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 caused by adjuvant endocrine therapy, over 52 weeks and optionally for an additional 2 years in women with, or at high risk for developing hormone-receptor positive breast cancer

Protocol Number:	21656
Protocol Version:	3.0
Amendment Number	Amendment 2 (Global)
Compound Number:	BAY 3427080 / elinzanetant
Short Title:	**O**verall **A**ssessment of efficacy and **S**afety of elinzanetant **I**n patients with vasomotor **S**ymptoms in women with, or at high risk for developing hormone-receptor positive breast cancer (OASIS-4)
Study Phase:	**3**
Acronym:	**OASIS 4**
Sponsor Name and Legal Registered Address:	Bayer Consumer Care AG, Peter-Merian-Strasse 84, 4052 Basel, Switzerland
Regulatory Agency Identifier Number(s):	EudraCT: 2022-000095-18
Amendment Date:	**10 MAY 2023**

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 (Global)	3.0	10 MAY 2023	
Amendment 1 (Global)	2.0	09 DEC 2022	
GBR-1	GBR-1	21 OCT 2022	To include changes specific to United Kingdom
ITA-1	ITA-1	30 SEP 2022	To include changes specific to Italy
Original Clinical Study Protocol	1.0	06 JUN 2022	

Protocol Amendment Summary of Changes Table

Amendment 2 (10 MAY 2023)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC and Article 2(2)(13) of the REGULATION (EU) No 536/2014 of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

There are no effective treatment options for vasomotor symptoms (VMS) caused by adjuvant endocrine therapy since hormone treatment is contraindicated in patients with or at high risk for developing hormone receptor (HR)-positive breast cancer. It is expected that elinzanetant will reduce the frequency and severity of VMS caused by adjuvant endocrine therapy. If these benefits are confirmed, patients will benefit from the continued treatment in the extension period of this study. Study participants who have completed the originally planned 52 weeks of treatment and who need to continue the intake of adjuvant endocrine therapy will be offered two additional years of treatment with elinzanetant.

A description of changes and a brief rationale is outlined in the table below.

Key Changes

Section # and Name	Description of Change	Brief Rationale
Section 1.1 Synopsis Section 1.2 Schema Section 1.3.2 Treatment and follow-up Section 1.3.3 Treatment extension Section 4.1 Overall Design Section 4.4 End of Study Definition Section 6.1 Study Intervention(s) Administered Section 6.6 Continued Access to Study Intervention after the End of the Study	Extension period was added. Participants who have completed 52 weeks of treatment and need to continue intake of their adjuvant endocrine therapy beyond the original treatment period of 52 weeks will be offered to continue with the study and study drug intake for 2 additional years.	There are no effective treatment options for VMS caused by adjuvant endocrine therapy since hormone treatment is contraindicated in patients with or at high risk for developing HR-positive breast cancer. It is expected that elinzanetant will reduce the frequency and severity of VMS caused by adjuvant endocrine therapy. If these benefits are confirmed, patients will benefit from the continued treatment in the extension period of this study that is expected to cover the period of regulatory approval for the extended indication until launch.

Section 6.8.1 Background therapy Section 7 Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal Section 8.1 Efficacy Assessments Section 8.1.2 Investigator collected Patient Reported Outcomes (RAVE) Section 8.2.5 Pregnancy Testing Section 9.5 Interim Analysis Section 10.1.5 Informed Consent Process		
Section 5.1 Inclusion Criteria	Footnote was added to explain that according to the prescription information of tamoxifen, females of reproductive potential need to be advised to use highly effective non-hormonal contraception during treatment with tamoxifen and for 9 months following the last dose of tamoxifen.	To follow a request from the German HA (BfArM) to address the need for long-lasting contraceptive methods after the last dose of tamoxifen.
Section 5.4 Screen Failures	Added wording to allow for rescreening in particular cases.	To follow practice used in Phase 3 studies of other Bayer compounds.
Section 6.8.3 Other Treatment Considerations Section 10.6 Appendix 6: Prohibited concomitant medications	The content of drug-drug interaction with P-gp substrates was updated.	Based on study 22081 P-gp substrates can be removed from the list of prohibited concomitant medications. No clinically relevant drug-drug interaction was observed.
Section 10.6 Appendix 6: Prohibited concomitant medications	The content of drug-drug interaction CCI [redacted]	CCI [redacted] were wrongly listed in the table.
Section 8.1.1.6 Beck Depression Inventory (BDI-II)	Instructions on AE reporting were updated.	Scores provide information and should be interpreted in connection with the clinical presentation. As the investigator sees the participant the interpretation of the score should be left to the discretion of the investigator.
Section 8.2.11 Suicidal thoughts or wishes: Beck's Depression Inventory (BDI-II)	Instructions on AE reporting were updated	Responses to item 9 with a 2 or a 3 should be interpreted in connection with the clinical presentation. As the investigator sees the participant the interpretation of the responses should be left to the discretion of the investigator.

Clarifications to the protocol

Section # and Name	Description of Change
Section 1.1 Synopsis Section 3 Objective, Endpoints and Estimands	Clarification for the reduction in frequency of moderate to severe HF was added.
Section 10.6 Appendix 6: Prohibited concomitant medications	Classification of drugs was added.

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

Section # and Name	Description of Change
Section 2.3.1 Risk Assessment	Subjects are also required to avoid pregnancy and to use highly-effective contraception during the study.
Section 10.1.7 Dissemination of Clinical Study Data	Bayer Trial Finder and EU Clinical Trials Register for interventional studies have been renamed to Bayer Clinical Trials Explorer and EU Clinical Trials Information System.

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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 caused by adjuvant endocrine therapy, over 52 weeks and optionally for an additional 2 years in women with, or at high risk for developing hormone-receptor positive breast cancer

Short Title: **O**verall **A**ssessment of efficacy and **S**afety of elinzanetant **I**n patients with vasomotor **S**ymptoms in women with, or at high risk for developing hormone-receptor positive breast cancer (OASIS-4)

Rationale: This is a phase 3 study to assess the efficacy and safety of elinzanetant for the treatment of vasomotor symptoms (VMS) caused by adjuvant endocrine therapy in women with, or at high risk for developing hormone-receptor positive breast cancer.

See country-specific requirements for Italy (ITA-1) in Section 10.8.1.1.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To evaluate the efficacy of elinzanetant for the treatment of VMS caused by adjuvant endocrine therapy in women with, or at high risk for developing hormone-receptor positive breast cancer	**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) **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) **Exploratory endpoints:** • Proportion of participants with at least 50% reduction in frequency of moderate to severe HF at Week 4 • Proportion of participants with at least 50% reduction in frequency of moderate to severe HF at Week 12

Objectives	Endpoints
Secondary	
• To evaluate the onset of efficacy of elinzanetant for the treatment of VMS caused by adjuvant endocrine therapy in women with, or at high risk for developing hormone-receptor positive breast cancer	**Secondary endpoints** • Mean change in frequency of moderate to severe HF from baseline to Week 1 (assessed by HFDD) • Mean change in frequency of moderate to severe HF from baseline over time (assessed by HFDD) **Exploratory endpoints:** Time to treatment response
• To evaluate the efficacy of elinzanetant in women with, or at high risk for developing hormone-receptor positive breast cancer on: ○ sleep quality ○ menopause related quality of life	**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 **Exploratory endpoints:** • Absolute values and changes from baseline in the PROMIS SD SF 8b over time • Absolute values and changes from baseline in MENQOL total score over time • Absolute values and changes from baseline in the ISI total score over time • Absolute values and changes from baseline in EQ-5D-5L single dimensions and health state VAS score over time. • Absolute values and changes from baseline in SF-36 acute domain, physical component summary (PCS) and mental component summary (MCS) scores over time • Absolute values and changes from baseline in the BDI-II total score over time
• To evaluate the safety of elinzanetant for the treatment of VMS caused by adjuvant endocrine therapy in women with, or at high risk for developing hormone-receptor positive breast cancer	**Other endpoints:** • Number of participants with TEAEs • Number of participants with abnormal laboratory parameters • Mean change in Sleepiness Scale, at Week 1, Week 4, Week 12, Week 26, Week 36 and Week 50 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, ISI=Insomnia Severity Index, MENQOL=Menopause Specific Quality of Life Scale, PROMIS SD SF 8b=Patient-reported Outcomes Measurement Information System Sleep Disturbance Short Form 8b, SAP = Statistical analysis plan, SF-36 acute = Short Form-36 Health Survey acute, TEAE = treatment emergent adverse event, VAS = Visual analog scale, VMS = Vasomotor symptoms

Overall Design:

This is a Phase 3 multi-center, multi-country, placebo-controlled, double blind, parallel group intervention study, in women with, or at high risk for developing hormone-receptor positive breast cancer.

Short Summary:

The purpose of this study is to investigate efficacy and safety of elinzanetant for the treatment of VMS caused by adjuvant endocrine therapy in women with, or at high risk for developing hormone-receptor positive breast cancer.

Study details include:

- Total study duration for an individual participant: approximately 62 weeks (plus potential washout period), including
    - Pre-screening / Washout period (if applicable)
    - Screening: approximately 6 weeks
    - Treatment: 52 weeks
    - Follow-up: 4 weeks
- Visit Frequency: Every 4 weeks until Week 16, then every 10 weeks until week 36 and end of treatment visit at week 52, including 6 phone call visits. See Section 1.3.2 for more details.
- Treatment extension (part C): Participants who complete the 52 weeks treatment phase will be offered to continue treatment for another 2 years. Visit frequency: every 24 weeks until week 156. See Section 1.3.3 for more details

Number of Participants:

Approximately 810 participants will be screened to achieve 405 participants randomly assigned to study intervention in a 2:1 ratio, resulting in estimated 365 participants evaluable for the primary efficacy analysis (243 and 122 evaluable participants in respectively the elinzanetant and placebo arm) after 12 weeks. The randomization will be stratified by women with breast cancer or high-risk for developing breast cancer and by type of treatment for the pre-existing condition at baseline (participants on tamoxifen and participants on aromatase inhibitors). 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, while staying on their current treatment, including their adjuvant endocrine therapy. There will be 2 arms in the study

- Elinzanetant for 52 weeks and optionally additional 2 years
- Placebo for 12 weeks, followed by elinzanetant for 40 weeks and optionally additional 2 years

Data Monitoring/Other Committee: Yes

1.2 Schema

Figure 1-1: Study Schema for participants not entering the 2 year treatment extension

