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Title Page

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Protocol Number: 21656

Compound Number: BAY 3427080 / elinzanetant

Short Title: Overall Assessment of efficacy and Safety of elinzanetant In patients with vasomotor Symptoms in women with, or at high risk for developing hormone-receptor positive breast cancer

Acronym: OASIS-4

Sponsor Name: Bayer Consumer Care AG

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This Statistical Analysis Plan is produced on a word-processing system and bears no signatures.
The approval of the Statistical Analysis Plan is documented in a separate signature document.

Table of Contents

Table of Tables

Table of Figures

Version History

This Statistical Analysis Plan (SAP) for Study 21656 is based on the protocol Version 3.0 dated 10 MAY 2023.

SAP Version	***Date***	***Change***	***Rationale***
1.0	19 FEB 2024	Not applicable	Original version
2.0	16 APR 2024	This amendment of the SAP includes correction of typos, clarifications of wording and analyses as well as adding of data handling rules. Major changes have been incorporated in following Sections:	Needed changes were identified during review of this document and of blinded data.
		1) Redundant text removed from Section 4.1. 2) Imputation of missing date -rules were added to procedures and some events in Section 4.1.1. 3) Intercurrent event "interruption/ discontinuation in intake of adjuvant endocrine therapy" was added to data rules in Section 4.1.2.	Duplicate text noticed during review of this document. Prior, during and post procedures as well as duration of adjuvant therapy and time from initial diagnosis were added in this SAP version and therefore imputation rules were added. The rule clarified.
		4) Formula for calculation of compliance for adjuvant endocrine therapy clarified in Section 4.5.1.1.	Wording revied to make it clear.

		5) Wording for biopsies shown at End of Treatment in Section 4.5.3.9 was clarified.	Clarified the text to better reflect the current TLF specification.
		6) Listing for phenotype/metabolizer status in genotyping analysis was added (Section 4.6.1.2).	Listing added to this SAP version.
		7) Population type was removed from subgroup analyses (Section 4.6.2).	During blinded data reviewed it was seen that there is only 1 subject in high-risk for developing breast cancer-group.
		8) Table 6–5: Preliminary list of prohibited concomitant medication by drug grouping (can be updated during the blind review meeting) was revised.	Updated based on blind data review.
		9) Duration of adjuvant endocrine therapy (from initiation of the therapy until baseline visit) was added to demographics (Section 6.5.1).	Added to this SAP version.
		10) Section 6.5.2: Source CRF for Hysterectomy or oophorectomy was revised and time from initial diagnosis was added.	Corrected from previous SAP version.
		11) Tables for prior, concomitant or post-treatment adjuvant	Added to this SAP version.

		endocrine therapy was added (Section 6.5.5)	
3.0	08 MAY 2024	This amendment of the SAP includes adding of data handling rule.	Needed changes were identified during review of this document and of blinded data.
		1) Table for unscheduled visit was added to analysis of breast imaging (Section 4.5.3.6)	Added to this SAP version.
		2) Table 6–5: Preliminary list of prohibited concomitant medication by drug grouping (can be updated during the blind review meeting) was revised.	Updated based on blind data review.

List of Abbreviations

Abbreviation	Definition
AE	Adverse event
AESI	Adverse events of special interest
AIC	Akaike's information criteria
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AR(1)	Autoregressive first order
AST	Aspartate aminotransferase
ATC	Anatomical therapeutic chemical classification
BDI	Beck Depression Inventory
BL	Baseline
BMI	Body mass index
BRM	Blind review meeting
CI	Confidence interval
CK	Creatinine kinase
CM	Concomitant medication
CMH	Cochran-Mantel-Haenszel
COVID-19	Coronavirus disease of 2019
CS	Compound symmetry
CSR	Clinical study report
DILI	Drug-induced liver injury
ECG	Electrocardiogram
eCRF(s)	Electronic case report form(s)
eDiary	Electronic diary
EIN	Endometrioid Intraepithelial Neoplasia
EMA	European Medicines Agency
ePROs	Electronic Participant-Reported Outcomes
EQ-5D-5L	European Quality of Life 5-dimension 5-level questionnaire
EoT	End of treatment
FAS	Full analysis set
FDA	Food and Drug Administration
GGT	Gamma-glutamyl transferase
GnRH	Gonadotropin-releasing hormone
HF(s)	Hot flash or Hot flashes
HFDD	Hot flash daily diary
HR	Hormone receptor
ICE(s)	Intercurrent event(s)
ICF	Informed consent form
ICH	International Council on Harmonization
INR	International normalized ratio
ISI	Insomnia severity index
IUD	Intrauterine Device
LDH	Lactate dehydrogenase
LPLV	Last patient last visit
LSMB	Liver Safety Monitoring Board
MAO-A	Monoamine oxidase A
MAR	Missing at random
MCMC	Monte Carlo Markov Chain
MedDRA	Medical dictionary for regulatory activities
MENQOL	Menopause-specific quality of life questionnaire
MI	Multiple imputation
MMRM	Mixed model repeated measures
PD	Pharmacodynamic

PK	Pharmacokinetics
PROMIS SD SF 8b	Patient-Reported Outcomes Measurement Information System Sleep Disturbance short-form 8b
PT	Preferred term
QTc	Corrected QT-interval
SAEs	Serious adverse events
SAF	Safety analysis set
SAP	Statistical analysis plan
SD	Standard deviation
SE	Standard error
SF-36v2.0 Acute	Short Form 36 Health Survey Version 2.0 Acute
SMQ	Standardized MedDRA Query
SOC	System organ class
SSRI	Selective serotonin reuptake inhibitors
TB	Total bilirubin
TEAE	Treatment emergent adverse event
ULN	Upper Limit Normal
UN	Unstructured
VAS	Visual analog scale
VMS	Vasomotor symptoms

1. Introduction

Vasomotor symptoms (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.

Elinzanetant (formerly NT-8141) 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.

The SAP describes all the analyses for Part A, Part B and Part C. Part C will be analyzed separately. Table, figure and listing specifications are contained in a separate documents.

There are no changes to the analyses described in the protocol.

1.1. Objectives, Endpoints, and Estimands

Objectives and endpoints are listed in Table 1–1.

Table 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* • Mean change in frequency of mild, moderate, and severe HF from baseline over time (assessed by HFDD)**
• 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 T-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 total T- and total raw scores over time • Absolute values and changes from baseline in MENQOL total, domain and single item scores 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 v2.0 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 • Mean change in frequency of nighttime awakening from baseline over time (assessed by HFDD)** • Mean change in proportion of days with participants rating of “quite a bit” or “very much” sleep disturbances experienced due to HF from baseline over time (assessed by HFDD)**
• 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

Objectives	Endpoints
• 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)

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 v2.0 Acute = Short Form-36 Health Survey Version 2.0 Acute, TEAE = treatment emergent adverse event, VAS = Visual analog scale,
VMS = Vasomotor symptoms

*Please see Section 4.4.1 for the definition of treatment response.

**Exploratory endpoints in addition to listed in the protocol.

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 1–2 (for further details regarding the identification of ICEs see Section 6.4)

Table 1–2 : 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.

Table 1–2 : Primary Estimand: ICEs and Strategies to Address Them

ICEs[a]	Reason for ICE	Strategy	Data handling method

AE = Adverse event, COVID-19 = Coronavirus disease of 2019, ICE = Intercurrent event, VMS = Vasomotor symptoms
a) ICEs will be reviewed at the Blinded Review Meeting prior to the study unblinding
b) Definition of temporary treatment interruption:
Week 1 = Treatment taken on <5/7 days during week 1 (day 2-8).
Week 4 = Treatment taken <80% during weeks 1-4 (day 1-28) OR treatment taken on <5/7 days during either Week 3 or 4.
Week 8 = Treatment taken <80% during weeks 1-8 (day 1-56) OR treatment taken on <5/7 days during either week 7 or 8.
Week 12 = Treatment taken <80% during weeks 1-12 (day 1-84) 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 week 1, weeks 3 and 4, week 7 and 8 or weeks 11 and 12 compared to baseline
For participants using aromatase inhibitor: reduction of at least 30% of planned daily dosage taken during week1, weeks 3 and 4, week 7 and 8 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.

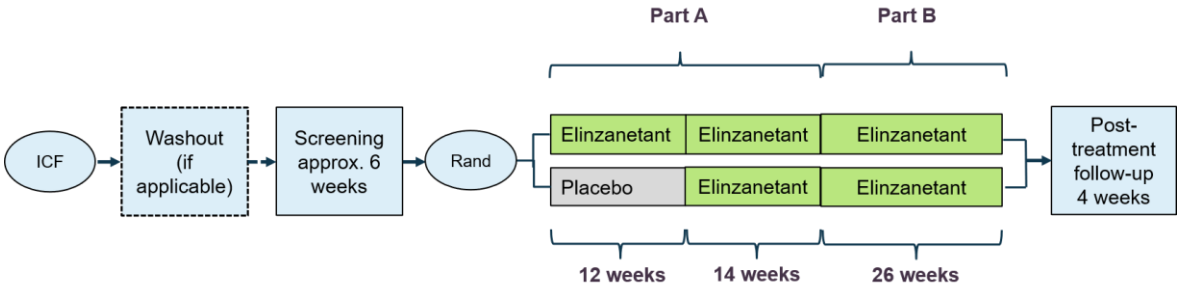
The key secondary endpoints will be handled using similar attributes except for the variables and population summary that are listed below:

- 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.

Treatment comparison will be based on differences in treatment group means.

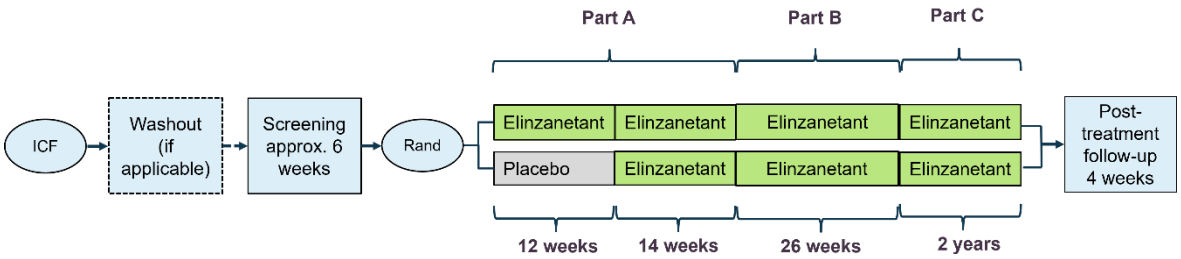
1.2. Study Design

Figure 1–1: Study Schema participants not 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 safety assessment will be performed.

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 safety assessment will be performed.

- Multi-center, multi-country, double-blind, randomized, parallel-group, placebo-controlled, Phase 3 intervention study in post-menopausal women, or at high risk for developing hormone-receptor positive breast cancer.
- Total study duration for all participants: approximately 62 weeks (plus potential washout period), including
    - Washout period (if applicable)

      After giving informed consent, but before starting formal screening procedures, participants will be withdrawn from prohibited concomitant medications.
    - Screening: approximately 6 weeks
    - Treatment: 52 weeks
    - Follow-up: 4 weeks
- Visit Frequency: Every 4-6 weeks
- Participants will be randomized 2:1 to either Elinzanetant 120 mg for 52 weeks or Placebo for 12 weeks, followed by elinzanetant 120 mg for 40 weeks

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

The analysis of part A is planned after the last participant completed part A (visit T9). This will be the final analysis for efficacy and safety of part A data and be based on cleaned and final data. Data from Part B will not be included in this analysis. Part B data will be analyzed together with Part A data after completion of the study (all subjects completed T13/End of treatment (EoT) and follow-up).

Participants who complete the 52 weeks treatment phase will be offered to continue treatment for another 2 years treatment extension (part C). Visit frequency: every 24 weeks until week 156. Part C will be analyzed separately.

2. 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.

2.1. Multiplicity Adjustment

As the hierarchical testing procedure follows a fixed sequence, it stops as soon as any of tests listed above 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.

3. Analysis Sets

For the purposes of analysis, the following analysis sets are defined in Table 3–1: Definition of analysis sets.

Table 3–1: Definition of 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.

In case of mis-randomization using wrong strata occurs, the correct stratification factors will be used in the analyses. In case more than 5 % are stratified incorrectly a sensitivity analysis for primary endpoints will be performed using randomized stratum.

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

Final decisions regarding the assignment of participants to analysis sets will be made during the review of study data and documented in the final list of important deviations, validity findings and assignment to analysis set(s).

Tables that are pre-specified to be displayed for FAS and SAF may be displayed for the FAS exclusively in case both analysis sets as well as the randomized intervention and the actual intervention received are identical.

4. Statistical Analyses

4.1. General Considerations

For a detailed description of the testing procedure including adjustments to the significance level, please see Section 2. The overall type I error rate will be controlled at 2.5 % one-sided. In general, confidence intervals (CI) will be two-sided with a confidence level of 95%.

The statistical evaluation will be performed by using the software SAS (release 9.4 or higher; SAS Institute Inc., Cary, NC, USA).

All variables will be analyzed by descriptive statistical methods. The number of data available and missing data, mean, standard deviation, minimum, median, and maximum will be calculated for metric data. The geometric mean and geometric SD will be provided instead of the arithmetic mean and SD for variables where lognormal distributions are assumed. Frequency tables will be generated for categorical data. Where appropriate, the data will also be presented by visit or week, including the analysis of the changes from baseline.

Variables recorded in the electronic case report form (eCRF) and relevant derived variables will be shown in subject data listings, whereby only randomized patients will be included. All data will be presented in the participant data listing as they are recorded on the eCRF, i.e., partially missing data will appear as such. Data from screening failures will only be shown in the 'Screening failure' listing.

Number of decimal places for summary statistics will be the following:

Table 4–1: Number of decimal places for summary statistics

Statistic	Number of digits
Minimum, maximum	Same as original data
Mean, median	1 more than in original data
SD	1 more than in original data
Frequencies (%)	1 digit
p-values	4 digits

4.1.1. Handling of Missing Data

This section describes the general handling of missing data. This includes data that would be meaningful for the analysis in terms of the study objectives but were not collected. The rules for handling the data that do not exist or are not considered meaningful for the analysis, because of an intercurrent event, are described in Section 4.2.1 and 4.2.3. No imputation of missing assessments will be performed for the secondary and exploratory endpoints unless it is specified otherwise.

All missing or partial data will be presented in the subject data listing as they are recorded on the eCRF or electronic diary (eDiary).

For the computation of durations, i.e., time between start and end date of certain events, and concomitant medication intake, a complete date is necessary.

The following rule will be applied to impute the missing start or end date of adverse events (AE)/ concomitant medications (CM)/procedures:

An imputation range will be defined as the earliest possible date (lower range) and the latest possible date (upper range) of the occurrence of AE/CM/procedures. If AE/CM/procedures end date is available, this will be used as the latest possible AE/CM/procedures occurrence date in the imputation range.

If the active treatment start date falls within imputation range, incomplete AE/CM/procedures start date will be imputed as the active treatment start date. If the active treatment start date does not fall within the imputation range, and the placebo treatment start date falls within the imputation range, an incomplete AE/CM/procedures start date is imputed as the placebo treatment start date. Otherwise, the partially missing AE/CM/procedures start date will be imputed to the earliest date of the imputation range. Completely missing start date will not be imputed. According to worst case criteria if there are completely missing AE/CM start dates, those AEs are considered treatment emergent and CMs as concomitant.

Partially missing AE/CM/procedures end date will be imputed as the latest possible date of AE/CM/procedures imputation range. Completely missing end date will not be imputed and presumed to be ongoing.

Missing start dates in certain events (for example date of initial diagnosis) will be imputed by replacing the missing information on the day and month of the event with the first day of the month and the first month of the year.

The date of permanent discontinuation of study medication will be collected in eCRF. In case of missing date, it will be determined based on last medication intake date before the discontinuation using available eDiary data.

Unless specified otherwise, participants with missing baseline assessments will be excluded from all analyses that require the respective baseline assessment.

4.1.1.1. Electronic Participant-Reported Outcomes (ePROs)

There are two types of missing data for ePRO measures: missing data at the ‘form’ level and missing data at the ‘item’ level. Form level missing refers to a participant missing an entire PRO assessment for a given time point (e.g. a given day for the HFDD and a given week for the PROMIS SD SF 8b). In general, form level data may be missing due to participant’s early withdrawal from the study, the inability to evaluate an endpoint at a particular time point, or non-compliance. By design of the eDiary, there will be no item level missing data for the respective ePRO questionnaires because the participants have to select an answer for an item in order to move on to the next item on the eDiary/electronic handheld device. This does not apply to the MENQOL (see below).

