Clinical Study Protocol ACER-801-201

ACER-801

A PHASE 2A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, DOSE-RANGING STUDY TO EVALUATE THE EFFICACY, SAFETY, AND PHARMACOKINETICS OF ACER-801 FOR TREATMENT OF MODERATE TO SEVERE VASOMOTOR SYMPTOMS (VMS) ASSOCIATED WITH MENOPAUSE

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Amendment 1: 14 March 2022

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IND Number: 147934

Sponsor
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CONFIDENTIAL

SPONSOR'S APPROVAL OF THE PROTOCOL

Reviewed and approved by:

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Signing Reason: I approve this document
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16-Nov-2022

Adrian Quartel, MD, FFPM
Chief Medical Officer
Acer Therapeutics Inc.

Date

INVESTIGATOR'S AGREEMENT

I have received and read the current version of the Investigator's Brochure (IB) for ACER-801 and this Protocol ACER-801-201. Having fully considered all the information available, I agree that it is ethically justifiable to give ACER-801 to selected subjects according to this protocol.

I understand that all information concerning ACER-801 supplied to me by the Sponsor, Acer Therapeutics Inc., and/or its agents in connection with this study and not previously published is confidential information. This includes the IB, clinical study protocol, case report forms, and any other preclinical and clinical data provided by the Sponsor.

I understand that no data are to be made public or published without prior knowledge and written approval by the Sponsor.

By my signature below, I hereby attest that I have read, understood, and agreed to abide by all the conditions, instructions and restrictions contained in Protocol ACER-801-201 and in accordance with Good Clinical Practice (CPMP/ICH/135/95), the Declaration of Helsinki, and all regulatory requirements for protection of human subjects in clinical studies and privacy requirements for the protection of individual and company data.

I acknowledge that the Sponsor of the study has the right to discontinue the study at any time.

_____

Investigator's Name (Printed)

_____ _____

Investigator's Signature Date

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Chief Medical Officer
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Date

1 SYNOPSIS

Name of Sponsor/Company:
Acer Therapeutics Inc.

Name of Investigational Product: ACER-801

Name of Active Ingredient:
Osanetant

Title of Study:
A Phase 2a Randomized, Double-Blind, Placebo-Controlled, Dose-Ranging Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of ACER-801 for Treatment of Moderate to Severe Vasomotor Symptoms (VMS) Associated with Menopause

Principal Investigator:
Jennifer Boston, MSN, APNP, A-GNP-BC

Investigational Site:
Spaulding Clinical Research, LLC

Phase of Development:
Phase 2a

Study Objectives:

Primary Objective:

The primary objectives are to:

- Evaluate the pharmacokinetic (PK) profile of ACER-801 and its metabolite at different doses
- Evaluate the safety profile of ACER-801 at different doses

Secondary Objectives:

The secondary objectives are to:

- Evaluate the effect of ACER-801 at different doses on the frequency of vasomotor symptoms associated with menopause compared to placebo
- Evaluate the effect of ACER-801 at different doses on the severity of vasomotor symptoms associated with menopause compared to placebo
- Evaluate the effect of ACER-801 at different doses on the hot flash severity score compared to placebo

Exploratory Objectives:

The exploratory objectives of this study are to evaluate:

- The effect of ACER-801 at different doses on change in hormones compared to placebo including:
    - luteinizing hormone (LH)
    - follicle stimulating hormone (FSH)
    - estradiol
    - testosterone
    - sex hormone binding globulin (SHBG)
    - adrenocorticotropic hormone (ACTH)
    - cortisol
    - thyroid-stimulating hormone (TSH)
    - triiodothyronine (T3) (Total and Free)
    - thyroxine (T4) (Total and Free)
- Changes in the number of night-time awakenings (NTA)
- Changes in blood bone density marker concentration
- Changes in blood markers associated with stress
- Changes in electrocardiogram (ECG) variables (heart rate, RR, PR, QRS, QT, QTcF, and QTcB)
- The relationship between PK exposure and measures of efficacy and/or safety

Methodology:
This is a Phase 2a, randomized, double-blind, placebo-controlled, dose-ranging study in post-menopausal women in which the pharmacokinetic (PK) profile of ACER-801 at different doses is evaluated and the efficacy of ACER-801 (50 mg twice daily [BID], 100 mg BID, and 200 mg BID) will be compared to placebo in approximately 40 to 56 subjects (10 to 14 subjects per treatment arm).

Subjects will enter a Screening Period to determine eligibility. Subjects will be required to complete hot flash diaries for 2 weeks prior to randomization. Eligible subjects will be admitted to a Clinical Research Unit (CRU) on Day -1 and remain in the clinic from Day-1 until discharge on Day 16 after completion of treatment and all study assessments or upon withdrawal from the study. The study includes a 14-day safety follow-up assessment (Day 28).

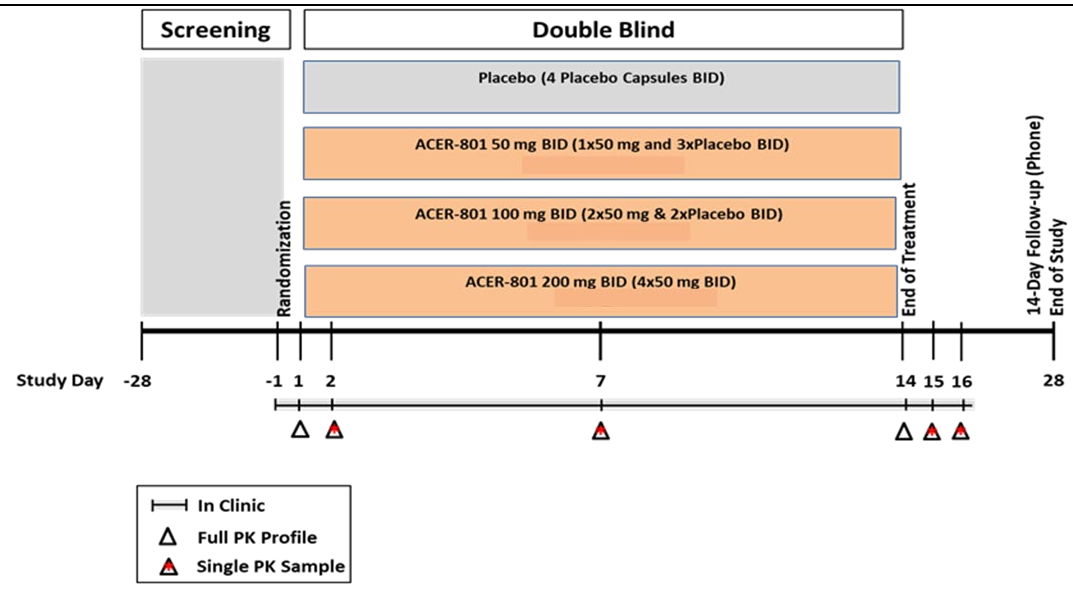
Subjects will be randomized in a 1:1:1:1 ratio to ACER-801 per one of the following dosing schedules prior to dosing:

- 50 mg BID,
- 100 mg BID,
- 200 mg BID, or
- Placebo administered orally for 14 consecutive days (28 doses).

Blood samples for PK (plasma) assessment will be collected for concentrations of ACER-801 and its metabolite at predose, 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 5.0, 6.0, 8.0, 12.0 (prior to evening dose), and 15.0 hrs post morning dose on Day 1 and Day 14, as well as predose (prior to morning dose) on Day 2 and Day 7. Plasma samples will also be collected 24 hrs (Day 15) and 48 hrs (Day 16) after the morning dose on Day 14.

Throughout the duration of the study (Day 1 through Day 16), subjects will be required to record the frequency and severity of hot flashes in a subject diary (continuous hot flash diary). Electrocardiographs using the Mortara Surveyor will be collected on Day -1, Day 1, and Day 14.

During the study, subjects will be closely monitored for safety including assessments of AEs, 12-lead ECGs, atrial oxygen saturation using pulse oximetry, vital signs (sitting and standing blood pressure (BP), heart rate, oral body temperature, and respiratory rate), clinical labs, and physical examinations.



Target Population:
Approximately 40 to 56 post-menopausal women aged 40-65, inclusive, who experience an average of 7 to 20 moderate to severe hot flashes per day (subjects must have 7 or more hot flashes on each day during the 2-week period prior to randomization) as determined by a continuous hot flash diary where events are recorded for 2 weeks prior to randomization will be included in this study. Subjects will have no active, ongoing health conditions that could cause difficulty in interpretation of hot flashes categorized as moderate to severe.

Study Duration:
This study consists of a 28-day Screening Period, a 14-day Treatment Period and a 14-day Safety Follow-Up Period.

Number of Subjects (planned):

- Total: approximately 40 to 56 subjects will be enrolled for the study
- Per treatment: approximately 10 to 14 subjects per treatment arm including study drug and placebo
- Randomization: 1:1:1:1 (treatment: 50 mg BID, 100 mg BID, and 200 mg BID of ACER-801; placebo)

Inclusion Criteria:
To be eligible to participate in this study, subjects must meet all of the following criteria:

1. Post-menopausal female subjects 40-65 years of age, inclusive.

Menopause will be defined as:

   a. At least 12 months of spontaneous, continuous amenorrhea, or
   b. At least 6 months of spontaneous, continuous amenorrhea with serum FSH levels > 40 mIU/mL at screening, or
   c. At least 6 weeks postsurgical bilateral oophorectomy with or without hysterectomy.

2. At baseline women:
   a) With an average of ≥ 7 and ≤ 20 moderate to severe hot flashes/day for 2 weeks prior to randomization (per continuous hot flash diary). The minimum number of hot flashes on each day during the 2 weeks prior to randomization must be at least 7.
   b) That have a change of < 50% in average 24-hour hot flash frequency 2 weeks prior to randomization.
      - Moderate: defined as sensation of heat with sweating, able to continue activity.
      - Severe: defined as sensation of heat with sweating, causing cessation of activity.
3. Able to understand and comply with the requirements of the study and sign Informed Consent forms.
4. Have not participated in any clinical research study evaluating another investigational drug, device or therapy within 30 days or within 5 half-lives (whichever is longer), of the investigational drug prior to consenting to study entry.

Exclusion Criteria:
To be eligible to participate in this study, subjects must not meet any of the following criteria:

1. Any active comorbid disease deemed by the investigator to be clinically significant, which could impact safety during study conduct including renal or hepatic impairment:
   a. Serum creatinine laboratory value greater than 1.2 times upper limit of normal (ULN) reference range (after adjustment for age) at Screening or Day -1 or subjects with renal function glomerular filtration rate (GFR) <60 mL/min/1.73m^2 based on the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.
   b. Total bilirubin greater than upper limit of normal reference range (with the exception of Gilbert's Syndrome) and/or alanine aminotransferase (ALT) >2 times ULN reference ranges and/or aspartate aminotransferase (AST) >2 times ULN reference ranges at Screening or Day -1.

Laboratory values may be repeated once to confirm results.

2. Any active medicinal (pharmaceutical or homeopathic) therapy considered by the investigator to potentially cause hepatic impairment leading to elevated:
   a. ALT and/or AST ranges.
3. Subjects with a prior medical history of or an increased risk of seizures, or who have a history of recent (within 6 months of Screening) head trauma that resulted in a loss of consciousness or concussion.
4. Any prior or ongoing history of arrhythmias.
5. Any ongoing cardiovascular disease including heart failure, coronary artery disease, uncontrolled hypertension, or uncontrolled diabetes (blood sugar level consistently over 100 mg/dL while fasting, higher than 180 mg/dL two hours after a meal, or random blood glucose levels higher than 200 mg/dL. Postmenopausal women with a history of hypertension must be medically cleared to participate in the study. Hypertension is defined as systolic blood pressure ≥130 mg Hg or diastolic blood pressure ≥80 mg over 3 readings on at least 2 different occasions, unless the participant receives medical clearance by her physician to participate in the trial.
6. Any clinically relevant ECG abnormalities at Screening, per Investigator discretion.
7. Use of any prohibited medications (see Section 5.3.2).
8. Any history of malignancy in the past 2 years.
9. Any active ongoing condition that could cause difficulty in interpreting vasomotor symptoms such as: infection that could cause pyrexia, pheochromocytoma, hypothyroidism, hyperthyroidism, carcinoid syndrome, alcohol abuse.
10. Body mass index (BMI) >35 kg/m^2.
11. Inability to complete questionnaires or continuous hot flash diary for any reason including psychiatric disorders and inability or unwillingness to use electronic devices.
12. History of hypothalamic dysfunction.
13. Any clinically significant or unstable medical or psychiatric condition that would interfere with the subject's ability to participate in the study including anxiety syndromes.
14. Any clinically significant abnormal laboratory test result(s) measured at Screening or on Day -1.
15. Participation in any clinical research study evaluating another investigational drug, device, or therapy within 30 days or within 5 half-lives (whichever is longer), of the investigational drug prior to consenting to study entry. If the subject is in an observational clinical study, no washout is required.
16. Subjects who, in the opinion of the investigator, should not participate in the study for any other reason.
17. Any known allergy or hypersensitivity to any of the ingredients in the study medication or to skin adhesives.
18. Current or planned use of other agents for treating hot flashes.
19. History or presence of alcohol abuse defined as consumption of more than 210 mL alcohol per week, or the equivalent of fourteen 4 ounce glasses of wine or fourteen 12 ounce cans/bottles of beer or wine coolers per week) within 6 months before Screening or positive alcohol test at Screening or Check-in (Day -1).
20. History or presence of substance abuse within the past 2 years or positive drug screen test at Screening or Check in (Day -1).
21. Presence of hepatitis B virus, hepatitis C virus (HCV), or human immunodeficiency virus (HIV) at Screening.
22. Current use or has used tobacco- or nicotine-containing products (e.g., cigarettes, cigars, chewing tobacco, snuff, vaping) within 30 days prior to first dose.
23. Known or suspected pregnancy on Day -1.

