmenopausal women suffering from HFs (8 arm study). A total of 356 subjects were randomized into this study with 43 to 45 subjects in each treatment group. There was a clinically relevant treatment effect observed at multiple doses. All groups were significantly different from placebo with respect to mean change in

the frequency of moderate to severe VMS at both weeks 4 and 12. The improvement relative to placebo at weeks 4 and 12 was greater than 2 HFs per day, indicative of a clinically relevant improvement, for all dose groups except 15 mg twice daily. All groups were significantly different from placebo with respect to mean change in the severity of moderate to severe VMS from baseline to week 4, but only 60 mg twice daily, 90 mg twice daily and 60 mg once daily demonstrated significance at week 12 in this study.

These data provide clinical evidence that, via antagonism of increased KNDy neuronal activity, fezolinetant produces a marked clinically significant reduction in VMS related the menopause and is very likely to exhibit similar activity in other hypoestrogenic states such as occur in women undergoing hormonal treatment for BC. More information can be found in the IB.

1.4 Summary of Key Safety Information for Fezolinetant

1.4.1 Nonclinical studies

In the nonclinical toxicology studies in rats and monkeys, fezolinetant was well tolerated and the no observed adverse event level (NOAEL) was considered to be 25 mg/kg per day in Cynomolgus monkeys as the most relevant species. Drug exposure (area under the curve) at this dose level in Cynomolgus monkey was similar to drug exposure levels measured in premenopausal women dosed at 540 mg/day. The main events that were observed in the nonclinical studies were considered to be related to the pharmacology of fezolinetant, including reduction of the ovarian activity in female monkeys.

Liver hypertrophy without increases in alanine aminotransferase (ALT) and bilirubin seen in rats was related to enzyme induction since this finding coincided with thyroid follicular cell hypertrophy. The liver finding is generally regarded as not predictive for humans. The NOAEL was 10 mg/kg. In monkeys, no liver changes were seen.

Adverse effects were observed at the high doses used in the nonclinical studies, at dose levels much higher than the clinical dosages. In monkeys, high doses of fezolinetant resulted in weight loss and a reduction in platelet counts, which resulted in observations of hemorrhage and regenerative anemia; these effects were recoverable with discontinuation of dosing. In rats, very high dose levels were associated with death and marked clinical signs and body weight loss during the first few days of treatment.

Exposure to the main human metabolite ES259564 was evaluated in the long-term toxicity studies in rats and monkeys and the metabolite is considered to be toxicologically qualified up to the human dose of 180 mg/day.

Fezolinetant did not show any genotoxic potential.

Reproductive toxicology studies on both rats and rabbits demonstrated significant litter loss in both animal species; however, the surviving embryos did not show any adverse effect on development. The litter loss in this case is regarded as a pharmacologic effect on the hormonal and reproductive status. A fertility and early embryonic development study was also

completed in female rats without any reported adverse events (AEs; NOAEL = 100 mg/kg per day).

1.4.2 Clinical Studies

The most frequently reported treatment-emergent adverse events (TEAEs) (i.e., in > 2 subjects [> 33.3%] per treatment group) following multiple ascending dosing for 21 days in healthy female subjects in the first in human study (ESN364-CPK-101) were: abdominal pain in 3 (50.0%) subjects each in placebo and in 180 mg fezolinetant treatment groups, nausea in 3 (50.0%) subjects in the 20 mg fezolinetant treatment group, headache in 3 (50.0%) and 4 (66.7%) subjects in the 60 and 180 fezolinetant treatment groups, respectively, and dry skin in 3 (50.0%) subjects in the 180 mg fezolinetant treatment group. The events of nausea and headache were only reported in the 20, 60 and/or 180 mg fezolinetant treatment groups and not in the placebo group. Clinical observations related to sex hormones were due to the mode of action of the investigational medicinal product: fezolinetant resulted in prolongation of the menstrual cycle in females for the first cycle after dosing for the 60 mg and 180 mg dose levels, with a median change from baseline of 7.5 and 9.5 days, respectively. Once withdrawn from the study drug, the normal menstrual cycle resumed immediately with cycle lengths comparable to the predose menstrual cycle.

The most frequent TEAEs (in > 2 [12.5%] subjects in the fezolinetant total group [16 subjects]) in the single dose Part 1 of the subsequent dose ranging phase 1 study (ESN364-CPK-102), were headache, paresthesia and nausea. The highest incidence for headache was after 360 and 900 mg intake, for paresthesia after 540 and 900 mg intake and for nausea after 900 mg intake. A severe headache was reported after 900 mg fezolinetant intake. Based on the results from Part 1, the maximum tolerated dose was considered to be 900 mg based on the occurrence of AEs (oral paraesthesia and severe headache). In the multiple dose administration (7 days) Part 2 in healthy female volunteers, the most frequent TEAEs (in > 2 [16.7%] subjects in the fezolinetant total group [540 and 720 mg combined]) were headache (4 [33.3%] subjects) and vaginal hemorrhage (3 [25.0%] subjects). In the single dose administration Part 3 in healthy male volunteers, the most frequent TEAE (in > 2 [28.6%] subjects in the fezolinetant total treatment groups [720 and 900 mg]) was oral paraesthesia (3 [42.9%] subjects).

The most frequently reported TEAEs in the phase 2a study (ESN364_HF_204) reported in > 2 patients in the fezolinetant group [90 mg bid]) were headache, palpitations, diarrhea and influenza. All TEAEs were at most moderate in severity. Treatment-related TEAEs were reported in 13 (30.2%) patients in the fezolinetant group and in 11 (25.0%) patients in the placebo group. Most treatment-related TEAEs were gastrointestinal disorders (abdominal discomfort, diarrhea and oral paraesthesia) reported in 6 (14.0%) patients in the fezolinetant group and 0 patients in the placebo group. Two patients discontinued treatment in the fezolinetant group (for 1 patient due to the TEAE fibromyalgia, depression, dry mouth, headache, palpitations, diarrhea and vomiting: and for 1 patient due to the TEAE headache and vertigo). None of the subjects in the placebo group permanently stopped the study medication due to a TEAE.

In the phase 2b ESN364_HF_205 study, overall fezolinetant was well tolerated. During this study the rates of TEAEs were comparable across all groups and most events were mild or moderate in severity. No deaths or treatment-related serious adverse events (SAEs) were reported.

The most common Medical Dictionary for Regulatory Activities (MedDRA) system organ classes (SOCs; ≥ 10% patients in any arm) in which TEAEs were reported were: gastrointestinal disorders, infections and infestations, general disorders and administration site conditions, investigations, nervous system disorders and skin and subcutaneous tissue disorders.

The active dose groups had a higher proportion of TEAEs reported as drug-related, but only 2 patients had severe drug-related TEAEs. TEAEs leading to discontinuations were reported in small numbers of patients across the treatment groups. A total of 5 patients discontinued due to changes in liver enzymes following ESN364; no discontinuations due to changes in liver enzymes occurred following placebo treatment.

Of the TEAEs of special interest, there was 1 patient with oral paresthesia (in the 30 mg bid group) and a few isolated cases of uterine bleeding with no reports of endometrial hyperplasia. There were 9 patients with ALT or AST > 3 × upper limit of normal (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 (TBL) > 2 × ULN, and consequently no Hy's law cases.

There were no clinically meaningful changes in hematology, coagulation, vital signs, electrocardiograms (ECG), bone turnover markers, endometrial assessments, or suicide status.

Overall in the clinical program to date, including indications other than MR-VMS, 7 treatment-emergent SAEs have been reported. These SAEs were assessed as not related to the study medication, except for a case of superficial thrombophlebitis reported in the phase 2a study in polycystic ovary syndrome (ESN364-PCO-201), which was assessed by the investigator as possibly related to the study medication; the study drug was interrupted and reinitiated after the event had resolved, with no recurrence of the event.

Given the limited safety information with fezolinetant, there are no expected serious adverse reactions (SARs) at the start of the phase 3 program. For up to date information regarding expected SARs, refer to the Reference Safety Information (RSI). The RSI for fezolinetant is contained in the IB, Section 5.3.2 Expected Serious Adverse Drug Reactions.

1.5 Risk Benefit Assessment

Fezolinetant is currently being developed for the treatment of VMS associated with the menopause (MR-VMS).

Based on recent advances in science, as well as the clinical data derived from 2 phase 2 clinical studies in women with VMS associated with the menopause, there are positive reasons to believe that fezolinetant can be an effective treatment for MR-VMS and treatment-resistant VMS.

When given to normally cycling healthy women, fezolinetant is capable of altering the menstrual cycle and decreasing the circulating levels of E2, LH, progesterone (P4) and testosterone. Since this study aims to include menopausal women, these effects will be of less importance because of the physiological changes that happen in the climacterium (anovulation with loss of P4 and E2 production and consequently increase of LH/FSH).

In terms of hormonal changes, a mild to moderate decrease of the already elevated LH and FSH plasma levels is anticipated. There are no known risks associated with this decrease of the gonadotropins in menopausal women.

Treatment with fezolinetant can cause adverse effects or other symptoms. Adverse effects that can be expected are those AEs that presented in fezolinetant clinical studies in healthy male and female volunteers, as well as in menopausal women.

Details of the AE profile from the completed clinical studies are presented in [Section 1.3 Fezolinetant Nonclinical and Clinical Data].

Across the completed phase 1 and 2a studies, there have been a small number of mild, transitory transaminase elevations observed both in patients/subjects who received either fezolinetant or placebo. There were no incidences of raised TBL and none of the patients/subjects experienced associated symptoms. In the recently completed phase 2b study ESN364_HF_205, transitory increases in transaminase enzymes, ALT/aspartate aminotransferase (AST), have been reported in 7 subjects between 4 and 8 weeks after start of study treatment and in 2 unique subjects during study follow-up. Subjects were reported to be asymptomatic throughout and there was no evidence of functional liver impairment. Although there were cases with evidence of significant underlying hepatic conditions and other confounding factors, independent expert review of the cases that met a stopping rule concluded that the study drug was probably the cause of the increased transaminase levels. In all cases, transaminase enzyme levels rapidly decreased, in 2 cases during continuing treatment with study medication.

Based on cases of increased AST and ALT > 5 × ULN in the phase 2b study ESN364_HF_205 that were assessed by external hepatic experts as related to the use of fezolinetant, liver injury has been categorized as an important potential risk. Monitoring of liver parameters is incorporated in the design of this protocol, including individual patient stopping rules and liver assessment per [Section 12.5]. Increased transaminases have not been observed at the dose selected for this study, i.e., 30 mg fezolinetant once daily [Section 2.2.2 Dose Rationale].

Severe thrombocytopenia has been reported in non-clinical studies but not in clinical studies and has been categorized as an important potential risk. To date, 1 clinical case of mind, pre-existing, thrombocytopenia has been reported (in phase 2a Study ESN364_HF_204). Platelet counts are included in the hematological monitoring during the course of the study.

Circumoral paresthesia has been reported by several subjects taking fezolinetant. Considering the reported cases in the phase 1 studies (ESN364-CPK-101 and ESN364-CPK-102) the occurrence of circumoral paresthesia is dose dependent for both intensity and duration,

usually starting within the first hour after drug intake, relatively short-lasting, with higher doses leading to a more intense and prolonged sensation. This type of paresthesia has been described as either plain paresthesia (oral, facial skin, tongue, scalp, lips), as a prickling sensation of the face, as a numbness of the tongue or as a tingling sensation (face, mouth, tongue).

Circumoral paraesthesia has been recognized in the clinical studies and categorized as a non-important identified risk. No specific additional monitoring is recommended.

Overall, the potential benefits of subjects receiving 30 mg or 45 mg once daily fezolinetant are considered to outweigh the potential risks. Although an important medical condition, VMS are not considered life-threatening and 52-week placebo treatment, which is also associated with improvement in VMS, is justifiable.

2 STUDY OBJECTIVE(S), DESIGN, AND ENDPOINTS

2.1 Study Objective(s)

2.1.1 Primary Objective

- To evaluate the long-term safety and tolerability of fezolinetant in women seeking treatment for relief of VMS associated with menopause.
- To evaluate the effect of fezolinetant on endometrial health after long-term treatment in women seeking treatment for relief of VMS associated with menopause.

2.1.2 Secondary Objective

- To evaluate the effect of fezolinetant on bone mineral density after long-term treatment in women seeking treatment for relief of VMS associated with menopause.

2.1.3 Exploratory Objectives

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

2.2 Study Design and Dose Rationale

2.2.1 Study Design

This is a 52-week randomized, placebo-controlled, double-blind, parallel-group, multicenter clinical study to assess the safety and tolerability of fezolinetant in women seeking treatment for VMS associated with menopause. The study visits will be performed on an outpatient basis.

This study will consist of a screening period (days -35 to -1, including the screening visit [visit 1] assessments), a 52 week treatment period (day 1 [visit 2] to week 52 [visit 15]) and a follow up visit (week 55 [visit 16]) 3 weeks after the last dose of study drug. An extra 15 screening days are allowed for repeat biopsy, if necessary (days -50 to -1, including the screening visit [visit 1] assessments).

The screening visit (visit 1) will occur up to 35 days prior to treatment initiation. Eligibility will be assessed via physical examination, clinical laboratory testing, urine pregnancy test, vital signs, ECG, Papanicolaou (Pap) test (or equivalent cervical cytology), mammography,

transvaginal ultrasound (TVU) and endometrial biopsy. To participate in the study, subjects must be seeking medical treatment for relief of VMS.

Subjects may be retested for assessments up to 1 time upon approval of the medical monitor within the current 35-day screening window and will retain the same subject screening identification number.

Subjects may be rescreened in this study, which will result in a new 35-day screening window and a new subject screening identification number, up to 1 time upon approval of the medical monitor. The following assessments do not need to be repeated at the rescreen provided they fall within the acceptable procedure completed time frame and all results meet inclusion and no exclusion criteria: TVU (acceptable 3 months from date of procedure); dual-energy X-ray absorptiometry (DXA) (acceptable 3 months from date of procedure); endometrial biopsy (acceptable 3 months from date of procedure); subject has documentation of a normal/negative or no clinically significant mammogram findings (obtained at screening or within the prior 12 months of trial enrollment [appropriate documentation includes a written report or an electronic report indicating normal/negative or no clinically significant mammographic findings]), ECG (acceptable 3 months from procedure); and documentation of a normal or not clinically significant Pap test (or equivalent cervical cytology) in the opinion of the investigator within the previous 12 months. Subjects who screen failed due to COVID-19 pandemic study suspension and have a documented evaluable endometrial biopsy from the original screening period do not have to undergo a repeat biopsy should they decide to rescreen.

Subjects who screened for the 2693-CL-0301 or the 2693-CL-0302 study who did not meet the minimum requirement for frequency and severity of VMS prior to randomization may be consented and screened for this study with a new 35-day screening window from the time of consent. For these subjects the following assessments that were completed and/or assessed do not need to be repeated provided they fall within the acceptable procedure completed time frame and all results meet inclusion and no exclusion criteria: TVU (acceptable 3 months from procedure); endometrial biopsy (acceptable 3 months from procedure); subject has documentation of a normal/negative or no clinically significant mammogram findings (obtained at screening or within the prior 12 months of trial enrollment [appropriate documentation includes a written report or an electronic report indicating normal/negative or no clinically significant mammographic findings]); ECG (acceptable 3 months from procedure); and documentation of a normal or not clinically significant Pap test (or equivalent cervical cytology) in the opinion of the investigator within the previous 12 months. These subjects will have to repeat screening labs and complete DXA procedure requirements.

A suction endometrial biopsy will be performed any time during the study in the case of uterine bleeding, in addition to the protocol-required time points.

At the end of treatment (EOT) (or the early discontinuation [ED] visit for subjects who withdraw from the study prior to completion), a TVU and a suction endometrial biopsy will be required. If a subject discontinues from the study, an endometrial biopsy is required at the discontinuation visit along with all other EOT procedures. During the treatment period, any

woman with an abnormal endometrial biopsy reported as disordered proliferative endometrium, endometrial hyperplasia or endometrial cancer will be referred to standard of care clinical management and followed to resolution, and the report of any medical or surgical procedures and the resultant pathology will be obtained. The investigator should record any such biopsy, and the associated diagnostic and therapeutic measures, as an AE. A mammogram at week 52/EOT/ED will be conducted if it coincides with the regularly scheduled routine screening mammogram of the patient, in accordance with local medical practice guidelines and the patient's primary care physician.

During the treatment period, subjects will return to the study site as indicated in the Schedule of Assessments [Table 1 Schedule of Assessments]. Site-based patient-related outcome (PRO) measures will be self-administered via an electronic device as indicated in the Schedule of Assessments. All assessments must be performed at the site and prior to all other required visit procedures. In the event a subject withdraws from the study prior to completion, all efforts to collect information on the site-based PRO measures should be made before or shortly after withdrawal.

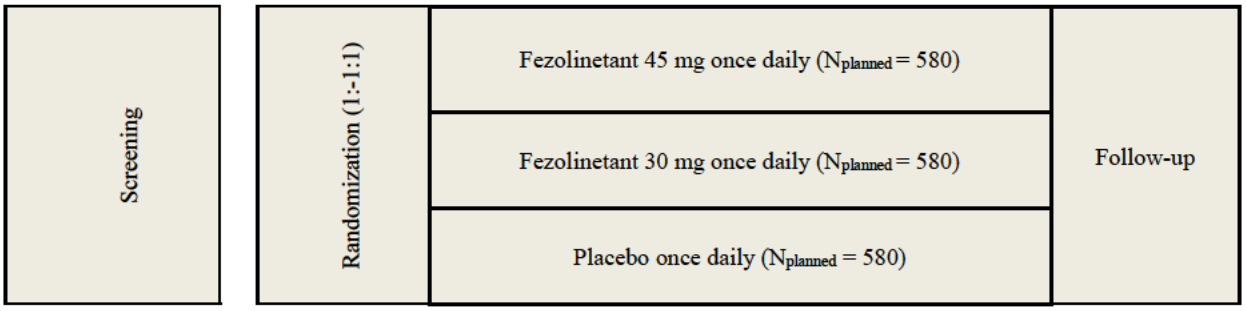
Following the completion of the treatment period (week 52 or ED), subjects will complete an EOT (or ED) visit and final safety follow-up visit 3 weeks after the last dose of study drug is administered (week 55 or 3 weeks following ED).

A Data Monitoring Committee (DMC) will oversee the safety of fezolinetant for the duration of the study.

The study drug will not be provided after study completion of the study without written approval from the sponsor.