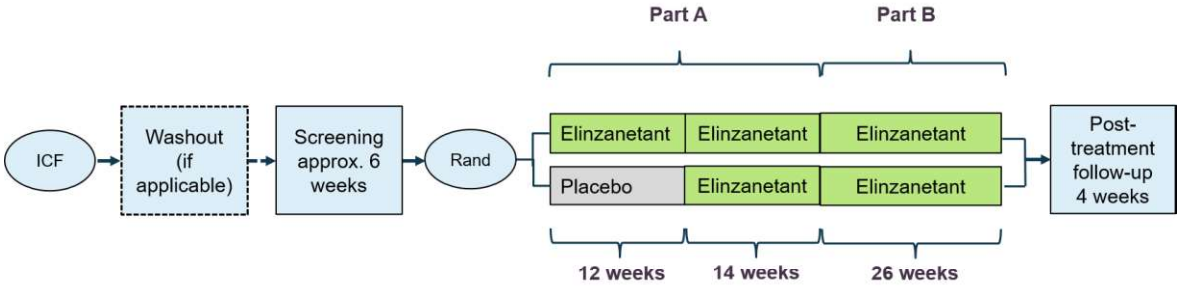
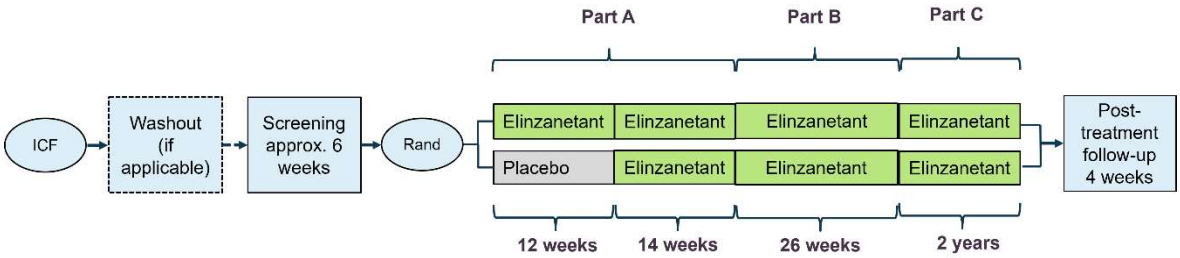


Figure 1-2: Study Schema for participants entering the 2 year treatment extension



Approx. = approximately, ICF = Signing of informed consent form, Rand. = randomization
After completion of Part A the final efficacy analysis and a preliminary safety assessment can be performed.

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 and needs to be performed between Pre-SCR and SCR-1 (See Section 4.1 for further details).
- All screening evaluations should typically be completed within 6 weeks after SCR-1 (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 education level	●	(●)[a]	
Medical history and concomitant medications	●	●	●
Gynecological and reproductive history including number of pregnancies and births	●	(●)[a]	
eDiary and eCOA instruments			
Dispensation and training of participant's hand-held device			●
Background medication intake documentation (see Section 6.8.1)			---------->
HFDD (twice daily)			---------->
Sleepiness Scale (daily in the evening)			---------->
BDI-II			●
Screening and randomization			
Inclusion/exclusion criteria	●	●	●
Safety			
Complete physical examination (including height and weight, see section 8.2.1)		●	
Vital signs		●	
12-lead ECG			●
Mammogram (if applicable, see Section 8.2.6)		●	
Cervical cytology (if applicable, see Section 8.2.7)		●	
Transvaginal ultrasound (if applicable, see Section 8.2.8)			●[b]
Endometrial biopsy (if applicable, see Section 8.2.9)			●[b]
Laboratory (including safety)			
Blood sampling (safety)		●	
Urine pregnancy test (if applicable, see Section 8.2.5)		●	●[b]
Urinalysis		●	

ECG = electrocardiogram, eCOA = Electronic clinical outcome assessment, Pre-SCR = pre-screening Visit, SCR=Screening Visit
Questionnaires: BDI-II=Beck Depression Inventory, HFDD=Hot Flash Daily Diary
a Only if Pre-screening visit is not performed
b A pregnancy test (unless participant has been confirmed post-menopausal or women of nonchildbearing potential (WONCBP)) and ultrasound must be performed before an endometrial biopsy is taken.

1.3.2 Treatment and follow-up

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

		Part A									Part B				
Visit name	**BL**	**T1**	**T2**	**T3**	**T4**	**T5**	**T6**	**T7**	**T8**	**T9**	**T10**	**T11**	**T12**	**T13/ EoT [a]**	**FU[e]**
In person (IP) or phone visit	**IP**	☎	**IP**	☎	**IP**	☎	**IP**	**IP**	☎	**IP**	☎	**IP**	☎	**IP**	**IP**
Visit Week	**1**	**2**	**4**	**6**	**8**	**10**	**12**	**16**	**20**	**26**	**30**	**36**	**42**	**52**	**56**
Visit window in days	1	8-14	22-28	36-42	50-56	64-70	85-90	106-112	127-140	176-182	197 - 210	246-252	281-294	351-364	386-399
Informed consent												(●)[f]		●[f]	
eDiary and eCOA instruments															
HFDD (twice daily, Section 8.1.1.1)	---------->							Week 25 & 26, Week 35 & 36 and Week 49 & 50							
Sleepiness scale (reported in the evening)	7 consecutive days during Weeks 1, 4, 12, 26, 36 and 50														
PROMIS SD SF 8b	once weekly		●		●		●	●		●		●		●	●
ISI	●		●		●		●	●		●		●		●	●
MENQOL	●		●		●		●	●		●		●		●	●
BDI-II			●		●		●	●		●		●		●	●
EQ-5D-5L	once weekly				●		●	●		●		●		●	●
SF-36 acute	●						●								
Vaginal bleeding diary (if applicable, see Section 8.1.1.8)	---------->														
Study drug/background medication intake documentation	---------->														
Check completeness of eDiary via web report	---------->														
Collection of hand-held device														●[f]	●
Screening and randomization															
Inclusion/exclusion criteria	●														
Participant randomization	●														
Safety/Laboratory															
AEs / concomitant medications	---------->														
Symptom-based physical examination (including weight)	●		●		●		●	●		●		●			●
Complete physical examination (including weight)														●	
Vital signs	●		●		●		●	●		●		●		●	●
Mammogram (if applicable, see Section 8.2.6)														●[b]	
Transvaginal ultrasound (if applicable, see Section 8.2.8)														●	
Endometrial biopsy (if applicable, see Section 8.2.9)														●	
Blood sample (safety)	●		●		●		●	●		●		●		●	●
Blood samples (E2)	●		●		●		●								
Blood samples (biomarker)	●						●								
Blood sample (PK elinzanetant/placebo)	●		●		●		●			●				●	
Blood sample (PK tamoxifen or Aromatase Inhibitor)	●		●		●		●			●				●	
Blood sample CYP2D6 genetics only from participants receiving tamoxifen (see Section 8.5 and 8.6)[d]	●														
Urine pregnancy test (if applicable, see Section 8.2.5)[c]	●		●		●		●	●	---------->					●	●

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

		Part A									Part B				
Visit name	**BL**	**T1**	**T2**	**T3**	**T4**	**T5**	**T6**	**T7**	**T8**	**T9**	**T10**	**T11**	**T12**	**T13/ EoT [a]**	**FU[e]**
In person (IP) or phone visit	**IP**	☎	**IP**	☎	**IP**	☎	**IP**	**IP**	☎	**IP**	☎	**IP**	☎	**IP**	**IP**
Visit Week	**1**	**2**	**4**	**6**	**8**	**10**	**12**	**16**	**20**	**26**	**30**	**36**	**42**	**52**	**56**
Visit window in days	1	8-14	22-28	36-42	50-56	64-70	85-90	106-112	127-140	176-182	197 - 210	246-252	281-294	351-364	386-399
Urinalysis														●	
Study intervention and study exit															
Study drug dispensing/training	●		●		●		●	●		●		●		●[f]	
Supervised study drug intake at site	●									●					
Study drug collection (if applicable)			●		●		●	●		●		●		●	
Study drug compliance		●	●	●	●	●	●	●	●	●	●	●	●	●	
Participant feedback survey	●						●							●	

AEs = adverse events, BL = baseline, CYP2D6 = Cytochrome P450 2D6, E2 = estradiol, eCOA = Electronic clinical outcome assessment, EoT = End of treatment Visit; FU = follow up, IP = In person; PK = pharmacokinetics, T = treatment

Questionnaires: BDI-II = Beck Depression Inventory, 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, PROMIS SD SF 8b = Patient-reported Outcomes Measurement Information System Sleep Disturbance Short Form 8b; SF-36 acute = Short Form-36 Health Survey acute

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 52 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 FU visit. If a participant discontinues from treatment but 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 no FU visit is needed after T13. 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 and patient 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 T13 or EoT.

c Urine pregnancy test will be performed at site at BL, T2, T4, T6, T7, T9, T11, T13/EoT and FU, and at home at week 20, 24, 30, 34, 40, 44 and 48. Home testing results will be documented in eDiary.

d If the blood sample for CYP2D6 genetics was not collected at BL visit it can be also collected at a later visit.

e Not applicable for participants continuing with the treatment extension (part C).

f Only applicable for participants continuing with the treatment extension (part C).

1.3.3 Treatment extension

Table 1-3 Treatment extension (for participants who completed the 52 weeks treatment phase, optionally)

	Part C					
Visit name	**T14**	**T15**	**T16**	**T17**	**EoT part C**	**FU part C**
In person (IP)	**IP**	**IP**	**IP**	**IP**	**IP**	**IP**
Visit Week	**58**	**82**	**107**	**131**	**156**	**160**
Visit window in days	402-409	573-580	744-751	915-922	1088-1095	1116-1123
Safety						
AEs / concomitant medications	---------->					
Question on adherence to adjuvant endocrine therapy	●	●	●	●	●	●
Dispensation of urine pregnancy test (if applicable, see Section 8.2.5)	●	●	●	●	●	
Study intervention						
Study drug dispensing	●	●	●	●		
Study drug collection	●	●	●	●	●	
Study drug compliance	●	●	●	●	●	

Table 1-3 Treatment extension (for participants who completed the 52 weeks treatment phase, optionally)

	Part C					
Visit name	**T14**	**T15**	**T16**	**T17**	**EoT part C**	**FU part C**
In person (IP)	**IP**	**IP**	**IP**	**IP**	**IP**	**IP**
Visit Week	**58**	**82**	**107**	**131**	**156**	**160**
Visit window in days	402-409	573-580	744-751	915-922	1088-1095	1116-1123

AEs = adverse events, EoT = End of treatment Visit; FU = follow up, IP = In person; T = treatment

1.3.4 PK sampling schedule

Table 1-4: PK sampling schedule for elinzanetant and tamoxifen or Aromatase Inhibitors

Visit	BL	T2	T4	T6	T9	EoT
Week	1	4	8	12	26	52
Study intervention[a] intake on visit days	at site	at home the evening before	at home the evening before	at home the evening before	at site and no dosing on the day before	at home the evening before
Documentation of date and time of study intervention[a]	on visit day	on the previous dosing days	on the previous dosing days	on the previous dosing days	on visit day and the previous dosing days	on the previous dosing days
PK sampling elinzanetant	post dose at: 0.5-3 hours	any time during the visit	any time during the visit	any time during the visit	pre-dose, and two samples between 0.5-4 hours post dose, at least 1 hour apart	any time during the visit
PK sampling tamoxifen OR Aromatase Inhibitor	prior to first elinzanetant dose	any time during the visit	any time during the visit	any time during the visit	prior to elinzanetant 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
a Tamoxifen OR Aromatase Inhibitor will be taken as prescribed by the doctor and the last intake (date and time) should be documented. Elinzanetant intake and documentation should be followed as described in this table.