4.1.1.1.1. Hot Flash Daily Diary (HFDD)

Participants’ assessments of HF will be collected at the timepoints indicated in the SoA and recorded electronically twice daily using the sponsor developed HFDD.

A diary day for the calculation of the frequency and severity of HF consists of the evening entry (Evening Hot Flash eDiary) and the morning entry (Morning Hot Flash eDiary) 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 will be calculated as the sum of hot flashes documented in both the evening and morning diary. Retrospective data entry is possible for a limited time. For the morning diary these retrospective entries will be allowed on the same day between 11:00AM and 11:59PM. For the evening diary the retrospective entry option will be available between midnight until 10:59AM on the day after the missed entry. If only the evening or morning entry is available, then only this will be used for that particular day.

For the evaluation of the frequency and severity of HF, the daily HF assessments will be aggregated to a mean daily frequency and a mean daily severity HF score from the data of a particular week (see Section 4.1.2.1). In case data is missing for more than 2 days within a week, the value for that particular week will be set to missing. Further details regarding imputation rules in case of missing week values are described in Section 4.2.1.

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

The PROMIS SD SF 8b will be filled out by the participants using the eDiary. All PROMIS SD SF 8b items must be answered to produce a valid total score. Handling of missing weekly assessments is described in Section 4.3.1.2.

4.1.1.1.3. Menopause Specific Quality of Life Scale (MENQOL)

The MENQOL will be filled out by the participants using the eDiary at the timepoints indicated in the SoA.

For the MENQOL, participants have the option to skip single questions (e.g. if they do not feel comfortable to complete them). Missing item score will be imputed, if the participant has responded to more than one half of the domain items (i.e. at least two items in the vasomotor domain, two items in the sexual domain, four items in the psychosocial domain and nine items in the physical domain of the MENQOL). The imputed score is calculated from values converted for analysis according to scoring table (Table 6–2) and rounded to a whole number. The imputed value is the mean for that item generated from the other subjects who responded as follows: For missing item score at baseline, all subjects who responded to the item are considered. For post-randomization, only the responses of the participants in the same treatment group are used. When data from other participants will be used for imputation half of the participants within a treatment group must have responded to the item before an imputed value can be calculated. If the participant answered ‘yes’ but did not indicate ‘how bothered’ she was (partially missing data), the value is imputed from her own answers by calculating the mean of her ‘bothered’ scores for all her ‘yes’ answers within that domain. If she answered ‘no’ to all other domain items, the imputed score would be generated from the mean of all the subjects who responded ‘yes’ to the same item as discussed above (Lewis, 2004). If missing item scores within a domain cannot be imputed (because participant responded to half or less than half of the domain items), the domain score will be set to missing and the total score will be calculated as the mean of the remaining available domains.

Further details of scoring and handling of missing weekly assessments are described in Section 6.1.3. and Section 4.3.1.

4.1.1.1.4. Beck Depression Inventory (BDI-II)

The BDI-II will be filled out by the participants using the eDiary at the timepoints indicated in the SoA. No imputation of missing assessments will be performed.

4.1.1.1.5. Insomnia Severity Index (ISI)

The ISI will be filled out by the participants using the eDiary at the timepoints indicated in the SoA. No imputation of missing assessments will be performed.

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

The EQ-5D-5L will be filled out by the participants using the eDiary at the timepoints indicated in the SoA. No imputation of missing assessments will be performed.

4.1.1.1.7. Short Form-36 Health Survey Acute (SF-36 acute)

The SF-36 acute will be filled out by the participants using the eDiary at the timepoints indicated in the SoA. Transformed and calculated scores are provided by external Vendor based on SF-36 manual.

4.1.1.1.8. Sleepiness scale

The Sleepiness Scale will be assessed together with the HFDD evening diary at bedtime at the timepoints indicated in the SoA. It consists of three items asking the participant to rate the degree of sleepiness felt in the morning (item 1), afternoon (item 2) and evening (item 3).

Missing item level responses will not be imputed, the average of item scores will be used to create a daily sleepiness score. A 7-day average score can be derived if a daily sleepiness score is available for at least 5 out of 7 of days, otherwise the 7-day average score will be set as missing. The baseline value will be calculated by aggregating all available days during the 14 days prior to start of treatment to a mean daily sleepiness. A minimum of 11 days should be available for the derivation of the baseline value.

4.1.2. Data Rules

Definition of baseline: The latest available valid measurement excluding unscheduled measurements at or before the start of treatment (for treated subjects) / randomization date (for randomized but not treated subjects). If the last observation available prior to randomization is the measurement from the Screening Visit, this would be used as the baseline value. In case a wash-out period was necessary, measurements taken during the pre-screening visit will not be used as a baseline value unless specified otherwise.

Change from baseline: To calculate the absolute change from baseline the baseline value will be subtracted from the value under treatment/follow-up, i.e.,

Absolute change = post baseline value – baseline value.

Some parameters will be additionally analyzed as relative change defined as

Relative change = 100 * [(post baseline value – baseline value) / baseline value].

Derivation of intercurrent event (ICE): Intercurrent events that occurred from randomization date (for randomized but not treated subjects) / start of treatment (for treated subjects) to day 84 inclusive will be flagged.

For the "permanent discontinuation of randomized drug", "intake of prohibited medication having impact on efficacy" and "interruption/ discontinuation in intake of adjuvant endocrine therapy", if the ICE occurs on or before the 5th day of the week, it will be flagged for the respective week. If the ICE occurs on the 6th or 7th day of the week, it will be flagged from the following week. For example, if the participant permanently discontinues from the randomized drug on the 2nd day of week 4, the ICE will be flagged from week 4 onwards. If the discontinuation from the randomized drug occurs on the 6th day of week 4, then the ICE will be flagged from week 5 onwards. For the ICEs "intake of prohibited medication having impact on efficacy" and "interruption/ discontinuation in intake of adjuvant endocrine therapy" , if the end date for the impact on efficacy occurs on the 1st or 2nd day of the week, the respective week should not be flagged. If the end date of impact on efficacy occurs on or after the 3rd day of the week, the week should be flagged.

The "permanent discontinuation of randomized drug" ICE will be flagged for participants who were randomized but not treated. These participants have an event at randomization for the Kaplan-Meier analysis on the time from randomization (for randomized but not treated subjects) / start of treatment (for treated subjects) to the first occurrence of the intercurrent event "Permanent discontinuation of randomized treatment". For the main analytical approach, the missing post-baseline data will be imputed as described in Section 4.2.1.

End-of-treatment ePRO assessments after premature treatment discontinuation:

Patient-Reported Outcome assessments (PROMIS SD SF 8b, MenQoL, EQ-5D-5L, BDI-II, ISI and SF-36 acute) are scheduled to occur during the following days:

Table 4–2: Scheduled assessment weeks for ePROs

Questionnaires	Assessment Week	Completion days* (inclusive)
PROMIS SD SF 8b, EQ-5D-5L	1	8-9
PROMIS SD SF 8b, EQ-5D-5L	2	15-16
PROMIS SD SF 8b, EQ-5D-5L	3	22-23
PROMIS SD SF 8b, EQ-5D-5L, MenQoL, ISI, BDI-II	4	29-30
PROMIS SD SF 8b, EQ-5D-5L, MenQoL, ISI, BDI-II	8	55-57
PROMIS SD SF 8b, EQ-5D-5L, MenQoL, ISI, BDI-II, SF-36 acute	12	83-85

*Completion days are referring to days from randomization.

First, scheduled assessments during the completion days will be assigned to the respective week.

Only in case no scheduled assessment is available for a particular week, assessments done at EoT, unscheduled timepoints or follow-up (in this order of priority) will be used, and they will be mapped to the next available, protocol-planned assessment week as described below.

- If the assessment occurs during the completion days as above, it will be assigned to the respective week.
- Up to and including Week 3 (only PROMIS SD SF 8b and EQ-5D-5L): If the EoT/ follow-up/ unscheduled assessment is on 5th day of the week or later, then the assessment will be mapped to the respective week (i.e., assessments on Days 6-7* will

be mapped to Week 1, Days 12-14 to Week 2 and Days 19-21 to Week 3). Otherwise, no mapping will occur, and the respective week will be considered missing. If multiple assessments are available within a particular week, the last assessment (i.e., the one closest to the scheduled assessment) will be used for mapping.

- From Week 4 onwards: a 2-week window will be used to map the available assessments to Week 4 (Days 15-28), Week 8 (Days 43-54*), or Week 12 (71-82*). A similar 2-week window will be used from Week 16 to Week 52. Within each 2-week-window, the last available assessment (i.e., the one closest to the scheduled assessment) will be used for mapping.

  *Week 1 = Days 2-8; Day 8 (week 1), Days 55/56 (week 8) and Days 83/84 (week 12) are scheduled assessments, and no mapping would be required, therefore, these days are not considered in the window for mapping.

- In case an assessment is assigned to Week 2 or 3 and to Week 4, based on the above rules, it will be shown for Week 2 or 3 in the descriptive tables. The Week 4 assessment will only be used in the model-based analyses.
- Assessments from follow-up visits will be shown as follow-up in the descriptive tables, and the value mapped to a specific treatment week will only be used in the model-based analyses.
- In the descriptive tables, data collected after premature discontinuation of treatment will not be shown for the respective treatment week. Assessments occurring up to 2 days after discontinuation (inclusive) will still be considered under treatment and shown for the respective week. Out of the assessment collected post treatment discontinuation (+ 2 days), the one closest to the planned time point of follow-up (i.e. discontinuation date + 28 days) will be shown as follow-up assessment. In case two assessments are equally close to that date, the first one will be selected.

Laboratory values <X or >X: For laboratory values lower than a limit of detection X which are given as <X , half the value of X will be used for analysis (i.e., values reported as "<X", "<X.X"," <X.XX" or etc. the value for analysis used will be derived by "X/2", "X.X/2"," X.XX/2" etc). Differences between 2 values <X will be assigned values of 0. Ratios between 2 values <X will be assigned a value of 1. For values which are higher than a limit of detection Y, given as Y, the value of Y will be used for analysis.

Repeated measurements at the same visit after start of treatment: If more than one post-randomization measurement is available for a given visit, the first available observation will be used in the data summaries and all observations will be presented in the data listings.

Start of treatment refers to the first drug intake and will be identified based on the eCRF entry.

Time to event: The randomization date (for randomized but not treated subjects) /start of study treatment (for treated subjects) will be used as the start date for the calculation of time to event. Therefore, the time of event will be defined as "date of event – randomization date (for randomized but not treated subjects) / start of study treatment (for treated subjects) +1".

Unscheduled Assessments: Extra assessments (e.g. laboratory data or vital signs) associated with non-protocol visits will be included in listings, but not in the summary tables or figures, unless specified otherwise.

Definition of phases: The following phase definitions are used for displaying treatment duration, compliance, exposure and adverse events**.** The two phases in the Part A of the study represent the approximately first 12 weeks of the study, in which participants receive either placebo or elinzanetant 120mg and the approximately 14 weeks when all participants receive elinzanetant (i.e. the participants in the placebo arm will switch to elinzanetant). The start and end date of the phases is defined as following:

- Phase 1 (Part A):
  - Start date = start of treatment for treated subjects / randomization date for subjects, randomized, but not treated
  - End date = first day of phase 2 study drug intake – 1 day (based on the eCRF entry)
    (*For participants who stayed in the study for at least 12 weeks and received the phase 2 study drug*);

    OR

    (For participants who have not received the drug phase 2 due to early discontinuation of randomized treatment or study withdrawal)

    [Week 12 assessment date or the post treatment phase end date, whichever is earlier

    (*this is for participants who discontinued from study drug but agreed to complete the assessments until Week 12*)

    or

    Study drug discontinuation date or EoT assessment date, whichever is later (*For participants who discontinued from randomized study drug before receiving phase 2 study drug and decided to go to the follow up period or withdraw from the study*)].

Note: HFDD morning diary and PRO questionnaires which were completed one day after the phase 1 end date will be assigned to phase 1. For participants who were randomized but not treated, the end date = randomization date.

- Phase 2 (Part A):
  - Start date = first day of phase 2 study drug intake (identified based on the eCRF entry)
  - End date = Visit T9 date (*For participants who completed the phase 2/Part A, i.e. 26 weeks*)
    or
    Study drug discontinuation date or EoT assessment date, whichever is later (*For participants who discontinue from treatment/study prematurely during the second phase*).

Note: HFDD morning diary and PRO questionnaires which were completed one day after the phase 2 end date will be assigned to phase 2.

In addition, Part B and Part C of the study will be defined as Phases 3 and 4 in the following way:

- Phase 3 (Part B):

- Start date = Visit T9 date +1
- End date = Visit T13 date (For participants who completed the phase 3/Part B, i.e. 52 weeks)
  or
  Study drug discontinuation date or EoT assessment date, whichever is later (For participants who discontinue from treatment/study prematurely during the third phase).

- Phase 4 (Part C):
  - Start date = Visit T13 +1 (i.e. start day of Part C) drug intake (identified based on the eCRF entry)
  - End date = end of treatment period date (For participants who completed the phase 4, i.e. Part C)

    or

    Study drug discontinuation date or EoT Part C assessment date, whichever is later (For participants who discontinue from treatment/study prematurely during the Part C).

4.1.2.1. Definition of Endpoints

Participants' assessments of HF will be recorded electronically twice daily using the Sponsor developed Hot Flash Daily Diary (HFDD). See details in Section 6.1.1.

Baseline value of frequency of moderate to severe HF:

The baseline value will be calculated by aggregating all 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). As per inclusion criteria 8 (see protocol), at least 11 days will be available for the derivation of the baseline value.

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 1 Days 2-8 will be used, 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 missing for more than 2 days within a week, the value for that particular week will be set to missing.

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 mean daily frequency of moderate to severe HF at Week 4 or Week 12, respectively, from the baseline value of the mean daily frequency of moderate to severe HF.

Baseline value of severity of moderate to severe HF:

The mean daily severity during baseline will be calculated for the available days 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. As per inclusion criteria 8 (see protocol), at least 11 days will be available for the derivation of the baseline value.

Severity of HF during treatment:

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

Similar to the frequency, the severity of HF for each week during the treatment period will be calculated using the available data during that particular week. Specifically, for Week 4 Days 22-28 will be used and for Week 12 Days 78-84 will be used (Day 1 corresponds to start of treatment). To obtain the post-baseline severity of HF during a particular week, the weekly data will be aggregated by averaging the mean daily severity of HF of the available days during that week. In case data is missing for more than 2 days within a week, the value for that particular week will be set to missing.

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.

4.1.3. Participant Disposition

The number of participants enrolled, randomized and valid for the FAS and SAF will be summarized overall and by treatment group, region, country and study site. A listing of the participants' assignment to the FAS and SAF and the reasons for exclusion will also be provided by treatment group.

Other summary statistics will include:

- number of screening failures and the reason for failed screening
- number of participants randomized but not treated (overall and by treatment group).
- number of participants who completed the study, i.e., completed all phases (screening, treatment and follow up) of the study including the last visit.

A disposition summary for each study period (screening, treatment (split by Part A (weeks 1-12 and weeks 13-26), Part B (weeks 27-52) and Part C) and follow-up period, see Section 1.2) will be presented summarizing the number of participants starting and completing the respective study period, the number of participants discontinuing it and the primary reason for discontinuation. This will also be presented overall and for each treatment group. The table will include COVID-19 pandemic associated reasons for discontinuation, i.e., the information whether decision for discontinuation was due to participant specific reasons or due to other reasons.

In addition, the number of participants with important deviations and validity findings will be presented overall and for each treatment group. The frequencies of each important deviation and validity finding will be presented by treatment group and in total.

Additionally, Kaplan-Meier plots for the time from randomization (for randomized but not treated subjects) / start of study treatment (for treated subjects) to the first occurrence of the intercurrent events "Permanent discontinuation of randomized treatment", "Intake of prohibited concomitant medication having impact on efficacy" and "Interruption/discontinuation in intake of adjuvant endocrine therapy" will be provided by treatment group, where applicable. If "Permanent discontinuation of randomized treatment" did not occur by day 84, the participant will be censored at week 12. If "Intake of prohibited concomitant medication having impact on efficacy" or "Interruption/discontinuation in intake of adjuvant endocrine therapy" did not occur by day 84, the participant will be censored at week 12 or at the time of dropping out of the study, whichever occurs earlier.