Approximately 1740 total subjects will be randomized into the study. Subjects will be randomized 1:1:1 into the following treatment groups:

- Fezolinetant 30 mg once daily (approximately 580 subjects)
- Fezolinetant 45 mg once daily (approximately 580 subjects)
- Placebo once daily (approximately 580 subjects)



a. Screening is to be performed up to 35 days prior to randomization.

FU: follow-up; V: visit.

* Refer to the schedule of assessments for visit 2b.

COVID-19 Consideration:

All attempts should be made to conduct the protocol-defined scheduled visits. In cases where a subject is unable to visit the clinic due to site closure related to the COVID-19 pandemic, the following alternative measures may be implemented to ensure subject safety and continuity of care while participating in the study:

- Telemedicine Conferences (telephone visits) to evaluate changes in a subject's medical condition or medications and completion of electronic patient-reported outcome questionnaires following the process defined in the *Notification of Pause and Screening Enrollment* memo released on 27 March 2020 provided to the site by the sponsor.
- Safety laboratory tests collected at a local lab including biochemistry, hematology, liver biochemistry and coagulation panel testing.
- Home healthcare services may be available in cases where arrangements are made in advance by the site upon request from the subject(s)

Due to the nature of the Screening (visit 1), Randomization, week 0 (visit 2) and EOT/ED week 52 (visit 15) visits, which include important study procedures, these visits must be conducted in the clinic. All other visits during the COVID-19 pandemic may be conducted utilizing all or some of the following services: home healthcare, telemedicine conferences (telephone visits) or safety laboratory tests collected at a local laboratory.

Subjects who screen failed due to the COVID-19 pandemic study suspension and have a documented evaluable endometrial biopsy from the original screening period do not have to undergo a repeat biopsy should they decide to rescreen.

2.2.2 Dose Rationale

A phase 2b dose-ranging study (ESN364_HF_205) assessing the effects of the potent and selective NK3 antagonist, fezolinetant, on VMS in post-menopausal females was recently completed.

From the ESN364_HF_205 study, 352 subjects were randomized and received at least 1 dose of study drug, 287 (81%) completed the study (placebo: 84%; fezolinetant: 80%). Discontinuations occurred most commonly for withdrawal of consent (6.7%) and AEs (5.9%).

The 4 co-primary efficacy endpoints for ESN364_HF_205 included the mean change in frequency and severity of moderate-to-severe VMS at weeks 4 and 12. VMS frequency and severity at weeks 4 and 12 were reduced in all fezolinetant groups. Differences from placebo in least squares mean changes from baseline in VMS daily frequency at week 4 were -1.9, -3.0, -2.8 and -3.5 for 15, 30, 60 and 90 mg twice daily and -2.3, -3.0 and -2.4 for 30, 60 and 120 mg once daily, respectively (common SE: 0.8; all $P < 0.05$, from a pairwise comparison against placebo without multiplicity adjustment). Differences at week 12 were -1.8, -2.1, -2.3, -2.6 and -2.1, -2.6, -2.1, respectively (common SE: approximately 0.7; all $P < 0.05$ from a pairwise comparison against placebo without multiplicity adjustment). The improvement relative to placebo at weeks 4 and 12 was greater than 2, indicative of a clinically meaningful improvement, for all dose groups except 15 mg twice daily. For HF severity, all treatment groups were statistically significant compared to placebo at week 4, while only the 60 mg twice daily, 90 mg twice daily and 60 mg once daily were statistically different from placebo at week 12. Unlike frequency, a clinically meaningful improvement in HF severity has not been established.

Fezolinetant was generally well-tolerated. No deaths or treatment-related serious adverse events (SAEs) were reported. The rates of TEAEs were comparable across groups and were mostly mild and moderate; however, overall the active dose groups had a higher proportion of AEs reported as treatment-related assessed by the site investigators. Nine subjects had ALT or AST elevations > 3 × ULN. There were no cases of TBL > 2 × ULN. Seven of the 9 subjects with transaminase elevations received total daily doses of 120 mg or greater.

A relationship between fezolinetant exposure (dose and concentration) and the incidence of liver parameter elevations appears to be present. Individual predicted exposures for subjects with transaminase elevations > 3 × ULN were compared to the broader distribution of fezolinetant exposure by treatment group. Subjects with ALT or AST elevations > 3 × ULN generally had steady-state C_{max} and C_{avg} concentrations toward the higher end of the distribution for each dose group. Most cases of ALT or AST elevations > 3 × ULN occurred at fezolinetant exposures anticipated from 120 mg total daily doses or higher. Two subjects receiving a 60 mg total daily dose (1 in 30 mg bid and 1 in 60 mg qd) experienced ALT or AST elevations > 3 × ULN. The subject in the 60 mg once daily dose group had an average concentration consistent with the 75% percentile of exposure for the 120 mg total daily dose. The transaminase elevation for the subject in the 30 mg twice daily group occurred at the follow-up visit, 3 weeks after the last dose. The subject had normal liver parameters throughout the study and the elevation was considered to be unlikely related to study drug.

Dose- and concentration-response models were developed to identify the minimum effective dose and the exposure-response relationship. Both the dose-response (Multiple Comparison Procedure – Modeling) and concentration-response (nonlinear mixed-effects models) analyses demonstrated increased improvements in HF frequency and HF severity with

increasing fezolinetant exposure. No clinically relevant difference was noted between predicted efficacy (frequency or severity) for the once daily and twice daily regimen given the same total daily dose.

Modeling and simulation suggests that although baseline does not impact the percentage reduction in HF frequency, it does impact the placebo-corrected change from baseline. In Study ESN364_HF_205, subjects were eligible for enrolment if they experienced more than an average 7 HFs per day over a week during the screening period; however, during the specific baseline period used for the analysis purpose, the same criterions was not required. This resulted in a decreased mean baseline compared to historical studies. At week 12, the model predicts a mean placebo-corrected change from baseline reduction in HF frequency of -1.74 and -1.95 for the 30 mg once daily and 45 mg once daily doses, respectively, at a mean baseline of 9.5 HFs per day. At a mean baseline more consistent with historical studies, the mean predicted placebo-corrected change from baseline reduction in HF frequency for 30 mg and 45 mg once-daily doses is -2.11 and -2.37, respectively, at week 12. In summary, once daily doses of ≥ 30 mg are predicted to have clinically meaningful population mean reductions in HF frequency based on historical baseline values. For HF severity based on the moderate and severe HFs, the model predicted placebo-corrected change from baseline for 30 mg and 45 mg once-daily doses was -0.34 and -0.41, respectively, at week 12. Based on these predicted reductions in HF severity and the increased sample size planned in the phase 3 studies, these proposed doses are anticipated that a statistically significant reduction in HF severity can be achieved compared to placebo.

In addition to the dose- and exposure-response analyses, drug-induced liver injury modeling software (DILIsym®) modeling was undertaken to better characterize and understand the increase in elevated transaminases noted for 9 subjects in Study ESN364-HF_205 and the potential for drug-induced liver injury (DILI). DILIsym predicted no cases of elevated transaminases greater than 3 × ULN for the 30 mg, 45 mg or 60 mg once-daily treatment regimens.

Based on the efficacy results and modeling and simulation analyses, the 30 mg once-daily dosing regimen is considered the lowest effective dose. In addition, a 45 mg once-daily dose, while not previously studied, is predicted to increase the probability of achieving efficacy endpoints while limiting the risk of potential exposure related transaminase elevations and DILI.

2.3 Endpoints

2.3.1 Primary Endpoint

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

- Frequency and severity of AEs
- Percentage of subjects with endometrial hyperplasia.
- Percentage of subject with endometrial cancer.

2.3.2 Secondary Endpoints

- Change from baseline in endometrial thickness at 12 months.
- Percentage of subjects with disordered proliferative endometrium.
- Change from baseline in bone mass 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: hematology, biochemistry and urinalysis.
- C-SSRS.
- ECG parameters.

2.3.3 Exploratory Endpoints

- Mean change on the Menopause-Specific Quality of Life (MENQOL) Total Score from baseline to specified time points (week 4, 12, 24 and 52).
- Mean change on the MENQOL 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) Total Score from baseline to specified time points (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).

3 STUDY POPULATION

3.1 Selection of Study Population

The study population will comprise women ≥ 40 and ≤ 65 years of age seeking treatment for VMS associated with menopause.

3.2 Inclusion Criteria

Subjects who meet all of the following criteria will be eligible to participate in the study:

1. 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.
2. Subject is born female, aged ≥ 40 years and ≤ 65 years of age at the screening visit.
3. Subject has a body mass index ≥ 18 kg/m^2 and ≤ 38 kg/m^2
4. 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.

5. Subject is seeking treatment for relief for VMS associated with menopause.
6. 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; hematology and biochemistry parameters; pulse rate and/or blood pressure; and ECG within the reference range for the population studied, or showing no clinically relevant deviations, as judged by the investigator.
7. Subject has documentation of a normal/negative or no clinically significant mammogram findings (obtained at screening or within the prior 12 months of trial enrollment). Appropriate documentation includes a written report or an electronic report indicating normal/negative or no clinically significant mammographic findings.
8. Subject is willing to undergo a TVU to evaluate the uterus and ovaries at screening and at week 52 (EOT). For subjects who are withdrawn from the study prior to completion, a TVU should be collected at the ED visit.
9. Subject is willing to undergo an endometrial biopsy at screening and at week 52 (EOT) or the ED visit for subjects who are withdrawn from the study prior to completion, and any time during the study in the case of uterine bleeding. The endometrial biopsy obtained at screening must be considered evaluable.
10. 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 12 months or at screening.
11. Subject has a negative urine pregnancy test at screening.
12. Subject has a negative serology panel (i.e., negative hepatitis B surface antigen, negative hepatitis C virus antibody and negative human immunodeficiency virus antibody screens) at screening.
13. Subject agrees not to participate in another interventional study while participating in the present study.

Waivers to the inclusion criteria will **NOT** be allowed.

3.3 Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from participation in the study:

1. Subject uses a prohibited therapy (strong or moderate CYP1A2 inhibitors, HRT, hormonal contraceptive, any treatment for VMS [prescription, over the counter or herbal]) or is not willing to wash out and discontinue such drugs for the full extent of the study.

2. Subject has a known substance abuse or alcohol addiction within 6 months of screening, as assessed by investigator.
3. Subject has previous or current history of a malignant tumor, except for basal cell carcinoma.
4. Subject's systolic blood pressure is ≥ 130 mmHg or diastolic blood pressure is ≥ 80 mmHg based on the average of 2 to 3 readings on at least 2 different occasions within the screening period.
    - Subjects who do not meet the criteria may, at the discretion of the investigator, be re-assessed after initiation or review of antihypertensive measures.
    - Subjects with a medical history of hypertension can be enrolled at the discretion of the investigator once they are medically cleared (stable and compliant).
5. Subject has a history of severe allergy, hypersensitivity or intolerance to drugs in general, including the study drug and any of its excipients.
6. 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.
7. Subject has an endometrial biopsy confirming presence of disordered proliferative endometrium, endometrial hyperplasia, endometrial cancer or other clinically significant findings in the opinion of the investigator at screening.
8. Subject has a history within the last 6 months of undiagnosed uterine bleeding.
9. Subject has a history of seizures or other convulsive disorders.
10. Subject has a medical condition or chronic disease (including history of neurological [including cognitive], hepatic, renal, cardiovascular, gastrointestinal, pulmonary [e.g., moderate asthma], endocrine or gynecological disease) or malignancy that could confound interpretation of the study outcome in the opinion of the investigator.
11. Subject has active liver disease, jaundice, elevated liver aminotransferases (ALT or AST), elevated total or direct bilirubin (DBL), elevated International Normalized Ratio (INR), or elevated alkaline phosphatase (ALP). Patients with mildly elevated ALT or AST up to 1.5 times the upper limit of normal (ULN) can be enrolled if total and DBL are normal. Patients with mildly elevated ALP (up to 1.5 × ULN) can be enrolled if cholestatic liver disease is excluded and no cause other than fatty liver is diagnosed. Patients with Gilbert's syndrome with elevated TBL may be enrolled as long as DBL, hemoglobin, and reticulocytes are normal.
12. Subject has creatinine > 1.5 × ULN; or estimated glomerular filtration rate using the Modification of Diet in Renal Disease formula ≤ 59 mL/min per 1.73 m^2 at the screening visit.
13. Subject has a history of suicide attempt or suicidal behavior within the last 12 months or has suicidal ideation within the last 12 months (a response of "yes" to questions 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 the time of visit 2 (randomization).

14. Subject has previously been enrolled in a clinical trial with fezolinetant.
15. 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.
16. Subject is unable or unwilling to complete the study procedures.
17. Subject has any condition which, in the investigator's opinion, makes the subject unsuitable for study participation.
18. This criterion has been removed.
19. This criterion has been removed.
20. Subject has had a partial or full hysterectomy.

Waivers to the exclusion criteria will **NOT** be allowed.

4 TREATMENT

4.1 Identification of Investigational Products

4.1.1 Study Drug

Fezolinetant study drug will be supplied in a blinded form by Astellas as fezolinetant 30 mg and 45 mg once daily tablets.

4.1.2 Comparative Drug

Placebo for fezolinetant will be supplied by Astellas in a blinded form to match the active drug tablets.

4.2 Packaging and Labeling

All study drug(s) used in this study will be prepared, packaged and labeled under the responsibility of qualified staff at APGD or sponsor's designee in accordance with APGD or sponsor's designee standard operating procedures (SOPs), Good Manufacturing Practice (GMP) guidelines, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) guidelines and applicable local laws/regulations.

Each kit will bear a label conforming to regulatory guidelines, GMP and local laws and regulations that identifies the contents as investigational drug.

A qualified person of Astellas Pharma Europe B.V. or sponsor's designee will perform the final release of the medication according to the requirements of the European Union (EU) Directive 2003/94/EC annex 13.

4.3 Study Drug Handling

Current ICH GCP Guidelines require the investigator to ensure that study drug deliveries from the sponsor are received by the investigator or designee and that:

- Such deliveries are recorded;
- Study drug is handled and stored according to labeled storage conditions;
- Study drug with appropriate expiry/retest and is only dispensed to study subjects in accordance with the protocol; and
- Any unused study drug is returned to the sponsor.

Study drug inventory and accountability records will be kept by the investigator, or designee. Study drug accountability throughout the study must be documented and reconciled. The following guidelines are therefore pertinent:

- The investigator or designee agrees not to supply study drugs to any persons except the eligible subjects in this study in accordance with the protocol;
- The investigator or designee (i.e., study drug manager) will keep the study drugs in a pharmacy or other locked and secure storage facility under controlled storage conditions, accessible only to those authorized by the investigator to dispense these study drugs;
- A study drug inventory will be maintained by the investigator or designee (i.e., study drug manager). The inventory will include details of material received and a clear record of when they were dispensed and to which subject;
- At the conclusion or discontinuation of this study, the investigator or designee (i.e., study drug manager) agrees to conduct a final drug supply inventory and to record the results of this inventory on the Drug Accountability Record. It must be possible to reconcile delivery records with those of used and/or returned study drug. Any discrepancies must be accounted for and documented. Appropriate forms of deliveries and returns must be signed by the site staff delegated this responsibility;
- The site staff must return study drug to the sponsor or designee at the end of the study or upon expiration unless otherwise approved by the sponsor.

4.4 Blinding

4.4.1 Blinding Method

This is a double blind study. Subjects will be randomized to receive fezolinetant 45 mg, fezolinetant 30 mg, 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. The randomization number will be assigned based on information obtained from the Interactive Response Technology (IRT).

4.4.2 Confirmation of the Indistinguishability of the Study Drugs

The appearance and the form of both the drug and packaging of fezolinetant 45 mg, fezolinetant 30 mg and placebo are identical.

4.4.3 Retention of the Assignment Schedule and Procedures for Treatment Code Breaking

The randomization list and study medication blind will be maintained by the IRT system.

4.4.4 Breaking the Treatment Code for Emergency

The treatment code for each randomized subject will be provided by the IRT in the event of a medical emergency requiring knowledge of the treatment assigned to the subject. The IRT will be programmed with blind-breaking instructions that may only be requested by the investigator or subinvestigators designated to have access to perform blind-break. In case of a medical emergency, the investigator has the sole responsibility for determining if unblinding of subject's treatment assignment is warranted. Subject safety must always be the first consideration in making such determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the sponsor prior to unblinding a subject's treatment assignment unless this could delay emergency treatment for the subject.

The investigator must have confirmed functionality to access code-break through the IRT system and must have a designated back up (e.g., redundant processes) to support emergency unblinding requirements.

Prior to randomization, subjects should be provided with information that includes the site emergency contact number and back-up contact number in case of a medical emergency. Any unblinding by the investigational staff must be reported immediately to the sponsor and include an explanation of why the study drug was unblinded. If unblinding is associated with a SAE the investigator is to follow the instructions in [Section 5.8.5 Reporting of Serious Adverse Events (SAEs)].

Care should be taken to limit knowledge of the randomization arm, in case this could affect the blinding of other subjects or future trial assessment for the subject.

4.4.5 Breaking the Treatment Code by the Sponsor

The sponsor may break the treatment code for subjects who experience a Suspected Unexpected Serious Adverse Reaction (SUSAR), in order to determine if the individual case or a group of cases requires expedited regulatory reporting. Individual Emergency Codes will be provided to the limited staff who are responsible to break the codes for all SUSAR cases for reporting purposes.

4.5 Assignment and Allocation

Subjects will be randomized in a 1:1:1 ratio of fezolinetant to placebo to a treatment arm according to the randomization schedules and stratified by smoking status (smoker or non-smoker) through IRT. The site personnel will dispense the treatment according to the IRT system's assignment. Specific procedures for randomization through the IRT are contained in the study procedures manual.

5 TREATMENTS AND EVALUATION

5.1 Dosing and Administration of Study Drug(s) and Other Medication(s)

5.1.1 Dose/Dose Regimen and Administration Period

Subjects will be screening up to 35 days prior to randomization. Informed consent will be obtained prior to randomization and before any study-related procedures are performed.

Subjects will be assigned study drug as a kit containing either fezolinetant or placebo at visits indicated in the schedule of assessments. Study drug intake will be done with a glass of room temperature tap water in the morning. The first intake of study drug will take place at the study site on day 1 (visit 2) under the supervision of the study staff.

On study visit days (except for EOT/ED week 52 [visit 15]) study drug will be taken at the study site, under the supervision of the study staff, after collection of predose blood samples. On all other days throughout the treatment period, subjects will be instructed to take their dose of study drug at home with water, in the morning.

