A Phase 3, Randomized, Placebo-controlled, 12-week Double-blind Study, followed by a Single-arm Open-label Treatment Period, to Assess the Efficacy and Safety of Fezolinetant in Women Suffering from Moderate to Severe Vasomotor Symptoms (Hot Flashes) Associated with Menopause

Skylight 1

ISN/Protocol 2693-CL-0301

Version 1.0

28 January 2019

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Sponsor: **Astellas Pharma Global Development, Inc. (APGD)**

1 Astellas Way
Northbrook, IL 60062

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I. SIGNATURES

1. SPONSOR'S SIGNATURES

Required signatures (e.g., protocol authors and contributors, etc.) are located in [Section 13 Sponsor Signatures].

2. INVESTIGATOR'S SIGNATURE

A Phase 3, Randomized, Placebo-controlled, 12-week Double-blind Study, followed by a Single-arm Open-label Treatment Period, to Assess the Efficacy and Safety of Fezolinetant in Women Suffering from Moderate to Severe Vasomotor Symptoms (Hot Flashes) Associated with Menopause

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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

24-hour Contact for Serious Adverse Events (SAEs) See [Section 5.5.5 Reporting of Serious Adverse Events] 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**
Medical Monitor/Study Physician:	Christopher Lademacher, MD, PhD Executive Medical Director, Medical Science Astellas Pharma Global Development, Inc. 1 Astellas Way Northbrook, IL 60062 USA Office: +1-224-205-5223 Mobile: +1-847-612-1701 Email: christopher.lademacher@astellas.com
Clinical Research Contact:	Danijela Dobric, PMP Clinical Study Manager Office: +1-224-205-5911 Cell: +1-847-420-3310 Email: danijela.dobric@astellas.com

III. LIST OF ABBREVIATIONS AND DEFINITION OF KEY TERMS

List of Abbreviations

Abbreviations	Description of abbreviations
^{14}C	carbon-14
ADME	absorption, disposition, metabolism and excretion
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
APGD	Astellas Pharma Global Development, Inc.
AST	aspartate aminotransferase
AT	serum aminotransferases
BC	breast cancer
bid	bis in die; twice daily
BSAP	bone specific alkaline phosphatase
CA	Competent Authorities
CAT	computerized adaptive test
cEC	concerned Ethics Committee
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CRO	contract research organization
C-SSRS	Columbia Suicide Severity Rating Scale
CTX	carboxy-terminal telopeptide of type I collagen
CYP1A2	cytochrome P450 1A2
DHEA	dehydroepiandrosterone
DILI	drug-induced liver injury
DMC	data monitoring committee
E2	estradiol
ECG	electrocardiogram
eCRF	electronic case report form
EEA	European Economic Area
eGFR	estimated glomerular filtration rate
EOT	end of treatment
ePRO	electronic patient-reported outcome
EQ-5D-5L	Euro-Qol 5D-5L
EMA	European Medicines Agency
ET	early termination
FAS	full analysis set
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	good clinical practice
GCS	Greene Climacteric Scale
GLP	good laboratory practice
GMP	good manufacturing practice

Abbreviations	Description of abbreviations
GnRH	gonadotropin-releasing hormone
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HF	hot flash
HFRDIS	Hot Flash Related Daily Interference Scale
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
hNK3	human neurokinin 3 receptor
HRT	hormone replacement therapy
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
INR	international normalized ratio
IRB	institutional review board
IRT	interactive response technology
KNDy	kisspeptin/neurokinin B/dynorphin
LA-CRF	liver abnormality case report form
LFT	liver function test
LH	luteinizing hormone
LLOQ	lower limit of quantification
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 observed adverse effect level
P1NP	procollagen type 1 amino-terminal propeptide
P4	progesterone
Pap	Papanicolaou
PGI-C	Patient Global Impression of Change
PGI-C SD	Patient Global Impression of Change in Sleep Disturbance
PGI-C VMS	Patient Global Impression of Change in Vasomotor Symptoms
PGI-S	Patient Global Impression of Severity
PGI-S SD	Patient Global Impression of Severity in Sleep Distrubance
PGx	pharmacogenomic
PRO	Patient-reported outcome
PROMIS SD SF 8b	Patient-reported Outcomes Measurement Information System Sleep Disturbance – Short Form 8b
PROMIS SRI SF 8a	Patient-reported Outcomes Measurement Information System Sleep-Related Impairment – Short Form 8a
PPS	per protocol set

Abbreviations	Description of abbreviations
QA	quality assurance
QC	quality control
RSI	reference safety information
(S)AE	adverse event or serious adverse event
SAE	serious adverse event
SAP	statistical analysis plan
SAR	serious adverse reaction
SHBG	sex hormone-binding globulin
SUSAR	suspected unexpected serious adverse reaction
TBL	total bilirubin
TEAE	treatment-emergent adverse event
TVU	transvaginal ultrasound
ULN	upper limit of normal
USM	urgent safety measure
VMS	vasomotor symptoms
WPAI-VMS	Work Productivity and Activity Impairment questionnaire specific to VMS

Definition of Key Study Terms

Terms	Definition of terms
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).
Enrollment/Randomization	After a subject has successfully completed the screening period and deemed eligible to move forward in the study, this subject will then be enrolled into the treatment period of the study. At that time, randomization will occur. Randomization is the process of assigning study subjects to 1 of 2 treatment arms using an element of chance to reduce bias. The randomization assignments in this study will be blinded. NOTE: The visit in which the subject is enrolled and administered the first dose of treatment (investigational product or placebo) is the baseline visit (day 1). NOTE: Unequal randomization is used to allocate subjects into groups at a differential rate (e.g., 3 subjects may be assigned to a treatment group for every 1 assigned to the control group).
Follow-up Period	Period of time after the last assessment of the protocol. Follow-up observations for sustained adverse events are conducted during this period.
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.
Screening	A process of active consideration of potential subjects for enrollment in a study. NOTE: This is conducted after the subject signs the informed consent form 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.
Screening period	Period of time before entering the investigational period, usually from the time when a subject signs the informed consent form 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.

Terms	Definition of terms
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:	28 January 2019, Version 1.0
Sponsor: Astellas Pharma Global Development	**Protocol Number:** 2693-CL-0301
Name of Study Drug: Fezolinetant	**Phase of Development:** Phase 3
Title of Study: A Phase 3, Randomized, Placebo-controlled, 12-week Double-blind Study, followed by a Single-arm Open-label Treatment Period, to Assess the Efficacy and Safety of Fezolinetant in Women Suffering from Moderate to Severe Vasomotor Symptoms (Hot Flashes) Associated with Menopause	
Planned Study Period: From Q3 2019 to Q3 2021	
Study Objective(s): Primary objective: • To evaluate the efficacy of fezolinetant versus placebo on the frequency and severity of moderate to severe vasomotor symptoms (VMS). o The estimand of the primary objective will use a hypothetical strategy and compare patients as though they had continued on the assigned treatment. Key secondary objective: • To evaluate the efficacy of fezolinetant versus placebo on patient-reported sleep disturbance. Secondary objectives: • To evaluate the effect of fezolinetant versus placebo on the frequency and severity of moderate to severe VMS at weekly time points. • To evaluate the safety and tolerability of fezolinetant. Exploratory objectives: • To evaluate pharmacokinetics of fezolinetant and metabolite ES259564. • To evaluate the effect of fezolinetant on pharmacodynamic markers. • To evaluate the efficacy of fezolinetant versus placebo on the frequency and severity of mild, moderate and severe VMS. • To evaluate the short-term and sustained effects of fezolinetant versus placebo on patient-reported sleep disturbance. • To evaluate the effect of fezolinetant versus placebo on the following patient-reported outcomes (PROs): global assessments of VMS and sleep disturbance, overall sleep-wake function, quality of life and work productivity.	
Planned Total Number of Study Centers and Location(s): Approximately 200 centers globally	
Study Population: Women ≥ 40 years and ≤ 65 years of age with moderate to severe VMS (≥ 50/week) associated with menopause.	
Number of Subjects to be Enrolled/Randomized: Approximately 300 subjects will be enrolled into this study. One hundred and fifty subjects will be randomized per treatment arm.	

Study Design Overview:

This is a randomized, 12- week double-blind, placebo-controlled, parallel group, multicenter clinical study to assess the efficacy and safety of fezolinetant in women suffering from moderate to severe VMS associated with menopause. Approximately 300 subjects will be enrolled into this study, 150 subjects per treatment arm. Duration of treatment is 52 weeks. The first 12 weeks of treatment will be double-blind. After completing 12 weeks of treatment, subjects will receive active treatment through end of study. Following the completion (or early termination [ET]) of the treatment period (week 52), subjects will complete an end of treatment (EOT; or ET) visit and final safety follow-up visit 3 weeks after the last dose of study drug is administered (week 55).

This study will consist of a screening period (days -35 to -1, including the screening visit [visit 1] and collection of VMS frequency and severity assessments), and a 52-week treatment period (day 1 [visit 2] to week 52 [visit 15]). The study will be performed on an outpatient basis. The screening visit (visit 1) will occur up to 35 days prior to randomization (visit 2). Eligibility will be assessed via physical examination, clinical laboratory testing, vital signs, electrocardiogram (ECG), Papanicolaou (Pap) test (or equivalent cervical cytology), mammography, transvaginal ultrasound (TVU) and endometrial biopsy (except for subjects who have had a partial [supracervical] or full hysterectomy). Endometrial biopsy will be performed at screening and at week 52/EOT.

Within the 10 days prior to randomization, subjects must have a minimum average of 7 to 8 moderate to severe hot flashes (HFs; VMS) per day, or 50 to 60 per week. Subjects are to record HFs for the entirety of the screening period. The electronic diary will be reviewed by study site staff at visit 2 to confirm study eligibility. Subjects may be rescreened 1 time, within the original screening period, upon approval of the medical monitor.

During the 52-week treatment period (visits 2 through 15), subjects will return to the study site every 4 weeks for assessments as indicated in the Schedule of Assessments. Subjects will record their VMS via their electronic dairy on a daily basis throughout their study participation.

Site-based PRO measures will be self-administered via an electronic device as indicated in the Schedule of Assessments. Assessments at visit 2 must occur prior to randomization/first dosing; assessments at weeks 4, 12, 24 and 52 must occur prior to dosing. All self-administered assessments will be performed first upon arrival at the site and prior to all other procedures. In the event a subject withdraws from the study, efforts to collect information on the site-based PRO measures should be made before or shortly after withdrawal.