The number of observed intercurrent events will be summarized by week and by treatment group and overall.

4.2. Primary Endpoints Analysis

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)

See definition in Section 4.1.2.1.Definition of Endpoints

4.2.1. Main Analytical Approach

The main estimand to answer the clinical question of the study is described in Section 1.1.

The frequency of moderate to severe HF and the change from baseline as well as the relative change (%) from baseline will be summarized using descriptive statistics (see Section 4.1) by treatment group and by week. Descriptive table will include participants on study treatment (a participant needs to have taken at least one dose of study drug during the week to be shown in the table). Post-treatment data will be used in the model-based analysis and shown in the listing only. The change from baseline over time in the frequency of HFs will be shown using line plots for means together with 95% CIs by treatment group.

Inference about the primary endpoints will be done based on a mixed model for repeated measures (MMRM). Prior to performing modeling with the MMRM, missing data will be handled in alignment with the estimand strategies for ICEs (described in Section 1.1).

Table 4–3 provides a detailed overview of the MMRM model for the change from baseline in frequency of HF. One of the stratification factors used at randomization, population type, will not be included in the analysis model because almost all participants are in the same category.

Table 4–3: Model description

Dependent variable:	Change from baseline in frequency of moderate to severe HF at Week 1, Week 4, Week 8 and Week 12
Covariates (continuous variables):	Baseline mean daily frequency of HF
Factors (class variables):	Treatment, Week
Stratification factor (class variables):	Type of treatment of pre-existing condition at baseline (tamoxifen or aromatase inhibitor)
Interaction terms:	Baseline*Week, Treatment*Week
Covariance structure:	Unstructured (UN) If the convergence cannot be attained with the unstructured correlation matrix, the following alternative structures will be attempted in the specified order: autoregressive(1) (AR(1)), and compound symmetry (CS). The first structure in this list with which the model converges will be used. If AR(1) structure is used, a random subject intercept will also be included in the model. This will need to be applied for each imputed dataset.
Equation	$Y_{ijkm} = \mu + \beta x_i + t_k + p_m + v_j + (tv)_{kj} + \alpha(xv)_{ij} + s_i + \varepsilon_{ijkm}$ where Y_{ijkm} is the change from baseline in frequency of HF to Week j for subject i (with treatment k and type of treatment m at baseline); μ is the intercept, β is the baseline covariate effect (baseline coefficient), x_i is the baseline frequency HF for subject i, t_k is the fixed effect of treatment k *(k=Elinzanetant, placebo)*, p_m is the fixed effect of type of treatment m at baseline *(m=Tamoxifen, Aromatase inhibitor)* v_j is the fixed effect of Week j *(j=1, 4, 8 & 12),* $(tv)_{jk}$ is the interaction effect of treatment k by Week j, α is the covariate effect for the interaction (xv) $(xv)_{ij}$ is the interaction effect of baseline frequency HF of subject i by Week j,

	$s_i \sim$ Normal $(0, \sigma_s^2)$ is the random effect of subject *i (only if AR(1) covariance structure is used),* $\varepsilon_{ijklm} \sim$ Normal $(0, \sigma^2)$ represents the residual variance component with corr $(\varepsilon_{ij}, \varepsilon_{ij'}) = \rho_{jj'}, j \neq j'$.

SAS code:	`PROC MIXED data=DATA;`
	`CLASS subject treatment week pretreatment;`
	`MODEL change = baseline treatment week pretreatment treatment*week baseline*week /ddfm=KR outp=resid s;`
	`REPEATED week / subject=subject type=un;`
	`RANDOM subject; /* only if AR(1) covariance structure is used */`
	`LSMEANS treatment*week /cl diff;`
	`ESTIMATE 'Elinzanetant - Placebo at Week 4' treatment 1 -1 treatment*week 0 1 0 0 0 -1 0 0 /cl;`
	`ESTIMATE 'Elinzanetant - Placebo at Week 12' treatment 1 -1 treatment*week 0 0 0 1 0 0 0 -1 /cl;`
	`ODS OUTPUT TESTS3=TYPE3 LSMeans=LSMEAN ESTIMATES=ESTIM;`
	`RUN;`

A treatment policy strategy will be applied to handle all of the ICEs in this trial in the main estimand. According to this strategy, all collected data should be utilized in the analysis irrespective of occurrence of the ICEs.

Although all study participants are expected to be followed after ICEs, some missing data may occur. Missing values that occur while participants continue on their randomized treatment and simply represent missed assessments will be assumed missing at random (MAR). Such missing values could be intermittent or monotone and will be imputed using a Monte Carlo Markov Chain (MCMC) multiple imputation (MI) method. For the baseline value to be imputed, at least 2 post-baseline values out of the 4 post-baseline values (i.e., Week 1, 4, 8 & 12) need to be available. Possible missing baseline values will be imputed together with other intermittent missing values. Absolute values will be used for imputation steps.

Due to study design it will be difficult to implement a modelling approach aligned with the treatment policy strategy with the imputation model estimated from participants who discontinue the randomized treatment and provide data. The number of such participants is expected to be too small for estimating a robust imputation model. Therefore, the washout method will be used to impute missing data from participants who experience the ICEs (i.e. permanent treatment discontinuation) (Wang et al. 2023).

A placebo-effect is expected to be seen with the placebo group while the elinzanetant treatment effect will consist of both the placebo-effect and the effect of elinzanetant. The washout method effectively ‘washes out’ any pre-ICE treatment effect of elinzanetant in participants with an ICE randomized to elinzanetant, while modeling the mean placebo effect. Missing data in participants randomized to placebo will be assumed MAR.

For participants randomized to elinzanetant, the imputation model will have the dependent variable as the endpoint measurement at week 4 with the baseline measurement and the stratification factor, type of treatment of pre-existing condition, at baseline. The multiple imputation model will be estimated only based on placebo participants who remain in the study through week 4 and have available data at week 4. Similarly, week 1, 8 and 12 values missing after an ICE will be imputed using the same model specification but with endpoint measurement at week 1, 8 or 12, respectively, as the dependent variable.

The imputation will be done using a regression model (PROC MI with MONOTONE REG) including covariates described above for each time point and using the MNAR statement to estimate the model from placebo participants only.

To impute missing data for participants randomized to placebo, using MAR assumption, the imputation will be done using a regression model including measurements from all timepoints before the time-point being imputed in addition to baseline measurement and the stratification factor (PROC MI with MONOTONE REG).

PROC MI will be run with the random seed setting SEED=21656 to produce 500 imputed datasets.

After the completion of imputation step, change from baseline values will be calculated and each imputed dataset will be analyzed using the MMRM model specified in Table 4–3 to obtain an estimate of the mean change from baseline and of the treatment effect. The results will be combined using the Rubin's rule (Rubin, 1987) to obtain an overall estimated mean change from baseline and an overall estimated treatment effect. A total of 500 multiple imputation steps will be used.

Details regarding how the ICEs will be identified and specifics regarding the reasons for the occurrence of ICE are described in Section 6.4. All the ICEs will be reviewed prior to study unblinding.

The results from the main analysis will be presented as the number of participants, estimated mean change from baseline and standard error (SE) for each treatment group at Weeks 4 and 12 as well as the estimated treatment difference (elinzanetant - placebo), SE of the difference, associated 95% CI and P-value (one-sided). A plot of the model-based estimates with SE will be provided by the treatment for Weeks 4 & 12.

4.2.2. Sensitivity Analyses

4.2.2.1. Assessment of normality assumption

The assumption for normality in the main analysis (see Section 4.2.1) will be evaluated by graphical tools (i.e., qqplot and plot of residuals against predicted values). This will be assessed based on the observed data before multiple imputation is applied.

For the case of extreme violations of the normality assumption, a non-parametric rank ANCOVA will be carried out as sensitivity analysis and the Hodges-Lehmann estimate will be calculated as an estimate of the treatment effect (see Stokes et al. 2012). This will be carried out separately for the primary endpoints, change from baseline of HF frequency at Week 4 and at Week 12. Specifically, a Cochran-Mantel-Haenszel score test will be applied

to the residuals of a regression model on rank-transformed data while adjusting for baseline and the stratification factor.

The methodology described in Stokes et al. (2012) will be applied as follows using the SAS pseudo code given below. First, the values of the change from baseline variable as well as baseline covariate will be transformed to standardized ranks by stratification factor (pre-treatment), using fractional ranks and mean method for ties:

```
proc rank data=datain nplus1 ties=mean out=ranks;
       by pre-treatment;
       var baseline change_from_baseline;
run;
```

Afterwards separate regression models will be fitted within each type of treatment of pre-existing condition at baseline using the standardized rank values of the change from baseline and the baseline as dependent and independent variable, respectively. Residuals from these regression models will be captured for further testing of differences between treatment groups:

```
proc reg data=ranks;
       by pre-treatment;
       model change_from_baseline = baseline;
       output out=residuals r=resid;
run;
```

Finally, the stratified Cochran-Mantel-Haenszel (CMH) test using the values of the residuals as scores will be used to compare the two treatment groups:

```
proc freq data=residuals;
       tables pre-treatment* treatment*resid / CMH2;
       ods output cmh=cmhstat;
run;
```

The non-parametric rank ANCOVA described above will be applied to each imputation dataset within the multiple imputation procedure described earlier. Before combining the results of the CMH test using Rubin's rule, a normalizing transformation using the Wilson-Hilferty transformation as described in Ratitch, Lipkovich et al. (2013) will be applied. Let $cmh^{(m)}$ be the CMH statistic computed for the mth imputed dataset and *df* the corresponding degrees of freedom associated with the CMH statistic. The standardized test statistic for the mth imputation $st\_cmh^{(m)}$ is then given by

$$st\_cmh^{(m)} = \frac{\sqrt[3]{\frac{cmh^{(m)}}{df}} - \left(1 - \frac{2}{9 \times df}\right)}{\sqrt{\frac{2}{9 \times df}}}$$

The corresponding standard error is equal to 1. This standardized statistic together with its standard error will be passed on to PROC MIANALYZE to perform a combined CMH test using Rubin's rule.

In addition to the assessment of the treatment effect based on the CMH statistic as described above, the Hodges-Lehmann estimate of the median difference will be provided as estimate of the magnitude of the unadjusted treatment effect. The Hodges-Lehman estimate together with its asymptotic standard error will be computed for each imputation dataset and subsequently Rubin's rule will be used to combine the results. The Hodges-Lehmann estimate can be obtained using the following pseudo SAS code:

```
proc npar1way hl;
        class treatment;
        var change_from_baseline;
        output out=HL;
run;
```

The two-sided p-value based on the non-parametric rank ANCOVA, as well as the Hodges-Lehmann based estimate of the size of the treatment effect together with the corresponding standard error and 95 % confidence interval will be reported. To assess statistical significance the p-value from the non-parametric rank ANCOVA will be used.

4.2.2.2. Tipping point analysis

A tipping point analysis will be applied to assess the sensitivity of the main analysis results to modeling of the missing data that occur in presence of ICEs as described in Section 4.2.1. This will be done by applying an unfavorable additive shift (referred to as delta adjustment) to the values imputed by the MI model (with MONOREG) for the main analysis in the elinzanetant arm. For the endpoints related to the frequency of HF, the adjustments will be applied with delta values of 1, 2, 3, 4, etc. in each successive tipping point iteration until a tipping point is attained. Additional details on the tipping point sensitivity analysis are provided in Section 6.3.

4.2.3. Supplementary Analyses

Two supplementary estimands are defined for this trial.

The hypothetical strategy will be used for handling temporary treatment interruption and permanent treatment discontinuation due to COVID-19, administrative and any other treatment unrelated reasons in both supplementary estimands. Intake of prohibited medications, discontinuation in intake of adjuvant endocrine therapy and permanent treatment discontinuation with initiation of alternative VMS treatment will be handled by the hypothetical strategy in the first supplementary estimand and by the composite strategy in the second supplementary estimand.

4.2.3.1. First Supplementary Analysis

The information about ICEs and strategies to address them for the first supplementary estimands is provided in Table 4–4. The other estimand attributes are the same as for the main estimand (see section 1.1).

Table 4–4: First Supplementary 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	**Hypothetical**, If participant complied with treatment.	Model outcomes during the ICE under the hypothetical scenario.
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	**Hypothetical**, If participant remained untreated.	Model outcomes after the ICE under the hypothetical scenario.
	Other treatment-unrelated reasons, including COVID-19	**Hypothetical,** If participant did not discontinue the randomized treatment.	Model outcomes after the ICE under the hypothetical scenario.
Intake of prohibited concomitant medication having impact on efficacy	All reasons	**Hypothetical,** If participant did not take prohibited concomitant medication/did not discontinued adjuvant endocrine therapy	Model outcomes under the hypothetical scenario during the period of confounding.
Interruption/Discontinuation in intake of adjuvant endocrine therapy[c]	No reasons collected	**Hypothetical**, If a participant did not discontinue taking their adjuvant endocrine therapy	Model outcomes under the hypothetical scenario during the period of confounding.

ICE=Intercurrent event, AE=Adverse event, VMS = Vasomotor symptoms
a) ICEs will be reviewed at the Blinded Review Meeting prior to the study unblinding
b) Definition of temporary treatment interruption:
Week 1 = Treatment taken on <5/7 days during week 1.
Week 4 = Treatment taken <80% during weeks 1-4 OR treatment taken on <5/7 days during either week 3 or 4.
Week 8 = Treatment taken <80% during weeks 1-8 OR treatment taken on <5/7 days during either week 7 or 8.
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 week 1, weeks 3 and 4, weeks 7 and 8 or weeks 11 and 12 compared to baseline
For participants using aromatase inhibitor: reduction of at least 30% of planned daily dosage taken during week 1, weeks 3 and 4, weeks 7 and 8 or weeks 11 and 12 compared to baseline

The details of data handling and missing data imputation for the first supplementary analysis of the primary endpoints are summarized in the Table 4–5. A pattern-mixture model using multiple imputation (MI) will be used to impute missing values that occur in presence of ICEs in a way that aligns with the ICE strategies.

The rows of Table 4–5 represent various patterns (subsets) of participants with a specific type of an ICE. For participants from each pattern who have missing data during the time frame of the ICE (Please see Sections 6.4.3 & 6.4.1 for the description of time frame for intake of prohibited medication and temporary treatment interruption ICEs. The time frame for the permanent treatment discontinuation is defined as the time after discontinuation.) or unobservable data under the assumed hypothetical scenario, a reference group is specified in the last column of the table.

Available data of participants from the corresponding reference group will be used to model the distribution of missing and unobservable data in each pattern. For the baseline value to be imputed, at least 2 post-baseline values out of the 4 post-baseline values (i.e. Week 1, 4, 8 & 12) need to be available. In case there are less than 10 participants with available post-ICE data in the defined reference group, at any intermediate time point, the missing data for that pattern will not be imputed at that time point. Additional details are provided in Section 6.2.

Table 4–5: First supplementary analysis data handling and missing data imputation strategy

Pattern ID	**ICE and the associated reason**	**ICE strategy and data handling**	**Reference group for modeling the distribution of missing or unobservable data**
1	Intake of prohibited medications Any reason	**Hypothetical strategy** If participant did not take prohibited concomitant medication. Discard the collected data after the intake of prohibited medication(s) for a certain time frame based on the medication class (See Section 6.4.2 for details).	Participants, from the same arm, who comply with treatment regimen[b] and have observed data at the time point that requires imputation.
	Temporary treatment interruption[a] Due to COVID-19/ administrative or any other treatment unrelated reasons	**Hypothetical strategy** If participant complied with treatment. Data collected for a specific assessment during/after a temporary treatment interruption will be discarded for that assessment Week only.	