In the event of a missed dose, the subject should skip the missed dose and continue with the next scheduled dose.

5.1.2 Increase or Reduction in Dose of the Study Drug(s)

Dose increases and decreases are not allowed.

5.1.3 Previous and Concomitant Treatment (Medication and NonMedication Therapy)

Medications for the treatment of VMS (including prescription medications, over the counter and herbal) taken during the 12 months prior to screening and other medication taken 90 days prior to the screening visit and up to the first dose of study medication (treatment period) will be documented in the appropriate electronic case report form (eCRF) as prior medication.

Medications taken after the first dose of study medication and through the last study-related activity will be documented on the appropriate CRF as concomitant medication. Prior and concomitant medications to be documented include but are not limited to: vitamins, herbal remedies (e.g., St. John’s wort, valerian), over the counter and prescription medications.

Subjects will be instructed not to take any concomitant medication without first consulting the investigator or study coordinator throughout the duration of the study.

5.1.3.1 Previous Medication (Drugs and Therapies)

For women who recently discontinued hormone therapy, the therapy must have been discontinued for at least the following durations prior to the screening visit:

- 1 week or longer for prior vaginal hormonal products (rings, creams, gels, inserts);
- 4 weeks or longer for prior transdermal estrogen alone or estrogen/progestin products;
- 8 weeks or longer for prior oral estrogen and/or progestin therapy;
- 8 weeks or longer for prior intrauterine progestin therapy;

- 3 months or longer for prior progestin implants and estrogen alone injectable drug therapy; or
- 6 months or longer for prior estrogen pellet therapy or progestin injectable drug therapy.

5.1.3.2 Concomitant Medications (Drugs and Therapies)

All concomitant medications and therapies (prescriptions, over the counter, and herbal), other than the study drug, administered from informed consent through 30 days post the last dose of study drug will be collected in the eCRF.

5.1.3.3 Prohibited Concomitant Medications

The following medications and therapies are prohibited throughout the study (from signing of informed consent through the last study-related activity):

- Use of hormonal medications such as hormone therapy, HRT or hormonal contraception or any treatment for VMS (prescription, over the counter or herbal).
- Investigational research products that have not been approved for any indication in the country where the subject is enrolled.
- Strong or moderate CYP1A2 inhibitors.

Refer to Appendix 12.4 List of Excluded Concomitant Medications for additional information.

5.1.4 Treatment Compliance

Study subjects should be counseled on the need to meet 100% compliance with study drug. The investigator or designee should ensure that study subjects meet this goal throughout the study period. Compliance will be verified by the accounting of study drug at each monthly visit after baseline. When study drug is administered at the research facility, it will be administered under the supervision of study personnel.

Compliance of the study drug will be monitored by the accounting of unused medication returned by the subject at visits. Compliance will be documented.

If compliance is 80%, the investigator or designee is to counsel the subject and ensure steps are taken to improve compliance. Subjects who are less than 80% compliant with the dosage regimen for any 2 consecutive visit periods during the study should be withdrawn from the study.

5.1.5 Criteria for Continuation of Treatment

Fezolinetant will not be made available after conclusion of the study.

5.1.6 Restrictions During the Study

There are no restrictions during the study.

5.2 Demographics and Baseline Characteristics

5.2.1 Demographics

Demographic and baseline characteristics will be collected during screening for all subjects according to the Schedule of Assessments [Table 1 Schedule of Assessments] and will include age, sex, race, ethnicity (US only), smoking status and prior HT use.

5.2.2 Medical History

A detailed medical history for each subject, including date of last menstruation and/or date of surgical sterilization, will be obtained at the screening visit. All relevant past and present conditions will be recorded for the main body systems, as well as prior surgical procedures.

Any untoward medical events that occur from the time of informed consent will be captured as AEs in the eCRF. A change in medical status or medical history from the time of signing informed consent is to be reported as an AE or SAE as appropriate.

5.2.3 Diagnosis of the Target Disease, Severity, and Duration of Disease

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);
- Having had bilateral oophorectomy ≥ 6 weeks prior to the screening visit

5.3 Order of Assessments

All PRO measures are to be self-administered electrically via the site tablet, at the site first upon arrival of the subject and prior to performing all other procedures including the C-SSRS. The frequency and timing of these assessments are appropriate for the population under study, study design and objectives, and type of questions asked. The assessments will be administered electronically via the site tablet on week 0 (visit 2), week 4 (visit 3), week 12 (visit 5), week 24 (visit 8) and week 52 (visit 15).

Screening (days -35 to day -1):

1. All screening procedures
2. Endometrial biopsy*

* An extra 15 screening days are allowed for repeat biopsy, if necessary (days -50 to -1, including the screening visit [visit 1] assessments).

Visit 2 through Visit 16:

The following sequence order will be in effect when more than 1 assessment is required at a time point:

1. Order of PROs to be administered:
    - MENQOL (baseline, week 4, week 12, week 24, week 52);
    - EQ-5D-5L (baseline, week 4, week 12, week 24, week 52).
2. The clinician administered C-SSRS.
3. Whenever vital signs, 12-lead ECGs and blood draws are scheduled for the same nominal time, the assessments should occur in the following order: 12-lead ECG, vital signs and blood draws.

5.4 Safety Assessments

5.4.1 Vital Signs

Vital sign parameters will be assessed at each study visit.

The vital sign parameters that will be assessed are body temperature (oral/tympanic), blood pressure (sitting) and pulse rate (sitting).

Any change from baseline in vital sign values occurring during the study that is considered to be clinically relevant or that requires concomitant medication, as judged by the investigator, should be recorded in the source documents and the AE section of the eCRF.

5.4.2 Columbia Suicide Severity Rating Scale

The C-SSRS is an assessment tool that evaluates suicidal ideation and behavior. A clinician will administer this measure electronically at the clinic visit. Administration should take place prior to any invasive procedures.

The C-SSRS will be collected at screening days -35 to -1 (visit 1), day 1 (visit 2), week 12 (visit 5), week 24 (visit 8), week 52 (visit 15/EOT) and the follow-up visit (week 55 [visit 16]).

5.4.3 Laboratory Assessments

Below is a table of the laboratory tests that will be performed during the conduct of the study. See [Table 1 Schedule of Assessments] for study visit collection dates.

Urine Pregnancy Test	**β-HCG**
Hematology	CBC: white blood cell count with differential (neutrophils, lymphocytes, eosinophils, monocytes, and basophils) hemoglobin hematocrit red blood cell count platelets reticulocytes
Biochemistry	Blood urea nitrogen Chloride Creatinine Inorganic phosphorus Sodium Bicarbonate Calcium Creatine kinase Estimated glomerular filtration rate Glucose Lactate dehydrogenase Potassium Uric acid
Table continued on next page	

Urine Pregnancy Test	**β-HCG**
Liver Biochemistry	Alanine aminotransferase Alkaline phosphatase Aspartate aminotransferase Albumin Gamma-glutamyltransferase Total bilirubin Direct bilirubin
Urinalysis	Protein Glucose pH Blood
Coagulation Panel	International normalized ratio Activated partial thromboplastin time Prothrombin time
Serology	HBsAg HCV antibody HIV antibody Anti-HBs Anti-HBc
Hormone Levels	LH FSH Estradiol SHBG Testosterone Total/Free Androstenedione DHEA Estrone

anti-HBc: antibody to hepatitis B core antigen; anti-HBs: antibody against hepatitis B antigen; β-HCG: beta human chorionic gonadotropin; BSAP: bone specific alkaline phosphatase; CBC: complete blood count; DHEA: dehydroepiandrosterone; FSH: follicle-stimulating hormone; HBsAG: hepatitis B virus surface antigen; HCV: hepatitis C virus; HIV: human immunodeficiency virus; LH: luteinizing hormone; SHBG: sex hormone-binding globulin

If the clinical laboratory results are outside the normal range, the investigator will document his/her assessment as clinically significant or not clinically significant.

Unscheduled tests or a repeat of abnormal laboratory test(s) may be performed if clinically indicated and to follow-up on suspected AEs.

Laboratory normal ranges will be outlined in the Laboratory manual and will be provided to all participating centers.

Clinical significance of out-of-range laboratory findings is to be determined and documented by the investigator/subinvestigator who is a qualified physician.

5.4.4 Papanicolaou Test

Pap tests will be performed at the screening visit (days -35 to -1 [visit 1]) only in the event that the subject does not have documentation of a normal/negative or no clinically significant findings Pap test (or equivalent cervical cytology) within the prior 12 months. Pap tests must show no clinically significant findings in order for subjects to be included in the study. Samples will be analyzed locally or at a central laboratory. For details on collection, handling and shipment instructions, refer to the laboratory manual.

5.4.5 Physical Examination

A full physical examination will be performed at screening (visit 1), day 1 (visit 2), week 52 (visit 15)/EOT and week 55 (visit 16)/follow-up which includes height (at the screening visit only), weight and waist circumference. A bimanual clinical pelvic and clinical breast examination will be performed at the screening visit. A bimanual clinical pelvic examination can be performed at any time in the study where clinically indicated. At week 2 (visit 3) thru week 48 (visit 14), a symptom directed physical exam will be conducted which includes weight and waist circumference.

5.4.6 Electrocardiogram

The 12-lead ECG will be captured at the time points shown in [Table 1 Schedule of Assessments]. The subject should rest in supine position for at least 10 minutes prior to the ECG.

5.5 Imaging

5.5.1 Mammogram

Mammograms will be performed at the screening visit (days -35 to -1 [visit 1]) only in the event that the subject does not have documentation of a normal/negative or no clinically significant findings mammogram within the prior 12 months of study enrollment. Mammograms must show no clinically significant findings in order for subjects to be included in the study. A mammogram at week 52/EOT/ED will be conducted if it coincides with the regularly scheduled routine screening mammogram of the patient, in accordance with local medical practice guidelines and the patient's primary care physician.

5.5.2 Dual-Energy X-Ray Absorptiometry (DXA)

Changes in BMD and TBS of hip and spine will be assessed by dual-energy X-ray absorptiometry (DXA) scan at screening (visit 1) and at week 52/EOT (visit 15).

The central DXA reader vendor will provide instructions for performing the DXA scans. The results will be transferred to the central DXA reader vendor, who will ensure that all data will be analyzed in the same way and will be blinded to the treatment allocation.

For practical reasons, the timing of DXA may vary from the actual time of the visit, depending on the DXA availability (DXA appointment). The screening visit (days -35 to -1 [visit 1]) DXA can be performed once the subject has been deemed eligible based on screening laboratory tests, or at visit 2, but must be performed before randomization. The week 52 (visit 15) DXA should be performed between week 50 and week 52, inclusive. For

subjects who are withdrawn from the study prior to completion, a DXA will be completed as soon as possible after study drug discontinuation (preferably within 2 weeks).

When DXA imaging is received, it goes through a quality control (QC) process to make sure the imaging parameters required for image review and assessment have been met. For TBS to be calculated, the DXA imaging is processed and analyzed as it would normally be and then evaluated using an automated algorithm to determine the TBS. TBS is a bone texture assessment that serves as a substitute for bone microarchitecture [Muschitz et al, 2015] and predicts fracture risk independent of BMD and clinical risk factors [McCloskey et al, 2016].

5.5.3 Transvaginal Ultrasound

Subjects will undergo a TVU to assess the uterus and ovaries at screening, at week 52 (EOT) and for subjects who withdraw from the study at the ED visit. The endometrium should be measured in the long axis or sagittal plane. The measurement is of the thickest echogenic area from 1 basal endometrial interface across the endometrial canal to the other basal surface. Care should be taken not to include the hypoechoic myometrium in this measurement. All TVUs will be centrally read.

5.6 Biopsies

5.6.1 Endometrial Biopsy

Subjects will undergo a suction endometrial biopsy at the following time points:

- Screening
- At week 52/EOT
- ED
- All cases of uterine bleeding during treatment

The screening endometrial biopsy must be evaluable.

Subjects that require a retest biopsy, for insufficient material or unevaluable only, will have an extended screening period and will be allowed an additional 15 days of screening (i.e., days -50 to -1). A maximum of 1 retest biopsy during screening is allowed.

Screening biopsy results are valid for study entry for up to 3 months from date of procedure for applicable subjects.

An endometrial biopsy is required at EOT or ED. For EOT/ED week 52 (visit 15) biopsies that are evaluated as insufficient material or unevaluable, a retest biopsy will be required. Any of the three pathologists can determine if a an EOT/ED is insufficient or unevaluable. However, if two pathologists read the EOT/ED endometrial biopsy as evaluable and issue the same diagnosis, and the 3rd pathologist reads the biopsy as insufficient or unevaluable, the biopsy does not need to be repeated.

During the treatment period, any woman with an abnormal endometrial biopsy reported as disordered proliferative endometrium, endometrial hyperplasia or endometrial cancer will be referred to standard of care clinical management and followed to resolution, and the report of any medical or surgical procedures and the resultant pathology will be obtained. The

investigator should record any such biopsy, and the associated diagnostic and therapeutic measures, as an AE.

Subjects with endometrial fibroids may be included in the study provided the endometrial biopsy result at screening is satisfactory and the investigator is confident no treatment will be required during the study.

Subjects will be allowed entry into the study on the primary endometrial result/diagnosis. A secondary and tertiary endometrial diagnosis will also be reported. A subject should discontinue the study if secondary or tertiary endometrial biopsy diagnosis is Category 2. All 3 pathology reports should be filed in the subject's source document. Please reference the central laboratory manual for further details and timing of biopsy specimen results.

All biopsies will be read concurrently by 3 independent expert pathologists from institutions with independent fiduciary and organizational reporting. Each pathologist should be blinded to the treatment group and to the readings of the other pathologists. For EOT/ED biopsies and all biopsies in cases of uterine bleeding during treatment the concurrence of 2 of the 3 pathologists is accepted as the final diagnosis. If there is no agreement among the 3 pathologists, the most severe pathologic diagnosis should be used as the final diagnosis.

The 3 independent expert pathologists should use the same standardized criteria for the diagnosis of endometrial hyperplasia or endometrial cancer, and endometrial polyps should be fully characterized as to glandular proliferation and atypia. The standardized criteria for histologic evaluation can be viewed in the FDA Draft Guidance for Industry, Estrogen and Estrogen/Progestin Drug Products to Treat Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms – Recommendations for Clinical Evaluation, 2003.

5.7 Patient-Reported Outcome, Pharmacodynamic and Pharmacokinetic Assessments

5.7.1 Patient-Reported Outcome Assessments

The following patient-reported outcomes (PROs) will be self-administered electronically at the site visit:

- MENQOL – assesses quality of life as it relates to menopausal symptoms
- EQ-5D-5L – assesses general health-related quality of life

All PRO measures will be administered in the local language. Only questionnaires provided by Astellas that have been linguistically validated and cognitively debriefed in the target language to which they have been translated will be used in this study.

All PRO measures must be self-administered at the site and prior to performing any other procedures including the C-SSRS. The assessments will be administered electronically via the site tablet on day 1, week 4, week 12, week 24 and week 52.

All sites and site personnel will undergo training to assist with any technology issues that arise due to electronic administration. Personnel will be trained on the acceptability of

defining terms for subjects if necessary; however, they will be instructed to not define a concept where the respondent's subjective interpretation is required (e.g., "my sleep quality").

Site personnel will be instructed to have subjects complete the PRO measures in a quiet room, to complete all questions before leaving the room, and to read the instructions provided. After completion, subjects will be asked to confirm their responses.

5.7.1.1 Menopause-Specific Quality of Life (MENQoL)

The MENQOL 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). Items pertaining to a specific symptom are rated as present or not present, and if present, how bothersome on a zero (not bothersome) to 6 (extremely bothersome) scale [Lewis et al, 2005].

Each item score ranges from 1 to 8, and each domain is scored separately; each domain mean ranges from 1 to 8 [Lewis et al, 2005; Hilditch et al, 1996]. The overall questionnaire score is the mean of the domain means. Higher scores represent more bothersome menopausal symptoms.

The questionnaire should take, on average, 7 minutes to complete with a range of 5 to 15 minutes based on the original English and French Canadian pretests [Lewis et al, 2005; Hilditch et al, 1996].

5.7.1.2 EQ-5D-5L with Visual Analog Scale (VAS)

The EQ-5D-5L is a 5-item standardized measure of health status that provides a simple, generic measure of health for clinical and economic appraisal [van Reenen et al., 2015]. This PRO measure comprises 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems and extreme problems. The subject is asked to indicate her health state by selecting the most appropriate statement in each of the 5 dimensions. This decision results in a 1-digit number that expresses the level selected for that dimension. The digits for the 5 dimensions can be combined into a 5-digit number that describes the patient's health state.

The EQ-5D-5L visual analog scale (VAS) is a subject-reported measure that records the respondent's self-rated health on a vertical VAS where the endpoint is labeled "Best imaginable health state" and "Worst imaginable health state." The scale ranges from 0 to 100, where 100 indicates the subject is in her best possible health state and 0 indicates the subject is in her worst possible health state. Subjects mark an 'X' on the scale to rate their health status that day.

This measure should take approximately 2 minutes to complete. Due to the electronic administration of this PRO, risk for missing data is mitigated.

5.7.2 Pharmacodynamic Assessments

Venous blood samples will be collected predose (on dosing visits) for pharmacodynamic assessments at day 1 (visit 2), week 4 (visit 3), week 12 (visit 5), week 24 (visit 8) and week 52 (visit 15/EOT) and at the follow-up visit (week 55 [visit 16]) [see Table 1 Schedule of Assessments]. Markers include LH, FSH, E2, SHBG, androstenedione, dehydroepiandrosterone, estrone and testosterone.

The exact date and time of blood sampling must be recorded in the source documents and on the eCRF. Serum will be collected and handled as specified in the central laboratory manual. After appropriate labeling, the serum samples will be stored below -20°C at the study site. Thereafter, the frozen serum samples will be transported/shipped on dry ice to the central laboratory for collection and storage below -20°C until analysis.

Further procedures for sample collection, shipment, processing and storage are described in the laboratory manual.

5.7.3 Pharmacokinetic Assessments

Venous blood samples will be collected for pharmacokinetic analysis of fezolinetant and metabolite ES259564 in plasma week 4 (visit 3) predose and 1 to 3 hours postdose, and predose at week 12 (visit 5), week 24 (visit 8) and week 52 (visit 15/EOT) [see Table 1 Schedule of Assessments].

