



CLINICAL STUDY PROTOCOL SJX-653-006

A PHASE 2, PROSPECTIVE, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED CLINICAL STUDY TO ASSESS THE EFFICACY, SAFETY, TOLERABILITY, AND PHARMACOKINETICS OF SJX-653 IN POSTMENOPAUSAL WOMEN WITH MODERATE TO SEVERE VASOMOTOR SYMPTOMS

Investigational Product:	SJX-653
Development Phase:	2
Date:	01 July 2020
Version No.:	2.0
Amendment	1.0
EudraCT Number:	2019-002281-12
Sponsor:	Sojournix, Inc. 400 Totten Pond Road, Suite 110 Waltham, MA 02451 USA

This clinical study will be conducted in accordance with the International Council for Harmonisation Guideline for Good Clinical Practice (E6).

CONFIDENTIALITY STATEMENT

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1. PROTOCOL SYNOPSIS AND SCHEDULE OF ASSESSMENTS

Name of Investigational Product: SJX-653
Name of Active Ingredient: 2-Ethylamino-8-fluoro-3-methyl-1-oxo-1,2-dihydroisoquinoline-4-carboxylic acid ((S)-cyclopropylphenylmethyl) amide
Protocol Title: A Phase 2, Prospective, Randomized, Double-Blind, Placebo-Controlled Clinical Study to Assess the Efficacy, Safety, Tolerability, and Pharmacokinetics of SJX-653 in Postmenopausal Women with Moderate to Severe Vasomotor Symptoms
Protocol Number: SJX-653-006
Development Phase: 2
Name of Sponsor/Company: Sojourntix, Inc.
Investigator/Study Sites: This study will be conducted at approximately 20 sites in Europe.
Study Objectives: Primary Objective: The primary objective of this study is to evaluate the effect of oral 20 mg SJX-653 once daily (QD) for 4 weeks in postmenopausal women (PMW) with moderate to severe vasomotor symptoms (VMS) on VMS frequency after 4 weeks of treatment. Secondary Objectives: <ul style="list-style-type: none">• Effect of SJX-653 on measures of VMS severity and frequency by study week• Safety and tolerability of SJX-653• Pharmacokinetics (PK) of SJX-653 Exploratory Objectives: <ul style="list-style-type: none">• Effect of SJX-653 on the following outcomes:<ul style="list-style-type: none">○ Measures of VMS severity and frequency by study day during the first week○ Daytime and nighttime measures of VMS severity and frequency by study week○ Sleep and Quality of Life (QoL).
Methodology: This is a multicenter, prospective, randomized, double-blinded, placebo-controlled, parallel-group, Phase 2 study of SJX-653 in PMW with moderate to severe VMS. PMW with moderate to severe VMS who sign an informed consent will undergo a Screening process for up to 4 weeks including a 14-day Run-in Period. During the Run-in Period, Baseline frequency and severity of VMS will be established by recording VMS in a hot flash (HF) electronic diary (eDiary). At the end of the Run-in Period, eligibility will be determined. Eligible subjects will be randomized in a 1:1 ratio to SJX-653 or placebo. Subjects will be dosed once daily (QD) with either 20 mg SJX-653 or matching placebo for 4 weeks. The Treatment Period will be followed by a 2-week Follow-up Period during which subjects must continue to adhere to all protocol restrictions, including prohibited medications and supplements. Data on efficacy, tolerability, safety, and PK will be collected. Subjects will also complete a QoL assessment (Hot Flash Related Daily Interference Scale [HFRDIS]) and a sleep questionnaire (Insomnia Severity Index [ISI]) on Day 1 to establish a baseline and then at subsequent visits per the Schedule of Assessments. Sampling of blood for PK analyses will occur per the Schedule of Assessments.

Safety and tolerability will be assessed by adverse event (AE) collection, physical examination, vital signs, 12-lead electrocardiogram (ECG), and safety laboratory tests per the Schedule of Assessments. The study design is illustrated in [Figure 1](#), the Schedule of Assessments is presented in [Table 1](#).