24. Positive COVID-19 test on Day -1.

Test Product, Dosage and Mode of Administration:
ACER-801 50 mg BID, 100 mg BID, 200 mg BID administered orally as 50 mg capsules
Oral

Reference, Dosage and Mode of Administration:
Placebo matched controls administered BID
Oral

Criteria for Evaluation:

Pharmacokinetics:
All blood samples for PK analysis will be analyzed by a central bioanalytical laboratory. Instructions for collection, processing, storing, and shipping of PK blood samples will be provided to the clinical unit by the bioanalytical laboratory.

Safety:
Subjects will be monitored throughout confinement and during the 2-week follow-up period for adverse reactions to the study treatments and/or procedures. Safety will be assessed by monitoring adverse events (AEs) and serious AEs (SAEs); vital signs; concomitant medications; physical examinations; ECGs; and clinical laboratory tests (hematology and coagulation, serum chemistry, and urinalysis). Ongoing AEs will be monitored (telephone call) until resolution or for 30 days, whichever is first. Abnormal lab findings will be closely monitored by the Sponsor and repeated as deemed necessary until resolution and followed up by the treating physician. All safety data will be reviewed by the Sponsor for any potential safety signals that would alter the safety profile of the molecule.

Statistical Methods:
Analysis Populations:

- The PK Population includes all randomized subjects who have evaluable PK samples.
- The Safety Population includes all randomized subjects receiving at least 1 dose of study treatment.
- The Modified Intent-to-Treat (mITT) Population includes all randomized subjects who receive study treatment with baseline and at least one post-baseline efficacy measurements.
- The Per-Protocol population includes all randomized subjects with baseline and efficacy measurement endpoint visits without any major protocol deviations that would have an impact on the efficacy measurements.

Pharmacokinetic Analyses:
Noncompartmental analysis (NCA) will be performed for the plasma concentrations of ACER-801 and its metabolite. Summary statistics for the PK parameters (C_{max}, t_{max}, AUC_{last}, AUC_{inf}, $AUC\tau$, Accumulation Ratio for C_{max} [AR_{Cmax}], Accumulation Ratio for AUC [AR_{AUC}], Metabolite Ratio of C_{max} [MR_{Cmax}], Metabolite Ratio of AUC [MR_{AUC}], $t_{1/2}$ of ACER-801 and its metabolite) will be determined for ACER-801 and its metabolite for the different dosing groups.

Safety Analyses:
All AEs/SAEs will be coded using the current version of the Medical Dictionary for Regulatory Activities to assign system organ class and preferred term classification, based on the original terms entered on the electronic case report form. The incidence of AEs will be summarized by system organ class, preferred term, relationship to study treatment, and severity for each study treatment. All AEs, including AEs that lead to premature discontinuation from the study and from study treatment SAEs, will be recorded.
All other safety measures including laboratory tests, vital signs, concomitant medication, medical history, physical examination, and ECG data will also be summarized descriptively (mean, standard deviation, median, minimum, and maximum). Laboratory tests will also be summarized by absolute and percent change from baseline and listed by clinical significance.
Concomitant medications will be coded using the most recent version of World Health Organization Drug Dictionary.

Efficacy Analyses:
The secondary endpoints are the change in frequency and severity of vasomotor symptoms and hot flash severity score at Week 1 and Week 2 relative to baseline.

Study Endpoints

Primary Objective: The primary objectives of this study are to:
- Evaluate the PK profile of ACER-801 and its metabolite at different doses
- Evaluate the safety profile of ACER-801 at different doses

Primary Endpoints	Assessments
• Pharmacokinetics (C_{max}, t_{max}, AUC_{last}, AUC_{inf}, AUCτ, AR_{Cmax}, AR_{AUC}, MR_{Cmax}, MR_{AUC}, $t_{1/2}$ of ACER-801 and its metabolite)	• Noncompartmental analysis
• Clinically significant changes in physical examination findings at Week 2 relative to Baseline • Clinically significant changes in clinical laboratory evaluations (hematology, coagulation, serum chemistry, urinalysis, hormones, bone density markers) during the 2-week treatment period relative to Baseline • Adverse events ≥5% • All SAEs and discontinuations	• Physical Examinations • Vital signs • Clinical laboratory assessments • AEs and SAEs

Secondary Objectives: The secondary objectives of this study are to:
- Evaluate the effect of ACER-801 at different doses on the frequency of vasomotor symptoms associated with menopause compared to placebo
- Evaluate the effect of ACER-801 at different doses on the severity of vasomotor symptoms associated with menopause compared to placebo
- Evaluate the effect of ACER-801 at different doses on the hot flash severity score compared to placebo

Secondary Endpoints	Assessments
• Change in frequency of vasomotor symptoms at Week 1 and Week 2 relative to Baseline • Change in severity of vasomotor symptoms at Week 1 and Week 2 relative to Baseline • Change in hot flash severity score at Week 1 and Week 2 relative to Baseline	• Continuous hot flash diary entries throughout the study

Exploratory Objectives:

The exploratory objectives of this study are to evaluate:
- The effect of ACER-801 at different doses on change in hormones compared to placebo
- Change in number of NTAs
- Change in blood bone density marker concentration
- Changes in blood markers associated with stress
- Change in ECG variables (heart rate, RR, PR, QRS, QT, QTcF, and QTcB)
- The relationship between PK exposure and measures of efficacy and/or safety

Exploratory Endpoints	Assessments
Change in hormones relative to Baseline	• LH • FSH • estradiol • testosterone • SHBG • ACTH • cortisol • TSH • T3 (Total and Free) • T4 (Total and Free)
Changes in the number of NTAs	Hot flash diary
Changes in bone density markers relative to Baseline	• Bone specific alkaline phosphatase (BSAP) • Osteocalcin • Amino-terminal propeptides of type 1 collagen (P1NP) • CTX
Changes in blood markers associated with stress relative to Baseline	• Catecholamines • Vasopressin • Gonadotropins • Prolactin • Insulin
Relationship between plasma exposure and changes in ECG variables	Graphical assessment of change in QT versus plasma exposure of ACER-801 and its metabolite.
Exposure-Response Relationship with Efficacy	Graphical assessment of efficacy or potential safety signals versus plasma exposure of ACER-801 and its metabolite.

Sample Size Justification: A sample size of approximately 10 to 14 subjects per arm (approximately 40 to 56 total) is considered sufficient to characterize the PK, safety and preliminary efficacy of ACER-801 based on study results from a dual neurokinin 1,3 receptor antagonists in postmenopausal women (Trower et al, 2020).

TABLE OF CONTENTS

SPONSOR'S APPROVAL OF THE PROTOCOL 3
INVESTIGATOR'S AGREEMENT 4
STUDY PERSONNEL CONTACT INFORMATION 5
1 SYNOPSIS 6
TABLE OF CONTENTS 13
LIST OF TABLES 17
LIST OF FIGURES 17
LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS 18
2 INTRODUCTION 20
2.1 Background 20
2.2 Safety Data 21
2.3 Rationale for Study Design and Dose for Investigational Product 21
3 STUDY OBJECTIVES AND PURPOSE 22
3.1 Primary Objective 22
3.2 Secondary Objectives 22
3.3 Exploratory Objectives 22
4 INVESTIGATIONAL PLAN 23
4.1 Overall Study Design 23
4.2 Number of Subjects and Target Population 24
4.3 Treatment Assignment 24
5 SELECTION AND WITHDRAWAL OF SUBJECTS 27
5.1 Inclusion Criteria 27
5.2 Exclusion Criteria 27
5.3 Study Restrictions 29
5.3.1 Concomitant Medications 29
5.3.2 Prohibited Concomitant Medications 29
5.4 Subject Withdrawal 30
5.5 Stopping Criteria for Subject Dosing 30
5.6 Study Termination Criteria 30
6 TREATMENT OF SUBJECTS 31
6.1 Investigational Product Treatment Regimen 31

6.2 Reference Product 31
6.3 Treatment Compliance 31
6.3.1 Return/Disposition of Clinical Supplies 31
6.4 Randomization and Blinding 32
6.4.1 Unblinding Procedures 32
6.5 Assignment of Site and Subject Numbers 32
6.6 Subject Management 32
6.6.1 Confinement 32
6.6.2 Meals and Dietary Restrictions 32
7 VISIT PROCEDURES 33
7.1 Screening Procedures (Day -28 to Day -1) 33
7.2 Check-In Procedures (Day -1) 33
7.3 Daily Study Procedures (Day 1 through Day 16) 34
7.4 Day 1 (Confined to CRU) 34
7.5 Day 2 35
7.6 Day 7 35
7.7 Day 14/End of Treatment 35
7.8 Day 15 36
7.9 Day 16/ET 36
7.10 End-of-Study Procedures for Subjects that Withdraw from the Study 36
7.11 14-Day Safety Follow-Up 36
7.12 Unscheduled Safety Visit 37
8 INVESTIGATIONAL PRODUCT MATERIALS AND MANAGEMENT 38
8.1 Treatments Administered 38
8.2 Identity of Investigational Product 38
8.3 Investigational Product Packaging, Storage, and Labeling 38
8.4 Investigational Product Receipt, Accountability, and Disposal 38
9 PHARMACOKINETICS 40
9.1 Blood Sampling 40
9.2 Analytical Method 40
10 EFFICACY ASSESSMENTS 41
10.1 Continuous Hot Flash Diary 41

10.2 Exposure-Response Analysis 41
11 ASSESSMENT OF SAFETY 42
11.1 Adverse Events and Serious Adverse Events 42
11.1.1 Definitions of Adverse Events 42
11.1.1.1 Adverse Event 42
11.1.2 Treatment-Emergent Adverse Event 43
11.2 Reporting of Adverse Events and Serious Adverse Events 44
11.2.1 Reporting of Adverse Events 44
11.2.2 Reporting of Serious Adverse Events 44
11.2.3 Additional Investigator Responsibilities for Serious Adverse Events 46
11.2.4 Notification of Post-Study Serious Adverse Events 46
11.2.5 Follow-Up of Adverse Events and Serious Adverse Events 46
11.2.6 Pregnancy and Follow-Up 46
11.3 Other Safety Parameters 47
11.3.1 Medical History 47
11.3.2 Vital Signs, Height, and Weight 47
11.3.3 Concomitant Medications 47
11.3.4 Physical Examination 48
11.3.5 Safety Electrocardiogram 48
11.3.6 Mortara Surveyor for Electrocardiographs 48
11.3.7 Clinical Laboratory Tests 48
11.3.8 Analytical Procedures 50
12 STATISTICS 51
12.1 Determination of Sample Size 51
12.2 Analysis Populations 51
12.3 Primary Endpoints 51
12.3.1 Pharmacokinetic Endpoints 51
12.3.2 Safety Endpoints 51
12.4 Secondary Endpoints 52
12.5 Exploratory Endpoints 52
12.5.1 Assessment of Hormone Changes 52
12.5.2 Night-Time Awakenings 52

12.5.3 Assessment of Changes in Blood Markers Associated with Stress 52
12.5.4 Markers of Bone Density 52
12.5.5 ECG 52
12.5.6 Exposure-Response Relationships 52
12.6 Statistical Analyses 52
12.6.1 Pharmacokinetic Analyses 52
12.6.2 Safety Analyses 53
12.6.3 Efficacy Analyses 53
12.6.4 Exploratory Analyses 53
12.7 Changes in the Conduct of the Study or Planned Analyses 53
13 ADMINISTRATIVE CONSIDERATIONS 54
13.1 Compensation, Insurance, and Indemnity 54
13.2 Ethical Considerations 54
13.2.1 Basic Principles 55
13.2.2 Institutional Review Board 55
13.2.3 Informed Consent 55
13.2.4 Subject Confidentiality and Data Protection 55
13.2.5 Quality Assurance/Quality Control 56
13.2.6 Study Monitoring 56
13.2.7 Audits and Inspections 57
13.2.8 Data Handling/Record Keeping 57
13.2.9 Report Format 57
13.2.10 Investigator Obligations 57
13.2.11 Adverse Event Reporting 58
13.2.12 Protocol Deviations 58
13.2.13 Regulatory Documentation 58
13.2.14 Archiving and Record Retention 59
14 PUBLICATION POLICY 60
15 LIST OF REFERENCES 61

LIST OF TABLES

Table 1 Schedule of Study Procedures 25
Table 2 Dosing Assignment 31
Table 3 Severity of Adverse Events 43
Table 4 Relationship of Adverse Events to Investigational Product 43
Table 5 List of Clinical Laboratory and Other Analytes to be Tested 49

LIST OF FIGURES

Figure 1 Study Design of ACER-801-201 24
Figure 2 Chemical Structure of ACER-801 38

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this protocol.

