Document Type:	Study protocol
Official Title:	A double-blind, randomized, placebo-controlled multicenter study to investigate efficacy and safety of elinzanetant for the treatment of vasomotor symptoms over 26 weeks in postmenopausal women
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Title Page

Protocol Title:

A double-blind, randomized, placebo-controlled multicenter study to investigate efficacy and safety of elinzanetant for the treatment of vasomotor symptoms over 26 weeks in postmenopausal women

Protocol Number:	21652
Protocol Version:	4.0
Amendment Number:	2
Compound Number:	BAY 3427080 / elinzanetant
Brief Title:	**O**verall **A**ssessment of efficacy and **S**afety of elinzanetant **I**n patients with vasomotor **S**ymptoms (OASIS-2)
Study Phase:	**3**
Acronym:	**OASIS 2**
Sponsor Name and	
Legal Registered Address:	Bayer Consumer Care AG, Peter-Merian-Strasse 84, 4052 Basel, Switzerland
Regulatory Agency	
Identifier Number(s):	EudraCT: 2020-004855-34
Protocol Date:	**22 JUN 2022**

Medical Monitor name and contact information will be provided separately.

Name: PPD MD, PhD Role: PPD

This is an electronically generated document that does not bear any sponsor signatures. The signature of the sponsor's medically responsible person is filed in the TMF and available on request.

Document History Table

DOCUMENT HISTORY			
Document	**Version**	**Date**	**Comments (if applicable)**
Amendment 2	4.0	22 JUN 2022	
Amendment 1	3.0	10 FEB 2022	
Clinical Study Protocol	2.0	15 JUN 2021	Version addressing feedback from FDA
Clinical Study Protocol	1.0	10 MAR 2021	Version submitted to FDA special protocol assessment

Protocol Amendment Summary of Changes Table

Amendment 2 (22 JUN 2022)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall rationale for Amendment 2:

Changes consist of three types, (i) they address comments from FDA, (ii) will help to clarify certain aspects of the protocol or (iii) they are minor corrections.

In addition, the sleep quality tracking substudy was removed due to technical difficulties.

Key changes

Section # and Name	Description of Change	Brief Rationale
Section 1.3.1 Schedule of activities, Table 1-1	Demography and baseline characteristics were updated to include educational level, and gynecological and reproductive history including numbers of pregnancy and birth.	Since start of the study, data have already been collected in the CRF as they are relevant for the analysis. Revised the study protocol to match information collected in the CRF.
Section 5.1 Inclusion criterion 6	A new sub-bullet was added: HPV testing in participants with “absence of endocervical/transformation zone component” will be used as an adjunctive test automatically. Participants can be included if they are negative for high-risk HPV strains.	Sub-criterion added to comply with ASCCP guidelines
Section 5.2 Exclusion Criteria	Re-test is allowed once in case of an abnormal INR value	Intake of concomitant medication may lead to abnormal INR values. INR can be repeated once in participants for whom no INR prolonging anticoagulant is recorded as prior and concomitant medication.

Section # and Name	Description of Change	Brief Rationale
Section 10.6 Prohibited concomitant medications	All vaginal hormonal products are prohibited from 4 weeks prior to Baseline visit, and not only those with systemic exposure.	Requested by FDA

Clarifications to the protocol

Section # and Name	Description of Change
Section 1.3.1 Schedule of activities	Instructions on wash-out of prior medication were clarified to ensure that hormonal therapies possibly affecting laboratory measurements of follicle-stimulating hormone and estradiol are washed out prior to SCR-1 visit.
Section 1.3.2 Treatment and Follow-up	Footnote **a** was reworded to clarify which Visits should be performed in case of premature discontinuation of study intervention.
Section 2.3.1 Risk Assessment	A new section on effects on reproductive function was added for completeness.
Section 5.4 Screen Failures	It was clarified that re-screening is allowed once if the inclusion/exclusion criteria, including related footnotes, have been changed via a protocol amendment.
Section 7.1.3 Temporary Discontinuation	Wording on permanent discontinuation of study intervention was clarified.
Section 7.2 Participant Discontinuation/Withdrawal from the Study	At the time of discontinuing from the study, if possible, End of Treatment visit procedures should be conducted, followed by FU visit as shown in the SoA and in particular described in footnote a) in Table 1–2.
Section 8.2.5 Pregnancy testing	Pregnancy testing will not be performed in participants who have undergone total hysterectomy and/or bilateral oophorectomy
Section 8.2.6 Mammogram	Women with bilateral mastectomy do not have to provide a mammogram provided that all breast tissue has been removed.
Section 8.2.6 Mammogram	A clarification was added that mammogram should be performed before any planned COVID-19 vaccination.
Section 8.2.7 Transvaginal ultrasound	TVU is not required in participants who have both a total hysterectomy as well as bilateral salpingo-oophorectomy since the organs that are meant to be assessed are absent. The assessment of ovaries should include diameters as well as details of cyst like structures, if applicable.
Section 8.2.8 Cervical cytology	Cervical smear will be performed only if the participant has an intact cervix.
Section 10.5.2 Close observation of participants with liver function test findings	In accordance with Table 10-2, a bullet point was added stating that close liver observation can be stopped if fragmentation reveals abnormal bone AP as reason for the increase of AP>2 x ULN.

Corrections of inconsistencies and minor corrections (editorial corrections not detailed)**:**

Section # and Name	Description of Change
Section 1.3 Schedule of Activities	Weight, hip and waist circumference were added to the screening safety assessments, in accordance with Section 8.2.1 Physical examinations.
Section 1.3.2 Treatment and follow-up	eDiary completeness will be checked until FU visit, and not only until EoT Visit.
Section 2.3.1 Risk Assessment	Information on abnormal involuntary muscle contractions and skeletal muscle toxicity were divided onto two separate rows.
Section 6.8.2 Other Treatment Considerations	Correction of a typo in OATP1B1/ B3
Section 8.1.1.7 Beck Depression Inventory (BDI-II)	A BDI score more than 19 at screening and not at baseline should be reported as “Depression” in medical history of the participant.
Section 10.6 Appendix 6: Prohibited concomitant medications	An erroneous footnote was removed from Table 10-5. Strong or moderate CYP3A4 inhibitors will not be determined by PK modelling but are identified based on published data and/or respective guidances.

In addition, minor editorial and formatting revisions have been made throughout the document.

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1. Protocol Summary

1.1 Synopsis

Protocol Title: A double-blind, randomized, placebo-controlled multicenter study to investigate efficacy and safety of elinzanetant for the treatment of vasomotor symptoms over 26 weeks in postmenopausal women

Brief Title: **O**verall **A**ssessment of efficacy and **S**afety of elinzanetant **I**n patients with vasomotor **S**ymptoms (OASIS-2)

Rationale: This is a pivotal phase 3 study to assess the efficacy and safety of elinzanetant for the treatment of vasomotor symptoms (VMS) related to menopause.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To evaluate the efficacy of elinzanetant for the treatment of VMS associated with the menopause	**<u>For regulatory submission in the US:</u>** **Primary endpoints** • Mean change in frequency of moderate to severe HF from baseline to Week 4 (assessed by HFDD) • Mean change in frequency of moderate to severe HF from baseline to Week 12 (assessed by HFDD) • Mean change in severity of moderate to severe HF from baseline to Week 4 (assessed by HFDD) • Mean change in severity of moderate to severe HF from baseline to Week 12 (assessed by HFDD) **<u>For all other regions except regulatory submission in the US:</u>** **Primary endpoints** • Mean change in frequency of moderate to severe HF from baseline to Week 4 (assessed by HFDD) • Mean change in frequency of moderate to severe HF from baseline to Week 12 (assessed by HFDD) **Key secondary endpoints** • Mean change in severity of moderate to severe HF from baseline to Week 4 (assessed by HFDD) • Mean change in severity of moderate to severe HF from baseline to Week 12 (assessed by HFDD) **<u>For all regions:</u>** **Exploratory endpoints:** • Proportion of participants with at least 50% reduction in frequency of HF at week 4 • Proportion of participants with at least 50% reduction in frequency of HF at week 12

Objectives	Endpoints
Secondary	
• To evaluate the onset of efficacy of elinzanetant for the treatment of VMS associated with the menopause	**Key secondary endpoints** • Mean change in frequency of moderate to severe HF from baseline to Week 1 (assessed by HFDD) **Secondary endpoints:** • Mean change in frequency of moderate to severe HF from baseline over time **Exploratory endpoints:** • Time to treatment response
• To evaluate the efficacy of elinzanetant in women treated for relief of VMS associated with the menopause on: ○ sleep quality ○ menopause related quality of life ○ depressive symptoms	**Key secondary endpoints:** • Mean change in PROMIS SD SF 8b total score from baseline to Week 12 • Mean change in MENQOL total score from baseline to Week 12 **Secondary endpoints:** • Mean change in BDI-II total score from baseline to Week 12 • Mean change in BDI-II total score from baseline to Week 26 **Exploratory endpoints:** • Absolute values and changes in the ISI total score over time • Absolute values of the PGI-C individual item scores over time • Absolute values and change in PGI-S individual item scores over time • Absolute values and change in EQ-5D-5L single dimensions and health state VAS score over time. • Absolute values and changes in the BDI-II total score over time
• To evaluate the safety of elinzanetant for the treatment of VMS associated with the menopause	• Number of participants with TEAEs • Mean change in Sleepiness Scale at Week 1, Week 4, and Week 12 compared to baseline

The full list of exploratory endpoints will be presented in the SAP

BDI-II=Beck Depression Inventory, EQ-5D-5L=European Quality of Life 5-dimension 5-level questionnaire, HF = Hot Flash, HFDD=Hot Flash Daily Diary, MENQOL=Menopause Specific Quality of Life Scale, PGI-C=Patient Global Impression of Change, PGI-S=Patient Global Impression of Severity, PROMIS SD SF 8b=Patient-reported Outcomes Measurement Information System Sleep Disturbance Short Form 8b, VAS = Visual analog scale

Overall Design:

This is a Phase 3 multi-center, multi-country, placebo-controlled, double blind, parallel group intervention study, in postmenopausal women with vasomotor symptoms.

Brief Summary:

The purpose of this study is to investigate efficacy and safety of elinzanetant for the treatment of vasomotor symptoms in postmenopausal women.

Study details include:

- Total study duration for an individual participant: approximately 36 weeks (plus potential wash-out period), including
  - Pre-screening / Wash-out period (if applicable)
  - Screening: approximately 6 weeks
  - Treatment: 26 weeks
  - Follow-up: 4 weeks
- Visit Frequency: Every 4-6 weeks

Number of Participants:

Approximately 1058 participants will be screened to achieve 370 participants randomly assigned to study intervention and 332 participants evaluable for the primary efficacy analysis, for an estimated 166 evaluable participants per study arm. See Section 9.2 for more details.

Intervention Groups and Duration:

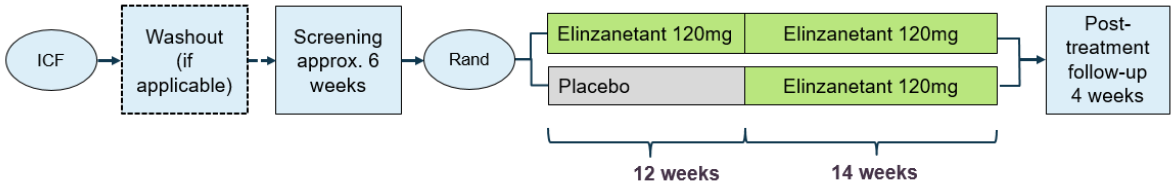
All participants will receive either 120 mg of elinzanetant or matching placebo orally once daily. There will be 2 arms in the study:

- Elinzanetant 120 mg for 26 weeks
- placebo for 12 weeks, followed by elinzanetant 120 mg for 14 weeks

Data Monitoring/Other Committee: Yes

1.2 Schema

Figure 1–1: Study Schema



Approx. = Approximately, ICF = Signing of informed consent form, Rand. = randomization

1.3 Schedule of Activities (SoA)

1.3.1 Screening

- The 3 visits in the table below can be combined, if possible according to organizational set-up at the study center.
- Depending on prior medication a wash-out period may be necessary. (See Section 4.1 for further details). Some hormonal therapies may affect the laboratory test results of estradiol and follicle-stimulating hormone. For participants in whom these two parameters are needed to determine menopausal status, the currently used hormonal therapy needs to be evaluated, and if necessary, the washout needs to be completed by SCR-1 visit.
- The duration between SCR-1 and baseline visit (see Table 1–2) should typically not exceed 6 weeks (see Section 5.5 for exceptions). The time required for central reading of endometrial biopsy samples needs to be considered for visit planning.

Table 1–1: Schedule of Activities – Pre-Screening and Screening

Visit name	Pre-SCR	SCR-1	SCR-2
In person or phone visit	**in person**	**in person**	**in person**
Baseline characteristics			
Informed consent	●	(●)[a]	
Demography including tobacco use and educational level	●	(●)[a]	
Medical history and concomitant medications, including history o menopause hormone therapy	●	●	●
Gynecological and reproductive history including number of pregnancies and births	●	(●)[a]	
eDiary and eCOA instruments			
Dispensation and training of participant's hand-held device			●
HFDD (twice daily)			---------->
Sleepiness Scale (daily in the evening)			---------->
BDI-II			●
eC-SSRS			●
Screening and randomization			
Inclusion/exclusion criteria	●	●	●
Safety			
Complete Physical examination (including height)		●	
Vital signs, weight, hip and waist circumference		●	
12-lead ECG			●
Mammogram (if applicable, see Section 8.2.6)		●	
Trans vaginal ultrasound			●[b]
Cervical cytology (if applicable, see Section 8.2.8)		●	
Endometrial biopsy (if applicable, see Section 8.2.9)			●[b]
Laboratory (including safety)			
Blood sampling (safety)		●	
Urine pregnancy test		●	●[b]
Urinalysis		●	

ECG = Electrocardiogram, eCOA = Electronic clinical outcome assessment Pre-SCR = pre-screening Visit, SCR=screening Visit

Questionnaires: BDI-II=Beck Depression Inventory, eC-SSRS = Electronic Columbia-Suicide Severity Rating Scale (patient rated), HFDD=Hot Flash Daily Diary,

a Only if Pre-screening visit is not performed

b Pregnancy test (only if participant has not been confirmed postmenopausal) and ultrasound has to be performed before an endometrial biopsy is taken. For participants who have been confirmed post-menopausal, no pregnancy test is needed at this visit.

1.3.2 Treatment and follow-up

Table 1–2: Schedule of Activities - Treatment and follow-up

Visit name	BL	T1	T2	T3	T4	T5	T6/EoT[a]	FU
In person (IP) or phone visit	**IP**	**IP**	**IP**	**IP**	**IP**	**phone**	**IP**	**IP**
Visit Week	**1**	**4**	**8**	**12**	**16**	**20**	**26**	**30**
Visit Day	1	22-28	50-56	85-90	106-112	134-140	176-182	204-217
Allowed window in days		-7	-7	+6	-7	-7	-7	±7
eDiary and eCOA instruments								
HFDD (twice daily)	---------->							
Sleepiness scale (7 consecutive days, reported in the evening)	during Week 1, Week 4, and Week 12							
PROMIS SD SF 8b	once weekly		●	●	●		●	●
ISI	●	●	●	●	●		●	●
MENQOL	●	●	●	●	●		●	●
BDI-II		●	●	●	●		●	●
EQ-5D-5L	once weekly		●	●	●		●	●
PGI-S	once weekly		●	●	●		●	●
PGI-C		●	●	●	●		●	●
eC-SSRS		●	●	●	●		●	●
Study drug intake documentation	---------->							
Check completeness of eDiary via web report	---------->							
Collection of hand-held device								●
Screening and randomization								
Inclusion/exclusion criteria	●							
Participant randomization	●							
Safety / laboratory								
AEs / concomitant medications	---------->							
Symptom-based physical exam	●	●	●	●	●			●
Complete physical exam							●	
Vital signs, weight, hip and waist circumference	●	●	●	●	●		●	●
Trans vaginal ultrasound							●	
Mammogram							●[b]	
Endometrial biopsy (if applicable, see Section 8.2.9)							●	
Blood sample (safety)	●	●	●	●	●		●	●
Blood sample (biomarkers)	●			●			●	
Blood sample (PK)	●				●		●	
Blood sample (pharmacogenetics - optional)	●							
Urinalysis							●	
Study intervention and study exit								
Study drug dispensing/training	●	●	●	●	●			
Study drug dispensing - DtP option						Monthly		
Supervised study drug intake at site	●				●			
Study drug collection (if applicable)		●	●	●	●		●	
Study drug compliance		●	●	●	●	●	●	
Participant feedback survey	●			●			●	

AEs = adverse events, BL=baseline, DtP = Direct to patient, eCOA = Electronic clinical outcome assessment, EoT = End of treatment, IP = in person, FU = follow up, PK = pharmacokinetics, T = treatment

Questionnaires: BDI-II=Beck Depression Inventory, eC-SSRS = Electronic Columbia-Suicide Severity Rating Scale (patient rated) , EQ-5D-5L=European Quality of Life 5-dimension 5-level questionnaire, HFDD=Hot Flash Daily Diary, ISI=Insomnia

Severity Index, MENQOL=Menopause Specific Quality of Life Scale, PGI-C=Patient Global Impression of Change, PGI-S=Patient Global Impression of Severity, PROMIS SD SF 8b=Patient-reported Outcomes Measurement Information System Sleep Disturbance Short Form 8b

a If a participant discontinues prematurely from treatment after the baseline visit, an EoT visit will be performed as soon as possible; it will comprise the same assessments as the Week 26 visit, and should be scheduled at the latest within 14 days after the discontinuation of the study drug. If the participant in addition decides to withdraw from the study, the EoT Visit will be followed after 4 weeks by the Follow-up Visit. If a participant discontinues from treatment prior to T3 and agrees to stay in the study, the next scheduled in person visit will cover the assessments expected to be performed during the FU visit, and, therefore, the participants who complete these visits after stopping the intake of study drug do not need to have a FU visit at the end of the visit schedule. The handheld device will be collected at the last scheduled IP visit.

b Mammogram should be performed if the time that has elapsed since the previous mammogram is in line with local medical guidelines for the frequency of mammograms in the respective age group. In case a non-study mammogram was conducted during the time of study participation, the result should be documented. In this case the mammogram will not be done at Visit T6 or EoT.