When PK samples must be taken pre-dose at Visit T9, the previous evening dose of study intervention will not be taken at home. On the day of BL visit and visit T9 with supervised study drug intake at the clinical site, the participant should not take any further study medication in the evening at home. Tamoxifen or aromatase inhibitors with or without the use of GnRH analogues will be used as prescribed by the participant's physician (e.g., oncologist, gynecologist, or general practitioner) and no change to this schedule should be made.

If the participant has mistakenly taken the evening dose prior to Visit T9 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 T9.

For participants prematurely discontinuing study treatment, a PK sample is neither required for elinzanetant nor for background treatment (tamoxifen or aromatase inhibitor) as part of the EoT activities.

2. Introduction

2.1 Study Rationale

This is a phase 3 study to assess the efficacy and safety of elinzanetant for the treatment of VMS caused by adjuvant endocrine therapy in women with, or at high risk for developing hormone-receptor positive breast cancer.

2.2 Background

VMS, commonly referred to as hot flashes (HF, also called “flushes”), are not only related to menopause. VMS are very common adverse reactions in women treated with adjuvant endocrine therapy such as tamoxifen and aromatase inhibitors (Arimidex SmPC 2021, Berkowitz et al. 2021, Biglia et al. 2003, Nolvadex SmPC 2021, Tamoxifen SmPC 2021).

Women with hormone receptor (HR)-positive breast cancer are treated for at least 5 years (up to 10 years) with adjuvant endocrine therapy, which substantially reduces the rate of disease recurrence and mortality (Davies et al. 2011, Davies et al. 2013). Tamoxifen is approved for the treatment of HR-positive breast cancer in both pre- and post-menopausal women. In post-menopausal women, aromatase inhibitors (such as anastrozole) have shown superior efficacy and safety over tamoxifen and are usually preferred (Cuzick et al. 2010). This strong benefit is reflected in current treatment guidelines, with all patients with HR-positive breast cancer being offered adjuvant endocrine therapy (Cardoso et al. 2019). Ovarian function suppression with gonadotropin-releasing hormone (GnRH) analogues or ovarian ablation may also be offered to premenopausal patients in combination with tamoxifen or an aromatase inhibitor (Cardoso et al. 2019).

Adjuvant endocrine therapy is also used for breast cancer prevention in women at high risk for developing breast cancer as clinically indicated although the level of evidence is weak (Paluch-Shimon et al. 2016). The use of adjuvant endocrine therapy for the prevention of breast cancer varies between countries and within countries.

Treatment-related side effects of adjuvant endocrine therapy negatively affect health-related quality of life and adherence to treatment and these side effects are often discussed by participants in online breast cancer forums (Berkowitz et al. 2021, Cella and Fallowfield 2008, Knobf 2006, Murphy et al. 2012, Runowicz et al. 2016).

Effective treatment options for VMS caused by adjuvant endocrine therapy are not available since hormone treatment is contraindicated in HR-positive breast cancer patients. Most self-management strategies for VMS such as relaxation, behavioral strategies, weight loss, and physical activity lack efficacy and are often based on weak or inconclusive evidence (Hall et al. 2021).

Elinzanetant (formerly NT-814[1]) is a dual neurokinin (NK)-1,3 receptor antagonist. Data indicate that VMS are triggered by hyperactivation of the KNDy neurons, which are part of the thermoregulatory pathway, due to withdrawal of estradiol caused by decreasing ovarian function in natural menopause or as a side effect of medical intervention (bilateral oophorectomy, antiestrogen treatments) (Rance et al. 2013, Zhang et al. 2021).

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 of HF in post-menopausal women. Furthermore, the SWITCH-1 study showed that the reduction in frequency of HF was associated with marked improvements on participant reported outcomes of sleep, mood and quality of life.

It is expected that elinzanetant will reduce the frequency and severity of VMS caused by adjuvant endocrine therapy. If these benefits are confirmed in this study, it is anticipated that elinzanetant will be available for the treatment of VMS in a high medical need population. Based on the phase 2 data elinzanetant has a quick onset of action and is expected to treat bothersome VMS.

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

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 for elinzanetant

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.
CCI [redacted] with narrow therapeutic range	CCI [redacted]	Will be managed through exclusion of participants taking the interacting concomitant medications during clinical trials.

[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.

Table 2-1: Risk assessment for elinzanetant

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Increase in plasma concentration of tamoxifen	Based on the available in-house PK data on the drug-drug interaction (DDI) of elinzanetant and midazolam and available literature, co-administration of elinzanetant and tamoxifen might lead to a maximum 2-fold increase of the tamoxifen plasma concentrations.	DDI study elinzanetant and tamoxifen is completed. The results from this DDI study together with the multiple dose simulations indicate no clinically relevant interaction between tamoxifen and its metabolites when continuously co-administered with elinzanetant with respect to safety and efficacy supporting the combined use in the ongoing Phase 3 study OASIS 4. Further PK data is being collected in the OASIS 4 study.
CCI [redacted]	CCI [redacted]	CCI [redacted]
CCI [redacted]	CCI [redacted]	CCI [redacted]
Phototoxicity	Preclinical safety finding. The in vitro 3T3 Neutral Red Uptake (NRU) 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 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.

Table 2-1: Risk assessment for elinzanetant

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Arrhythmias	A possible signal with respect to an increased incidence of 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 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 database.
Effects on reproductive function	There was no evidence of developmental or reproductive toxicity in embryo-fetal toxicity studies at doses up to CCI in rats or up to CCI in rabbits representing CCI 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 CCI, which exceeds human exposure at the anticipated therapeutic dose of 120 mg/day CCI. The dose free of findings represents CCI the human exposure. 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	Subjects are informed of these effects on reproductive function. Subjects are also required to avoid pregnancy and to use highly-effective contraception during the study.
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 VMS during the first 12 weeks of treatment. After 12 weeks participants randomized to placebo will be switched to active treatment.	Participants are not expected to suffer undue medical consequences from absence of treatment during the first 12 weeks. 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, CCI 3A4, DDI = drug-drug interaction, ECG = Electrocardiogram, GGT = Gamma glutamyl transferase, LDH = Lactate dehydrogenase, PK = Pharmacokinetics, VMS = Vasomotor symptoms

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 caused by endocrine adjuvant therapy. These benefits may include

- reduction in frequency of VMS,

- sleep-related benefits,
- improvement of mood and health-related quality of life.

Participants who are randomized to the placebo group are expected to benefit from participation in the study since after 12 weeks all participants will receive active treatment.

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 caused by adjuvant endocrine therapy.

3. Objectives, Endpoints and Estimands

Objectives and endpoints are listed in Table 3-1.

Table 3-1: Objectives and endpoints

Objectives	Endpoints
Primary	
• To evaluate the efficacy of elinzanetant for the treatment of VMS caused by adjuvant endocrine therapy in women with, or at high risk for developing hormone-receptor positive breast cancer	**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) **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) **Exploratory endpoints:** • Proportion of participants with at least 50% reduction in frequency of moderate to severe HF at Week 4 • Proportion of participants with at least 50% reduction in frequency of moderate to severe HF at Week 12

Objectives	Endpoints
Secondary	
• To evaluate the onset of efficacy of elinzanetant for the treatment of VMS caused by adjuvant endocrine therapy in women with, or at high risk for developing hormone-receptor positive breast cancer	**Secondary endpoints** • Mean change in frequency of moderate to severe HF from baseline to Week 1 (assessed by HFDD) • Mean change in frequency of moderate to severe HF from baseline over time (assessed by HFDD) **Exploratory endpoints:** Time to treatment response
• To evaluate the efficacy of elinzanetant in women with, or at high risk for developing hormone-receptor positive breast cancer on: ○ sleep quality ○ menopause related quality of life	**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 **Exploratory endpoints:** • Absolute values and changes from baseline in the PROMIS SD SF 8b over time • Absolute values and changes from baseline in MENQOL total score over time • Absolute values and changes from baseline in the ISI total score over time • Absolute values and changes from baseline in EQ-5D-5L single dimensions and health state VAS score over time. • Absolute values and changes from baseline in SF-36 acute domain, physical component summary (PCS) and mental component summary (MCS) scores over time • Absolute values and changes from baseline in the BDI-II total score over time
• To evaluate the safety of elinzanetant for the treatment of VMS caused by adjuvant endocrine therapy in women with, or at high risk for developing hormone-receptor positive breast cancer	**Other endpoints:** • Number of participants with TEAEs • Number of participants with abnormal laboratory parameters • Mean change in Sleepiness Scale, at Week 1, Week 4, Week 12, Week 26, Week 36 and Week 50 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 caused by adjuvant endocrine therapy 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, PK = Pharmacokinetics, PROMIS SD SF 8b=Patient-reported Outcomes Measurement Information System Sleep Disturbance Short Form 8b, SAP = Statistical analysis plan, SF-36 acute = Short Form-36 Health Survey acute, TEAE = treatment emergent adverse event, VAS = Visual analog scale, VMS = Vasomotor symptoms

Estimands

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

- Population: women aged 18-70 with VMS caused by adjuvant endocrine therapy, as described by the inclusion/exclusion criteria detailed in the protocol.
- Variable: Efficacy will be assessed based on 2 primary endpoints as listed below:
  - Change in frequency of moderate to severe HFs from baseline to Week 4
  - Change in frequency of moderate to severe HFs from baseline to Week 12.
- 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.
Interruption/ discontinuation in intake of adjuvant endocrine therapy[c]	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

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

ICEs[a]	Reason for ICE	Strategy	Data handling method

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.
c) Definition of interruption/discontinuation in intake of adjuvant endocrine therapy:
For participants using tamoxifen: reduction of at least 50% of planned daily dosage taken during weeks 3 and 4 OR weeks 11 and 12 compared to baseline
For participants using aromatase inhibitor: reduction of at least 30% of planned daily dosage taken during weeks 3 and 4 OR weeks 11 and 12 compared to baseline

- Population level summary:
  - Mean change in frequency of moderate to severe HFs from baseline to Week 4.
  - Mean change in frequency of moderate to severe HFs from baseline to Week 12.