A pharmacokinetic collection will be obtained for any subjects with signal of elevated transaminases (> 3 × ULN) during their visit for repeat blood draw. The sample will be held for potential analysis based on the patient's clinical outcome. The exact date and time of the pharmacokinetic sampling must be recorded in the source documents and on the eCRF, as well as the exact time of last drug intake before the samples were taken. This means that for a predose blood sample, the time of the morning drug intake of the day before needs to be recorded, and for the postdose samples, the exact time of the morning dose on the very same day needs to be recorded.

Further procedures for sample collection, shipment, processing, and storage are described in the laboratory manual.

5.7.4 Caffeinated Beverage Intake

Subjects' intake of caffeinated beverages (e.g., coffee) will be recorded to explore the interaction of fezolinetant with caffeine (a weak CYP1A2 inhibitor).

History of average caffeinated beverage intake will be collected at baseline. At each clinic visit, the caffeinated beverage intake within the past 24 hours will be recorded. Details on data collection procedures will be provided in the eCRF completion guidelines.

5.8 Adverse Events and Other Safety Aspects

5.8.1 Definition of Adverse Events

An AE is any untoward medical occurrence in a subject administered a study drug, and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product whether or not considered related to the medicinal product.

In order to identify any events that may be associated with study procedures and could lead to a change in the conduct of the study, Astellas collects AEs even if the subject has not received study drug treatment. AE collection begins after the signing of the informed consent and will be collected until 21 days after the last dose of study drug or the subject is determined to be a screen failure.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrences.

5.8.1.1 Abnormal Laboratory Findings

Any abnormal laboratory test result (e.g., hematology, clinical chemistry or urinalysis) or other safety assessment (e.g., ECGs, radiographic scans, vital signs measurements or physical examination), including those that worsen from baseline, that is considered to be clinically significant in the medical and scientific judgment of the investigator and not related to underlying disease, is to be reported as an (S)AE.

Any clinically significant abnormal laboratory finding or other abnormal safety assessment which is associated with the underlying disease does not require reporting as an (S)AE, unless judged by the investigator to be more severe than expected for the subject's condition.

Repeating an abnormal laboratory test or other safety assessment, in the absence of any of the above criteria, does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.

5.8.1.2 Potential Cases of Drug-Induced Liver Injury

Refer to [Appendix 12.5 Liver Safety Monitoring and Assessment] for detailed instructions on DILI. Abnormal values in AST and/or ALT concurrent or with abnormal elevations in TBL that meet the criteria outlined in [Appendix 12.5 Liver Safety Monitoring and Assessment], in the absence of other causes of liver injury, are considered potential cases of DILI (potential Hy's Law cases). Any subject discontinuations due to liver safety are always to be considered important medical events and reported per [Section 5.8.5 Reporting of Serious Adverse Events].

5.8.1.3 Disease Progression and Study Endpoints

Under this protocol, the following event(s) will not be considered as an(S)AE:

- Pre-planned and elective hospitalizations or procedures for diagnostic, therapeutic, or surgical procedures for a pre-existing condition that did not worsen during the course of the clinical trial. These procedures are collected per the eCRFs Completion Guidelines.

5.8.2 Definition of Serious Adverse Events (SAEs)

An AE is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Results in death;
- Is life-threatening (an AE is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death);
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions;
- Results in congenital anomaly, or birth defect;
- Requires inpatient hospitalization (except for planned procedures as allowed per study) or leads to prolongation of hospitalization (except if prolongation of planned hospitalization is not caused by an AE). Hospitalization for treatment/observation/examination caused by AE is to be considered as serious);
- Discontinuation due to increases in liver enzymes [Section 6.1]; and
- Other medically important events (defined in paragraph below).

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These events, including those that may result in disability/incapacity, usually are considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

5.8.2.1 Always Serious Adverse Events

The sponsor has a list of events that they classify as "always serious" events. If an AE is reported that is considered by the sponsor to be an SAE per this classification as "always serious", additional information on the event (e.g., investigator confirmation of seriousness, causality) will be requested.

5.8.3 Criteria for Causal Relationship to Study Drug

A medically qualified investigator is obligated to assess the relationship between the study drug and each occurrence of each (S)AE. This medically qualified investigator will use medical judgment as well as the RSI (See Section 1.4 Summary of Key Safety Information for Fezolinetant) to determine the relationship. The causality assessment is one of the criteria used when determining regulatory reporting requirements.

The medically qualified investigator is requested to provide an explanation for the causality assessment for each (S)AE and must document in the medical notes that he/she has reviewed the (S)AE and has provided an assessment of causality.

Following a review of the relevant data, the causal relationship between the study drug and each (S)AE will be assessed by answering '**yes**' or '**no**' to the question "**Do you consider that there is a reasonable possibility that the event may have been caused by the study drug.**"

When making an assessment of causality, the following factors are to be considered when deciding if there is evidence and/or arguments to suggest there is a 'reasonable possibility' that an (S)AE may have been caused by the study drug (rather than a relationship cannot be ruled out) or if there is evidence to reasonably deny a causal relationship:

- Plausible temporal relationship between exposure to the study drug and (S)AE onset and/or resolution. Has the subject actually received the study drug? Did the (S)AE occur in a reasonable temporal relationship to the administration of the study drug?
- Plausibility; i.e., could the event been caused by the study drug? Consider biologic and/or pharmacologic mechanism, half-life, literature evidence, drug class, preclinical and clinical study data, etc.
- Dechallenge/Dose reduction/Rechallenge:
    - Did the (S)AE resolve or improve after stopping or reducing the dose of the suspect drug? Also consider the impact of treatment for the event when evaluating a dechallenge experience.
    - Did the (S)AE reoccur if the suspected drug was reintroduced after having been stopped?
- Laboratory or other test results; a specific lab investigation supports the assessment of the relationship between the (S)AE and the study drug (e.g., based on values pre-, during and post-treatment)
- Available alternative explanations independent of study drug exposure; such as other concomitant drugs, past medical history, concurrent or underlying disease, risk factors including medical and family history, season, location, etc. and strength of the alternative explanation

There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, it is very important that the medically qualified investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor. With limited or insufficient information about the event to make an informed medical judgment and in absence of any indication or evidence to establish a causal relationship, a causality assessment of 'no' is to be considered. In such instance, the investigator is expected to obtain additional information regarding the event as soon as possible and to re-evaluate the causality upon receipt of additional information. The medically qualified investigator may revise his/her assessment of causality in light of new information regarding the SAE and shall send an SAE follow-up report and update the eCRF with the new information and updated causality assessment.

5.8.4 Criteria for Defining the Severity of an Adverse Event

The investigator will use the following definitions to rate the severity of each AE

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

5.8.5 Reporting of Serious Adverse Events (SAEs)

The collection of AEs and the expedited reporting of SAEs will start following receipt of the informed consent and will continue until 21 days after last administration of study drug or the subject is determined to be a screen failure.

In the case of a SAE, the investigator must contact the sponsor by fax or email immediately (within 24 hours of awareness).

The investigator must complete and submit an SAE worksheet containing all information that is required by local and/or regional regulations to the sponsor by email or fax immediately (within 24 hours of awareness).

The SAE worksheet must be signed by a medically qualified investigator (as identified on Delegation of Authority Log). Signature confirms accuracy and completeness of the SAE data as well as the investigator causality assessment including the explanation for the causality assessment.

If the SAE is associated with emergency unblinding as outlined in Section 4.4.4 Breaking the Treatment Code for Emergency this is to be recorded on the SAE worksheet. Within the SAE worksheet, the investigator is to include when unblinding took place in association with the SAE.

For contact details, see [Section II Contact Details of Key Sponsor's Personnel]. Fax or email the SAE/Special Situations Worksheet to:

Astellas Pharma Global Development Inc.
Pharmacovigilance
Fax number: (+1) 888-396-3750
Alternate fax number: (+1) 847-317-1241
Email: safety-US@astellas.com

If there are any questions, or if clarification is needed regarding the SAE, please contact the sponsor's medical monitor/study physician or his/her designee [Section II Contact Details of Key Sponsor’s Personnel].

Follow-up information for the event should be sent promptly (within 7 days of the initial notification).

Full details of the SAE should be recorded on the medical records, SAE/Special Situation Worksheet and on the (e)CRF.

The following minimum information is required:

- International Study Number (ISN)/Study number,
- Subject number, sex and age,
- The date of report,
- A description of the SAE (event, seriousness criteria),
- Causal relationship to the study drug (including reason), and
- The drug provided (if any) <blinded regimen is also an option>

The sponsor or sponsor's designee will medically evaluate the SAE and determine if the report meets the requirements for expedited reporting based on seriousness, causality, and expectedness of the events (e.g., SUSAR reporting) according to current local/regional regulatory requirements in participating countries. The sponsor or sponsor's designee will submit expedited safety reports (e.g., IND Safety Reports, SUSAR, CIOMS-I) to Competent Authorities (CA) and concerned Ethics Committee (cEC) per current local regulations, and will inform the investigators of such regulatory reports as required. Investigators must submit safety reports as required by their IRB/local IEC within timelines set by regional regulations (e.g., EMA, FDA) where required. Documentation of the submission to and receipt by the IRB/ local IEC of expedited safety reports should be retained by the site.

The sponsor will notify all investigators responsible for ongoing clinical studies with the study drug of all SUSARs that require submission per local requirements IRB/local IEC/head of the study site.

The investigator or designee should provide written documentation of IRB/IEC notification for each report to the sponsor.

5.8.6 Follow-up of Adverse Events

All AEs occurring during or after the subject has discontinued the study are to be followed up until resolved or judged to be no longer clinically significant, or until they become chronic to the extent that they can be fully characterized by the investigator.

If after the protocol defined AE collection period [see Section 5.8.1 Definition of Adverse Event], an AE progresses to a SAE, or the investigator learns of any (S)AE including death, where he/she considers there is reasonable possibility it is related to the study drug treatment or study participation, the investigator must promptly notify the sponsor.

5.8.7 Adverse Events of Special Interest

AEs of special interest are AEs the sponsor may wish to carefully monitor. These AEs may be serious or non-serious and are not considered SAEs unless they meet the SAE definition in Section 5.8.1 Definition of Adverse Events. AEs of special interest should be reported on the eCRF as such.

If the AE of special interest meets the definition of an SAE, they are to be collected via the SAE/Special Situation worksheet and reported within 24 hours as described in Section 5.8.5 Reporting of Serious Adverse Events (SAEs). Adverse events of special interest in this study will include:

- AE of uterine bleeding
- Endometrial hyperplasia/cancer or disordered proliferative endometrium
- AE of thrombocytopenia
- AE of liver test evalations
- AE of bone fractures/bone loss ≥ 7%
- AEs of abuse liability
- AEs of depression
- AEs of wakefulness
- AEs of effect on memory

5.8.8 Special Situations

Certain Special Situations observed in association with the study drug(s), such as incorrect administration (e.g., wrong dose of study drug, comparator, or background therapy) are collected, as Protocol Deviation per [Section 8.3 Major Protocol Deviations] or may require special reporting, as described in the subsections below.

Special Situations are not considered AEs, but do require to be communicated to Astellas as per the timelines defined below.

If a Special Situation is associated with, or results in, an AE, the AE is to be assessed separately from the Special Situation and captured as an AE in the eCRF. If the AE meets the definition of a SAE, the SAE is to be reported as described in [Section 5.8.5 Reporting of Serious Adverse Events] and the details of the associated Special Situation are to be included in the clinical description on the SAE worksheet.

Special Situations relevant to this protocol are:

- Pregnancy
- Lack of Efficacy [refer to Section 5.8.8.2 Lack of Efficacy]
- Medication Error, Overdose and “Off label use”
- Misuse/abuse
- Suspected Drug-Drug interaction

5.8.8.1 Pregnancy

If a female subject becomes pregnant during the study dosing period or within 30 days from the discontinuation of dosing, the investigator is to report the information to the sponsor according to the timelines in **[**Section 5.8.5 Reporting of Serious Adverse Events] using the Pregnancy Reporting Form and in the eCRF.

The expected date of delivery or expected date of the end of the pregnancy, last menstruation, estimated conception date, pregnancy result and neonatal data etc., should be included in this information.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or termination (including elective termination) of a pregnancy is to be reported for a female study subject as an AE in the eCRF or SAE per [Section 5.8.5 Reporting of Serious Adverse Events].

Additional information regarding the outcome of a pregnancy when also categorized as an SAE is mentioned below:

- "Spontaneous abortion" includes miscarriage, abortion and missed abortion;
- Death of a newborn or infant within 1 month after birth is to be reported as an SAE regardless of its relationship with the study drug;
- If an infant dies more than 1 month after the birth, is to be reported if a relationship between the death and intrauterine exposure to the study drug is judged as ″possible″ by the investigator;
- Congenital anomaly (including anomaly in miscarried fetus).

Unless a congenital anomaly is identified prior to spontaneous abortion or miscarriage, the embryo or fetus should be assessed for congenital defects by visual examination. (S)AEs experienced by the newborn/infant should be reported via the Pregnancy Reporting Form. Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date.

5.8.8.2 Lack of Efficacy

If lack of efficacy of the study drug is suspected, the investigator must forward the Special Situation worksheet to the sponsor by fax or email immediately (within 24 hours of awareness) and any associated (S)AEs are to be reported in the eCRF. If the AE meets the definition of a SAE, the SAE is also to be reported as described in [Section 5.8.5 Reporting of Serious Adverse Events] together with the details of the lack of efficacy.

5.8.8.3 Medication Error, Overdose and “Off-Label Use”

If a Medication Error, Overdose or “Off-Label Use” (i.e., use outside of what is stated in the protocol) is suspected, refer to Section 8.3 Major Protocol Deviations. Any associated (S)AEs are to be reported in the eCRF. If the AE meets the definition of a SAE, the SAE is also to be reported as described in [Section 5.8.5 Reporting of Serious Adverse Events] together with the details of the medication error, overdose and/or “Off-Label Use.”

In the event of suspected fezolinetant overdose, the subject should receive supportive care and monitoring. The medical monitor/expert should be contacted as applicable.

5.8.8.4 Misuse/Abuse

If misuse or abuse of the study drug(s) is suspected, the investigator must forward the Special Situation worksheet to the sponsor by fax or email immediately (within 24 hours of awareness). Any associated (S)AEs are to be reported in the eCRF. If the AE meets the definition of a SAE, the SAE is also to be reported as described in [Section 5.8.5 Reporting of Serious Adverse Events] together with details of the misuse or abuse of the study drug(s).

5.8.8.5 Suspected Drug-Drug Interaction

If a suspected drug-drug interaction associated with the study drug(s) is suspected, the investigator must forward the Special Situation worksheet to the sponsor by fax or email immediately (within 24 hours of awareness). Any associated (S)AEs are to be reported in the eCRF. If the AE meets the definition of a SAE, the SAE is also to be reported as described in [Section 5.8.5 Reporting of Serious Adverse Events] together with details of the suspected drug-drug interaction.

5.8.9 Supply of New Information Affecting the Conduct of the Study

When new information becomes available necessary for conducting the clinical study properly, the sponsor will inform all investigators involved in the clinical study as well as the regulatory authorities. Investigators should inform the IRB/IEC of such information when needed.

The investigator will also inform the subjects, who will be required to sign an updated informed consent form (ICF) in order to continue in the clinical study.

5.8.10 Urgent Safety Measures

An urgent safety measure (USM) is an intervention, which is not defined by the protocol and can be put in place with immediate effect without needing to gain prior approval by the sponsor, relevant CA, IRB/IEC, where applicable, in order to protect study participants from any immediate hazard to their health and/or safety. Either the investigator or the sponsor can initiate an USM. The cause of an USM can be safety, product or procedure related.

5.8.11 Reporting Urgent Safety Measures

In the event of a potential USM, the investigator must contact the Astellas Study Physician (within 24 hours of awareness). Full details of the potential USM are to be recorded in the subject's medical records. The sponsor may request additional information related to the event to support their evaluation.

If the event is confirmed to be an USM the sponsor will take appropriate action to ensure the safety and welfare of the patients. These actions may include but are not limited to a change in study procedures or study treatment, halting further enrollment in the trial, or stopping the study in its entirety. The sponsor or sponsor's designee will notify CA and cEC within the timelines required per current local regulations, and will inform the investigators as required. When required, investigators must notify their IRB/IEC within timelines set by regional regulations.

5.9 Test Drug Concentration

Blood samples for pharmacokinetics of fezolinetant and metabolite ES259564 will be collected from every subject. Pharmacokinetic samples will be taken predose at week 4 (visit 3), week 12 (visit 5), week 24 (visit 8), week 52 (visit 15), as well as any subject with a signal of elevated (> 3 × ULN) aminotransferases [Appendix 12.4 List of Excluded

Concomitant Medications]. Pharmacokinetic samples will be taken 1 to 3 hours postdose at week 4 (visit 3).

Details on sampling, processing, storage and shipment procedures will be provided in a separate central laboratory manual.

5.10 Other Measurements, Assessments or Methods

Not applicable

5.11 Total Amount of Blood

Blood samples will be taken for the purposes of clinical laboratory tests, serology tests (screening only), pharmacokinetic samples, and pharmacodynamics samples. Repeat and additional blood samples may be taken if required. For each patient, the expect blood volume to be drawn will be approximately 175 mL over the course of the clinical study.

6 DISCONTINUATION

6.1 Discontinuation of Individual Subject(s) From Study Treatment

A discontinuation from treatment is a subject who enrolled in the study and for whom study treatment is permanently discontinued for any reason. The reason for discontinuation from study treatment must be documented in the subject's medical records.

A subject **must** discontinue study treatment for any of the following reasons:

- Withdrawal of informed consent
- Lost to follow-up
- If, for safety reasons, it is in the best interest of the subject that she be withdrawn, in the investigator's opinion
- Development of a medical condition that requires concomitant treatment with a prohibited therapy
- Development of seizures or other convulsive disorders
- Breaking of the randomization code during administration of the study drug by the investigator or by a member of the site staff. If the code is broken by the sponsor for safety reporting purposes or early time point analysis, the subject may remain in the study.
- Confirmed (within 72 hours from the notification of test result) decrease in platelets below 75,000 mm^3, which does not normalize after 7 days or immediate withdrawal in case of platelets below 50,000 mm^3.
- Development of severe hepatic abnormality defined as ALT or AST > 8 × ULN
- Confirmed (within 72 hours from the notification of test result) severe hepatic abnormality for any of the following:
    - ALT or AST > 5 × ULN for more than 2 weeks;
    - ALT or AST > 3 × ULN **AND** TBL > 2 × ULN or INR > 1.5 × ULN, and INR > 1.5; or

  - ALT or AST > 3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (> 5% increase from baseline).
- The subject becomes pregnant.
- Category 2 results of secondary or tertiary screening endometrial biopsy diagnosis.