Abbreviation	Description
ACTH	Adrenocorticotropic hormone
AE	Adverse event
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AR_{Cmax}	Accumulation ratio for C_{max}
AR_{AUC}	Accumulation ratio for AUC
AUC_{inf}	Area under the concentration curve from t_0 to infinite time
AUC_{last}	Area under the concentration curve from dosing to the time of the last measured concentration
AUC_{τ}	Area under the plasma concentration-time curve from time zero to the end of the dosing interval
AST	Aspartate aminotransferase
BID	Twice daily
BMI	Body mass index
BP	Blood pressure
BSAP	Bone specific alkaline phosphatase
CFR	Code of Federal Regulations
C_{max}	Maximum concentration
COVID-19	Coronavirus disease 2019
CRA	Clinical research associate
CRU	Clinical Research Unit
CTCAE	Common Terminology Criteria for Adverse Events
CTD	Common Technical Document
CTX	Collagen Type- C-Telopeptide
CYP3A4	Cytochrome P450 3A4
CYP2D6	Cytochrome P450 2D6
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EOS	End of study
ET	Early termination
FDA	Food and Drug Administration
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
HbsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HEENT	Head, eyes, ears, nose, and throat
HIV	Human immunodeficiency virus
HRT	Hormone replacement therapy
IB	Investigator's Brochure

Abbreviation	Description
ICF	Informed consent form
ICH	International Conference on Harmonization
ICMJE	International Committee of Medical Journal Editors
IRB	Institutional review board
iVMS	Induced vasomotor symptoms
LH	luteinizing hormone
MDRD	Modification of diet in renal disease
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-to-Treat Population
MR_{Cmax}	Metabolite:parent ratio of C_{max}
MR_{AUC}	Metabolite:parent ratio of AUC
NCA	Noncompartmental analysis
NKA	Neurokinin A
NKB	Neurokinin B
NK	Neurokinin
NK3R	Neurokinin 3receptor
NTA	Night-time awakenings
OTC	Over the counter
P1NP	Amino terminal propeptides of type 1 collagen
PK	pharmacokinetic(s)
QD	Once daily
SAE	Serious adverse event
SAP	Statistical analysis plan
SHBG	Sex hormone binding globulin
SNRI	Serotonin and norepinephrine reuptake inhibitors
SOP	Standard operating procedure
SP	Substance-P
SSRI	Selective serotonin reuptake inhibitor
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event
T_{max}	Time to reach maximum concentration
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal
US	United States
VMS	Vasomotor symptoms
WHODDrug	World Health Organization Drug Dictionary

2 INTRODUCTION

Acer acquired the rights to osanetant (SR142801), a selective non-peptide neurokinin 3 receptor (NK3R) antagonist, from Sanofi on December 2018 and has since renamed the compound ACER-801. ACER-801 is being investigated for the prevention/treatment of moderate/severe vasomotor symptoms (VMS) in patients with medically or surgically induced VMS (iVMS).

The efficacy and safety of ACER-801 in subjects with iVMS has not been evaluated to date. Osanetant (SR142801) has been studied in a total of 23 completed clinical studies conducted by Sanofi with osanetant doses ranging from 5 mg to 1000 mg in healthy subjects and 50 mg to 200 mg once daily (QD) in patients with schizophrenia, major depressive disorder, Parkinson's disease, panic disorder, and asthma. In these studies, osanetant was found to be well tolerated, with minimal safety issues.

2.1 Background

Neurokinin B (NKB) belongs to a group of neuropeptides, called tachykinins or neurokinins (NKs), that includes substance-P (SP), and neurokinin A (NKA). The biological effects of tachykinins are mediated through specific receptors denoted NK1, NK2, and NK3. NKB is the preferred endogenous ligand of tachykinin NK3 receptors. The tachykinin NK3 receptors (NK3R) are located primarily in the brain, while a few receptors are also present in the peripheral nervous system. The NK receptor pathway in the hypothalamus, including NK3, has been shown to play a role in the etiology of VMS (Prague 2017; Skorupskaite, 2018).

VMS are generally defined as hot flashes, flushing and night sweats that most often occur in women entering or in menopause. VMS are causally related to decreased estradiol concentrations mainly in the systemic circulation and subsequently also in the hypothalamic temperature regulating center. The lack of estrogens alters neurotransmitter activity, especially in the serotonergic and noradrenergic pathways. Because sex steroids act as potent neuromodulators, the substitution of ovarian steroids by hormone replacement therapy (HRT) is currently the most effective treatment option for VMS.

Clinical studies with a dual NK1/NK3 antagonist (NT-814) and selective NK3 antagonists (fezolinetant and MLE4901 [pavinetant]) in menopausal women significantly reduced VMS (Trower, 2020; Fraser, 2020; Santoro, 2020, Prague, 2017). Based on the demonstrated role of the NK pathway in the etiology of VMS, it is hypothesized that administration of the NK3 receptor antagonist, ACER-801, will result in similar findings by modulating the NKB pathway directly.

While VMS associated with menopause can often be treated with HRT, there are subjects who experience VMS who are not in menopause and in whom HRT is not the preferred or acceptable treatment. VMS can be induced (iVMS) with the use of hormonal cancer therapies and certain surgical procedures. Under these situations, VMS can appear immediately and be severe and, in many instances, HRT therapy is not the preferred treatment.

ACER-801 may be a novel, non-hormonal, centrally acting therapy for iVMS.

2.2 Safety Data

To date, no studies have been conducted with ACER-801 in subjects with iVMS.

Safety data are summarized for completed clinical studies conducted with osanetant by Sanofi. These studies were conducted in healthy subjects and patients with schizophrenia, major depressive disorder, Parkinson's disease, panic disorder, and asthma.

Osanetant was evaluated in 23 completed Phase 1 and Phase 2 studies. In single- and repeat-dose Phase 1 studies, approximately 400 subjects were exposed to doses ranging from 5 mg to 1000 mg in single dose studies and from 5 mg to 1000 mg (500 mg twice daily [BID]) in repeat-dose studies in which subjects received osanetant for up to 21 days.

In the 7 completed Phase 2 studies, a total of 821 patients were exposed to osanetant, including patients with depression (up to 200 mg QD for 6 weeks), patients with panic disorder (200 mg QD for 4 weeks), patients with schizophrenia (200 mg QD for 16 weeks), patients with asthma (200 mg QD for 6 weeks), and patients with Parkinson's disease (100 or 200 mg QD for 9 days).

Data from these studies demonstrated no major safety concerns after single-dose and repeat-dose administration up to 400 mg QD in healthy subjects, and 200 mg QD in the patient population. In controlled clinical trials, there is no evidence to date for liver function test abnormalities or weight loss, as noted in the toxicology studies.

The incidence of adverse events (AEs) was similar in the osanetant and placebo groups in completed Phase 1 and 2 trials. In patients, the serious adverse events (SAEs) reported in the osanetant group were mainly related to the condition being treated. Adverse events most frequently reported in osanetant-treated patients were headache, nausea, dyspepsia, insomnia, dizziness, and abdominal pain. These incidences were comparable in the osanetant and placebo groups.

Additional details can be found in the Investigator's Brochure.

2.3 Rationale for Study Design and Dose for Investigational Product

A 200 mg BID dose was chosen as the maximum dose based on previous studies in healthy subjects where a 400 mg QD dose up to 21 days was shown to be safe. The subjects in this study will be healthy with no outstanding medical issues who present with moderate to severe VMS.

3 STUDY OBJECTIVES AND PURPOSE

3.1 Primary Objective

The primary objectives are to:

- Evaluate the pharmacokinetic (PK) profile of ACER-801 and its metabolite at different doses
- Evaluate the safety profile of ACER-801 at different doses

3.2 Secondary Objectives

The secondary objectives are to:

- Evaluate the effect of ACER-801 at different doses on the frequency of vasomotor symptoms associated with menopause compared to placebo
- Evaluate the effect of ACER-801 at different doses on the severity of vasomotor symptoms associated with menopause compared to placebo
- Evaluate the effect of ACER-801 at different doses on the hot flash severity score compared to placebo

3.3 Exploratory Objectives

The exploratory objectives are to evaluate:

- The effect of ACER-801 at different doses on change in hormones compared to placebo including:
  - luteinizing hormone (LH)
  - follicle stimulating hormone (FSH)
  - estradiol
  - testosterone
  - sex hormone binding globulin (SHBG)
  - adrenocorticotropic hormone (ACTH)
  - cortisol
  - thyroid-stimulating hormone (TSH)
  - Triiodothyronine (T3) (Total and Free)
  - Thyroxine (T4) (Total and Free)
- Changes in the number night-time awakenings (NTA)
- Change in blood bone density marker concentration
- Changes in blood markers associated with stress
- Change in electrocardiogram (ECG) variables (heart rate, RR, PR, QRS, QT, QTcF, and QTcB)
- The relationship between PK exposure and measures of efficacy and/or safety

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design

This is a Phase 2a, randomized, double-blind, placebo-controlled, dose-ranging study in post-menopausal women in which the pharmacokinetic (PK) profile of ACER-801 at different doses is evaluated and the efficacy of ACER-801 (50 mg twice daily [BID], 100 mg BID, and 200 mg BID) will be compared to placebo in approximately 40 to 56 subjects (approximately 10 to 14 subjects per treatment arm).

Subjects will enter a Screening Period to determine eligibility. Subjects will be required to complete hot flash diaries for 2 weeks prior to randomization. Eligible subjects will be admitted to a Clinical Research Unit (CRU) on Day -1 and remain in the clinic from Day -1 until discharge on Day 16 after completion of treatment and all study assessments or upon withdrawal from the study. The study includes a 14-day safety follow-up assessment (Day 28) (Figure 1).

Subjects will be randomized in a 1:1:1:1 ratio to ACER-801 per one of the following dosing schedules prior to dosing:

- 50 mg BID
- 100 mg BID,
- 200 mg BID, or
- placebo administered orally for 14 consecutive days (28 doses).

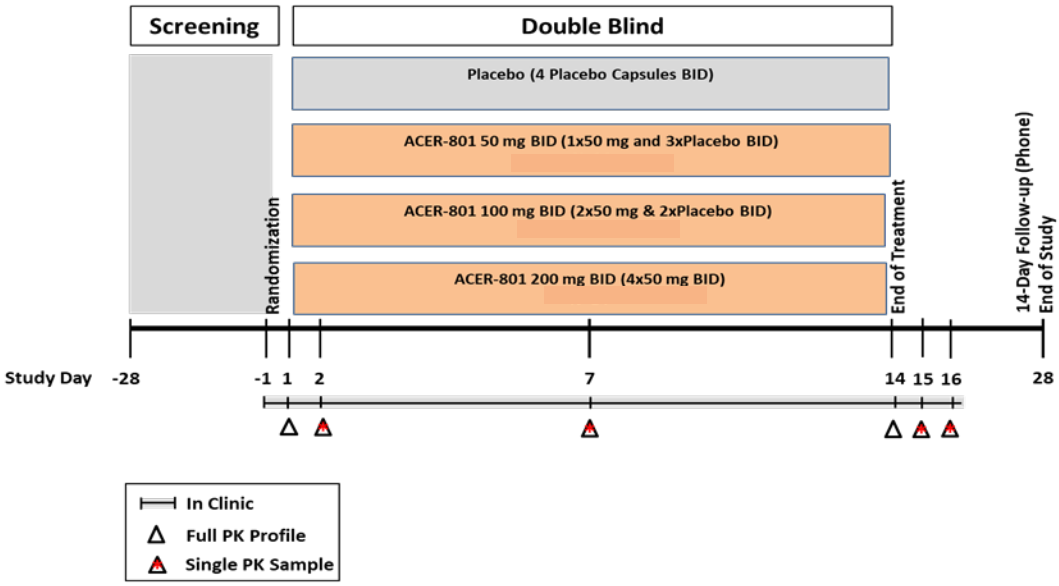
Blood samples for PK (plasma) assessment will be collected for concentrations of ACER-801 and its metabolite at predose, 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 5.0, 6.0, 8.0, 12.0 (prior to evening dose), and 15.0 hrs post morning dose on Day 1 and Day 14, as well as predose (prior to morning dose) on Day 2 and Day 7. Plasma samples will also be collected 24 hrs (Day 15) and 48 hrs (Day 16) after the morning dose on Day 14.

Throughout the duration of the study (Day 1 through Day 16), subjects will be required to record the frequency and severity of hot flashes in a subject diary (continuous hot flash diary).

Electrocardiographs using the Mortara Surveyor will be collected on Day -1, Day 1, and Day 14.

During the study, subjects will be closely monitored for safety including assessments of AEs, 12-lead ECGs, atrial oxygen saturation using pulse oximetry, vital signs (sitting and standing blood pressure (BP), heart rate, oral body temperature, and respiratory rate), clinical labs, and physical examinations.

Figure 1 Study Design of ACER-801-201



An overview of the study procedures is presented in Study Duration

This study consists of a 28-day Screening Period, a 14-day Treatment Period, and a 14-day Safety Follow-Up Period.

4.2 Number of Subjects and Target Population

Approximately 40 to 56 post-menopausal women aged 40-65, inclusive, who experience an average of 10 to 20 moderate to severe hot flashes per day as determined by a continuous hot flash diary where events are recorded for 2 weeks prior to randomization will be included in this study. Subjects will have no active, ongoing health conditions that could cause difficulty in interpretation of hot flashes categorized as moderate to severe.

4.3 Treatment Assignment

Subjects will be randomly assigned in a blinded manner to 1 of 4 treatment arms (placebo or 50 mg BID, 100 mg BID, or 200 mg BID ACER-801).

Table 1 Schedule of Study Procedures

		In Clinic									EOS
	Screening Visit		PK Days			PK Day		PK Days			14-Day Safety Follow up (±4 days)[12]
Activity	Day -28 to Day -1[13]	Day -1[2]	Day 1[2]	Day 2	Day 3 -Day 6	Day 7	Day 8- Day 13	Day 14/ EOT	Day 15	Day 16/ ET[11]	
Informed consent[1]	X										
Eligibility criteria review	X	X[2]									
Fasting[3]	X	X	X	X		X		X		X	
Admission		X									
COVID-19 test		X									
Medical history	X	X									
Concomitant medication review	Continuous Collection										
Physical exam	X		X							X	
Vital signs[4]	X	X	X	X	X	X	X	X	X	X	
Weight	X	X								X	
Height	X										
Serum pregnancy testing		X									
Standard Urine drug Screen	X	X									
Virology (HIV antibody, HBsAg, and HCV)	X										
FSH (for eligibility)	X										
Randomization[5]		X	X								
12-lead ECG for Safety[16]	X	X	X							X	
Electrocardiographs using the Mortara Surveyor[15]		X	X					X			
Blood bone density marker concentration			X					X			
Biochemistry/ Hematology, Coagulation[14]	X	X	X			X		X		X	
Provide instructions on recording of hot flashes[6]	X										
Continuous hot flash diary[6]	X	X	X	X	X	X	X	X	X	X	
Record bedtime and morning wake-up time in hot flash diary[6]	X	Continuous Collection									
Catecholamines, vasopressin, gonadotropins, prolactin, insulin[14]			X					X		X	
SHBG, estradiol, testosterone, ACTH, cortisol, TSH, total and free T3 and total and free T4, FSH[14]			X					X			
Urinalysis[14]	X	X				X		X		X	
LH[7, 10]		X	X	X				X			

Table 1 Schedule of Study Procedures

		In Clinic									EOS
	Screening Visit		**PK Days**			**PK Day**		**PK Days**			**14-Day Safety Follow up (±4 days)[12]**
Activity	**Day -28 to Day -1[13]**	**Day -1[2]**	**Day 1[2]**	**Day 2**	**Day 3 -Day 6**	**Day 7**	**Day 8-Day 13**	**Day 14/ EOT**	**Day 15**	**Day 16/ ET[11]**	
Dosing [8]			X	X	X	X	X	X			
PK[9, 10]			X	X		X		X	X	X	
Discharge										X	
AE collection	Continuous AE Collection										

AE=adverse event; ACTH=adrenocorticotropic hormone; CTX = Collagen Type- C-Telopeptide; EOT=end of treatment; ET=early termination; EOS=end of study; FSH=follicle stimulating hormone; LH=luteinizing hormone; PK=pharmacokinetics; SHBG=sex hormone binding globulin; TSH=thyroid stimulating hormone; T3=triiodothyronine; T4=thyroxine.