1.3.3 PK sampling schedule

Table 1–3: PK sampling schedule

Visit	BL	T4	T6/EoT
Week	1	16	26
Study intervention intake on visit days	at site	at site and no dosing on the day before	at home the evening before
Documentation of date and time of study intervention	on visit day	on visit day and the previous dosing day	on the previous dosing day
PK sampling	post dose at: 0.5-3 hours	pre-dose, and two samples between 0.5-4 hours post dose, at least 1 hour apart.	any time during the visit

BL= baseline, EoT = End of treatment, T = treatment, PK = Pharmacokinetics

When PK samples must be taken pre-dose at Visit T4, the previous evening dose of study intervention will not be taken at home. On the day of BL visit and visit T4 with supervised study drug intake at the clinical site, the participant should not take any further study medication in the evening at home.

If the participant has mistakenly taken the evening dose prior to Visit T4 instead of intake at the clinical site, the participant will not receive a supervised study drug intake, and should take the study drug in the evening as usual. In this case, PK sampling for all three samples, to be taken at least 1 hour apart (between each sampling), will be done at any time during Visit T4.

For participants prematurely discontinuing study treatment, a PK sample is not required as part of the EoT activities.

2. Introduction

2.1 Study Rationale

This is a pivotal phase 3 study to assess the efficacy and safety of elinzanetant for the treatment of VMS related to menopause.

2.2 Background

VMS, commonly referred to as hot flashes (HF, also called "flushes"), are one of the most common, bothersome and distressing symptoms felt by women during the menopause transition, and the leading cause for seeking medical attention during this particular phase of a woman's life (Pachman et al. 2010). Effective treatment options are mostly limited to hormone therapy, which despite being effective is associated with safety concerns such as increased risk of hormone-dependent cancers and cardiovascular adverse effects, including thrombotic risk (BIJUVA® Prescribing Information 2018, PREMARIN® Prescribing information 2017). A low dose of the anti-depressant paroxetine is approved in US for treatment of VMS but has limited efficacy and a range of safety and tolerability concerns that prevent its widespread usage (BRISDELLE® Prescribing Information 2017).

Since hormone treatment is not an option for many women suffering from moderate and severe VMS, either because of contraindications or personal preferences, there is a strong medical need for an effective non-hormonal treatment option with improved benefit / risk balance.

Elinzanetant (formerly NT-814[1]) is a dual neurokinin (NK)-1,3 receptor antagonist. Data indicate that HF may be treated by targeting the neuroendocrine factors that trigger the VMS (Rance et al. 2013).

Two previous studies, RELENT-1 (NCT02865538 2020) and SWITCH-1 (814-PM-02) (NCT03596762 2020), have shown elinzanetant to be significantly better than placebo in reducing the frequency and severity of HF. Furthermore, the SWITCH-1 study showed that the reduction in frequency and severity of HF was associated with marked improvements on participant reported outcomes of sleep, mood and quality of life.

If these benefits are confirmed in further studies, it is anticipated that elinzanetant will be a relevant improvement compared to currently available non-hormonal therapies. The efficacy is expected to be comparable to that seen with hormone therapy, but with a quicker onset of action and without the serious side effects associated with hormonal therapy. It is also anticipated to result in greater efficacy and a better tolerability profile than anti-depressants used for treating VMS.

A detailed description of the chemistry, pharmacology, efficacy, and safety of elinzanetant is provided in the IB.

[1] The compound was initially developed by GSK, then NeRRe Therapeutics Ltd. on behalf of KaNDy Therapeutics Ltd. On 08 SEP 2020 Bayer AG acquired KaNDy Therapeutics Ltd. and continues development of elinzanetant.

2.3 Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected AEs of elinzanetant may be found in the IB.

2.3.1 Risk Assessment

Table 2–1: Risk assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention elinzanetant		
Somnolence or fatigue	Mild to moderate somnolence and fatigue identified as common (1-10% of participants) in the previous studies.	Participants will be generally dosed in the evening to limit the occurrence of these reactions and will be advised to avoid driving or use of machinery if affected.
Concomitant use of strong CYP3A4 inhibitors Concomitant use of CYP3A4 substrates with narrow therapeutic range	Elinzanetant is moderate to sensitive substrate for the CYP3A4 enzyme and a weak inhibitor of CYP3A4.	Will be managed through exclusion of participants taking the interacting concomitant medications during clinical trials
Abnormal involuntary muscle contraction	Observed in a repeat dose study in rats at all doses but not in subsequent longer-term studies in rat and cynomolgus monkeys. These findings are considered unlikely to be relevant safety findings but will continue to be monitored in clinical studies. In the SWITCH-1 study, there were 2 non-serious cases of muscle spasm, both mild in severity, at dosages of 120 and 160mg. Both were assessed as related to the study intervention by the investigator.	Continuous AE monitoring
Skeletal muscle toxicity	The reactions were observed in a repeat dose study in rats at high doses but not in subsequent longer-term studies in rat and cynomolgus monkey. These findings are considered unlikely to be relevant safety findings but will continue to be monitored in clinical studies.	Continuous AE monitoring together with evaluation of related laboratory parameters (CK, AST, LDH) at specific time points will ensure proper evaluation of the risk during the study.

Table 2–1: Risk assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Phototoxicity	Preclinical safety finding. The in vitro 3T3 Neutral Red Uptake phototoxicity assay showed a potentially phototoxic effect. However, this test has a high rate of false-positives and poor positive predictive value. One participant in the SWITCH-1 study who received 160 mg of elinzanetant reported a mild skin reaction that was potentially consistent with photosensitivity. The event resolved after 15 days despite continued treatment with elinzanetant. No particular precautions to avoid sunlight had been taken.	Investigators and participants will be advised of the potential for skin sensitivity and to be vigilant to any possible reactions. Measures are to be taken to avoid strong sunlight should such reactions occur.
Increase in liver enzymes	Two participants were withdrawn from the SWITCH-1 study because of increased liver enzymes, although both were subsequently found to be noncompliant with the elinzanetant treatment. There was one further participant participating in the 814-1-05 study who was found to have increased transaminases. The participant had abnormal GGT at screening and fatty liver.	Defined exclusion criteria. Regular monitoring of liver parameters during the study. Defined strategy for close observation and defined stopping criteria for participants with increased liver parameters during the study.
Arrhythmias	A possible signal with respect to an increased incidence if arrhythmias was identified in Phase 1 studies in healthy male volunteers but has not been substantiated in subsequent studies, including through Holter monitoring conducted over an extended period in all participants who participated in the RELENT-1 study.	12 lead ECG will be performed during screening for all participants to exclude relevant preexisting arrhythmias. If clinically indicated, unscheduled 12-lead ECGs can be performed at any point during the study. Unscheduled ECGs must be recorded in the eCRF.
Effects on reproductive function	There was no evidence of developmental or reproductive toxicity in embryo-fetal toxicity studies at doses up to 100 mg/kg/day in rats or up to 140 mg/kg/day in rabbits representing about 11- or 1-times the human exposure in rats or rabbits, respectively. In a female rat fertility and early embryonic development study, increased percentage of pre-implantation and post-implantation embryo loss, reduced litter size and lower fetal body weights were seen at the dose of 100 mg/kg/day, which exceeds human exposure at the anticipated therapeutic dose of 120 mg/day by a factor of 11. The dose free of findings represents 3-times the human exposure.	Subjects are informed of these effects on reproductive function. Subjects are also required to avoid pregnancy during the study.

Table 2–1: Risk assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	Elinzanetant reduced plasma estradiol, progesterone and luteinizing hormone in pre-menopausal females. These effects were correlated in one of the studies with delayed or irregular menses	
Study Procedures		
No relevant risks are expected related to the study procedures	All study procedures are routine medical procedures in this participant population.	All study procedures will be conducted by appropriately trained staff.
Other		
Non-effective treatment for participants who are randomized to placebo.	Participants who are randomized to placebo will not receive active treatment for 3 months.	Participants are not expected to suffer undue medical consequences from absence of treatment. Participants who discontinue study treatment will be encouraged to remain in the study for further data collection.

AE = Adverse event, AST = Aspartate-aminotransferase, CK = Creatinine kinase, CYP3A4 = Cytochrome P450 isoenzyme 3A4, ECG = Electrocardiogram, GGT = Gamma glutamyl transferase, LDH = Lactate dehydrogenase

2.3.2 Benefit Assessment

Based on the mode of action, pre-clinical, and clinical data it is expected that treatment with elinzanetant will provide relevant clinical benefits to women with VMS. These benefits may include

- reduction in frequency and severity of VMS,
- sleep-related benefits,
- improvement of mood and health-related quality of life.

It is expected that efficacy related to VMS will be comparable to that seen with hormone therapy, with the anticipation that the onset of effect will be more rapid. Furthermore, it is anticipated that treatment with elinzanetant will not be associated with some of the contraindications limiting the use of hormone treatment in the target population.

Participants who are randomized to the placebo group are still expected to have some benefit from participation in the study as they will receive a thorough medical evaluation. All participants on placebo will receive active treatment with elinzanetant in the second part of the study.

2.3.3 Overall Benefit: Risk Conclusion

Taking into account the measures taken to minimize risk to participants in this study, the potential risks identified in association with elinzanetant are justified by the anticipated benefits that may be afforded to participants with VMS.

3. Objectives, Endpoints and Estimands

Objectives and endpoints are listed in Table 3–1.

Based on available FDA (FDA 2003) and EMA (EMA 2005) guidance on the treatment of VMS associated with menopause the requirements regarding the primary endpoints for efficacy trials are different. Therefore, following the ICH E17 guidance on multiregional trials (EMA 2017), a differing set of primary and key secondary endpoints have been defined for the two regions. Details can be found in the table below.

Table 3–1: Objectives and endpoints

Objectives	Endpoints
Primary	
• To evaluate the efficacy of elinzanetant for the treatment of VMS associated with the menopause	**For regulatory submission in the US:** **Primary endpoints** • Mean change in frequency of moderate to severe HF from baseline to Week 4 (assessed by HFDD) • Mean change in frequency of moderate to severe HF from baseline to Week 12 (assessed by HFDD) • Mean change in severity of moderate to severe HF from baseline to Week 4 (assessed by HFDD) • Mean change in severity of moderate to severe HF from baseline to Week 12 (assessed by HFDD) **For all other regions except regulatory submission in the US:** **Primary endpoints** • Mean change in frequency of moderate to severe HF from baseline to Week 4 (assessed by HFDD) • Mean change in frequency of moderate to severe HF from baseline to Week 12 (assessed by HFDD) **Key secondary endpoints** • Mean change in severity of moderate to severe HF from baseline to Week 4 (assessed by HFDD) • Mean change in severity of moderate to severe HF from baseline to Week 12 (assessed by HFDD) **For all regions:** **Exploratory endpoints:** • Proportion of participants with at least 50% reduction in frequency of HF at week 4 • Proportion of participants with at least 50% reduction in frequency of HF at week 12

Objectives	Endpoints
Secondary	
• To evaluate the onset of efficacy of elinzanetant for the treatment of VMS associated with the menopause	**Key secondary endpoints** • Mean change in frequency of moderate to severe HF from baseline to Week 1 (assessed by HFDD) **Secondary endpoints:** • Mean change in frequency of moderate to severe HF from baseline over time **Exploratory endpoints:** • Time to treatment response
• To evaluate the efficacy of elinzanetant in women treated for relief of VMS associated with the menopause on: ○ sleep quality ○ menopause related quality of life ○ depressive symptoms	**Key secondary endpoints:** • Mean change in PROMIS SD SF 8b total score from baseline to Week 12 • Mean change in MENQOL total score from baseline to Week 12 **Secondary endpoints:** • Mean change in BDI-II total score from baseline to Week 12 • Mean change in BDI-II total score from baseline to Week 26 **Exploratory endpoints:** • Absolute values and changes in the ISI total score over time • Absolute values of the PGI-C individual item scores over time • Absolute values and change in PGI-S individual item scores over time • Absolute values and change in EQ-5D-5L single dimensions and health state VAS score over time. • Absolute values and changes in the BDI-II total score over time
• To evaluate the safety of elinzanetant for the treatment of VMS associated with the menopause	• Number of participants with TEAEs • Mean change in Sleepiness Scale at Week 1, Week 4, and Week 12 compared to baseline
Other pre-specified	
• To evaluate variability in exposure in relation to the efficacy and safety for elinzanetant	• Systemic exposure of elinzanetant in plasma via sparse PK sampling
• To further investigate elinzanetant (e.g., mode-of-action-related effects, safety) and to further investigate pathomechanisms deemed relevant to VMS and associated health problems	• Various biomarkers (e.g., diagnostic, safety, pharmacodynamic, monitoring, or potentially predictive biomarkers)

The full list of exploratory endpoints will be presented in the SAP.

BDI-II=Beck Depression Inventory, EQ-5D-5L=European Quality of Life 5-dimension 5-level questionnaire, HF = Hot Flash, HFDD=Hot Flash Daily Diary, ISI = Insomnia severity index, MENQOL=Menopause Specific Quality of Life Scale, PGI-C=Patient Global Impression of Change, PGI-S=Patient Global Impression of Severity, PK = Pharmacokinetics, PROMIS SD SF 8b=Patient-reported Outcomes Measurement Information System Sleep Disturbance Short Form 8b, SAP = Statistical analysis plan, TEAE = treatment emergent adverse event, US = United States, VAS = Visual analog scale, VMS = Vasomotor symptoms

Estimands

The attributes of the main estimand for the primary endpoints are as following:

- Population: Post menopause women aged 40-65 with VMS as described by the inclusion/exclusion criteria detailed in the protocol.
- Variable: Efficacy will be assessed based on 2 or 4 primary endpoints depends on the region (regulatory submission in the US only/all regions) as listed below:
    - Change in frequency of moderate to severe HF from baseline to Week 4 (all regions).
    - Change in frequency of moderate to severe HF from baseline to Week 12 (all regions).
    - Change in severity of moderate to severe HF from baseline to Week 4 (regulatory submission in the US only).
    - Change in severity of moderate to severe HF from baseline to Week 12 (regulatory submission in the US only).
- Treatment: 120 mg elinzanetant, Placebo
- ICEs: see Table 3–2

Table 3–2 : Primary Estimand: ICEs and Strategies to Address Them

ICEs[a]	Reason for ICE	Strategy	Data handling method
Temporary Treatment interruption[b]	AEs (treatment related/unrelated)	**Treatment policy**	Utilise the collected data after ICE.
	COVID-19 and administrative reasons	**Treatment policy**	Utilise the collected data after ICE.
Permanent discontinuation of randomized treatment	AEs (treatment related/unrelated) or Lack of efficacy		
	For participants who remained untreated/on background therapy.	**Treatment policy**	Utilise the collected data after ICE.
	For participants who initiate alternative VMS treatment	**Treatment policy**	Utilise the collected data after ICE.
	Other treatment-unrelated reasons, including COVID-19	**Treatment policy**	Utilise the collected data after ICE.
Intake of prohibited concomitant medication having impact on efficacy	All reasons	**Treatment policy**	Utilise the collected data after ICE.

AE = Adverse event, COVID-19 = Coronavirus disease of 2019, ICE = Intercurrent event, VMS = Vasomotor symptoms
a) ICEs will be reviewed at the Blinded Review Meeting prior to the study unblinding
b) Definition of temporary treatment interruption:
Week 1 = Treatment taken on <5/7 days during week 1.
Week 4= Treatment taken <80% during weeks 1-4 OR treatment taken on <5/7 days during either week 3 or 4.
Week 12= Treatment taken <80% during weeks 1-12 OR treatment taken on <5/7 days during either week 11 or 12.

- Population level summary:
  - Mean change in frequency of moderate to severe HF from baseline to Week 4 (all regions).
  - Mean change in frequency of moderate to severe HF from baseline to Week 12 (all regions).
  - Mean change in severity of moderate to severe HF from baseline to Week 4 (regulatory submission in the US only).

- Mean change in severity of moderate to severe HF from baseline to Week 12 (regulatory submission in the US only).

The key secondary endpoints will be handled using similar attributes except for the variables and population summary that are listed below:

- Variable:
  - Change in severity of moderate to severe HF from baseline to Week 4 (all regions except regulatory submission in the US)
  - Change in severity of moderate to severe HF from baseline to Week 12 (all regions except regulatory submission in the US)
  - Change in frequency of moderate to severe HF from baseline to Week 1 (all regions)
  - Change in PROMIS SD SF 8b total score from baseline to Week 12 (all regions).
  - Change in MENQOL total score from baseline to Week 12 (all regions).
- Population level summary:
  - Mean change in severity of moderate to severe HF from baseline to Week 4 (all regions except regulatory submission in the US).
  - Mean change in severity of moderate to severe HF from baseline to Week 12 (all regions except regulatory submission in the US).
  - Mean change in frequency of moderate to severe HF from baseline to Week 1 (all regions).
  - Mean change in PROMIS SD SF 8b total score from baseline to Week 12 (all regions).
  - Mean change in MENQOL total score from baseline to Week 12 (all regions).

4. Study Design

4.1 Overall Design

This is a multi-center, multi-country, double-blind, randomized, parallel-group, placebo-controlled, Phase 3 intervention study in post-menopausal women with VMS.

The study includes a wash-out period (if applicable), approximately 6-week screening, a 26-week treatment and a 4-week follow-up period.

Wash-out: After giving informed consent, participants will be withdrawn from prohibited concomitant medications (see Section 10.6) at Pre-SCR visit if needed.

Screening: Screening period starts at SCR-1 Visit. The screening period may also be used to obtain a mammogram, if required.

Randomization: After screening, eligible participants will be randomized into 2 arms, as depicted below.

- elinzanetant 120 mg for 26 weeks
- placebo for 12 weeks, followed by elinzanetant 120 mg for 14 weeks

The randomization will be stratified by region: North America and rest of the world.

Treatment: Participants will receive either 120 mg of elinzanetant, or matching placebo orally once daily. More details are provided in Section 6. Participant feedback surveys will be conducted to evaluate their experience with study assessments and overall satisfaction of participating in the study. These surveys will be conducted at timepoints defined in the SoA, and in addition may be conducted throughout the study. Participants will be required to consent prior to completing any study surveys. Results will be reported separately.

Follow-Up: The treatment phase will be followed by a 4-week safety follow-up period.