2	Temporary treatment interruption[a] Due to AE	**Treatment policy strategy** Utilize all the collected data in the analysis.	Participants, from the same arm, who have available data before and during the treatment interruption. MI will be used to model change from a time point before treatment interruption to a time point with treatment interruption (Copy Increment from Reference imputation strategy).
3	Permanent treatment discontinuation Due to AE/lack of efficacy	**Treatment policy/Hypothetical strategy** If participant remained untreated/on background therapy after permanent discontinuation of the randomized treatment, use the treatment policy strategy and utilize the collected data. Otherwise, if participant initiated an alternative treatment, use the hypothetical strategy under the hypothetical scenario "If participant did not initiate an alternative treatment after permanent discontinuation of randomized treatment". Discard data after the ICE.	Missing values that occur after the ICE will be imputed using a similar MI model as used in the main analysis of the primary endpoint, i.e., the wash-out method (Wang et al. 2023).
4	Permanent treatment discontinuation Due to COVID-19/ administrative or any other treatment unrelated reasons Interruption/Discontinuation in intake of adjuvant endocrine therapy	**Hypothetical strategy** If participant did not discontinue the randomized treatment due to the specified reason. Any data collected after permanent treatment discontinuation will be discarded. **Hypothetical strategy** If participant did not stop adjuvant endocrine therapy Discard the collected data after the stop of adjuvant endocrine therapy.	All other participants from the same arm (i.e., participants without a similar ICE at the time point that requires imputation).

a) If more than one interruption for different reasons is recorded during the specified weeks (please see the definition of ICE in Section 1.1), the data handling rule and missing data imputation will be performed based on the reason in the following pre-specified order: 1) AE, 2) Due to COVID-19/ administrative or any other treatment unrelated reasons.

b) Complying with treatment regimen is defined as having no ICEs (i.e., no early discontinuation of randomized treatment, no treatment interruption in the respective week (definition in Table 1–2), no intake of prohibited concomitant medications and no reduction from baseline in adjuvant endocrine therapy).

Missing values that occur in the time frame outside of any identified ICE and simply represent missed assessments will be assumed missing at random (MAR). Such missing values are likely to be intermittent and will be imputed using a Monte Carlo Markov Chain (MCMC) MI method for imputation of non-monotone missing data. Additional details are provided in Section 6.2.

A pattern-mixture model using multiple imputation will be applied to impute missing and unobservable data to mimic the distribution of observed data in the appropriate reference group as described in Table 4–5, conditional on covariates and partially observed data. The imputations will be done sequentially in patterns 1 through 4. The reference group for imputation in patterns 3 and 4 may contain participants who have some values imputed during the imputation of preceding patterns. Consequently, the MI model for pattern 4 will reflect a mixture of participants, some of which fully comply with the randomized treatment and some with other types of ICEs. Additional details of the pattern-mixture modeling with multiple imputation are provided in Section 6.2.

Each imputed dataset will be analyzed using the MMRM model specified in Table 4–3 to obtain an estimate of the treatment effect. The results will be combined using Rubin's rule (Rubin, 1987) to obtain an overall estimated treatment effect.

The same baseline covariates will be included in the imputation and the analysis step as specified in Section 4.2.1.

The results from the supplementary analysis will be presented in a similar way as to the main analysis (see Section 4.2.1).

4.2.3.2. Second Supplementary Analyses

The details of the second supplementary estimand can be found in Table 4–6 and Table 4–7. Similar analyses steps (i.e. imputation, modeling and combining results) as for the first supplementary analysis will be applied to the secondary supplementary analysis (see Section 4.2.3.1).

For the intake of prohibited medication and permanent treatment discontinuation after which participants initiated alternative VMS treatments and interruption/discontinuation in intake of adjuvant endocrine therapy, the composite strategy will be used to handle the data. The attributes for this estimand are the same as the main estimand except for following:

- Variable:
    - Change in frequency of moderate to severe HF from baseline to Week 4 in the absence of ICEs (i.e. intake of prohibited medication or initiation of alternative

VSM treatment after permanent discontinuation of randomized treatment or interrupted/discontinued adjuvant endocrine therapy) or no change from baseline otherwise.

- Change in frequency of moderate to severe HF from baseline to Week 12 in the absence of ICEs (i.e. intake of prohibited medication or initiation of alternative VSM treatment after permanent discontinuation of randomized treatment or interrupted/discontinued adjuvant endocrine therapy) or no change from baseline otherwise.

- Intercurrent Events (ICEs): see Table 4–6

Table 4–6: Second Supplementary 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	**Hypothetical** If participant complied with treatment	Model outcomes during the ICE under the hypothetical scenario.
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	**Composite** Treatment failure (i.e. no change from baseline)	Model outcomes after the ICE under the treatment failure.
	Other treatment-unrelated reasons, including COVID-19	**Hypothetical** If participant did not discontinue the randomized treatment.	Model outcomes after the ICE under the hypothetical scenario.
Intake of prohibited concomitant medication having impact on efficacy	All reasons	**Composite** Treatment failure (i.e. no change from baseline)	Model outcomes under the treatment failure during the period of confounding.
Interruption/Discontinuation in intake of adjuvant endocrine therapy [c]	No reasons collected	**Composite** Treatment failure (i.e. no change from baseline)	Model outcomes under the treatment failure during the period of confounding.

ICE=Intercurrent event, AE=Adverse event, VMS = Vasomotor symptoms

a) ICEs will be reviewed at the Blinded Review Meeting prior to the study unblinding

b) Definition of temporary treatment interruption:
Week 1 = Treatment taken on <5/7 days during week 1.
Week 4 = Treatment taken <80% during weeks 1-4 OR treatment taken on <5/7 days during either week 3 or 4.
Week 8 = Treatment taken <80% during weeks 1-8 OR treatment taken on <5/7 days during either week 7 or 8.
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 week 1, weeks 3 and 4, weeks 7 and 8 or weeks 11 and 12 compared to baseline

For participants using aromatase inhibitor: reduction of at least 30% of planned daily dosage taken during week 1, weeks 3 and 4, weeks 7 and 8 or weeks 11 and 12 compared to baseline

Table 4–7: Second supplementary estimand data handling and missing data imputation strategy.

Pattern ID	ICE and the associated reason	ICE strategy and data handling	Reference group for modeling the distribution of missing or unobservable data
N/A	Intake of prohibited medications and Interruption/Discontinuation in intake of adjuvant endocrine therapy [c] Any reason	**Composite strategy** Treatment failure (i.e. no change from baseline.) Discard the collected data after the intake of prohibited medication(s) for a certain time frame based in the medication class (See Section 6.4.3 for details) and assign the value of zero change from baseline. Discard the collected data after interruption/discontinuation of adjuvant endocrine therapy and assign the value of zero change from baseline.	**N/A**
1	Temporary treatment interruption[a] Due to COVID-19 /administrative or any other treatment unrelated reasons	**Hypothetical strategy** If participant complied with treatment. Data collected for a specific assessment during/after a temporary treatment interruption will be discarded for that assessment Week only.	Participants, from the same arm, who comply[b] with treatment regimen and have observed data at the time point that requires imputation. **(same as the first supplementary analysis)**
2	Temporary treatment interruption Due to AE	**Treatment policy strategy** Utilize all the collected data in the analysis.	Participants, from the same arm, within the same pattern who have available data before and during the treatment interruption. MI will be used to model change from a time point before treatment interruption to a time point

			with treatment interruption (Copy Increment from Reference imputation strategy). **(same as the first supplementary analysis)**
3	Permanent treatment discontinuation (Due to AE/lack of efficacy)	**Treatment policy strategy** If participant remained untreated/on background therapy after permanent discontinuation of the randomized treatment, use the treatment policy strategy and utilize the collected data.	Missing values that occur after the ICE will be imputed using a similar MI model as used in the main analysis of the primary endpoint, i.e., ,the wash-out method (Wang et al. 2023) **(same as the first supplementary analysis)**
		Composite strategy Otherwise, if participant initiated an alternative treatment, use the composite strategy assuming treatment failure (i.e. no change from baseline). Discard data after the ICE and assign the value of zero change from baseline	N/A
4	Permanent treatment discontinuation. Due to COVID-19 /administrative or any other treatment unrelated reasons	**Hypothetical strategy** If participant did not discontinue the randomized treatment due to the specified reason. Any data collected after permanent treatment discontinuation will be discarded.	All other participants from the same arm (i.e., participants without a similar ICE at the time point that requires imputation). **(same as the first supplementary analysis)**

a) If more than one interruption for different reasons is recorded during the specified weeks (please see the definition of ICE in Section 1.1), the data handling rule and missing data imputation will be performed based on the reason in the following pre-specified order: 1) AE, 2) Due to COVID-19/ administrative or any other treatment unrelated reasons.

b) Complying with treatment regimen is defined as: 1) on treatment (i.e., no earlier discontinuation of randomized treatment); 2) has no treatment interruption in the respective week (according to the definition in Table 1–2) and 3) has not taken any prohibited meds.

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 week 1, weeks 3 and 4, weeks 7 and 8 or weeks 11 and 12 compared to baseline

For participants using aromatase inhibitor: reduction of at least 30% of planned daily dosage taken during week 1, weeks 3 and 4, weeks 7 and 8 or weeks 11 and 12 compared to baseline

4.3. Secondary Endpoints Analysis

4.3.1. Key Secondary Endpoints

The key secondary efficacy endpoints in this study are:

- Mean change in PROMIS SD SF 8b total T-score from baseline to Week 12
- Mean change in MENQOL total score from baseline to Week 12

4.3.1.1. Definition of Endpoints

4.3.1.1.1. Patient-reported Outcomes Measurement Information System Sleep Disturbance Short Form 8b (PROMIS SD SF 8b) related endpoints

- Mean change in PROMIS SD SF 8b total T-score from baseline to Week 12

Participants responses to the 8 single items of the instrument are scored 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) and aggregated to derive total raw scores ranging from 8-40. These total raw scores are then converted into total T-scores using a look-up table for comparison with population norms. Higher scores indicate greater level of sleep disturbances. See further details in Section 6.1.2.

4.3.1.1.2. Menopause Specific Quality of Life Scale (MENQOL) related endpoints

- Mean change in MENQOL total score from baseline to Week 12

Participants responses to the 29 items will be scored individually on a scale indicating whether the participant experienced the symptom (yes/no). If they select yes, they rate how bothered they were by the symptom using a 6-point verbal descriptor scale. The items assess four domains of symptoms and functioning: vasomotor symptoms, psychosocial functioning, physical functioning, and sexual functioning. Domain scores are calculated as mean of single item converted scores. The MENQOL total score is the mean of the domain mean scores. Higher scores indicate greater bother. See details in Section 6.1.3.

4.3.1.2. Main Analytical Approach

The same clinical questions are posed in respect of each primary and key secondary endpoint, and hence the data handling rules selected in respect of the ICEs are the same (detailed in Section 4.2.1). The key secondary endpoints will be analyzed using a mixed model with repeated measures (MMRM) model analogous to the main analysis of primary endpoints (see Section 4.2.1). For PROMIS SD SF 8b T-scores are used. For MENQOL week 1 data will not be collected, the analysis will be adjusted accordingly.

PROMIS SD SF 8b total scores (converted as T-scores), total raw scores and MENQOL total scores will be summarized descriptively by treatment group and week using the number of non-missing observations, arithmetic mean and standard deviation, median, minimum and maximum. The absolute values at various weeks and the corresponding change from baseline per week will be summarized accordingly. The change from baseline over time will be shown using line plots for means together with 95% CIs by treatment group.

Graphical summaries with the absolute change from baseline on the x-axis and proportion of participants achieving this reduction on the y-axis, by treatment group, for week 4 and 12 will be presented for the MENQOL total score and for the PROMIS SD SF 8b total T-score.

PROMIS SD SF 8b raw scores for each item will be summarized by a frequency table with the number of observations and percentage by treatment group and week. Bar charts will also be created by treatment group and week.

4.3.1.3. Sensitivity Analyses

The sensitivity analysis similar to described in Section 4.2.2 will be performed for key secondary endpoints.

For tipping point analysis, the adjustments will be applied with the following delta values:

- PROMIS SD SF 8b total T-score, delta values of 3, 6, 9, etc.
- MENQOL total score, delta values of 0.5, 1, 1.5, etc.

4.3.1.4. Supplementary Analyses

The two supplementary estimands defined for the primary endpoints will also be used for the key secondary endpoints (see Section 4.2.3).

4.3.2. Secondary Endpoints

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

The frequency and severity of moderate to severe HF and the change as well as the relative change (%) from baseline will be summarized using descriptive statistics as described in Section 4.2.1. Further details with regards to the frequency of HF and baseline values can be found in Section 4.1.2.1.

If a participant discontinues/interrupts use of adjuvant endocrine therapy, mean change in frequency of moderate to severe HF from baseline over time will be additionally presented in presence or in absence of adjuvant endocrine therapy (by treatment group and by week). Absence of adjuvant endocrine therapy is defined similar to ICE “interruption/discontinuation of adjuvant endocrine therapy”; For participants using tamoxifen, reduction of at least 50% and for or participants using aromatase inhibitors, reduction of at least 30% of planned daily dosage taken during each particular week compared to baseline.

4.4. Exploratory Endpoints Analysis

For all exploratory endpoints, the ICEs will be handled according to the treatment policy. No missing data imputation is planned for these endpoints.

4.4.1. HFDD related exploratory endpoints

The following exploratory endpoints based on the HFDD will be analyzed by descriptive statistical methods as described in Section 4.1 by treatment group.

- 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
- Time to treatment response
- Mean change in frequency of mild, moderate, and severe HF from baseline over time (assessed by HFDD)
- Mean change in frequency of nighttime awakenings from baseline over time (assessed by HFDD)
- Mean change in proportion of days with participants rating of "quite a bit" or "very much" sleep disturbances experienced due to HF from baseline over time (assessed by HFDD).

The proportion of participants with at least 50 % reduction in frequency of moderate to severe HF at week 4 and 12 will be calculated as the proportion of participants whose baseline value for the frequency of moderate to severe HF is reduced by ≥ 50 % at week 4 and 12, respectively.

A graphical summary with % change (0 to 100) in the frequency and severity of moderate to severe HF from baseline on the x-axis and proportion of participants achieving this reduction on the y-axis, by treatment group, for week 4 and 12 will also be provided. Similarly, a graphical summary with absolute change in the frequency and severity of moderate to severe HF from baseline on the x-axis and proportion of participants achieving this reduction on the y-axis, by treatment group, for week 4 and 12 will also be produced.

To assess the treatment response, threshold value for 50% reduction from baseline of the frequency of moderate to severe HF will be considered. The time to first occurrence (i.e., the first week after baseline) of a reduction of the baseline value by 50% will be analyzed. If the required reduction by week 12 is not observed, the participant will be censored at week 12. Similarly, participants that drop out of the study before achieving the required reduction, will be censored at the time of dropping out (i.e., at the last evaluable week, defined as a week with at least 5 days of diary data, before dropping out). Kaplan-Meier estimates of the time to treatment response including a 95% confidence interval (calculated based on a normal approximation and using the Greenwood formula for the standard deviation) and cumulative incidence plots based on the Kaplan-Meier estimator will be presented by treatment group. Furthermore, the proportion of treatment responders will be summarized by treatment group. In addition, the proportion of treatment responders will be presented at Week 26 and at Week 50.

The mean change in frequency of mild, moderate, and severe HF from baseline will be calculated similar to the mean change in frequency of moderate to severe HF described in Section 4.1.2.1, but will also include mild HF in the calculation. Specifically, the baseline value of the frequency of mild, moderate, and severe HF 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 mild, moderate, and severe HF during the 14 days prior to start of treatment) /

(total number of available days with data). As per inclusion criteria 8 (see protocol), at least 11 days will be available for the derivation of the baseline value. Similarly, the frequency of mild, moderate, and severe HF for each week during the treatment period will be calculated using the available data during that particular week and aggregated to a mean daily frequency as (total number of mild, moderate, and severe HF during that week) / (total number of available days with data during that week). In case data is missing for more than 2 days within a week, the value for that week will be set to missing and no imputation of missing values will be performed. The mean change from baseline will then be calculated as the difference in the mean daily frequency of mild, moderate, and severe HF for a given week from the corresponding baseline value.

Summary statistics for the frequency of mild, moderate, and severe HFs as well as the absolute change from baseline will be presented by week and by treatment group. The change from baseline over time in the frequency of mild, moderate, and severe HFs will be shown using line plots by treatment group.