Independent Review: An independent Data Monitoring Committee (DMC) will be established for this study. Members of the DMC will be independent of the study Investigators. The DMC will comprise relevant medical experts (including a specialist in VMS/women's health), an independent statistician, and additional representatives (to be defined in the DMC Charter). The DMC will review safety data at regular intervals according to the DMC Charter. The DMC Charter will establish meeting frequency, scope and method of data review, maintenance of blind, and the decision-making process, prior to the start of the study. In the event that potential safety issues are identified, the DMC may recommend modification of the study design or study termination, which will be communicated to the Investigators, Institutional Review Boards/Independent Ethics Committees (IRBs/IECs), and regulatory agencies by the Sponsor, in accordance with legal and regulatory requirements.

Investigational Product: SJX-653 Tablet, 10 mg dose strength.

Reference Drug (Placebo): Matching placebo tablets containing excipient only.

Mode of Administration: Oral in the morning with water.

Frequency of administration: QD

Number of Subjects (planned): Approximately 66 subjects are planned for randomization in the study, assuming a drop-out rate of 12%. Eligible subjects will be randomized in a 1:1 ratio to SJX-653 or placebo.

Duration of Subject Participation: Participation will be approximately 10 weeks: up to 4 weeks for Screening (including a 14-day Run-in Period), a 4-week Treatment Period, and a 2-week safety Follow-up Period.

Inclusion/Exclusion Criteria:

Inclusion Criteria

Subjects must meet the following criteria for inclusion:

1. Have voluntarily agreed to participate in this study and signed a consent form before Screening procedures begin.
2. Be a postmenopausal female, 40 to 65 years of age (inclusive) at the Screening Visit, defined as:
 - Spontaneous amenorrhea for at least 12 months, OR
 - 6 months of spontaneous amenorrhea with serum FSH level >40 mIU/mL, OR
 - 6 weeks past a postsurgical bilateral oophorectomy with or without hysterectomy.

All PMW must have a serum FSH >40 mIU/mL at Screening.

3. Have had VMS for 3 months prior to Screening.
4. Be compliant with daily HF eDiary completion, as measured by HF eDiary completion on at least 12 days during the 14-day Run-in Period.
5. Have an average of at least 7 moderate to severe VMS per day at Baseline, calculated from daily HF eDiary data of at least 12 days during the Run-in Period, with at least 4 of those days with 7 or more moderate to severe VMS per day.

The following definitions for severity are used:

- **Mild:** Sensation of heat without sweating/dampening; if at night, do not wake up but later notice damp sheets or clothing.
 - **Moderate:** Sensation of heat with sweating/dampness, but able to continue activity; if at night, wake up because hot and/or sweating, but no action is necessary other than rearranging the bed sheets.
 - **Severe:** Sensation of heat with sweating causing disruption of current activity; if at night, wake up hot and sweating and need to take action (eg, removing layer of clothes, open the window, or get out of bed).
6. Have a body mass index between 18 and 35 kg/m², inclusive.
 7. Have a clinical breast exam without clinically significant finding at Screening.
 8. For Subjects 50-65 years old, have documentation (written or electronic report) of a satisfactory mammogram result at Screening within applicable intervals stated in local breast cancer screening guidelines. Subjects 40-49 years old require a mammogram within the same intervals.
 9. Have documentation (written or electronic report) of a normal Pap smear (or equivalent cervical cytology) in combination with Human Papilloma virus (HPV) testing, or a Pap smear of no clinical significance in the opinion of the Investigator, at Screening within applicable intervals stated in local cervical cancer prevention guidelines.
 10. Be willing to undergo a transvaginal ultrasound to assess endometrial thickness at Screening and at Week 4 (EOT). This is not required for subjects who have had a partial (supracervical) or full hysterectomy.
 11. Have an endometrial thickness ≤ 4 mm by transvaginal ultrasound at Screening
 12. Subjects must be willing to undergo an endometrial biopsy if they have unexplained bleeding during the study or an endometrial thickness >4 mm at the EOT Visit. An endometrial biopsy is not required for subjects who have had a partial (supracervical) or full hysterectomy.