4.2 Scientific Rationale for Study Design

A double-blind placebo-controlled design is considered necessary to differentiate drug effects from the natural course of disease, the effects of study participation, and background safety findings. Experience from multiple studies of women with postmenopausal VMS have shown that a placebo response of up to 60% can be expected (Newton et al. 2014). Therefore, comparison to placebo is relevant to describe the true treatment effect of elinzanetant.

Placebo is considered acceptable because post-menopausal VMS are uncomfortable and disruptive to affected individuals, but not life-threatening or life-limiting. The use of placebo is also considered adequate by both the US FDA and EU Committee for Medicinal Products for Human Use (CHMP) disease-specific guidelines (EMA 2005, FDA 2003).

The definitions and clinical outcome assessment strategy of VMS are based on the FDA VMS and Vulvar and Vaginal Atrophy Clinical Evaluation Guidance (FDA 2003), and the CHMP 'Guideline on clinical investigation of medicinal products for hormone replacement therapy of estrogen deficiency symptoms in postmenopausal women'.

4.2.1 Patients' Input into Design

Feedback was collected from patient population through a patient Advisory Board and patient surveys with the intent to:

- Identify potential hurdles to recruitment, adherence with the study procedures, and participant retention
- Confirm the relevance of the investigated endpoints for patients with VMS
- Seek input on the content and visual design of study-related awareness and educational materials

4.3 Justification for Dose

The clinical development program has broadly evaluated doses ranging from 1.5 mg to 300 mg. The free base form of elinzanetant in a soft-gel capsule formulation was evaluated at doses between 25 mg and 160 mg once daily. A dose of 120 mg per day has been shown to be optimal with respect to efficacy, safety and receptor pharmacology.

The 120 mg once daily dose was effective on a range of measures in the SWITCH-1 study and was more effective than the two lower doses studied (40 mg and 80 mg once daily). There was no relevant additional benefit from a higher dose (160 mg once daily).

The plasma concentrations achieved with the 120 mg dose are associated with full occupancy of central NK1 receptors throughout a dose interval at steady state as demonstrated in a human PET study. Although it is not possible to assess NK3 receptor occupancy directly, as a suitable NK3 PET ligand does not exist, the achieved concentrations are also very likely to fully occupy central NK3 receptors. For details, refer to the IB.

4.4 End of Study Definition

The end of the study is defined as the date of the last scheduled visit of the last participant in the study globally.

The primary completion date is the date when the last participant completes Visit T3.

A participant is considered to have completed the study if she has completed all phases of the study including the last visit.

5. Study Population

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion Criteria

Participants are eligible to be included in the study only if all the following criteria apply:

Age

1. Females aged 40 to 65 years, inclusive, at signing of informed consent.

Type of Participant and Disease Characteristics

2. Postmenopausal, defined as:
   a. at least 12 months of spontaneous amenorrhea prior to signing of informed consent, or
   b. at least 6 months of spontaneous amenorrhea prior to signing of informed consent with serum FSH levels > 40 mIU/mL **and** a serum estradiol concentration of < 30 pg/mL, or
   c. at least 6 months after hysterectomy at signing of informed consent with serum FSH levels > 40 mIU/mL[2] **and** a serum estradiol concentration of < 30 pg/mL, or
   d. surgical bilateral oophorectomy with or without hysterectomy at least 6 weeks prior to signing of informed consent.
3. Moderate to severe HF associated with the menopause and seeking treatment for this condition.
4. Negative urine pregnancy test at screening.

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[2] In women between 40 and 50 years of age, who are hysterectomized but who have intact ovaries, a second FSH test should be performed within around 1-3 weeks to confirm the postmenopausal status (second value should also be >40mIU/mL)

5. In good general health, in the opinion of the investigator, based on the medical history, physical examination, 12-lead ECG, vital signs, gynecological ultrasound[3], endometrial biopsy, mammogram, clinical laboratory tests, eC-SSRS, BDI and other assessments completed during screening.
6. Normal or clinically insignificant cervical cytology not requiring further follow-up:
    a. A cervical cytology sample has to be obtained during screening, or
    b. A documented normal result has to be available from cervical cytology conducted within 12 months prior to signing of informed consent.
    c. HPV testing in participants with ASCUS will be used as an adjunctive test automatically. Participants with ASCUS can be included if they are negative for high-risk HPV strains.
    d. HPV testing in participants with "absence of endocervical/transformation zone component" will be used as an adjunctive test automatically. Participants can be included if they are negative for high-risk HPV strains.
7. BMI between 18 and 38 kg/m^2 at screening
8. Participant has a screening mammogram performed, unless she is able to provide a written normal mammogram result obtained no more than 6 months prior to the start of screening.
9. Participant has completed HFDD for at least 11 days during the two weeks preceding baseline visit, and participant has recorded at least 50 moderate or severe HF (including night-time HF) over the last 7 days that the HFDD was completed (assessed at the Baseline Visit).

Informed Consent

10. Capable of giving signed informed consent as described in Section 10.1.5 which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

5.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

1. Any clinically significant prior or ongoing history of arrhythmias, heart block and QT prolongation either determined through clinical history or on ECG evaluation.

[3] Women with an ovarian cyst/cysts that need further diagnostic procedures to rule out the possibility of malignancy during screening should be excluded from participation.

2. Any clinically significant abnormal laboratory test result(s) measured during screening (single re-test allowed, except for tests listed in inclusion criteria 2 and exclusion criteria 10[4]).
3. Any active ongoing condition that could cause difficulty in interpreting VMS such as: infection that could cause pyrexia, pheochromocytoma, carcinoid syndrome.
4. Current or history (except complete remission for 5 years or more) of any malignancy (except basal and squamous cell skin tumours). Women receiving adjuvant endocrine therapy (e.g. tamoxifen, aromatase inhibitors, GnRH analogues) cannot be enrolled in this study.
5. Uncontrolled or treatment-resistant hypertension. Women with mild hypertension can be included in the study if they are medically cleared prior to study participation.[5]
6. Untreated hyperthyroidism or hypothyroidism.
    - Treated hyperthyroidism with no abnormal increase of thyroid function laboratory parameters and no relevant clinical signs for > 6 months before signing of informed consent is acceptable.
    - Treated hypothyroidism with normal thyroid function test results during screening and a stable (for ≥ 3 months before signing of informed consent) dose of replacement therapy is acceptable.
7. Any unexplained post-menopausal uterine bleeding.
8. Clinically relevant abnormal findings on mammogram[6].
9. Renal impairment greater than moderate (i.e. estimated glomerular filtration rate < 30 mL/min/1.73m^2) at screening
10. Abnormal liver parameters (presence of at least one of the following criteria):
    - AST > 2 x ULN
    - ALT > 2 x ULN
    - AP > 2 x ULN
    - TBL > ULN unless explained by Gilbert's syndrome
    - INR > ULN unless explained by, e.g., intake of anticoagulants [4]
    - Diagnosis of hepatitis B infection, i.e., Hbs-antigen positive at screening
    - Diagnosis of hepatitis C infection, i.e., hepatitis C-antibodies and HCV-RNA positive at screening.

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4 Re-test of INR will be allowed once.

5 Hypertension is defined as systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥80 mmHg over three readings on at least two different occasions. "Medically cleared" includes stable disease and compliance with treatment, if the blood pressure is SBP≤139mmHg and DBP≤89mmHg at screening period.

6 Clinically relevant abnormal finding is defined as any finding that requires further follow-up or diagnostic procedures per local guidelines.

11. Disordered proliferative endometrium, endometrial hyperplasia, polyp, or endometrial cancer diagnosed based on endometrial biopsy during screening (see Section 8.2.9)
12. Any other history, condition, therapy, or uncontrolled intercurrent illness which could in the opinion of the investigator affect compliance with study requirements.

Prior/Concomitant Therapy

13. Has used and is unwilling to wash-out use of any of the prohibited concomitant medications, as specified in Section 10.6.
14. Inability to comply with the use of prohibited medications as described in Sections 6.8.1 and 10.6.

Prior/Concurrent Clinical Study Experience

15. Concurrent (or within 2 months prior to signing of ICF) participation in a clinical study with an investigational medicinal product (including medical devices).

Other Exclusions

16. At screening a suicidal ideation in the past 6 months (as indicated by "Yes" on item 4 or item 5 of the suicidal ideation section of the eC-SSRS) or suicidal behavior in the past 6 months (indicated by "Yes" on any item of the suicidal behavior section of the eC-SSRS).
17. Clinically relevant drug or alcohol abuse within 12 months of signing of informed consent[7].
18. Dependent on the investigator, the contract research organisation(s) or Sponsor for education or employment (e.g. family members, employees, people who receive grants/education).
19. Known hypersensitivity to elinzanetant or any of the excipients in the formulation.
20. Inability to comply with the study procedures for any reason, including the following examples: language comprehension, psychiatric illness, general inability to get to the study site.

5.3 Lifestyle Considerations

No restrictions to lifestyle are required.

[7] Clinically relevant alcohol or drug abuse is behavior that meets the DSM-5 criteria for substance use disorder (DSM-5:Diagnostic and Statistical Manual of Mental Disorders).

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, date of informed consent, date of last visit, screen failure details, history of menopause hormone therapy, and eligibility criteria based on completed procedures.

Re-screening is allowed once only. Re-screening can be performed in the following case:

- If the inclusion/exclusion criteria, including related footnotes, preventing participant's initial attempt to participate have been changed via a protocol amendment.

The investigator should ensure that the repeated screening procedures do not expose the participant to an unjustifiable health risk.

The participant must sign a new ICF for re-screening, even if the content was not changed after the previous consenting. Re-screened participant will be assigned a new participant number.

5.5 Criteria for Temporarily Delaying Randomization

If a participant is otherwise eligible, acute intercurrent conditions (e.g. current febrile illness, quarantine for suspicion of COVID-19) may allow to postpone start of study intervention in a participant to a time when the condition has resolved.

A delayed assessment or report of procedures required for assessment of eligibility (e.g. ECG, mammogram, endometrial biopsy) would constitute a reason for postponing randomization.

Under these circumstances, the screening period may be extended until these conditions have resolved or the delayed assessment is available.

6. Study Intervention(s) and Concomitant Therapy

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

6.1 Study Intervention(s) Administered

Table 6–1: Study Interventions

Arm name	Elinzanetant	Placebo
Intervention Name	BAY 3427080 / elinzanetant	Placebo
Type	Drug	N/A
Dose Formulation	soft gel capsule	soft gel capsule
Unit Dose Strength(s)	60 mg	N/A
Dosage Level(s)	two capsules daily (120 mg)	two capsules daily
Route of Administration	oral	oral
Use	experimental	placebo
Packaging and Labeling	Study Intervention will be provided in an Alu-Alu blister with 12 soft gel capsules. 5 blisters will be placed into 1 box containing capsules for treatment of one month. Each box will be labeled as required per country requirement	
Current name	BAY 3427080	N/A
Former Name	NT-814	

Alu = Aluminium; N/A = Not applicable

Study intervention will be dispensed at the study visits summarized in the SoA.

The first dose should be taken supervised during the Baseline Visit on the day of randomization. In general, study treatment will be taken once daily before going to bed in all treatment arms, with or without food. For requirements on drug intake for PK sampling, please refer to section 1.3.3.

If a participant forgets to take a dose in the evening, then the dose can be taken at any time up to 2 AM the same night. After this time, the dose should not be taken and will be considered a missed dose.

Returned study intervention may not be re-dispensed to a different participant.

6.2 Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
2. Only participants randomized in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
3. The investigator or the head of the institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records). Drug returns, accountability, reconciliation and destruction return information will be captured in IxRS.
4. Further guidance and information for the final disposition of unused study interventions are provided in Investigator Site File.

5. Interim pick-up appointments may be introduced to allow for monthly in person dispense in accordance with Sponsor, if needed. Where DtP distribution of study intervention occurs at selected sites and visits, the investigator delegates distribution responsibility to the sponsor. The investigator maintains responsibility and control for dispensing via IxRS by confirming whether or not DtP distribution of study intervention can be triggered. The sponsor contracts a distribution provider to conduct DtP distribution of study intervention including the delegation of storage and handling as needed until handover to the participant.

Local destruction (if any) of the study drug must be properly documented consistent with the sponsor's agreed and specified procedures. Written instructions on medication destruction will be made available to affected parties as applicable.

6.3 Measures to Minimize Bias: Randomization and Blinding

Participants who meet all eligibility criteria will be centrally assigned to randomized study intervention using IxRS. Before the study is initiated, the log in information and directions for the IxRS will be provided to each site. The randomization schedule will be computer generated by the sponsor or delegate. Once a randomization number has been assigned it must not be re-assigned.

Participants will be randomly assigned to receive study intervention as described in Section 9.2. Investigators will remain blinded to each participant's assigned study intervention throughout the course of the study.

Unblinding

The IxRS will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the responsibility for determining if unblinding of a participant's intervention assignment is warranted.

If the investigator is unavailable, and a treating physician not associated with the study requests emergency unblinding, the emergency unblinding requests are forwarded to the emergency medical advice 24 hours/7-day service. Participant safety must always be the first consideration in making such a determination.

If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the sponsor prior to unblinding a participant's intervention assignment unless this could delay emergency treatment of the participant.

If a participant's intervention assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and case report form, as applicable.

In case of unblinding, only those individuals who are required to know treatment allocation may be given this information. All others must remain blinded to treatment, including the participant.

Pharmacometrics staff may be unblinded according to Bayer standard operating procedures. Pharmacokinetic and exposure-response analysis might be performed using population approaches (popPK and popPK/PD, e.g., by non-linear mixed effect modeling). Analysis and report will be done under a separate cover. This evaluation might be started prior to database lock. If this is applicable, appropriate measures will be taken to maintain blinding of the study

team, e.g., data will be stored separately, and members of the study team will neither have access to the randomization list nor to individual data.

Sponsor global pharmacovigilance staff may unblind the intervention assignment for any participant with an SAE/SUSAR. If the SAE/SUSAR requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the report, identifying the participant's intervention assignment, may be sent to investigators in accordance with local regulations and/or sponsor policy.

An independent data analysis center will provide unblinded safety data to the independent Data Safety Monitoring Board.

6.4 Study Intervention Compliance

When participants self-administer study intervention(s) at home, compliance with study intervention will be assessed at each visit. Compliance will be assessed by review of daily diary entries and confirmatory capsule counts during study visits and documented in the source documents and relevant form. Deviation(s) from the prescribed dosage regimen should be recorded.

A record of the quantity of study intervention dispensed to and administered by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays will also be recorded. If the participant is unable to continue taking the study intervention as required, she should contact the study site.

Study drug intake documenting

Participants will document the number of study medication capsules taken, together with the HFDD evening diary once daily at bedtime using the 'Study drug intake documentation' on the electronic hand-held device during the treatment period as indicated in the SoA.

6.5 Dose Modification

Not applicable, all participants receiving active treatment will stay on the same dose.

6.6 Continued Access to Study Intervention after the End of the Study

No access to study intervention is planned after the end of the study.

6.7 Treatment of Overdose

For this study, any dose of elinzanetant greater than 240 mg within a 24-hour time period will be considered an overdose.

There is no known specific treatment (no antidote) for an overdose with elinzanetant. An overdose should be treated as clinically indicated based on signs and symptoms.

Overdose *per se* will not be reported as an AE and/or SAE unless it is associated with clinically relevant signs and/or symptoms, or an intentional overdose taken with possible suicidal and/or self-harming intent (see Sections 10.3.1 and 10.3.2).

In the event of an overdose, the investigator should:

- Contact the Sponsor immediately.

- Evaluate the participant to determine, in consultation with the Medical Monitor, whether study intervention should be interrupted or whether the dose should be reduced.
- Closely monitor the participant for any AE/SAE and laboratory abnormalities until stabilization and/or resolution.
- Obtain a plasma sample for PK analysis as soon as possible from the date of the last dose of study intervention if requested by the Medical Monitor (determined on a case-by-case basis).
- Document the quantity of the excess dose as well as the duration of the overdose in the eCRF.

Decisions regarding dose interruptions will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

6.8 Concomitant Therapy

Any medications (including over-the-counter or prescription medicines, contrast media, vaccines), vitamins and/or herbal supplements that the participant uses during the study participation must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.8.1 Prohibited concomitant medications

Section 10.6 presents a comprehensive (but not exhaustive) list of prohibited concomitant medications (recently approved drugs may not be included in the list and should be checked on a case-by-case basis). The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.8.2 Other Treatment Considerations

Based on preclinical data, an increase in exposure of drugs that are sensitive substrates of OATP1B1/1B3, P-gp or BCRP during co-administration of elinzanetant due to inhibition of those transporters by elinzanetant could not be excluded. Results from a clinical drug-drug interaction study with the BCRP and OATP1B1/B3 substrate rosuvastatin showed no clinically relevant effect on the pharmacokinetics of rosuvastatin when administered together with elinzanetant. Therefore, medications that are substrates of BCRP and/or OATP1B1/1B3 can be administered together with elinzanetant without restrictions.

In the absence of clinical drug-drug interaction data with P-gp substrates including but not limited to fexofenadine, dabigatran, digoxin, the following precautionary measures have to be implemented:

Participants receiving a combination of elinzanetant and P-gp substrates should be closely monitored for signs and symptoms of adverse events due to increased exposure of the co-administered P-gp substrate. Dose modification of sensitive P-gp substrates should be considered based on the prescriber information or such compounds should be avoided.

Vitamin D and calcium supplements

Postmenopausal women should take sufficient Vitamin D and Calcium (e.g. by food or supplement intake). 400 IU vitamin D, along with 500 mg to 1000 mg of calcium daily during the study period is considered sufficient. Investigators and study coordinators will be trained on the importance of vitamin D and calcium use. Participants will be counseled at every visit on the importance of taking vitamin D and calcium during the treatment period. If necessary, the dose of calcium or vitamin D supplementation may be modified or discontinued at the discretion of the investigator. The intake of vitamin D and calcium should be documented on the concomitant medication eCRF throughout the study.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

7.1 Discontinuation of Study Intervention

It may be necessary for a participant to permanently discontinue study intervention. If study intervention is permanently discontinued prior to Visit T3, the participant will be asked to remain in the study without receiving the study intervention until Visit T3 has been reached. As a general rule, all procedures scheduled for the end-of-treatment visit should be performed at the time of premature discontinuation of study intervention and documented. In case this is considered not medically appropriate for certain procedures (e.g. for invasive procedures if only short time has elapsed since the last scheduled assessment) this should be documented by the investigator. All scheduled study visits and procedures, except for study intervention, should continue if agreed by the participant. PK sampling is also not required. For participants who agree to continue in the study, any medication used after discontinuation of study intervention must be documented.