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

Inclusion/Exclusion Criteria:

Inclusion:

Subject who meets 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 (including withdrawal of prohibited medication, if applicable).
2. Subject is born female, aged ≥ 40 years and ≤ 65 years of age at the screening visit.
3. Subject has a body mass index between 18 kg/m^2 to 38 kg/m^2 (extremes included).

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 [FSH] > 40 IU/L); or
   - Having had bilateral oophorectomy ≥ 6 weeks prior to the screening visit (with or without hysterectomy).
5. Within the 10 days prior to randomization, subject must have a minimum average of 7 to 8 moderate to severe HFs (VMS) per day, or 50 to 60 per week.
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 findings mammogram (obtained at screening or within the prior 9 months of study 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), and for subjects who are withdrawn from the study prior to completion, a TVU at the ET visit. This is not required for subjects who have had a partial (supra-cervical) or full hysterectomy.
9. Subject is willing to undergo an endometrial biopsy at screening and at week 52 (EOT), for subjects with uterine bleeding, and for subjects who are withdrawn from the study prior to completion. This is not required for subjects who have had a partial (supracervical) or full hysterectomy.
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 9 months or at screening.
11. Subject has a negative urine pregnancy test at screening.
12. Subject has a negative serology panel (including hepatitis B surface antigen, hepatitis C virus antibody and human immunodeficiency virus antibody screens).
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.

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 1A2 [CYP1A2] inhibitors, hormone replacement therapy [HRT], hormonal contraceptive or any treatment for VMS [prescription, over the counter or herbal]) or is not willing to wash out and discontinue use of such drugs for the full duration of study conduct.
2. Subject has known substance abuse or alcohol addiction within 6 months of screening, as assessed by the investigator.
3. Subject has previous or current history of a malignant tumor, except for basal cell carcinoma.
4. Subject has uncontrolled hypertension as assessed by the investigator.

5. Subject has history of severe allergy, hypersensitivity or intolerance to drugs in general, including the study drug and any of its excipients.
6. For subjects with a uterus: Subject has an unacceptable result from the TVU assessment at screening (i.e., full length of endometrial cavity cannot be visualized or presence of a clinically significant finding).
7. For subjects with a uterus: Subject has an endometrial biopsy confirming presence of endometrial hyperplasia, endometrial cancer or other clinically significant findings in the opinion of the investigator at screening. A biopsy with insufficient material for evaluation is acceptable provided the endometrial thickness is no greater than 4 mm.
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 or elevated liver function tests > 1.5 times the upper limit of normal (ULN) including alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TBL), alkaline phosphatase or lactate dehydrogenase (LDH).
12. Subject has creatinine > 1.5 × ULN; or estimated glomerular filtration rate (eGFR) using the Modification of Diet in Renal Disease formula ≤ 59 mL/min per 1.73 m^2 at screening.
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 question 4 or 5 on the suicidal ideation portion of the Columbia Suicide Severity Rating Scale [C-SSRS]), or who is at significant risk to commit suicide, as assessed by the investigator at screening and at visit 2 (randomization).
14. Subject has had previous exposure 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 or relative is the investigator or other site staff directly involved in the conduct of the study.
18. Subject is an employee of Astellas.
19. Subject has any condition, which in the investigator's opinion, makes the subject unsuitable for study participation.

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

Investigational Product(s):

Fezolinetant 30 mg

Dose(s):

30 mg once daily

Mode of Administration:

Oral

Comparative Drug(s):

Placebo to match once daily

Dose(s):

Not applicable

Mode of Administration:

Oral

Concomitant Medication Restrictions or Requirements:

Medication for VMS 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.

Subjects taking prohibited medications who are willing to discontinue these medications as medically indicated and based upon the investigator's recommendation, may wash-out over a period of 5 half-lives on a schedule determined by the investigator.

Medications taken after the first dose of study medication through the last study-related activity will be documented on the appropriate eCRF 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) and over the counter and prescription medication.

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.

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 defined 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 International Normalized Ratio (INR) > 1.5 × ULN and INR > 1.5 (If INR testing is applicable/evaluated)
  - 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 subject becomes pregnant

Study Discontinuation:

The sponsor may terminate this study 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.

Endpoints for Evaluation:

Co-primary:

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

Key Secondary:

- Mean change in the Patient-reported Outcomes Measurement Information System Sleep Disturbance – Short Form 8b (PROMIS SD SF 8b) Total Score from baseline to week 12

Secondary:

- Mean change in the frequency of moderate and severe VMS from baseline to each week up to week 12
- Mean change in the severity of moderate and severe VMS from baseline to each week up to week 12
- Mean percent reduction in the frequency of moderate and severe VMS from baseline to each week up to week 12
- Percent reduction ≥ 50% and at 100% in the frequency of moderate and severe VMS from baseline to each week up to week 12
- Mean change in the frequency of moderate to severe VMS from baseline to week 24 (descriptive)
- Mean change in the severity of moderate to severe VMS from baseline to week 24 (descriptive)

Exploratory:

- Mean change in the frequency of mild, moderate and severe VMS from baseline to each week up to week 12
- Mean change in the severity of mild, moderate and severe VMS from baseline to each week up to week 12
- Mean percent reduction in the frequency of mild, moderate and severe VMS from baseline to each week up to week 12
- Percent reduction ≥ 50% and at 100% in the frequency of mild, moderate and severe VMS from baseline to each week up to week 12
- Change in serum concentrations of sex hormones and sex hormone-binding globulin (SHBG) from baseline to each visit
- Mean change in serum concentrations of bone specific alkaline phosphatase (BSAP), procollagen type 1 amino-terminal propeptide (P1NP) and carboxy-terminal telopeptide of type I collagen (CTX) from baseline to each visit
- Plasma concentrations of fezolinetant and metabolite ES259564 at pre-specified time points
- Mean score on the Patient Global Impression of Change (PGI-C) in VMS at each visit
- Mean change on the PROMIS SD SF 8b total score from baseline at each visit
- Mean change on the Patient-reported Outcomes Measurement Information System Sleep-Related Impairment – Short Form 8a (PROMIS SRI SF 8a) total score from baseline at each visit
- Mean change on the Patient Global Impression of Severity in Sleep Disturbance (PGI-S SD) from baseline at each visit
- Mean score on the Patient Global Impression of Change in Sleep Disturbance (PGI-C SD) to each week up to week 12
- Mean change on the Menopause-Specific Quality of Life (MENQOL) total score from baseline to each week up to week 12
- Mean change on the MENQOL domain scores from baseline to each week up to week 12
- Mean change on the Euro-Qol 5D-5L (EQ-5D-5L) total score and Visual Analog Scale (VAS) from baseline to each week up to week 12
- Mean change on the Work Productivity and Activity Impairment questionnaire specific to VMS (WPAI-VMS) domain scores from baseline to each week up to week 12

NOTE: Assessments after the 12 week placebo–controlled period are descriptive only, because there is no placebo control.

Statistical Methods:

Sample size justification:

A total of 300 subjects are planned to be randomized; 150 subjects in each treatment arm.

For a pairwise comparison of the primary endpoint of mean daily frequency using a 2-sample t-test at a 2-sided 5% alpha, 100 subjects would provide at least 80% power to detect differences from placebo of -2.0 or larger, assuming a SD of 5.

For a pairwise comparison of the primary endpoint of mean severity using a 2-sample t-test at a 2-sided 5% alpha, 100 subjects would provide at least 80% power to detect differences from placebo of -0.40 or larger, assuming a SD of 1.

Assuming approximately 32% of subjects discontinue prematurely, the number of subjects will be increased from 100 to 150 subjects per arm. This sample size would also provide over 95% power to detect a difference of 4.3 from placebo on the key secondary endpoint of the PROMIS sleep disturbance questionnaire, using a 2-sample t-test at a 2-sided 5% alpha assuming a SD of 7 [Avis et al, 2016].
Efficacy: For each of the 4 co-primary efficacy endpoints, a mixed models repeated measures analysis of covariance (MMRM) will be used with treatment group, pooled center, and smoking status (current vs. former/never) as factors, with baseline weight and baseline measurement as covariates, consistent with the hypothetical strategy used for the estimand, which is to compare patients as though they had continued on the assigned treatment. Comparisons between the active doses and placebo will be calculated based on least-squares mean contrasts using a 2-tailed 95% confidence interval (CI). NOTE: All 4 co-primary variables should be successful for a given dose-level. The PROMIS SD scale will be analyzed using MMRM will be used including treatment group as factor and baseline measurement as covariate, similar to the analysis of the co-primary endpoints. If the co-primary analysis of the co-primary efficacy endpoints is statistically significant between fezolinetant and placebo, the statistical test will be performed on the key secondary efficacy endpoint between fezolinetant and placebo with alpha = 0.05.
Pharmacokinetics: Plasma concentrations of fezolinetant and metabolite ES259564 will be listed and summarized using descriptive statistics by scheduled time point. Mean fezolinetant plasma concentration and mean metabolite ES259564 plasma concentration will be plotted against scheduled time-point. Pharmacokinetics may be evaluated by a population pharmacokinetics 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: Serum hormone concentration and changes from baseline will be listed and summarized using descriptive statistics by scheduled time point. Mean serum hormone concentration and changes from baseline will be plotted against scheduled time-point. Pharmacodynamic data and efficacy data may be evaluated by a population pharmacodynamic 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.
Safety: Safety will be assessed by examining the incidence of adverse events, physical examinations findings, the clinician-administered C-SSRS, TVU's, endometrial biopsies, vital signs, ECGs, clinical laboratory tests, and bone marker concentrations over time.
Interim Analysis: No interim analysis is planned for this study.

12-week Analysis and 52-week Analysis:

Given the design, a 12-week treatment analysis will occur to assess efficacy and safety during the double-blind treatment phase. This will occur after all subjects have completed 12 weeks of treatment. Efficacy and safety data will be analyzed, excluding the endpoints measured after 12 weeks. Since all primary and secondary analyses only based on data through week 12, no alpha adjustment is required as the information fraction at the 12-week analysis is 100%.

Once the entire 52-week study is completed and locked, additional efficacy and safety will be summarized without statistical comparison to placebo.