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

- Variable:
  - Change in PROMIS SD SF 8b total score from baseline to Week 12
  - Change in MENQOL total score from baseline to Week 12
- Population level summary:
  - 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.

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 women with, or at high risk for developing hormone-receptor positive breast cancer.

Main study (part A+B): The study includes a wash-out period (if applicable), approximately 6-week screening, a 52-week treatment and a 4-week follow-up period.

Treatment extension (part C): Participants who completed the 52 weeks treatment phase are offered to continue treatment for 2 additional years.

See country-specific requirements for Italy (ITA-1) in Section 10.8.1.1.

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: The 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 with a 2:1 ratio in a stratified way into 2 arms, as depicted below.

- elinzanetant
- placebo for 12 weeks, followed by elinzanetant for 40 weeks

The randomization will be stratified by women with breast cancer or high-risk for developing breast cancer and by type of treatment for the pre-existing condition at baseline (participants on tamoxifen and participants on aromatase inhibitors).

The investigator will receive an email notification if a participant responded to item 9 of the BDI-II 'Suicidal Thoughts or Wishes' with a 2 = 'I would like to kill myself' or a 3 = 'I would kill myself if I had the chance'. If this happens at screening the participant cannot be randomized. If this happens after randomization the participant can continue in the study at the discretion of the investigator. Any suicidal ideation should be reported as an adverse event and treated according to local clinical practice.

Treatment: Participants will receive either 120 mg (2x 60 mg soft gel capsules) of elinzanetant or matching placebo orally once daily. More details are provided in Section 6. Participant 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.

Follow-Up: The treatment phase will be followed by a 4-week safety follow-up period in participants who do not continue with the treatment extension (part C) and completed with the FU visit.

Treatment extension (part C): Participants who completed 52 weeks of treatment and decide to continue in the study will receive 120 mg (2x 60 mg soft gel capsules) of elinzanetant orally once daily. Treatment in part C will start the day after last medication intake in the main study, i.e., without interruption of treatment.

Follow-Up (part C): The treatment extension (part C) will be followed by a 4-week safety follow-up period and completed with the FU part C visit.

4.2 Scientific Rationale for Study Design

A double-blind placebo-controlled design up to the primary endpoint at week 12 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.

A placebo-controlled period of 12-weeks to assess efficacy at week 4 and week 12 is considered acceptable because VMS caused by adjuvant endocrine therapy negatively affect health-related quality of life and adherence to treatment. The use of placebo is also considered adequate by both the EU Committee for Medicinal Products for Human Use (CHMP) and US FDA disease-specific guidelines (EMA 2005, FDA 2003). For women

experiencing VMS caused by adjuvant endocrine therapy, no approved active comparator is available.

Participants will remain on the treatment regimen for the underlying condition, i.e. adjuvant endocrine therapy.

The study includes multiple efficacy and safety endpoints in a population of patients with different degrees of moderate to severe VMS caused by adjuvant endocrine therapy, with the intention of reflecting the future patient population. These assess relevant aspects for the treatment of women with VMS and safety topics that were identified based on the mode of action of elinzanetant as well as available pre-clinical and clinical data.

Study participants who have completed the originally planned 52 weeks of treatment and who need to continue the intake of adjuvant endocrine therapy will be offered two additional years of treatment with elinzanetant. There are no effective treatment options for VMS caused by adjuvant endocrine therapy since hormone treatment is contraindicated in patients with or at high risk for developing HR-positive breast cancer. It is expected that elinzanetant will reduce the frequency and severity of VMS caused by adjuvant endocrine therapy. If these benefits are confirmed, patients will benefit from the continued treatment in the extension period of this study.

4.2.1 Patients' Input into Design

Feedback was collected from patient population through a patient Insights 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 that included post-menopausal women 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.

VMS are triggered by hyperactivation of the KNDy neurons, which are part of the thermoregulatory pathway, due to withdrawal of estradiol caused by decreasing ovarian function in natural menopause or as a side effect of medical intervention (bilateral oophorectomy, antiestrogen treatments). Based on the full receptor occupancy the hyperactivation of the KNDy neurons causing VMS can be antagonized by elinzanetant in both post-menopausal women and in women who are treated with adjuvant endocrine therapy.

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 T6.

A participant is considered to have completed the main study if she

- has completed all phases of part A+B (including EoT visit at week 52) and the FU IP visit at week 56 or
- has completed all phases of part A+B (including EoT visit at week 52) and continues in part C.

A participant is considered to have completed the study if she has completed all phases 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 18 to 70 years, inclusive, at signing of informed consent.

Type of Participant and Disease Characteristics

2. Women experiencing VMS caused by adjuvant endocrine therapy that they are expected to use for the duration of the study
    a. Tamoxifen with or without the use of GnRH analogues or
    b. Aromatase inhibitors with or without the use of GnRH analogues

    The participant should be on stable adjuvant endocrine therapy at least 6 weeks prior to baseline.

    Switching or dose modification of adjuvant endocrine therapy is only allowed after Visit T6.
3. Women must have
    a. a personal history of hormone-receptor positive breast cancer or
    b. a high risk for developing breast cancer

See country-specific requirements for Italy (ITA-1) in Section 10.8.1.1.

4. Negative urine pregnancy test at Screening and at Baseline if participant has not been confirmed post-menopausal or WONCBP.
5. In good general health (apart from the condition that resulted in adjuvant endocrine therapy), in the opinion of the investigator, based on the results of the 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. Human papilloma virus (HPV) testing in participants with atypical squamous cells of undetermined significance (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/m2 at screening.
8. Participant has completed HFDD for at least 11 days during the two weeks preceding baseline visit, and participant has recorded at least 35 moderate to severe HF (including night-time HF) over the last 7 days that the HFDD was completed (assessed at the Baseline Visit).

Sex and Contraceptive/Barrier Requirements

9. Contraceptive use by women (except for post-menopausal women or WONCBP) should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

    - A female participant is eligible to participate if she is not pregnant or breastfeeding, and one of the following conditions applies:
        - Is a WONCBP as defined in Section 10.4.1

    OR

        - Is a WOCBP and using a highly effective contraceptive method as described in Section 10.4.2 during the study intervention period (the contraceptive methods must be used through the end of exposure [for at least 8 days after the last dose of elinzanetant[2]]). The investigator should evaluate the potential for contraceptive method failure (e.g., noncompliance, recently initiated) in relationship to the first dose of study intervention.

[2] Tamoxifen can cause fetal harm when administered to a pregnant woman. Therefore, according to the prescription information of tamoxifen, females of reproductive potential need to be advised to use highly effective non-hormonal contraception during treatment with tamoxifen and for 9 months following the last dose of tamoxifen.

- A WOCBP must have a negative highly sensitive urine pregnancy test within 4 weeks before the first dose of study intervention, see Section 8.2.5.
  - If a urine test performed at site cannot be confirmed as negative (e.g., an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.
- Additional requirements for pregnancy testing during and after study intervention are located in Section 8.2.5.
- The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

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. Initial diagnosis of metastatic hormone-receptor positive breast cancer (stage IV) or recurrence under adjuvant endocrine therapy of hormone-receptor positive breast cancer.
2. Current or history (except complete remission for 5 years or more prior to signing informed consent) of any malignancy, except for hormone-receptor positive breast cancer (Stage 0-III), basal and squamous cell skin tumours.
3. Surgery or non-surgical (e.g., chemotherapy, radiotherapy, immunotherapy) treatment for breast cancer within the last 3 months prior to signing informed consent (except use of tamoxifen, aromatase inhibitors, GnRH analogues).
4. Planned surgery, chemotherapy, radiotherapy, or immunotherapy within the duration of the study (reconstructive breast surgery allowed after week 12).
5. Current pregnancy or less than 3 months since delivery, abortion or stop of lactation prior to signing informed consent.
6. Any clinically significant prior or ongoing history of arrhythmias, heart block and QT prolongation either determined through clinical history or on ECG evaluation.
7. Any active ongoing condition that could cause difficulty in interpreting VMS such as: infection that could cause pyrexia, pheochromocytoma, carcinoid syndrome.
8. Any unexplained vaginal bleeding.

9. Mammogram with clinically relevant malignant or suspicious findings that will require surgery, radiotherapy or chemotherapy as per local guidelines (mammogram should not be older than 12 months prior to signing informed consent). If a mammogram is not possible after partial mastectomy an ultrasound could be performed instead.
10. Any clinically significant abnormal laboratory test result(s) measured during screening (single re-test allowed, except for tests listed in-exclusion criterion 11[3]).
11. 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 anti-coagulants[3],
    - 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.
12. 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.
13. Renal impairment greater than moderate (i.e. estimated glomerular filtration rate < 30 mL/min/1.73m2) at screening.
14. Disordered proliferative endometrium, endometrial hyperplasia, polyp, or endometrial cancer diagnosed based on endometrial biopsy during screening (see Section 8.2.9).
15. Current arterial or venous vascular event (e.g. MI, TIA, stroke, DVT), i.e. within the last 6 months prior to signing informed consent.
16. Any other history, condition, therapy, or intercurrent illness which could in the opinion of the investigator affect compliance with study requirements.
17. Women with an ovarian cyst/cysts that need further diagnostic procedures to exclude the possibility of malignancy during screening.

[3] Re-test of INR will be allowed once.

Prior/Concomitant Therapy

18. Any other contraindication listed in the local labeling for medication used as adjuvant endocrine therapy.
19. Has used and is unwilling to wash-out use of any of the prohibited concomitant medications, as specified in Section 10.6.
20. Intake of medication prohibited due to potential drug-drug interaction, see Sections 6.8.2 and 10.6.