See the SoA for data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed.

For withdrawal from study see Section 7.2.

7.1.1 Liver Chemistry Stopping Criteria

Discontinuation of study intervention for abnormal liver tests is required by the investigator when a participant meets one of the conditions outlined in Section 10.5 or in the presence of abnormal liver chemistries not meeting protocol-specified stopping rules if the investigator believes that it is in best interest of the participant. See Section 10.5 for further details.

7.1.2 Platelet count Stopping Criteria

In the case of platelet counts below 50,000/mm^3, study intervention must be discontinued immediately. In the case of platelet counts between 50,000/mm^3 and 75,000/mm^3, a retest should be performed within 72 hours of the initial test results. If values do not normalize within 7 days, study intervention must be discontinued.

7.1.3 Temporary Discontinuation

In the event that a participant experiences an AE which the investigator believes is treatment related and which the participant finds intolerable, a break in dosing of up to one week is permitted. If, on reintroduction of the study medication, the AE recurs and remains intolerable, the study drug will be permanently withdrawn. A break in dosing will not result in extension of the overall dosing period.

Temporary discontinuation is also allowed in the following two cases:

- Temporary discontinuation of study intervention for an intercurrent illness, at the discretion of the investigator.
- In the event of a trial-continuity issue (e.g. caused by a pandemic), the sponsor may provide additional guidance in study-specific communication.

7.1.4 Rechallenge

Study intervention may be restarted after a temporary interruption if deemed clinically appropriate by the investigator in collaboration with the Sponsor's Medical Monitor.

7.1.4.1 Study Intervention Restart or Rechallenge After Liver Stopping Criteria Met

Study intervention restart or rechallenge after liver chemistry stopping criteria are met by any participant in this study is not allowed.

7.2 Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time at her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, or compliance reasons.
  - If a participant is tested positive for SARS-CoV-2 infection while on study, the investigator will have to decide whether staying in the study is compatible with participant and site personnel safety and wellbeing. In most cases, temporary discontinuation (see section 7.1.3) may be an appropriate solution. The decision should also take into account possible interaction between the study intervention and potential treatment for SARS-CoV-2 infection.
- At the time of discontinuing from the study, if possible, End of Treatment visit procedures should be conducted, followed by FU visit as shown in the SoA and in particular described in footnote a) in Table 1–2.
  - Participants who have been randomized but not yet started study intervention do not need to undergo further study procedures other than return of supplies, before their study participation terminates.
  - For withdrawal during the follow-up period, the participant should undergo the assessments scheduled for the next visit (FU Visit)
- The participant will be permanently discontinued both from the study intervention and from the study at that time.

- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

For withdrawal from study intervention see Section 7.1

7.3 Lost to Follow Up

A participant will be considered lost to follow-up if she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, she will be considered to have withdrawn from the study.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix 1.

8. Study Assessments and Procedures

- Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (e.g., cervical smear or mammogram) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.
- Laboratory/analyte results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.

- In the event of a significant trial-continuity issue (e.g. caused by a pandemic), alternate strategies for participant visits, assessments, medication distribution and monitoring may be implemented by the sponsor or the investigator, as per local health authority / ethics requirements.

8.1 Efficacy Assessments

In this clinical trial, efficacy will be assessed using clinical outcome assessments. As these are responded to by the study participants themselves, they are considered PROs. The PROs used in the study are described in Section 8.1.1.

Planned time points for all efficacy assessments are provided in the SoA.

8.1.1 Electronic Participant-Reported Outcomes (ePROs)

During the study visits, ePROs are to be completed prior to any other procedure. An ePRO is an electronically applied measurement based on a report that comes directly from the participant about the status of the participant's health condition without interpretation of the response by a clinician or anyone else. In this trial ePROs will be used for the assessment of different endpoints. These endpoints will be collected using an electronic participant hand-held device during the entire study duration both for entries at home (including days of the study visits), and at study visits at the study site, as indicated in the SoA. Additionally, data will be collected on tablet computers which will be used by the participants during the study visits at the study sites. Web-based back-up versions may be applied in addition.

ePROs collected on the participant's hand-held device

The following ePROs will be collected on a hand-held device in the following sequence:

- Morning HFDD
- PROMIS SD SF 8b
- ISI
- MENQOL
- BDI-II
- EQ-5D-5L
- PGI-S and PGI-C
- Evening HFDD
- Sleepiness Scale (See Section 8.2.10)
- Study drug intake documentation (See Section 6.4)

After BL visit up to Visit T3 (inclusive) PROMIS SD SF 8b, ISI, MENQOL, BDI-II, EQ-5D-5L, PGI-S and PGI-C will be open for completion by the participant at pre-defined days in the study, as roughly reflected in the SoA. Exact days will be described in a participant guidance document. From Visit T4 onwards these ePROs will be completed by the participant during the study visits.

ePRO collected on a tablet computer at the study sites

The following ePRO will be collected on a tablet computer:

- eC-SSRS (See Section 8.2.11)

Time for completion

Time for completion of each item of the different ePROs is conservatively estimated with approximately 30 seconds per individual item. The daily completion time, therefore, ranges from approximately 5 min during normal days during the study without study visits to a maximum of 47 min on the days of the study visits when all/most questionnaires are to be completed.

Data entry into the electronic devices during the visits at the study sites must be performed prior to any other study related activity.

Dispense of the participant's hand-held device, data entry and transmission

The device will be dispensed at the time point specified in the SoA.

The specific time window for data entry into the participant hand-held device is ePRO-specifically technically regulated and alarms will be set as appropriate to remind the participant to complete the ePROs respectively. The participants will be asked to fill in the questionnaires at specified time intervals as detailed in the SoA.

Participants' data entries from the hand-held device will be transmitted automatically by wireless connection to the electronic diary provider's database and later by the vendor to Sponsor's Data Management. Automatic continuous checking of the data transfer will be performed, and completeness of diary entries will be monitored, so that a failure to make entries is detected by the data-logging system and a warning will be sent to the study site. The ePRO device will be returned to the site when a participant leaves the study.

Training of participants

During screening, participants will be trained on the use of the hand-held device and tablet computer. Retraining will be performed as needed during the course of the study. The participants will be asked to confirm their understanding on the use of the device and completion of the ePRO before data entry on the hand-held device / the tablet computer is activated. Participants will be educated regarding the importance of their timely and accurate completion of the ePROs during all study visits. The participants will be instructed to complete the ePROs on their own without any input from others at the pre-specified timepoints, in a quiet place in one sitting, following the instructions on the ePROs.

Ongoing technical support during the entire study duration will be provided by the study site staff to prevent missing data entry to the extent possible. Beyond this technical support, no other help should be given to participants regarding the completion of the ePROs at home and at the study site.

Training of and by study site staff, 24-hour help desk

The study site staff will be instructed to explain the importance of completing the ePROs to the participants.

The study site staff will be trained regarding the use of the participant hand-held device and the tablet computer at the site, and in resolving technical issues with these devices during the Investigator Meeting and site initiation process. Educational material will be available in the ePRO portal and the Investigator Site File. The study site staff will provide a standardized technical training on the handling of the participant hand-held device and the tablet computer to the participants during SCR-2, and retraining will be performed as needed during the course of the trial. The study site staff will assist the participants in case of any technical queries during the entire study duration.

In addition to the technical support by the study site staff, a 24-hour help desk by the ePRO provider will be available during the entire study duration to respond to urgent technical questions.

Measures to further prevent missing participants' hand-held device entries

In case one entry on the HFDD, the Sleepiness Scale or the study intervention intake documentation was missed (for morning diaries in case this was not completed when getting up in the morning; for evening diaries, Sleepiness Scale and the study intervention intake documentation in case this was not completed in the evening when going to bed), retrospective data entry is possible for a limited time. For the morning diary these retrospective entries will be allowed on the same day between 11:00AM and 11:59PM. For the evening diary, the Sleepiness Scale and the Study intervention intake documentation, the entry option will be available between midnight until 10:59AM on the day after the missed entry.

When the study site becomes aware of missing participant hand-held device entries, the study site staff will contact the participant who have missed a defined number of consecutive entries (provided separately) immediately, and ask for reasons for failure in data entry and transfer. The study site staff will remind the participants of the importance of the twice daily eDiary entry.

Further to the automatic continuous checking of completeness of the participant hand-held device entries, at all the study visits following SCR-2, the participant hand-held device entries will be checked, and the checks documented by the study site personnel for completeness.

8.1.1.1 Hot Flash Daily Diary (HFDD)

Participants' assessments of HF will be recorded electronically twice daily using the Sponsor developed HFDD. Following the assessment schedule indicated in the SoA, the HFDD will be completed in the morning after waking up (morning diary) and each evening at bedtime (evening diary) on the hand-held device. The HFDD items assess the number of mild, moderate, and severe HF experienced during the day and during the night. In addition, the number of awakenings during the night and disturbance of sleep due to HF will be documented in the morning diary.

Mild HF are defined as a "sensation of heat without sweating", moderate HF are defined as a "sensation of heat with sweating, but able to continue activity", and severe HF are defined as a "sensation of heat with sweating, causing cessation (stopping) of activity". For information on assessment of eligibility and efficacy with HFDD see Section 10.8.1.

8.1.1.2 Patient-reported Outcomes Measurement Information System Sleep Disturbance Short Form 8b (PROMIS SD SF 8b)

The PROMIS SD SF 8b includes 8 items assessing sleep disturbance over the past 7 days (Yu et al. 2011). Items assess sleep quality, sleep depth and restoration associated with sleep, perceived difficulties with getting to sleep or staying asleep and perceptions of the adequacy of and satisfaction with sleep. Participants respond to the items on a 5-point scale from not at all, never or very poor to very much, always or very good. Four of the items are scored reversely. Total scores range from 8 to 40, with higher scores indicating greater severity of sleep disturbance. The individual items for a respondent can be summed and raw scores can be converted into T-scores for comparison with population norms.

In this study the PROMIS SD SF 8b will be applied electronically and responded to by the participants at home and during selected in person visits using the hand-held device at the timepoints indicated in the SoA.

For information on assessment and validity of PROMIS SD SF 8b see Section 10.8.2.

8.1.1.3 Menopause Specific Quality of Life Scale (MENQOL)

The MENQOL questionnaire is comprised of 29 items assessing the presence of menopausal symptoms and the impact of menopause on health-related quality of life over the past week (Hilditch et al. 2008). The items assess four domains of symptoms and functioning: VMS, psychosocial functioning, physical functioning, and sexual functioning. For each item, the participant indicates if they have experienced the symptom (yes/no). If they select yes, they rate how bothered they were by the symptom using a six-point verbal descriptor scale, with response options ranging from 0 'not at all bothered' to 6 'extremely bothered'.

Based on the individual responses, item scores, domain scores, and a total MENQOL score are calculated. Each score ranges from 1-8, higher scores indicate greater bother. For the converted score see Section 10.8.3

In this study the MENQOL will be applied electronically and responded to by the participants at home and during selected in person visits at timepoints indicated in the SoA.

8.1.1.4 Patient Global Impression of Severity (PGI-S) and Change (PGI-C)

The PGI-S includes 3 items assessing the frequency of moderate to severe HF, the severity of HF, and the severity of sleep problems using a 5-point response scale (No HF to Very Often for the frequency item; No HF/sleep problems to Very severe for severity items). The recall period for the PGI-S items is “the past 7 days”. Each item is scored independently.

The PGI-C includes 3 items assessing change in frequency of HF, change in the severity of HF, and change in the severity of sleep problems since the participant started taking the study medication. A 5-point response scale is used ranging from e.g. ‘much less’ to ‘much more’ for the change in frequency item and ‘much better’ to ‘much worse’ for change in severity and sleep problems. Each item is scored independently.

Both instruments, the PGI-S and the PGI-C are self-invented by the sponsor with the objective to serve as reference measures for the planned psychometric analysis of the HFDD, the PROMIS SD SF 8b and the MENQOL using data from this study. Psychometric analysis will be detailed and reported separately.

In this study the PGI-S and PGI-C will be applied electronically and responded to by the participants at home and during selected in person visits at timepoints indicated in the SoA.

8.1.1.5 European Quality of Life 5-dimension 5-level questionnaire (EQ-5D-5L)

The EQ-5D-5L is a self-administered preference-based generic measure of health status which includes five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. For the EQ-5D-5L descriptive system, participants provide a rating for each question on a five-point Likert scale: having no problems, having slight problems, having moderate problems, having severe problems and being unable to do/having extreme problems. In addition, patients are asked to self-rate their own health today on a vertical 0-100 unit visual analogue scale (VAS), with 0 corresponding to "the worst health you can imagine", and 100 corresponding to "the best health you can imagine".

In this study the EQ-5D-5L will be applied electronically and responded to by the participants at home and during selected in person visits at the timepoints indicated in the SoA.

8.1.1.6 Insomnia Severity Index (ISI)

The ISI is a seven item instrument that quantifies the participant perception of insomnia severity, along with the impact of insomnia on daytime functioning in adults in the last two weeks (Bastien et al. 2001). The items refer to: severity of sleep onset, sleep maintenance and early morning wakening problems, satisfaction with sleep pattern, noticeability of sleep problems by others, distress caused by the sleep difficulties and interference of sleep difficulties with daytime functioning. It is scored on a five point Likert scale from 0 to 4 depending on the item (0=’none’, 4=’very severe’ (Items 1-3); 0=’very satisfied’, 4=’very dissatisfied (Item 4)’; 0=’not at all noticeable’, 4=’very much noticeable’ (Item 5); 0=’not at all worried’, and 4=’very much worried’ (Item 6); 0=’not at all interfering’, 4=’very much interfering’ (Item 7). The scores for each item are summed to produce the total score (maximum 28).

Total score categories:

0–7 = No clinically significant insomnia

8–14 = Subthreshold insomnia

15–21 = Clinical insomnia (moderate severity)

22–28 = Clinical insomnia (severe)

In this study the ISI will be applied electronically and responded to by the participants at home and during selected in person visits at timepoints indicated in the SoA.

8.1.1.7 Beck Depression Inventory (BDI-II)

The BDI-II is an established and widely used measure for assessment of depression. Additionally, it provides conceptual coverage and some concepts in the emotional experience of postmenopausal women.

The BDI-II consists of 21 items to assess the severity of depression over the past 2 weeks (Beck et al. 1996). Each item is a list of four statements arranged in increasing levels of severity about a particular symptom of depression. Items use a 4-point verbal response scale ranging from 0 (not at all) to 3 (extreme form of each symptom); specific response options are tailored to the aspect of depression being measured in each item. A total score ranging from 0 to 63 is calculated with scores of 0-13 indicating mild minimal range, 14 – 19 mild depression, 20 – 28 indicating moderate and 29 – 63 severe depression (higher score = greater depression).

A BDI score of more than 19 during screening should be reported as "Depression" in the medical history of the participant or as AE if reported thereafter. The investigator will receive an email notification if a BDI of >19 is reported. The participant can be enrolled in the study when in the opinion of the investigator the depression does not affect compliance with study requirements. In addition, any depression should be treated according local clinical practice.

In this study the BDI-II will be applied electronically and responded to by the participants at home and during selected in person visits at timepoints indicated in the SoA.

8.2 Safety Assessments

Planned time points for all safety assessments are provided in the SoA.

8.2.1 Physical Examinations

- A complete physical examination will be performed at visits indicated in the SoA. It will include, at a minimum, gynecological examination, and assessments of the Cardiovascular, Respiratory, Gastrointestinal and Neurological systems. Gynecological examination is to be done according to local guidelines/common clinical practice.
- A symptom-based physical examination will be performed as indicated in the SoA, in a response to new symptoms, or changes in symptoms.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.
- Height will be measured at screening only.
- Weight, hip and waist circumference will be recorded at visits indicated in the SoA.
- Abnormal physical examination findings, including overweight/obesity when BMI > 30, are to be recorded either as medical history or as adverse events.

8.2.2 Vital Signs

- Pulse rate, and systolic and diastolic blood pressure will be assessed.
- Vital signs measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (e.g., television, cell phones).
- Vital signs should be taken before blood collection for laboratory tests.

- Blood pressure and pulse rate measurements will be assessed once in a sitting position with a completely automated device. Manual techniques will be used only if an automated device is not available.
- In case of abnormal results, repeat measurements should be performed to adequately document potential findings, e.g. hypertension.[8]

8.2.3 Electrocardiograms

- ECGs should be obtained using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals according to Bazett's formula and/or Fridericia's formula.
- A single 12-lead ECG will be obtained for eligibility check only at screening. If clinically indicated, unscheduled 12-lead ECGs can be performed at any point during the study. Unscheduled ECGs must be recorded in the eCRF.
- The interpretation of the tracing must be made locally by a qualified physician.
- Each ECG tracing should be labeled with the study number, participant number, and date and kept in the source documents at the study site.
- Clinically relevant abnormalities should be reported as AEs as appropriate (e.g. new onset atrial fibrillation).

8.2.4 Clinical Safety Laboratory Assessments

- See Section 10.2 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.
- The investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory reports must be filed with the source documents.
- Abnormal laboratory findings associated with the underlying disease are not considered clinically significant unless judged by the investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 7 days after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or the medical monitor.
    - If clinically significant values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified, and the sponsor notified.
    - All protocol-required laboratory tests, as defined in Section 10.2, must be conducted in accordance with the laboratory manual and the SoA.

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[8] Hypertension is defined as systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥80 mmHg over three readings on at least two different occasions.

- If laboratory values from non-protocol specified laboratory tests performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (e.g., SAE or AE or dose interruption), then the results must be recorded according to the eCRF completion guideline.

8.2.5 Pregnancy Testing

None of the participants of the study are women of childbearing potential. Nevertheless, a pregnancy test will be performed to confirm eligibility in all participants except those who have undergone total hysterectomy and/or bilateral oophorectomy.

8.2.6 Mammogram

Mammogram will be performed at timepoints indicated in Section 1.3.