Exclusion Criteria

Subjects are to be excluded from the study if they meet any of the following criteria:

1. Have clinically significant history or evidence of poorly controlled cardiovascular, respiratory, hepatic, renal, gastrointestinal, endocrine, neurological, immunological, or psychiatric disorder(s), or have any other medical condition that, in the Investigator's opinion, would make subjects unsuitable for participation in the study.
2. Have manifest or suspected active COVID-19 infection
 - Have tested positive for presence of SARS-CoV-2 based on a RT-PCR or other validated test, or
 - Have clinical symptoms suggestive of COVID-19 infection, or
 - Have to comply with quarantine requirements per local Public Health directive
3. A history of diagnosis of major depressive disorder in the 3 years prior to Screening, or are on antidepressant, anxiolytic or antipsychotic treatment with the following exception:
 - Selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs) treatment for mild depression and/or mild anxiety are allowed provided medication is stable and well-tolerated in the 3 months prior to the Screening Visit and does not change during study participation.
 - SSRIs and SNRIs for treatment of VMS are prohibited (see Exclusion Criterion 26)

4. Have a history of suicide ideation or attempt in the past 3 years.
5. Have a sleep disorder other than insomnia due to VMS (eg, narcolepsy, sleep apnea, restless leg syndrome).
6. Have clinical or biochemical evidence of active hepatitis or other significant hepatic or biliary disease (eg, chronic hepatitis, cirrhosis, autoimmune hepatitis, primary biliary cholangitis, primary sclerosing cholangitis, nonalcoholic steatohepatitis, nonalcoholic fatty liver disease, or hereditary liver disease).
7. Have any of the following abnormal laboratory values at Screening:
 - Alanine aminotransferase ($>1.5 \times$ upper limit of normal [ULN]),
 - Aspartate aminotransferase ($>1.5 \times$ ULN),
 - Gamma glutamyl transpeptidase ($>1.5 \times$ ULN),
 - Total bilirubin ($>1.0 \times$ ULN) (subjects with Gilbert's syndrome can be enrolled if other LFTs are within stated limits),
 - Alkaline phosphatase $>1.5 \times$ ULN, provided cholestatic or other liver disease is excluded,
 - Estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m² (CKD-EPI 2009 calculation; Levey 2009).
8. Have tested positive for human immunodeficiency virus antigen or antibodies, hepatitis C antibodies, hepatitis B core antibodies or hepatitis B surface antigen (HBsAg), or hepatitis E virus RNA (reverse transcriptase polymerase chain reaction) at Screening.
9. Have any gastrointestinal, liver, kidney or other disorder that would significantly interfere with the absorption, distribution, metabolism, or excretion (ADME) of drugs in the opinion of the Investigator, including surgery (eg, short bowel syndrome, gastric or intestinal bypass surgery).
10. Have a history of alcohol abuse or a history of substance abuse.
11. Smoking >10 cigarettes per day.
12. Regularly working night shifts.
13. Have a history of hypersensitivity to more than two chemical classes of drugs, or known hypersensitivity to SJX-653 or any of its excipients.
14. Systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure as ≥ 90 mmHg, based on the median of a total of 4 to 6 readings, from 2 to 3 readings taken on 2 different occasions.
15. Have poorly controlled Type II diabetes mellitus as defined by a glycosylated hemoglobin (HbA1c) $>8.0\%$ despite standard care. Subjects with Type I diabetes and subjects on insulin treatment are excluded.
16. Have a history of or are on treatment for hyperthyroidism or hypothyroidism, or have abnormal thyroid tests (T3, T4, thyroid-stimulating hormone) at Screening. Subjects with subclinical hypothyroidism, and subjects on stable treatment for hypothyroidism for a least 3 months prior to Screening with normal thyroid function test results at Screening are allowed.
17. Have clinically significant abnormal ECG or QT interval prolongation (corrected for heart rate using Fridericia formula [QTcF] prolongation >470 ms) at Screening.
18. Have a history of endometrial hyperplasia or uterine/endometrial cancer.
19. Have current unexplained uterine bleeding.
20. Have a history of cancer prior to Screening (other than local, treated basal cell or squamous cell carcinoma).