6.1.1 Lost to Follow Up

Every reasonable effort is to be made to contact any subject lost to follow-up during the course of the study to complete study-related assessments, record outstanding data, and retrieve study drug.

6.2 Discontinuation of the Site

If an investigator intends to discontinue participation in the study, the investigator must immediately inform the sponsor.

6.3 Discontinuation of the Study

The sponsor may terminate this study or treatment arm, prematurely, either in its entirety or at any study site, for reasonable cause provided that written notice is submitted in advance of the intended termination. Advance notice is not required if the study is stopped due to safety concerns. If the sponsor terminates the study for safety reasons, the sponsor will immediately notify the investigator and subsequently provide written instructions for study termination.

7 STATISTICAL METHODOLOGY

A Statistical Analysis Plan (SAP) will be written to provide details of the analysis, along with specifications for tables, listings and figures to be produced. The SAP will be finalized before the database hard lock. Changes from the analyses planned in SAP that affect the statistical analysis will be documented in the Clinical Study Report (CSR).

In general, continuous data will be summarized with descriptive statistics (number of subjects, mean, SD, minimum, median and maximum), and frequency and percentage for categorical data.

7.1 Sample Size

The primary objective of this study is to assess long-term safety and tolerability. The sample size in this study is not calculated based on the statistical power for efficacy evaluation to detect treatment difference.

The total sample size will be 1740, which will be randomly assigned 1:1:1 to a fezolinetant 45 mg once daily group (580), fezolinetant 30 mg once daily group or placebo group (580) This sample size would provide high probability to observe events of special interest that has with a fairly low background event rate that is less than 1%. With the sample size, the following table illustrates the probability of observing 1 or more events, 2 or more events and 3 or more events for different background event rate.

	Fezolinetant 45 mg once daily/Fezolinetant 30 mg once daily/Placebo		
Sample Size (1:1:1)	**n = 580**		
Background Event Rate	**Prob(#>=3)**	**Prob(#>=2)**	Prob(#>=1)
0.10%	2.11%	11.53%	44.03%
0.20%	11.18%	32.29%	68.69%
0.30%	25.33%	51.94%	82.49%
0.40%	40.94%	67.43%	90.22%
0.50%	55.46%	78.62%	94.54%
0.60%	67.63%	86.28%	96.95%
0.70%	77.16%	91.35%	98.30%
0.80%	84.27%	94.62%	99.05%
0.90%	89.38%	96.69%	99.47%

Prob(#>=1) means the probability of observing 1 or more events.

Prob(#>=2) means the probability of observing 2 or more events.

Prob(#>=3) means the probability of observing 3 or more events.

In addition, if an assumed background rate of 0.26% such as for endometrial hyperplasia, this sample size would provide the final number of evaluable subjects to demonstrate that the point estimate is less than or equal to 1% and upper bound of 1-sided 95% CI to be ≤ 4% with at least 95% probability assuming up to 60% (including baseline, ED and subject refusal of endometrial biopsy at EOT) of subjects may not have evaluable biopsy data.

7.2 Analysis Sets

7.2.1 Full Analysis Set (FAS)

The full analysis set (FAS) will consist of all subjects who are randomized and receive at least 1 dose of study drug. This will be the primary analysis set for efficacy analyses. The randomized treatment for each subject will be used for summaries by treatment group based on the FAS, even if a subject erroneously received a different treatment.

7.2.2 Safety Analysis Set (SAF)

The safety analysis set (SAF) consists of all randomized subjects who took at least 1 dose of study drug, and will be used for safety analyses. A subject erroneously receiving a treatment different from their randomized treatment will be assigned to the treatment group that the patient received as first dose.

7.2.3 Pharmacokinetic Analysis Set (PKAS)

The pharmacokinetic analysis set (PKAS) consists of the administered population for which sufficient plasma concentration data is available to facilitate derivation of at least 1 pharmacokinetic parameter and for whom the time of dosing on the day of sampling is known. Additional subjects may be excluded from the PKAS at the discretion of the pharmacokineticist. Any formal definitions for exclusion of subjects or time-points from the

PKAS will be documented in the in the Classification Specifications and determined the Classification Meeting.

7.2.4 Pharmacodynamic Analysis Set (PDAS)

The pharmacodynamic analysis set (PDAS) will include the subjects from the administered population for whom sufficient pharmacodynamic measurements were collected. The PDAS will be used for all analyses of pharmacodynamic data.

7.3 Demographics and Baseline Characteristics

The demographic summary will include age, sex, race, ethnicity, smoking status and prior HT use. Baseline characteristics include caffeine used, weight, body mass index, diagnosis of the target disease, severity and duration of disease. Demographics and baseline characteristics will be summarized by treatment group as well as for all treatment groups combined.

7.3.1 Subject Disposition

The number of subjects who are screened, randomized and treated will be summarized. The number and percentage of subjects who completed and discontinued treatment and reasons for treatment discontinuation will be presented for all randomized subjects and subjects in the SAF by treatment group and overall. All disposition details and dates of first and last evaluations for each subject will be listed.

7.3.2 Previous and Concomitant Medications

All previous and concomitant medications will be summarized.

7.3.3 Medical History

Medical history for each subject will be presented in a listing.

7.4 Analysis of Efficacy

No efficacy data will be collected for this study.

7.5 Analysis of Exploratory Endpoints

The exploratory endpoints include the MENQOL and the EQ-5D-5L which will be assessed at baseline and weeks 4, 12, 24 and 52. The exploratory endpoints will be analyzed for the FAS set. Summary statistics will be provided by treatment group.

The exploratory variables include the effect of fezolinetant on the following:

- Mean change on the MENQOL Total Score from baseline to specified time points.
- Mean change on the MENQOL Domain Scores from baseline to specified time points.
- Mean change on the EQ-5D-5L Total Score from baseline to specified time points.
- Change from baseline to specified time points in serum concentrations of sex hormones and SHBG [see Section 7.2.4 Pharmacodynamic Analysis Set (PDAS)].
- Plasma concentrations of fezolinetant and the fezolinetant metabolite ESN259564 at specified time points [see Section 7.2.3 Pharmacokinetic Analysis Set (PKAS)].

For the treatment comparison of continuous endpoints, a mixed model for repeated measures (MMRM) will be used. The model will include treatment, visit, 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 visit and an interaction of baseline measurement by visit., with an unstructured variance-covariance.

7.6 Analysis of Safety

Overall long-term safety of fezolinetant will be the primary objective of this study. The safety assessments include adverse events, laboratory assessments, vital signs, C-SSRS, Pap test, physical examination, ECG, endometrial health assessment and imaging (mammogram, DXA, TVU). Safety analysis will be conducted on the SAF.

Primary Safety Variables:

The primary variable will require the evaluation of the safety of fezolinetant on the following:

- Frequency and severity of AEs
- Percentage of subjects with endometrial hyperplasia
- Percentage of subjects with endometrial cancer

Secondary Safety Variables:

- Change from baseline in endometrial thickness at 12 months
- Percentage of subjects with disordered proliferative endometrium
- Change from baseline in BMD and TBS at hip and spine at 12 months
- Vital signs: sitting systolic and diastolic blood pressure and pulse rate
- Laboratory tests: hematology, biochemistry and urinalysis
- C-SSRS
- ECG parameters

For each AE of special interests a summary statistics will be provided and the rate, odds ratio, and their corresponding 2-sided 95% confidence intervals will be presented. For the treatment comparison of bone density and endometrial thickness, an analysis of covariance model will be used. The model will include treatment and smoking status (current vs former/never) as factors, with baseline weight and baseline as covariates.

7.6.1 Adverse Events

A TEAE is defined as an AE observed after starting administration of the study drug and 21 days after the last dose of study drug.

The number and percentage of subjects with treatment-emergent AEs, SAEs, AEs leading to withdrawal of treatment and AEs related to study drug will be summarized by SOC, preferred term and treatment group. The number and percentage of AEs by severity will also be summarized. All AEs will be listed.

A study drug-related TEAE is defined as any TEAE with a causal relationship of YES by the investigator.

AEs will be coded using MedDRA. An AE with onset at any time from first dosing until last scheduled procedure will be classified as treatment-emergent for inclusion in the summary tabulations.

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

7.6.2 Laboratory Assessments

For quantitative laboratory measurements descriptive statistics will be used to summarize results and change from baseline for subjects in the SAF by treatment group and time point.

Shifts relative to normal ranges from baseline to each time point during treatment period in lab tests will also be tabulated. Laboratory data will be displayed in listings.

Number and percentage of subjects with platelets < 150x10^9/L will be separately summarized for each treatment group. The liver safety assessments will be summarized by the categories below based on the measurements from ALP, ALT, TBL, AST and their combination. These parameters will be based on measurements from a central laboratory.

The subject's highest value during the treatment period will be used.

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

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

7.6.3 Vital Signs

Descriptive statistics will be used to summarize vital sign results and changes from baseline for subjects in the SAF by treatment group and visit.

7.6.4 Physical Examination

Physical examination will be listed by treatment group.

7.6.5 Routine 12-lead Electrocardiograms

The 12-lead ECG results will be summarized by treatment group and time point.

All ECG interpretations will be displayed in listings.

7.6.6 Endometrial Health Assessment

Data collected based on endometrial biopsy and endometrial thickness from transvaginal ultrasound images will be summarized by treatment group and time point.

Endometrial hyperplasia, cancer and disordered proliferative endometrium endpoints will be analyzed for endometrial health analysis set (EH set) which is defined as SAF subjects who have 1 year evaluable biopsy. Further details for EH set including the analysis window for post-baseline evaluable biopsy will be defined in the SAP. Rates (percentage of subjects) and 1-sided 95% confidence intervals with these abnormal findings will be calculated.

For thickness, change from baseline to 52-week will be calculated and each fezolinetant group will be compared to placebo using an analysis of covariance (ANCOVA) model with treatment and smoking status as factors and baseline weight and baseline value as covariates. This analysis will be done on SAF set.

7.6.7 Imaging

DXA (BMD, TBS) data will be summarized by treatment group.

7.7 Analysis of Pharmacokinetics

Descriptive statistics (e.g., n, mean, SD, minimum, median, maximum, coefficient of variation [CV], geometric mean and geometric CV) on the actual values will be summarized for plasma concentrations of fezolinetant and the major metabolite ES259564 by visit and treatment arm. Pharmacokinetics may be evaluated by a population pharmacokinetic approach. All details of population analyses will be described in a separate analysis plan and a separate report will be written. When deemed necessary, data from this study may be combined with data from other studies.

7.8 Analysis of Pharmacodynamics

Individual serum hormone concentration values and actual sampling times relative to study drug intake will be listed. Descriptive statistics (number of subjects, mean, SD, median, minimum and maximum) on the actual values and changes from baseline values will be summarized by assessment timepoint and by treatment arm. Pharmacodynamic data and efficacy data may be evaluated by a population pharmacodynamics or population pharmacokinetic/pharmacodynamic approach. All details of population analyses will be described in the SAP. When deemed necessary, data from this study may be combined with data from other studies.

7.9 Major Protocol Deviations

Major protocol deviations as defined in [Section 8.3 Major Protocol Deviations] will be summarized for all randomized subjects by treatment group and total as well as by site. A data listing will be provided by site and subject.

The major protocol deviation criteria will be uniquely identified in the summary table and listing.

7.10 Interim Analysis (and Early Discontinuation of the Clinical Study)

No formal interim analysis is planned for this study.

7.11 Additional Conventions

The start and stop dates of AEs and concomitant medication will be imputed. The imputed dates will be used to allocate the concomitant medication and AEs to a treatment group, in addition to determining whether an AE is/is not treatment emergent. Listings of the AEs and concomitant medications will present the actual partial dates; imputed dates will not be shown. See the SAP for details of the definition for analysis windows to be used for analyses by visit.

8 OPERATIONAL CONSIDERATIONS

8.1 Data Collection

The investigator or site designee will enter data collected using an Electronic Data Capture system. In the interest of collecting data in the most efficient manner, the investigator or site designee should record data (including laboratory values, if applicable) in the eCRF within 5 days after the subject's visit.

The investigator or site designee is responsible to ensure that all data in the eCRFs and queries are accurate and complete and that all entries are verifiable with source documents. These documents should be appropriately maintained by the site.

The monitor should verify the data in the eCRFs with source documents and confirm that there are no inconsistencies between them.

Laboratory tests are performed at a central laboratory. Central Laboratory data will be transferred electronically to the sponsor or designee at predefined intervals during the study. The Central laboratory will provide the sponsor or designee with a complete and clean copy of the data.

ECG results are performed at a central ECG reading. Central ECG read data will be transferred electronically to the sponsor or designee at predefined intervals during the study. The central ECG laboratory will provide the sponsor or designee with a complete and clean copy of the data.

TVU central results are performed by a central TVU reader. Central TVU read data will be transferred electronically to the sponsor or designee at predefined intervals during the study. The central TVU imaging facility will provide the sponsor or designee with a complete and clean copy of the data.

Endometrial biopsies will be analyzed by central pathologists. Central biopsy readings will be transferred electronically to the sponsor or designee at predefined intervals during the study. The central pathology facility will provide the sponsor or designee with a complete and clean copy of the data.

All procedures conducted under the protocol must be documented. For screen failures, the minimum demographic data (sex, birth date, race and informed consent date), outcome of eligibility assessment (inclusion and exclusion criteria), reason for screen failure and AEs details must be documented.

The investigator or designee will be responsible for source data completion and that all data and queries are accurate, complete and are verifiable with the source. The source should be appropriately maintained by the clinical unit.

Electronic data sources and any supporting documents should be available for review/retrieval by the sponsor/designee at any given time.

8.1.1 Electronic Clinical Outcome Assessment/Electronic Patient-Reported Outcome

Subject questionnaires will be completed by the subject on an electronic device and the collected electronic source data will be hosted at the vendor. The investigator or site designee should review the questionnaire data while the subject is at the site.

The questionnaire data will be transferred electronically to sponsor or designee at predefined intervals during the study. The vendor will provide the investigator with a complete and clean copy of their site's data and will provide the sponsor or designee with a complete and clean copy of the study data. The ownership of this data is with the investigator and subsequently any changes requested to these subject reported data will be made using a Data Clarification Form to the vendor. The requested change must be supported by documented evidence at site.

8.2 Screen Failures

For screen failures the demographic data, reason for failing, informed consent, inclusion and exclusion criteria and AEs will be collected in the eCRF.

8.3 Major Protocol Deviations

A protocol deviation is generally an unplanned excursion from the protocol that is not implemented or intended as a systematic change. Deviations from the protocol are to be recorded. A protocol waiver is a documented prospective approval of a request from an investigator to deviate from the protocol. Protocol waivers are strictly prohibited.

The investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol and must protect the rights, safety and well-being of subjects. The investigator should not implement any deviation from, or changes of, the protocol, unless it is necessary to eliminate an immediate hazard to subjects.

A major protocol deviation is 1 that may potentially impact the completeness, accuracy or reliability of data contributing to the primary endpoint or affect the rights, safety or well-being of a subject. Major protocol deviations will have additional reporting requirements.

When a major deviation from the protocol is identified for an individual subject, the investigator or designee must ensure the sponsor is notified. The sponsor will follow up with the investigator, as applicable, to assess the deviation and the possible impact to the safety

and/or efficacy or pharmacokinetic parameters of the subject to determine subject continuation in the study.

The major protocol deviation criteria that will be summarized at the end of the study are as follows:

PD1 - Entered into the study even though the subject did not satisfy entry criteria

PD2 - Developed withdrawal criteria during the study and was not withdrawn

PD3 - Received wrong treatment or incorrect dose

PD4 - Received excluded concomitant treatment

The investigator will also assure that deviations meeting IRB/IEC and appropriate regulatory authorities' criteria are documented and communicated appropriately. All documentation and communications to the IRB/IEC and appropriate regulatory authorities will be provided to the sponsor and maintained within the Trial Master File.

9 END OF TRIAL

The end of the study is defined as the last visit or scheduled procedure shown in the Schedule of Assessments for the last study participant in the study.

10 STUDY ORGANIZATION

10.1 Data Monitoring Committee

A DMC will evaluate the safety data of subjects enrolled on a periodic basis during this study. DMC members will be clinicians with expertise in Women's Health studies and are not investigators participating in the study or Astellas employees. A statistician will also be and DMC member. A separate charter will outline the activities of this committee.

An independent data analysis center will provide analysis for the DMC. DMC members may include advice from other external advisors.

10.2 Other Study Organization

A Liver Safety Monitoring Committee consisting of independent hepatologists experienced in the assessment of drug induced liver injury will be formed. This committee will conduct an independent review of individual subject cases that meet the individual withdrawal criteria pertaining to elevated transaminases or other liver health markers and advise the study sponsor whether the individual reviewed cases meet the criteria of a potential DILI. A separate charter will outline the activities of this committee.

11 REFERENCES

Crandall CJ, Manson JE, Hohensee C, Horvath S, Wactawski-Wende J, LeBlanc ES, et al. Association of genetic variation in the tachykinin receptor 3 locus with hot flashes and night sweats in the Women's Health Initiative Study. Menopause. 2017;24(3):252-61.

de Villiers TJ, Hall JE, Pinkerton JV, Cerdas Perez S, Rees M, Yang C, et al. Revised global consensus statement on menopausal hormone therapy. Climacteric. 2016;19:313-5.

FDA Draft Guidance, Estrogen and Estrogen/Progestin Drug Products to Treat Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms – Recommendations for Clinical Evaluation, 2003 at https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm071643.pdf

Hilditch JR, Lewis J, Peter A, van Mark B, Ross A, Franssen E, et al. A menopause-specific quality of life questionnaire: development and psychometric properties. Maturitas. 1996;24:161-75.

Hrabovszky E. Neuroanatomy of the human hypothalamic kisspeptin system. Neuroendocrinology. 2014;99(1):33-48.

Kronenberg F. Hot flashes: epidemiology and physiology. Ann N Y Acad Sci.1990;592:52-86.

Kronenberg F. Hot flashes: phenomenology, quality of life, and search for treatment options. Exp Gerontol. 1994; 29:319-36.

Lehman MN, Coolen LM, Goodman RL. Minireview: Kisspeptin/neurokinin B/dynorphin (KNDy) cells of the arcuate nucleus: A central node in the control of gonadotropin-releasing hormone secretion. Endocrinology. 2010;151(8):3479-89.

Lewis JE, Hilditch JR, Wong CJ. Further psychometric property development of the Menopause-Specific Quality of Life questionnaire and development of a modified version, MENQOL-Intervention questionnaire. Maturitas. 2005;50:209-21.