[1] Informed consent must be signed by the subject before the start of any study procedure.

[2] Key inclusion/exclusion criteria must be re-assessed before conducting any other baseline assessments. All baseline assessments to be conducted on Day -1 (and/or Day 1 as indicated) to be conducted prior to dosing unless otherwise indicated (See Section 7).

[3] Subjects will be required to fast for approximately 8 hours prior to their Screening Visit and Day 16. Subjects will be required to fast for 12 hours prior collection of laboratory sample for CTX on Day 1 and Day 14. CTX blood sample must be collected prior to dosing. Subjects will be required to fast for 4 hours post morning dose on Day 1 and Day 14. Subjects will also be required to fast for 8 hours prior to Day -1 and from midnight prior to dosing (approximately 8 hours) Day 2 and Day 7. Water will be allowed *ad libitum.*

[4] Vital signs, including oral body temperature, pulse oximetry, respiratory rate, and sitting and standing BP and heart rate, will be performed daily during the study period approximately 60 minutes prior to am dosing. The minimal positional time for collection of the orthostatic vital signs is approximately 5 minutes sitting and approximately 2 minutes standing prior to collection of vital signs.

[5] Randomization can occur on Day -1 or Day 1 but must occur before dosing.

[6] Continuous hot flash diary: Instructions on the use of the continuous hot flash diary will be provided at Screening. Subjects are required to record the frequency and severity of the hot flash (scale 1 to 3) in a continuous hot flash diary for 2 weeks prior to randomization (during the day and at night). Subjects will record the frequency and severity of hot flash while in the clinic Day -1 to Day 16 (during the day and the night). Subjects are also to record the time they went to sleep, and morning wake up time.

[7] Luteinizing hormone (LH) sampling on Day-1 and predose and every 60 mins starting at 60 minutes after dose 0 to 8 hrs Day 1, Day 2, and Day 14.

[8] Study drug will be administered twice daily, approximately 12 hours apart (morning and evening dose) from Day 1 through Day 14. All applicable study procedures must be completed prior to administration of the morning study drug. Subjects will be required to fast for 12 hours prior to study drug administration and for 4 hours post morning dose on Days 1 and 14. Subjects will be required to fast for 8 hours prior to morning study drug administration on Days 2 and 7. No fasting is required on Days 3 – 6 or Days 8 – 13.

[9] PK Sampling at predose, 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 5.0, 6.0, 8.0, 12.0 (prior to evening dose) and 15.0 hours post morning dose on Day 1 and Day 14, as well as predose (morning) on Day 2 and Day 7. Plasma samples will also be collected 24 hours (Day 15) and 48 hours (Day 16) after the morning dose on Day 14.

[10] Predose samples for PK and LH to be taken within 30 minutes prior to dose administration.

[11] Where possible, all subjects who are withdrawn or withdraw from the study early will undergo the Early Termination Visit assessments.

[12] 14-Day Safety Follow-up Visit; subjects will be contacted by telephone 14 days (±4 days) following the final dose of study drug on Day 14, unless deemed by the investigator that a clinic visit is more appropriate to follow up an adverse event.

[13] If the Screening Period is >28 days the following procedures must be repeated such that the most recent evaluation occurs within 28 days of their scheduled randomization: biochemistry, hematology, coagulation, vital signs, 12-lead ECG, physical examination. If the subject has completed (or partially completed) the continuous Hot Flash Diary this must still be repeated, and a new continuous hot flash diary started on the new planned Day -15 and completed for the 2 weeks up to Day -2. Eligibility will be assessed on the repeated continuous hot flash diary, not the initial one. If the subject had not started completing their screening continuous hot flash diary at the time screening was put on hold, they will start this screening continuous hot flash diary on the re-scheduled Day -15.

[14] To be collected predose on dosing days.

[15] Time and duration of Mortara Surveyor ECG collection must be identical on Day -1, Day 1, and Day 14 and must be planned in relation to predose and 15 hrs postdose PK time points.

[16] The safety ECG readings will be performed approximately 1 hour after the scheduled morning dose on dosing days.

5 SELECTION AND WITHDRAWAL OF SUBJECTS

5.1 Inclusion Criteria

To be eligible to participate in this study, subjects must meet all the following criteria:

1. Post-menopausal female subjects 40-65 years of age, inclusive.
   Menopause will be defined as:
   a. At least 12 months of spontaneous, continuous amenorrhea, or
   b. At least 6 months of spontaneous, continuous amenorrhea with serum FSH levels > 40 mIU/mL at screening, or
   c. At least 6 weeks postsurgical bilateral oophorectomy with or without hysterectomy.
2. At baseline women:
   a. With an average of ≥ 7 and ≤ 20 moderate to severe hot flashes/day for 2 weeks prior to randomization (per continuous hot flash diary) (Sloan, 2012). The minimum number of hot flashes on each day during the 2 weeks prior to randomization must be at least 7.
   b. That have a change of < 50% in average 24-hour hot flash frequency 2 weeks prior to randomization.

- Moderate: defined as sensation of heat with sweating, able to continue activity.
- Severe: defined as sensation of heat with sweating, causing cessation of activity.

3. Able to understand and comply with the requirements of the study and sign Informed Consent forms.
4. Have not participated in any clinical research study evaluating another investigational drug, device or therapy within 30 days or within 5 half-lives (whichever is longer), of the investigational drug prior to consenting to study entry.

5.2 Exclusion Criteria

To be eligible to participate in this study, subjects must not meet any of the following criteria:

1. Any active comorbid disease deemed by the investigator to be clinically significant, which could impact safety during study conduct including renal or hepatic impairment:
   a. Serum creatinine laboratory value greater than 1.2 times upper limit of normal (ULN) reference range (after adjustment for age) at Screening or Day -1 or subjects with renal function glomerular filtration rate (GFR) <60 mL/min/1.73m^2 based on the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.
   b. Total bilirubin greater than upper limit of normal reference range (with the exception of Gilbert's Syndrome) and/or alanine aminotransferase (ALT) >2 times ULN reference ranges and/or aspartate aminotransferase (AST) >2 times ULN reference ranges at Screening or Day -1.

   Laboratory values may be repeated once to confirm results.
2. Any active medicinal (pharmaceutical or homeopathic) therapy considered by the investigator to potentially cause hepatic impairment leading to elevated:
   c. ALT and/or AST ranges.

3. Subjects with a prior medical history of or an increased risk of seizures, or who have a history of recent (within 6 months of Screening) head trauma that resulted in a loss of consciousness or concussion.
4. Any prior or ongoing history of arrhythmias.
5. Any ongoing cardiovascular disease including heart failure, coronary artery disease, or uncontrolled hypertension or uncontrolled diabetes (blood sugar level consistently over 100 mg/dL while fasting, higher than 180 mg/dL two hours after a meal, or random blood glucose levels higher than 200 mg/dL). Postmenopausal women with a history of hypertension must be medically cleared to participate in the study. Hypertension is defined as systolic blood pressure ≥130 mg Hg or diastolic blood pressure ≥80 mg over 3 readings on at least 2 different occasions, unless the participant receives medical clearance by her physician to participate in the trial.
6. Any clinically relevant ECG abnormalities at Screening, per Investigator discretion.
7. Use of any prohibited medications (see Section 5.3.2).
8. Any history of malignancy in the past 2 years.
9. Any active ongoing condition that could cause difficulty in interpreting vasomotor symptoms such as: infection that could cause pyrexia, pheochromocytoma, hypothyroidism, hyperthyroidism, carcinoid syndrome, alcohol abuse.
10. Body mass index (BMI) >35 kg/m^2.
11. Inability to complete questionnaires or continuous hot flash diary for any reason including psychiatric disorders and inability or unwillingness to use electronic devices.
12. History of hypothalamic dysfunction.
13. Any clinically significant or unstable medical or psychiatric condition that would interfere with the subject's ability to participate in the study including anxiety syndromes.
14. Any clinically significant abnormal laboratory test result(s) measured at Screening or on Day -1.
15. Participation in any clinical research study evaluating another investigational drug, device, or therapy within 30 days or within 5 half-lives (whichever is longer), of the investigational drug prior to consenting to study entry. If the subject is in an observational clinical study, no washout is required.
16. Subjects who, in the opinion of the investigator, should not participate in the study for any other reason.
17. Any known allergy or hypersensitivity to any of the ingredients in the study medication or to skin adhesives.
18. Current or planned use of other agents for treating hot flashes.
19. History or presence of alcohol abuse (defined as consumption of more than 210 mL alcohol per week, or the equivalent of fourteen 4 ounce glasses of wine or fourteen 12 ounce cans/bottles of beer or wine coolers per week) within 6 months before Screening or positive alcohol test at Screening or Check in (Day -1).
20. History or presence of substance abuse within the past 2 years or positive drug screen test at Screening or Check in (Day -1).
21. Presence of hepatitis B virus, hepatitis C virus (HCV), or human immunodeficiency virus (HIV) at Screening.
22. Current use or has used tobacco-or nicotine-containing products (e.g., cigarettes, cigars, chewing tobacco, snuff, vaping) within 30 days prior to first dose.
23. Known or suspected pregnancy on Day -1.

24. Positive COVID-19 test on Day -1.

5.3 Study Restrictions

5.3.1 Concomitant Medications

All concomitant medications taken during the study will be recorded in the electronic case report form (eCRF) with indication, dose information, and dates of administration.

5.3.2 Prohibited Concomitant Medications

Subjects using the following medications will be excluded from the study:

- Drugs that may cause hepatoxicity as assessed by the PI and/or Sponsor.
- Any antidepressants (e.g., selective serotonin reuptake inhibitors [SSRI], serotonin and norepinephrine reuptake inhibitors [SNRIs]) within 4 weeks of Screening Visit
- NK receptor antagonists within 2 weeks of Screening visit
- Women on tamoxifen (or other estrogen modulating drugs) or receiving
- Chemotherapy/radiation therapy within 4 weeks of Screening or planned antineoplastic
- Chemotherapy/radiation therapy
- Drugs or herbal medications that could be associated with hot flash like symptoms including nicotinic acid, calcium channel blockers, clonidine, opioid drugs, black cohosh within 2 weeks of Screening Visit
- Drugs that are highly protein bound e.g., Warfarin and digoxin within 4 weeks of screening visit, use of non-steroidal anti-inflammatory drugs from the time of signing informed consent
- Use of any of the following hormonal treatment before Screening Visit:
  - 1 week or longer for prior vaginal hormonal products (rings, creams, gels)
  - 4 weeks or longer for prior transdermal estrogen alone or estrogen/progestin products
  - 12 weeks or longer for prior oral estrogen and/or progestin therapy
  - 3 months or longer for prior progestin implants and estrogen alone injectable drug
  - therapy
  - 6 months or longer for prior estrogen pellet therapy or progestin injectable drug therapy
- Subjects using the following medications within 2 weeks prior to first dosing (or within 5 times the half-life of that medication, whichever is longer) will be excluded from the study:
  - Inhibitors of CYP3A4 (including but not limited to macrolide antibiotics, HIV protease inhibitor, azole antifungal drugs, cyclosporine, calcium channel inhibitor, cimetidine)
  - Inducers of CYP3A4 (including but not limited to rifampicin, carbamazepine, efavirenz, bosentan, modafinil, St. John's Wort)
- Medications with narrow therapeutic index that are metabolized by CYP3A4 and/or CYP2D6 are not allowed from screening until up to 5 half-lives after last dose of ACER-801 is administered.

Subjects will be required to inform the study investigator of any regularly taken medications (prescription or over the counter (OTC)), including hormone replacement therapy, natural and

herbal products, vitamin, mineral or dietary supplement, taken within 2 weeks (or less than 5 times the half-life of that medication, whichever is longer) prior to first dosing. Use of such medications should be reviewed with the medical monitor and permitted on a case-by-case basis.

5.4 Subject Withdrawal

Subjects are free to withdraw from the study at any time for any reason.

In addition, subjects may be withdrawn from the study by the investigator for the following reasons:

- Aes
- Withdrawal of consent
- Protocol violation
- Lost to follow-up
- Other
- If it is in the subject's best interest according to the investigator

The clinical study report will include the reason(s) and relevant details(s) for subject withdrawals.

5.5 Stopping Criteria for Subject Dosing

Study drug will be withdrawn from the subject if the following stopping criteria are met:

- 5≥ ULN ALT/AST and total bilirubin ≤2 ULN BILI
- 3≥ ULN ALT/AST and total bilirubin ≥2 ULN BILI

5.6 Study Termination Criteria

The Sponsor or designee will review pooled and individual subject data during the course of the study. A single occurrence of the following safety events will trigger an ad hoc meeting to review individual cases:

- Hepatic toxicity such as marked elevations in transaminases or simultaneous elevations in hepatic transaminases and bilirubin (i.e., Hy's Law)
- Severe renal impairment
- Severe cardiovascular dysfunction such as arrhythmia or other abnormalities as indicated by ECG readings

If the Sponsor or its designee determines that the event is drug-related and a clear safety signal has been identified, early termination of the study may occur.