- Prior mammogram results may be used for eligibility if obtained no more than 6 months prior to start of screening. Women with bilateral mastectomy do not have to provide a mammogram provided that all breast tissue has been removed.
- At end of treatment, a mammogram should be performed if the time that has elapsed since the previous mammogram is in line with local medical guidelines for the frequency of mammograms in the respective age group.
- In case a non-study mammogram was conducted during the time of study participation, the result should be documented.
- Since unilateral axillary lymphadenopathy is a frequent mild side effect of COVID-19 vaccination, it is recommended to perform the mammogram at the screening visit prior to any planned Covid-19 vaccination or to delay the screening visit for a certain period according to local guidance. In addition, it is recommended to schedule a COVID-19 vaccination after the EoT mammogram (if a mammogram is required, see above).

8.2.7 Transvaginal ultrasound (TVU)

- Ultrasound examination should be performed, by a physician/examiner well experienced in gynecology or with corresponding qualification based on local clinical practice. TVU is not required in participants who had both a total hysterectomy and a bilateral salpingo-oophorectomy.
- The following safety parameters will be measured and recorded:
  - Endometrial thickness (measured in the medio-sagittal section as double-layer in millimeters)
  - Overall safety assessment of the pelvic organs, especially for evaluation of the uterus, ovaries (including diameters as well as details of cyst like structures, if applicable) and fallopian tubes (abnormalities to be reported as AE/SAE)
- In case of any suspicious finding, further diagnostic investigations should be performed at the discretion of the investigator.

- The minimum documentation will include printouts and/or electronic format with images from the ultrasound machine showing the endometrium in sagittal section and both ovaries. The images have to be labeled unambiguously, containing at least the study number, participant number, time point, endometrial thickness, and laterality (left/right) for ovaries. If the printouts are on thermo-sensitive paper, they need to be copied as they will fade over time.

8.2.8 Cervical cytology

- Cervical smear will only be performed before randomization to ensure eligibility and is not a safety endpoint.
- Cervical smear will be performed only if the participant has an intact cervix.
- Cervical smear performed during the last 12 months prior to signing of informed consent can be used for the screening assessment.
- Participants with ASCUS are eligible for the study if they have negative result for high-risk HPV strains from an HPV deoxyribonucleic acid test.
- Cervical smear can be repeated once in case of insufficient material in the sample.
- If cervical smear and endometrial biopsy are scheduled for the same day, cervical smear should be conducted first.

8.2.9 Endometrial biopsy

Timing and sampling of endometrial biopsy

- Endometrial biopsy is to be performed only when applicable (i.e. women with intact uterus) at timepoints indicated in the SoA. All endometrial biopsies must be collected by qualified personnel.
- Each participant should have an endometrial biopsy with a normal result (disordered proliferative endometrium, hyperplasia, polyp and malignant findings will be considered as abnormal) documented at screening.
- If postmenopausal status has not been confirmed prior to the endometrial biopsy, a urine pregnancy test and a transvaginal ultrasound must be performed before conducting the biopsy.
- If a cervical smear sample is collected at the same visit, it must be performed before performing the biopsy.
- Unscheduled biopsy should be performed in case of an abnormal finding in the TVU and/or if the participant has experienced post-menopausal bleeding during the study.
- The sterilized, disposable device Pipelle de Cornier will be used – a flexible and transparent polypropylene sheath with an internal plunger for aspiration. This device allows for gentle tissue sampling, without hysteroscopy, and generally requires no local anesthesia or cervical dilatation.

- If necessary for pain prophylaxis or relief relating to the endometrial biopsy procedure, the use of an analgesic is permitted and will be documented as concomitant medication.

Assessment of endometrial biopsies

All biopsy samples will be processed via the central laboratory and will be evaluated independently by three pathologists who are blinded with regard to treatment assignment.

If the baseline biopsy is interpreted by at least one of the reviewing pathologists to contain findings that constitute an exclusion criterion, the participant must be excluded from the study. Details can be found in the Operational Manual for Pathology Reads.

Study sites will be informed about the individual diagnoses of the three pathologists to allow for clinical follow-up.

In case a sample is considered "not evaluable" by two or more of the pathologists, a repeat sample will be requested by the central laboratory.

- At screening, an evaluable sample is required for inclusion. Women with a diagnosis of disordered proliferative endometrium, endometrial hyperplasia, polyp, or malignant neoplasm by any of the three pathologists will not be included.
- At end-of-treatment, the requirement for a repeat biopsy after a non-evaluable sample is at the discretion of the investigator. The decision should take into account endometrial thickness and clinical findings.

8.2.10 Sleepiness Scale

The sleepiness scale is a Sponsor developed questionnaire containing 3 items assessing the degree of sleepiness experienced by the participant in the morning, in the afternoon and in the evening of the same day. The Sleepiness Scale will be assessed together with the HFDD evening diary at bedtime during selected time periods, using the electronic hand-held device. In case one entry on the Sleepiness Scale was missed, retrospective data entry is possible for a pre-defined period of time (see Section 8.1.1, subsection "Measures to further prevent missing participants' hand-held device entries").

Participants respond to the items using a 5-point verbal rating scale ("0"=not at all; "4"=very much). For the assessment of sleepiness 7-day averages of daily individual single item scores and 7-day averages of an aggregated overall sleepiness score will be used.

During the screening period assessments will be done daily in the evenings together with the HFDD assessment.

During the treatment period the assessments will be done on 7 consecutive evenings at timepoints indicated in the SoA.

8.2.11 Suicidal ideation and behavior: Electronic Columbia-Suicide Severity Rating Scale (eC-SSRS)

Suicidal ideation and behavior will be monitored by eC-SSRS questionnaire. Use of the eC-SSRS is required by the US FDA in clinical trials of new compounds with a central mode of action.

The eC-SSRS is a fully structured participant rated questionnaire designed and developed for computer administration. Participants respond to standardized clinical questions presented in a uniform fashion and adhering to the original C-SSRS clinical conventions. The eC-SSRS assesses lifetime suicidality during an initial baseline evaluation, and then prospectively monitors ideations and behaviors at subsequent follow-up assessments. The eC-SSRS assesses the severity and frequency of suicidal ideation and behavior. The information collected in the eC-SSRS is classified into a set of 11 categories for suicidal ideation and suicidal behavior, and self-injurious behavior without suicidal intent.

See Exclusion Criteria 16 for information on when the participant should not be randomized based on suicidal behavior or ideation.

The investigator will receive an email notification if a participant has a "Yes" score on item 4 or item 5 of the suicidal ideation section of the eC-SSRS or "Yes" on any item of the suicidal behavior section. If this happens after randomization, the participant can continue the study at the discretion of the investigator. The investigator has to report this as an adverse event. In addition, any suicidal ideation and/or behavior should be treated according to local clinical practice.

8.3 Adverse Events (AEs), Serious Adverse Events (SAEs) and Other Safety Reporting

The definitions of adverse events (AEs) and serious adverse events (SAEs) can be found in Section 10.3.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up all AEs (see Section 7).

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 10.3.

8.3.1 Time Period and Frequency for Collecting AE and SAE Information

(S)AEs will be collected from the start of study intervention until the last follow-up visit at the time points specified in the SoA (Section 1.3). (S)AEs which are related to protocol-required study procedures (eg, (S)AE related to invasive study procedures) will be recorded as (S)AEs from the signing of the ICF.

Any medical occurrences/conditions that begin in the period between signing ICF and the start of study intervention, and which are not related to a protocol-required study procedure, will be recorded on the Medical History/Current Medical Conditions, not as AEs.

All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours of learning of the event, as indicated in Section 10.3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

8.3.2 Method of Detecting AEs and SAEs

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

8.3.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, and AEs of special interest (as defined in Section 8.3.6), will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Section 10.3.

8.3.4 Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/ IEC, and investigators.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.
- For all studies except those using medical devices, investigator safety reports must be prepared for SUSARs according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

8.3.5 Pregnancy

All the participants will be confirmed with postmenopausal status including hormonal level at baseline. In case of a suspected pregnancy, a pregnancy test should be performed. In the unlikely event of a pregnancy the following applies:

- Details of all pregnancies in participants will be collected after the start of study intervention and until end of Follow-up.

- If a pregnancy is reported, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the pregnancy.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs, and will be reported as such.
- The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate, and the information will be forwarded to the sponsor.
- Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.3.4. While the investigator is not obligated to actively seek this information in former participants, he or she may learn of an SAE through spontaneous reporting.
- Any participant who becomes pregnant while participating in the study will discontinue study intervention or be withdrawn from the study.

See Section 10.4 for details on collection of pregnancy information.

8.3.6 Adverse Events of Special Interest

The following are defined as AESI in this study, if the event takes place after the first intake of study intervention:

- Any condition triggering close liver observation according to Section 10.5.

  Any increase in liver enzymes meeting the following criteria needs to be reported as an adverse event to the sponsor within 24 hours of the investigator's awareness for expedited reporting to the health authorities:

  - ALT and/or AST >8x ULN OR
  - ALT and/or AST >3x ULN with total bilirubin >2x ULN

  The investigator may consider whether the observed increase in liver values would qualify as SAE.
- Somnolence or fatigue: Mild somnolence has been identified as a possible adverse reaction to elinzanetant. Participants will be instructed neither to drive nor operate machinery if they experience somnolence or fatigue. As a precautionary measure, participants are dosed in the evening before going to bed.
- Phototoxicity: A signal with respect to potential phototoxicity warrants monitoring of participants for skin reactions to sunlight. In case such a reaction occurs, exposure to strong sunlight should be avoided.
- Post-menopausal uterine bleeding: Any participants experiencing post-menopausal bleeding after randomization should undergo a transvaginal ultrasound with subsequent investigation and management (including endometrial biopsy, if indicated) according to the investigator's clinical judgement and usual practice (unexplained

post-menopausal bleeding prior to randomization will exclude the participant from the study).

8.4 Pharmacokinetics

Blood samples for measurement of elinzanetant and its main metabolites in plasma for PK are to be collected at the time points given in Table 1–3. The date and time of study drug intake on the previous dosing days prior to the PK sampling as indicated in Table 1–3, the time of the supervised drug intake, and the time of all blood samples are to be documented.

If, for any reason, PK samples are taken outside of the pre-specified time window, the exact time that the sample was taken must be recorded. These time deviations are not to be considered as important deviations.

If a participant discontinues study treatment permanently, no blood sampling for PK is required. PK analyses are based on a population modeling approach. Blood samples are considered valid for the population PK analysis under the following conditions:

- The dose amount and time of drug intake prior to the blood sample is known
- The time of the blood sample collection is known.

The samples are to be collected and processed as described in detail in the respective Sample Handling Sheets as a part of a separate Laboratory manual.

Plasma concentrations of elinzanetant are determined using a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS). Quality control and calibration samples are analyzed concurrently with study samples. The results of calibration samples, quality control samples, and study samples will be reported in the Bioanalytical Reports, which will be included in the Clinical Study Report for this study. A re-opening of the database may become necessary in order to include the results of the PK measurements. In addition, selected metabolites may be quantified in plasma using a validated analytical method and evaluated and reported as described for elinzanetant.

The bioanalyst will be unblinded for analysis of study samples. Placebo samples will not be analyzed.

Plasma concentration information that would unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

Population pharmacokinetic analysis of elinzanetant

Based on the plasma concentrations, the variability in elinzanetant PK will be analyzed using population PK modeling. Optionally, a population PK/PD model could be used to describe the effect of elinzanetant exposure on PD data related to efficacy and safety such as frequency of VMS and endocrine hormone levels. This analysis might start prior to database lock (eg, at the moment that approximately 80% of the expected PK samples have been measured). The final population PK model that will be applied to describe the PK of elinzanetant in the study population may be linked to relevant PD parameters (eg, frequency of VMS, endocrine hormone levels) obtained in this study to investigate the relationship between elinzanetant exposure and response.

Population or nonlinear mixed effects PK models describe the relationship between dose, time, and the elinzanetant plasma drug concentration. A previously developed population PK model for elinzanetant based on Phase 1 and 2 data will be applied to all valid PK samples to evaluate the relationship between variability in PK and covariates, (ie, intrinsic [eg, body weight, race] and extrinsic factors [eg, concomitant medication]) that are of clinical relevance. If necessary, the population PK model will be adapted to adequately fit the data. Individual PK parameters of elinzanetant will be calculated.

A separate Modeling and Simulation (M&S) Analysis Plan, providing details of the model development and evaluation will be provided before the start of the population PK analysis. Evaluation of the data will be presented in a separate M&S Report.

Appropriate measures will be taken to maintain blinding of the study team (eg, data access will be restricted to specific people involved in the analysis and members of the study team will neither have access to the randomization list nor to individual data).

8.5 Genetics

Genetic as well as non-genetic analyses may be part of the biomarker investigations in this study, if approved by local ECs / IRBs and competent authorities.

Pharmacogenetic investigations may be of any kind, except for whole genome sequencing.

8.6 Biomarkers

In this study, genetic as well as non-genetic biomarkers (e.g., related to the mode of action or the safety of the study intervention and similar drugs) may be investigated. This applies to further biomarkers deemed relevant to VMS and associated health problems. These investigations may include e.g., diagnostic, safety, pharmacodynamic, monitoring, or potentially predictive biomarkers.

8.6.1 PD /safety biomarkers from blood

The following table gives an overview on sample types collected:

Sample type	Description
Biomarker plasma	**For PD / safety (optional assessment)**
Biomarker serum	**For PD / safety (optional assessment)**
Biomarker whole blood	**For pharmacogenetics testing**

- **Timing** – see the SoA planned time points of sample collection.
  Sampling time points may also be moved or removed.
- **Sample handling and storage** – details on the collection, processing, shipment and storage of samples will be provided in separate documents (e.g. sample handling sheets or lab manual). Samples may be stored for a maximum of 15 years (or according to local regulations) following the end of the study at a facility selected by the sponsor to enable further analyses.

- **Reporting** – the results of biomarker investigations may be reported separately (e.g. in a biomarker evaluation report).

8.6.2 Functional Biomarkers - Sleep efficiency measurement

As of Amendment 1 sleep quality tracking substudy has been removed from the protocol.

8.7 Immunogenicity Assessments

Not applicable

8.8 Health Economics

Although Health Economics parameters are not evaluated in this study, the EQ-5D-5L will be assessed (see Section 8.1.1.5). The EQ-5D-5L VAS and the single-dimension will be assessed descriptively. A preference weighted or utility score with the aim to support economic models can be calculated in a further step independent of this study, using statistical algorithms producing utility values ranging from dead (0 or depending on the algorithm used lower than 0) to full health (1).

9. Statistical Considerations

9.1 Statistical Hypotheses

The hypotheses for the primary and key secondary efficacy endpoints, are defined as:

H1- H_{01}: $\mu_{1P} \leq \mu_{1V}$ versus H_{11}: $\mu_{1P} > \mu_{1V}$ where μ_{1P} and μ_{1V} stand for the mean change from baseline in the placebo (P) and verum (V) group in HF frequency at week 4.

H2- H_{02}: $\mu_{2P} \leq \mu_{2V}$ versus H_{12}: $\mu_{2P} > \mu_{2V}$ where μ_{2P} and μ_{2V} stand for the mean change from baseline in the placebo (P) and verum (V) group in HF frequency at week 12.

H3- H_{03}: $\mu_{3P} \leq \mu_{3V}$ versus H_{13}: $\mu_{3P} > \mu_{3V}$ where μ_{3P} and μ_{3V} stand for the mean change from baseline in the placebo (P) and verum (V) group in HF severity at week 4.

H4- H_{04}: $\mu_{4P} \leq \mu_{4V}$ versus H_{14}: $\mu_{4P} > \mu_{4V}$ where μ_{4P} and μ_{4V} stand for the mean change from baseline in the placebo (P) and verum (V) group in HF severity at week 12.

H5- H_{05}: $\mu_{5P} \leq \mu_{5V}$ versus H_{15}: $\mu_{5P} > \mu_{5V}$ where μ_{5P} and μ_{5V} stand for the mean change from baseline in the placebo (P) and verum (V) group in PROMIS SD SF 8b at week 12.

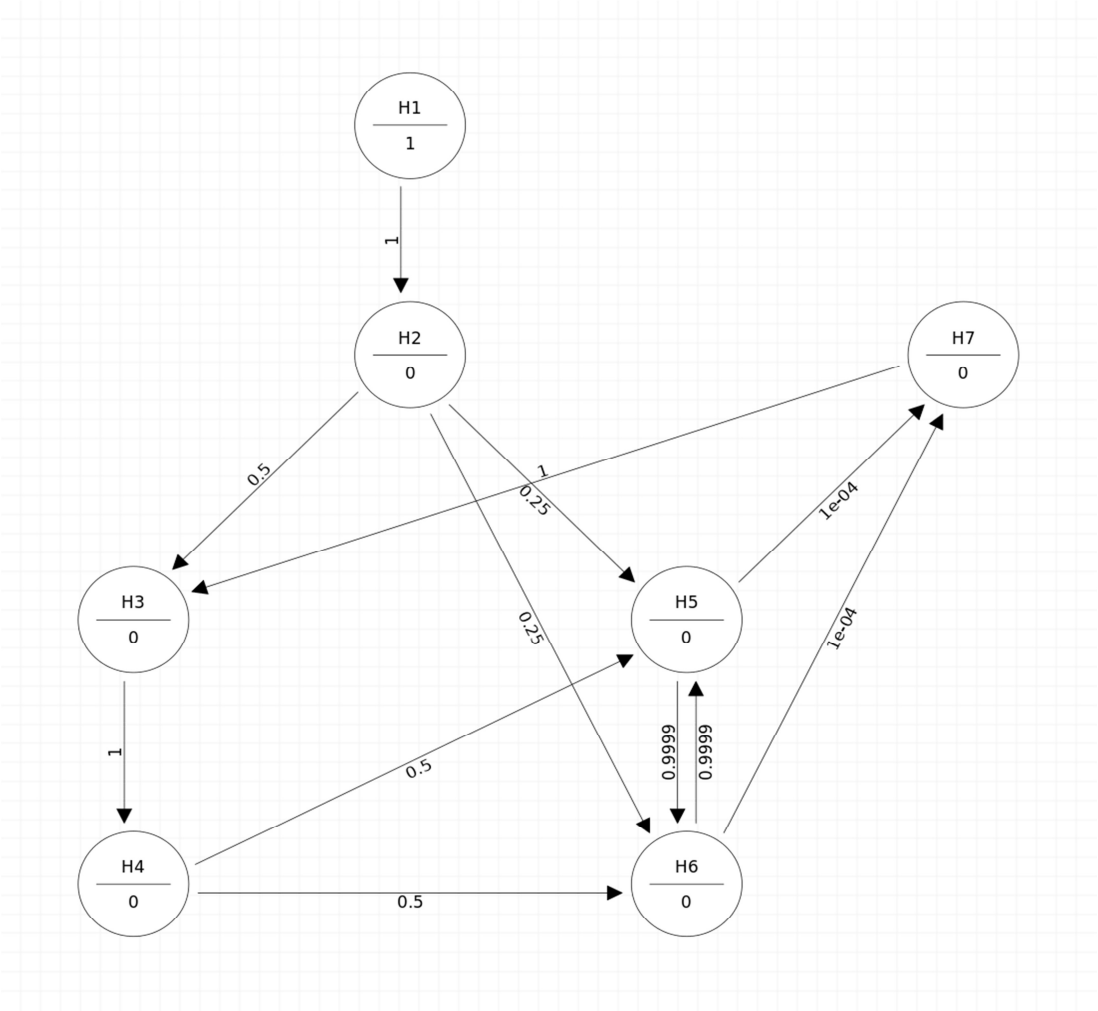
H6- H_{06}: $\mu_{6P} \leq \mu_{6V}$ versus H_{16}: $\mu_{6P} > \mu_{6V}$ where μ_{6P} and μ_{6V} stand for the mean change from baseline in the placebo (P) and verum (V) group in HF frequency at week 1.