V. FLOW CHART AND SCHEDULE OF ASSESSMENTS

Flow Chart

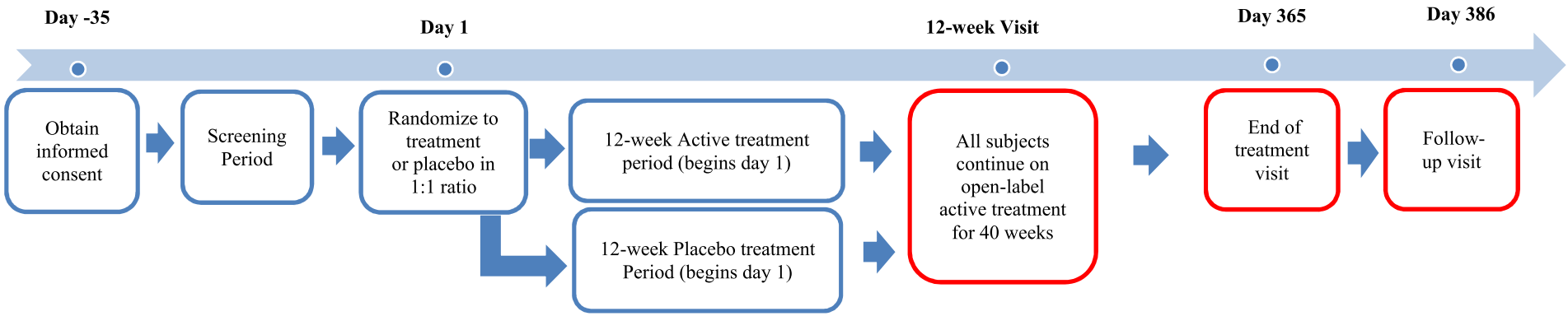


Table 1 Schedule of Assessments

Assessments	**Screening Visit**	**Treatment Period**						**Follow-up Visit**
Study Visit	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visits 6, 7, 8, 9, 10, 11, 12, 13 and 14	Visit 15/ EOT	Visit 16
Visit weeks	-5 to -1		Week 4	Week 8	Week 12	Weeks 16, 20, 24, 28, 32, 36, 40, 44 and 48	Week 52	Week 55[b]
Visit days	Days -35 to -1[a]	Day 1 (Randomization)	Day 29	Day 57	Day 85	Day 113, 141, 169, 197, 225, 253, 281, 309 and 337	Day 365	Day 386
Visit Window[c]	-	-	± 3	± 3	± 3	± 3	± 3	± 3
Informed consent[d]	X							
Informed consent PGx[d]	X							
Inclusion/exclusion criteria	X	X						
Medical history/concomitant diseases	X							
ePRO's Assessment[e]								
PGI-C VMS[e]			X		X	X[e]	X	
PROMIS SD SF 8b[e]		X	X		X	X[e]	X	
PGI-S SD[e]		X	X		X	X[e]	X	
PGI-C SD[e]			X		X	X[e]		
PROMIS SRI SF 8a[e]		X	X		X	X[e]	X	
MENQOL[e]		X	X		X	X[e]	X	
EQ-5D-5L[e]		X	X		X	X[e]	X	
WPAI-VMS[e]		X	X		X	X[e]	X	
Study Procedures:								
C-SSRS (clinician-administered)[f]	X	X			X	X[f]	X	X
Screening mammogram[g]	X							
Demographic data[h]	X							
Physical examination[i]	X	X	X[j]	X[j]	X	X[j]	X	X
Urine pregnancy test	X							
Clinical laboratory[k] and urinalysis	X	X	X	X	X	X	X	X
Vital signs[l]	X	X	X	X	X	X	X	X
12-lead ECG[m]	X	X			X		X	

Table continued on next page

Assessments	**Screening Visit**	**Treatment Period**						**Follow-up Visit**
Study Visit	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visits 6, 7, 8, 9, 10, 11, 12, 13 and 14	Visit 15/ EOT	Visit 16
Visit weeks	-5 to -1		Week 4	Week 8	Week 12	Weeks 16, 20, 24, 28, 32, 36, 40, 44 and 48	Week 52	Week 55[b]
Visit days	Days -35 to -1[a]	Day 1 (Randomization)	Day 29	Day 57	Day 85	Day 113, 141, 169, 197, 225, 253, 281, 309 and 337	Day 365	Day 386
Visit Window[c]	-	-	± 3	± 3	± 3	± 3	± 3	± 3
Pap test (or equivalent cervical cytology)[n]	X							
TVU[o]	X						X	
Endometrial biopsy[o]	X						X	
Serology[p]	X							
Blood pharmacodynamic sample[q]		X	X		X	X[q]	X[q]	X
Blood pharmacokinetic sample[r]			X		X	X[r]	X[r]	
Blood PGx sample[s]			X					
VMS diary[t]	X	X	X	X	X	X	X	X
ePRO training	X							
Randomization		X						
Bone marker[u]		X					X	X
Dispense study drug[v]		X	X	X	X	X		
Study drug compliance and accountability[w]		X	X	X	X	X	X	
Concomitant medications and AEs[x]	X	X	X	X	X	X	X	X

AE: adverse event; BSAP: bone specific alkaline phosphatase; C-SSRS: Columbia Suicide Severity Rating Scale; CTX: C-telopeptides of type 1 collagen; E2: estradiol; ECG: electrocardiogram; ; ePRO: electronic patient-reported outcomes; EQ-5D-5L: EuroQol group 5 Dimensions questionnaire; EOT: end of treatment; ET: early termination; FSH: follicle-stimulating hormone; HBsAG: hepatitis B virus surface antigen; HCV: hepatitis C virus; HIV: human immunodeficiency virus; LH: luteinizing hormone; MENQOL: Menopause-Specific Quality of Life; P1NP: N terminal pro-peptides of type 1 collagen; Pap test: Papanicolaou test; PGI-C SD: Patient Global Impression of Change in Sleep Disturbance; PGI-C VMS: Patient Global Impression of Change in vasomotor symptoms; PGI-S SD: Patient Global Impression of Severity in Sleep Distrubance; PGx: pharmacogenomic; PROMIS SD SF 8b: Patient-reported Outcomes Measurement Information System Sleep Disturbance – Short Form 8b; PROMIS SRI SF 8b: Patient-reported Outcomes Measurement Information System Sleep-Related Impairment – Short Form 8b; SHBG: sex hormone-binding globulin; TVU: transvaginal ultrasound; VMS: vasomotor symptom; WPAI-VMS: Work Productivity and Activity Impairment questionnaire specific to vasomotor symptoms

Footnotes continued on next page

a. The screening visit is to occur within 35 days of randomization (day 1 [visit 2]). Subjects will record daily VMS during the screening period in an electronic diary. To qualify for the study, within 10 days prior to randomization, subject must have a minimum average of 7 to 8 moderate to severe hot flashes (VMS) recorded per day, or 50 to 60 per week. Subjects may be rescreened 1 time upon approval of the medical monitor. The following assessments do not need to be repeated at the rescreen provided they still fall within the acceptable time window: TVU, endometrial biopsy, mammogram, ECG and Pap test (or equivalent cervical cytology).

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 done. Subjects who do not consent to PGx sampling are not excluded from participating in the study.

e. ePRO assessments will be self-administered at the study site first upon arrival and before any other study assessments/procedures are performed; assessments at visit 2 must occur prior to randomization/first dosing; Assessment PGI-C SD will occur at visits 3 and 5 and must occur prior to dosing. The remaining assessments will occur at visits 3, 5, 8 and 15 and must occur prior to dosing. In the event a subject withdraws from the study, efforts to collect information on the site-based ePRO measures should be made before or shortly after withdrawal.

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

g. Only in the event the subject does not have a normal/negative or no clinically significant findings mammogram from previous 9 months on record.

h. Includes age, race, sex and smoking status.

i. At the screening visit height, weight and waist circumference will be measured, along with a bimanual clinical pelvic and clinical breast examination. The bimanual clinical pelvic examination can be performed at any time in the study where clinically indicated.

j. At week 4 (visit 3) thru week 8 (visit 4) and weeks 16 (visit 6) thru week 48 (visit 14) a symptom directed physical exam will be conducted which includes weight and waist circumference.

k. Includes biochemistry, coagulation (at the screening visit and week 52 [visit 15]/EOT only) and hematology panel. Blood samples for clinical laboratory tests should be taken in a fasted state.

l. Includes oral/tympanic temperature, sitting blood pressure and pulse rate (after 5 minutes of rest).

m. 12-lead ECG. The subject should rest in supine position for at least 10 minutes prior to the ECG measurement.

n. 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 9 months on record.

o. Endometrial biopsy will be performed at screening and at week 52/EOT and in the case of uterine bleeding during treatment, except for subjects who have had a partial (supracervical) or full hysterectomy. Subject may schedule the endometrial biopsy on a separate day, within the screening period, after all other screening procedures have been completed.

p. For HBsAG, anti-HCV antibodies and anti-HIV antibodies.

Footnotes continued on next page

q. Pharmacodynamic samples will be taken predose at day 1 (visit 2), week 12 (visit 5), week 16 (visit 6), week 24 (visit 8) and week 52 (visit 15), as well as predose and 3 hours postdose at week 4 (visit 3). The week 4 (visit 3) 3 hours postdose pharmacodynamic sample may be shifted to a later date (prior to week 12) in case the subject cannot accommodate the sampling schedule at that visit. The pharmacodynamic sample should be taken at the same time as the 3-hour postdose pharmacokinetic sample. A pharmacodynamic sample will be taken at the follow-up visit (week 55 [visit 16]) as well. Markers include LH, FSH, E2, SHBG, androstenedione, dehydroepiandrosterone, estrone and testosterone.

r. Pharmacokinetic samples to be taken at predose, 1 h (± 30 min) post dose and 3 h (± 30 min) postdose week 4 (visit 3) and week 16 (visit 6), as well as predose, week 12 (visit 5), week 24 (visit 8) and week 52 (visit 15). The indicated time windows for week 4 (visit 3) pharmacokinetic sampling will allow for flexibility. If this visit is missed, the samples can be taken at the next visit (prior to week 12).

s. While scheduled for week 4 (visit 3), PGx sample can be taken at any time during the study after signed informed consent and enrollment into the study.

t. The VMS diary will be kept by subjects. Subjects will record the VMS frequency and severity of each VMS in the ePRO diary on a daily basis from the screening visit (days -35 to -1 [visit 1]) through the follow-up visit (week 55 [visit 16]). Night sweats should be recorded no later than in the morning upon awakening to start a new day.

u. Includes BSAP, P1NP and CTX.

v. Subjects will be assigned study drug as a kit in blister packaging. 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 dose of study drug at home, 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 interactive response technology.