Prior/Concurrent Clinical Study Experience

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

Other Exclusions

22. At screening a response of 2 (I would like to kill myself) or 3 (I would kill myself if I had the chance) on BDI-II item 9 (Suicidal thoughts or wishes).
23. Clinically relevant recreational/illicit drug or alcohol abuse within 12 months of signing of informed consent[4].
24. 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).
25. Known hypersensitivity to elinzanetant or any of the excipients in the formulation.
26. 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.
27. Wish for pregnancy during the study period.

5.3 Lifestyle Considerations

No restrictions to lifestyle are required.

5.4 Screen Failures

A screen failure occurs when a participant consents to participate in the clinical study but is 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, and eligibility criteria based on completed procedures.

[4] 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).

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once. Rescreening will not be allowed in participants who failed because of any of the following criteria:

- Inclusion criterion 8
- Exclusion criteria: 1, 6, 9, 10, 11, 13, 14, 18, 22, and 25.

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., post-vaccine delay for mammogram, delayed result or repeated endometrial biopsy, technical ePRO issues) would constitute a reason for postponing randomization. Under these circumstances and to keep the treatment-free screening period as short as possible, the baseline visit will be scheduled as soon as reasonably possible, once the issue or condition is resolved and all screening results available. In case the screening period is extended to more than 8 weeks, a new blood sample has to be taken for assessment of eligibility.

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 Intervention(s) Administered

Intervention Label	Elinzanetant	Placebo
Intervention Name	BAY 3427080 / elinzanetant	Placebo
Intervention Description	60 mg capsule, 120 mg, qd	two capsules, qd
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	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 Former Name	BAY 3427080 NT-814	N/A

Alu = Aluminium; N/A = Not applicable; qd = Once daily

Table 6-2: Study Arm(s)

Arm Title	Elinzanetant	Placebo
Arm Type	experimental	placebo
Arm Description	Participants will receive 120 mg elinzanetant orally once daily for 52 weeks and optionally for additional 2 years.	Participants will receive placebo orally once daily for the first 12 weeks. 120 mg elinzanetant will be administered from week 13 to 52 and optionally for additional 2 years.
Associated Intervention Labels	Elinzanetant	Placebo or Elinzanetant

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 both treatment arms, with or without food. For requirements on drug intake for PK sampling, please refer to Section 1.3.4.

If a participant forgets to take a dose in the evening, then the dose can be taken at any time up to 2AM 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. Study intervention may only be dispensed to a study participant of child bearing potential after ruling out pregnancy (urine pregnancy test with negative result).

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 an 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. A Liver Safety Monitoring Board will assess the blinded cases that enter Close Liver Observation.

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

Study participants who have completed the main study of 52 weeks of treatment will be offered to continue with the study and study drug intake for 2 additional years (treatment extension). No general access to study intervention is planned after the end of the study. Investigators can request post trial access for their study participants, if deemed necessary.

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:

- 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 Background therapy

As per inclusion criterion 2, all participants experience VMS caused by adjuvant endocrine therapy, i.e. either “tamoxifen with or without the use of GnRH analogues” or “aromatase inhibitors with or without the use of GnRH analogues”.

These background therapies are considered as Auxiliary Medicinal Products (not an Investigational Product) and are authorized in all participating countries. Please refer to the current prescribing information / Summary of Product Characteristics (SmPC).

These drugs will be used as prescribed by the participant’s physician (e.g., oncologist, gynecologist, or general practitioner) for the treatment of breast cancer or for the prevention of developing breast cancer. The European Society for medical oncology clinical practice guideline for breast cancer prevention and screening says that adjuvant endocrine therapy should be administered as clinically indicated although the level of evidence is weak (Paluch-Shimon et al. 2016). The use of adjuvant endocrine therapy for the prevention of breast cancer varies between countries and within countries.

These drugs will be supplied locally (by the site or local pharmacy) during the course of the study as per local laws and regulations. In case of local shortages the sponsor may supply background medication as a risk mitigation to ensure that participants can continue the study as planned.

These Auxiliary Medicinal Products will be recorded in the prior and concomitant medication pages of the eCRF.

Participants will document these background medication intakes on a daily basis in the eDiary (using hand-held device) as indicated in the SoA, i.e. until EoT visit (week 52). A participant who completed the 52 weeks treatment period will be offered 2 additional years of treatment extension (part C). During the part C the intake will not any longer need to be documented on a daily basis. Instead some general information will be collected during the visits (see Section 8.1.2).

The participant should be on stable adjuvant endocrine therapy at least 6 weeks prior to baseline and, until the week 12 visit (T6), it is not permitted to switch or to modify dose of adjuvant endocrine therapy (e.g., switch from tamoxifen to an aromatase inhibitor, or switch from one aromatase inhibitor to another aromatase inhibitor).

6.8.2 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.

6.8.3 Other Treatment Considerations

Based on preclinical data, an increase in exposure of drugs that are sensitive substrates of OATP1B1/1B3, P-glycoprotein or breast cancer resistance protein (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. Results from a clinical drug-drug interaction study with the sensitive P-gp substrate dabigatran etexilate (study 22081) showed no clinically relevant interaction. Therefore, medications that are substrates of P-gp can be administered together with elinzanetant without restrictions.

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, and if the investigator considers it medically justified, the participant may remain in the study without receiving the study intervention. 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.

Treatment extension (part C):
Participants who prematurely discontinue from treatment during part C are asked to return to the EoT part C and FU part C visit.

For withdrawal from study see Section 7.2.

7.1.1 Pregnancy

The participants must discontinue study intervention in case of pregnancy (See Section 8.3.5).

7.1.2 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.
No lab samples are taken during part C. In case the participant meets one of these thresholds in lab samples taken outside of the study these criteria apply.

7.1.3 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.
No lab samples are taken during part C. In case the participant meets one of these thresholds in lab samples taken outside of the study these criteria apply.

7.1.4 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.

7.1.5 Rechallenge

Study intervention may be restarted after a temporary interruption if deemed clinically appropriate by the investigator in collaboration with the Sponsor's representative (e.g. medical monitor).

7.1.5.1 Study Intervention Restart or Rechallenge After Liver Stopping Criteria Met

Section 7.1.5.1 is not applicable for the treatment extension (part C).

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 7.1.4) 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.
  - If a participant discontinues treatment with tamoxifen/aromatase inhibitors in the main study (part A+B), the investigator will decide whether the participant should be withdrawn from the study.
    - If a participant discontinues treatment with tamoxifen/aromatase inhibitors during treatment extension (part C), she should be withdrawn from the study.
- At the time of discontinuing from the study, if possible, End of Treatment visit (either EoT or EoT part C visit) procedures should be conducted, followed by a 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 (Section 1.3). Protocol waivers or exemptions are not allowed.
- 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 screen 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 (Section 1.3).

The efficacy assessments described in Section 8.1.1 are not conducted during treatment extension (part C) of the study.

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. 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
- SF-36 acute
- Evening HFDD
- Sleepiness Scale (See Section 8.2.10)
- Study drug intake documentation (See Section 6.4)
- Background medication intake documentation (See Section 6.8.1)
- Vaginal bleeding diary[5]
- Result of home urine pregnancy test (independent of above sequence)

After BL visit up to Visit T6 (inclusive) the PROMIS SD SF 8b, the MENQOL, the BDI-II, the EQ-5D-5L and the SF-36 acute 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 T7 onwards these ePROs will be completed by the participant during the study visits.

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 6 min during normal days during the study without study visits to a maximum of 60 min on the one day when all/most questionnaires are to be completed.

[5] Only to be completed by women who use tamoxifen monotherapy as adjuvant endocrine therapy and who had in addition a menstrual bleeding in the 3 months prior to the Baseline Visit.

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. 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 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 time points, 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 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 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 urgent technical questions.

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

In case one entry on the HFDD, the Sleepiness Scale, the Study/background medication intake or the vaginal bleeding diary was missed (for morning diaries in case this was not completed when getting up in the morning; for evening diaries, Sleepiness Scale, study/background medication intake and vaginal bleeding diary 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 11:00 AM and 11:59 PM. For the evening diary, the Sleepiness Scale, the Study/background medication intake documentation, and the vaginal bleeding diary, the entry option will be available between midnight until 10:59 AM 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 participants 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. 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 at time points indicated in the SoA. 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".

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 handheld device at the time points indicated in the SoA.

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 participants indicate 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.

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

8.1.1.4 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 study participants at home and during selected in person visits at the timepoints indicated in the SoA.

8.1.1.5 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 study participants at home and during selected in person visits at timepoints indicated in the SoA.

8.1.1.6 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).

The investigator will receive an email notification if a BDI of >19 is reported. The investigator may consider reporting an adverse event based on the clinical presentation. 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 to local clinical practice. See details in Section 8.2.11 for eligibility criteria based on BDI-II.

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

8.1.1.7 Short Form-36 Health Survey Acute (SF-36 acute)

The SF-36 acute is a widely used measure of general health status with well-documented reliability, validity, and responsiveness in the general population as well as in various disease indications. It consists of 36 items which are responded to using item specific 1-5 or 1-3 Likert scales. The acute version has a recall period of 1 week. The items are comprising 8 domains: physical function, role physical, bodily pain, general health, vitality, social functioning, role of emotional and mental health and two composite scores, the physical component score (PCS) and mental component score (MCS). Scores from individual items of each subscale are combined to form a subscale rating and are transformed to a 0 to 100 scale. Higher scores indicate better quality of life. Reference values derived in a healthy population, distributed by age and gender, are available.

In this study the SF-36 acute will be applied electronically and responded to by the study participants at home and during selected in person visits at the timepoints indicated in the SoA.

8.1.1.8 Vaginal bleeding diary

The vaginal bleeding diary will be completed only by pre-menopausal women who use tamoxifen monotherapy as adjuvant endocrine therapy and who had in addition a vaginal bleeding in the 3 months prior to the Baseline Visit. The vaginal bleeding diary will be completed only during the placebo-controlled period of 12 weeks. It will be filled in daily using the electronic hand-held device.

The vaginal bleeding diary is a frequently used PRO instrument designed to assess the participant's experience of vaginal bleeding symptoms. The vaginal bleeding diary will be completed daily by the participant each evening in the electronic hand-held device, when the participant is to reflect on her experiences in the past 24 hours. Participants will be asked to rate their vaginal bleeding as follows:

- None (no vaginal bleeding)
- Spotting (less than associated with normal menstruation relative to the participant's experience, with no need for sanitary protection (except for panty liners))
- Light (less than associated with normal menstruation relative to the participant's experience, with need for sanitary protection)
- Normal (like normal menstruation relative to the participant's experience)
- Heavy (more than normal menstruation relative to the participant's experience)

Findings from the vaginal bleeding diary data only need to be documented as an AE, if they lead to a special diagnosis, treatment or to a drop-out.