The mean change in frequency of nighttime awakenings from baseline over time is based on the number of nighttime awakenings during the previous night that is being assessed every morning as part of the HFDD. The baseline value of the nighttime awakenings will be calculated by averaging the nighttime awakenings from the available days during the 14 days prior to start of treatment to a mean daily frequency as (total number of nighttime awakenings during the 14 days prior to start of treatment) / (total number of available days with morning data). Similarly, the frequency of nighttime awakenings for each week during the treatment period will be calculated using the available data during that particular week and averaged to a mean daily frequency as (total number of nighttime awakenings during that week) / (total number of available days with morning data during that week). In case morning data is missing for more than 2 days within a week, the value for that week will be set to missing and no imputation of missing values will be performed. The mean change from baseline will then be calculated as the difference in the mean daily frequency of nighttime awakening for a given week from the corresponding baseline value. A graphical summary (i.e. cumulative distribution function) with absolute change (0 to 100) in the frequency of nighttime awakenings from baseline on the x-axis and proportion of participants achieving this reduction on the y-axis, by treatment group, for week 4 and 12 will also be provided.

Summary statistics for the frequency of nighttime awakenings as well as the absolute change from baseline will be presented by week and by treatment group. The change from baseline over time in the frequency of nighttime awakenings will be shown using line plots for means together with 95% CIs by treatment group.

Sleep disturbances due to HF are assessed every morning as part of the HFDD. Participants provide a rating of their sleep disturbances due to HF in the previous night as

- ‘not at all’
- ‘a little bit’
- ‘somewhat’
- ‘quite a bit’
- ‘very much’

To calculate the mean change in proportion of days with ‘quite a bit’ or ‘very much’ sleep disturbance due to HF, the number of days with participants having reported ‘quite a bit‘ or ’very much‘ sleep disturbance will be used. The baseline value of the proportion of days with ‘quite a bit’ or ‘very much’ sleep disturbances due to HF will be calculated based on the available days during the 14 days prior to start of treatment as (number of days with sleep disturbance due to HF rated as ‘quite a bit’ or ‘very much’)/ (total number of available days with morning data). The on-treatment value for the sleep disturbances due to HF for each week will be calculated using the available data during that particular week as (number of days with sleep disturbance due to HF rated as ‘quite a bit’ or ‘very much’ during that week) / (total number of available days with morning data during that week). In case morning data is missing for more than 2 days within a week, the value for that week will be set to missing and no imputation of missing values will be performed. Mean change in proportion of days with participants having reported ’quite a bit‘ or ’very much‘ sleep disturbance due to HF from baseline will then be calculated as the difference in the mean sleep disturbance value for a given week from the corresponding baseline value.

Summary statistics for the proportion of days with participants having reported ’quite a bit‘ or ’very much‘ sleep disturbance due to HF as well as the absolute change from baseline will be presented by week and by treatment group. The change from baseline over time of the proportion of days with participants having reported ’quite a bit‘ or ’very much‘ sleep disturbance due to HF will be shown using line plots for means together with 95% CIs by treatment group.

4.4.2. PROMIS SD SF 8b

- Absolute values and changes from baseline in the PROMIS SD SF 8b total T- and raw scores over time

Details on this instrument can be found in Section 6.1.2.

The absolute values and the change from baseline in the PROMIS SD SF 8b total T- and raw scores over time will be summarized by week and treatment group using descriptive statistical methods as described in Section 4.1.

4.4.3. MenQoL

- Mean change in MENQOL domain and single item scores from baseline over time

Details on this instrument can be found in Section 6.1.3.

The absolute values and the change from baseline will be summarized by week and by treatment group using descriptive statistical methods as described in Section 4.1. The change from baseline over time of domain scores will be shown using line plots for means together with 95% CIs by treatment group. Converted scores will be shown in the tables.

4.4.4. Insomnia Severity Index (ISI)

- Absolute values and changes in the ISI total score over time

Details on this instrument can be found in Section 6.1.4.

The absolute values for the total score and the change from baseline will be summarized using descriptive statistical methods as described in Section 4.1 by week and treatment group. In addition, Severity of insomnia presented in categories (i.e. “No clinically significant insomnia”, “Subthreshold insomnia”, “Clinical insomnia (moderate severity)” and “Clinical insomnia (severe)” as defined in Section 6.1.4) will be summarized with frequency tables by treatment group, as well as change from baseline to each week will be described using shift tables.

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

- Absolute values and change in EQ-5D-5L single dimensions and health state VAS score over time

Details on this instrument can be found in Section 6.1.5.

The answers to the 5 dimensions will be summarized in frequency tables by week and by treatment group. The change from baseline will be described using shift tables. The health state VAS values and the change from baseline will be analyzed using descriptive statistical methods as described in Section 4.1 by week and treatment group.

Hebrew EQ5D-5L VAS scale was reversed for 12 subjects. They are included in the planned analysis, but sensitivity analysis will be performed, where those 12 subjects will be excluded.

4.4.6. Short Form-36 Health Survey Acute (SF-36 Acute)

- Absolute values and changes from baseline in SF-36 acute domain, physical component summary (PCS) and mental component summary (MCS) scores over time

Details on this instrument can be found in Section 6.1.6.

Each domain a raw score, a standardized score and PCS and MCS scores, as well as change from baseline, will be summarized using descriptive statistics by treatment group and by week.

4.4.7. Beck Depression Inventory (BDI-II)

- Absolute values and changes in the BDI-II total score over time

Calculation of the BDI-II total score is described in Section 6.1.7. The absolute values and the change from baseline will be summarized using descriptive statistical methods as described in Section 4.1 by week and by treatment group. The change from baseline in categories from BDI-II total score (0-13: none to minimal depression, 14-19: mild depression, 20-28: moderate depression and 29-63: severe) will be described using a shift table.

4.4.8. Bleeding diary

Bleeding diary data will be listed.

4.5. Safety Analyses

4.5.1. Extent of Exposure

The analyses described in this section will be presented for the SAF and the FAS.

Treatment duration will be defined as the number of days from the day of first study drug intake up to and including the day of last study drug intake and will be summarized using descriptive statistics by treatment group and by study drug. For the display by Week 1-12, the treatment duration ends on the end of treatment phase 1 or on the day of last study drug intake, whatever is earlier. For the display by Week 13-26, the treatment duration starts on the first day of treatment phase 2. For the display by Week 27-52, the treatment duration starts on the Visit T9 + 1. The duration of extension period (Part C) starts on the Visit T13 + 1. (As defined in Section 4.1.2.)

The extent of exposure to elinzanetant will be summarized as the total amount of study drug intake in grams and the average daily dose in mg using descriptive statistics per treatment group.

The compliance (as percentage) will be calculated as:

100 * Number of capsules taken / Number of planned capsules

The number of planned capsules is calculated as:

treatment duration * 2

All capsules, including the placebo capsules, will be counted. For participants who withdraw prematurely from the study drug, compliance will be calculated up to the time of last dose. The compliance will be summarized descriptively by treatment group. In addition, percent of compliance will be categorized into 3 groups, less than 80%, 80 to 120% and greater than 120%, and the categories will be summarized by treatment group and by study drug.

Treatment duration will be presented based on the data collected via the eCRF. If the date for end of exposure is not available in eCRF, the last day of drug intake from eDiary will be used to determine the end of exposure. Extent of exposure and compliance will be calculated and presented based on the ePRO daily instrument ‘Study drug intake documentation’ and on the eCRF ‘Drug Accountability’ and ‘Drug Exposure’ pages. The summaries for treatment duration, exposure and compliance will be presented for weeks 1-12, 13-26, 27-52 and overall, (i.e., for the entire 26 (Part A)/52 (Part B) weeks). Treatment duration, exposure and compliance summaries will be shown separately for Part C.

4.5.1.1. Extent of exposure of adjuvant endocrine therapy

The compliance (%) of adjuvant endocrine therapy will be summarized descriptively by treatment group for weeks 1-12, 13-26, 27-52 and overall. The compliance (as percentage) will be calculated as:

> 100 * Number of days the medication taken / (Number of available daily diary data with adjuvant endocrine therapy intake during treatment period* Daily dosage during baseline)

During Part C at each visit, the investigator will ask the participant about adherence to the prescribed intake 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 intake will be summarized using frequency table by visit.

4.5.2. Adverse Events

Adverse events (AEs) will be collected from the start of study intervention until the last follow-up. (Serious) Adverse event ((S)AEs) which are related to protocol required study procedures (e.g. (S)AE related to invasive study procedures) will be recorded as (S)AEs from the signing of the Informed consent form (ICF) (pre-treatment (S)AEs). 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 AEs will be summarized using the Medical Dictionary for Regulatory Activities (MedDRA) preferred terms (PT) grouped by system organ class (SOC) (the current version at the time of analysis) and classified into pre-treatment AEs, treatment-emergent (TEAE) and post-treatment AEs. Pre-treatment and post-treatment AEs will be shown by treatment group. Descriptive analysis for TEAEs will be performed for Week 1-12, 13-26, 27-52 and overall week 1-26, 27-52 and 1-52 by study drug.

Incidences of TEAEs and TESAEs per 100 person-years will be summarized by study drug and by study period (weeks 1-12, 13-26, 27-52 and overall elinzanetant for weeks 1-26 and 1-52).

The rate per 100 person-years is calculated as

> Rate per 100 person-years = number of subjects with an event / (total drug exposure in years / 100),

where 365.25 days are taken as one year.

A TEAE is defined as any adverse event occurring or worsening on or after the date of the first dose of study drug up to 14 days after the date of the last dose of study drug. AEs will be flagged as TEAE except for AEs for which there is clear evidence that the AE starts before date of first study drug intake (pre-treatment AEs) or after the date of last study drug intake + 14 days (post-treatment AEs).

If the severity of a previously reported event worsens or if the relationship to study intervention/protocol required procedures changes, two separate events should be reported.

Worsening of an AE is defined as follows:

- AE intensity is worsened (e.g. moderate to severe)
- AE changed to a serious event
- AE ends with death

In case an AE starts before the date of last study drug intake + 14 days and worsens after last study drug intake +14 days, it will be considered as two AEs, a TEAE and a post-treatment AE.

Partially missing onset AE date will be imputed following a worst-case approach as described in Section 4.1.1.

In case of events with different intensity within a subject, the maximum reported intensity will be used. If the same event is considered as both unrelated and related to the study drug within a subject, the event will be reported as related to study drug. If the drug relationship is missing, the event will be considered as being related to the study drug.

The tabulation will follow in principle the Bayer Global Standard Tables catalogue (v4.0 or later). SAEs and Adverse events of special interest (AESI) will be summarized in the same way as described for TEAEs. A separate table summarizing TEAEs that occurred in more than 5% of the subjects will be provided.

In addition, subjects with a COVID-19 as an adverse event will be listed.

Adverse events of special interest (AESI)

AESI will only be identified by Standardized MedDRA Query (SMQ) searches and PTs and AESI 'any condition triggering close liver observation' also via eCRF as further detailed in Section 6.6. The following AEs are included:

1. Any condition triggering close liver observation (as listed in Protocol section 10.5)
2. Somnolence or fatigue
3. Phototoxicity
4. Post-menopausal uterine bleeding (women without hysterectomy are considered)

4.5.3. Additional Safety Assessments

4.5.3.1. Physical examination

Weight will be summarized by treatment group and by visit, including change from baseline, using descriptive statistics as described in Section 4.1. The absolute values by visit and by treatment group will be shown using boxplots.

4.5.3.2. Vital signs

Vital signs (pulse rate, systolic blood pressure and diastolic blood pressure) will be summarized by treatment group for each visit, including change from baseline where appropriate, using descriptive statistics as described in Section 4.1. The absolute values by visit and by treatment group will be shown using boxplots. In addition, for systolic and diastolic blood pressure the line-plots depicting the mean change from baseline ±95% CI by treatment group as well as scatter plot showing blood pressure values at week 12 and at Week 52/EoT against baseline by treatment group will be provided.

4.5.3.3. Electrocardiograms

Unscheduled electrocardiograms ECGs will be shown in data listings only. Both Bazett's formula, Fridericia's formula and/or calculations based on linear regression techniques will be shown for corrected QT-interval (QTc), when available.

4.5.3.4. Clinical laboratory

The tabulation of clinical laboratory data will be presented by treatment group for each visit according to the Bayer Global Standard Tables catalogue (version 4.0 or later). It includes:

- Summary statistics of continuous laboratory parameters, and their changes from baseline
- Frequency tables for categorical laboratory parameters

The distribution of laboratory values by treatment group for each visit will be presented graphically with boxplots. Line plots depicting the mean change from baseline ± 95% CI will be provided for CK, LDH, estradiol, HbA1c, total cholesterol, HDL, LDL and TG and for liver parameters: AST, ALT, ALP, Total bilirubin and INR.

Treatment-emergent (i.e. 14 days from the last drug intake) high and low laboratory abnormalities will be summarized for Week 1-12, 13-26, 27-52 and overall week 1-26, 27-52 and 1-52 by study drug.. Both scheduled and unscheduled laboratory measurements will be used in treatment-emergent abnormal laboratory tables.

Central laboratory will be considered for descriptive analysis. Local laboratory measurements will be listed, if available.

4.5.3.4.1. Liver monitoring

The following parameters will be investigated in addition to the standard lab presentations:

- Aspartate aminotransferase (AST) (in U/L),
- Alanine aminotransferase (ALT) (in U/L),
- Alkaline phosphatase (ALP) (in U/L),
- Total Bilirubin in serum (in mg/dL)
- International normalized ratio (INR).

Frequency tables presenting number and percentage of subjects by treatment group for baseline and post-baseline (both scheduled and unscheduled measurements can be used), will be presented for the following categorizations (where ULN stands for “Upper Limit of Normal”):

- For ALT and AST, separately:
  - ≥1×ULN, ≥3×ULN, ≥ 5×ULN, ≥ 8×ULN, ≥ 10×ULN, ≥ 20×ULN
- For ALT and AST combined (if at least one of ALT and AST falls into the category):
  - ≥ 3×ULN, ≥ 5×ULN, ≥8×ULN, ≥ 10×ULN, ≥ 20×ULN
- For Total bilirubin:
  - ≥1×ULN, ≥2×ULN, ≥ 5×ULN, ≥8×ULN
- For ALP:
  - ≥1.5×ULN, ≥2.0×ULN, ≥3.0×ULN
- For INR:

- ≥1.5, ≥2

Frequency tables presenting number and percentage of participants by treatment group for post-baseline will be presented for the following combinations of ALT/AST and Total bilirubin or INR,

Relative to ULN:

- ALT or AST ≥3×ULN and ≥1.5×ULN in Total bilirubin
- ALT or AST ≥ 3×ULN for and ≥2×ULN in Total bilirubin
- ALT or AST ≥3×ULN followed by ≥2×ULN in Total bilirubin (measured within 30 days afterwards) (Hy's Law criteria).
- ALT or AST ≥3×ULN and ≥1.5 for INR
- ALT or AST ≥5×ULN for more than 2 weeks
- ALT or AST ≥8×ULN
- ALT or AST ≥ 3×ULN with the appearance of any signs or symptoms based on close liver observation eCRF page.
- ALP ≥ 2×ULN and Total Bilirubin ≥2×ULN

Relative to baseline (BL):

- ALT ≥3×BL or AST ≥3×BL and Total bilirubin ≥2×BL
- ALT ≥3×BL or AST ≥3×BL
- ALT ≥5×BL or AST ≥5×BL
- ALT ≥2×BL or AST ≥2×BL and Total bilirubin ≥2×BL
- ALP ≥2×BL and Total bilirubin ≥2×BL

Time to event analysis

Cumulative incidence estimates for the time to first occurrence of ALT ≥ 3×ULN and to first occurrence of ALP ≥ 3×ULN will be derived. If no such an increase is observed, the observation is censored at the last visit date. Tables with the number of subjects under risk, cumulative number of subjects with ALT ≥3×ULN and ALP ≥ 3xULN, and estimated probability for an event including 95% CIs (two-sided) will be presented. Furthermore, cumulative incidence curves will be provided by treatment group. If a participant does not have any post-baseline data, she will be censored at baseline.

Figures

Hepatocellular drug-induced liver injury (DILI) screening plot will be displayed to identify cases of possible serious hepatocellular DILI. In the plot each patient is plotted based on their maximum postbaseline Total bilirubin (y-axis) and transaminase values (ALT or AST, whichever is higher. Together with the plot a frequency table for patients in each quadrant (Potential Hy's Law, Cholestasis, Temple's corollary) will be shown.

Cholestatic drug-induced liver injury screening plot will be shown to identify significant ALP elevation in the setting of hepatic dysfunction. Maximum postbaseline Total bilirubin is

plotted against maximum postbaseline ALP. Similar to above a frequency table for patients in each quadrant (Total bilirubin ≥ 2xULN and ALP ≥ 2xULN, Total bilirubin ≥ 2xULN and ALP < 2xULN, Total bilirubin < 2xULN and ALP ≥ 2xULN) will be shown.