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

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 (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 lasts 4 to 10 minutes 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 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 (human neurokinin 1 and human neurokinin) 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-0009) 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 orally intake, fezolinetant showed generally dose proportional pharmacokinetics at doses between 20 and 60 mg once daily in female subjects. Peak concentration (C_{max}) was generally reached within 1 to 4 hours postdose with terminal half-life ($t_{1/2}$) ranging between 4 to 6 hours in healthy subjects and patients. With a once daily dose regimen, steady state in plasma concentrations are approximately achieved by 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 CYP1A2 enzyme, to form the major metabolite ES259564. A strong CYP1A2 inhibitor (fluvoxamine) increased fezolinetant AUC and C_{max} approximately 9-fold and 1.8-fold, respectively, while smoking can decrease AUC and C_{max} to a geometric LS mean ratio of 48.29% and 71.74%, respectively (study 2693-CL-0006).

In a recently completed mass balance study (ESN364_CPK_103), the routes of excretion of fezolinetant were 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 (study 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}, comparing 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 the 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 of 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

Table continued on next page

Study Number	Development Phase	Description	Location	Number of Subjects/Patients Randomized
ESN364_HF_204	2a	Proof of concept study in MR-VMS	Belgium	Fezolinetant 90 mg twice daily = 43 Placebo = 44
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 Fezolinetnat 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

^{14}C-ESN-364 ADME: absorption, disposition, metabolism and excretion of ^{14}C-ESN-364; MAD: multiple ascending dose; MR-VMS: menopause-related vasomotor symptoms; SAD: single ascending dose; VMS: vasomotor symptoms

Source: Fezolinetant (ESN364) Investigator's Brochure

In patients, 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 HF (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 HF 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 to 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 Study Drugs

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 (AUC) at this dose level in Cynomolgus monkeys 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 pre-dose 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, paraesthesia and nausea. The highest incidence for headache was after 360 and 900 mg intake, for paraesthesia 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 2 b 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 SAEs were reported. The most common MedDRA 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 aspartate aminotransferase (AST) > 3× ULN. Of these, 3 patients had ALT or AST > 8 × ULN (60 mg bid, 90 mg bid and 60 mg qd). There were no cases of total bilirubin (TBL) > 2 × ULN, and consequently no Hy's law cases.

There were no clinically meaningful changes in hematology, coagulation, vital signs, electrocardiograms (ECGs), 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.

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/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 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 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 above 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 12.4. Increased transaminases have not been observed at the dose selected for the phase 3 studies (i.e., 30 mg fezolinetant qd).

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 mild, 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 and/or lips), as a prickling sensation of the face, as a numbness of the tongue or as a tingling sensation (face, mouth and/or tongue).

Circumoral paraesthesia has been recognized in the phase 1 and 2 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 once daily fezolinetant are considered to outweigh the potential risks. Although an important medical condition, VMS are not considered life-threatening and 12 week placebo treatment, which also is associated with improvement in VMS, is justifiable.

2 STUDY OBJECTIVES, DESIGN AND ENDPOINTS

2.1 Study Objectives

2.1.1 Primary Objective

- To evaluate the efficacy of fezolinetant versus placebo on the frequency and severity of moderate to severe VMS.
    - The estimand of the primary objective will use a hypothetical strategy and compare patients as though they had continued on the assigned treatment.

2.1.2 Key Secondary Objective

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

2.1.3 Secondary Objectives

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

2.1.4 Exploratory Objectives

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

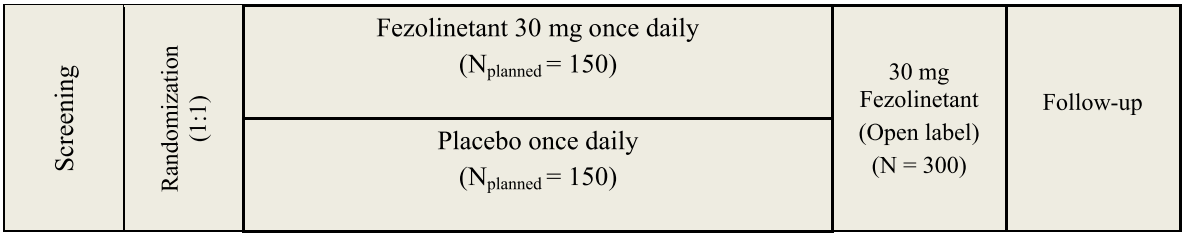
2.2 Study Design and Dose Rationale

2.2.1 Study Design

This is a randomized, 12- week double-blind, placebo-controlled, parallel group, multicenter clinical study to assess the efficacy and safety of fezolinetant in women suffering from moderate to severe VMS associated with menopause. Approximately 300 subjects will be enrolled into this study, with 150 subjects per treatment arm (see Figure 1):

- Fezolinetant 30 mg once daily
- Placebo once daily

Figure 1 Study Schematic



V: visit

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

Duration of treatment is 52 weeks. The first 12 weeks of treatment will be double-blind. After completing 12 weeks of treatment, subjects will receive active treatment through end of study. Following the completion (or early termination [ET]) of the treatment period (week 52), subjects will complete an end of treatment (EOT; or ET) visit and final safety follow-up visit 3 weeks after the last dose of study drug is administered (week 55).

This study will consist of a screening period (days -35 to -1, including the screening visit [visit 1] and collection of VMS frequency and severity assessments) and a 52-week treatment period (day 1 [visit 2] to week 52 [visit 15]). The study will be performed on an outpatient basis. The screening visit (visit 1) will occur up to 35 days prior to randomization (visit 2). Eligibility will be assessed via physical examination, clinical laboratory testing, vital signs, ECG, Papanicolaou (Pap) test (or equivalent cervical cytology), mammography, transvaginal ultrasound (TVU) and endometrial biopsy (except for subjects who have had a partial [supracervical] or full hysterectomy). Endometrial biopsy will be performed at screening and at week 52/EOT.

Within the 10 days prior to randomization, subjects must have a minimum average of 7 to 8 moderate to severe HFs (VMS) per day, or 50 to 60 per week. Subjects are to record HFs for the entirety of the screening period. The electronic diary will be reviewed by study site staff at visit 2 to confirm study eligibility. Subjects may be rescreened 1 time, within the original screening period, upon approval of the medical monitor.

During the 52-week treatment period (visits 2 through 15), subjects will return to the study site every 4 weeks for assessments as indicated in the Schedule of Assessments [Table 1]. Subjects will record their VMS via their electronic dairy on a daily basis throughout their study participation.

Site-based PRO measures will be self-administered via an electronic device as indicated in the Schedule of Assessments [Table 1]. Assessments at visit 2 must occur prior to randomization/first dosing; assessments at weeks 4, 12, 24 and 52 must occur prior to dosing. All self-administered assessments will be performed first upon arrival at the site and prior to all other procedures. In the event a subject withdraws from the study, efforts to collect information on the site-based PRO measures should be made before or shortly after withdrawal.

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

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 week 4 and week 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 is not well-defined.

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 total bilirubin > 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 bid 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 possible dose response curves. Both the dose-response (Multiple Comparison Procedure – Modelling) 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. At week 12, the model predicts a mean placebo-corrected change from baseline reduction in HF frequency of -1.74 for a 30 mg once-daily dose at baseline values similar to study ESN364_HF_205. The criteria used to define the baseline in study ESN364_HF_205 permitted subjects to participate in the study with a baseline of < 7 HFs per day. This resulted in a decreased mean baseline and larger variability in baseline compared to historical studies. At a baseline more consistent with historical studies, the mean predicted placebo-corrected change from baseline reduction in HF frequency for a 30 mg once daily dose is -2.11 at week 12. In summary, 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, the model predicted placebo-corrected change from baseline for a 30 mg once daily dose was -0.34 at week 12.

Based on the efficacy results and modeling and simulation analyses, the 30 mg once-daily dosing regimen is considered the lowest effective dose. Additionally, based on the safety data analysis on drug-induced liver injury (DILI), this dose is selected for evaluation in subsequent phase 3 studies. However, co-administration of strong or moderate CYP1A2 inhibitors can substantially increase fezolinetant concentration. Therefore, strong and moderate CYP1A2 inhibitors are prohibited in the study to minimize safety risk.

2.3 Endpoints

2.3.1 Co-primary Endpoints

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

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

2.3.2 Key Secondary Endpoints

The key secondary efficacy objective examines the effect of fezolinetant versus placebo on the following:

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

2.3.3 Secondary Endpoints

The secondary efficacy objectives examine the effect of fezolinetant versus placebo on the following:

- Mean change in the frequency of moderate and severe VMS from baseline to each week up to week 12
- Mean change in the severity of moderate and severe VMS from baseline to each week up to week 12
- Mean percent reduction in the frequency of moderate and severe VMS from baseline to each week up to week 12
- Percent reduction ≥ 50% and at 100% in the frequency of moderate and severe VMS from baseline to each week up to week 12
- Mean change in the frequency of moderate to severe VMS from baseline to week 24 (descriptive)
- Mean change in the Severity of moderate to severe VMS from baseline to week 24 (descriptive)

2.3.4 Exploratory Endpoints

- Mean change in the frequency of mild, moderate and severe VMS from baseline to each week up to week 12
- Mean change in the severity of mild, moderate and severe VMS from baseline to each week up to week 12
- Mean percent reduction in the frequency of mild, moderate and severe VMS from baseline to each week up to week 12
- Percent reduction ≥ 50% and at 100% in the frequency of mild, moderate and severe VMS from baseline to each week up to week 12

- Change in serum concentrations of sex hormones and sex hormone-binding globulin (SHBG) from baseline to each visit
- Mean change in serum concentrations of bone specific alkaline phosphatase (BSAP), procollagen type 1 amino-terminal propeptide (P1NP) and carboxy-terminal telopeptide of type I collagen (CTX) from baseline to each visit
- Plasma concentrations of fezolinetant and metabolite ES259564 at pre-specified time points
- Mean score on the Patient Global Impression of Change (PGI-C) in VMS at each visit
- Mean change on the PROMIS SD SF 8b total score from baseline at each visit
- Mean change on the Patient-reported Outcomes Measurement Information System Sleep-Related Impairment – Short Form 8a (PROMIS SRI SF 8a) total score from baseline at each visit
- Mean change on the Patient Global Impression of Severity in Sleep Disturbance (PGI-S SD) from baseline at each visit
- Mean score on the Patient Global Impression of Change in Sleep Disturbance (PGI-C SD) to each week up to week 12
- Mean change on the Menopause-Specific Quality of Life (MENQOL) total score from baseline to each week up to week 12
- Mean change on the MENQOL domain scores from baseline to each week up to week 12
- Mean change on the Euro-Qol 5D-5L (EQ-5D-5L) total score and Visual Analog Scale (VAS) from baseline to each week up to week 12
- Mean change on the Work Productivity and Activity Impairment questionnaire specific to VMS (WPAI-VMS) domain scores from baseline to each week up to week 12

NOTE: Assessments after the 12 week placebo-controlled period are descriptive only, because there is no placebo control.