8.1.2 Investigator collected Patient Reported Outcomes (RAVE)

Only applicable for treatment extension (part C) of the study.

During each visit, the investigator will ask the participant about adherence to the prescribed intake schedule of the adjuvant endocrine therapy (tamoxifen/aromatase inhibitor) during the past 6 months by use of a five-point Likert scale: none of the time, a little of the time, some of the time, most of the time, all the time.

The investigator will document the participant's responses in her patient file and enter the response in the eCRF.

8.2 Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Section 1.3).

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 Visit only.
- Weight will be recorded at all in person visits.
- 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.[6]

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.

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[6] Hypertension is defined as systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg over three readings on at least two different occasions.

- 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.
    - 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

All women who are not confirmed post-menopausal or who are WOCBP should have pregnancy tests performed according to the SoA. See Section 10.4.1 for definitions.

In these participants a urine pregnancy test will be performed to confirm eligibility at Screening and at Baseline prior to the first study drug intake. Afterwards, urine pregnancy tests will be performed during all site visits. Additionally, the participant is asked to conduct home urine pregnancy testing as indicated in the SoA and document the results in the eDiary. If the home urine pregnancy test is positive or cannot be confirmed as negative (e.g., an ambiguous result) after repeating at home, the participant should contact the site immediately. Further investigations will be performed at the discretion of the investigator. Reference is made to Section 8.3.5 in the unlikely event that a pregnancy is detected during the study. The home pregnancy tests will be provided by the sponsor.

Treatment extension (part C):

No urine pregnancy tests will be performed during the site visits. The participant is asked to conduct home urine pregnancy testing once a month, e.g., when starting a new package. If the home urine pregnancy test is positive or cannot be confirmed as negative (e.g., an ambiguous result) after repeating at home, the participant should contact the site immediately. Further investigations will be performed at the discretion of the investigator. Reference is made to Section 8.3.5 in the unlikely event that a pregnancy is detected during the study. The home pregnancy tests will be provided by the sponsor.

8.2.6 Mammogram

Mammogram will be performed at time points indicated in Section 1.3.

- Prior mammogram results may be used for eligibility if obtained no more than 12 months prior to signing informed consent and the results should be documented in the eCRF.
- Women with bilateral mastectomy do not have to provide a mammogram provided that all breast tissue has been removed. If a mammogram is not possible after partial mastectomy an ultrasound could be performed instead.
- Mammograms should be obtained during the study in alignment with local medical guidelines for the follow up of the specific participant and the results should be documented in the eCRF.
- At the 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 follow up of the specific participant and the results should be documented in the eCRF.
- 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 any planned COVID-19 vaccination after the EoT mammogram (if a mammogram is required, see above).

8.2.7 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.
- Cervical smear is not required in participants with total hysterectomy (condition needs to be recorded in the eCRF).

8.2.8 Transvaginal ultrasound (TVU)

- Transvaginal ultrasound should be performed as indicated in the SoA or if the participant has symptoms (e.g. unexplained vaginal bleeding) and endometrial biopsy will be considered depending on the endometrial thickness (see Section 8.2.9)

- Ultrasound examination should be performed by a physician/examiner well experienced in the procedure 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.
- If TVU is not possible due to vulvo-vaginal atrophy (e.g. in women who use aromatase inhibitors) an abdominal or transrectal ultrasound is allowed.
- The following safety parameters will be measured and recorded:
    - Endometrial thickness (measured in the medio-sagittal section as double-layer in millimeters)
    - Overall 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.
- TVU is not required in participants with total hysterectomy and bilateral salpingo-oophorectomy (these conditions need to be recorded in the eCRF).

8.2.9 Endometrial biopsy

Timing and sampling of endometrial biopsy

- Endometrial biopsy is to be performed only when applicable as outlined below at time points indicated in the SoA.
- Endometrial biopsy should be performed by a physician/examiner well experienced in the procedure or with corresponding qualification based on local clinical practice
- Endometrial biopsy should be performed if the participant has an intact uterus and has symptoms (e.g. unexplained vaginal bleeding)
- Endometrial biopsy should be considered if:
    - the endometrial thickness assessed by TVU is ≥7 mm for pre-menopausal women. According to the Royal College of Obstetricians and Gynaecologists guidance (Royal College of Obstetricians and Gynaecologists 2016), endometrial hyperplasia is unlikely if the endometrial thickness <7 mm. The final decision to perform an endometrial biopsy should be based on the investigator's clinical judgement and usual clinical practice.
    - the endometrial thickness assessed by TVU is ≥4 mm for post-menopausal women.
- If an endometrial biopsy was taken at screening, the result should be normal in order for the participant to be randomized (disordered proliferative endometrium, hyperplasia, polyp and malignant findings will be considered as abnormal).

- 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 unexplained bleeding during the study.
- 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.

- Women with a diagnosis of disordered proliferative endometrium, endometrial hyperplasia, polyp or malignant neoplasm by any of the three pathologists will not be included in the study.
- 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.
- Any abnormal endometrial biopsy findings should be followed-up and treated according to local clinical practice.

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 assessment will be done on 7 consecutive evenings at time points indicated in the SoA.

8.2.11 Suicidal thoughts or wishes: Beck's Depression Inventory (BDI-II)

Suicidal thoughts or wishes will be assessed at screening by the BDI-II item 9. For further details regarding the BDI-II, please refer to Section 8.1.1.6.

See Exclusion Criterion 22 for information on when the participant should not be randomized based on suicidal ideation.

The investigator will receive an email notification if a participant responded to item 9 with a 2 (I would like to kill myself) or a 3 (I would kill myself if I had the chance). If this happens after randomization the participant can continue the study at the discretion of the investigator. The investigator has to consider reporting an adverse event based on the clinical presentation. In addition, any suicidal ideation 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, Institutional Review Boards (IRB)/Independent Ethics Committees (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 suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

8.3.5 Pregnancy

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 study 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.

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 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, for tamoxifen and its metabolites and for the aromatase inhibitors (i.e. anastrozole) in plasma for PK are to be collected at the time points given in Table 1-4. The date and time of study drug intake and adjuvant endocrine therapy on the previous dosing days prior to the PK sampling as indicated in Table 1-4, the time of the supervised intake of elinzanetant, 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 has to 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 study drug intake and adjuvant endocrine therapy 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, tamoxifen and its metabolites or aromatase inhibitors (i.e. anastrozole) are determined using a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS). Quality control (QC) and calibration samples are analyzed concurrently with study samples. The results of calibration samples, QC 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.

Pharmacometric 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 will 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.

The PK data and the relationship of the elinzanetant exposure parameters (e.g. C_{max}, AUC) with treatment effects might be evaluated using pharmacometric approaches (e.g. non-linear mixed effect modeling) including potential influence of relevant subject co-variables. 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.

8.5 Genetics

In this study a CYP2D6 genotyping analysis will be performed in all participants treated with tamoxifen. The CYP2D6 enzyme is one of the main enzymes involved in converting tamoxifen into its major active metabolite, endoxifen. Genetic variation in the CYP2D6 gene (various CYP2D6 alleles will be determined) may lead to increased ("ultrarapid metabolizer"), decreased ("intermediate metabolizer"), or absent ("poor metabolizer") enzyme activity.

8.6 Biomarkers

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

PD /safety biomarkers from blood

BM samples (see below) will be collected within the first 12 weeks of the study.

The following table gives an overview on sample types collected:

Sample type	Description
Biomarker plasma	**Blood sample to provide plasma for biomarker analyses**
Biomarker serum	**Blood sample to provide serum for biomarker analyses**
Biomarker whole blood	**For CYP2D6 polymorphism (only collected from tamoxifen participants)**

- **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).

8.7 Immunogenicity Assessments

Not applicable.

8.8 Health Economics

EQ-5D-5L data will be collected; VAS and single-dimensions will be assessed descriptively (see Section 8.1.1.4). 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 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.

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

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 PROMIS SD SF 8b total score at week 12.

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 MENQOL total score at week 12.

For the confirmatory efficacy analysis, a hierarchical testing approach will be applied, involving the two primary efficacy variables and the two key secondary variables.
The type I error rate will be controlled at a one-sided α=0.025 level. For a positive study outcome, both tests for primary variables need to be significant. As the hierarchical testing procedure follows a fixed sequence, it stops as soon as any of these tests cannot be rejected at an alpha level of 0.025 and all further tests after failing to reject one null hypothesis in the testing sequence will be considered exploratory. This fixed sequence procedure accounts for the multiplicity created by carrying out multiple tests. Moreover, all other endpoints will be summarized descriptively and therefore no multiplicity adjustment is needed.

9.2 Sample Size Determination

Approximately 405 participants will be randomly assigned to study intervention in a 2:1 ratio. Of these, 270 participants will be randomly assigned to elinzanetant and the other

135 participants will be randomly assigned to the placebo arm. The randomization will be stratified by women with a personal history of hormone-receptor positive breast cancer or women at high-risk for developing breast cancer (maximum of 10% of participants for high-risk developing breast cancer) and by type of treatment of pre-existing condition at baseline (at least 40% of participants on tamoxifen and at least 40% of participants on aromatase inhibitors in both population groups, i.e. breast cancer and high-risk for developing breast cancer). Assuming a drop-out rate of 10 % in the first 3 months, this will result in approximately 243 evaluable participants in the elinzanetant arm and approximately 122 participants in the placebo arm who completed 12 weeks of treatment. Assuming a yearly drop-out rate of 30% in the elinzanetant arm, approximately 189 participants will be available that were treated for 1 year.

The number of participants needed for this study is based on the total number of participants needed for the safety evaluation. Following the ICH E1 guideline (EMA 1995), a total of 1,500 participants are required that were exposed to at least one dose of elinzanetant 120 mg. Of these 1,500 participants 300-600 should have been treated for at least 6 months and approximately 100 for 1 year. Based on the number of participants that are available from previous phase 1 and phase 2 studies, together with the number of participants that are planned to be enrolled in ongoing and upcoming phase 3 studies, the number of participants needed for the elinzanetant arm in this study is 270, also taking into account that participants in the placebo arm receive elinzanetant after 3 months and the drop-out rates described above.