Individual patient presentations

If a patient met close liver observation criteria at any time point, a plot for her individual time course in the following laboratory parameters will be presented: 1) ALT, AST, Total bilirubin and ALP relative to ULN over time and 2) absolute values for INR over time. It will be indicated within the plot on which days the study drug and adjuvant endocrine therapy was taken (i.e. start and stop dates of treatment intake), in addition all AEs and CM 6 months (182 days) prior to the first onset of close liver observation will be shown in the first plot. Furthermore, listing will be provided for INR (absolute values) and for liver-related parameters, i.e. ALT, AST, Total and direct bilirubin,ALP, GGT, CK and LDH (with results relative to ULN).

The liver injury criteria

All subjects meeting close liver observation criteria will be assessed by Liver Safety Monitoring Board (LSMB). Number of subjects fulfilling the liver injury criteria per LSMB manual will be presented with a frequency table.

4.5.3.5. Pregnancy test

Pregnancy test results will be listed.

4.5.3.6. Breast imaging – Mammogram/Ultrasound

A frequency table for mammogram/ultrasound findings (normal/abnormal) at screening, at Week 52/EoT and at unscheduled visits will be produced by treatment group.

4.5.3.7. Transvaginal ultrasound

Number and percentage of subjects with ultrasound performed and result of overall assessment at each visit (baseline and Week 52/EoT) will be presented by treatment group.

Endometrial thickness will be summarized by treatment group for each visit, including change from baseline, using descriptive statistics for women without hysterectomy.

Number and percentage of subjects that developed ovarian cyst during the study will be presented by treatment group.

4.5.3.8. Cervical cytology

A frequency table for cervical smears findings at screening will be provided by treatment group.

4.5.3.9. Endometrial biopsy

Analyses will present the number and percentage of either participants or biopsies for women without hysterectomy. Biopsies taken at EoT (including biopsies taken at Week 52 or at

earlier EoT visit) or at Unscheduled visit will be further divided in the tables for subjects treated for at least 326 days and for subjects treated less than 326 days.

Presentations will be done for

- the Majority read
- All reads (Reader #1 - #3)

Majority read: Majority read will be determined for main results and subcategories (see Table 4–8). First, adequacy (for part II and III) of tissue will be investigated by all readers. If at least 2 of the 3 readers consider the tissue adequate/sufficient, the majority for the main results will be assessed. If there is a majority with respect to the main result, majority of the respective subcategories will be determined. If no majority result is available (3 different results in 3 readers, 2 different results in 2 readers), either "no consensus" or the worst case will be presented. Table 4–8 presents an overview of the biopsy results including the approach which is used in case no majority is available. Other observations will be listed only.

All read: All read results will be based on all biopsies with results from at least one reader.

Table 4–8: Overview of biopsy endpoints including majority result handling and worst case

Part		**Endpoint**	**No majority available**
Main results			
I		Adequate endometrial tissue	- *(not possible)*
II	Main diagnosis	Benign endometrium Endometrial Hyperplasia (WHO 2014 classification) Malignant Neoplasm	Worst case: List is ordered by severity, from low to high
III		Endometrial Polyp	Worst case: yes
Subcategories			
II	Main diagnosis	Benign endometrium (select one) •Atrophic • Inactive • Proliferative • Disordered Proliferative • Secretory • Menstrual • Endometritis • Other, specify	"no consensus"
		Endometrial Hyperplasia (WHO 2014 classification) (select one) • Hyperplasia without atypia • Atypical hyperplasia / Endometrioid Intraepithelial Neoplasia (EIN)	Worst case: Atypical hyperplasia / Endometrioid Intraepithelial Neoplasia
		Malignant Neoplasm • Endometrial Neoplasm • Other Malignant Neoplasm	"no consensus"
III		Endometrial Polyp (select one) • Atrophic • Functional • Hyperplastic	"no consensus"

4.5.3.10. 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, using the electronic handheld device together with the HFDD evening diary assessment. In case one entry on the Sleepiness Scale was missed, retrospective data entry is possible for a pre-defined period of time (the entry option will be available between midnight until 10:59AM on the day after the missed entry. During the screening period assessments will be done daily. During the treatment period the assessment will be done on 7 consecutive evenings during Weeks 1, 4, 12, 26, 36 and 50.

Participants respond to the items using a 5-point verbal rating scale (from "0" = not at all, to"4" = very much). Daily sleepiness score will be calculated by averaging daily individual item scores (i.e. morning, afternoon and evening scores).

Descriptive summaries for 7-day average of daily individual single item scores and 7-day averages of a daily sleepiness score and corresponding change from baseline values will be created by treatment group and overall for each week. 7-day averages can be derived, if daily score at least 5 out of 7 days is available, otherwise average score will be set as missing.

The baseline sleepiness score will be derived from days with available data within the 14-day period before randomization. A minimum of 11 days should be available for the derivation of the baseline value.

4.6. Other Analyses

Other pre-specified objectives in this study are:

- To evaluate variability in exposure in relation to the efficacy and safety for elinzanetant
- To further investigate elinzanetant (e.g., mode-of-action-related effects, safety) and to further investigate pathomechanisms deemed relevant to VMS and associated health problems

These will be evaluated accordingly by:

- Systemic exposure of elinzanetant in plasma via sparse pharmacokinetic (PK) sampling
- Various biomarkers (e.g., diagnostic, safety, pharmacodynamic, monitoring, or potentially predictive biomarkers)

4.6.1. Other Variables and/or Parameters

4.6.1.1. Pharmacokinetics

PK analyses will be described in a separate document and the results will be presented outside CSR. Only concentration data will be provided in a listing (Section 10).

4.6.1.2. Genetics

Genetic as well as non-genetic analyses may be part of the biomarker investigations in this study, if approved by local Ethics Committees / Institutional Review Boards and competent authorities.

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

The analysis will be described in a separate document and the results will be presented outside CSR. Only the phenotype/metabolizer status for subjects with Tamoxifen as an adjuvant endocrine therapy treatment will be listed among section 10.

4.6.1.3. PD /safety biomarkers from blood

The analyses for pharmacodynamic (PD)/safety biomarkers from blood will be described in a separate document and the results will be included in the CSR.

4.6.1.4. Psychometric properties of selected questionnaires

In case needed, data from the study might be used to assess psychometric properties of scores form HFDD, PROMIS SD SF 8b and the MENQOL to be described in a separate document and the results will be presented outside CSR.

4.6.2. Subgroup Analyses

Exploratory subgroup analyses using descriptive statistics will be provided for the primary and key secondary endpoints for the following subgroups:

- Type of treatment for the pre-existing condition at baseline (tamoxifen, aromatase inhibitors)
- Race
- Ethnicity
- BMI (<18.5, 18.5 to <25, 25 to <30, >= 30 kg/m2)
- Smoking history (Never, Former, Current; derived from habitual cigarette smoking and any other tobacco/nicotine from the CRF)

For the key secondary endpoints based on the PROMIS SD SF8b these exploratory subgroup analyses will only be presented for the total T-scores. For the MENQOL, they will be presented for the total scores and the vasomotor symptoms subdomain score.

Descriptive statistics for PROMIS SD SF 8b total T-scores will be provided for the following subgroups based on Insomnia Severity Index (ISI) administered at baseline (see Section 6.1.4 more details on ISI):

- 0-14 = No clinically significant and subthreshold insomnia
- 15–21 = Clinical insomnia (moderate severity)
- 22–28 = Clinical insomnia (severe)

4.7. Interim Analyses

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. Data cutting rules are defined in the separate document, which is signed before database closure. Data from Part B will not be included in this analysis. No multiplicity adjustment is needed since the primary efficacy analysis will be final after the evaluation of part A data. Final CSR will include Part A and Part B. Part B data will be analyzed for available endpoints. Treatment extension (part C) will be analyzed and reported separately from Parts A and B.

4.8. Changes to Protocol-planned Analyses

Not applicable.

5. 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.

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 5–1. The data from placebo arm in SWITCH-1 study (NCT03596762, 2020) was used for assumption of standard deviation.

Table 5–1: 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

6. Supporting Documentation

6.1. Appendix 1: Additional information on scoring and measurement properties of the HFDD, the PROMIS SD SF 8b, MENQOL and BDI-II

6.1.1. 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. 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".

6.1.2. 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 (scored from 1 to 5) from "not at all", "never", "very poor" to "very much", "always" or "very good". Four of the items are scored reversely. The individual item scores for a participant will be summed to derive a total raw score. Total raw scores range from 8 to 40, with higher scores indicating greater severity of sleep disturbance. Total raw scores will be converted into T-scores for comparison with population norms (United States general population). The conversion table is provided in Table 6–1. (PROMIS Sleep Disturbance – Scoring Manual). T-scores will be used in the confirmatory analysis.

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 once weekly during the weeks 1-4 and thereafter at weeks 8, 12, 16, 26, 36, 52 and 56 (i.e. Follow-up).

Table 6–1: Sleep Disturbance 8b - Conversion Table

Sleep Disturbance 8b *Short Form Conversion Table*		
Raw Score	**T-score**	**SE***
8	28.9	4.8
9	33.1	3.7
10	35.9	3.3
11	38.0	3.0
12	39.8	2.9
13	41.4	2.8
14	42.9	2.7
15	44.2	2.7
16	45.5	2.6
17	46.7	2.6
18	47.9	2.6
19	49.0	2.6
20	50.1	2.5
21	51.2	2.5
22	52.2	2.5
23	53.3	2.5
24	54.3	2.5
25	55.3	2.5
26	56.3	2.5
27	57.3	2.5
28	58.3	2.5
29	59.4	2.5
30	60.4	2.5
31	61.5	2.5
32	62.6	2.5
33	63.7	2.6
34	64.9	2.6
35	66.1	2.7
36	67.5	2.8
37	69.0	3.0
38	70.8	3.2
39	73.0	3.5
40	76.5	4.4

*SE = Standard Error on T-score metric

6.1.3. 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). 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'. The conversion table is provided in Table 6–2.

Table 6–2: MENQOL - conversion table

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

Domain scores are calculated by averaging the converted individual item scores (range 1-8) related to the respective domain. (Domains: Vasomotor - items 1 to 3, Psychosocial – items 4 to 10, Physical- items 11- to 26, Sexual – items 27 to 29.) For a MENQOL total score the aggregated mean of the mean domain scores is calculated. Higher scores indicate greater bother. MENQOL total score, domain scores and individual item scores will be summarized in this study.

In this study the MENQOL will be applied electronically and responded to by the participants at home and during selected in person visits at weeks 1 (i.e. baseline), 4, 8, 12, 16, 26, 36, 52 and 56 (i.e. Follow-up).

6.1.4. 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 seven questions are with respect to:

- difficulty falling asleep
- difficulty staying asleep
- problems waking up too early
- satisfaction/dissatisfaction with current sleep pattern
- noticeability of sleep problems by others
- worries/distress caused by the sleep difficulties
- extent of interference of sleep difficulties with daily functioning.

It is scored on a five-point Likert scale from 0 to 4 depending on the item:

- Items 1-3: 0='none' to 4='very severe'
- Item 4: 0='very satisfied' to 4='very dissatisfied'
- Item 5: 0='not at all noticeable' to 4='very much noticeable'

- Item 6: 0=’not at all worried’ to 4=’very much worried’
- Item 7: 0=’not at all interfering’ to 4=’very much interfering’ (Item 7)

The scores for each item are summed to produce the total score (maximum 28) which allow categorization of severity of insomnia.

Total score categories:

0–7 = No clinically significant insomnia

8–14 = Subthreshold insomnia

15–21 = Clinical insomnia (moderate severity)

22–28 = Clinical insomnia (severe)

6.1.5. EQ-5D-5L

The EQ-5D-5L is a self-administered preference-based generic measure of health status which includes five dimensions (EQ-5D-5L User guide):

1. mobility
2. self-care
3. usual activities
4. pain/discomfort
5. anxiety/depression.

Participants provide a rating for each question on a five-point Likert scale:

- for items 1-3: no problems, slight problems, moderate problems, severe problems, unable to do
- for item 4: no pain, slight pain, moderate pain, severe pain, extreme pain
- for item 5: not anxious or depressed, slightly anxious or depressed, moderately anxious or depressed, severely anxious or depressed, extremely anxious or depressed.

In addition, participants 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".

6.1.6. 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.

Descriptive analysis will base on the single item level assessment, aggregation of single item scores to the 8 health domains respectively, and calculations: the psychometrically-based physical component summary (PCS) and the mental component summary (MCS) scores. Transformed and calculated scores are provided by external Vendor.

6.1.7. BDI-II

The BDI-II consists of 21 items to assess the severity of depression over the past 2 weeks (Beck et al. 1996). The 21 items are with respect to various symptoms of depression, specifically:

- Sadness
- Pessimism
- Past Failure
- Loss of Pleasure
- Guilty Feelings
- Punishment Feelings
- Self-Dislike
- Self-Criticalness
- Suicidal Thoughts or Wishes
- Crying
- Agitation
- Loss of Interest
- Indecisiveness
- Worthlessness
- Loss of Energy
- Changes in Sleeping Pattern
- Irritability
- Changes in Appetite
- Concentration Difficulty
- Tiredness or Fatigue
- Loss of Interest in Sex

Each item consists of a list of four response options arranged in increasing levels of severity, except for “Changes in Sleeping Pattern” and “Changes in Appetite” which contain 7 response options each. For the items with 4 response options, each item is rated on a 4-point verbal response scale ranging from 0 (not at all) to 3 (extreme form of each symptom). The items with 7 response options are also scored from 0 to 3 as

Response option 1 → score=0

Response option 2 or 3 → score=1

Response option 4 or 5 → score=2

Response option 6 or 7 → score=3.

The total score ranging from 0 to 63 is calculated by summing up the ratings to the 21 items.

6.2. Appendix 2: Pattern-mixture modeling approach for supplementary analysis

A pattern mixture modeling approach (Little, 1993) will be used in combination with multiple imputation (Ratitch, O'Kelly et al., 2013; Wang et al. 2023) to handle missing and unobservable data that occur in presence of ICEs in a way that aligns with the estimand strategy for each type of ICE.

We will use a reference-based pattern imputation approach which makes use of observed data from the reference group for estimating the multiple imputation model for each pattern that requires distinct assumptions about a plausible distribution of missing/unobservable data. The reference group consists of participants who are expected to have similar outcomes to those with missing/unobservable values after conditioning on baseline covariates and, in some cases, partially observed data. Pattern definitions and the corresponding reference groups that will be used for the supplementary analysis of the primary and key secondary endpoints are specified in Table 4–5 and Table 4–7.

The pattern-mixture multiple imputation and analysis method will be implemented by a series of steps using SAS PROC MI, MIXED, and MIANALYZE:

1. Imputation: Impute missing and unobservable values at baseline, Week 1, 4, 8 and 12 (see Table 4–5 and Table 4–7 for definition of patterns):

Impute intermittent (non-monotone) missing values that occur outside of the time frame of any ICE as well as missing and unobservable values that occur in presence of ICEs in pattern 1.

A joint multivariate normal multiple imputation model will include outcomes at baseline, Week 1, 4, 8 and 12, as well as the fixed, categorical effects of treatment and stratification factor (type of treatment of pre-existing condition at baseline).
This step will be implemented using PROC MI with the MCMC statement and the following options: “CHAIN = MULTIPLE” and “SEED = 21656” to produce 500 imputed datasets. The input dataset will contain all participants with missing/unobservable data targeted by this step as described above and participants from the reference group, i.e., participants who complied with the randomized treatment (please see the definition of compliance in Table 1–2). Partially imputed data will serve as input to complete imputation in patterns 3 and 4.

Impute missing values occurring during an ICE associated with pattern 2.

A multiple imputation regression model will be used to model change from a time point before treatment interruption to a time point during treatment interruption as the dependent variable (change equal to pre-interruption value minus value at the time point of interruption). The model will include as predictors the baseline value, value before treatment interruption, and the fixed, categorical effects of treatment and stratification factor (type of treatment of pre-existing condition at baseline). Because the number of participants in this pattern is expected to be small, modeling of change in outcome from pre-interruption to during interruption will be done by pooling data across time points where treatment interruptions occur. Missing values at a time point *k* will be replaced by adding the change value predicted by the imputation model to the participant's value at the time point *(k-1)* prior to treatment interruption.
This step will be implemented with PROC MI and MONOTONE REG statement explicitly specifying the model described above. The input dataset will include all participants in pattern 2 and participants with temporary interruption due to treatment unrelated reasons from pattern 1 who have observed data before and during the interruption.