3 STUDY POPULATION

3.1 Selection of Study Population

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

3.2 Inclusion Criteria

Subject who meets 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 (including withdrawal of prohibited medication, if applicable).
2. Subject is born female, aged ≥ 40 years and ≤ 65 years of age at the screening visit.
3. Subject has a body mass index between 18 kg/m^2 to 38 kg/m^2 (extremes included).

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 (with or without hysterectomy).
5. Within the 10 days prior to randomization, subject must have a minimum average of 7 to 8 moderate to severe HFs (VMS) per day, or 50 to 60 per week.
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 findings mammogram (obtained at screening or within the prior 9 months of study 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), and for subjects who are withdrawn from the study prior to completion, a TVU at the ET visit. This is not required for subjects who have had a partial (supra-cervical) or full hysterectomy.
9. Subject is willing to undergo an endometrial biopsy at screening and at week 52 (EOT), for subjects with uterine bleeding, and for subjects who are withdrawn from the study prior to completion. This is not required for subjects who have had a partial (supracervical) or full hysterectomy.
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 9 months or at screening.
11. Subject has a negative urine pregnancy test at screening.
12. Subject has a negative serology panel (including hepatitis B surface antigen, hepatitis C virus antibody and human immunodeficiency virus antibody screens).
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

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 CYP1A2 inhibitors, HRT, hormonal contraceptive or any treatment for VMS [prescription, over the counter or herbal]) or is not willing to wash out and discontinue use of such drugs for the full duration of study conduct.
2. Subject has known substance abuse or alcohol addiction within 6 months of screening, as assessed by the investigator.
3. Subject has previous or current history of a malignant tumor, except for basal cell carcinoma.
4. Subject has uncontrolled hypertension as assessed by the investigator.
5. Subject has history of severe allergy, hypersensitivity or intolerance to drugs in general, including the study drug and any of its excipients.
6. For subjects with a uterus: Subject has an unacceptable result from the TVU assessment at screening (i.e., full length of endometrial cavity cannot be visualized or presence of a clinically significant finding).
7. For subjects with a uterus: Subject has an endometrial biopsy confirming presence of endometrial hyperplasia, endometrial cancer or other clinically significant findings in the opinion of the investigator at screening. A biopsy with insufficient material for evaluation is acceptable provided the endometrial thickness is no greater than 4 mm.
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 or elevated liver function tests > 1.5 times the ULN including ALT, AST, TBL, alkaline phosphatase or lactate dehydrogenase (LDH).
12. Subject has creatinine > 1.5 × ULN; or estimated glomerular filtration rate (eGFR) using the Modification of Diet in Renal Disease formula ≤ 59 mL/min per 1.73 m^2 at screening.
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 question 4 or 5 on the suicidal ideation portion of the Columbia Suicide Severity Rating Scale [C-SSRS]), or who is at significant risk to commit suicide, as assessed by the investigator at screening and at visit 2 (randomization).
14. Subject has had previous exposure 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 or relative is the investigator or other site staff directly involved in the conduct of the study.
18. Subject is an employee of Astellas.
19. Subject has any condition, which in the investigator's opinion, makes the subject unsuitable for study participation.

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

4 TREATMENT(S)

4.1 Identification of Investigational Product(s)

4.1.1 Study Drug(s)

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

4.1.2 Comparative Drug(s)

Placebo will be supplied by Astellas in a blinded form to match the active fezolinetant 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 Astellas Pharma Global Development, Inc. (APGD) or sponsor's designee in accordance with APGD or sponsor's designee Standard Operating Procedures (SOPs), Good Manufacturing Practice (GMP) guidelines, ICH 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 BV or sponsor's designee will perform the final release of the medication according to the requirements of the 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 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 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. 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 termination of this study, the investigator or designee 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

The first 12 weeks of the study are double blind. Subjects will be randomized to receive fezolinetant or placebo in a blinded fashion such that the investigator, sponsor's study management team, clinical staff, nor the subject will know which agent is being administered. 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 the fezolinetant are identical to those of their matching placebo.

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 an SAE the investigator is to follow the instructions in [Section 5.5.5 Reporting of Serious Adverse Events**].**

Care should be taken to limit knowledge of the randomization arm, in case this could affect the blinding of other subjects or future study 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 ratio to a treatment arm according to the randomization schedules and stratified by smoking status (active 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 screened up to 35 days prior to randomization. Informed consent/ authorization will be obtained prior to randomization and before any study-related procedures are performed.

Subjects will be assigned study drug as a kit at visits indicated in the Schedule of Assessments [Table 1]. Each kit will contain blister packages (or wallets) 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 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.

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)

Medication for VMS 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.

Subjects taking prohibited medications who are willing to discontinue these medications as medically indicated and based upon the investigator's recommendation, may washout over a period of 5 half-lives on a schedule determined by the investigator.

Medications taken after the first dose of study medication through the last study-related activity will be documented on the appropriate eCRF 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) and over the counter and prescription medication.

Subjects are 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)

Before starting study drug, prescription medications, over the counter or herbal for the treatment of VMS should be washed out after consultation with the prescribing physician and as per package insert guidance to ensure clinical safety. A minimum of 5 half-lives is required prior to screening.

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 and 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 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) 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 or moderate CYP1A2 inhibitors.

Refer to [Appendix 12.3 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. 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 considered to 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 protocol restrictions.

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] and will include age, sex, race, 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.

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 ICF 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); or
- Having had bilateral oophorectomy ≥ 6 weeks prior to the screening visit (with or without hysterectomy);
- Within the 10 days prior to randomization, subject has a minimum average of 7 to 8 moderate to severe HFs (VMS) per day, or 50 to 60 per week.

5.3 Efficacy | Pharmacodynamics | Pharmacokinetics | Assessments

5.3.1 Efficacy Assessment

5.3.1.1 Vasomotor Symptom Diary

Daily HF data will be collected using an electronic HF diary [Section 8.1 Data Collection], which should be completed daily by study participants. The HF diary is a validated, interactive, real-time vendor hosted system available for use 24 hours per day for data entry. This electronic diary will be the only source document for the 4 co-primary endpoints. Subjects will be provided with a reference guide within the diary, which includes the definitions of mild, moderate and severe HFs. These definitions are as follows [FDA Guidance for Industry, 2003]:

- Mild: sensation of heat without sweating
- Moderate: sensation of heat with sweating, able to continue activity
- Severe: sensation of heat with sweating, causing cessation of activity

The real-time system will generate daily compliance reports for each subject. The compliance reports tabulate the date and time of each HF entry and the number of HFs entered at each time point.

5.3.2 Key Secondary Efficacy Assessment

The PROMIS is a National Institutes of Health Roadmap initiative designed to improve PRO measures using state-of-the-science methods. The PROMIS SD SF 8b [PROMIS SD, 2015] assesses self-reported sleep disturbance over the past 7 days and includes perceptions of restless sleep; satisfaction with sleep; refreshing sleep; difficulties sleeping, getting to sleep or staying asleep; amount of sleep; and sleep quality. Because it assesses the patient's

experience of sleep disturbance, the measure does not focus on specific sleep-disorder symptoms or ask patients to report objective measures of sleep (e.g., total amount of sleep, time to fall asleep and amount of wakefulness during sleep). Responses to each of the 8 items range from 1 to 5, and the range of possible summed raw scores is 8 to 40. Higher scores on the PROMIS SD SF 8b indicate more of the concept measured (disturbed sleep).

Subjects will complete the PROMIS SD SF 8b electronically via a tablet at each site and without assistance from anyone else. This instrument will be self-administered; proxy responses will not be allowed.

While administration time for the PROMIS SD SF 8b has not been quantified, it is anticipated that the measure can be completed in approximately 2 minutes. In a study of patients with systemic sclerosis [Khanna et al, 2012], 11 PROMIS item banks, including the SD item bank, were administered via computerized adaptive test (CAT). The average number of items completed for each CAT-administered item bank ranged from 5 to 8, and the average time to complete each CAT-administered item bank ranged from 48 seconds to 1.9 minutes per subject (average time = 11.9 minutes per subject for 11 banks) [Khanna et al, 2012]. The expected administration time of approximately 2 minutes is also in line with the 'rule of thumb' that 3 to 5 items can be completed per minute [Hays & Reeve, 2008].The PROMIS SD SF 8b should take approximately 2 minutes to complete.

Due to the electronic administration of this PRO, risk for missing data is mitigated.

5.3.3 Patient-reported Outcome Assessments

The following PROs will be self-administered electronically at the site visit:

- PROMIS SD SF 8b – assesses sleep disturbance
- PROMIS SRI SF 8a – assesses sleep-related impairment
- PGI scales – assess patient-perceived global impressions of severity in sleep disturbance and change in VMS and sleep disturbance
- MENQOL – assesses quality of life as it relates to menopausal symptoms
- EQ-5D-5L – assesses general health-related quality of life
- WPAI-VMS – assesses VMS-related work productivity and activity impairment

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 will be self-administered at the site and prior to performing all other procedures including the C-SSRS.

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.

5.3.3.1 Patient Global Impression Scale

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

The PGI-C VMS asks: “Compared to the beginning of this study, how would you rate your HFs/night sweats now?” Subject ratings range from (1) much better to (7) much worse. The PGI-C SD asks: Compared to the beginning of this study, how well are you sleeping now?” Subject ratings range from (1) much better to (7) much worse. The PGI-S SD asks: “How would you rate the severity of any problems you currently have while sleeping at night?” Subject ratings range from (1) no problems to (4) severe problems.

Each PGI measure should take less than 1 minute to complete. Due to the electronic administration of these PROs, risk for missing data is mitigated.