H7- H_{07}: $\mu_{7P} \leq \mu_{7V}$ versus H_{17}: $\mu_{7P} > \mu_{7V}$ where μ_{7P} and μ_{7V} stand for the mean change from baseline in the placebo (P) and verum (V) group in MENQOL at week 12.

The data collected after Week 12 will be summarized in a descriptive manner.

A multiplicity adjustment strategy is defined in this trial using the graphical method (Bretz et al. 2009). The multiplicity adjustment strategy controls the overall Type I error rate at a one-sided $\alpha = 0.025$ level under any joint distribution of the test statistics corresponding to the above listed null hypotheses. The testing strategy for the seven null hypotheses is depicted in Figure 9–1.

Figure 9–1: Testing strategy for the seven hypotheses



The testing of the hypotheses will stop if the null hypothesis for either of the primary endpoints on the frequency of VMS at Week 4 or 12 (H1 & H2) is not rejected. Given successful rejection of the first two primary endpoints at α, a weighted version of the Holm test will be applied to the significance level for the remaining hypotheses. H3 and H4 as the second important hypotheses are weighted as 0.5 in the testing strategy and will be sequentially tested in the second stage at $\alpha/2$. H5 & H6 were considered equally important and weighted at 0.25 each. H7 will be tested last only if H5 and H6 are successfully rejected. The level of significance for H5, H6, H7 depends on the outcome of the test for H3 & H4.

9.2 Sample Size Determination

A total of 370 participants (185 per arm) will be randomized in a 1:1 ratio to both arms. Assuming a drop-out rate of 10 % in the first 3 months, this will result in approximately 332 evaluable participants (166 per arm), who completed 12 weeks of treatment. The drop-out rate in months 4-6 is also expected to be 10 %, which will result in approximately 298 participants (149 per arm), who completed 6 months of treatment.

Non-evaluable participants are defined as participants that do not contribute data for the efficacy analysis, for example due to missing baseline information or due to missing weekly data after randomization.

Screen failures are defined in Section 5.4. Assuming an overall screen failure rate of 65%, approximately 1058 participants need to be enrolled to achieve the required number of 370 randomized participants. More participants might be enrolled in case the screen failure rate is higher than anticipated. Additionally, further patients may be enrolled in case of an exceptionally high drop-out rate due to a trial-continuity issue.

A formal sample size estimation was performed for the efficacy analyses. The sample size was determined to power the study on the primary and key secondary endpoints listed in Section 3 (Table 3–1) and in Section 9.1 at a minimum of 90%.

The sample size has been determined via simulation.

For each endpoint, the distribution of the effect for the placebo and treatment arms were built.

For endpoints 1, 2, 3, 4 & 6 (see the ordering in Section 9.1), we used the data from placebo arm in SWITCH-1 study (NCT03596762 2020) to build a distribution for the effect of placebo in the study. The placebo arm distribution then was shifted by the estimated treatment effect (from SWITCH-1) to represent the distribution of effects for the treatment arm.

For endpoints 5 & 7, there is limited data available in this population and therefore, a standard normal distribution (mean=0, SD=1) was assumed for the placebo arm effect. A treatment effect of 0.4 is selected based on clinical team input.

The assumed treatment effect and characteristics of the placebo distributions are presented in Table 9–1.

Table 9–1: Assumed treatment effect and characteristics of the placebo distributions

Endpoint	Treatment effect Treatment vs. placebo	Distribution of the placebo arm	Distribution parameters
1 – CFB HF Freq W4	-3.5	Normal	Mean= -2.29, SD= 3.632
2 – CFB HF Freq W12	-2	Normal	Mean= -4.43, SD= 4.29
3 – CFB HF Sev W4	-0.22	Mixture normal (Two normal distributions weighted equally at 0.5)	Mean1= -0.543, SD1= 0.562, Mean2= -0.105, SD2= 0.123
4 – CFB HF Sev W12	-0.26	Mixture normal (Two normal distributions weighted equally at 0.5)	Mean1= -0.897, SD1= 0.733, Mean2= -0.128, SD2= 0.185
5 – CFB PROMIS SD SF 8b W12	-0.4	Standard Normal	Mean= 0, SD= 1
6 – CFB HF Freq W1	-2.36	Generalised normal	Psi= -0.43, Kappa= 0.628, Alpha= 2.277
7 – CFB MENQOL W12	-0.4	Standard Normal	Mean= 0, SD= 1

CFB = change from baseline, Freq. = Frequency; HF = hot flashes, MENQOL = Menopause-specific quality of life questionnaire, PROMIS SD SF 8b = Patient-Reported Outcomes Measurement Information System Sleep Disturbance short-form 8b, Sev = Severity, SD = standard deviation, W = week

A patient level data were simulated from the joint distributions of the endpoints. For each simulated study, the treatment effect was tested for the endpoints using a two sample T-test, where the assumption of normality is met, or a Wilcoxon sum-ranked otherwise. The power

was calculated as the total number of rejected null-hypotheses out of the number of simulated studies for each endpoint. The significance level (α) for the tests was adjusted based on the multiplicity strategy. A fixed level of correlation, 0.3, was assumed between the endpoints.

Under the assumptions given in Table 9–1, the study should be powered to achieve a statistical significance for all seven primary and key secondary endpoints at a minimum of 90% with 166 participants per arm.

9.3 Analysis Set

For the purposes of analysis, the following analysis sets are defined in Table 9–2.

Table 9–2: Definition of the analysis sets.

Analysis Set	Description
Enrolled	All participants who sign the informed consent form.
Full Analysis Set (FAS)	All randomized participants.
Safety Analysis Set (SAF)	All participants who receive at least one dose of study intervention.

Efficacy analyses will be based on the FAS and participants will be analyzed according to the randomized intervention. Safety analyses will be performed on the SAF and here participants will be analyzed according to the intervention received.

Documentation of validity findings and assignment of participants to analysis sets will be performed according to the sponsor's applicable Standard Operating Procedures.

Details on additional subsets which may be of interest will be provided in the SAP.

9.4 Statistical Analyses

9.4.1 General Considerations

SAP will be finalized prior to database lock and will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

If not otherwise indicated, the statistical analyses will be performed using SAS and R; the version used will be specified in the SAP.

The endpoints/variables collected in the study will be analyzed using descriptive statistics as appropriate. Continuous variables will be analyzed using at least the following descriptive statistics: number of non-missing observations, arithmetic mean and standard deviation, median, minimum and maximum. Discrete data will be analyzed using frequency tables.

Intercurrent Events (ICEs)

Important ICEs for this study are defined as:

a. Temporary treatment interruption, defined as:

   Week 1 = Treatment taken on <5/7 days during week 1.

Week 4= Treatment taken <80% during weeks 1-4 OR treatment taken on <5/7 days during either week 3 or 4.

Week 12= Treatment taken <80% during weeks 1-12 OR treatment taken on <5/7 days during either week 11 or 12.

b. Permanent treatment discontinuation of randomized treatment

c. Intake of prohibited concomitant medications having impact on efficacy.

The impact of these ICEs on the study results and its interpretation is addressed in Table 3–2 where the main estimand for the primary and key secondary endpoints are defined.

We considered a low impact of the COVID-19 pandemic on missing assessments of the frequency and severity of HF due to the use of eDiary. The eDiary should be completed at home and therefore, there is no need for participants to attend the clinic for the assessment of HF related endpoints.

COVID-19 is included as a reason for occurrence of the important ICEs in the study estimand strategy (Table 3–2).

Definitions required for the calculation of frequency and severity of HF:

Baseline values for the frequency and severity of moderate to severe HF will be calculated using the available data assessed via the HFDD during the 14 days prior to the baseline visits. As per inclusion criteria 9, at least 11 days must be available for the derivation of the baseline value.

A diary day for the calculation of the frequency and severity of HF consists of the evening entry and the morning entry of the subsequent day. A day will be considered available for the calculation of the frequency and severity of HF, if at least the evening or the morning entry (of the subsequent day) is not missing. The daily number of hot flashes per day will be calculated as the sum of the evening and morning entries (of the subsequent day). If only the evening or morning entry is available, then only this will be used for that particular day.

9.4.2 Primary Endpoint(s)

The primary efficacy endpoints for regulatory submission in the US in this study are:

- Mean change in frequency of moderate to severe HF from baseline to Week 4 (assessed by HFDD)
- Mean change in frequency of moderate to severe HF from baseline to Week 12 (assessed by HFDD)
- Mean change in severity of moderate to severe HF from baseline to Week 4 (assessed by HFDD)
- Mean change in severity of moderate to severe HF from baseline to Week 12 (assessed by HFDD)

The primary efficacy endpoints for all regions outside the US are:

1. Mean change in frequency of moderate to severe HF from baseline to Week 4 (assessed by HFDD)
2. Mean change in frequency of moderate to severe HF from baseline to Week 12 (assessed by HFDD)

9.4.2.1 Calculations related to the primary endpoints

Baseline value of frequency of moderate to severe HF:

The baseline value will be calculated by aggregating the available days during the 14 days prior to start of treatment to a mean daily frequency as (total number of moderate to severe HF during the 14 days prior to start of treatment) / (total number of available days with data)

Frequency of moderate to severe HF during treatment:

The frequency of moderate to severe HF for each week during the treatment period will be calculated using the available data during that particular week. Specifically, for Week 4 Days 22-28 will be used and for Week 12 Days 78-84 will be used (Day 1 corresponds to start of treatment). These data will be aggregated to a mean daily frequency as (total number of moderate to severe HF during that week) / (total number of available days with data during that week). In case data is not available for more than 2 days within a week, the value for that particular week will be set to missing. Further details will be specified in the SAP.

Mean change in frequency of moderate to severe HF from baseline to Week 4 and Week 12:

This will be calculated as the difference in the frequency of moderate to severe HF at Week 4 or Week 12, respectively, from the baseline value of the frequency of moderate to severe HF.

Baseline value of severity of moderate to severe HF:

The mean daily severity during baseline will be calculated as [(2 x number of moderate HF) + (3 x number of severe HF)] / (total number of moderate to severe hot flashes on that day). When no moderate or severe HF are reported for a particular day, the mean severity for that day will be set to 0. The baseline value will be calculated by averaging the mean daily severity of the available days during the 14 days prior to start of treatment.

Severity of HF during treatment:

The mean daily severity during treatment will be calculated as [(1 x number of mild HF) + (2 x number of moderate HF) + (3 x number of severe HF)] / (total number of mild, moderate and severe hot flashes on that day). When no HF are reported for a particular day, the mean severity for that day will be set to 0.

Similar to the frequency, the severity of HF for each week during the treatment period will be calculated using the available data during that particular week. Specifically, for Week 4 Days 22-28 will be used and for Week 12 Days 78-84 will be used (Day 1 corresponds to start of treatment). To obtain the post-baseline severity of HF during a particular week, the weekly data will be aggregated by averaging the mean daily severity of HF of the available days during that week. In case data is not available for more than 2 days within a week, the value for that particular week will be set to missing. Further details will be specified in the SAP.

Mean change in severity of moderate to severe HF from baseline to Week 4 and Week 12:

This will be calculated as the difference in the severity of HF at Week 4 or Week 12, respectively, from the baseline value of the severity of moderate to severe HF.

9.4.2.2 Primary analysis of the primary efficacy endpoints

The same clinical questions are posed in respect of each primary and secondary endpoint, and hence the strategies selected in respect of the ICEs are the same (Table 3–2).

The primary endpoints will be analyzed using a mixed model with repeated measures (MMRM) on the change from baseline scores at different Weeks including Week 1, 4, 8 and 12. Baseline, treatment and Week will be included as covariates in the model. The interaction terms baseline*Week and treatment* Week will also be included. More details on model diagnostics, alternative modeling approaches, main and sensitivity analysis, and details of the missing data handling/imputation will be given in the SAP.

9.4.3 Secondary Endpoints

The key secondary efficacy endpoints in this study are:

- Mean change in severity of moderate to severe HF from baseline to Week 4 (assessed by HFDD) (all regions except regulatory submission in the US)
- Mean change in severity of moderate to severe HF from baseline to Week 12 (assessed by HFDD) (all regions except regulatory submission in the US)
- Mean change in PROMIS SD SF 8b total score from baseline to Week 12
- Mean change in frequency of moderate to severe HF from baseline to Week 1
- Mean change in MENQOL total score from baseline to Week 12

The calculation of the mean change in severity of moderate to severe HF from baseline to Week 4 and 12 will be done as described in Section 9.4.2.1. The calculation of the mean change in frequency of moderate to severe HF from baseline to Week 1 will be done analogously to the calculations for Week 4 and 12 described in Section 9.4.2.1. The calculation of the frequency of moderate to severe HF for Week 1 will be based on Days 2-8 on treatment, where Day 1 corresponds to start of treatment.

The calculation of the total scores for the PROMIS SD SF 8b and for the MENQOL will be done according to the respective questionnaire guidelines. Details will be provided in the SAP.

Same estimand strategy applies to the key secondary endpoints (detailed in Table 3–2).

The key secondary endpoints will be analyzed using a similar modeling approach as the primary endpoints (see Section 9.4.2.2).

Additional secondary efficacy endpoints are defined in Section 3. Details for the analysis of these secondary endpoints will be provided in the SAP.

9.4.4 Exploratory Endpoints

The analysis of the exploratory endpoints will be described in the SAP. Additional exploratory endpoints may be specified in the SAP.

9.4.5 Other Safety Analysis

All safety analyses will be descriptive and will be performed on the SAF. Safety data will be summarized descriptively for each treatment group.

All AEs will be coded using the latest version prior to data base lock of the Medical Dictionary for Regulatory Activities (MedDRA).

Further details on safety analyses will be described in the SAP.

9.4.6 Other Analysis

Exploratory subgroup analyses using descriptive statistics will be provided for the primary and secondary endpoints by region. Further subgroup analyses including additional subgroups (e.g. by BMI) may be specified in the SAP.

9.5 Interim Analysis

No interim analysis is planned for this study. Blinded data may be used for evaluation of psychometric and other measurement properties of PRO instruments.

10. Supporting Documentation and Operational Considerations

10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
    - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
    - Applicable ICH Good Clinical Practice (GCP) Guidelines
    - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants. Any substantial modification of the protocol will be submitted to the competent authorities as substantial amendments for approval, in accordance with ICH Good Clinical Practice and national and international regulations.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of ICH guidelines, the IRB/IEC, and all other applicable local regulations

10.1.2 Data Safety Monitoring Board

An independent data safety monitoring board (DSMB) will be established for the elinzanetant development program to perform ongoing safety surveillance. The DSMB will monitor the general safety of the ongoing Phase 3 trials and relevant additional data at an appropriate frequency as provided in the DSMB charter and make recommendations to the sponsor regarding steps to ensure the safety of the trial participants. Details will be described in the DSMB charter.

10.1.3 Liver Safety Monitoring Board

An independent liver safety monitoring board(LSMB) will be established for the elinzanetant development program to perform ongoing surveillance regarding hepatic safety. Independent hepatologists experienced in the assessment of drug induced liver injury (DILI) will conduct an independent review of available clinical data, i.e. blinded individual cases pertaining to elevated transaminases or other liver health markers on a regular basis. The LSMB will advise the DSMB and the sponsor whether the individual cases meet the criteria of a potential DILI, and whether any other actions are necessary to ensure participant safety. Details will be described in the LSMB charter. Case evaluations of the LSMB will be included in the ongoing safety surveillance of the DSMB (see section 10.1.2).

10.1.4 Financial Disclosure

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

10.1.5 Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participants and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.

- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participants.

Participants who are rescreened are required to sign a new ICF.

10.1.6 Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records, datasets or biological samples that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.7 Dissemination of Clinical Study Data

Result summaries of Bayer's sponsored clinical trials in drug development phases 2, 3 and 4 and Phase 1 studies in patients are provided in the Bayer Trial Finder application after marketing authorization approval in line with the position of the global pharmaceutical industry associations laid down in the "Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases". In addition, results of clinical drug trials will be provided on the publicly funded website www.ClinicalTrials.gov and EU Clinical Trials Register in line with the applicable regulations.

Bayer commits to sharing upon request from qualified scientific and medical researchers patient-level clinical trial data, study-level clinical trial data, and protocols from clinical trials in patients for medicines and indications approved in the United States (US) and European Union (EU) on or after January 01, 2014 as necessary for conducting legitimate research.

All Bayer-sponsored clinical trials are considered for publication in the scientific literature irrespective of whether the results of the clinical trials are positive or negative.

10.1.8 Data Quality Assurance

- All participant data relating to the study will be recorded on eCRF unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.