6 TREATMENT OF SUBJECTS

6.1 Investigational Product Treatment Regimen

ACER-801 will be prepared by the pharmacist at the clinical study site.

ACER-801 is only available as a 50 mg capsule. To maintain the blind, subjects randomized to 50 mg and 100 mg ACER-801 will also receive placebo capsules for a total of 4 capsules BID to match the total number of capsules used for the 200 mg BID treatment group (Table 2).

Table 2 Dosing Assignment

	Morning		Evening	
Randomization	**ACER-801**	**PBO**	**ACER-801**	**PBO**
	# of capsules	**# of capsules**	**# of capsules**	**# of capsules**
50 mg BID	1	3	1	3
100 mg BID	2	2	2	2
200 mg BID	4	0	4	0
Placebo BID	0	4	0	4

6.2 Reference Product

The reference product used in this study will be placebo-matched controls. Placebo-matched controls will look identical to ACER-801 capsules.

6.3 Treatment Compliance

Study drug will be administered as described in Section 6.1, Section 6.2, and the Pharmacy Manual. A witness from the study team will verify that the treatment has been ingested and this information will be recorded in source documentation for each subject.

The quantity received, dispensed, returned, used, lost, etc. will be recorded on the dispensing log provided for the study.

6.3.1 Return/Disposition of Clinical Supplies

Unused study drug must be kept in a secure location for final accountability and reconciliation by Acer or its designee. The investigator must provide an explanation for any destroyed or missing study drug or study materials.

Unused study drug may be destroyed on site, per the clinical unit's standard operating procedures (SOPs), but only after Acer or its designee has granted approval in writing. Acer or its designee must account for all study drug in a formal reconciliation process prior to study drug destruction. If study is drug destroyed on site this must be documented, and documentation must be provided to Acer or its designee and retained in the investigator's study files. The clinical unit should return unused study drug only if instructed to do so by Acer or its designee. The return of study drug or study drug materials must be accounted for on a Study Drug Returns Form provided by Acer or its designee.

All study drug and study drug materials should be stored, inventoried, reconciled, and destroyed or returned according to applicable state and federal regulations, study procedures and applicable SOPs.

6.4 Randomization and Blinding

Subjects will be blinded to the study drug and will be randomized 1:1:1:1 to ACER-801 50 mg BID, 100 mg BID, 200 mg BID or placebo.

6.4.1 Unblinding Procedures

The patient, the Investigator, and other members of the staff involved with the study will remain blinded to study treatment. The study treatment blind shall not be broken by the investigator/designee unless information concerning the study medication is necessary for the medical treatment of the subject. For unblinding a subject, the randomization information for unblinding can be obtained by contacting the clinical site pharmacist (or designee).

6.5 Assignment of Site and Subject Numbers

When a subject is successfully enrolled and randomly assigned to treatment, they will receive a unique identification number and their personal identification (name other identifying information) will be protected, however, the sponsor (or designee) and regulatory authorities have authorization to review source documents which may contain identifying information of study subjects.

6.6 Subject Management

6.6.1 Confinement

Subjects will be housed in the clinical unit from Day -1 until Day 16.

6.6.2 Meals and Dietary Restrictions

Subjects must refrain from eating grapefruit, grapefruit juice, Seville oranges and pomelos within 7 days prior to Day -1 until after their final follow-up visit. Other than this restriction subjects should maintain their usual diet when not in the clinic.

Subjects are required to fast from overnight prior to dosing (approximately 8 hours) prior to Screening and Day 16.

Subjects are required to fast from overnight approximately 8 hours prior to Screening and Day -1.

Subjects will be required to fast overnight for approximately 12 hours on Day 1 and Day 14 and continue to fast until 4 hours post dose.

Subjects will be required to fast overnight prior to morning dosing (approximately 8 hours) on Days 2, and 7. Water will be allowed ad libitum. No fasting is required on Days 3- 6 or Days 8-13 or 15.

7 VISIT PROCEDURES

An informed consent form (ICF) must be signed before any study-related procedures are performed. The AE reporting period will begin at the time the ICF is signed. The treatment-emergent AE (TEAE) reporting period will begin at the time study drug is first administered on Day 1 of the study.

7.1 Screening Procedures (Day -28 to Day -1)

Within 28 days of Day -1, after subjects have provided a signed voluntary written ICF, subjects will be screened for enrollment into the study. The following study evaluations will be performed at screening:

- Written informed consent
- Inclusion/exclusion criteria
- Document fasting period (minimum of 8 hours)
- Concomitant medication review
- Medical history and demographic data
- Urine drug screen
- Virology testing
- Physical examination
- Vital signs
- Weight
- Height (determine BMI for eligibility)
- 12-lead ECG (for safety)
- Biochemistry. Hematology, and coagulation
- Urinalysis
- FSH for eligibility
- Instructions for continuous hot flash diary
- Continuous hot flash diary reporting for 2 weeks prior to randomization (including hot flashes during the day and night)
- Daily recording of bedtime and morning wake up time for 2 weeks prior to randomization.
- AE monitoring (after the ICF has been signed)

The screening visit assessments must be performed within 28 days prior to Day -1 to determine whether the subject meets all the inclusion criteria and none of the exclusion criteria. Subjects who do not fulfill all eligibility criteria will not be enrolled in the study.

7.2 Check-In Procedures (Day -1)

The AE reporting period will begin at the time of the signing of the ICF and continues through the Follow-up phone call.

Subjects will be admitted to the CRU where they will reside from Day -1 to Day 16. All study procedures, including study drug administration, will occur in the CRU. On Day -1, the following procedures will be performed:

- Check-in to clinical unit (start of confinement in clinical unit)
- Confirmation of inclusion/exclusion criteria
- Collect continuous hot flash diary information to confirm eligibility
- Document fasting period (minimum of 8 hours)
- Concomitant medication review
- Medical history
- COVID-19 test
- Vital signs
- Weight
- 12-lead ECG (for safety)
- Urine drug screen
- Serum pregnancy testing
- Electrocardiographs using the Mortara Surveyor (time and duration of ECG collection must be identical on Day -1, Day 1, and Day 14 and must be planned in relation to predose and 15 hrs postdose PK time points)
- Daily recording of bedtime and morning wake up time.
- Biochemistry, hematology, and coagulation
- Continuous hot flash diary reporting (including hot flashes during the day and night)
- LH
- Urinalysis
- AE monitoring
- Randomization can occur on Day -1 or Day 1 (prior to dosing)

7.3 Daily Study Procedures (Day 1 through Day 16)

Subjects will be instructed to perform the below procedures during the study.

Reporting of hot flashes and nighttime awakenings are to be performed independently without consultation with other study subjects or staff unless there is a question regarding initial instructions.

- Concomitant medication review
- Continuous hot flash diary reporting (including hot flashes during the day and night)
- Daily recording of bedtime and morning wake up time
- Vital signs
- AE monitoring
- Administer study drug in the morning (am) and the evening (pm) (Day 1 am through Day 14 pm)

7.4 Day 1 (Confined to CRU)

In addition to study procedures outlined in Section 7.3, all study procedures must be performed prior to morning study administration unless otherwise indicated.

- Document fasting period (minimum of 12 hours) prior to administration of morning study drug and 4 hours after dosing
- Randomization (prior to dosing on Day 1 or Day -1)
- Physical exam

- Electrocardiographs using the Mortara Surveyor (duration and time of collection must be the same on Day -1, Day 1, and Day 14)
- Blood bone density markers
- Biochemistry, hematology, and coagulation
- Catecholamines, vasopressin, gonadotropins, prolactin, insulin collection
- Estradiol, testosterone, SHBG, ACTH, cortisol, TSH, T3 (Total and Free), T4 (Total and Free), FSH collection
- LH assessment
- PK assessment (30 min predose)

Post morning dose:

- 12-lead ECG (for safety) (1-hour post-morning dose)
- PK assessments
- LH assessment (every 60 mins starting at 60 minutes after dose 0 to 8 hrs)

7.5 Day 2

In addition to study procedures outlined in Section 7.3, all study procedures must be performed prior to morning study administration unless otherwise indicated.

- Confirm fasting (8 hours prior to dosing)
- LH assessment
- PK assessment (30 min predose)

Post morning dose:

- LH assessment (every 60 mins starting at 60 minutes after dose 0 to 8 hrs)

7.6 Day 7

In addition to study procedures outlined in Section 7.3, all study procedures must be performed prior to morning study administration unless otherwise indicated.

- Confirm fasting (8 hours prior to dosing)
- Biochemistry, hematology, and coagulation
- Urinalysis
- PK assessment (30 min predose)

7.7 Day 14/End of Treatment

In addition to study procedures outlined in Section 7.3, all study procedures must be performed prior to morning study administration unless otherwise indicated.

- Confirm fasting (minimum of 12 hours prior to administration of morning study drug and 4 hours after)
- Electrocardiographs using the Mortara Surveyor (duration and time of collection must be the same on Day -1, Day and Day 14)
- Biochemistry, hematology, and coagulation
- Blood bone density marker concentration
- Catecholamines, vasopressin, gonadotropins, prolactin, insulin collection

- Estradiol, testosterone, SHBG, ACTH, cortisol, TSH, T3 (Total and Free), T4 (Total and Free), FSH collection
- Urinalysis
- LH assessment
- PK assessment (30 min predose)
- Removal of mortara surveyor after completion of procedures

Post morning dose:

- PK assessments (post morning dose)
- LH assessment (every 60 mins starting at 60 minutes after dose 0 to 8 hrs)

7.8 Day 15

In addition to study procedures outlined in Section 7.3, the following study procedures will be performed.

- 24-hr PK blood draw (relative to the morning dose on Day 14)

7.9 Day 16/ET

In addition to study procedures outlined in Section 7.3, the following study procedures will be performed.

- Confirm fasting (8 hours prior to lab draws)
- Physical exam
- Weight
- 12-lead ECG (for safety)
- Biochemistry, hematology, and coagulation
- Catecholamines, vasopressin, gonadotropins, prolactin, insulin collection
- Urinalysis
- 48-hr PK sample (relative to the morning dose on Day 14)
- Discharge

7.10 End-of-Study Procedures for Subjects that Withdraw from the Study

Subjects that withdraw from the study must have all EOS/early termination (ET) procedures performed. Subjects should be encouraged to remain at the clinical unit until Day 16 for EOS/ET procedures. The purpose of this visit is to conduct final assessments on or as near as possible to the final day of dosing.

7.11 14-Day Safety Follow-Up

All subjects will be contacted by telephone 14 days (±4 days) following the final dose of study drug on Day 14. The subject will be queried regarding their overall health and well-being. This telephone contact may be used to verify the resolution of any Aes that were ongoing at the time of the Day 16/ET visit. Any follow-up deemed medically necessary will be conducted as an unscheduled/safety visit, detailed in Section 7.12.

Abnormal lab findings will be closely monitored by the Sponsor and repeated as deemed necessary until resolution and followed up by the treating physician. All safety data will be

reviewed by the Sponsor for any potential safety signals that would alter the safety profile of the molecule.

7.12 Unscheduled Safety Visit

The investigator may schedule an unscheduled/safety visit at the clinical unit at any time, if clinically warranted. Unscheduled and/or repeat assessments, including additional laboratory tests or investigations, may be conducted. The medical monitor should be contacted, as appropriate.

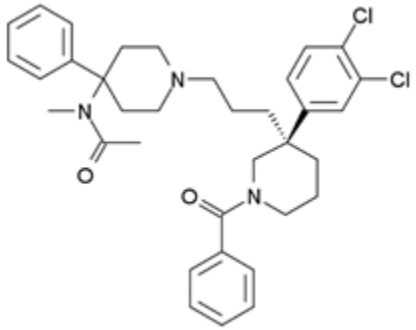
8 INVESTIGATIONAL PRODUCT MATERIALS AND MANAGEMENT

8.1 Treatments Administered

ACER-801 (osanetant) (Figure 2) is a white to almost white powder. ACER-801 is freely soluble in dichloromethane, sparingly soluble in acetonitrile and 2-propanol, and practically insoluble in water.

8.2 Identity of Investigational Product

Figure 2 Chemical Structure of ACER-801



All investigational product will be manufactured according to Good Manufacturing Practices.

8.3 Investigational Product Packaging, Storage, and Labeling

The molecular formula of ACER-801 is $C_{35}H_{41}N_3O_2Cl_2$

The molecular weight of anhydrous ACER-801 is 606.63 g.

ACER-801 capsules are stored in high density polyethylene bottles with a child resist cap.

The clinical supplies as packaged should be stored between 15-25 °C (59-77 °F), limited excursions permitted up to 30 °C (86 °F).

8.4 Investigational Product Receipt, Accountability, and Disposal

Acer's representative will send investigational product to the clinical unit under appropriate storage conditions. All shipments of investigational product should be unpacked, and the contents reviewed immediately upon receipt. If it is not possible to verify the contents immediately, they must be stored under the appropriate storage conditions until verification of the contents is possible (ideally, within 1 business day from receipt). The pharmacist or designee should verify the investigational product against the shipment documentation. The pharmacist or designee should contact Acer immediately to report any concerns regarding the shipment.

All investigational product will be provided for use only in this study and is not to be used for any other purpose. The investigator or designee will maintain a full record of investigational product accountability, including records of individual subject dispensing and final return or disposition (as directed by Acer).

Unused study drug may be destroyed on site, per the clinical unit's SOPs, but only after Acer or its designee has granted approval in writing. Acer or its designee must account for all study drug in a formal reconciliation process prior to study drug destruction. All study drug destroyed on site must be documented, and documentation must be provided to Acer or its designee and retained in the investigator's study files. The clinical unit should return unused study drug only if instructed to do so by Acer or its designee. The return of study drug or study drug materials must be accounted for on a study drug returns form provided by Acer or its designee.