5.3.3.2 PROMIS SRI SF 8a

The PROMIS SRI SF 8a [PROMIS Sleep-Related Impairment, 2015] is an 8-item PRO measure that evaluates self-reported perceptions of alertness, sleepiness and tiredness during usual waking hours and the perceived functional impairments during wakefulness associated with sleep problems or impaired alertness. Though this measure does not directly assess cognitive, affective or performance impairment, it does measure waking alertness, sleepiness and function within the context of overall sleep-wake function. The PROMIS SRI SF 8a is a universal rather than disease-specific instrument, and has a 7-day recall period.

Responses to each of the 8 items on the PROMIS SRI SF 8a range from 1 to 5, and the range of possible summed raw scores is 8 to 40. Higher scores indicate more of the concept measured (sleep-related impairment).

The PROMIS SRI SF 8a should take up to 2 minutes to complete. Due to the electronic administration of this PRO, risk for missing data is mitigated.

5.3.3.3 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 pre-tests [Lewis et al, 2005; Hilditch et al, 1996].

5.3.3.4 EQ-5D-5L with Visual Analog Scale

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 [EuroQol Research Foundation, 2018; van Reenen & Janssen, 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 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.

5.3.3.5 WPAI-VMS

The WPAI-VMS is a 6-item PRO measure that examines VMS-related work productivity and activity in the preceding 7 days [Reilly Associates, 2013; Reily et al, 1993]. It consists of 4 domains: absenteeism (the percentage of work time missed because of VMS in the past 7 days), presenteeism (the percentage of impairment experienced while at work in the past 7 days because of VMS), overall work productivity loss (overall work impairment measured by combining absenteeism and presenteeism to determine the total percentage of missed time) and activity impairment (the percentage of impairment in daily activities because of VMS in the past 7 days). If the subject is unemployed, only 2 of the 6 items on this questionnaire require completion.

WPAI-VMS outcomes are expressed as impairment percentages, with higher numbers indicating greater impairment and less productivity (i.e., worse outcomes) [Reilly Associates, 2013].

The WPAI-VMS should take 2 minutes to complete. Due to the electronic administration of this PRO, risk for missing data is mitigated.

5.3.4 Pharmacodynamic Assessments

Venous blood samples will be collected for pharmacodynamic assessments starting at day 1 (visit 2), through week 52 (visit 15/EOT) and at the follow-up visit (week 55 [visit 16]).

Pharmacodynamic samples will be taken predose at day 1 (visit 2), week 12 (visit 5), week 16 (visit 6), week 24 (visit 8) and week 52 (visit 15), as well as predose and 3 hours postdose at week 4 (visit 3). The week 4 (visit 3) 3 hours postdose pharmacodynamic sample should be shifted to a later date (prior to week 12) in case the subject cannot accommodate the sampling schedule at that visit. The pharmacodynamic sample should be taken at the same time as the 3-hour postdose pharmacokinetic sample. A pharmacodynamic sample will be taken at the follow-up visit (week 55 [visit 16]), as well. 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 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.

5.3.5 Pharmacokinetic Assessments

Venous blood samples will be collected for pharmacokinetic analysis of fezolinetant and metabolite ES259564 in plasma predose, 1 h (± 30 min) postdose and 3 h (± 30 min) postdose at week 4 (visit 3) and week 16 (visit 6), as well as predose week 12 (visit 5), week 24 (visit 8) and week 52 (visit 15) [see Table 1 Schedule of Assessments]. The indicated time windows for week 4 (visit 3) pharmacokinetic sampling will allow for flexibility. If this visit is missed, the samples can be taken at the next visit.

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.

5.3.6 Pharmacogenomic sample

While pharmacogenomic (PGx) sampling is scheduled for week 4 (visit 3), PGx sample can be taken at any time during the study after signed ICF and enrollment into the study [see Table 1 Schedule of Assessments]. PGx samples will be stored for potential future analysis. Any PGx sample taken during screening will be destroyed in the event of a screen failure.

5.4 Safety Assessment

Safety will be assessed by examining the incidence of AEs, physical examinations findings, the clinician-administered C-SSRS, TVU's, endometrial biopsies, vital signs, ECGs, clinical laboratory tests and bone marker concentrations over time.

5.4.1 Vital Signs

Vital sign parameters will be assessed at each study visit [see Table 1 Schedule of Assessments].

The vital sign parameters that will be assessed are body temperature (oral/tympanic), blood pressure 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 administered at screening (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]) [see Table 1 Schedule of Assessments].

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.

Screening	**Urine Pregnancy Test**	**β-HCG**	
All Visits	Hematology	CBC: white blood cell count with differential (neutrophils, lymphocytes, eosinophils, monocytes and basophils) hemoglobin hematocrit red blood cell count platelets	
Table continued on next page			

Screening	Urine Pregnancy Test	β-HCG	
All Visits	Biochemistry	Blood urea nitrogen Chloride Creatinine Inorganic phosphorus Sodium Bicarbonate Calcium Creatine kinase Estimated glomerular filtration rate Glucose Lactate dehydrogenase Potassium Uric acid	
All Visits	Liver Biochemistry	Alanine aminotransferase Alkaline phosphatase Aspartate aminotransferase Albumin Gamma-glutamyl transferase Total bilirubin	Reference Lab Manual
All Visits	Urinalysis	Protein Glucose pH Blood	
Screening Visit 15/EOT	Coagulation Panel	International normalized ratio Activated partial thromboplastin time Prothrombin time	
Screening	Serology	HBsAg HCV antibody HIV antibody	
Visit 2 Visit 15/EOT Visit 16/FU	Bone Marker	BSAP PINP CTX	
Visit 2 Visit 3 Visit 5 Visit 6 Visit 8 Visit 15/EOT Visit 16/FU	Hormone Levels	LH FSH E2 SHBG Testosterone Total/Free Androstenedione DHEA Estrone	

β-HCG: beta human chorionic gonadotropin; BSAP: bone specific alkaline phosphatase; CBC: complete blood count; CTX: carboxy-terminal telopeptide of type I collagen; DHEA: dehydroepiandrosterone; E2: estradiol; ET: early termination; FSH: follicle-stimulating hormone; HBsAG: hepatitis B virus surface antigen; HCV: hepatitis C virus; HIV: human immunodeficiency virus; LH: luteinizing hormone; PINP: Procollagen Type 1 N-Terminal Propeptide; 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.

5.4.4 Physical Examination

A full physical examination will be performed at screening visit 1, visit 5 (week 12), end-of-treatment visit 15 (week 52) and at the follow-up visit 16 (week 55), 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 visit 3 (week 4) through visit 4 (week 8) and visit 6 (week 16) through visit 14 (week 48) a symptom directed physical exam will be conducted, which includes weight and waist circumference.

5.4.5 Electrocardiogram

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

5.4.6 Imaging

5.4.6.1 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 9 months of study enrollment. Mammograms must show no clinically significant findings in order for subjects to be included in the study.

5.4.6.2 Transvaginal Ultrasound

This is not required for subjects who have had a partial (supra-cervical) or full hysterectomy. All other subjects will undergo a TVU to assess endometrial thickness at screening, at week 12 (EOT) and for subjects who are withdrawn from the study at the ET 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 read by a local reader followed by a central reading.

5.4.7 Endometrial Biopsy

Subjects will undergo a suction endometrial biopsy at the following timepoints (except for subjects who have had a partial [supracervical] or full hysterectomy):

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

In the event an inadequate specimen is obtained at screening, 1 repeat biopsy may be performed if technically possible. If the biopsy is abnormal at week 52 (EOT), subjects will have a repeat biopsy 4 weeks later, if clinically indicated. 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.

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. 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 Guidance for Industry, Estrogen and Estrogen/Progestin Drug Products to Treat Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms – Recommendations for Clinical Evaluation, 2003.

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 9 months. Pap tests must show no clinically significant findings in order for subjects to be included in the study. Samples will be analyzed at a central laboratory. For details on collection, handling and shipment instructions, refer to the laboratory manual.

5.4.8 Order of Assessments

All PRO measures must be self-administered at the site first upon arrival 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 following sequence order will be in effect when more than 1 assessment is required at a time point:

Screening (day -35 to day -1)

1. All screening procedures (except biopsy)
2. Endometrial biopsy

After Randomization (day 1 to day 386)

1. All PRO measures will be administered in the following order, at visits indicated in the Schedule of Assessments [Table 1]:
    - PGI-C VMS
    - PROMIS SD SF 8b
    - PGI-S SD
    - PGI-C SD
    - PROMIS SRI SF 8b
    - MENQOL

- EQ-5D-5L
- WPAI-VMS

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.

5.5 Adverse Events and Other Safety Aspects

5.5.1 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 ICF 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.

5.5.1.1 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, 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 (adverse event or serious adverse event).

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.

5.5.1.2 Potential Cases of Drug-induced Liver Injury

Refer to [Appendix 12.4 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 12.4 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) and are always to be considered important medical events and reported per [Section 5.5.5 Reporting of Serious Adverse Events].

5.5.1.3 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 study. These procedures are collected per the eCRFs Completion Guidelines.

5.5.2 Definition of Serious Adverse Events

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.)
- 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 1 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.

5.5.2.1 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.

5.5.3 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 Reference Safety Information [see Section 1.4 Summary of Key Safety Information for Study Drugs] to determine the relationship. The causality assessment is 1 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.

5.5.4 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

5.5.5 Reporting of Serious Adverse Events

The collection of AEs and the expedited reporting of SAEs will start following receipt of the ICF and will continue until 21 days after the 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 in 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 eCRF.

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)

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, Council for International Organizations of Medical Sciences-I (CIOMS-I) form] to Competent Authorities (CAs) 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, which require submission per local requirements to IRB/local IEC.

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

The investigator may contact the sponsor's medical monitor/study physician for any other problem related to the safety, welfare or rights of the subject.

5.5.6 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 5.5.1 Definition of Adverse Events], 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.

5.5.7 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 5.5.7 Adverse Events of Special Interest] and should be reported on the eCRF as such. AEs of special interest in this study will include:

- Uterine bleeding
- Endometrial hyperplasia/cancer
- Thrombocytopenia
- Elevation in ALT and/or AST > 3 × ULN
- Bone fractures

5.5.8 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 deviations 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 5.5.5 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
- Medication error, overdose and “off-label use”
- Misuse/abuse
- Suspected drug-drug interaction

5.5.8.1 Pregnancy

If a female subject becomes pregnant during the study dosing period or within 28 days from the discontinuation of dosing, the investigator is to report the information to the sponsor according to the timelines in **[**Section 5.5.5 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 5.5.5 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.