- Guidance on completion of eCRFs will be provided in the eCRF Completion Guidelines.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- QTLs will be pre-defined in the integrated data review plan to identify systematic issues that can impact participant safety and/or reliability of study results. These pre-defined parameters will be monitored during the study and important deviations from the QTLs and remedial actions taken will be summarized in the clinical study report.
- Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (e.g., Contract Research Organizations).
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.1.9 Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the eCRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in the Source Data Location List.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF, excluding ePRO data.
- Study monitors will perform ongoing source data verification and source data review according to the monitoring plan to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.10 Study and Site Start and Closure

First Act of Recruitment

The first participant's signature of informed consent is considered the first act of recruitment and will be the study start date.

Study/Site Termination

The sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

For study termination:

- Discontinuation of further study intervention development
- Recommendation by the DSMB (see Section 10.1.2) to stop the development program or an individual trial within the program.

For site termination:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the investigator
- Total number of participants included earlier than expected.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.1.11 Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2 Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 10–1 will be performed by the central laboratory, unless otherwise indicated.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 10–1: Clinical laboratory tests

Panel	Parameters (by category)
Safety parameter	
Hematology:	red blood cell count, white blood cell count, hematocrit, hemoglobin, mean corpuscular volume, platelet count and WBC differentials.
Clinical chemistry:	sodium, potassium, glucose, urea (blood urea nitrogen), creatinine, creatine kinase (CK), albumin, calcium, phosphate, bilirubin (total and direct), alkaline phosphatase, aspartate transaminase (AST), alanine transaminase (ALT), gamma glutamyl transferase (GGT), total cholesterol, high density lipoprotein (HDL) cholesterol, low density lipoprotein (LDL) cholesterol, triglycerides, bicarbonate, magnesium, chloride, total protein, hemoglobin A1c, lactate dehydrogenase (LDH)
Coagulation:	prothrombin time (Quick), INR, activated partial thromboplastin time (aPTT)
Hormones:	follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol (E2), progesterone (P), prolactin, thyroid-stimulating hormone (TSH), triiodothyronine (T3), thyroxine (T4), free triiodothyronine (FT3), free thyroxine (FT4), sex hormone-binding globulin (SHBG), total testosterone (tT)
Bone markers	bone-specific alkaline phosphatase (BALP), procollagen type 1 N-terminal pro-peptide (P1NP), vitamin D (serum 25-hydroxyvitamin D), osteocalcin
Urine analysis	pH, urobilinogen, blood/hemoglobin, total protein, ketone, bilirubin, nitrite, glucose, leukocytes
Screening/Start of Intervention parameters	
Urine pregnancy test	Beta human chorionic gonadotropin (β-hCG)
Virology	Hepatitis B virus surface antigens and Hepatitis C antibodies, HCV-RNA (HCV-mRNA automatically tested if anti-HCV is positive)
Endometrial Biopsy	Histological analysis of endometrium
Cervical Cytology	Cervical smear (HPV-DNA automatically tested if ASCUS is reported from cervical cytology)
	High risk HPV-DNA
BM, PK & PG	
Pharmacogenetics	Genetics (only consented participants)
Pharmacokinetics	pre-and post-dose PK samples
Biomarkers	For biomarkers, serum and plasma samples needed

ASCUS = atypical squamous cells of undetermined significance; BM = Biomarkers, DNA = Deoxyribonucleic acid; HCV = Hepatitis C virus; HPV-DNA = Human papilloma virus; INR = International normalized ratio; mRNA = Messenger ribonucleic acid, PG = Pharmacogenomics, PK = Pharmacokinetics, RNA = ribonucleic acid; WBC = White blood cell count

See section 10.5 for additional parameters to be assessed in case of increased ALT or AST.

Investigators must document their review of each laboratory safety report.

10.3 Appendix 3: AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1 Definition of AE

AE Definition

- An AE is any untoward medical occurrence in a clinical study participant, associated with the use of study intervention, whether or not considered related to the study intervention.
- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) associated with the use of study intervention.

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected intervention-intervention interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.
- "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

Events <u>NOT</u> Meeting the AE Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2 Definition of SAE

An SAE is defined as any AE that, at any dose:	
a.	**Results in death**
b.	**Is life-threatening** • The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c.	**Requires inpatient hospitalization or prolongation of existing hospitalization** • In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. • Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
d.	**Results in persistent or significant disability/incapacity** • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e.	**Is a congenital anomaly/birth defect**

f. Other situations:

- Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment for allergic bronchospasm, blood dyscrasias, convulsions, or development of intervention dependency or intervention abuse.

10.3.3 Recording and Follow-Up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information.
- It is not acceptable for the investigator to send photocopies of the participant's medical records to the sponsor in lieu of completion of the AE/SAE eCRF page.
- There may be instances when copies of medical records for certain cases are requested by the sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to sponsor.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

- The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:
- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort to interfere with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

  An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to sponsor. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission** of the SAE data to sponsor.
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide sponsor with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally submitted documents.
- The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

10.3.4 Reporting of SAEs

SAE Reporting to sponsor via an Electronic Data Collection Tool
• The primary mechanism for reporting an SAE to sponsor will be the electronic data collection tool. • If the electronic system is unavailable, then the site will use the paper SAE data transmission (see next section) to report the event within 24 hours. • The site will enter the SAE data into the electronic system as soon as it becomes available. • After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data. • If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the local pharmacovigilance contact person by telephone. • Contacts for SAE reporting can be found in the investigator site file.

SAE Reporting to Sponsor via Paper Data Collection Tool
• Email transmission of the SAE paper data collection tool is the preferred method to transmit this information to the sponsor's Pharmacovigilance department. • In rare circumstances and if email transmission is not feasible, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE data collection tool within the designated reporting time frames. • Contacts for SAE reporting can be found in the Investigator Site File.

10.4 Appendix 4: Collection of Pregnancy Information

This study does not include Woman of Childbearing Potential (WOCBP). Therefore, cases of pregnancy are not expected. In the unlikely event that a pregnancy is detected during the study, the following procedures should be adhered to.

Collection of Pregnancy Information:

- The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. The initial information will be recorded on the appropriate form and submitted to the sponsor within 24 hours of learning of a participant's pregnancy.

- The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
  - While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
  - A spontaneous abortion (occurring at <22 weeks gestational age) or still birth (occurring at >22 weeks gestational age) is always considered to be an SAE and will be reported as such.
- Any post-study pregnancy related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.3.4. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue study intervention or be withdrawn from the study.

10.5 Appendix 5: Liver Safety Actions and Follow-up Assessments

10.5.1 Liver safety -related monitoring and discontinuation criteria

Investigators and participants should pay special attention to non-specific symptoms which may be associated with liver dysfunction; including anorexia, nausea, fatigue, right upper abdominal discomfort, vomiting, malaise, jaundice, fever, and rash.

- Information on these symptoms should be asked for in case of abnormal liver laboratory values (Table 10–2) or any other suspicion of liver dysfunction.
- Participants should be regularly reminded to contact the investigator immediately if they are concerned about such symptoms, and unscheduled visits for evaluation should be considered
- In the case of increased liver values defined in Table 10–2, a retest may be performed within 72 hours of the initial test results. If the abnormal liver values are confirmed in the retest, liver safety monitoring should be initiated.

Table 10–2: Liver Safety-Related Monitoring and Discontinuation Criteria

Lab result	Measures
ALT or AST > 3 x ULN	Initiate close observation as defined in Section 10.5.2. Consider withdrawal of study intervention if the participant does not adhere to procedures required for close observation[a]
AP>2 x ULN[b]	Initiate close observation as defined in Section 10.5.2. Consider withdrawal of study intervention if the participant does not adhere to procedures required for close observation
ALT or AST > 3 x ULN **and** TBL > 2 x ULN	Withdraw study intervention and initiate close observation as defined in Section 10.5.2.
ALT or AST > 3 x ULN and INR > 1.5 x ULN	Withdraw study intervention and initiate close observation as defined in Section 10.5.2.
ALT or AST > 3 ULN **with** appearance of fatigue, nausea, vomiting, right upper abdominal quadrant pain or tenderness, fever, rash and/or eosinophilia (>5%)	Withdraw study intervention and initiate close observation as defined in Section 10.5.2.
ALT or AST > 5 x ULN for more than 2 weeks	Withdraw study intervention and initiate close observation as defined in Section 10.5.2.
ALT or AST > 8 x ULN	Withdraw study intervention and initiate close observation as defined in Section 10.5.2.

ALT = alanine aminotransferase; AP = Alkaline phosphatase; AST = aspartate aminotransferase; INR= international normalized ratio, TBL = total bilirubin, ULN = upper limit of normal (all referring to serum/plasma)
[a] in case visits for close observation could not be arranged with a frequency deemed adequate by the investigator, despite of reasonable efforts
[b] Close observation can be stopped if bone AP value is reported as abnormal

10.5.2 Close observation of participants with liver function test findings

- Abnormal laboratory results and clinical signs and symptoms resulting in close liver observation should be reported as adverse event.
    - Any increase in liver enzymes meeting the following criteria needs to be reported as an adverse event to the sponsor within 24 hours of the investigator's awareness for expedited reporting to the health authorities:
        - ALT and/or AST >8x ULN OR
        - ALT and/or AST >3x ULN with total bilirubin >2x ULN
    - The investigator may consider whether the observed increase in liver values would qualify as SAE (see Section 8.3.6).
- It is critical to initiate close observation immediately upon detection and confirmation of early signals of possible drug-induced liver injury, and not to wait until the next scheduled visit or monitoring interval
- Procedures to be taken resemble workup/ documentation along the guideline of the US FDA for assessment of potential drug-induced liver injury (FDA Guidance for Industry 2009). Objectives are to:
    - Ensure participant safety
    - Identify possible non-study-intervention-related causes of liver injury
- A close observation has to be initiated during intervention or follow-up phase if liver function tests meet the criteria in Table 10–2. Close observation includes:

- Sampling for the first batch of laboratory parameters (Table 10–3).
- Repeating follow-up samplings (Table 10–3) 2 to 3 times per week. Frequency of retesting can decrease to once a week or less if abnormalities stabilize.
- Obtaining a detailed history of the symptoms and prior or concurrent diseases
- Obtaining a history of concomitant drug use (including nonprescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets.
- Ruling out acute viral hepatitis, autoimmune or alcoholic hepatitis, nonalcoholic steatohepatitis, hypoxic/ischemic hepatology and biliary tract disease. Unless an obvious and firm non-drug induced liver injury diagnosis has already been made additional procedures, e.g. ultrasound examinations should be performed. If requested, tests will be done retrospectively using residual blood/serum samples collected at visits before laboratory abnormalities occurred.
- Obtaining a history of exposure to environmental chemical agents
- Obtaining additional tests to evaluate liver function as required (e.g. INR, direct bilirubin measurements)
- Considering gastroenterology or hepatology consultations

- Data for any findings are to be recorded in the corresponding eCRF pages
- Stopping criteria for close observation:
  - 2 consecutive normal/baseline results for liver enzymes in addition to availability of results from detailed close liver observation lab panel, related procedures, relevant medical and medication history and the reporting of signs and symptoms related to elevated liver enzymes, or
  - a confirmed clinical diagnosis explaining the elevated liver enzymes, or
  - if fragmentation reveals abnormal bone AP as reason for the increase of AP>2 x ULN.

Table 10–3 lists the samples to be taken during close observation for liver safety. The samples are to be taken as needed.

Table 10–3: Samples during close observation for liver safety

First batch of parameters to be taken when initiating close observation for liver safety[a]
Albumin
Alkaline phosphatase (AP)
Alanine-aminotransferase (ALT)
Aspartate-aminotransferase (AST)
Complete blood count including WBC with differentials
Cholinesterase
Conjugated (direct) bilirubin
Creatine kinase (CK)
GGT
Hemoglobin
INR
Lactate dehydrogenase (LDH)
PT
Total bilirubin
HDL-cholesterol

Table 10–3: Samples during close observation for liver safety

LDL-cholesterol
Total cholesterol
Triglycerides
Anti-hepatitis A virus IgM antibodies.
Hepatitis B virus surface antigen (if positive, automatically test below antibodies related to HBV and HDV) - Anti-hepatitis B surface antibodies - Anti-hepatitis B core total antibodies - Anti-hepatitis B IgM antibodies - Hepatitis B PCR (viral copies) - HDV antibodies (if positive, automatically test HDV RNA)
Anti-HCV antibodies)
Hepatitis C RNA
Anti-HDV antibodies (if positive, automatically test HDV RNA)
Anti-HEV IgM (if positive, automatically test HEV RNA)
Anti-cytomegalovirus IgM antibodies
Anti-Epstein-Barr Virus IgM antibodies
HSV IgM (anti-HSV IgM)
IgG level (gamma globulins)
IgA
IgM
c-Antineutrophil cytoplasmic antibodies
c-Antineutrophil perinuclear antibodies
Anti-mitochondrial antibodies
Anti-nuclear antibodies
Anti-Smooth muscle antibodies
A1AT level
Ceruloplasmin
Ferritin
Iron
Total iron binding capacity
Follow-up samples during close observation for liver safety[b]
Albumin
Alkaline phosphatase
Alanine-aminotransferase
Aspartate-aminotransferase
WBC with differentials
Cholinesterase
Creatine kinase
Conjugated (direct) bilirubin
Total bilirubin
Gamma-glutamyl transferase
INR
LDH

a) First sample after AST or ALT > 3 X ULN or AP>2xULN
b) Additional parameters/tests may be added as medically justified
A1AT = Alpha-1 antitrypsin; GGT = Gamma-glutamyl transferase; INR = International normalized ratio; HBV = hepatitis B virus; HCV = Hepatitis C virus, HDL = high-density lipoprotein; HDV = hepatitis D virus; HEV = hepatitis E virus; HSV = herpes simplex virus; IgA = immunoglobulin A; IgG = immunoglobulin G; IgM = immunoglobulin M, LDH = lactate dehydrogenase; LDL = low density lipoprotein; PCR = Polymerase chain reaction; PT = prothrombin time; RNA = ribonucleic acid; ULN = Upper limit of normal; WBC = White blood cell count

10.6 Appendix 6: Prohibited concomitant medications

Table 10–4: Prohibited concomitant medication potentially confounding efficacy

Prohibited from the time shown until 1 week after the last dose of study drug	
	Hormonal therapies
From 4 weeks prior to Baseline Visit	Vaginal hormonal products (rings, creams, gels and including DHEA or analogues thereof)
From 4 weeks prior to Baseline Visit	Transdermal estrogen alone or estrogen/progestin products
From 8 weeks prior to Baseline Visit	• Oral estrogen and/or progestin therapy • Selective estrogen receptor modulators • Intrauterine progestin therapy
From 12 weeks prior to Baseline Visit	• Progestin implants and estrogen alone injectable drug therapy • Use of adjuvant endocrine therapy (e.g. tamoxifen, aromatase inhibitors, GnRH analogues)
From 24 weeks prior to Baseline Visit	Estrogen pellet therapy or progestin injectable drug therapy
	Non-hormonal therapies
From 4 weeks prior to Baseline Visit	• Anti-depressant drugs with effect on vasomotor symptoms (eg paroxetine, other including selective serotonin reuptake inhibitors, serotonin norepinephrine reuptake inhibitors and tri-cyclic antidepressants, alpha agonists [clonidine], methyldopa, gabapentin, pregabalin, medicinal cannabis or derivatives) • Over the counter/herbal treatments including traditional Chinese medicine for treatment of menopausal symptoms. • Oxybutynin/ Oxybutynin hydrochloride

DHEA = Dehydroepiandrosteronacetat, ICF = Informed consent form

Table 10–5: Prohibited concomitant medication potentially affecting PK

Prohibited from the time shown until 1 week after the last dose of study medication	
From 1 week prior to Baseline Visit CYP3A4 substrates with a narrow therapeutic range	alfentanil, astemizole, cisapride, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, terfenadine
From 2 weeks prior to Baseline Visit: Strong (or moderate) inhibitors of CYP3A4	See Table 10–6 for examples of most common moderate or potent CYP3A4 inhibitors
From 4 weeks prior to Baseline Visit: Strong (or moderate) inducers of CYP3A4	See Table 10–7 for examples of most common moderate or potent CYP3A4 inducers
From 1 week prior to Baseline Visit: P-glycoprotein inhibitors	azithromycin, conivaptan, cyclosporine, diltiazem, erythromycin, ketoconazole, quinidine, ranolazine, amiodarone, carvedilol, clarithromycin, dronedarone, itraconazole, lapatinib, propafenone, quinidine,
From 1 week prior to Baseline Visit: P-glycoprotein substrates with a narrow therapeutic range	Digoxin

CYP3A4 = Cytochrome P450 isoenzyme 3A4, PK = Pharmacokinetics

Table 10–6 and Table 10–7 list examples of the most common medication regarded as potent CYP3A4 inhibitors or inducers.

Table 10–6: Examples of clinical inhibitors for CYP3A4

Strong inhibitors	Moderate inhibitors	Weak inhibitors
▪ boceprevir ▪ clarithromycin ▪ cobicistat ▪ danoprevir and ritonavir ▪ elvitegravir and ritonavir	▪ aprepitant ▪ ciprofloxacin ▪ conivaptan ▪ crizotinib ▪ cyclosporine	▪ chlorzoxazone ▪ cilostazol ▪ cimetidine ▪ clotrimazole ▪ fosaprepitant
▪ grapefruit juice	▪ diltiazem	▪ istradefylline
▪ idelalisib ▪ indinavir and ritonavir ▪ itraconazole ▪ ketoconazole	▪ dronedarone ▪ erythromycin ▪ fluconazole ▪ fluvoxamine	▪ ivacaftor ▪ lomitapide ▪ ranitidine ▪ ranolazine
▪ lopinavir and ritonavir	▪ imatinib	▪ ticagrelor
▪ nefazodone	▪ tofisopam	
▪ nelfinavir ▪ paritaprevir and ritonavir and (ombitasvir and/or dasabuvir) ▪ posaconazole ▪ ritonavir	▪ verapamil	
▪ saquinavir and ritonavir ▪ telaprevir ▪ tipranavir and ritonavir ▪ telithromycin		
▪ troleandomycin ▪ voriconazole		

Source: (FDA 2020)

Table 10–7: Examples of clinical inducers for CYP3A4

Strong inducers	Moderate inducers	Weak inducers
▪ apalutamide ▪ carbamazepine ▪ enzalutamide ▪ mitotane	▪ bosentan ▪ efavirenz ▪ etravirine ▪ phenobarbital	▪ armodafinil ▪ modafinil ▪ rufinamide
▪ phenytoin ▪ rifampin ▪ St. John's wort	▪ primidone	

Source: (FDA 2020)

10.7 Appendix 7: Sleep Quality Tracking Substudy

As of Amendment 1 sleep quality tracking substudy has been removed from the protocol.