The clinical research associate (CRA) who serves as the study monitor will review accountability records against investigational product dispensed and that remaining in stock during on-site monitoring visits, and when the study is completed or if it is prematurely terminated. The CRA will retrieve documentation detailing and confirming the return or destruction of the investigational product. If the investigational product is to be returned to Acer's vendor for destruction, the CRA will also prepare the investigational product for shipment.

9 PHARMACOKINETICS

All blood samples for PK analysis will be processed by a central bioanalytical laboratory. Instructions for collection, processing, storing, and shipping of PK blood samples will be provided to the clinical unit by the bioanalytical laboratory.

9.1 Blood Sampling

Blood samples will be collected for measurement of plasma concentrations of ACER-801 and its metabolite at the following time points:

Day 1 and Day 14: predose (within 30 minutes prior to dosing) and at
0.5; 1.0; 1.5; 2.0; 2.5; 3.0; 4.0; 5.0; 6.0; 8.0; 12.0 (prior to evening dose), and 15.0 hrs post morning dose

Day 2 and Day 7: predose (within 30 minutes prior to dosing)

Day 15 and Day 16: 24 hrs and 48 hrs after the morning dose on Day 14

Plasma samples will be stored at approximately -80°C for PK analyses for up to 12 months after the end of the study.

The actual time of study drug ingestion and each blood sample collection must be recorded.

9.2 Analytical Method

A validated bioanalytical method will be used for sample analysis.

10 EFFICACY ASSESSMENTS

Subjects will record VMS, including NTA, in a continuous hot flash diary during the Screening Period (2 weeks prior to Day -1) to assess eligibility. During confinement subjects will record VMS using a continuous hot flash diary. A description of the methods for VMS assessments is described in Sections 10.1 and 10.2.

10.1 Continuous Hot Flash Diary

During the 2 weeks prior to randomization, subjects will be asked to complete the continuous hot flash diary (during the day and at night). Subjects also will be required to record daily bedtime and morning wake up time. This will require recording the occurrence and severity of the hot flash (on a scale from 1 to 3).

While in the clinic (Day -1 to Day 16), subjects will continue to record the occurrence and severity (scale of 1 to 3) of each hot flash in the continuous hot flash diary (during the day and at night). Subjects also will be required to record daily bedtime and morning wake up time.

10.2 Exposure-Response Analysis

Graphical representation between efficacy measurements and plasma concentrations of ACER-801 and its metabolite will be generated to determine any potential relationships.

11 ASSESSMENT OF SAFETY

Subjects will be monitored throughout confinement for adverse reactions to the study treatments and/or procedures. Safety will be assessed by monitoring Aes/serious Aes (SAEs); vital signs; concomitant medications; physical examinations; ECGs; and clinical laboratory tests.

All Aes, whether observed by the investigator, reported by the subject, noted from laboratory findings, or identified by other means, will be recorded from the time of check-in until the subject completes the EOS assessments. Recording Aes/SAEs in the electronic data capture (EDC) system is the method for reporting Aes/SAEs. All Aes/SAEs will be recorded in the EDC.

11.1 Adverse Events and Serious Adverse Events

11.1.1 Definitions of Adverse Events

11.1.1.1 Adverse Event

An AE is defined as any untoward medical occurrence associated with the use of the investigational product in humans, whether or not considered related to investigational product. An AE can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with any use of the investigational product, without any judgment about causality and irrespective of route of administration, formulation, or dose, including an overdose.

Adverse events include but are not limited to: (1) a worsening or change in nature, severity, or frequency of condition(s) present at the start of the study; (2) subject deterioration due to primary illness; (3) intercurrent illness; and (4) drug interaction.

Subjects should be questioned in a general way, without leading the subject or asking about the occurrence of any specific symptom. The investigator should attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. The diagnosis and not the individual signs/symptoms should be documented as the AE. For example, if the underlying disease process is a stroke, it would not be appropriate to record the AE by describing the symptoms “sudden numbness, dizziness, and difficulty speaking”. The AE medical term of “stroke or cerebrovascular accident” should be recorded as it more accurately describes the AE.

All Aes must be graded for severity (i.e., intensity) using Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. The investigator will determine the severity of each AE and will record it on the AE eCRF, using the categories defined in Table 3. It should be noted that the term “severe” used to grade intensity is not synonymous with the term “serious”. The assessment of severity is made regardless of investigational product relationship or of the seriousness of the AE. When reporting Aes, reference should be made to the CTCAE manual for guidance on appropriate grading.

Table 3 Severity of Adverse Events

Grade	Clinical Description of Severity
1 = Mild	Asymptomatic or mild symptoms, clinical or diagnostic observations only, or intervention not indicated.
2 = Moderate	Minimal, local, or noninvasive intervention indicated; or limiting age-appropriate instrumental activities of daily living[a]
3 = Severe	Medically significant but not immediately life-threatening, hospitalization or prolongation of hospitalization indicated, disabling, or limiting self-care activities of daily living[b]
4 = Life threatening	Life-threatening consequences. Urgent intervention indicated.
5 = Death	Death related to AE.

[a] Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
[b] Self-care activities of daily living refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

The investigator will document their opinion of the relationship of the AE to treatment with the investigational product using the criteria outlined in Table 4. An AE for which there is a "reasonable possibility" that the investigational product caused the AE is otherwise referred to as suspected adverse reaction. "Reasonable possibility" means there is evidence to suggest a causal relationship between the investigational product and the AE.

If the relationship between the AE/SAE and the investigational product is determined to be "definite", "probable", or "possible", the event will be considered to be related to the investigational product for the purposes of expedited regulatory reporting.

Table 4 Relationship of Adverse Events to Investigational Product

Relationship	Description
Definite	A reaction that follows a reasonable temporal sequence from administration of the investigational product or in which the investigational product level has been established in body fluids or tissue; that follows a known or expected response pattern to the suspected investigational product; and that is confirmed by improvement on stopping or reducing the dosage of the investigational product, and reappearance of the reaction on repeated exposure.
Probable	A reaction that follows a reasonable temporal sequence from administration of the investigational product; that follows a known or expected response pattern to the suspected investigational product; that is confirmed by stopping or reducing the dosage of the investigational product; and that could not be reasonably explained by the known characteristics of the subject's clinical state.
Possible	A reaction that follows a reasonable temporal sequence from administration of the investigational product; that follows a known or expected response pattern to the suspected investigational product; but that could readily be produced by a number of other factors.
Unlikely	An event that does not follow a reasonable temporal sequence from administration of the investigational product; that does not follow a known or suspected response pattern to the suspected investigational product; and that could reasonably be explained by known characteristics of the subject's clinical state.
Not Related	Any event that does not meet the above criteria.

11.1.2 Treatment-Emergent Adverse Event

A TEAE is any event not present before administration of study drug or any event that was already present but worsens in either intensity or frequency following exposure to the study drug.

Serious Adverse Event

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

- Death
- Is immediately life threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Results in a congenital abnormality or birth defect
- Is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above

Events not considered to be SAEs are hospitalizations for:

- Routine monitoring of the studied indication and not associated with any deterioration in condition or AE
- Elective treatment for a pre-existing condition that did not worsen
- Respite care or observation when there is no AE associated with the hospitalization

11.2 Reporting of Adverse Events and Serious Adverse Events

11.2.1 Reporting of Adverse Events

All AE data will be collected from the time that signed informed consent is obtained until the subject fully completes her/his study participation of the study. Ongoing Aes will be monitored (telephone call) until resolution or for 30 days, whichever is first.

Abnormal lab findings will be closely monitored by the Sponsor and repeated as deemed necessary until resolution and followed up by the treating physician. All safety data will be reviewed by the Sponsor for any potential safety signals that would alter the safety profile of the molecule.

All Aes, whether assessed by the investigator to be related or unrelated to the study drug, must be documented in the subject's medical records, in accordance with the investigator's normal clinical practice and on the AE electronic case report form (eCRF). Each AE is to be evaluated for duration, intensity, frequency, seriousness, outcome, other actions taken, and relationship to the investigational product.

11.2.2 Reporting of Serious Adverse Events

In agreeing to the provisions of this protocol, the investigator accepts all legal responsibilities for immediate reporting of SAEs to Acer.

Any SAE, whether or not considered related to study drug, will also be reported immediately (within 24 hours) to Acer or the Acer designee Drug Safety Department by email (drugsafety@acertx.com) using the study-specific SAE Report Form and will be entered into the EDC system within 24 hours. A study-specific SAE report form (paper) will be used if the EDC system is not available.

The reporting period for SAEs is the period from the time of check-in through check-out and within 30 days after the last dose of study drug.

Any medication or other therapeutic measures used to treat the event will be recorded on the appropriate eCRF page in addition to the outcome of the SAE. Investigators should not wait to collect additional information that fully documents the event before notifying Acer or the Acer

designee Drug Safety Department of an SAE. Acer or the Acer designee may be required to report certain SAEs to regulatory authorities within 7 calendar days of being notified about the event; therefore, it is important that investigators submit additional information requested by Acer or the Acer designee as soon as it becomes available.

Reporting of SAEs to the institutional review board (IRB) will be conducted in accordance with the SOPs and policies of the IRB. Adequate documentation must be provided to Acer or the Acer designee showing that the IRB was properly notified.

All SAEs must be reported to Acer. SAEs are reported by entering the SAE data into the study specific EDC system. Entering the SAE data into the EDC system will automatically notify Acer of the event. If an SAE occurs in a subject during the study, in the event the EDC system is inaccessible, the following Acer personnel is to be contacted:

Alka Chawla, MD
Telephone: 1-408-482-4903
Fax: 1-866-511-8891
Email: drugsafety@acertx.com

If an SAE is reported by telephone, an SAE Report Form must also be completed in the EDC system as soon as the EDC system is accessible. At a minimum, the following information should be provided at the time of the initial report:

- Subject number
- Event term
- At least 1 criterion classifying the event as serious
- Name and title of the reporting individual
- Causal relationship to the investigational product

The investigator will assess whether the event is causally related to the investigational product. Acer will also assess whether the event is causally related to the investigational product, in addition to assessing the overall safety profile of the investigational product. Acer will notify the appropriate regulatory agencies of expedited safety reports that occur during the study within the time frames required by each regulatory agency.

An SAE assessed with a possible, probable, or definite causal relationship to the investigational product and unexpected according to the IB, is known as a suspected unexpected serious adverse reaction (SUSAR) and will be expeditiously reported to regulatory authorities and investigators, as appropriate.

Following the initial report, any additional information obtained by the investigator about the SAE must be reported promptly to Acer in the same manner as described above for the initial SAE report. Any supporting source documentation should be emailed to drugsafety@acertx.com as soon as possible.

The investigator is responsible for submitting information on expedited safety reports received from Acer to their local IRB, as directed by the local-country requirements.

Documentation of the submissions to IRBs must be retained in the appropriate study files. As instructed by Acer, expedited safety reports should be retained in the appropriate investigative site study files, or with the IB.

11.2.3 Additional Investigator Responsibilities for Serious Adverse Events

The safety data recorded in the EDC represent the official record of all Aes and SAEs reported in the study. The investigator should comply with requests by the medical monitor or other Acer personnel to record the SAE on the subject's AE EDC. Other supporting documents such as radiology reports, hospital discharge summaries, and autopsy reports should also be provided, when appropriate. Additionally, upon request by Acer, the investigator should provide input into the SAE narrative and provide timely information to ensure prompt follow-up and closure of the SAE report.

The investigator and supporting personnel responsible for subject care should discuss with the medical monitor any need for supplemental investigations of SAEs. The results of these additional assessments must be reported to the medical monitor.

11.2.4 Notification of Post-Study Serious Adverse Events

If an investigator becomes aware of an SAE that may be attributable to the investigational product at any time after the end of the study, Acer should be notified immediately (i.e., within 24 hours).

All SAEs that occur within 30 days following the cessation of investigational product, whether or not they are related to the study, must be reported to Acer within 24 hours.

11.2.5 Follow-Up of Adverse Events and Serious Adverse Events

All Aes must be followed during the study until the AE resolves, is no longer of clinical concern, has stabilized or is otherwise explained, or the subject is lost to follow-up. Ongoing Aes will be monitored (telephone call) until resolution or for 30 days, whichever is first.

Abnormal lab findings will be closely monitored by the Sponsor and repeated as deemed necessary until resolution and followed up by the treating physician. All safety data will be reviewed by the Sponsor for any potential safety signals that would alter the safety profile of the molecule.

Any Aes ongoing at the final visit that are deemed to be possibly, probably, or definitely related to the investigational product or of other clinical significance must be followed for as long as necessary to adequately evaluate the safety of the subject or until the event stabilizes, resolves, or is no longer of clinical concern. If resolved, a resolution date for the AE should be documented on the eCRF. The investigator must ensure that follow-up includes any supplemental investigations indicated to elucidate the nature and/or causality of the AE. This may include additional laboratory tests or investigations or consultation with other healthcare professionals, as considered clinically appropriate, by the investigator.

11.2.6 Pregnancy and Follow-Up

Pregnancies are not considered Aes in and of themselves; however, if a female subject becomes pregnant while she is enrolled in the clinical study, she must interrupt/discontinue investigational product immediately and Acer must be notified within 24 hours of the investigator learning of the pregnancy by completing the pregnancy follow-up section in the EDC. Entering the pregnancy report into the EDC system will automatically notify Acer of the pregnancy.

In the situation that the EDC is not functioning, the medical monitor should be notified by telephone and a pregnancy notification form may be emailed to Acer at drugsafety@acertx.com. The investigator remains responsible for entering the pregnancy information into the EDC when the EDC becomes functional.

The subject and neonate must be followed for outcome information and/or as considered appropriate by the investigator and Acer. The investigator should notify Acer of the outcome of the pregnancy by completing pregnancy follow-up section in the EDC. In the situation that the EDC is no longer available due to study closure, a pregnancy outcome form should be completed and faxed or emailed to Acer. Thereafter, the subject and infant must be followed as considered appropriate by the investigator and Acer.