5.5.8.2 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 5.5.5 Reporting of Serious Adverse Events] together with the details of the medication error, overdose and/or “off-label use”.

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

5.5.8.3 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 5.5.5 Reporting of Serious Adverse Events] together with details of the misuse or abuse of the study drug(s).

5.5.8.4 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 5.5.5 Reporting of Serious Adverse Events] together with details of the suspected drug-drug interaction.

5.5.9 Supply of New Information Affecting the Conduct of the Study

When new information becomes available and/or 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 ICF in order to continue in the clinical study.

5.5.10 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 CAs, 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.

5.5.11 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 study 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.

5.6 Test Drug Concentration

Blood plasma samples for pharmacokinetics of fezolinetant and metabolite ES259564 will be collected from every subject.

A single pharmacokinetic sample will be collected at each of the following time points [Table 3].

Table 3 Pharmacokinetic Time Points

Visit	Time Point
Visit 3, Visit 6	pre-dose, 1 hour and 3 hour postdose
Visits 5, 8 and 15	pre-dose

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

5.7 Other Measurements, Assessments or Methods

5.7.1 Blood Sample for Future Pharmacogenetic Analysis (Retrospective Pharmacogenetic Analysis)

PGx research may be conducted in the future to analyze or determine genes of relevance to clinical response, pharmacokinetics and toxicity/safety issues. After randomization [see Table 1 Schedule of Assessments], a sample of whole blood for possible retrospective PGx analysis will be collected. Samples will be shipped to a sponsor designated banking contract research organization (CRO). PGx samples will be kept for up to 15 years, or as specified in the ICF.

Details on sample collection, labeling, storage and shipment procedures will be provided in a separate laboratory manual.

See [Appendix 12.6 Pharmacogenetic Analysis With Banked Sample] for further details on the banking procedures.

5.8 Total Amount of Blood

Blood samples will be taken for the purposes of clinical laboratory tests, serology tests (screening only), pharmacokinetic samples, pharmacodynamic samples, PGx samples (if applicable) and bone markers. Repeat and additional blood samples may be taken if required. For each patient, the expected blood volume to be drawn will be approximately 250 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 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 International Normalized Ratio (INR) > 1.5 × ULN and INR > 1.5 (If INR testing is applicable/evaluated)
    - 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 subject becomes pregnant

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 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

As described above, the first 12 weeks of treatment will be double-blind, with a 12-week analysis conducted after all subjects complete 12 weeks of treatment. After completing 12 weeks of treatment, subjects will receive active treatment through end of 52-week study.

Given the design, a 12-week treatment analysis will occur to assess efficacy and safety during the double-blind treatment phase. This will occur after all subjects have completed 12 weeks of treatment. Efficacy and safety data will be analyzed, excluding the endpoints measured after 12 weeks. Since all primary and secondary analyses only based on data through week 12, no alpha adjustment is required as the information fraction at the 12-week analysis is 100%.

Once the entire 52-week study is completed and locked, additional efficacy and safety will be summarized without statistical comparison to placebo.

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 hard lock for the12-week treatment analysis at the latest. Any changes from the analyses planned in SAP will be justified in the clinical study report.

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

A total of 300 subjects are planned to be randomized; 150 subjects in each treatment arm.

The phase 2b dose-ranging study included 7 active doses. In this study, the observed least-squares mean difference between fezolinetant and placebo in change from baseline to week 12 (and week 4) in mean daily frequency of moderate to severe VMS ranged from -1.8 to -3.0.

For a pairwise comparison using a 2-sample t-test at a 2-sided 5% alpha, 100 subjects would provide at least 80% power to detect the following effect sizes assuming a SD of 5:

Assumed treatment difference in mean daily frequency	Power for pairwise test
-2.0	80%
-2.3	89%
-2.5	94%

For change from baseline to week 12 (and week 4) in mean severity of moderate to severe VMS, the observed mean treatment differences in the phase 2b study ranged from -0.2 and -1.0.

For a pairwise comparison using a 2-sample t-test at a 2-sided 5% alpha, 100 subjects would provide the at least 80% power to detect the following effect sizes assuming a SD of 1:

Assumed treatment difference in mean severity	Power for pairwise test
-0.40	80%
-0.46	89%
-0.50	94%

NOTE: The combined power for testing all 4 co-primary endpoints will be lower than the power for each considered individually; however, the co-primary endpoints are correlated (especially the same endpoint at different time points) and this will serve to limit the potential reduction of power.

Assuming approximately 32% of subjects discontinue prematurely, the number of subjects will be increased from 100 to 150 subjects per arm.

This sample size would also provide over 95% power to detect a difference of 4.3 from placebo on the key secondary endpoint of the PROMIS sleep disturbance questionnaire, using a 2-sample t-test at a 2-sided 5% alpha assuming a SD of 7 [Avis et al, 2016].

7.2 Analysis Sets

Detailed criteria for analysis sets will be laid out in classification specifications and the allocation of subjects to analysis sets will be determined prior to database hard-lock.

For each treatment group, the number and percentage of subjects will be characterized for all randomized subjects and by each analysis set.

7.2.1 Full Analysis Set

The full analysis set (FAS) will consist of all subjects who are randomized and receive at least 1 dose of study drug and have at least 1 post baseline electronic diary measurement. 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 Per Protocol Set

The per protocol set (PPS) will consist of the subset of the FAS who do not meet criteria for PPS exclusion. These criteria are to capture relevant non-adherence to the protocol, in a manner that might reasonably impact the primary analysis, and will be defined in the SAP. A full list of criteria will be decided and assessed prior to database lock and unblinding. The PPS will be a secondary analysis set for efficacy analyses. Select demographic and baseline characteristics may also be summarized for the PPS.

7.2.3 Safety Analysis Set

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.

7.2.4 Pharmacokinetic Analysis Set

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. The PKAS will be used for all summaries and analyses of the pharmacokinetic data.

7.3 Demographics and Baseline Characteristics

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 and percentage of subjects who completed and discontinued treatment and reasons for treatment discontinuation will be presented for all randomized subjects and for subjects in the SAF by treatment group and overall. Similar tables for screening disposition and investigational period disposition will also be presented for all randomized subjects 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 presented in a listing.

7.3.3 Medical History

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

7.4 Analysis of Efficacy

Efficacy analysis will be conducted on the FAS and PPS. The interpretation of results from statistical tests will be based on the FAS. The PPS will be used to assess the robustness of the results from the statistical tests based on the FAS.

All statistical comparisons will be conducted using 2-sided tests at the $\alpha = 0.05$ significance level unless specifically stated otherwise. There are additional testing details below regarding the 4 co-primary endpoints and the key secondary endpoint. All null hypotheses will be of no treatment difference, all alternative hypotheses will be 2-sided, unless specifically stated otherwise.

7.4.1 Analysis of Co-primary Endpoint

7.4.1.1 Co-primary Analysis

The 4 co-primary efficacy endpoints are the mean change in the frequency of moderate to severe VMS and the mean change in severity of VMS (per 24 hours) from baseline to week 4 and week 12.

For each of the 4 co-primary efficacy endpoints, a mixed models repeated measures analysis of covariance (MMRM) will be used with treatment group, pooled center and smoking status (current vs. former/never) as factors, with baseline weight and baseline measurement as covariates. MMRM will use all available on-treatment data to inform mean treatment effect estimates without requiring explicit imputation for missing data (i.e., for discontinued subjects). This analysis will use a restricted maximum likelihood–based repeated-measures approach. The treatment difference will be estimated at all study weeks. This approach is consistent with the hypothetical strategy used for the estimand, which is to compare patients as though they had continued on the assigned treatment.

Comparisons between the active doses and placebo will be calculated based on least-squares mean contrasts using a 2-tailed 95% confidence interval (CI). NOTE: All 4 co-primary variables should be successful for a given dose-level.

The hypothesis for each pairwise comparison is given as follows:

H0: The change from baseline at week 4 (or 12) for fezolinetant and placebo are the same

H1: The change from baseline at week 4 (or 12) for fezolinetant and placebo are not the same

The co-primary analysis will use the FAS.

Frequency of moderate or severe VMS events will be calculated as the sum of moderate or severe VMS events per day.

Severity of moderate to severe VMS events will be calculated using a weighted sum defined as follows:

([number of moderate VMS events × 2] + [number of severe VMS events × 3])

Daily frequency and severity per week (e.g., week 4, week 12) will be calculated as the average frequency or severity over 7 days. The specific windows will be defined in the SAP.

Within the 10 days prior to randomization, subjects must have a minimum average of 7 to 8 moderate to severe HFs (VMS) per day, or 50 to 60 per week.

7.4.1.2 Sensitivity Analysis of Co-primary Endpoints

A supportive analysis will be carried out for the co-primary efficacy endpoints based on the PPS. The method used for this analysis will be identical to the co-primary analysis described in [Section 7.4.1.1 Co-primary Analysis]. Week 4 analyses will be performed on PPS4 and the week 12 analyses will be performed on PPS12.

For subjects in the efficacy analysis populations with missing co-primary efficacy endpoints, multiple imputation by fully conditional specification methods will be used as a sensitivity analysis. The imputation model will use subject demographics (age, sex, race, baseline weight and smoking status) and baseline and post-baseline mean number and severity of VMS. These imputed data will be analyzed using, an analysis of covariance (ANCOVA) with treatment group, pooled center and smoking status (current vs former/never) as factors, with baseline weight and baseline measurement as covariates. These ANCOVA models will be run separately for each of the 4 co-primary endpoints.

The analysis for each of the co-primary endpoints will be conducted using a simplified MMRM model with treatment group as a factor and baseline measurement as a covariate.

7.4.1.3 Subgroup Analysis

The simplified MMRM for the co-primary efficacy endpoints analyses will be repeated, including but not limited to, smoking status, body mass index and race.

7.4.2 Analysis of Secondary Endpoints

The analysis of secondary efficacy endpoints will be based on the FAS. For efficacy endpoints collected at visits, the last non-missing assessment prior to the first dose of study treatment (investigational product or placebo) is the baseline.

7.4.2.1 Key Secondary Endpoint

The PROMIS SD scale will be analyzed using MMRM will be used including treatment group as factor and baseline measurement as covariate, similar to the secondary analysis of the co-primary endpoints.

If all the co-primary endpoints are statistically significant between fezolinetant and placebo, the statistical test will be performed on the key secondary efficacy endpoint between fezolinetant and placebo with alpha = 0.05.