Impute missing and unobservable data occurring during an ICE associated with pattern 3.

Missing values that occur after the ICE in pattern 3 will be imputed using a similar MI model as used in the main analysis of the primary endpoint as described in Section 4.2.1, that is, the wash-out method (Wang, et al. 2023).

Impute missing and unobservable data occurring during an ICE associated with pattern 4.

If there are any intermittently missing data in this pattern, they will be imputed using PROC MI with the MCMC statement and "CHAIN = MULTIPLE" option to perform partial imputation and obtain a monotone missing pattern. The remaining monotone unobservable data in this pattern will be imputed using multiple imputation regression models for outcome at each affected time point. The model will include as predictors the baseline value, values at time points before treatment discontinuation, and the fixed, categorical effects of treatment and stratification factor (type of treatment for pre-existing condition). The input dataset will include all participants in the analyses set, their observed values and values imputed on previous steps outlined above. That is, the MI model for pattern 4 will reflect a mixture of participants, some of which fully comply with the randomized treatment and some with other types of ICEs.

If an unobserved/missing value is imputed below 0, a post processing step will be applied to set the imputed value 0.

In order to impute a missing value at baseline (as part of the imputation of intermittent missing values), a minimum of 2 post-baseline values (out of 4) should have been observed for the participant.

At the end of the four imputation steps, 500 datasets will be produced and each imputed dataset will be analyzed as described in the analysis step below.

2. Analysis: Estimate of the treatment difference based on each imputed dataset, using the analysis model for the primary endpoints (i.e. MMRM as specified in Section 4.2.1).

The estimated treatment difference at Week 4 and 12 from all imputed datasets will be saved and combined in the next step as described below.

3. Combining results of analyses from multiple imputed datasets: The results of the MMRM analysis on 500 imputed datasets will be combined using Rubin's rule to derive the final estimate for the treatment difference, its 95% CI and p-value (one-sided). This will be done using SAS PROC MIANALYZE.

6.3. Appendix 3: Tipping point analysis

A tipping point analysis will be applied by applying an unfavorable additive shift (referred to as delta adjustment) to values imputed to fill in the missing and unobservable data that occur in presence of ICEs. Delta adjustment will be applied only to imputed values in the elinzanetant arm. No delta adjustment will be applied to missing values that occur outside of the time frame of any ICE. The following steps will be implemented for primary endpoint, i.e., frequency of HF:

1. The imputation step will be done as described in Section 4.2.1.
2. Prior to the analysis step, each imputed value in the elinzanetant arm that occurs in the time frame of an ICE would have a value of "delta" added to it (see Section 4.2.2 for settings of delta for each type of endpoint). The same value of delta will be applied at each time point.
3. Observed, imputed, and adjusted data will be analyzed and results combined as described in Section 4.2.1.
4. The steps for imputation, modeling, combining the results will be repeated with increasing settings of "delta" (see Section 4.2.1) for each primary endpoint until the estimated treatment difference at Week 4 or Week 12 is no longer statistically significant at the 0.025 one-sided level. The corresponding "delta" setting will be selected as the tipping point for that endpoint.

6.4. Appendix 4: Details regarding the identification of intercurrent events

6.4.1. Temporary treatment interruption

Per definition (see Section 1.1), the ICE "temporary treatment interruption" will only be considered for week 1, week 3 and 4, week 7 and 8, and week 11 and 12. Specifically, temporary treatment interruption is defined as

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

- Treatment taken <80% during weeks 1-8 OR treatment taken on <5/7 days during either week 7 or 8 for Week 8
- Treatment taken <80% during weeks 1-12 OR treatment taken on <5/7 days during either week 11 or 12 for Week 12.

The criterion for treatment taken on 5/7 days during the corresponding two weeks, as defined above, is met, if in any selected 7 consecutive days within those weeks, the treatment has been taken for less than 5 days (i.e., at least 3 missed intakes).

If the criterion is met, an ICE flag will be placed for the corresponding visit week for HFDD. For PROMIS and MenQoL, the ICE flag will be placed only if the questionnaire is filled in after the third drug missed intake day.

To identify whether < 80 % treatment was taken, planned compliance during weeks 1-4 will be calculated as

100 * Number of capsules taken / 56

where 56 is based on two tablets per day over 28 days. Planned compliance during weeks 1-8 will be calculated as

100 * Number of capsules taken / 112

where 112 is based on two capsules per day over 56 days.

Planned compliance during weeks 1-12 will be calculated as

100 * Number of capsules taken / 168

where 168 is based on two capsules per day over 84 days.

To calculate the number of days per week with treatment intake, a day where at least one capsule was taken, will be considered as a day with treatment intake.

For the identification of the ICE temporary treatment interruption, the compliance and daily treatment intake will be calculated based on the ePRO instrument ‘Study drug intake documentation’.

Regarding the reasons, AEs that lead to a treatment interruption, together with start and end date, will be collected on the respective eCRF page. Similarly, reasons related to COVID-19 or administrative reasons will also be collected in the eCRF.

The reasons for temporary treatment interruption will be reviewed during blind review of the data. The observed temporary treatment interruptions together with the corresponding reason will be presented in data listings.

6.4.2. Permanent discontinuation of randomized treatment

The reasons for permanent discontinuation of randomized treatment will be collected on the corresponding eCRF page, among others with AE or lack of efficacy as possible options. A permanent discontinuation of randomized treatment will be considered to be due to “other treatment unrelated reasons” if AE or lack of efficacy was not selected as reason and any of the following was selected:

- Non-compliance with study device

- Site terminated by sponsor
- Technical problems
- Pregnancy
- Subject decision
- Subject decision: unwillingness to comply with study procedures
- Lost to follow-up
- Other
- COVID-19 pandemic related: subject specific
- COVID-19 pandemic related: other
- Non-compliance with study drug
- Randomized by mistake

The observed permanent discontinuations of randomized treatment together with corresponding reason will be presented in data listings.

Discontinuation due to AE or lack of efficacy may be handled differently depending on estimand for participants who remained untreated/background therapy and for participants who initiate alternative VMS treatment. The treatment status (i.e., remained untreated/on background therapy vs. initiate alternative VMS treatment) should be captured for all participants who discontinued from randomized drug irrespective of the reason for discontinuation.

Table 6–3: Preliminary list of alternative VMS treatment (can be updated during blind review meeting)

DGCODEL0	DGNAME0	DGCODEL1	DGNAME1	DGCODEL2	DGNAME2	Duration of impact with respect to efficacy[a] (considered up to 12 weeks[b])
		5	Hormone replacement therapy	2	Oestrogens	1, From 1st dose to 4 weeks after the last dose if the route is vaginal, intravaginal, cutaneous, nasal or transdermal. 2, From 1st dose to 8 weeks after the last dose if the route

						is oral, sublingual or intrauterine, 3, From 1st dose to 12 weeks or longer if the route is subcutaneous or intradermal.
		5	Hormone replacement therapy	3	Progestogens	1, From 1st dose to 4 weeks after the last dose if the route is vaginal, intravaginal, cutaneous, nasal or transdermal. 2, From 1st dose to 8 weeks after the last dose if the route is oral, sublingual or intrauterine, 3, From 1st dose to 12 weeks or longer if the route is subcutaneous, intradermal or intramuscular.
1633	Drugs for psychiatric disorders	111	Antidepressants	113	Selective serotonin reuptake inhibitors (SSRI)	From 1st dose to 4 weeks after the last dose

*In this column, the terms "1st dose" and "last dose" both refer to the start date and stop date of certain doses of concomitant medication. If the dose was changed, a new start date and/or stop date were reported.
** No further differentiation if duration of impact is longer than 12 weeks since ICEs are considered in the analysis only for the first 12 weeks of the study.

Table 6–4: Preliminary list of alternative VMS treatment by drug names (can be updated during blind review meeting)

WHO Drug Name	WHO Drug Record Number	WHO Drug Sequence Number 1	WHO Drug Sequence Number 2	Duration of impact with respect to efficacy[a] (considered up to 12 weeks[b])
OXYBUTIN	005389	02	057	From 1st dose to 4 weeks after the last dose

[a]In this column, the terms "1st dose" and "last dose" both refer to the start date and stop date of certain doses of concomitant medication. If the dose was changed, a new start date and/or stop date were reported.
[b] No further differentiation if duration of impact is longer than 12 weeks since ICEs are considered in the analysis only for the first 12 weeks of the study.

Although more alternative treatment options may be available, only drug groupings/ drug names are listed that were reported in OASIS 1-4 studies as of finalization of this statistical analysis plan.

6.4.3. Intake of prohibited concomitant medication having impact on efficacy

Drug groupings, individual drugs and manual review will be used to identify whether any prohibited concomitant medication as defined in the protocol were used that influence efficacy. All here listed drug groupings/ drug names were reported in OASIS 1-4 studies as of finalization of this statistical analysis plan, although other medications may also be prohibited per the protocol.

1. For the change from baseline at Week 1 any intake of prohibited medication during Week 1 that has an effect on HF will be considered an intercurrent event.
2. For weeks 4, 8, and 12, not only intake in the respective week but also, intake that occurred prior to week 4, 8, and 12 should be considered as an intercurrent event if within the washout period of the prohibited drug.

A similar approach will be used for the endpoints related to sleep quality (mean change in PROMIS SD SF 8b total score from baseline) and to the menopause related quality of life (mean change in MENQOL total score from baseline) with respect to any prohibited medication that has an effect on sleep quality and menopause related quality of life, respectively.

The list of prohibited concomitant medication together with the assumed relevant time period for their effect will be reviewed during blind review of the data and finalized prior to unblinding.

Table 6–5: Preliminary list of prohibited concomitant medication by drug grouping (can be updated during the blind review meeting)

Any additional condition, so that considered as prohibited and considered as intercurrent event	DGCODEL0	DGNAME0	DGCODEL1	DGNAME1	DGCODEL2	DGNAME2	Duration of impact with respect to efficacy[a] (considered up to 12 weeks[b])
If newly started or dose modified or stopped during the first 12 weeks of study period			5	Hormone replacement therapy	2	Oestrogens	1, From 1st dose to 4 weeks after the last dose if the route is vaginal, intravaginal, cutaneous, nasal or transdermal. 2, From 1st dose to 8 weeks after the last dose if the route is oral, sublingual or intrauterine, 3, From 1st dose to 12 weeks or longer if the route is subcutaneous or intradermal.
If newly started or dose modified or stopped during the first 12 weeks of study period			5	Hormone replacement therapy	3	Progestogens	1, From 1st dose to 4 weeks after the last dose if the route is vaginal, intravaginal, cutaneous, nasal or transdermal. 2, From 1st dose to 8 weeks after the last dose if the route is oral, sublingual or intrauterine, 3, From 1st dose to 12 weeks or longer if the route is subcutaneous,

							intradermal or intramuscular.
Any other than tamoxifen or aromatase inhibitor or GnRH agonists and GnRH antagonist ; if newly started or dose modified or stopped during the first 12 weeks of study period			772	Cancer therapies	738	Endocrine antineoplastic therapy	From 1st dose to 12 weeks after the last dose (All other cancer therapies are excluded, only tamoxifen, aromatase inhibitors, GnRH agonists and GnRH antagonist are allowed.[c])
If newly started or dose modified or stopped during the first 12 weeks of study period	1633	Drugs for psychiatric disorders	111	Antidepressants	114	Monoamine oxidase (MAO) inhibitors, non-selective	From 1st dose to 4 weeks after the last dose
If newly started or dose modified or stopped during the first 12 weeks of study period	1633	Drugs for psychiatric disorders	111	Antidepressants	115	Monoamine oxidase A (MAO-A) inhibitors	From 1st dose to 4 weeks after the last dose

If newly started or dose modified or stopped during the first 12 weeks of study period	1633	Drugs for psychiatric disorders	111	Antidepressants	112	Non-selective monoamine reuptake inhibitors	From 1st dose to 4 weeks after the last dose
If newly started or dose modified or stopped during the first 12 weeks of study period	1633	Drugs for psychiatric disorders	111	Antidepressants	113	Selective serotonin reuptake inhibitors (SSRI)	From 1st dose to 4 weeks after the last dose
	45	Drugs interacting with CYP3A	240	CYP3A inducers	225	Moderate CYP3A inducers	From 1st dose to 4 weeks after the last dose Considered not to have an influence on efficacy, if route is auricular(otic), ophthalmic or conjunctival.
	45	Drugs interacting with CYP3A	240	CYP3A inducers	265	Strong CYP3A inducers	From 1st dose to 4 weeks after the last dose
If newly started or dose modified or stopped during the first 12 weeks of	1633	Drugs for psychiatric disorders	111	Antidepressants	1830	Antidepressant Serotonin Norepinephrine Reuptake Inhibitors (SNRI)	From 1st dose to 4 weeks after the last dose

study period							

[a]In this column, the terms "1st dose" and "last dose" both refer to the start date and stop date of certain doses of concomitant medication. If the dose was changed, a new start date and/or stop date were reported.
[b] No further differentiation if duration of impact is longer than 12 weeks since ICEs are considered in the analysis only for the first 12 weeks of the study.
[c] Tamoxifen (ATC =L02BA), aromatase inhibitors (ATC = L02BG), GnRH agonists (DGCODEL1 = 108, DGCODEL2 = 109) GnRH antagonists (DGCODEL1 = 108, DGCODEL2 = 110)

In addition, the following concomitant medications are considered prohibited:

Table 6–6: Preliminary list of prohibited concomitant medication by drug names (can be updated during the blind review meeting)

Any additional condition, so that considered as prohibited and considered as intercurrent event	WHO Drug Name	WHO Drug Record Number	WHO Drug Sequence Number 1	WHO Drug Sequence Number 2	Duration of impact with respect to efficacy[a] (considered up to 12 weeks[b])
If newly started or dose modified or stopped during the first 12 weeks of study period	ARMOUR THYROID	000537	01	011	From 1st dose to 12 weeks after the last dose
If newly started or dose modified or stopped during the first 12 weeks of study period	NATURE THROID	000537	01	027	From 1st dose to 12 weeks after the last dose
If newly started or dose modified or stopped during the first 12 weeks of study period	LEVOTHYROXINE	000680	01	001	From 1st dose to 12 weeks after the last dose
If newly started or dose modified or stopped during the first 12 weeks of study period	L-THYROXINE	000680	01	006	From 1st dose to 12 weeks after the last dose
If newly started or dose modified or stopped during the first 12 weeks of study period	L-THYROXIN	000680	01	014	From 1st dose to 12 weeks after the last dose
If newly started or dose modified or stopped	LEVAXIN	000680	02	002	From 1st dose to 12 weeks after the last dose

during the first 12 weeks of study period					
If newly started or dose modified or stopped during the first 12 weeks of study period	SYNTHROID	000680	02	005	From 1st dose to 12 weeks after the last dose
If newly started or dose modified or stopped during the first 12 weeks of study period	EUTHYROX	000680	02	007	From 1st dose to 12 weeks after the last dose
If newly started or dose modified or stopped during the first 12 weeks of study period	THYROXIN	000680	02	014	From 1st dose to 12 weeks after the last dose
If newly started or dose modified or stopped during the first 12 weeks of study period	LEVOTHYROXINE [LEVOTHYROXINE SODIUM]	000680	02	020	From 1st dose to 12 weeks after the last dose
If newly started or dose modified or stopped during the first 12 weeks of study period	THYREX	000680	02	028	From 1st dose to 12 weeks after the last dose
If newly started or dose modified or stopped during the first 12 weeks of study period	THYROHORMONE	000680	02	029	From 1st dose to 12 weeks after the last dose
If newly started or dose modified or stopped during the first 12 weeks of study period	T4	000680	02	031	From 1st dose to 12 weeks after the last dose
If newly started or dose modified or stopped during the first 12 weeks of study period	LETROX	000680	02	046	From 1st dose to 12 weeks after the last dose
If newly started or dose modified or stopped during the first 12 weeks of study period	UNITHROID	000680	02	052	From 1st dose to 12 weeks after the last dose