Loprinzi CL, Kugler JW, Sloan JA, Mailliard JA, La Vasseur BI, Barton DL, et al. Venlafaxine in management of hot flashes in survivors of breast cancer: a randomised controlled trial. Lancet. 2000;356:2059-63.

Loprinzi CL, Sloan JA, Perez EA, Quella SK, Stella PJ, Mailliard JA, et al. Phase III evaluation of fluoxetine for treatment of hot flashes. J Clin Oncol. 2002;20:1578-83.

McCloskey EV, Oden A, Harvey NC, Leslie WD, Hans D, Johansson H, et al. A meta-analysis of trabecular bone score in fracture risk prediction and its relationship to FRAX. J Bone Mineral Res. 2016;31(5):940-8.

Millar RP, Newton CL. Current and future applications of GnRH, kisspeptin and neurokinin B analogues. Nat Rev Endocrinol. 2013;9:451-66.

Muschitz C, Kocijana R, Haschka J, Pahr D, Kaider A, Pietschmann P, et al. TBS reflects trabecular microarchitecture in premenopausal women and men with idiopathic osteoporosis and low-traumatic fractures. Bone. 2015;79:259-66.

Rance NE, Young WS III. Hypertrophy and increased gene expression of neurons containing neurokinin-B and substance-P messenger ribonucleic acids in the hypothalami of postmenopausal women. Endocrinology. 1991;128:2239-47.

Rance NE. Menopause and the human hypothalamus: Evidence for the role of kisspeptin/neurokinin B neurons in the regulation of estrogen negative feedback. Peptides. 2009;30:111-22.

Rance NE, Dacks PA, Mittelman-Smith MA, Romanovsky AA, Krajewski-Hall SJ. Modulation of body temperature and LH secretion by hypothalamic KNDy (kisspeptin, neurokinin B and dynorphin) neurons: A novel hypothesis on the mechanism of hot flushes. Front Neuroendocrinol. 2013;34(3):211-27.

Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, Kooperberg C, Stefanick M L, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: Principal results from the Women's Health Initiative randomized controlled trial. JAMA. 2002;288:321-33.

Ruka KA, Burger LL, Moenter SM. Both estrogen and androgen modify the response to activation of neurokinin-3 and κ -opioid receptors in arcuate kisspeptin neurons from male mice. Endocrinology. 2016;157(2):752-63.

Stearns V, Isaacs C, Rowland J, Crawford J, Ellis MJ, Kramer R, et al. A pilot trial assessing the efficacy of paroxetine hydrochloride (Paxil) in controlling hot flashes in breast cancer survivors. Ann Oncol. 2000;11:17-22.

Stearns V, Beebe KL, Iyengar M, Dube E. Paroxetine controlled release in the treatment of menopausal hot flashes: A randomized controlled trial. JAMA. 2003;289(21):2827-34.

Thurston RC and Joffe H. Vasomotor symptoms and menopause: Findings from the study of Women's Health Across the Nation. Obstet Gynecol Clin North Am. 2011;38(3):489-501.

van Reenen M and Jannssen B. EQ-5D-5L User Guide: basic information on how to use the EQ-5D-5L instrument. Version 2.1. April 2015. Available at https://euroqol.org/wp-content/uploads/2016/09/EQ-5D-5L_UserGuide_2015.pdf. Accessed 11 October 2018.

12 APPENDICES

12.1 Ethical, Regulatory, and Study Oversight Considerations

12.1.1 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, ICH guidelines, applicable regulations and guidelines governing clinical study conduct and the ethical principles that have their origin in the Declaration of Helsinki.

12.1.2 Institutional Review Board (IRB)/Independent Ethics Committee (IEC)/ Competent Authorities (CA)

GCP requires that the clinical protocol, any protocol amendments, the IB, the informed consent and all other forms of subject information related to the study (e.g., advertisements used to recruit subjects) and any other necessary documents be reviewed by an IEC/IRB. The IEC/IRB will review the ethical, scientific and medical appropriateness of the study before it is conducted. IEC/IRB approval of the protocol, informed consent and subject information and/or advertising, as relevant, will be obtained prior to the authorization of drug shipment to a study site.

Any substantial amendments to the protocol will require IRB/IEC approval before implementation, except for changes necessary to eliminate an immediate hazard to subjects.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

12.1.3 Protocol Amendment and/or Revision

Any changes to the study that arise after approval of the protocol must be documented as protocol amendments: substantial amendments and/or nonsubstantial amendments. Depending on the nature of the amendment, either IRB/IEC, Competent Authority approval or notification may be required. The changes will become effective only after the approval of the sponsor, the investigator, the regulatory authority, and the IRB/IEC (if applicable).

Amendments to this protocol must be signed by the sponsor and the investigator. Written verification of IRB/IEC approval will be obtained before any amendment is implemented. Modifications to the protocol that are administrative in nature do not require IRB/IEC approval, but will be submitted to the IRB/IEC for their information, if required by local regulations.

If there are changes to the informed consent, written verification of IRB/IEC approval must be forwarded to the sponsor. An approved copy of the new informed consent must also be forwarded to the sponsor.

12.1.4 Financial Disclosure

Investigators and subinvestigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

12.1.5 Informed Consent of Subjects

12.1.5.1 Subject Information and Consent

The investigator or his/her representative will explain the nature of the study to the subject and answer all questions regarding this study. Prior to any study-related screening procedures being performed on the subject, the informed consent statement will be reviewed, signed and dated by the subject, the person who administered the informed consent and any other signatories according to local requirements. A copy of the signed ICF will be given to the subject and the original will be placed in the subject's medical record. An entry must also be made in the subject's dated source documents to confirm that informed consent was obtained prior to any study-related procedures and that the subject received a signed copy.

The signed consent forms will be retained by the investigator and made available (for review only) to the study monitor and auditor regulatory authorities and other applicable individuals upon request.

1. Supply of New and Important Information Influencing the Subject's Consent and Revision of the Written Information. The investigator or his/her representative will immediately inform the subject orally whenever new information becomes available that may be relevant to the subject's consent or may influence the subject's willingness to continue to participate in the study (e.g., report of serious drug adverse drug reaction). The communication must be documented in the subject's medical records and whether the subject is willing to remain in the study or not must be confirmed and documented.
2. The investigator must update the subject's ICF and submit it for approval to the IRB/IEC. The investigator or his/her representative must obtain written informed consent from the subject on all updated ICFs throughout their participation in the study. The investigator or his/her designee must re-consent subjects with the updated ICF even if relevant information was provided orally. The investigator or his/her representative who obtained the written informed consent and the subject should sign and date the ICF. A copy of the signed ICF will be given to the subject and the original will be placed in the subject's medical record. An entry must be made in the subject's records documenting the re-consent process.

12.1.6 Source Documents

Source data must be available at the site to document the existence of the study subjects and to substantiate the integrity of study data collected. Source data must include the original documents relating to the study, as well as the medical treatment and medical history of the subject.

The investigator is responsible for ensuring the source data are attributable, legible, contemporaneous, original, accurate and complete whether the data are hand-written on paper or entered electronically. If source data are created (first entered), modified, maintained, achieved, retrieved or transmitted electronically via computerized systems (and/or other kind of electric devices) as part of regulated clinical trial activities, such systems must be compliant with all applicable laws and regulations governing use of electronic records and/or electronic signatures. Such systems may include, but are not limited to, electronic medical/health records, protocol related assessments, AE tracking, and/or drug accountability.

Paper records from electronic systems used in place of electronic format must be certified copies. A certified copy must be an exact copy and must have all the same attributes and information as the original. Certified copies must include signature and date of the individual completing the certification. Certified copies must be a complete and chronological set of study records (including notes, attachments, and audit trail information (if applicable). All printed records must be kept in the subject file and available for archive.

12.1.7 Record Retention

The investigator will archive all study data (e.g., subject identification code list, source data, CRFs and investigator's file) and relevant correspondence. These documents are to be kept on file for the appropriate term determined by local regulation (for US sites, 2 years after approval of the NDA or discontinuation of the IND). The sponsor will notify the site/investigator if the NDA/MAA/J-NDA is approved or if the IND/IMPD/CHIKEN TODOKE is discontinued. The investigator agrees to obtain the sponsor's agreement prior to disposal, moving or transferring of any study-related records. The sponsor will archive and retain all documents pertaining to the study according to local regulations.

Data generated by the methods described in the protocol will be recorded in the subjects' medical records and/or study progress notes.

12.1.8 Subject Confidentiality and Privacy

Individual subject medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited unless otherwise the subject provides written consent or approval. Additional medical information may be given only after approval of the subject to the investigator or to other appropriate medical personnel responsible for the subject's well-being.

The sponsor shall not disclose any confidential information on subjects obtained during the performance of their duties in the clinical study without justifiable reasons.

Even though any individuals involved in the study, including the study monitors and auditors, may get to know matters related to subject's privacy due to direct access to source documents, or from other sources, they may not leak the content to third parties.

The sponsor affirms the subject's right to protection against invasion of privacy. Only a subject identification number will identify subject data retrieved by the sponsor. However, the sponsor requires the investigator to permit the sponsor, sponsor's representative(s), the IRB/IEC and when necessary, representatives of the regulatory health authorities to review and/or to copy any medical records relevant to the study.

The sponsor agrees to comply and process personal data in accordance with all applicable privacy laws and regulations, including, without limitation, the Personal Information Protection Law in Japan and Privacy laws in the US. If the services will involve the collection or processing of personal data (as defined by applicable data protection legislation) within the European Economic Area (EEA), then the sponsor shall serve as the controller of such data, as defined by the European Union (EU) Data Protection Directive, and the investigator and/or third party shall act only under the instructions of the sponsor in regard to personal data. If the sponsor is not based in the EEA, the sponsor must appoint a third party to act as its local data protection representative or arrange for a co-controller established in the EU for data protection purposes in order to comply with the Directive.

12.1.9 Arrangement for Use of Information and Publication of the Clinical Study

Information concerning the study drug, patent applications, processes, unpublished scientific data, the IB and other pertinent information is confidential and remains the property of the sponsor. Details should be disclosed only to the persons involved in the approval or conduct of the study. The investigator may use this information for the purpose of the study only. It is understood by the investigator that the sponsor will use the information obtained during the clinical study in connection with the development of the drug and therefore may disclose it as required to other clinical investigators or to regulatory agencies. In order to allow for the use of the information derived from this clinical study, the investigator understands that he/she has an obligation to provide the sponsor with all data obtained during the study.

Publication of the study results is discussed in the clinical study agreement.

12.1.10 Insurance of Subjects and Others

The sponsor has covered this study by means of an insurance of the study according to national requirements. The name and address of the relevant insurance company, the certificate of insurance, the policy number and the sum insured are provided in the investigator's file.

12.1.11 Signatory Investigator for Clinical Study Report

ICH E3 guidelines recommend and EU Directive 2001/83/EC requires that a final study report which forms part of a marketing authorization application be signed by the representative for the coordinating investigator(s) or the principal investigator(s). The representative for the coordinating investigator (s) or the principal investigator(s) will have the responsibility to review the final study results to confirm to the best of his/her knowledge

it accurately describes the conduct and results of the study. The representative for coordinating investigator(s) or the principal investigator(s) will be selected from the participating investigators by the sponsor prior to database lock.

12.2 Procedure for Clinical Study Quality Control

12.2.1 Clinical Study Monitoring

The sponsor or delegated contract research organization (CRO) is responsible for monitoring the clinical study to ensure that subject's human rights, safety, and well-being are protected, that the study is properly conducted in adherence to the current protocol and GCP, and study data reported by the investigator/subinvestigator are accurate and complete and that they are verifiable with study-related records such as source documents. The sponsor is responsible for assigning study monitor(s) to this study for proper monitoring. They will monitor the study in accordance with planned monitoring procedures.

12.2.2 Direct Access to Source Data/Documents

The investigator and the study site must accept monitoring and auditing by the sponsor or delegated CRO, as well as inspections from the IRB/IEC and relevant regulatory authorities. In these instances, they must provide all study-related records including source documents when they are requested by the sponsor monitors and auditors, the IRB/IEC or regulatory authorities. The confidentiality of the subject's identities shall be well protected consistent with local and national regulations when the source documents are subject to direct access.

12.2.3 Data Management

Data Management will be coordinated by the Data Science of the sponsor in accordance with the SOPs for data management. All study-specific processes and definitions will be documented by Data Management. eCRF completion will be described in the eCRF instructions. Coding of medical terms and medications will be performed using MedDRA and World Health Organization Drug Dictionary, respectively.

12.2.4 Quality Assurance

The sponsor is implementing and maintaining quality assurance (QA) and QC systems with written SOPs to ensure that studies are conducted and data are generated, documented, recorded, and reported in compliance with the protocol, GCP and applicable regulatory requirement(s). Where applicable, the QA and QC systems and written SOPs of the CRO will be applied.

The sponsor or sponsor’s designee may arrange to audit the study at any or all study sites and facilities. The audit may include on-site review of regulatory documents, CRFs and source documents. Direct access to these documents will be required by the auditors.

To support quality around subject safety and reliability of study results, quality tolerance limits (QTLs) are defined and monitored. QTLs represent the acceptable variation of study data, taking into consideration the current state of medical and statistical knowledge about the variables to be analyzed as well as the statistical design of the study. It is a level, point, or value associated with a parameter that should trigger an evaluation if a deviation is detected to determine if there is a possible systematic issue (i.e., a trend has occurred). The QTLs defined for this study, information regarding the QTL limit and limit justification, as well as associated activities are documented in STL-3458 QTL monitoring plan.

12.3 Contraception Requirements

WOCBP participants who choose complete abstinence must continue to have pregnancy tests, as specified in Schedule of Assessments.

WOMEN OF CHILDBEARING POTENTIAL DEFINITIONS AND METHODS OF CONTRACEPTION DEFINITIONS (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile.

Women in the following categories are not considered WOCBP

- Premenarchal
- Premenopausal female with 1 of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy
- Post-menopausal

Documentation of any of these categories can come from the site personnel's review of the female subject's medical records, medical examination, or medical history interview.

A postmenopausal state is defined as at least 12 months after last regular menstrual bleeding without an alternative medical cause.

- In case the last regular menstrual bleeding cannot be clearly determined, confirmation with repeated FSH measurements of at least > 40 IU/L (or higher per local institutional guidelines), is required.

Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status by repeated FSH measurements before study enrollment.

CONTRACEPTION GUIDANCE FOR FEMALE PARTICIPANTS OF CHILD BEARING POTENTIAL

One of the highly effective methods of contraception listed below is required at the time of informed consent and until the end of relevant systemic exposure, defined as 21days after the final study drug administration.[a]

Highly Effective Contraceptive Methods (Failure rate of < 1% per year when used consistently and correctly)[b]

Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b]

- oral
- intravaginal
- transdermal

Progestogen-only hormonal contraception associated with inhibition of ovulation

- oral
- injectable
- implantable

Hormonal methods of contraception containing a combination of estrogen and P4, vaginal ring, injectables, implants and intrauterine hormone-releasing systems

- intrauterine device
- bilateral tubal occlusion

[a] Local laws and regulations may require use of alternative and/or additional contraception methods.

[b] Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies.

12.4 List of Excluded Concomitant Medications

These lists are not inclusive of all possible prohibited medications. In case of doubt, the Investigator must contact the local medical monitor.

- Use of hormonal medications such as hormone therapy, HRT or hormonal contraception or any treatment for menopausal symptoms (prescription, over the counter or herbal) is not allowed during the study.
- Investigational research products that have not been approved for any indication in the country where the subject is enrolled.

Strong CYP1A2 Inhibitors (AUCr > 5)	
Inhibitor	**Therapeutic Class**
Angelica root - Bai Zhi (Angelica dahurica radix)	Herbal Medications
ciprofloxacin	Antibiotics
clinafloxacin	Antibiotics
enoxacin	Antibiotics
fluvoxamine	SSRIs
oltipraz	Cancer Chemopreventive Agents
rofecoxib	NSAIDS
zafirlukast	Antiasthmatics
Moderate CYP1A2 Inhibitors (AUCr ≥ 2 and AUCr ≤ 5)	
Inhibitor	**Therapeutic Class**
3,4-methylene-dioxymethamphetamine (MDMA)	Recreational Drugs
etintidine	H-2 Receptor Antagonists
genistein	Food Products
idrocilamide	Muscle Relaxants
methoxsalen (8-methoxypsoralen)	Antipsoriatics
mexiletine	Antiarrhythmics
osilodrostat	Adrenal Steroidogenesis Inhibitors
oral contraceptives	Oral Contraceptives
phenylpropanolamine	Vasoconstrictors
pipemidic acid	Antibiotics
propafenone	Antiarrhythmics
propranolol	Alpha/Beta Adrenergic Antagonists
troleandomycin	Antibiotics
vemurafenib	Kinase Inhibitors

AUCr: area under the concentration-time curve ratio; CYP: cytochrome P450; MDMA: 3,4-methylene-dioxymethamphetamine; NSAID: nonsteroidal anti-inflammatory drugs; SSRI: Selective serotonin reuptake inhibitors.

Estrogen-Only Medicines	
Brand Name	Generic Name
Alora	Estradiol
Cenestin	Synthetic Conjugated Estrogens
Climara	Estradiol
Delestrogen	Estradiol Valerate
Divigel	Estradiol
Elestrin	Estradiol
Enjuvia	Synthetic Conjugated Estrogens
Esclim	Estradiol
Estrace	Estradiol
Estraderm	Estradiol
Estrasorb	Estradiol
Estring	Estradiol
EstroGel	Estradiol
Evamist	Estradiol
Femring	Estradiol Acetate
Femtrace	Estradiol Acetate
Menest	Esterified Estrogen
Menostar	Estradiol
(only used to prevent osteoporosis)	
Minivelle	Estradiol
Ogen	Estropipate
Ortho-Est	Estropipate
Premarin	Conjugated Estrogens
Vagifem	Estradiol
Vivelle	Estradiol
Vivelle-Dot	Estradiol
Progestin-Only Medicines	
Brand Name	Generic Name
Prometrium	Micronized Progesterone
Aygestin	norethindrone acetate
Provera	Medroxyprogesterone Acetate

Estrogen-Only Medicines	
Combination Estrogen and Progestin Medicines	
Brand Name	Generic Name
Activella	Estradiol/
	Norethindrone Acetate
Angeliq	Estradiol/ Drospirenone
Climara Pro	Estradiol/
	Levonorgestrel
Combipatch	Estradiol/
	Norethindrone Acetate
Jinteli	Ethinyl Estradiol/
	Norethindrone Acetate
Mimvey	Estradiol/
	Norethindrone Acetate
Femhrt	Norethindrone Acetate/
	Ethinyl Estradiol
Prefest	Estradiol/
	Norgestimate
Prempro	Conjugated Estrogen/
	Medroxyprogesterone
Premphase	Conjugated Estrogen/
	Medroxyprogesterone
Combination Estrogen and Hormone Medicines	
Brand Name	Generic Name
Duavee	Conjugated Estrogen/ Bazedoxifene

12.5 Liver Safety Monitoring and Assessment

Any subject enrolled in a clinical study with active drug therapy and reveals an increase of serum aminotransferases (AT) to > 3 × ULN or bilirubin > 2 × ULN should undergo detailed testing for liver enzymes (including at least ALT, AST, ALP and TBL). Testing should be repeated within 72 hours of notification of the test results. For studies for which a central laboratory is used, alerts will be generated by the central laboratory regarding moderate and severe liver abnormality to inform the investigator and study team. Subjects should be asked if they have any symptoms suggestive of hepatobiliary dysfunction.