Screen failures are defined in Section 5.4. Assuming a screen failure rate of 50% approximately 810 participants need to be enrolled to achieve the required number of 405 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 justification was performed for the primary efficacy endpoints using the one-sided two-Sample T-test (equal variance) assuming at least approximate normal distribution and taking into account the drop-out rate of 10% in the first 3 months as described above. The power with treatment differences (i.e. mean change in frequency of moderate to severe HF from baseline to Week 4 or 12), with N=243 in the elinzanetant arm and N=122 in the placebo arm and assumed standard deviations are provided in Table 9-1. The data from placebo arm in SWITCH-1 study (NCT03596762 2020) was used for assumption of standard deviation.

Table 9-1: Sample size justification

Primary efficacy endpoint	Standard deviation	Treatment difference Elinzanetant vs. placebo	Power %
Mean change in frequency of moderate to severe HF from baseline to Week 4	3.632	-1.00	69.67 %
		-1.50	96.01%
		-2.00	>99.9 %
Mean change in frequency of moderate to severe HF from baseline to Week 12	4.29	-1.00	55.38 %
		-1.50	88.16 %
		-2.00	98.71 %
Mean change in PROMIS SD SF 8b total score from baseline to Week 12	1.00	-0.4	94.90 %
Mean change in MENQOL total score from baseline to Week 12	1.00	-0.4	94.90 %

nQuery Version 9.1.0.0 was used for sample size calculation.
HF = Hot Flash, MENQOL=Menopause Specific Quality of Life Scale, PROMIS SD SF 8b=Patient-reported Outcomes Measurement Information System Sleep Disturbance Short Form 8b

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 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 statistical analysis plan (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 and secondary endpoints.

If not otherwise indicated, the statistical analyses will be performed using SAS; 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. Where appropriate 95 % confidence intervals will be provided. Discrete data will be analyzed using frequency tables. Further details will be described in the SAP.

Intercurrent Events

Important Intercurrent Events (ICEs) for this study are defined as:

a. Temporary treatment interruption in the week 4 defined as treatment taken <80% during weeks 1-4 OR treatment taken on <5/7 days during either week 3 or 4.

   Temporary treatment interruption in the week 12 defined as 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.

d. Interruption/discontinuation in intake of adjuvant endocrine therapy defined as follows:

   - For participants using Tamoxifen: reduction of at least 50% of planned daily dosage taken during weeks 3 and 4 OR weeks 11 and 12 compared to baseline
   - For participants using Aromatase inhibitor: reduction of at least 30% of planned daily dosage taken during weeks 3 and 4 OR weeks 11 and 12 compared to baseline

The impact of these ICEs on the study results and its interpretation is addressed in Table 3-2 where the primary estimand for the primary endpoint is defined.

A low impact of the COVID-19 pandemic on missing assessments of the frequency and severity of HFs is considered 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 HFs related endpoints.

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

The number of deaths are considered to be small and therefore the impact of death as a potential ICEs is expected to be negligible. That will be monitored throughout the trial until the blind review and if deemed necessary, the estimand will be adjusted in the SAP before the study unblinding.

The number of observed intercurrent events will be summarized by treatment group and overall, for each intercurrent event.

9.4.2 Primary Endpoint

The primary efficacy endpoints for 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)

9.4.2.1 Calculations related to the frequency and severity of HF

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.

The baseline value of 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 criterion 8, at least 11 days will be available for the derivation of the baseline value.

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 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). 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 primary estimand to be applied to primary efficacy endpoints is described in Table 3-2.

The primary endpoint will be analyzed using a mixed model with repeated measures (MMRM) model on the change from baseline scores at various weeks including Week1, Week 4, Week 8 and Week 12. Baseline, treatment, week, population type (women with a personal history of hormone-receptor positive breast cancer or women at high-risk for developing breast cancer) and the type of treatment of pre-existing condition at baseline (stratification factors for randomization) 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 PROMIS SD SF 8b total score from baseline to Week 12
- Mean change in MENQOL total score from baseline to Week 12

The secondary efficacy endpoints in this study are:

- 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)
- Mean change in frequency of moderate to severe HF from baseline to Week 1
- Mean change in frequency of moderate to severe HF from baseline over time (assessed by HFDD)

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.

The same clinical questions are posed in respect of each primary and key secondary endpoint, and hence the 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).

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.

Details for the analysis of the secondary endpoints will be provided in the SAP.

9.4.4 Exploratory / Other Endpoints

The analysis of the exploratory / other safety and efficacy 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 database 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

Subgroup analyses may be specified in the SAP.

9.5 Interim Analysis

Blinded data may be used for evaluation of psychometric and other measurement properties of PRO instruments.

The analysis of part A is planned after the last participant completed part A. This will be the final analysis for efficacy and safety of part A data based on cleaned and final data and will be reported together with part B data. No multiplicity adjustment is needed since the primary efficacy analysis will be final after the evaluation of part A data. Part B data will be analyzed for available endpoints and reported together with the data from part A in one report. Treatment extension (part C) will be analyzed and reported separately from parts A and B. Further details will be given in the SAP.

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 (CIOMS) 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) has been 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 are described in the DSMB charter.

10.1.3 Liver Safety Monitoring Board

An independent liver safety monitoring board (LSMB) has been 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 are 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

Detailed description of the recruitment strategy will be provided in country-specific documentation as required.

- 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.
- It may be considered to apply an eConsent process in some countries. The consenting will still take place at the site (no remote consenting). Instead of a paper version the informed consent information will be provided in an electronic format.
- If the participant decides to take part in the treatment extension, she will sign a separate ICF.

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 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 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.
- The contract between sponsor and study sites specifies responsibilities of the parties related data protection, including handling of data security breaches and respective communication and cooperation of the parties.
- Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.

10.1.7 Dissemination of Clinical Study Data

Result Summaries of Bayer's sponsored clinical studies in drug development phases 2, 3 and 4 and Phase 1 studies in patients are provided in the Bayer Clinical Trials Explorer 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 Information System (CTIS) in line with the applicable regulations.

In accordance with the current EU regulation, result summaries will be submitted within one year from the end of the studies in adult populations in all participating countries. No

preliminary data analysis (e.g., on EU data only) will be performed, as this might compromise data integrity and the scientific validity of the study.

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 electronic CRF 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 CRF.
- Guidance on completion of CRFs will be provided in the CRF 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.
- Quality tolerance limits (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 CRF 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

Study Start

The study start date is the date on which the clinical study will be open for recruitment of participants.

The start of a clinical study in EU is defined as the date on which the first site is declared by the sponsor to be ready to enroll in a country and clinical study will be open for recruitment of participants.

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, magnesium, chloride, total protein, hemoglobin A1c, lactate dehydrogenase (LDH), Estimated Glomerular Filtration Rate (eGFR, only at screening)
Coagulation:	prothrombin time (Quick), INR, activated partial thromboplastin time (aPTT)
Hormones:	thyroid-stimulating hormone (TSH), triiodothyronine (T3), thyroxine (T4), free triiodothyronine (fT3), free thyroxine (fT4), estradiol (E2) only at BL, T2, T4, T6.
Bone markers	bone-specific alkaline phosphatase (BALP),
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)[a]
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	CYP2D6 genotyping (only from participants treated with tamoxifen)
Pharmacokinetics	pre-and post-dose PK samples
Biomarkers	For biomarkers, serum and plasma samples needed

ASCUS = atypical squamous cells of undetermined significance; BM = biomarker, CYP2D6 = Cytochrome P450 2D6, 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
a Only if the urine pregnancy test does not show a final conclusive negative result a serum pregnancy test is required.

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.
- Sign, symptoms, or the clinical sequelae of suspected medication errors, misuse and abuse of either study intervention or a concomitant medication. Medication errors, misuse and abuse per se will not be reported as an AE/SAE, unless it is resulting in AE/SAE. Such medication errors, misuse and abuse 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 NOT 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

10.4.1 Definitions

Woman of Childbearing Potential (WOCBP)

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

Women in the following categories are considered WOCBP (fertile)

1. Following menarche
2. From the time of menarche until becoming postmenopausal unless permanently sterile (see below).

A postmenopausal state is defined as:

- ≥12 months of spontaneous amenorrhea in the absence of other physiological or pathological causes (e.g. pregnancy, thyroid disease, hyperprolactinemia) or
- Surgical menopause as a result of bilateral oophorectomy with or without hysterectomy at least 6 weeks prior to signing of informed consent

Permanent sterilization methods (for the purpose of this study) include:

- Documented hysterectomy
- Documented bilateral salpingectomy
- For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), investigator discretion should be applied to determining study entry.

Note: Documentation can come from the site personnel's: review of the participant's medical records, medical examination, or medical history interview.

If fertility is unclear (e.g., amenorrhea in athletes, post-chemotherapy amenorrhea) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Woman of Nonchildbearing Potential (WONCBP)

Women in the following categories are considered WONCBP:

1. Pre-menopausal female with permanent infertility due to one of the following:
    - Documented hysterectomy
    - Documented bilateral salpingectomy
    - Documented bilateral oophorectomy
    - For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), investigator discretion should be applied to determining study entry.
2. Postmenopausal women (see definition above)

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview

10.4.2 Contraception Guidance

This study does include Woman of Childbearing Potential (WOCBP) and accordingly these women must use highly effective contraception during the entire study participation. Reference is made to Section 10.4.3 in the unlikely event that a pregnancy is detected during the study.

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
Highly Effective Methods[b] That Have Low User Dependency *Failure rate of < 1% per year when used consistently and correctly.*
• Intrauterine device without hormonal release (IUD)
• Bilateral tubal occlusion
• Azoospermic partner (vasectomized or due to a medical cause) *Azoospermia is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.* Note: documentation of azoospermia for a male partner can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
Highly Effective Methods[b] That Are User Dependent *Failure rate of < 1% per year when used consistently and correctly.*
Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)*
a) Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies. b) Failure rate of < 1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly.

The table below presents contraceptive methods that are **not** considered highly effective and these should **not** be used during the study.

CONTRACEPTIVES NOT ALLOWED DURING THE STUDY INCLUDE:
Effective Methods That Are Not Considered Highly Effective *Failure rate of ≥ 1% per year when used consistently and correctly.*
• Male or female condom with or without spermicide
• Cervical cap, diaphragm, or sponge with spermicide
• A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods)[c]
Note: Periodic abstinence (calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception.