21. Have any significant illness requiring hospitalization or emergency treatment within 4 weeks prior to the Screening Visit or during the Screening Period, as determined by the Investigator.
22. Are pregnant or lactating.
23. Are taking any drugs considered moderate or strong inducers and/or inhibitors of cytochrome P450 3A4 (CYP3A4).
24. Started statin therapy less than 3 months prior to Screening, or are not on a stable and well-tolerated dose in the 3 months prior to Screening.
25. Have used any of the following hormonal treatments during the timeframes listed prior to the start of the Run-in Period:
 - Vaginal hormonal products (rings, creams, gels): 7 days
 - Transdermal estrogen or estrogen/progestin products: 4 weeks
 - Oral estrogen or estrogen/progestin therapy: 8 weeks
 - Intrauterine progestin therapy: 8 weeks
 - Progestin implants: 3 months
 - Estrogen injectable drug therapy: 3 months
 - Estrogen pellet therapy: 6 months
 - Progestin injectable drug therapy: 6 months
26. Are taking any nonhormonal medication for treatment of VMS in the 8-week period prior to the start of the Run-in Period, including SSRIs, SNRIs, drugs with structural resemblance to gamma-aminobutyric acid (including but not limited to gabapentin and pregabalin), or clonidine.
27. Have used herbal supplements or over-the-counter (OTC) medications for treatment of VMS 8 weeks prior to the start of the Run-in Period. Any other herbal supplements or OTC supplements that could interfere with the study objectives require a 28-day wash-out period prior to the start of the Run-in Period.
28. Are taking any antiestrogens, selective estrogen receptor modulators, or aromatase inhibitors.
29. Are taking any antigonadotropin medication.
30. Are legally or mentally incapacitated.
31. Are not a suitable clinical study candidate per Investigator assessment; e.g., perceived willingness or ability to comply with protocol and study procedures.
32. Are currently participating in another drug or device clinical study or have received the last dose/device intervention in such a study within 90 days or 5 half-lives (whichever is longer) prior to the Screening Visit.
33. Have previously received SJX-653 in another clinical study.
34. Are directly involved in the conduct of the study.

Study Endpoints

Primary Endpoint:

Mean change in average daily frequency of moderate to severe VMS in the intent-to-treat (ITT) population from Baseline to Week 4.

Secondary Endpoints:

Efficacy

- Mean change and percent change of the following parameters of VMS frequency and severity from Baseline by study week through End of Study (EOS):
 - Average daily frequency of moderate to severe VMS.
 - Average daily frequency of all VMS (mild, moderate, and severe).
 - Average daily severity score for moderate to severe VMS.
 - Average daily severity score for all VMS (mild, moderate, and severe).
 - Average daily VMS score for moderate to severe VMS.
 - Average daily VMS score for all VMS (mild, moderate, and severe).
- “Study week” refers to all weeks in the study from Baseline through EOS.

Safety

- Incidence and severity of AEs and serious AEs for SJX-653.
- Change from Baseline to worst (parameter dependent) and last values in vital sign parameters.
- Change from Baseline in clinical laboratory values.
- Change from Baseline in physical examination and ECG.

Pharmacokinetics

- Assessment of C_{trough} concentration at steady state.