Definition of Liver Abnormalities

Confirmed abnormalities will be characterized as moderate and severe where ULN:

	ALT or AST		**TBL**
Moderate	> 3 × ULN	or	> 2 × ULN
Severe	> 3 × ULN	and	> 2 × ULN

In addition, the subject should be considered to have severe hepatic abnormalities for any of the following:

- ALT or AST > 8 × ULN;
- ALT or AST > 5 × ULN for more than 2 weeks;
- ALT or AST > 3 × ULN **AND** TBL > 2 × ULN or INR > 1.5; or
- ALT or AST > 3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (> 5% increase above baseline).

The investigator may determine that abnormal liver test results, other than as described above, may qualify as moderate or severe abnormalities and require additional monitoring and follow-up.

Follow-up Procedures

Confirmed moderate and severe abnormalities in hepatic tests should be thoroughly characterized by obtaining appropriate expert consultations, detailed pertinent history, physical examination and laboratory tests. The site staff is to complete the liver abnormality case report form (LA-CRF). Subjects with confirmed liver aminotransferases (ALT or AST) should be followed as described below.

Confirmed moderately abnormal liver tests should be repeated 2 to 3 times weekly then weekly or less if abnormalities stabilize or the study drug has been discontinued and the subject is asymptomatic.

Severe liver test abnormalities as defined above, in the absence of another etiology, are considered an important medical event and should be reported as a SAE. The sponsor should be contacted and informed immediately of all subjects for whom severe hepatic liver function abnormalities possibly attributable to study drug are observed.

To further assess abnormal hepatic laboratory findings, the investigator is expected to:

- Obtain a more detailed history of symptoms and prior or concurrent diseases. Symptoms and new-onset diseases is to be recorded as "AEs" within the eCRF. Illnesses and conditions such as hypotensive events, and decompensated cardiac disease that may lead to secondary liver abnormalities should be noted. Nonalcoholic steatohepatitis is seen in obese hyperlipoproteinemic and/or diabetic patients, and may be associated with fluctuating AT levels. The investigator should ensure that the medical history form captures any illness that predates study enrollment that may be relevant in assessing hepatic function.
- Obtain a history of concomitant drug use (including nonprescription medication, complementary and alternative medications), alcohol use, recreational drug use and special diets. Medications, is to be entered in the eCRF. Information on alcohol, other substance use and diet should be entered on the LA-CRF or an appropriate document.
- Obtain a history of exposure to environmental chemical agents.
- Based on the subject's history, other testing may be appropriate including:
    - Acute viral hepatitis (A, B, C, D, E or other infectious agents),
    - Ultrasound or other imaging to assess biliary tract disease,
    - Other laboratory tests including INR and DBL.
- Consider gastroenterology or hepatology consultations.
- Submit results for any additional testing and possible etiology on the LA-CRF or an appropriate document.

Study Treatment Discontinuation

In the absence of an explanation for increased liver aminotransferases (ALT or AST) tests, such as viral hepatitis, preexisting or acute liver disease, or exposure to other agents associated with liver injury, the subject may be discontinued from study treatment. The investigator may determine that it is not in the subject's best interest to continue study treatment. Study treatment must be discontinued and event reported as an SAE if:

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

Subjects who develop a signal for liver injury will be monitored every 2 to 4 weeks if the study drug is discontinued. If the subject remains on study drug, they will be closely monitored for liver biochemistry results.

Subjects with a signal of elevated (> 3 × ULN) transaminases will have pharmacokinetic samples drawn in addition to repeat blood draws for liver biochemistry monitoring. These samples can be held for potential analysis based on the subject's clinical outcome.

In addition, if close monitoring for a subject with moderate or severe hepatic laboratory tests is not possible, study treatment should be discontinued.

***Hy's Law Definition**: Drug-induced jaundice caused by hepatocellular injury, without a significant obstructive component, has a high rate of bad outcomes, from 10 to 50% mortality (or transplant).

The 2 "requirements" for Hy's Law are:

1. Evidence that a drug can cause hepatocellular-type injury, generally shown by an increase in transaminase elevations higher 3 × ULN (2 × ULN elevations are too common in treated and untreated patients to be discriminating).
2. Cases of increased bilirubin (at least 2 × ULN) in people with concurrent transaminase elevations to at least 3 × ULN (but it is almost invariably higher) and no evidence of intra- or extra-hepatic bilirubin obstruction (elevated ALP) or Gilbert's syndrome [Temple, 2006].

FDA Guidance for Industry titled "Drug-induced Liver Injury: Premarketing Clinical Evaluation" issued by the FDA on July 2009:

FDA Guidance for Industry:

1. The drug causes hepatocellular injury, generally shown by a higher incidence of 3-fold or greater elevations above the ULN of ALT or AST than the (nonhepatotoxic) control drug or placebo.
2. Among trial subjects showing such AT elevations, often with ATs much greater than 3 × ULN, one or more also show elevation of serum TBL to > 2 × ULN, without initial findings of cholestasis (elevated serum ALP).
3. No other reason can be found to explain the combination of increased AT and TBL, such as viral hepatitis A, B, or C; preexisting or acute liver disease; or another drug capable of causing the observed injury.

References

Temple R. Hy's law: Predicting Serious Hepatotoxicity. Pharmacoepidemiol Drug Saf. 2006 April;15(Suppl 4):241-3.

12.6 Common Serious Adverse Events

For this protocol, there is no list of common SAEs anticipated for the study population for the purposes of IND safety reporting.

12.7 Clinical Study Continuity

INTRODUCTION

The purpose of this appendix is to provide acceptable alternate methods to assess safety and efficacy parameters, as appropriate, in the event the clinical study is interrupted at the country, state, site or participant level during any crisis (e.g., natural disaster, pandemic).

BENEFIT-RISK RATIONALE

Maintaining the safety of clinical study participants and delivering continuity of care in the clinical study setting is paramount during any crisis. The site is expected to follow the protocol and associated Schedule of Assessments [Table 1] unless the site principal investigator discusses the need with the Astellas medical monitor to implement the alternate measures.

The approach outlined within this appendix defines which assessments are required to maintain a favorable benefit/risk to the participant, to maintain overall study integrity and to provide acceptable alternate methods to complete the study required assessments and procedures if study activities are unable to be performed as described in [Section 5 Treatments and Evaluation] due to a crisis.

INFORMED CONSENT

Participants who need to follow any or all of the alternate measures outlined in this Appendix will be required to provide informed consent which explicitly informs them of the nature of, and rationale for these changes, and gain their agreement to continue participation in the study prior to the implementation of any of these changes. In the event the urgency of implementing the alternate measures does not allow for the participant to provide written consent prior to implementation, the principal investigator or designee will obtain oral agreement from the subject followed by written documentation as soon as is feasible. A separate addendum to the study informed consent will be provided to document the participant's consent of the changes.

PARTICIPANT PROCEDURES ASSESSMENT

Sites with participants who are currently enrolled into this clinical study may consider implementing the alternate methods outlined below if one or more of the following conditions are met due to the crisis:

- Regional or local travel has been restricted, inclusive of mandatory shelter in place measures, which makes participant travel to/from the study site nearly impossible
- Site facilities have been closed for clinical study conduct
- Site has been restricted to treating patients with conditions outside of the scope of the study
- Site personnel have temporarily relocated the conduct of the study to a location that place a burden on the participant with respect to time and travel

- Participant(s) have temporarily relocated from the current study site to an alternate study site to avoid placing a burden on the participant with respect to travel
- Participant(s) have temporarily relocated from their home location and the new distances from the site would cause undue burden with respect to time and travel
- Participant has risk factors for which traveling to the site poses an additional risk to the participant's health and safety

Adherence to the original protocol as reflected in the Schedule of Assessment [Table 1] is expected, where plausible, in the case of a crisis. The alternate measures as noted in Table 3 below are only permissible in the event of a crisis, and after discussing the need with the Astellas medical monitor to implement the alternate measures. This is to allow for continuity of receiving investigational medicinal product (IMP) and maintaining critical safety and efficacy assessments for patients participating in the study at a time of crisis.

If one or more of the alternate measures noted below is implemented for a participant, the site should document in the participant's source document the justification for implementing the alternate measure and the actual alternate measures that were implemented, along with the corresponding time point(s).

Table 3 Alternative Schedule of Assessments in Response to a Crisis

Assessments	Alternate Approaches	Treatment Period									Follow-up Visit
Study Visit		**Visit 2b**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visits 9, 10, 11, 12, 13 and 14**	**Visit 15/ EOT/ED**	**Visit 16**
Time of Visit		**Week 2**	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24**	**Weeks 28, 32, 36, 40, 44 and 48**	**Week 52**	**Week 55**
Visit days		**Day 15**	**Day 29**	**Day 57**	**Day 85**	**Day 113**	**Day 141**	**Day 169**	**Day 197, 225, 253, 281, 309 and 337**	**Day 365**	**Day 386**
Visit Window (days)		**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**-14 /+ 6**	**± 3**
Mammogram	If imaging is delayed, should be completed as soon as possible.	Please refer to protocol schedule of assessments.									
Demographic data	Remote/Virtual/Telemedicine Visits allowed	Please refer to protocol schedule of assessments.									
Urine pregnancy test	Visit collection of samples at local facility acceptable if results can be made available to investigative site. To be completed at local laboratory.	Please refer to protocol schedule of assessments.									
Clinical laboratory	Visit collection of samples at local facility acceptable if results can be made available to investigative site. To be completed at local laboratory.	Please refer to protocol schedule of assessments.									
Serology	Visit collection of samples at local facility acceptable if results can be made available to investigative site. To be completed at local laboratory.	Please refer to protocol schedule of assessments.									
Blood pharmacodynamic sample	Delay the measurements to subsequent visit.	Please refer to protocol schedule of assessments.									
Blood pharmacokinetic sample	Delay the measurements to subsequent visit.	Please refer to protocol schedule of assessments.									

Table continued on next page

Assessments	**Alternate Approaches**	**Treatment Period**									**Follow-up Visit**
Study Visit		**Visit 2b**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visits 9, 10, 11, 12, 13 and 14**	**Visit 15/ EOT/ED**	**Visit 16**
Time of Visit		**Week 2**	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24**	**Weeks 28, 32, 36, 40, 44 and 48**	**Week 52**	**Week 55**
Visit days		**Day 15**	**Day 29**	**Day 57**	**Day 85**	**Day 113**	**Day 141**	**Day 169**	**Day 197, 225, 253, 281, 309 and 337**	**Day 365**	**Day 386**
Visit Window (days)		**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**-14 /+ 6**	**± 3**
C-SSRS	Remote/Virtual/Telemedicine Visits allowed	Please refer to protocol schedule of assessments.									
EQ-5D-5L	Remote/Virtual/Telemedicine Visits allowed for non-dosing visits	Please refer to protocol schedule of assessments.									
MENQoL	Remote/Virtual/Telemedicine Visits allowed for non-dosing visits	Please refer to protocol schedule of assessments.									
ePRO training	Remote/Virtual/Telemedicine Visits allowed for non-dosing visits	Please refer to protocol schedule of assessments.									
Dispense study drug	Patients can be brought into the clinic earlier to provide additional study drug. Courier service directly to patient allowed.	Please refer to protocol schedule of assessments.									
Study drug compliance and accountability	Patients can be brought into the clinic earlier to provide additional study drug. Courier service directly to patient allowed.	Please refer to protocol schedule of assessments.									
Concomitant medications and AEs	Remote/Virtual/Telemedicine Visits allowed for non-dosing visits	Please refer to protocol schedule of assessments.									

AE: adverse event; C-SSRS: Columbia Suicide Severity Rating Scale; ED: early discontinuation; EOT: end of treatment; ePRO: electronic patient-reported outcome; EQ-5D-5L: Euro-Qol 5D-5L; MENQoL: Menopause-Specific Quality of Life.

INVESTIGATIONAL MEDICINAL PRODUCT SUPPLY

If any of the conditions outlined above in the Participants Procedures Assessment are met, one or all of the following mitigating strategies will be employed, as needed, to ensure continuity of IMP supply to the participants:

- Increase stock of IMP on site to reduce number of shipments required, if site space will allow.
- Direct-to-Participant shipments of IMP from the site to the participant's home.
- Bringing the participant to the site earlier.

DATA COLLECTION REQUIREMENTS

Additional data may be collected in order to indicate how participation in the study may have been affected by a crisis and to accommodate data collection resulting from alternate measures implemented to manage the conduct of the study and participant safety.

- Critical assessments for safety and efficacy based on study endpoints to be identified as missing or altered (performed virtually, at alternative locations, out of window, or other modifications) due to the crisis.

13 ATTACHMENT 1: NONSUBSTANTIAL AMENDMENT 3

I. The purpose of this amendment is:

Nonsubstantial Changes
1. Update End of Treatment (EOT) Visit Window
DESCRIPTION OF CHANGE:
The EOT visit window is expanded from 0/+6 to -14/+6 and a footnote is added to the endometrial biopsy at Visit 15/EOT/early discontinuation.
RATIONALE:
This is to provide more flexibility to investigators and subjects in scheduling the EOT/ED visit, to ensure that there is appropriate opportunity to collect all EOT/ED assessments. In case of an EOT/ED endometrial biopsy that is evaluated as 'insufficient material' or 'unevaluable', the extended visit window will enable a retest biopsy to be conducted within the visit window.
2. Clarification of Visit 15/EOT/ED Endometrial Biopsy Procedures
DESCRIPTION OF CHANGE:
Language is added to clarify that EOT/ED endometrial biopsies that are evaluated as 'insufficient material' or 'unevaluable' a retest biopsy is required. In addition, language was also added to clarify when a repeat biopsy is required.
RATIONALE:
This change is made to further optimize the collection of EOT/ED endometrial biopsies for the primary objective/endpoint of the study and provide clarity on when a repeat biopsy is required.
3. Add Clarification for Pharmacokinetic Sample at Week 52
DESCRIPTION OF CHANGE:
A statement added to the footnote for Blood Pharmacokinetic Sample in the schedule of assessments to clarify that the last dose of study drug should be administered the day prior to the week 52 (visit 15) visit.
RATIONALE:
This revision is made for clarification.
4. Update Timing of Week 52 Dual-Energy X-Ray Absorptiometry (DXA)
DESCRIPTION OF CHANGE:
In Section 5.5.2 and the schedule of assessments, the timing of the week 52 DXA is changed to 'between week 50 and 52.'

RATIONALE:
This revision is made to align with the timing of the adjusted Visit 15/EOT/ED visit window.
5. Clarification of Recording an Abnormal Endometrial Biopsy as an Advese Event (AE)
DESCRIPTION OF CHANGE:
Added that the investigator should record any abnormal biopsies and the associated diagnostic and therapeutic measures, as an AE.
RATIONALE:
Clarification provided to investigator so abnormal endometrial biopsies can be followed to resolution.
6. Removed Platelet Reduction as AE of Special Interest
DESCRIPTION OF CHANGE:
Platelet reduction is removed as an AE of special interest
RATIONALE:
Not consistent with the statistical analysis plan.
7. Removed Significance Testing
DESCRIPTION OF CHANGE:
Removed the significance testing for dichotomized endpoints.
RATIONALE:
The confidence intervals for odds ratio and rate is sufficient for interpretation.
8. Add Appendix for Clinical Study Continuity
DESCRIPTION OF CHANGE:
A Clinical Study Continuity appendix is added to the protocol (Appendix 12.7). This appendix contains procedures for continuity of care during a crisis (e.g., natural disaster or a pandemic).
RATIONALE:
This appendix is added to provide acceptable alternate methods to assess safety and efficacy parameters in the event the clinical study is interrupted at the country, state, site or participant level during any crisis (e.g., natural disaster or pandemic). This is an appendix that is being standardized throughout Astellas. The procedures that are included in this appendix are aligned with what was already included in the previous version of the protocol.

9. Minor Administrative-type Changes
DESCRIPTION OF CHANGE:
Include minor administrative-type changes (e.g., typos, format, numbering and consistency throughout the protocol) and updated list of abbreviations.
RATIONALE:
To provide clarifications to the protocol and to ensure complete understanding of study procedures.