7.4.2.2 Secondary Endpoints

For percent reduction at weeks 4 and 12, an MMRM model as described in [Section 7.4.1.2 Secondary Analysis of Co-Primary Endpoints] will be used.

For each of the secondary responder endpoints, logistic regression will be used for the analysis for each week and endpoint. A missing value will be imputed as a nonreponder.

7.4.3 Analysis of Exploratory Endpoints

Percent reduction, PROMIS (SD and SRI total scores), MENQOL total, EQ-5D domain scores and WPAI-VMS total score will be assessed using an MMRM model as described in [Section 7.4.1.2 Secondary Analysis of Co-Primary Endpoints]. Percent reduction and absolute reduction will be analyzed as described for the secondary responder endpoints. PGI-S and PGI-C will be analyzed using Cochran Mantel Haenszel test with PGI-S using the baseline score. The median change in serum concentrations of sex hormones and sex hormone-binding globulin (SHBG) from baseline to weeks 4 and 12 and the mean change in serum concentrations of BSAP, P1NP and CTX from baseline to week 12 will be summarized.

NOTE: Assessments after the 12-week placebo-controlled period are descriptive only, because there is no placebo control.

7.5 Analysis of Safety

Safety will be assessed by examining the incidence of AEs, physical examinations findings, the clinician-administered C-SSRS, TVU's, endometrial biopsies, vital signs, ECGs, clinical laboratory tests and bone marker concentrations over time.

7.5.1 Adverse Events

AEs will be coded using MedDRA.

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 system organ class, preferred term and treatment group. The number and percentage of AEs by severity will also be summarized.

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

7.5.2 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.

The liver safety assessments will be summarized by the categories below based on the measurements from alkaline phosphatase (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 TL > 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.

7.5.3 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 time point.

7.5.4 Physical Examination

Physical examination will be listed by treatment group.

7.5.5 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.

7.5.6 Endometrial Health Assessment

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

7.6 Analysis of Pharmacokinetics

Descriptive statistics (e.g., n, mean, SD, minimum, median, maximum, coefficient of variation [CV], geometric mean and geometric CV) will be provided for plasma concentrations of fezolinetant and the major metabolite ES259564 by time point. Plasma concentration data of fezolinetant may be subjected to population pharmacokinetic analysis. 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. The results of the population pharmacokinetic analysis will not be reported in the clinical study report, but in a separate population pharmacokinetic report.

7.7 Analysis of Pharmacodynamics

Serum concentrations of sex hormones and SHBG will be summarized using descriptive statistics (number of subjects, mean, SD, median, minimum and maximum) for each visit and time point and for change from the baseline to each postdose visit, if applicable. Detailed information on the statistical analysis of pharmacodynamic data, such as transformations and nature of descriptive statistics used, will be provided in the SAP for this study.

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

No formal interim analysis is planned for this study.

7.9 Additional Conventions

Missing data may be the result of missing week 4/week 12 frequency/severity of VMS measurements or the result of patients discontinuing treatment prior to week 4/week 12. Missing at random will be assumed. Details will be provided in the SAP.

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 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 facility. 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.

All procedures conducted under the protocol must be documented. For screen failures, the minimum demographic data (sex, birth date/age, race and ICF 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 diaries and questionnaires as descried in [Section 5.3.3 Patient-reported Outcomes Assessments] 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 will review the diaries and questionnaire data throughout the study to ensure completion and protocol compliance.

The diary and 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. For this study, it has been decided that there are justifiable scientific reasons (e.g., recall bias) for not allowing the following variables or type of data to be changed after the original data has been entered and submitted, greater than 24 hours ago, as a change could potentially impact the data integrity of this study: HF diary entries and associated severities.

8.2 Screen Failures

For screen failures the demographic data, reason for failing, ICF, 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. All 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 one that may potentially impact the completeness, accuracy or reliability of data contributing to the primary endpoint or affect the rights, safety or well-being of a 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 applicable regulatory authorities will be provided to the sponsor and maintained within the trial master file.

9 END OF STUDY

The end of the study is defined as the last visit or scheduled procedure shown in the Schedule of Assessments [Table 1] 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 and are not investigators participating in the study or Astellas employees. A statistician will also be an 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 DILI 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.

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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/Independent Ethics Committee/Competent Authorities

Good Clinical Practice (GCP) requires that the clinical protocol, any protocol amendments, the IB, the ICF 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, ICF 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 non-substantial amendments. Depending on the nature of the amendment, either IRB/IEC, CA 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 ICF, written verification of IRB/IEC approval must be forwarded to the sponsor. An approved copy of the new ICF 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 or her guardian or legal representative, and answer all questions regarding this study. Prior to any study-related screening procedures being performed on the subject, the ICF will be reviewed and signed and dated by the subject or her guardian or legal representative, the person who administered the ICF 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 ICFs 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.

12.1.5.2 Supply of New and Important Information Influencing the Subject's Consent and Revision of the Written Information

1. 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 their 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 study 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, eCRFs 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 is approved or if the IND 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

The privacy of subjects must always be respected. Every possible measure should be taken to ensure the privacy of subjects and to minimize the potential impact of the clinical study on the subject. The specific measures should be provided in this section.

For clinical research performed at a facility that is not a covered entity under Health Insurance Portability and Accountability Act (HIPAA), language consistent with the principles of HIPAA should be included in the ICF to describe the provisions in place to protect subject privacy and to seek consent for use of private information obtained during the study.

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 sponsor shall serve as the controller of such data, as defined by the EU Data Protection Directive, and investigator and/or third party shall act only under the instructions of the sponsor in regard to personal data. If sponsor is not based in the EEA, 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 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 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 Data Science or designee 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 WHO Drug Dictionary, respectively.

12.2.4 Quality Assurance

The sponsor is implementing and maintaining quality assurance (QA) and quality control (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 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**
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
Table continued on next page	

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 (only used to prevent osteoporosis)	Estradiol
Minivelle	Estradiol
Ogen	Estropipate
Ortho-Est	Estropipate
Premarin	Conjugated Estrogens
Vagifem	Estradiol
Vivelle	Estradiol
Vivelle-Dot	Estradiol
Table continued on next page	

Progestin-Only Medicines	
Brand Name	**Generic Name**
Prometrium	Micronized Progesterone
Aygestin	Norethindrone acetate
Provera	Medroxyprogesterone Acetate
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

12.4 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 × ULN, and INR > 1.5 (If INR testing is applicable/evaluated), 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 function 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 functions 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 abnormal liver function tests (LFTs) should be followed as described below.

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

Severe hepatic liver function abnormalities as defined above, in the absence of another etiology, may be considered an important medical event and may be reported as a SAE. The sponsor should be contacted and informed 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, direct bilirubin.
- 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 LFTs, 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. Discontinuation of study treatment should be considered 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 > 1.5) (If INR testing is applicable/evaluated).
- 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).

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) with concurrent transaminase elevations at least 3 × ULN and no evidence of intra- or extra-hepatic bilirubin obstruction (elevated ALP) or Gilbert’s syndrome [Temple, 2006].

FDA Guidance for Industry, “Drug-Induced Liver Injury: Premarketing Clinical Evaluation,” 2009:

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 study subjects showing such AT elevations, often with ATs much greater than 3 × ULN, 1 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):241-43.

Guidance for Industry titled “Drug-Induced Liver Injury: Premarketing Clinical Evaluation” issued by FDA on July 2009.

12.5 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.

12.6 Pharmacogenomic Analysis with Banked Sample

INTRODUCTION

PGx research aims to provide information regarding how naturally occurring differences in a subject's gene and/or expression of genes based on genetic variation may impact what treatment options are best suited for the subject. Through investigation of PGx by technologies such as genotyping, gene sequencing, statistical genetics and Genome-Wide Association Studies, the relationship between gene profiles and a drug's kinetics, efficacy or toxicity may be better understood. As many diseases may be influenced by 1 or more genetic variations, PGx research may identify which genes are involved in determining the way a subject may or may not respond to a drug.

OBJECTIVES

The PGx research that may be conducted in the future with acquired blood samples is exploratory. The objective of this research will be to analyze or determine genes of relevance to clinical response, pharmacokinetics and/or toxicity/safety issues.

By analyzing genetic variations, it may be possible to predict an individual subject's response to treatment in terms of efficacy and/or toxicity.

SUBJECT PARTICIPATION

Subjects who have consented to participate in this study participate in this PGx sub-study. Subjects must provide written consent prior to providing any blood samples that may be used at a later time for PGx analysis.

SAMPLE COLLECTION AND STORAGE

Subjects who consent to participate in this sub-study will provide 1 tube of whole blood of approximately 4 to 6 mL per Astellas' instructions. Each sample will be identified by the unique subject number. Samples will be shipped to a designated banking CRO as directed by Astellas.

PGx ANALYSIS

Details on the potential PGx analysis cannot be established yet. Astellas may initiate the PGx analysis if evidence suggests that genetic variants may be influencing the drug's kinetics, efficacy and/or safety.

DISPOSAL OF PGx SAMPLES/DATA

All PGx samples collected will be stored for a period of up to 15 years following study database hardlock. If there is no requirement for analysis, the whole blood sample will be destroyed after the planned storage period. The subject has the right to withdraw consent at any time. When a subject's withdraw notification is received, the PGx sample will be destroyed. The results of any PGx analysis conducted on a sample prior to its withdrawal will be retained at Astellas indefinitely unless otherwise specified by local regulation.

INFORMATION DISCLOSURE TO THE SUBJECTS

Exploratory PGx analysis may be conducted following the conclusion of the clinical study, if applicable. The results of the PGx analysis will not be provided to any investigators or subjects, nor can the results be requested at a later date. Any information that is obtained from the PGx analysis will be the property of Astellas.

13 SPONSOR SIGNATURES

ELECTRONIC SIGNATURE PAGE

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01/30/2019 15:18:38	James Young	Signature as Document Originator
Full Name / Legal Name	James Young	
01/30/2019 15:25:25	Danijela Dobric	Signature as Document Originator
Full Name / Legal Name	Danijela Dobric	
01/30/2019 20:54:24	Christopher Lademacher	(For Disclosure) Responsible Officer
Full Name / Legal Name	Christopher Lademacher	
Full Name / Legal Name		
Full Name / Legal Name		
Full Name / Legal Name		
Full Name / Legal Name		
Full Name / Legal Name		
Full Name / Legal Name		
Full Name / Legal Name		

*UTC: Coordinated Universal Time