Exploratory Endpoints:

- Mean change and percent change of parameters of VMS frequency and severity from Baseline by study day through Week 1.
- Mean change and percent change of daytime and nighttime VMS frequency and severity from Baseline by study week through EOS.
- Change in ISI score from Baseline to Week 4.
- Change in HFRDIS total score from Baseline to Week 2 and 4.

Statistical Methods: A formal statistical analysis plan will be developed and finalized before database lock.

Analysis populations

- ITT – all subjects randomized.
- Per Protocol (PP) – all subjects in the ITT who completed the 4-week assessments with no major protocol violations that may impact the interpretation of the primary efficacy endpoint.
- Safety (SAF) – all subjects who received at least 1 dose of study drug (Investigational drug or placebo).
- PK – all subjects in the SAF who had at least 1 evaluable PK sample collected.

The primary endpoint will be assessed using Mixed effect Model Repeat Measurement (MMRM) with Baseline VMS frequency as a covariate. Secondary and exploratory endpoints assessing change in continuous endpoints over time will use MMRM for individual time points and trends over time. Safety endpoints will be summarized using descriptive statistics.

Sample size considerations: Sample size requirements were calculated under the following assumptions for the primary efficacy endpoint:

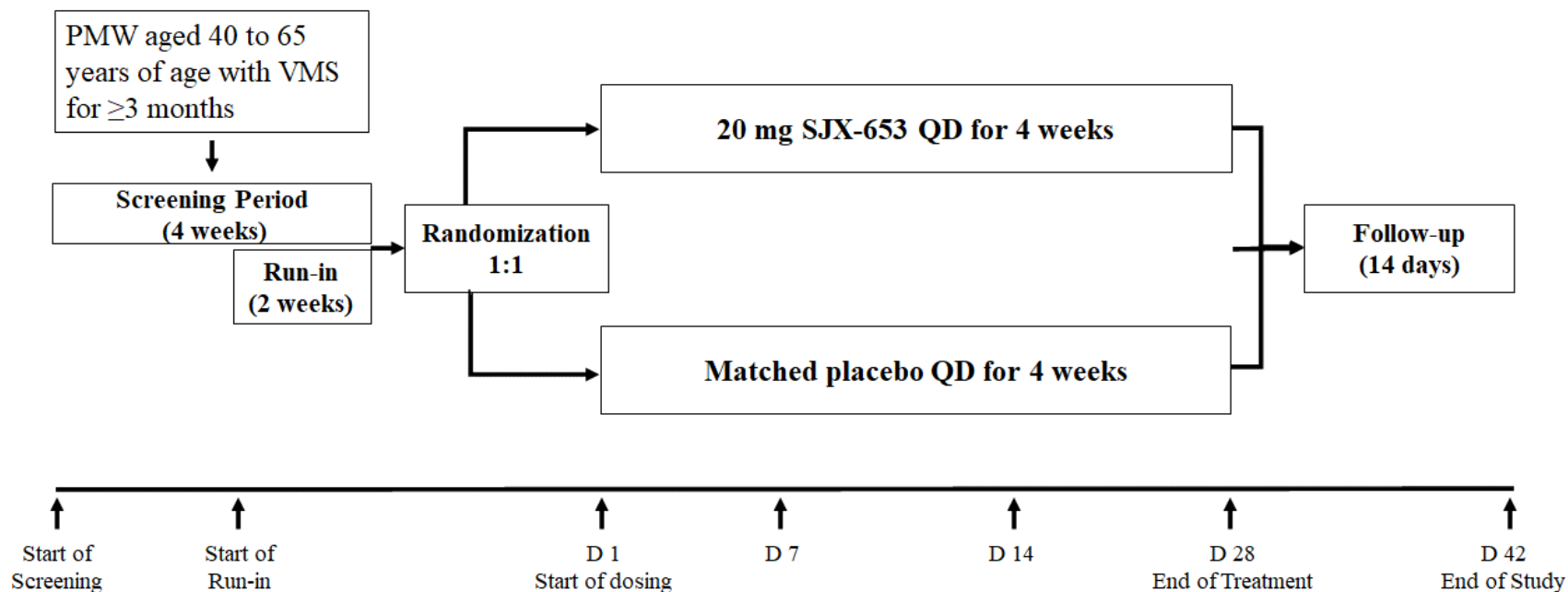
- Two sided $\alpha=0.05$
- Target power=80%.
- Unpaired t-test with two treatment arms (placebo and 20 mg SJX-653).
- Pooled standard deviation = 4.0 based on the change from Baseline to Week 4 for placebo and 20 mg SJX-653.
- Drop-out rate of 12%.
- Mean improvement in placebo group from an average daily frequency of 10 moderate to severe VMS/day to 6.0 moderate to severe VMS/day at Week 4.
- Mean improvement in 20 mg SJX-653 group from an average daily frequency of 10 moderate to severe VMS/day to 3.0 moderate to severe VMS/day at Week 4