10.4.3 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 as defined in Table 10-2, a retest should 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)
Bone-specific alkaline phosphatase (BALP)
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
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

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

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 1 week prior to Baseline Visit	Vaginal hormonal products (rings, creams, gels)
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 • Intrauterine progestin therapy
From 12 weeks prior to Baseline Visit	Progestin implants and estrogen alone injectable drug therapy
From 24 weeks prior to Baseline Visit	Estrogen pellet therapy or progestin injectable drug therapy
	Non-hormonal therapies
From 12 weeks prior to Baseline Visit	adjuvant endocrine therapy other than tamoxifen, aromatase inhibitors or GnRH analogues (e.g., CDK 4/6 inhibitor, toremifene, fulvestrant). The participant is allowed to switch to CDK 4/6 inhibitors[redacted] after 12 weeks of treatment with the study intervention (i.e., after the placebo-controlled period ends).
From 4 weeks prior to Baseline Visit	Antidepressant drugs: Participants are permitted to continue to use antidepressant drugs and over the counter/herbal treatments (see details below) when the dose has been stable for at least 4 weeks and when it is anticipated to be stable for the duration of the study. In addition, the drug has been prescribed solely for the management of another disorder (e.g., neuropathic pain, depression). Participants are not allowed to start with these drugs during the study: • Anti-depressant drugs with effect on vasomotor symptoms (e.g., 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 vasomotor symptoms. Others: • Oxybutynin/ Oxybutynin hydrochloride

CDK = Cyclin-dependent kinases, CYP2D6 = Cytochrome P450 2D6, GnRH = Gonadotropin-releasing hormone

CCI

Table 10-6 and Table 10-7 list examples of the most common medication regarded as

CCI

10.7 Appendix 7: Additional information on scoring and measurement properties of the HFDD, the PROMIS SD SF 8b and the MENQOL

10.7.1 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.

10.7.2 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.

10.7.3 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

Response	Converted Score
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.

10.8 Appendix 8: Country/region-specific Requirements

10.8.1 Italy

10.8.1.1 ITA-1: Country/region-specific Changes Valid for Italy only

Overall Rationale

This section implements country-specific modifications of the original protocol, dated 30 SEP 2022, to meet local requirement in Italy.

10.8.1.1.1 Overview of Changes

A description of changes and a brief rationale is outlined in the table below:

Section # and Name	Description of Change	Brief Rationale
Section 1.1 Synopsis Section 4.1 Overall design Section 5.1 Inclusion Criteria	Only women treated with adjuvant endocrine therapy for hormone receptor-positive breast cancer are included in the study.	To follow the request from the Italian Medicines Agency AIFA. Only women treated with adjuvant endocrine therapy for hormone receptor-positive breast cancer should be included in the study.

10.8.1.1.2 Changes to the Protocol Text

10.8.1.1.2.1 Section 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 caused by adjuvant endocrine therapy, over 52 weeks in women with, or at high risk for developing hormone-receptor positive breast cancer

Short Title: **O**verall **A**ssessment of efficacy and **S**afety of elinzanetant **I**n patients with vasomotor **S**ymptoms in women with, or at high risk for developing hormone-receptor positive breast cancer (OASIS-4)

Rationale: This is a phase 3 study to assess the efficacy and safety of elinzanetant for the treatment of vasomotor symptoms (VMS) caused by adjuvant

endocrine therapy in women with, or at high risk for developing hormone-receptor positive breast cancer.

Note: In Italy only women with hormone-receptor positive breast cancer are allowed to participate in the study.

[…]

10.8.1.1.2.2 Section 4.1 Overall Design

This is a multi-center, multi-country, double-blind, randomized, parallel-group, placebo-controlled, Phase 3 intervention study in women with, or at high risk for developing hormone-receptor positive breast cancer.

The study includes a wash-out period (if applicable), approximately 6-week screening, a 52-week treatment and a 4-week follow-up period.

Note: In Italy only women with hormone-receptor positive breast cancer are allowed to participate in the study.

[…]

10.8.1.1.2.3 Section 5.1 Inclusion Criteria

[…]

Type of Participant and Disease Characteristics

[…]

3. Women must have a personal history of hormone-receptor positive breast cancer

[…]

10.8.2 United Kingdom

10.8.2.1 GBR-1: Country/region-specific Changes Valid for United Kingdom only

Overall Rationale

This section implements country-specific modifications of the original protocol, dated 21 OCT 2022, to meet local requirement in United Kingdom.

10.8.2.1.1 Overview of Changes

A description of changes and a brief rationale is outlined in the table below:

Section # and Name	Description of Change	Brief Rationale
Section 5.1 Inclusion Criteria	The contraceptive methods must be used through the end of exposure (for at least 8 days after the last dose of elinzanetant).	To follow the request from Medicines and Healthcare products Regulatory Agency (MHRA). The contraceptive methods must be used through the end of exposure (for at least 8 days after the last dose of elinzanetant).

10.8.2.1.2 Changes to the Protocol Text

10.8.2.1.2.1 Section 5.1 Inclusion Criteria

[…]

Sex and Contraceptive/Barrier Requirements

9. Contraceptive use by women (except for post-menopausal women or WONCBP) should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

    - […]
        - […]

    OR

        - Is a WOCBP and using an acceptable contraceptive method as described in Section 10.4.2 during the study intervention period (the contraceptive methods must be used through the end of exposure (for at least 8 days after the last dose of elinzanetant)).
        […]

10.9 Appendix 9: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the table of contents (TOC).

Amendment 1 (09 DEC 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 because it impacts the safety of participants of the study.

Below is a description of the change and a brief rationale.

Key Changes

Section # and Name	Description of Change	Brief Rationale
Section 1.3.2 Treatment and follow-up	Add blood sample (safety) at T9	In the original version of the clinical study protocol a tick for collecting a blood sample 'safety' test at Visit T9 in week 26 was missing in the schedule of activities (Table 1-2).
Section 1.3.2 Treatment and follow-up Section 1.3.3 PK sampling schedule	Add PK sampling at T4 and T6	Longitudinal PK data of tamoxifen/aromatase inhibitors in relation to elinzanetant exposure is required to be able to detect potential drifts in the exposure.
Section 1.3.3 PK sampling schedule	PK sampling at BL was updated to prior to first elinzanetant dose	True baseline PK values for tamoxifen/aromatase inhibitors in the absence of elinzanetant are required in order to quantify the influence of elinzanetant on the exposure of these comedications.

Section 2.3.1 Risk Assessment Section 5.1 Inclusion Criteria	DDI study elinzanetant and tamoxifen is completed. The results from this DDI study together with the multiple dose simulations indicate no clinically relevant interaction between tamoxifen and its metabolites when continuously co-administered with elinzanetant with respect to safety and efficacy supporting the combined use in the ongoing Phase 3 study OASIS 4. Further PK data is being collected in the OASIS 4 study. Maximum daily dose of 20mg was removed for tamoxifen.	Tamoxifen is indicated for treatment of adult patients with estrogen receptor-positive metastatic breast cancer in doses of 20 and in some countries up to 40 mg daily. Based on the results of the DDI interaction study with elinzanetant and tamoxifen there is no need to exclude women using 40 mg tamoxifen from participation in this study.
Section 5.1 Inclusion Criteria	To ensure that contraceptive protection is used throughout the entire time of exposure, it was requested that a highly effective contraceptive method is to be used until at least 8 days after the last dose of elinzanetant.	To follow the request from Medicines and Healthcare products Regulatory Agency (MHRA). The contraceptive methods must be used through the end of exposure (for at least 8 days after the last dose of elinzanetant).
Section 6.6 Continued Access to Study Intervention after the End of the Study	No general access to study intervention is planned after the end of the study. Investigators can request post trial access for their patients, if deemed necessary.	There is no treatment available for VMS in this patient population. If it is in the interest of the study participant to continue with study drug the investigator can request post-trial access.

Clarifications to the protocol

Section # and Name	Description of Change
Section 5.5 Criteria for Temporarily Delaying Randomization	In case the screening period is extended to more than 8 weeks, a new blood sample has to be taken for assessment of eligibility.
Section 10.6 Prohibited concomitant medications	CCI [redacted] after 12 weeks of treatment with the study intervention is allowed.

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

Section # and Name	Description of Change
Section 5.1 Inclusion Criteria	The contraceptive method was updated to a highly effective contraceptive method, in accordance with Section 10.4.2 Contraception Guidance.
Section 1.3.1 Screening Section 8.2.5 Pregnancy Testing	Footnote b was removed at SCR-1 in Table 1-1. The text of in all participants except those who have undergone total hysterectomy and/or bilateral oophorectomy was removed in Section 8.2.5 since the scope of the pregnancy tests was described above.

10.10 Appendix 10: Abbreviations and Definitions

Definitions:

Throughout this document, terms study drug 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
ASCUS	Atypical squamous cells of undetermined significance
AST	Aspartate-aminotransferase
AUC	Area under the concentration vs. time curve from zero to infinity after single (first) dose
BCRP	Breast Cancer Resistance Protein
BDI	Beck Depression Inventory
BL	Baseline
BM	Biomarker(s)
BMI	Body mass index
CD	Compact disc
CHMP	Committee for Medicinal Products for Human Use
CK	Creatinine kinase
COVID-19	Coronavirus disease of 2019
CYP2D6	Cytochrome P450 2D6
CCI	[redacted]
DDI	Drug-drug interaction
DNA	Deoxyribonucleic acid
DSM-5	Diagnostic and Statistical Manual of Mental Disorders
DSMB	Data Safety Monitoring Board
DVT	Deep vein thrombosis
EC(s)	Ethics committee(s)
ECG	Electrocardiogram
eCOA(s)	Electronic clinical outcome assessments
eCRF(s)	Electronic case report form(s)
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
FU	Follow up
GCP	Good clinical practice
GGT	Gamma glutamyl transferase
GnRH	Gonadotropin-releasing hormone
HA	Health authority

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
IRB	Institutional review board
ISI	Insomnia Severity Index
IUD	Intrauterine device
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 (once)
LSMB	Liver Safety Monitoring Board
MCS	Mental component summary
MedDRA	Medical dictionary for drug regulatory affairs
MENQOL	Menopause-specific quality of life questionnaire
MI	Myocardial infarction
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
OCT	Organic cation transporter
PCR	Polymerase chain reaction
PCS	Physical component summary
PD	Pharmacodynamic(s)
PET	Positron emission tomography
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
QC	Quality control
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
SCR-1	Screening visit 1
SCR-2	Screening visit 2
SF-36 acute	Short Form-36 Health Survey Acute
SoA	Schedule of activities
SUSAR	Suspected unexpected serious adverse reaction(s)
TBL	Total bilirubin
TEAE(s)	Treatment-emergent adverse event(s)
TIA	Transient ischemic attack
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
WONCBP	Women of Nonchildbearing potential

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