Completing the pregnancy report in the EDC is not a substitute for reporting an AE/SAE when an AE/SAE has occurred. In the situation when an AE/SAE has occurred, the AE/SAE reporting procedures described in Section 11.2 must also be followed.

11.3 Other Safety Parameters

11.3.1 Medical History

A complete medical history will be obtained from the subject at screening (Table 1). Demographic characteristics (age, sex, race, and ethnicity) will also be recorded.

Medical history will include specific information relating to any prior or existing medical conditions or surgical procedures involving the following systems: general appearance; dermatologic; head, eyes, ears, nose, and throat (HEENT); lymphatic; cardiovascular; respiratory; gastrointestinal; genitourinary; musculoskeletal; and neurological. A history of alcohol or drug abuse in the previous 6 months will be collected.

Investigators will query subjects for smoking and tobacco use history. Investigators will also query subjects regarding current alcohol intake (i.e., number of drinks per day).

11.3.2 Vital Signs, Height, and Weight

To monitor subject safety, heart rate, blood pressure, body temperature, pulse oximetry, and respiratory rate will be measured for each subject as indicated in Table 1. Vital signs will be measured while subjects are in a sitting position and standing position.

The minimal positional time for collection of the orthostatic vital signs is approximately 5 minutes sitting and approximately 2 minutes standing prior to collection of vital signs.

When the time of vital signs monitoring coincides with a blood draw, vital signs will be taken within approximately 10 minutes of the scheduled blood draw and 60 minutes prior to the morning dose. Vital signs may be taken at other times if deemed necessary. Height and weight will be measured at screening to calculate BMI.

11.3.3 Concomitant Medications

All prescription and over-the-counter medications taken by a subject during the 30-day period before screening will be recorded at screening. All medications taken by subjects during the study will also be recorded. If drug therapy other than that specified in this protocol is required, a

decision to continue or discontinue the subject from the study will be made by the investigator, based on the time the medication was administered and its pharmacology and PK. Any concomitant medications added or discontinued will be recorded at screening and throughout the study (Table 1).

11.3.4 Physical Examination

Physical examinations will be performed for each subject as indicated in Table 1, and can be performed at other times, if deemed necessary. A full physical exam may include, but is not limited to evaluation of general appearance, cardiovascular and respiratory system, upper and lower extremities, genitourinary system, abdominal examination, HEENT, and a general neurologic physical exam. Assessment of other systems may be conducted as clinically indicated.

11.3.5 Safety Electrocardiogram

A 12-lead safety ECG (after 5 minutes in supine position) will be performed for each subject as indicated in Table 1 and can be performed at other times, if deemed necessary. The ECG readings will be performed approximately 1 hour after the scheduled morning dose on dosing days.

11.3.6 Mortara Surveyor for Electrocardiographs

A Mortara Surveyor will be used to collect ECG information (in triplicate) at timepoints coinciding with PK Samples. The extracted ECGs will then be blindly reviewed at a later time by an ECG core laboratory reader to determine changes in ECG variables (heart rate, RR, PR, QRS, QT, QTcF and QTcB). Graphical representations between ECG variables (e.g., QTcF) and plasma concentrations of ACER-801 and its metabolite will be generated.

The time and duration of ECG collection must be identical on Day -1, Day 1, and Day 14 and must be planned in relation to predose and 15 hrs postdose PK time points.

11.3.7 Clinical Laboratory Tests

Hematology and coagulation; serum chemistry; urinalysis; urine screening for drugs of abuse, cotinine, and alcohol will be performed for each subject as indicated in Table 1 and Table 5. Clinical laboratory tests may be repeated once for subjects who had previous clinical laboratory test results that revealed clinically significant abnormalities per the investigator's request. Pregnancy tests may be reported in the event of any positive or equivocal test result. If a pregnancy test is positive, Acer must be notified, and the subject will be followed as outlined in Section 11.2.6, until pregnancy outcome. Additional tests may be performed at other times, if deemed necessary. Blood samples may also be used for the assessment of tachykinin peptides, including NKB, NKA, and substance P.

Virology testing will include testing for the presence of HIV antibody, HbsAg, and HCV as indicated in Table 1. Blood samples will be appropriately processed, and laboratory reports will be made available to the investigator in a timely manner to ensure appropriate clinical review and subject inclusion/exclusion based upon results. Procedures for handling and shipping of all laboratory samples will be included in a laboratory manual provided by the central laboratory facility.

All clinical laboratory tests will be performed at the clinical unit) (instructions in the Study Reference Manual and Laboratory Manual).

Abnormalities in clinical laboratory tests that are considered clinically significant by the investigator will be considered Aes and recorded on the AE eCRF. In addition, ALT and AST elevations greater than 5 times the upper limit of normal (i.e., Grade 3 or higher based on CTCAE) will be considered clinically significant for the purposes of this study and reported as Aes.

Any clinically significant abnormal clinical laboratory test results, including test results obtained through Day 16/ET, will be repeated. For any repeat analysis, the abnormal value will be followed regularly until: (1) the value returns to screening or Day -1 values or within normal range; (2) a valid reason, other than Aes related to the study drug, is identified; or (3) the investigator determines that the abnormal value is no longer clinically significant or that further follow-up us no longer deemed medically necessary.

The list of clinical laboratory tests and other analytes to be tested is provided in Table 5.

The total amount of blood taken for the entire study will be approximately 508 mL.

Table 5 List of Clinical Laboratory and Other Analytes to be Tested

Assessment	Analyte
Central Laboratory (Clinical Site)	
Hematology	Hemoglobin, hematocrit, white blood count with differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils), platelet count, red blood cell count (including mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration)
Coagulation	Prothrombin time, partial thromboplastin time, international normalized ratio
Serum chemistry	Albumin, alkaline phosphatase, total bilirubin, ALT, AST, blood urea nitrogen, calcium, carbon dioxide, chloride, potassium, sodium, total cholesterol, creatinine, gamma glutamyl transferase, glucose, lactate dehydrogenase, phosphorus, total protein, uric acid
Virology	HIV antibody types 1 and 2, HCV antibody, HbsAg
Peptides	Neurokinin B
Hormones	Catecholamines, vasopressin, gonadotropins, estradiol, testosterone, FSH, LH, ACTH, cortisol, TSH, T3 (Total and Free), T4 (Total and Free), prolactin, SHBG, and insulin
Bone Density markers	BSAP, osteocalcin, amino terminal propeptide of type 1 collagen (P1NP) and Collagen Type- C-Telopeptide (CTX)
Urinalysis	pH, specific gravity, protein, glucose, ketones, bilirubin
Drugs of abuse, cotinine, and alcohol	Drugs of abuse including cocaine, amphetamines, barbiturates, opiates, benzodiazepines, cannabinoids, methadone, cotinine (nicotine), and alcohol
Pregnancy test	Serum pregnancy test
COVID-19 screen	As per site policy.
PK Laboratory	
PPD	ACER-801, metabolite

Note: Blood samples may also be used for the assessment of tachykinin peptides, including NKB, NKA, and substance P.

Abbreviations: ACTH = adrenocorticotropic hormone; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BSAP = Bone specific alkaline phosphatase COVID-19 = coronavirus disease 2019; FSH = follicle stimulating hormone; HbsAG = hepatitis B surface antigen; HCV = hepatitis C virus; HIV = human immunodeficiency virus; LH =luteinizing hormone; PK = pharmacokinetic; SHBG = sex hormone binding globulin; TSH = thyroid-stimulating hormone; T3 = triiodothyronine; T4 = thyroxine.

11.3.8 Analytical Procedures

Whenever possible, all samples from each subject will be analyzed on the same standard curve. Standard and quality control samples will be included in each batch of study samples assayed. Samples with drug concentrations greater than the upper limit of the validated range of the assay will be diluted with the appropriate drug-free biological fluid and re-assayed; those which are below the lower limit of this range will be reported as being below the lower limit of quantification. The analysts will not have access to the randomization scheme.

Analytical results will be presented in tabular form in the final report and chromatographic and derived data will also be provided. Additionally, accuracy, precision, and linearity data for each standard curve and all quality control samples will be presented. Representative chromatograms and standard curve graphs will be included.

12 STATISTICS

The PK, safety, and efficacy data will be presented using descriptive statistics and figures. A statistical analysis plan (SAP), providing details about the specific planned analyses and hypothesis tests will be prepared and approved by Acer and its designees before study database lock and unblinding of subject treatment assignments. An alpha of 0.05 will be used for hypothesis testing with no adjustment for multiplicity.

12.1 Determination of Sample Size

A sample size of approximately 10 to 14 subjects per arm (approximately 40 to 56 total) is considered sufficient to characterize the PK, safety and preliminary efficacy of ACER-801 based on study results from a dual neurokinin 1,3 receptor antagonists in postmenopausal women (Trower et. al, 2020).

12.2 Analysis Populations

- The PK Population includes all randomized subjects who have evaluable PK samples.
- The Safety Population includes all randomized subjects receiving at least 1 dose of study treatment.
- The Modified Intent-to-Treat (mITT) Population includes all randomized subjects who receive study treatment with baseline and at least one post-baseline efficacy measurements.
- The Per-Protocol population includes all randomized subjects with baseline and efficacy measurement endpoint visits without any major protocol deviations that would have an impact on the efficacy measurements.

12.3 Primary Endpoints

12.3.1 Pharmacokinetic Endpoints

The pharmacokinetic endpoints are:

- C_{max}, t_{max}, AUC_{last}, AUC_{inf}, $AUC\tau$, Accumulation Ratio for C_{max} (AR_{Cmax}), Accumulation Ratio for AUC (AR_{AUC}), Metabolite Ratio of C_{max} (MR_{Cmax}), Metabolite Ratio of AUC (MR_{AUC}), $t_{1/2}$ of ACER-801 and its metabolite

12.3.2 Safety Endpoints

Safety endpoints are:

- Clinically significant changes in physical examination findings at Week 2 relative to Baseline
- Clinically significant changes in clinical laboratory evaluations (hematology, coagulation, serum chemistry, urinalysis, hormones, bone density markers) during the 2-week treatment period relative to Baseline
- Adverse events ≥5%
- All SAEs and discontinuations

12.4 Secondary Endpoints

The secondary endpoints are:

- Change in frequency of vasomotor symptoms at Week 1 and Week 2 relative to Baseline
- Change in severity of vasomotor symptoms at Week 1 and Week 2 relative to Baseline
- Change in hot flash severity score at Week 1 and Week 2 relative to Baseline

12.5 Exploratory Endpoints

The exploratory endpoints are:

12.5.1 Assessment of Hormone Changes

- The change in clinical laboratory assessments from Baseline for LH, FSH, estradiol, testosterone, SHBG, ACTH, cortisol, TSH, T3 (Total and Free) and T4 (Total and Free), will be assessed. Summary statistics of changes in the hormone levels relative to baseline will be generated.

12.5.2 Night-Time Awakenings

- The change in the number of NTAs throughout the study will be assessed.

12.5.3 Assessment of Changes in Blood Markers Associated with Stress

- The change from Baseline to Week 2 in catecholamines, vasopressin, gonadotropins, prolactin, and insulin.

12.5.4 Markers of Bone Density

- The change from Baseline in bone density makers, including BSAP, osteocalcin, CTX, and P1NP will be summarized.

12.5.5 ECG

- The change in ECG variables (heart rate, RR, PR, QRS, QT, QTcF, and QTcB) will be assessed.
- Relationship between plasma exposure and changes in ECG variables

12.5.6 Exposure-Response Relationships

- Exploratory exposure-response relationships for efficacy (e.g., VMS), QT, and potentially safety relative to the plasma exposure of ACER-801 and its metabolite will be assessed.

12.6 Statistical Analyses

12.6.1 Pharmacokinetic Analyses

Noncompartmental analysis (NCA) will be performed for the plasma concentrations of ACER-801 and its metabolite. Summary statistics for the PK parameters (C_{max}, T_{max}, AUC_{last},

AUC_{inf}, AUCτ, AR_{Cmax}, AR_{AUC}, MR_{Cmax}, MR_{AUC}, $t_{1/2}$) will be determined for ACER-801 and its metabolite for the different dosing groups.

12.6.2 Safety Analyses

All AEs/SAEs will be coded using the current version of the Medical Dictionary for Regulatory Activities to assign system organ class and preferred term classification, based on the original terms entered on the electronic case report form. The incidence of AEs will be summarized by system organ class, preferred term, relationship to study treatment, and severity for each study treatment. All AEs, including AEs that lead to premature discontinuation from the study and from study treatment and SAEs, will be recorded.

All other safety measures including laboratory tests, vital signs, concomitant medication, medical history, physical examination, and ECG data will also be summarized descriptively (mean, standard deviation, median, minimum, and maximum). Laboratory tests will also be summarized by absolute and percent change from baseline and listed by clinical significance.

Concomitant medications will be coded using the most recent version of World Health Organization Drug Dictionary.

12.6.3 Efficacy Analyses

The secondary endpoints are the change in frequency and severity of vasomotor symptoms and hot flash severity score at Week 1 and Week 2 relative to Baseline.

12.6.4 Exploratory Analyses

The exploratory analyses will include summary statistics.

12.7 Changes in the Conduct of the Study or Planned Analyses

Only Acer or its designee may modify the protocol. Any change in study conduct requested by the investigator will be made only after consultation with Acer or its designee, who will then issue a formal protocol amendment to implement the change. The only exception may occur when the investigator considers that a subject's safety is compromised without immediate action. In these circumstances, immediate approval of the chairman of the IRB must be sought, and the investigator should inform Acer or its designee and the full IRB within 2 working days after the emergency occurs. With the exception of minor administrative or typographical changes, the IRB must review and approve all amendments. Amendments that have an impact on subject risk or the study objectives, or require revision of the ICF, must receive approval from the IRB prior to their implementation.