If newly started or dose modified or stopped during the first 12 weeks of study period	LEVOTIROXINA [LEVOTHYROXINE SODIUM]	000680	02	054	From 1st dose to 12 weeks after the last dose
If newly started or dose modified or stopped during the first 12 weeks of study period	L-THYROXIN HENNING	000680	02	058	From 1st dose to 12 weeks after the last dose
If newly started or dose modified or stopped during the first 12 weeks of study period	TIROXIN [LEVOTHYROXINE SODIUM]	000680	02	062	From 1st dose to 12 weeks after the last dose
If newly started or dose modified or stopped during the first 12 weeks of study period	L THYROXIN	000680	02	070	From 1st dose to 12 weeks after the last dose
If newly started or dose modified or stopped during the first 12 weeks of study period	EUTIROX	000680	02	074	From 1st dose to 12 weeks after the last dose
If newly started or dose modified or stopped during the first 12 weeks of study period	LEVOTHYROXIN	000680	02	081	From 1st dose to 12 weeks after the last dose
If newly started or dose modified or stopped during the first 12 weeks of study period	TIROSINT	000680	02	087	From 1st dose to 12 weeks after the last dose
If newly started or dose modified or stopped during the first 12 weeks of study period	EUTHYROX N	000680	02	138	From 1st dose to 12 weeks after the last dose
If newly started or dose modified or stopped during the first 12 weeks of study period	LEVOTIROXIN	000680	02	145	From 1st dose to 12 weeks after the last dose
If newly started or dose modified or stopped	L THYROX	000680	02	163	From 1st dose to 12 weeks after the last dose

during the first 12 weeks of study period					
If newly started or dose modified or stopped during the first 12 weeks of study period	TIROSINT SOL	000680	02	219	From 1st dose to 12 weeks after the last dose
If newly started or dose modified or stopped during the first 12 weeks of study period	LIOTHYRONINE	001433	01	001	From 1st dose to 12 weeks after the last dose
If newly started or dose modified or stopped during the first 12 weeks of study period	LIOTHYRONIN	001433	02	020	From 1st dose to 12 weeks after the last dose
	CLONIDINE	001711	01	001	From 1st dose to 4 weeks after the last dose
	CLONIDINE HYDROCHLORIDE	001711	02	001	From 1st dose to 4 weeks after the last dose
	DIXARIT	001711	02	002	From 1st dose to 4 weeks after the last dose
	CLONIDINE HCL	001711	02	048	From 1st dose to 4 weeks after the last dose
	CANNABIS SATIVA	002377	01	001	From 1st dose to 4 weeks after the last dose
	CANNABIS SATIVA	002377	01	002	From 1st dose to 4 weeks after the last dose
	MARIJUANA	002377	01	002	From 1st dose to 4 weeks after the last dose
	CBD OEL	002377	08	003	From 1st dose to 4 weeks after the last dose
	OXYBUTIN	005389	02	057	From 1st dose to 4 weeks after the last dose
	DRIPTAN	005389	02	126	From 1st dose to 4 weeks after the last dose

	GABAPENTIN	010030	01	001	From 1st dose to 4 weeks after the last dose
	NEURONTIN [GABAPENTIN]	010030	01	002	From 1st dose to 4 weeks after the last dose
	GABRION	010030	01	024	From 1st dose to 4 weeks after the last dose
	GABAPENTINE	010030	01	045	From 1st dose to 4 weeks after the last dose
	GABA [GABAPENTIN]	010030	01	226	From 1st dose to 4 weeks after the last dose
	PREGABALIN	016141	01	001	From 1st dose to 4 weeks after the last dose
	LYRICA	016141	01	002	From 1st dose to 4 weeks after the last dose
	PRAGIOLA	016141	01	249	From 1st dose to 4 weeks after the last dose
	EGZYSTA	016141	01	314	From 1st dose to 4 weeks after the last dose
	PREATO	016141	01	722	From 1st dose to 4 weeks after the last dose
	CANNABIDIOL	079492	01	001	From 1st dose to 4 weeks after the last dose
If newly started or dose modified during the first 12 weeks of study period	THYRONAJOD	109689	02	006	From 1st dose to 12 weeks after the last dose
If newly started or dose modified during the first 12 weeks of study period	LEVOTHYROXINE;POTASSIUM IODIDE	109689	03	001	From 1st dose to 12 weeks after the last dose
If newly started or dose modified during the first 12 weeks of study period	LEVOTHYROXINE AND LIOTHYRONINE [LEVOTHYROXINE;LIOTHYRONINE]	131345	01	008	From 1st dose to 12 weeks after the last dose

If newly started or dose modified during the first 12 weeks of study period	NOVOTHYRAL	131345	03	007	From 1st dose to 12 weeks after the last dose

[a] In this column, the terms "1st dose" and "last dose" both refer to the start date and stop date of certain doses of concomitant medication. If the dose was changed, a new start date and/or stop date were reported.
[b] No further differentiation if duration of impact is longer than 12 weeks since ICEs are considered in the analysis only for the first 12 weeks of the study.

6.4.4. Interruption or discontinuation in intake of adjuvant endocrine therapy

Interruption or discontinuation in intake of adjuvant endocrine therapy will be defined by comparing tablets taken during baseline for two weeks and at selected weeks as follows:

For participants using tamoxifen: reduction of at least 50% of planned daily dosage (tablets taken during the 14 days prior start of treatment, i.e. during baseline) taken during week1, weeks 3 and 4, weeks 7 and 8 or weeks 11 and 12 compared to baseline.

For participants using aromatase inhibitor: reduction of at least 30% of planned daily dosage (tablets taken during the 14 days prior start of treatment, i.e. during baseline) taken during week1, weeks 3 and 4, weeks 7 and 8 or weeks 11 and 12 compared to baseline.

6.5. Appendix 5: Population characteristics

In general, descriptive statistics by treatment group and overall will be presented for variables defined in this section. For continuous variables, number of observations, mean, standard deviation, minimum, median, and maximum will be presented. For categorical variables, number and percentage of participants will be presented. Listings will be provided as appropriate.

6.5.1. Demographics and baseline characteristics

All demographic and baseline characteristics will be summarized by treatment group and overall. The descriptive statistics will be presented for the SAF and FAS.

Demographic and baseline assessments to be summarized will include:

- Population type (breast cancer, high-risk for developing breast cancer)
- Type of treatment for the pre-existing condition at baseline (tamoxifen, aromatase inhibitors)
- Duration of adjuvant endocrine therapy (from initiation of the therapy until baseline visit)
- Age (at inclusion), region/country, race, ethnicity
- Categorized age
    - <40 years, 40-49 years , 50-59 years, 60-65 years, >65 years

- Weight (kg), height (cm), body mass index (BMI; kg/m^2)
- Categorized BMI (< 18.5, 18.5 to < 25, 25 to < 30, ≥ 30 kg/m^2)
- Smoking history (Never, Former, Current)
- Level of educational

Demographic and baseline characteristics will be summarized also for the following subgroups:

- Type of treatment for the pre-existing condition at baseline (tamoxifen, aromatase inhibitors)
- Race
- Ethnicity
- Smoking history (Never, Former, Current)
- BMI (< 18.5, 18.5 to < 25, 25 to < 30, ≥ 30 kg/m^2)

6.5.2. Reproductive and Menstrual History and Breast cancer classification at baseline

Reproductive and menstrual history will include information on number of pregnancies, number of births and years being amenorrheic and number of participants with hysterectomy or oophorectomy. Hysterectomy or oophorectomy are based on Prior and concomitant procedures -CRF. (For hysterectomy the PTs Hysterectomy, Hysterosalpingectomy, Hysterosalpingo-oophorectomy and Radical hysterectomy are considered. For oophorectomy the PTs Hysterosalpingo-oophorectomy, Oophorectomy, Oophorectomy bilateral, Salpingo-oophorectomy, Salpingo-oophorectomy bilateral, Salpingo-oophorectomy unilateral are considered.)

Breast cancer classification will include information on time from initial diagnosis, histology, laterality, stage and grading of the disease.

These variables will be analyzed descriptively, separately for each treatment group and overall based on the SAF and FAS.

6.5.3. Protocol deviations

Important deviations from the protocol and validity findings and the resulting assignment of subjects to the analysis sets (see Section 3) are agreed upon in the blind review meeting (BRM). The documentation of important deviations, validity findings and the assignment of subject data to analysis sets will be performed according to the sponsor's applicable Standard Operating Procedures and/or Instruction Manuals. The definition for important deviations and validity findings will be provided in the 'Specification of assessment criteria and identification requirements' before unblinding the data.

Identification of important deviations and validity findings will be done periodically while the study is running, concluding with the completion of the final list during the BRM. Any

changes to the statistical analysis prompted by the results of BRM will be documented in an amendment and, if applicable, in a supplement to this SAP.

The list of important deviations and validity findings will only be final after assessment of conditional findings, which are validity findings that can only be identified after unblinding of study treatment.

6.5.4. Medical history

For medical history the MedDRA (current version at the time of analysis) will be used. Medical history findings (i.e., previous diagnoses, diseases or surgeries) not pertaining to the study indication, starting before start of treatment and considered relevant to the study will be tabulated by primary SOC and PT by treatment group and overall. Medical history will be presented for SAF.

All new or worsened findings after start of study treatment should be documented on the AE eCRF page.

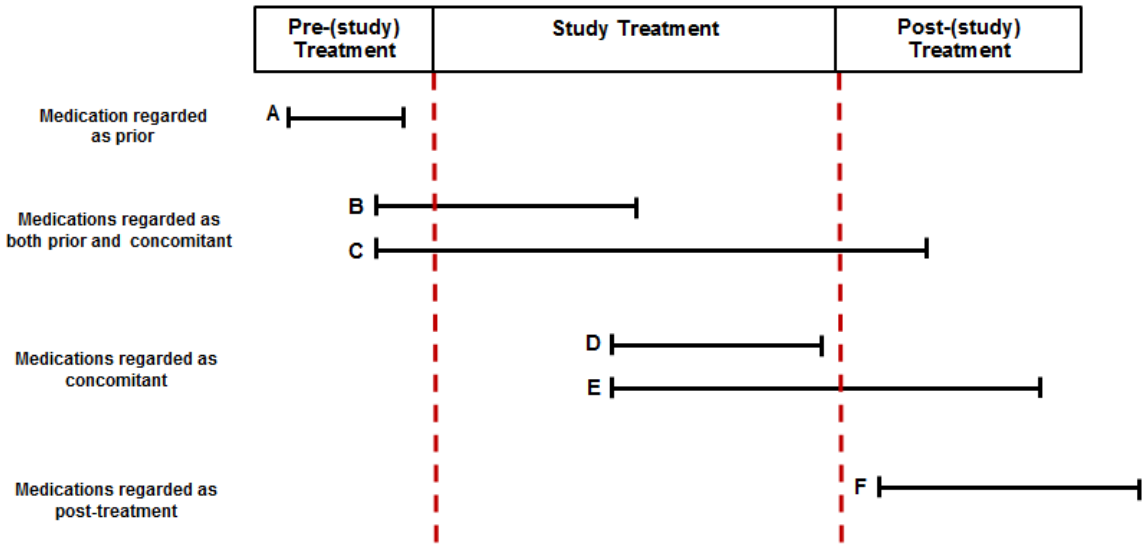
6.5.5. Prior, concomitant and post-treatment medication

For prior/concomitant/post-treatment medications, the following definitions in accordance with the Global Standards Catalogue (v4.0 or later) will be used in the analysis (see Figure 6–1):

- Prior medication: Medication taken before start of the study drug intake, (regardless of when it ended).
- Concomitant medication: Medication taken during treatment phase, i.e. between first and last study drug intake (regardless of when it started or ended).
- Post-treatment medication: Start of medication is after last study drug intake.

Partially missing dates will be imputed as described in Section 4.1.1.

Figure 6–1: Categories of concomitant medication (example)



Categories are prior medication (A, B, C), concomitant medication (B, C, D, E) and post-treatment medication (F).
Source: Global Standards Catalogue V4.0

Medication, recorded as prior, concomitant or post-treatment medication in the eCRF, will be coded according to the World Health Organization Drug Dictionary WHODRUG Global (current version at the time of analysis), to the respective Drug Codes with their corresponding Anatomical Therapeutic Chemical (ATC) classification. In addition, prior, concomitant or post-treatment adjuvant endocrine therapy will be shown by ATC classification and Standardized Medication Name.

The number of subjects taking prior, concomitant or post-treatment medication will be analyzed using frequency tables and shown by treatment group. Analysis of prior, concomitant and post-treatment medication will be done on the SAF.

6.6. Appendix 6: Coding conditions applicable for AESI

AESI	Search
Potential AESI – Liver event "Any condition triggering close liver observation" according to protocol Section 10.5 results in true AESIs of liver events. The search specified here is beyond the protocol definition of the AESI and will be considered together with the assessment by the Liver Safety Monitoring Board to determine a true AESI.	SMQ Cholestasis and jaundice of hepatic organ SMQ Drug related hepatic disorders – severe events only SMQ Liver related investigations, signs and symptoms SMQ Liver-related coagulation and bleeding disturbances In addition, include AESIs ticked at AE-CRF.
Somnolence or fatigue	a) Somnolence MLG: PT Somnolence PT Hypersomnia b) Fatigue (MGL Decreased general strength and energy) PT Asthenia PT Decreased activity PT Fatigue PT Fatigue management PT Mental fatigue PT Physical deconditioning PT Sluggisheness In addition to MLGs above, include PT Sleep disorder due to general medical condition, hypersomnia type
Phototoxicity	BMQ Photosensitivity reactions
Post-menopausal uterine bleeding	MLG Female genital tract bleeding PT Abnormal uterine bleeding PT Abnormal withdrawal bleeding PT Cervix haematoma uterine PT Cervix haemorrhage uterine PT Coital bleeding PT Haematocoele female PT Haematosalpinx PT Haemorrhagic ovarian cyst PT Ovarian haematoma PT Ovarian haemorrhage PT postmenopausal haemorrhage PT Unexpected vaginal bleeding on hormonal IUD PT Uterine haematoma PT Uterine haemorrhage PT Vaginal haematoma PT Vaginal haemorrhage PT Vulval haematoma PT Vulval haematoma evacuation PT Vaginal haemorrhage PT Withdrawal bleed

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Title Page

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

SAP (incl. version and date): V3.0 08 MAY 2024

Compound Number: BAY 3427080 / elinzanetant

Sponsor Name: Bayer Consumer Care AG

Legal Registered Address: Peter-Merian-Strasse 84, 4052 Basel, Switzerland

Regulatory Agency Identifier Number(s):

Registry	**ID**
EudraCT	2020-004908-33

Date: 25 OCT 2024
Version: 1.0

This Statistical Analysis Plan is produced on a word-processing system and bears no signatures.
The approval of the Statistical Analysis Plan is documented in a separate signature document.

Table of Contents

1. Supplementary analyses to complement pre-planned analyses

This supplementary analysis is being conducted to be able to differentiate possible safety events during placebo-controlled phase (week 1-12) vs. when all subjects received elinzanetant 120 mg (week 13 onwards).

To address this, the following additional analyses will be contacted.

- Tables and figures representing liver monitoring (Section 4.5.3.4.1 in the SAP v3.0) will be shown by week 1-12 and by treatment group (elinzanetant 120 mg and placebo) and by week 1-52 (elinzanetant 120 mg). In addition, exposure adjusted incidence rates per 100 person-years will be calculated.

  Formula for exposure adjusted incidence rate =

  (number of participants with event / sum of exposure days) * 100.

  Where sum of exposure days = sum of time to first event for participants if an event occurred + sum of treatment duration with time after treatment up to end of observation for participants without event. Results are provided per 100 person-years, where one person-year is defined as 365.25 days.

- Tables for the following (Sections 4.5.3.6, 4.5.3.7, 4.5.3.9 in the SAP v3.0):
  - Breast imaging – Mammogram/Ultrasound
  - Transvaginal ultrasound
  - Endometrial biopsies

  will be shown by treatment group, in addition end of treatment (EoT) and unscheduled visit will be divided into week 1-12 and week 13-52.

Title Page

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In addition, adverse events (AEs) related to abuse potential, including drug abuse and dependence, as well as drug withdrawal, that occur while on-treatment and post-treatment will be presented. AEs will be categorized by primary System Organ Class (SOC) and Preferred Terms (PTs) for Week 1-12, 13-26, 27-52 and overall week 1-26 and 1-52 by study drug. On-treatment AEs are defined as AEs with an onset between first and last study drug intake date. For abuse potential, post-treatment AEs are all AEs with an onset after the last study drug intake date. Events are assigned to the study drug the participant received last.