II. Amendment Summary of Changes:

II Contact Details of Key Sponsor's Personnel
WAS:
PPD ICON Clinical Research PPD
IS AMENDED TO;
PPD ICON Clinical Research PPD

III List of Abbreviations and Definition of Key Terms *List of Abbreviations*	
ADDED:	
IMP	**investigational medicinal product**

V Flow Chart and Schedule of Assessments

Table 1 Schedule of Assessments

WAS:

Assessments	Screening Visit[a,x]	Randomi-zation[x]	Treatment Period									Follow-Up Visit[b]
Study Visit	Visit 1	Visit 2	Visit 2b	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visits 9, 10, 11, 12, 13 and 14	Visit 15/ EOT/ED[x]	Visit 16
Time of Visit	Week -5 to -1	Week 0	Week 2	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Weeks 28, 32, 36, 40, 44 and 48	Week 52	Week 55
Visit days	Days -35 to -1	Day 1	Day 15	Day 29	Day 57	Day 85	Day 113	Day 141	Day 169	Day 197, 225, 253, 281, 309 and 337	Day 365	Day 386
Visit Window (days)[c]	-35 to -1	-	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	+ 6	± 3
Endometrial biopsy[n]	X										X	
DXA[o]	X										X	
Serology[p]	X											
Blood pharmacodynamic sample[q]		X		X		X			X		X	X
Blood pharmacokinetic sample[r]				X[r]		X			X		X	
C-SSRS[s]	X	X				X			X		X	X
EQ-5D-5L[t]		X		X		X			X		X	
MENQoL[t]		X		X		X			X		X	
Dispense study drug[u]		X		X	X	X	X	X	X	X		
Study drug compliance and accountability[v]		X		X	X	X	X	X	X	X	X	
Concomitant medications and AEs[w]	X	X	X	X	X	X	X	X	X	X	X	X

n. Endometrial biopsy will be performed at screening and at week 52/EOT and in the case of uterine bleeding during treatment. Subject may schedule the endometrial biopsy on a separate day, within the screening period. Subjects that require a retest biopsy due to insufficient or unevaluable result, will have an extended screening period and will be allowed an additional 15 days of screening (i.e., days -50 to -1). Screening biopsy results are valid for study entry up to 3 months from date of procedures for applicable subjects. Subjects who screen failed due to the COVID-19 pandemic study suspension and have a documented evaluable endometrial biopsy from the original screening period do not have to undergo a repeat biopsy should they decide to rescreen. If a subject discontinues from the study, an endometrial biopsy will be performed at the discontinuation visit along with all other EOT procedures.

p. For practical reasons, the timing of DXA may vary from the actual time of the visit, depending on the DXA availability (DXA appointment). The screening visit (days -35 to -1 [visit 1]) DXA can be performed once the subject has been deemed eligible based on screening laboratory tests, or at visit 2 but must be performed before randomization. The week 52 (visit 15) DXA should be performed between week 51 and week 52, inclusive. For subjects who are withdrawn from the study prior to completion, a DXA will be completed as soon as possible after study drug discontinuation

(preferably within 2 weeks).

s. Pharmacokinetic samples to be taken predose at week 4 (visit 3), week 12 (visit 5), week 24 (visit 8), and at EOT/ED week 52 (visit 15) and at 1 to 3 hour postdose at week 4 (visit 3). A predose sample will be collected for any subject with a signal of elevated (> 3 × ULN) transaminases.

v. Subjects will be assigned study drug as a kit containing either fezolinetant or placebo. Study drug intake will be done with a glass of room temperature tap water. The first intake of study drug will take place at the study site on day 1 (visit 2) under the supervision of the study staff. On study visit days, the daily dose of study drug will be taken at the study site, under the supervision of the study staff, after collection of predose blood samples. On all other days throughout the treatment period, subjects will be instructed to take their study drug at home, in the morning with water.

IS AMENDED TO:

Assessments	Screening Visit[a,x]	Randomi-zation[x]	Treatment Period									Follow-~~U~~up Visit[b]
Study Visit	Visit 1	Visit 2	Visit 2b	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visits 9, 10, 11, 12, 13 and 14	Visit 15/ EOT/ED[xv]	Visit 16
Time of Visit	Week -5 to -1	Week 0	Week 2	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Weeks 28, 32, 36, 40, 44 and 48	Week 52	Week 55
Visit days	Days -35 to -1	Day 1	Day 15	Day 29	Day 57	Day 85	Day 113	Day 141	Day 169	Day 197, 225, 253, 281, 309 and 337	Day 365	Day 386
Visit Window (days)[c]	-35 to -1	-	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	**-14**/+ 6	± 3
Endometrial biopsy[n]	X[n]										X[o]	
DXA[op]	X										X	
Serology[pq]	X											
Blood pharmacodynamic sample[qr]		X		X		X			X		X	X
Blood pharmacokinetic sample[rs]				X[r]		X			X		X	
C-SSRS[st]	X	X				X			X		X	X
EQ-5D-5L[tu]		X		X		X			X		X	
MENQoL[tu]		X		X		X			X		X	
Dispense study drug[uv]		X		X	X	X	X	X	X	X		
Study drug compliance and accountability[vw]		X		X	X	X	X	X	X	X	X	
Concomitant medications and AEs[wx]	X	X	X	X	X	X	X	X	X	X	X	X

v. Endometrial biopsy will be performed at screening and ~~at week 52/EOT and~~ in the case of uterine bleeding during treatment. Subject may schedule the endometrial biopsy on a separate day, within the screening period. Subjects that require a retest biopsy due to insufficient or unevaluable result, will have an extended screening period and will be allowed an additional 15 days of screening (i.e.,

days -50 to -1). Screening biopsy results are valid for study entry up to 3 months from date of procedures for applicable subjects. Subjects who screen failed due to the COVID-19 pandemic study suspension and have a documented evaluable endometrial biopsy from the original screening period do not have to undergo a repeat biopsy should they decide to rescreen. ~~If a subject discontinues from the study, an endometrial biopsy will be performed at the discontinuation visit along with all other EOT procedures.~~

o. Endometrial biopsy is required at EOT or ED. For EOT/ED week 52 (visit 15) biopsies that are evaluated as insufficient material or unevaluable , a retest biopsy will be required. Any of the three pathologists can determine if a EOT/ED biopsy is insufficient or unevaluable. However, if two pathologists read the EOT/ED endometrial biopsy as evaluable and issue the same diagnosis, and the 3rd pathologist reads the biopsy as insufficient or unevaluable, the biopsy does not need to be repeated.

~~o~~**p** For practical reasons, the timing of DXA may vary from the actual time of the visit, depending on the DXA availability (DXA appointment). The screening visit (days -35 to -1 [visit 1]) DXA can be performed once the subject has been deemed eligible based on screening laboratory tests, or at visit 2 but must be performed before randomization. The week 52 (visit 15) DXA should be performed between week **50**~~51~~ and week 52, inclusive. For subjects who are withdrawn from the study prior to completion, a DXA will be completed as soon as possible after study drug discontinuation (preferably within 2 weeks).

~~r~~**s** Pharmacokinetic samples to be taken predose at week 4 (visit 3), week 12 (visit 5), week 24 (visit 8), and at EOT/ED week 52 (visit 15) and at 1 to 3 hour postdose at week 4 (visit 3). A predose sample will be collected for any subject with a signal of elevated (> 3 × ULN) transaminases. **For the week 52 (visit 15) PK/PD samples, the last dose of study drug should be administered the day prior to the week 52 (visit 15) visit. Sites should collect week 52 (visit 15) PK/PD samples approximately at the same time when study drug would typically be given on site.**

v. Subjects will be assigned study drug as a kit containing either fezolinetant or placebo. Study drug intake will be done with a glass of room temperature tap water. The first intake of study drug will take place at the study site on day 1 (visit 2) under the supervision of the study staff. On study visit days **(except for EOT/ED week 52 [visit 15**]), the daily dose of study drug will be taken at the study site, under the supervision of the study staff, after collection of predose blood samples. On all other days throughout the treatment period, subjects will be instructed to take their study drug at home, in the morning with water.

IV Synopsis, Study Design Overview and 2 Study Objectives, Design, and Endpoints *2.2.1 Study Design*
WAS:
At the end of treatment (EOT) (or the early discontinuation [ED] visit for subjects who withdraw from the study prior to completion), a TVU and a suction endometrial biopsy will be performed. If a subject discontinues from the study, an endometrial biopsy will be performed at the discontinuation visit along with all other EOT procedures.
IS AMENDED TO:
At the end of treatment (EOT) (or the early discontinuation [ED] visit for subjects who withdraw from the study prior to completion), a TVU and a suction endometrial biopsy will be performed. If a subject discontinues from the study, an endometrial biopsy ~~will be~~ **is** ~~performed~~ **required** at the discontinuation visit along with all other EOT procedures.

IV Synopsis, Study Design Overview and 2 Study Objectives, Design, and Endpoints *2.2.1 Study Design*
WAS:
At the end of treatment (EOT) (or the early discontinuation [ED] visit for subjects who withdraw from the study prior to completion), a TVU and a suction endometrial biopsy will be performed. If a subject discontinues from the study, an endometrial biopsy will be performed at the discontinuation visit along with all other EOT procedures. During the treatment period, any woman with an abnormal endometrial biopsy reported as disordered proliferative endometrium, endometrial hyperplasia or endometrial cancer will be referred to standard of care clinical management and followed to resolution, and the report of any medical or surgical procedures and the resultant pathology will be obtained.
IS AMENDED TO:
At the end of treatment (EOT) (or the early discontinuation [ED] visit for subjects who withdraw from the study prior to completion), a TVU and a suction endometrial biopsy will be ~~performed~~ **required**. If a subject discontinues from the study, an endometrial biopsy ~~will be performed~~ **is required** at the discontinuation visit along with all other EOT procedures. During the treatment period, any woman with an abnormal endometrial biopsy reported as disordered proliferative endometrium, endometrial hyperplasia or endometrial cancer will be referred to standard of care clinical management and followed to resolution, and the report of any medical or surgical procedures and the resultant pathology will be obtained. **The investigator should record any such biopsy, and the associated diagnostic and therapeutic measures, as an AE.**

5 Treatments and Evaluation *5.1.1 Dose/Dose Regimen and Administration Period*
WAS:

On study visit days study drug will be taken at the study site, under the supervision of the study staff, after collection of predose blood samples. On all other days throughout the treatment period, subjects will be instructed to take their dose of study drug at home with water, in the morning.
IS AMENDED TO:
On study visit days **(except for EOT/ED week 52 [visit 15])** study drug will be taken at the study site, under the supervision of the study staff, after collection of predose blood samples. On all other days throughout the treatment period, subjects will be instructed to take their dose of study drug at home with water, in the morning.

5 Treatments and Evaluation *5.5.2 Dual-Energy X-Ray Absorptiometry (DXA)*
WAS:
The week 52 (visit 15) DXA should be performed between week 51 and week 52, inclusive.
IS AMENDED TO:
The week 52 (visit 15) DXA should be performed between week **50**~~51~~ and week 52, inclusive.

5 Treatments and Evaluation *5.6.1 Endometrial Biopsy*
ADDED:
An endometrial biopsy is required at EOT or ED. For EOT/ED week 52 (visit 15) biopsies that are evaluated as insufficient material or unevaluable, a retest biopsy will be required. Any of the three pathologists can determine if a an EOT/ED is insufficient or unevaluable. However, if two pathologists read the EOT/ED endometrial biopsy as evaluable and issue the same diagnosis, and the 3rd pathologist reads the biopsy as insufficient or unevaluable, the biopsy does not need to be repeated.…… **The investigator should record any such biopsy, and the associated diagnostic and therapeutic measures, as an AE.**

5 Treatments and Evaluation *5.8.7 Adverse Events of Special Interest*
WAS:

Adverse events of special interest in this study will include:

- AE of uterine bleeding
- Endometrial hyperplasia/cancer or disordered proliferative endometrium
- AE of thrombocytopenia or platelets< 15000/uL
- AE of liver test evalations
- AE of bone fractures/bone loss ≥ 7%
- AEs of abuse liability
- AEs of depression
- AEs of wakefulness
- AEs of effect on memory

IS AMENDED TO:

Adverse events of special interest in this study will include:

- AE of uterine bleeding
- Endometrial hyperplasia/cancer or disordered proliferative endometrium
- AE of thrombocytopenia ~~or platelets< 15000/uL~~
- AE of liver test evalations
- AE of bone fractures/bone loss ≥ 7%
- AEs of abuse liability
- AEs of depression
- AEs of wakefulness
- AEs of effect on memory

7 Statistical Methodology
7.6.2 Laboratory Assessments

WAS:

The liver safety assessments will be summarized by the categories below based on the measurements from ALP, ALT, TBL, AST and their combination. These parameters will be based on measurements from a central laboratory.

IS AMENDED TO:

Number and percentage of subjects with platelets < 150x10^9/L will be separately summarized for each treatment group. The liver safety assessments will be summarized by the categories below based on the measurements from ALP, ALT, TBL, AST and their combination. These parameters will be based on measurements from a central laboratory.

12 Appendices

ADDED:

12.7 Clinical Study Continuity

INTRODUCTION

The purpose of this appendix is to provide acceptable alternate methods to assess safety and efficacy parameters, as appropriate, in the event the clinical study is interrupted at the country, state, site or participant level during any crisis (e.g., natural disaster, pandemic).

BENEFIT-RISK RATIONALE

Maintaining the safety of clinical study participants and delivering continuity of care in the clinical study setting is paramount during any crisis. The site is expected to follow the protocol and associated Schedule of Assessments [Table 1] unless the site principal investigator discusses the need with the Astellas medical monitor to implement the alternate measures.

The approach outlined within this appendix defines which assessments are required to maintain a favorable benefit/risk to the participant, to maintain overall study integrity and to provide acceptable alternate methods to complete the study required assessments and procedures if study activities are unable to be performed as described in [Section 5 Treatments and Evaluation] due to a crisis.

INFORMED CONSENT

Participants who need to follow any or all of the alternate measures outlined in this Appendix will be required to provide informed consent which explicitly informs them of the nature of, and rationale for these changes, and gain their agreement to continue participation in the study prior to the implementation of any of these changes. In the event the urgency of implementing the alternate measures does not allow for the participant to provide written consent prior to implementation, the principal investigator or designee will obtain oral agreement from the subject followed by written documentation as soon as is feasible. A separate addendum to the study informed consent will be provided to document the participant's consent of the changes.

PARTICIPANT PROCEDURES ASSESSMENT

Sites with participants who are currently enrolled into this clinical study may consider implementing the alternate methods outlined below if one or more of the following conditions are met due to the crisis:

- **Regional or local travel has been restricted, inclusive of mandatory shelter in place measures, which makes participant travel to/from the study site nearly impossible**
- **Site facilities have been closed for clinical study conduct**
- **Site has been restricted to treating patients with conditions outside of the scope of the study**
- **Site personnel have temporarily relocated the conduct of the study to a location that place a burden on the participant with respect to time and travel**
- **Participant(s) have temporarily relocated from the current study site to an alternate study site to avoid placing a burden on the participant with respect to travel**

- **Participant(s) have temporarily relocated from their home location and the new distances from the site would cause undue burden with respect to time and travel**
- **Participant has risk factors for which traveling to the site poses an additional risk to the participant's health and safety**

Adherence to the original protocol as reflected in the Schedule of Assessment [Table 1] is expected, where plausible, in the case of a crisis. The alternate measures as noted in Table 3 below are only permissible in the event of a crisis, and after discussing the need with the Astellas medical monitor to implement the alternate measures. This is to allow for continuity of receiving investigational medicinal product (IMP) and maintaining critical safety and efficacy assessments for patients participating in the study at a time of crisis.

If one or more of the alternate measures noted below is implemented for a participant, the site should document in the participant's source document the justification for implementing the alternate measure and the actual alternate measures that were implemented, along with the corresponding time point(s).

12 Appendices

ADDED:

Table 3 Alternative Schedule of Assessments in Response to a Crisis

Assessments	Alternate Approaches	Treatment Period									Follow-up Visit
Study Visit		Visit 2b	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visits 9, 10, 11, 12, 13 and 14	Visit 15/ EOT/ED	Visit 16
Time of Visit		Week 2	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Weeks 28, 32, 36, 40, 44 and 48	Week 52	Week 55
Visit days		Day 15	Day 29	Day 57	Day 85	Day 113	Day 141	Day 169	Day 197, 225, 253, 281, 309 and 337	Day 365	Day 386
Visit Window (days)		± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	-14 /+ 6	± 3
Mammogram	If imaging is delayed, should be completed as soon as possible.	Please refer to protocol schedule of assessments.									
Demographic data	Remote/Virtual/Telemedicine Visits allowed	Please refer to protocol schedule of assessments.									
Urine pregnancy test	Visit collection of samples at local facility acceptable if results can be made available to investigative site. To be completed at local laboratory.	Please refer to protocol schedule of assessments.									
Clinical laboratory	Visit collection of samples at local facility acceptable if results can be made available to investigative site. To be completed at local laboratory.	Please refer to protocol schedule of assessments.									
Serology	Visit collection of samples at local facility acceptable if results can be made available to investigative site. To be completed at local laboratory.	Please refer to protocol schedule of assessments.									
Blood pharmacodynamic sample	Delay the measurements to subsequent visit.	Please refer to protocol schedule of assessments.									

Blood pharmacokinetic sample	**Delay the measurements to subsequent visit.**	**Please refer to protocol schedule of assessments.**
C-SSRS	**Remote/Virtual/Telemedicine Visits allowed**	**Please refer to protocol schedule of assessments.**
EQ-5D-5L	**Remote/Virtual/Telemedicine Visits allowed for non-dosing visits**	**Please refer to protocol schedule of assessments.**
MENQoL	**Remote/Virtual/Telemedicine Visits allowed for non-dosing visits**	**Please refer to protocol schedule of assessments.**
ePRO training	**Remote/Virtual/Telemedicine Visits allowed for non-dosing visits**	**Please refer to protocol schedule of assessments.**
Dispense study drug	**Patients can be brought into the clinic earlier to provide additional study drug. Courier service directly to patient allowed.**	**Please refer to protocol schedule of assessments.**
Study drug compliance and accountability	**Patients can be brought into the clinic earlier to provide additional study drug. Courier service directly to patient allowed.**	**Please refer to protocol schedule of assessments.**
Concomitant medications and AEs	**Remote/Virtual/Telemedicine Visits allowed for non-dosing visits**	**Please refer to protocol schedule of assessments.**

AE: adverse event; C-SSRS: Columbia Suicide Severity Rating Scale; ED: early discontinuation; EOT: end of treatment; ePRO: electronic patient-reported outcome; EQ-5D-5L: Euro-Qol 5D-5L; MENQoL: Menopause-Specific Quality of Life.

12 Appendices
ADDED:
INVESTIGATIONAL MEDICINAL PRODUCT SUPPLY **If any of the conditions outlined above in the Participants Procedures Assessment are met, one or all of the following mitigating strategies will be employed, as needed, to ensure continuity of IMP supply to the participants:** ● **Increase stock of IMP on site to reduce number of shipments required, if site space will allow.** ● **Direct-to-Participant shipments of IMP from the site to the participant's home.** ● **Bringing the participant to the site earlier.** **DATA COLLECTION REQUIREMENTS** **Additional data may be collected in order to indicate how participation in the study may have been affected by a crisis and to accommodate data collection resulting from alternate measures implemented to manage the conduct of the study and participant safety.** **Critical assessments for safety and efficacy based on study endpoints to be identified as missing or altered (performed virtually, at alternative locations, out of window, or other modifications) due to the crisis.**

III. Nonsubstantial Amendment Rationale:

Rationale for Nonsubstantial Designation
All revisions made to the protocol do not impact the safety or scientific value of the clinical study.

14 SPONSOR SIGNATURES

Attachment 1	Electronic Sponsor Signatures