When a protocol amendment substantially alters the study design or the potential risks or burden to subjects, the ICF will be amended and approved by the IRB, and all active subjects will again provide written informed consent.

13 ADMINISTRATIVE CONSIDERATIONS

13.1 Compensation, Insurance, and Indemnity

There will be no charge to subjects to be in this study. Acer will pay all costs of tests, procedures, and treatments that are part of the study. In addition, Acer may defer the cost of travel if the company determines that the costs will impose a hardship on subjects. Acer will not pay for any hospitalizations, tests, or treatments for medical problems of any sort, whether or not related to the study subject's disease that is not part of this study. Costs associated with hospitalizations, tests, and treatments should be billed and collected in the way that such costs are usually billed and collected.

The investigator should contact Acer or its designee immediately upon notification that a subject has been injured by the study drug or by procedures performed as part of the study. Any subject who experiences a study-related injury should be instructed by the investigator to seek medical treatment at a prespecified institution.

The treating physician should bill the subject's health insurance company or other third-party payer for the cost of this medical treatment. If the subject has followed the investigator's instructions, Acer will pay for reasonable and necessary medical services to treat the injuries caused by the study drug or study procedures if these costs are not covered by health insurance or another third party that usually pays these costs. In some jurisdictions, Acer is obligated by law to pay for study-related injuries without prior recourse to third party payer billing. If this is the case, Acer will comply with the law.

13.2 Ethical Considerations

The final study protocol, including the final version of the ICF and/or other subject information, must be approved or given a favorable opinion in writing by an IRB. The investigator must submit written IRB approval to Acer before they can enroll any subject into the study. The investigator is responsible for providing the IB and any other available safety information and information about payments and compensation available to subjects to the IRB for review.

The investigator is responsible for informing the IRB of any amendment to the protocol in accordance with local requirements. A favorable opinion on amendments will be obtained prior to implementation, unless the amendment is necessary to reduce immediate risk to study participants. In addition, the IRB must approve all advertising used to recruit subjects for the study. The protocol must be reapproved by the IRB/upon receipt of amendments and annually, as local regulations require.

The investigator is also responsible for providing the IRB with reports of any reportable serious adverse drug reactions from any other study conducted with the investigational product, according to local regulations and guidelines. Acer will provide this information to the investigator.

The clinical trial will not be initiated, and study drug supplies will not be shipped to the clinical unit, until appropriate documents from the IRB, confirming unconditional approval of the protocol, ICF, and all recruiting materials, are obtained by the investigator and copies are received by Acer or its designee. The approval must refer to the study by protocol title and number, identify the documents reviewed, and include the date of review. The investigator will

provide appropriate reports on the progress of the study to Acer or its designee and to the IRB in accordance with applicable governmental regulations and in agreement with policy established by Acer or its designee.

Progress reports and notifications of SAEs will be provided to the IRB according to local regulations and guidelines. Investigators or Acer or its designee will provide reports to the IRB as requested, at a minimum annually, and after the study is complete.

13.2.1 Basic Principles

This research will be carried out in accordance with CFR, Good Clinical Practice (GCP), 21 CFR Parts 50 and 312, the principles enunciated in the Declaration of Helsinki, and the International Council for Harmonisation (ICH) harmonized tripartite guideline regarding GCP.

13.2.2 Institutional Review Board

This protocol will be reviewed by an IRB and the study will not start until the IRB has approved the protocol or a modification thereof. The IRB is constituted and operates in accordance with the principles and requirements described in the US CFR (21 CFR Part 56). The board must be ICH compliant.

13.2.3 Informed Consent

A properly written and executed ICF in compliance with the Declaration of Helsinki, ICH GCP, and the appropriate US and local regulations will be obtained from each subject prior to enrolling the subject in the study. A copy of the approved ICF and, if applicable, a copy of the approved subject information sheet, must be received by Acer or its designee prior to delivery of study drug and prior to conducting any study procedures.

The purpose of the study, the procedures to be carried out, and the potential hazards will be described to the subjects in non-technical terms. The subject should be given the opportunity to ask questions and allowed time to consider the information provided. Subjects will be required to read, sign, and date an ICF summarizing the discussion prior to screening and will be assured that they may withdraw from the study at any time without jeopardizing their medical care. Subjects will be given a copy of their ICF.

13.2.4 Subject Confidentiality and Data Protection

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and Acer and their agents. This confidentiality is extended to cover testing of biological samples in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study, or the data will be released to any unauthorized third party without prior written approval of Acer.

The study monitor (e.g., CRA, medical monitor), other authorized representatives of Acer, representatives of the IRB, or regulatory inspectors may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical

study site will permit access to such records. An agreement for disclosure of any such information will be obtained in writing and is included in the statement of informed consent.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept secured against unauthorized access for as long a period as dictated by local IRB and institutional regulations.

The investigator will maintain a list of subject's names and identifying information (e.g., subject's hospital number, unique subject number). This list will not be collected by Acer but may be viewed or audited by Acer or regulatory authorities.

The ICF will explain that study data will be securely stored in a computer database, maintaining confidentiality in accordance with national data protection legislation. All data computer processed by Acer or designee will be identified by unique subject number/randomization code/site number only.

When personal data on subjects are stored or processed by computer, the data must be secured, and password protected to prevent disclosure to unauthorized third parties. The pertinent sections of the data protection laws in the country in which the protocol is being conducted will be complied with in full.

The ICF will explain that, for data verification purposes, authorized representatives of Acer, regulatory authorities, or IRB may require direct access to parts of the hospital or study center records relevant to the study, including subject's medical history.

13.2.5 Quality Assurance/Quality Control

SOPs will be adhered to for all activities relevant to the quality of the study.

All clinical data will undergo a 100% quality control check prior to clinical database lock. Edit checks are then performed as a validation routine using SAS® to check for missing data, data inconsistencies, data ranges, etc. Corrections are made prior to statistical database lock.

13.2.6 Study Monitoring

Qualified individuals designated and/or approved by Acer will monitor all aspects of the study for compliance with applicable government regulations. Following written SOPs, the monitors will verify that the clinical trial is conducted, and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements (e.g., Good Laboratory Practices, Good Manufacturing Practices.

Study records at the clinical unit will be monitored at regular intervals by the CRA. The role of the CRA is to aid the investigator in the maintenance and documentation of complete, accurate, legible, well organized, and easily retrievable data. In addition, the CRA will ensure the investigator's understanding of all applicable regulations concerning the clinical evaluation of the investigational product and will ensure an understanding of the protocol, reporting responsibilities and the validity of the data. This will include ensuring that full and appropriate essential documentation is available.

In order to perform this role, the CRA must perform source data verification and as such must be given access to the subject's primary source documentation (e.g., paper or electronic medical

records such as consent to participate in the study, visit dates, screening and randomization numbers, demographic information, medical history, disease history, physical examination, vital signs, laboratory assessments [copy of laboratory reports], AEs/SAEs, concomitant medications, dates of dispensing investigational product, and ECGs) that support data entries in the eCRF. The eCRF must be completed promptly after each visit to allow the progress and results of the study to be closely followed by the medical monitor.

The investigator may exercise judgment in allowing the CRA access to particular sections of the subject's medical records if these are deemed irrelevant to the performance, observations, or conduct of this study.

Independent audits may be conducted by an Acer Quality representative to ensure monitoring practices are performed consistently and that monitors are following the GCPs and applicable SOPs.

13.2.7 Audits and Inspections

The investigator should understand that it may be necessary for an Acer Quality representative, the IRB and/or regulatory agencies to conduct one or more site audits during or after the study. The investigator will be informed if an audit is to take place and be advised as to the scope of the audit. Representatives of regulatory agencies may conduct an inspection of the study. If informed of such an inspection, the investigator should notify Acer or its designee immediately. The investigator will provide direct access to all trial related sites, pharmacy, clinical staff, source data/documents, clinical supplies and reports for the purpose of monitoring and auditing by Acer, and inspection by local and regulatory authorities.

13.2.8 Data Handling/Record Keeping

The Spaulding Clinical standard eCRF will be supplied. All raw data generated in connection with this study, together with the original copy of the final report, will be retained by the Spaulding Clinical until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period; however, if required by the applicable regulatory requirements or by an agreement with Acer. It is the responsibility of Acer to inform the investigator/institution as to when these documents no longer need to be retained.

13.2.9 Report Format

According to the ICH Harmonised Tripartite Guideline (Organization of the Common Technical Document (CTD) for the Registration of Pharmaceuticals for Human Use M4), the final report will be written according to the ICH E3 Guideline (Structure and Content of Clinical Study Reports).

13.2.10 Investigator Obligations

The investigator or a medically trained designee will be responsible for obtaining written informed consent and for the care of the subjects for the duration of the study. If the investigator

is not present in the study center during the assessment, they will leave instructions for the study center personnel and a telephone number where they can be reached.

The investigator will be responsible for the medical follow up of subjects, as applicable.

13.2.11 Adverse Event Reporting

The investigator is responsible for recording AEs reported by the subject or discovered by any other means during the study. In agreeing to the provisions of this protocol, the investigator accepts all legal responsibilities for immediate reporting of SAEs to Acer.

13.2.12 Protocol Deviations

The investigator is not permitted to deviate from the protocol in any significant way without proper notification to Acer (or designee). Only Acer may amend the protocol. Any change in study conduct considered necessary by the investigator will be made only after consultation with Acer, who will then issue a formal protocol amendment to implement the change and obtain regulatory approval. The only exception is when the investigator considers a subject's safety to be compromised if immediate action is not taken.

As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH E6:

- 4.5 Compliance with Protocol, Sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, Section 5.1.1
- 5.20 Noncompliance, Sections 5.20.1 and 5.20.2.

It is the responsibility of the site to use continuous vigilance to identify and report deviations within one working day of identification of the protocol deviation. All deviations must be addressed in study source documents. Protocol deviations must be sent to the local IRB per their guidelines. The site PI/study staff is responsible for knowing and adhering to their IRB requirements.

13.2.13 Regulatory Documentation

The following regulatory documentation must be completed or provided, and maintained by the Sponsor and the CRO:

- Approved ICF (all versions)
- IRB approvals (of protocol/amendments, subject questionnaires, etc.)
- Form FDA 1572
- Current medical license of investigators
- Curriculum vitae of investigators
- Laboratory certification and reference ranges
- Financial disclosure forms

13.2.14 Archiving and Record Retention

Investigators must retain all study records required by Acer and by the applicable regulations in a secure and safe facility. Any study documents stored elsewhere should have their location referenced in the investigator site file. The investigator must consult an Acer representative before disposal of any study records and must notify Acer of any change in the location, disposition, or custody of the study files. The investigator/institution must take measures to prevent accidental or premature destruction of essential documents, that is, documents that individually and collectively permit evaluation of the conduct of a study and the quality of the data produced, including paper copies of study records (e.g., subject charts) as well as any original source records that are electronic, as required by applicable regulatory requirements.

All documents relating to the study, source documents and subject medical files (retained per country specific regulations), completed study subject log, and confidential subject identification list will be retained by the investigator until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product.

The investigator/institution should retain subject identification codes for at least 15 years after the completion or discontinuation of the study. Subject files and other source data must be kept for the maximum period of time permitted by the hospital, institution, or private practice, but not less than 15 years. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an Acer agreement. Acer must be notified and will assist with retention should the investigator/institution be unable to continue maintenance of subject files for the full 15 years. Acer is responsible for informing the investigator/institution as to when these documents no longer need to be retained.

14 PUBLICATION POLICY

After completion of the study, the data may be considered for reporting at a scientific meeting or for publication in a scientific journal in accordance with current publication authorship guidelines, including those of the International Committee of Medical Journal Editors (ICMJE). Decisions regarding authorship will appropriately reflect the contribution made by personnel of Acer Therapeutics Inc., the investigators, and other individuals involved. Acer Therapeutics Inc. will be primarily responsible for publication decisions and activities and will work with the investigators to determine how the manuscript is written and edited, the number and order of authors, the publication to which it will be submitted, and any other related issues. Acer Therapeutics Inc. has final approval authority over all such issues. The data from this study are the exclusive property of the Acer Therapeutics Inc. and considered confidential. The data cannot be published without prior written authorization from Acer Therapeutics, Inc., but data and any publication thereof will not be unreasonably withheld. It is understood that if needed, a reasonable delay in timing of submission by Acer, or exclusion of confidential information of Acer, to allow for protection of intellectual property is appropriate.

15 LIST OF REFERENCES

Fraser GL, Lederman S, Waldbaum A, et al. A Phase 2b, Randomized, Placebo-Controlled, Double-Blind, Dose-Ranging Study of the Neurokinin 3 Receptor Antagonist Fezolinetant for Vasomotor Symptoms Associated with Menopause. Menopause 2020;27:382-392.

Prague JK, Roberts RE, Comninos AN, et al. Neurokinin 3 Receptor Antagonism Rapidly Improves Vasomotor Symptoms with Sustained Duration of Action. Lancet 2017;389: 1809-1820.

Santoro N, Waldbaum A, Lederman S, et al. Effect of the Neurokinin 3 Receptor Antagonist Fezolinetant on Patient-Reported Outcomes in Postmenopausal Women with Vasomotor Symptoms: Results of a Randomized, Placebo-Controlled, Double-Blind, Dose-Ranging Study (VESTA). Menopause 2020;27:1350-1356.

Skorupskaite K, George JT, Veldhuis JD, et al. Neurokinin 3 Receptor Antagonism Reveals Roles for Neurokinin B in the Regulation of Gonadotropin Secretion and Hot Flashes in Postmenopausal Women. Neuroendocrinology 2018;106:148-157.

Sloan JA, Loprinzi CL, Novotny PJ, et al. Methodologic Lessons Learned from Hot Flash Studies. J Clin Oncol 2001;19(23):4280-90.

Trower M et al. Effects of NT-814, A Dual Neurokinin 1 and 3 Receptor Antagonist, on Vasomotor Symptoms in Postmenopausal Women: A Placebo-Controlled, Randomized Trial. Menopause 2020; 27 498-505.