10.8 Appendix 8: Additional information on scoring and measurement properties of the HFDD, the PROMIS SD SF 8b and the MENQOL

10.8.1 HFDD

Rules for assessment of eligibility and efficacy using scores from the HFDD are detailed in section 9.4

The HFDD was acknowledged for use by regulatory agencies to appropriately assess frequency and severity of HF. Instruments similar to the HFDD are well established and have been used in competitive clinical trials.

10.8.2 PROMIS SD SF 8b

The mean of the total PROMIS SD SF 8b score will be used for assessing a key secondary efficacy endpoint.

The PROMIS SD SF 8b is a generic measure of sleep disturbances which showed good measurement properties in conditions other than VMS. It also has appropriate conceptual coverage of concepts relevant for VMS as the cause of sleep disturbance and it currently supports secondary endpoints in other development programs assessing VMS.

10.8.3 MENQOL

The mean of the total MENQOL score will be used for assessing a key secondary efficacy endpoint. For each item, the participant indicates if they have experienced the symptom (yes/no). If they select yes, they rate how bothered they were by the symptom using a six-point verbal descriptor scale, with response options ranging from 0 'not at all bothered' to 6 'extremely bothered'.

Item scores are converted to a score ranging from 1 to 8 in the following manner:

Response	Converted Score
The participant responded ‘NO’, she did not experience the problem	1
The participant experienced the problem and rated it as ‘0’ on the bothered scale;	2
The participant experienced the problem and rated it as ‘1’ on the bothered scale;	3
The participant experienced the problem and rated it as ‘2’ on the bothered scale;	4
The participant experienced the problem and rated it as ‘3’ on the bothered scale;	5
The participant experienced the problem and rated it as ‘4’ on the bothered scale;	6
The participant experienced the problem and rated it as ‘5’ on the bothered scale;	7
The participant experienced the problem and rated it as ‘6’ on the bothered scale;	8

Domain scores are calculated by averaging the converted individual item scores (range 1-8) related to the respective domain). For a total MENQOL score the aggregated mean of the mean domain scores is calculated. Higher scores indicate greater bother.

The MENQOL is widely used in menopausal clinical trials. There is some evidence available for content validity and other measurement properties in postmenopausal populations.

10.9 Appendix 9: Ancillary Medical Devices Used in the Study

As of Amendment 1 there are no ancillary medical devices used in this study.

10.10 Appendix 10: Abbreviations

Definitions:

Throughout this document, terms “study drug”, “study medication” and “study intervention” are used interchangeably.

Abbreviations:

A1AT	Alpha-1 antitrypsin
AE(s)	Adverse event(s)
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
AP	Alkaline phosphatase
aPTT	Activated partial thromboplastin time
ASCCP	American Society for Colposcopy and Cervical Pathology
ASCUS	Atypical squamous cells of undetermined significance
AST	Aspartate-aminotransferase
BCRP	Breast Cancer Resistance Protein
BDI-II	Beck Depression Inventory, Version II
BL	Baseline
BM	Biomarker(s)
BMI	Body mass index
CD	Compact disc
CFB	Change from baseline
CHMP	Committee for Medicinal Products for Human Use
CK	Creatinine kinase
COVID-19	Coronavirus disease of 2019
CYP3A4	Cytochrome P450 isoenzyme 3A4
DBP	Diastolic blood pressure
DHEA	Dehydroepiandrosteronacetat
DILI	Drug induced liver injury
DNA	Deoxyribonucleic acid
DSM-5	Diagnostic and Statistical Manual of Mental Disorders
DSMB	Data safety monitoring board
DtP	Direct to patient
EC(s)	Ethics committee(s)
ECG	Electrocardiogram
eCOA(s)	Electronic clinical outcome assessments
eCRF(s)	Electronic case report form(s)
eC-SSRS	Electronic Columbia Suicide Severity Rating Scale
EMA	European Medicines Agency
EoT	End of treatment
ePRO(s)	Electronic patient reported outcome(s)
EQ-5D-5L	European Quality of Life 5-dimension 5-level questionnaire
EU	European Union
FAS	Full analysis set
FDA	Food and Drug Administration
FSH	Follicle stimulating hormone
FU	Follow up
GCP	Good clinical practice
GGT	Gamma glutamyl transferase

GnRH	Gonadotropin-releasing hormone
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HDL	High density lipoprotein
HDV	Hepatitis D virus
HEV	Hepatitis E virus
HF(s)	Hot flash(es)
HFDD	Hot Flash Daily Diary
HPV	Human papilloma virus
HSV	Herpes simplex virus
IB	Investigator brochure
ICE(s)	Intercurrent event(s)
ICF	Informed consent form
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent ethics committee
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IgM	Immunoglobulin M
INR	International normalized ratio
IP	In person
IRB	Institutional review board
ISI	Insomnia Severity Index
IU	international unit
IxRS	Interactive voice – web response system
LC-MS/MS	Liquid chromatography and tandem mass spectrometry
LDH	Lactate dehydrogenase
LDL	Low density lipoprotein
LH	Luteinizing hormone
LSMB	Liver safety monitoring board
MAR	Missing at random
MedDRA	Medical dictionary for drug regulatory affairs
MENQOL	Menopause-specific quality of life questionnaire
MMRM	Mixed model repeated measures
mRNA	Messenger RNA
N/A	Not applicable
NK / NK1 / NK3	Neurokinin / neurokinin 1 / neurokinin 3
OATP	Organic-anion-transporting polypeptide
PCR	Polymerase chain reaction
PD	Pharmacodynamic(s)
PET	Positron emission tomography
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
PK	Pharmacokinetic(s)
PopPK	Population pharmacokinetics
pre-SCR	Pre-screening visit
PRO	Participant reported outcome
PROMIS SD SF 8b	Patient-Reported Outcomes Measurement Information System Sleep Disturbance short-form 8b
PT	Prothrombin time
QTc	Corrected QT value
QTL(s)	Quality tolerance limit(s)
RNA	Ribonucleic acid
SAE(s)	Serious adverse event(s)
SAF	Safety analysis set
SAP	Statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus -2
SAS	Statistical analysis software
SBP	Systolic blood pressure

SCR-1	Screening visit 1
SCR-2	Screening visit 2
SD	Standard deviation
SoA	Schedule of activities
SUSAR	Suspected unexpected serious adverse reaction(s)
TBL	Total bilirubin
TEAE(s)	Treatment-emergent adverse event(s)
TMF	Trial master file
TSH	Thyroid-stimulating hormone
TVU	Transvaginal ultrasound
ULN	Upper limit of normal
US	United States
VAS	Visual analog scale
VMS	Vasomotor symptoms
WBC	White blood cell count
WOCBP	Women of childbearing potential

10.11 Appendix 11: Protocol amendment history

10.11.1 Amendment 1

Amendment 1 (10 FEB 2022)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall rationale for Amendment 1:

Changes consist of three types, (i) they address comments from authorities (FDA and Portuguese Health Authority) during the initial CTA review process, (ii) will help to clarify certain aspects of the protocol or (iii) they are minor corrections.

In addition, the sleep quality tracking substudy was removed due to technical difficulties.

Key changes

Section # and Name	Description of Change	Brief Rationale
Section 1.3.1 Screening Section 1.3.2 Treatment and Follow-up Section 3 Objectives, Endpoints and Estimands Section 8.6.2 Functional Biomarkers – Sleep efficiency measurement Section 10.7 Appendix 7: Sleep Quality Tracking Substudy Section 10.9. Appendix 9: Ancillary Medical Devices Used in the Study Section 11 References	Sleep quality tracking substudy has been removed.	Due to technical difficulties with the selected device, the sleep quality tracking substudy has been removed from this study.

Section # and Name	Description of Change	Brief Rationale
Section 5.2 Exclusion criteria	Exclusion criterion 2 was modified as follows: Any clinically significant abnormal laboratory test result(s) measured during screening (single re-test allowed, except for tests listed in *inclusion criteria 2* and exclusion criteria *10*)	Retesting for FSH and serum estradiol concentration is not allowed.
Section 5.2 Exclusion criteria Section 10.6 Appendix 6: Prohibited concomitant medications	Exclusion criterion 4 was modified as follows: Women with current or previous history *(except complete remission for 5 years or more)* of any malignancy (except basal and squamous cell skin tumours) will be excluded. *Women receiving adjuvant endocrine therapy (e.g. tamoxifen, aromatase inhibitors, GnRH analogues) cannot be enrolled in this study.*	Women with a previous history of any malignancy (except basal and squamous cell skin tumors) that is longer than 5 years ago will be allowed to participate in the study. The most frequently reported adverse reaction of adjuvant endocrine therapy are hot flushes and these women will therefore be excluded from participation in this study.
Section 5.2 Exclusion criteria Section 10.2 Appendix 2 Clinical laboratory tests	Exclusion criteria 6 was modified to exclude *current* untreated hypo- or hyperthyroidism, instead of history of untreated hypo- or hyperthyroidism. Definition for acceptable treated hyperthyroidism was added. Triiodothyronine (T3), thyroxine (T4), free triiodothyronine (FT3) and free thyroxine (FT4) were added to the hormone laboratory tests.	The word current was added to clarify the precise exclusion criteria. A definition for treated hyperthyroidism was added for clarification. To correctly diagnose untreated hyperthyroidism and hypothyroidism, and to monitor thyroid function through the study.
Section 5.2 Exclusion criteria	Exclusion criteria 10 was modified to allow women with Gilbert's syndrome to be enrolled.	This change was requested by FDA, since Gilbert's syndrome affects up to 7% of the US population.
Section 6.8.2 Other treatment considerations	Instructions regarding drugs that are sensitive substrates of OATP1B1/1B3, P-gp or BCRP during co-administration of elinzanetant were updated to allow administration of BCRP and/or OATP1B1/1B3 together with elinzanetant without restrictions.	New clinical data not present at the time of the initial CSP finalization was added. The new clinical data are more relevant than the previously available preclinical data, allowing revision of the medication restrictions.
Section 7.1 Discontinuation of study intervention	~~In rare instances,~~ it may be necessary for a participant to permanently discontinue study intervention.	This change was requested by the Portuguese Health Authority.
Section 7.2 Participant discontinuation/withdrawal from the study	A participant may withdraw from the study at any time at her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, or compliance reasons. ~~This is expected to be uncommon.~~	This change was requested by the Portuguese Health Authority.

Section # and Name	Description of Change	Brief Rationale
Section 8.2.6 Mammogram	Mammogram should be done either prior to COVID-vaccinations, or it should be delayed for a certain period after a vaccination, according to local guidelines.	Since unilateral axillary lymphadenopathy is a frequent mild side effect of COVID-19 vaccination, it is recommended to perform the mammogram at the screening visit prior to any Covid-19 vaccination or to delay the screening visit according to local guidelines.
Section 8.3.6 Adverse events of special interest Section 10.5.2 Close observation of participants with liver function test findings	Any increase in liver enzymes meeting the following criteria needs to be reported to the sponsor within 24 hours of the investigator's awareness for expedited reporting to the health authorities: • ALT and/or AST >8x ULN OR • ALT and/or AST >3x ULN with total bilirubin >2x ULN	This change was requested by FDA as part of the comprehensive liver safety follow-up.
Section 9.4.2.2 Primary analysis of the primary efficacy endpoints	The primary endpoints will be analyzed using a mixed model with repeated measures (MMRM) on the change from baseline scores at different Weeks including also Week 8.	Week 8 is used in the MMRM-analysis to get equally spaced visits.
Section 10.5.1 Liver safety - related monitoring and discontinuation criteria Section 10.5.2 Close observation of participants with liver function test findings	Close liver observation was added in cases where AP>2xULN.	Added as precautionary measure as recommended by the Liver Safety Monitoring Board.
Section 10.5.2 Close observation of participants with liver function test finding	HCV-RNA was added to the parameters for samples during close liver observation that will be done immediately at the onset of the close liver observation and not only when antigen testing is positive. Liver imaging has been indicated as a standard procedure in evaluation testing for competing causes of liver injury unless an obvious and firm non-drug induced liver injury diagnosis has already been made.	These changes were requested by FDA to exclude drug induced liver injury as soon as possible.

Section # and Name	Description of Change	Brief Rationale
Section 10.6 Appendix 6: Prohibited concomitant medications	Use of adjuvant endocrine therapy (e.g. tamoxifen, aromatase inhibitors, GnRH analogues) is not allowed during this study.	Women with a previous history of any malignancy (except basal and squamous cell skin tumors) that is longer than 5 years ago will be allowed to participate in the study. Vasomotor symptoms are a frequent side effect of adjuvant endocrine therapy and therefore women with a history of breast cancer who use adjuvant endocrine therapy cannot be included in the study.
Section 10.6 Appendix 6: Prohibited concomitant medications	Vaginal hormonal products with systemic exposure are not allowed from 4 weeks prior to baseline.	Vaginal hormonal products with local effect and no systemic exposure will not influence the efficacy analysis and should be allowed in the study considering the characters of the target population (prevalence of atrophic vagina).
Section 10.6 Appendix 6: Prohibited concomitant medications	Oxybutynin / Oxybutynin hydrochloride are added to prohibited concomitant medications	Oxybutynin / Oxybutynin hydrochloride is used of label for the treatment of VMS and would therefore have an effect on the efficacy outcome.
Section 10.6 Appendix 6: Prohibited concomitant medications	Progestin implants and estrogen alone injectable drug therapy are prohibited 12 weeks prior to *baseline visit* instead of screening visit.	The time point of counting the washout period should be consistent with other drugs that may affect the efficacy, so adjust that to baseline visit.
Section 10.6 Appendix 6: Prohibited concomitant medications	Timepoints for prohibited concomitant medications potentially affecting PK were revised to allow for greater flexibility in using these drugs.	This change allows greater flexibility in using these drugs.

Clarifications to the protocol

Section # and Name	Description of Change
Section 1.3.2 Treatment and follow-up	Hand-held device will not be returned at the EoT Visit. The participants need the hand-held device at the FU-visit to complete the questionnaires.
Section 1.3.2 Treatment and follow-up Section 8.2.1 Physical Examinations	A clarification was made that weight, hip and waist circumference will be recorded at visits indicated in the SoA.
Section 1.3.3 PK sampling schedule	Clarification that all three PK samples at Visit T4 will be taken even if the participant has mistakenly taken the evening dose prior to Visit T4.

Section # and Name	Description of Change
Section 4.1 Overall design	Wash-out: After giving informed consent, ~~but before starting screening procedures.~~ participants will be withdrawn from prohibited concomitant medications.
Section 5.1 Inclusion criteria	Footnote 2 in inclusion criterion 2c was revised for clarity, and it was precised that the value from the retest should also be >40mIU/mL.
Section 5.1 Inclusion criteria	A footnote was added to inclusion criterion 5 provide guidance to rule out possibility of malignancy during screening.
Section 5.2 Exclusion criteria	Exclusion criteria 7 was modified to clarify that women with any unexplained post-menopausal uterine bleeding should be excluded.
Section 6.3 Measures to Minimize Bias: Randomization and Blinding	A further explanation was added that an independent data analysis center will provide unblinded safety data to the independent Data Safety Monitoring Board.
Section 6.8 Concomitant Therapy	*Dates* ~~Times~~ of administration including start and end dates must be recorded.
Section 8.1.1 Electronic Participant-Reported Outcomes (ePROs)	Following clarifications were added: Participants data entries will be transferred automatically to the eDiary provider's database, *and later by the vendor* to Sponsor's database. Educational material will be available *in the ePRO portal* and the Investigator site file. Clarification was added that a missed entry of the study intervention intake may also be added retrospectively.
Section 8.1.1.6 Insomnia Severity Index (ISI)	Clarification was added that participants answer to ISI both *at home* and at the site visits.
Section 8.1.1.7 Beck Depression Inventory (BDI-II)	A sentence was added stating that the investigator will receive a notification if a BDI of >19 is reported. Furthermore, it was also clarified that the participants will fill in the questionnaire both at in person visits and at home during the study.
Section 10.5.2 Close observation of participants with liver function test finding	The Section heading was modified to include all liver test findings.
Section 10.6 Appendix 6: Prohibited concomitant medications	All timepoints were converted to weeks.

Corrections of inconsistencies and minor corrections (editorial corrections not detailed)**:**

Section # and Name	Description of Change
Section 1.3.2 Treatment and Follow-up	Correction of a typo. FU treatment window stated days 204-210, which is a 7 day window, while the visit window is given as 14 days. Visit window was corrected to days 204-217.
Section 1.3.3 PK sampling schedule	Correction of an inconsistency: PK sample is not required at EoT visit if the participant discontinues study intervention prematurely.
Section 2.3.1 Risk assessment	The number of non-serious muscle spasm cases in the SWITCH-1 study was corrected to be 2.
Section 5.2 Exclusion criteria	Typo correction to the exclusion criteria 2: to refer to correct criterion about liver parameters.
Section 5.2 Exclusion criteria	In exclusion criteria 9 the eGFR unit of measurement was corrected to read mL/min/1.73m^2.
Section 6.2 Preparation/Handling/ Storage/Accountability	Wording on DtP distribution was corrected.
Section 8.1.1 Electronic participant reported outcomes (ePROs)	The order of the ePROs that are collected in the study was corrected.
Section 8.2.8 Cervical Cytology	Correction of an inconsistency: Cervical smear performed during the last 12 months *prior to signing of informed consent* can be used for the screening assessment.
Section 8.2.11 Suicidal ideation and behavior: Electronic Columbia-Suicide Severity Rating Scale (eC-SSRS)	Typo correction: Corrected reference to exclusion criteria for information on when the participant should not be randomized based on suicidal behavior or ideation.
Section 9.4.2.2	Statistical model was changed to include baseline*Week interaction, instead of baseline*treatment.
Section 9.4.3 Secondary Endpoints	The calculation of the mean change in severity of moderate to severe HF from baseline to Week 4 and 12 will be done instead of calculation of the mean change in frequency.

Administrative changes

Section # and Name	Description of Change
Title page	Amendment number was added on the protocol title page.

In addition, minor editorial and formatting revisions have been made throughout the document.

10.11.2 Amendment 2

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC). A separate file with tracked changes against the last integrated protocol version is available upon request.

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