Under these assumptions, approximately 29 subjects per group need to complete the study to detect a mean 3.0 moderate to severe VMS /day improvement for 20 mg SJX-653 over placebo in the ITT Population. Approximately 66 (33+33) eligible subjects will initially be randomized 1:1 (20 mg SJX-653: placebo) to achieve 58 (29+29) subjects reaching Week 4.

Adjustment for Multiplicity: No adjustment for multiplicity is planned; Secondary and exploratory endpoints, being supportive in nature, will be tested at 2-sided $\alpha=0.05$ each (nominal testing). Inferential analysis associated with secondary and exploratory endpoints will be considered as supportive.

Missing data: There will be no imputation of missing safety endpoints unless specified otherwise. Missing efficacy endpoints will be handled using MMRM.

Figure 1: Study Schema



Abbreviations: D = Day; PMW = postmenopausal women; QD = once daily; VMS = vasomotor symptoms.
Vertical upwards arrows indicate study Visit days. See Schedule of Assessment for permissible Visit windows.
Randomization is on Day 1, the Start of dosing.

Table 1: Schedule of Assessments

	Screening Period		Treatment Period				Follow-Up
	Screening	Run-In	Baseline	Study Visit		End of Treatment/ Early Termination ¹	End of Study
Study Day	-30 to -15	-14 to -1	1 ±2	7 ±2	14 ±2	28±3	42±3
Study Week	-4 to -2	-2 to -1		1	2	4	6
Visit Location²	Clinic	Phone option	Clinic	At home option	At home option	Clinic	At home option
Events							
Informed consent form signed	X						
Review inclusion/exclusion criteria & medical history	X		X				
Demographics	X						
Physical examination ³	X		X			X	
Randomization			X				
Height and weight ⁴	X		X			X	
Concomitant medications	X	X	X	X	X	X	X
Adverse event monitoring	X	X	X	X	X	X	X
HIV and hepatitis tests	X						
Pregnancy test (urine)	X		X			X	
Drugs of abuse screening ⁵	X		X			X	X
Vital signs ⁶	X		X	X	X	X	X
12-lead ECG	X		X			X	
Hematology	X		X		X	X	X
Total serum chemistry ⁷	X		X		X	X	X
LFTs only				X			
Urinalysis	X		X		X	X	X
COVID-19 testing ⁸	X		X		X	X	X
E2, SHBG, LH, FSH ⁹	X ¹⁰		X	X	X	X	X
Endometrial biopsy ¹¹						X	
Transvaginal ultrasound ¹²		X				X	
Mammogram ¹³		X					

	Screening Period		Treatment Period				Follow-Up
	Screening	Run-In	Baseline	Study Visit		End of Treatment/ Early Termination ¹	End of Study
Study Day	-30 to -15	-14 to -1	1 ±2	7 ±2	14 ±2	28±3	42±3
Study Week	-4 to -2	-2 to -1		1	2	4	6
Visit Location²	Clinic	Phone option	Clinic	At home option	At home option	Clinic	At home option
Events							
Pap smear and HPV testing ¹⁴	X						
Plasma PK collection ¹⁵				X		X	
Dispensing of medication			X				
Drug accountability and compliance check				X	X	X	
Dosing of medication in clinic ¹⁶			X			X	
Recording of VMS frequency/severity in daily HF eDiary ¹⁷	→						
Recording of body temperature in daily eDiary ¹⁸			→				
HFRDIS			X		X	X	
ISI			X			X	

Abbreviations: ALP = alkaline phosphatase; BP = blood pressure; ECG = electrocardiogram; eDiary = electronic diary; EOS = End of Study; EOT = End of Treatment; ET = Early Termination; E2 = estradiol; FSH = Follicle Stimulating Hormone; HDL-C = high density lipoprotein – cholesterol; HF = hot flash; HFRDIS = Hot Flash Related Daily Interference Scale; HIV = human immunodeficiency virus; INR = international normalized ratio; ISI = Insomnia Severity Index; LDL-C = low density lipoprotein – cholesterol; LFT = liver function test; LH = luteinizing hormone; PK = pharmacokinetic; PT = prothrombin time; SHBG = sex hormone binding globulin; VMS = vasomotor symptoms.

Footnotes are on the following page.

- ¹ Participants who discontinue study treatment and/or the study prior to the scheduled EOT Visit on Day 28 should attend an Early Termination Visit. The procedures at this Early Termination Visit will be the same as those specified for EOT.
- ² The Run-In visit may be conducted by phone. During Treatment and Follow-up Period, Day 7, 14, and/or Day 42 (EOS) visits may be conducted either in-clinic or at home.
- ³ Clinical breast examination will be performed only at Screening. Gynecological examination to be performed at Screening and Day 28 (EOT).
- ⁴ Height will be measured at Screening only.
- ⁵ Drugs of abuse panel (see [Appendix 4](#)).
- ⁶ Vital signs (supine BP and heart rate, and aural body temperature); vital signs should be taken after the subject has been resting for at least 5 minutes. BP assessment for eligibility must be based on the median of a total of 4 to 6 readings, based on 2-3 readings from two different occasions.
- ⁷ Total Cholesterol, HDL-C, LDL-C, triglycerides, and fasted glucose will only be collected at Screening and Day 28 (EOT). PT/INR will only be collected at Screening.
- ⁸ Testing for presence of virus (SARS-CoV-2) at Screening, Baseline (Day 1), Days 14, 28 (EOT), and 42 (EOS). COVID-19 antibody testing only at Screening, EOT, and EOS.
- ⁹ At the discretion of the Sponsor, other analyses including but not limited to hormone assessments may be performed.
- ¹⁰ FSH level to confirm eligibility. All postmenopausal women must have a serum FSH >40 mIU/mL at Screening.
- ¹¹ Endometrial biopsy to be performed only if endometrial thickness is >4 mm as measured by transvaginal ultrasound at Day 28 (EOT). Subjects with uterine bleeding during the study must also undergo an endometrial biopsy.
- ¹² Transvaginal ultrasound not required for women who have had a partial (supracervical) or full hysterectomy.
- ¹³ For mammograms, the Screening Period can be extended by 2 weeks
- ¹⁴ Pap smear or equivalent cervical cytology, and HPV screening will be processed at the central laboratory.
- ¹⁵ PK sampling to occur prior to dosing on Day 28 (EOT), and on Day 7 if possible.
- ¹⁶ Medication will be dosed in the clinic on Days 1 (Baseline) and 28 (EOT).
- ¹⁷ Subjects are expected to complete the daily HF eDiary every day from Screening through Day 42 (EOS).
- ¹⁸ Subjects are expected to record daily body temperature in eDiary from Day 1(Baseline) through Day 28 (EOT).