Document Type:	Clinical Study Protocol
Official Title:	A randomized, parallel-group treatment, Phase 2, double-blind, pilot study to investigate the efficacy and safety of elinzanetant compared with placebo for treatment of sleep disturbances associated with menopause
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Title Page

Protocol Title:

A randomized, parallel-group treatment, Phase 2, double-blind pilot study to investigate the efficacy and safety of elinzanetant compared with placebo for treatment of sleep disturbances associated with menopause.

Protocol Number:	22423
Protocol Version:	2.0
Amendment Number:	Amendment 1
Compound Number:	BAY 3427080 / elinzanetant
Short Title:	A pilot study to assess the effects of elinzanetant on sleep disturbances associated with menopause
Study Phase:	**2**
Acronym:	**NIRVANA**

Sponsor Name and

Legal Registered Address:

Bayer Consumer Care AG, Peter-Merian-Strasse 84, 4052 Basel, Switzerland

Regulatory Agency Identifier Number(s):

EU-CT number: 2023-504955-28-00

Protocol Date: **21 SEP 2023**

Name: PPD Role: PPD

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

Medical Monitor name and contact information will be provided separately.

Document History Table

DOCUMENT HISTORY			
Document	**Version**	**Date**	**Comments (if applicable)**
Amendment 1	2.0	21 SEP 2023	Version addressing FDA comments dated 17 AUG 2023.
Clinical Study Protocol	1.0	13 JUN 2023	Initial version.

Protocol Amendment Summary of Changes Table

Amendment 1 (21 SEP 2023)

This amendment/modification is considered to be substantial based on the relevant criteria of the European Union clinical trial legislation.

Overall Rationale for the Amendment:

The changes address comments from FDA.

Key changes

Section # and Name	Description of Change	Brief Rationale
Section 5.1 Inclusion Criteria	Inclusion criterion 2 was changed to only include women who are in post-menopausal period AND hysterectomized.	To address comments from FDA.
Section 5.1 Inclusion Criteria	Criterion 12 was added: Normal breast cancer screening result available prior to start of treatment in line with the method and frequency recommended in the respective country. The time elapsed since the last screening examination should be sufficiently short that no further routine screening examination needs to be scheduled during the course of the study.	To address a comment from FDA.
Section 5.1 Inclusion Criteria	Criterion 13 was added: In individuals with a cervix: normal cervical cancer screening result available prior to start of treatment in line with the method and frequency recommended in the respective country. The time elapsed since the last screening examination should be sufficiently short that no further routine screening examination needs to be scheduled during the course of the study.	To address a comment from FDA.
Section 5.2 Exclusion Criteria	Criterion 21 was added: Current diagnosis of the following pre-malignant conditions: cervical dysplasia; breast atypia including atypical ductal hyperplasia, atypical lobular hyperplasia, lobular carcinoma in situ; cirrhosis of the liver; and nodular hepatic lesions.	To address a comment from FDA.
Section 8 Study Assessments and Procedures	A bullet was added: If cervical cancer screening or breast cancer screening results are not available at the time of signing of ICF, they can be performed locally.	Changed to match the updated inclusion criteria.
Section 8.3.4 Pregnancy Testing	Pregnancy testing is not performed in participants who have undergone hysterectomy AND bilateral oophorectomy.	Changed to match the updated inclusion criteria.
Section 8.4.6 Adverse Events of Special Interest	Wording related to post-menopausal bleeding was adjusted.	Changed to match the updated inclusion criteria.
Section 10.5.3 Follow-up assessments	Wording related to pregnancy as a reason for elevated AP levels was removed.	Changed to match the updated inclusion criteria.
Section 10.7 Washout periods for hormonal therapies and prohibited concomitant medications	Intrauterine progestin therapy was removed from the washout period table.	Changed to match the updated inclusion criteria.

Administrative changes

Section # and Name	Description of Change
Title page	Amendment details have been added to the title page

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

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List of Abbreviations and Definitions of Terms

Abbreviations:

AE(s)	Adverse event(s)
AESI	Adverse event of special interest
AHI	Apnea hypopnea index / Respiratory Irregularity Index (for Sleepiz One+)
ALT	Alanine aminotransferase
AP	Alkaline phosphatase
AST	Aspartate aminotransferase
BCRP	Breast Cancer Resistance Protein
BL	Baseline
BMI	Body mass index
CFR	Code of Federal Regulations
CIOMS	The Council for International Organizations of Medical Sciences
CK	Creatine kinase
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	Coronavirus disease of 2019
CRF	Case report form
CT	Computed tomography
CTIS	EU Clinical Trials Information System
CYP3A4	Cytochrome P450 isoenzyme 3A4
ECG	Electrocardiogram
eCOA(s)	Electronic clinical outcome assessments
eCRF(s)	Electronic case report form(s)
eC-SSRS	Electronic Columbia-Suicide Severity Rating Scale
eDiary	Electonic diary
EMA	European Medicines Agency
EoT	End of treatment
ePRO(s)	Electronic patient-reported outcome(s)
ERCP	Endoscopic retrograde cholangiopancreatography
EU	European Union
FDA	Food and Drug Administration
FU	Follow-up
GAD-7	General Anxiety Disorder-7
GCP	Good clinical practice
GGT	Gamma glutamyl transferase
Hbs-antigen	Hepatitis B virus surface antigen
HCV	Hepatitis C virus
HF(s)	Hot flash(es)
HFDD	Hot Flash Daily Diary
HT	Hormone therapy
IB	Investigator brochure
ICE(s)	Intercurrent event(s)
ICF	Informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
(I)EC	(Independent) ethics committee
IMM	IRT and Medication Manager
INR	International normalized ratio
IP	In person
IRB	Institutional review board
IRT	Interactive Response Technology
ISI	Insomnia Severity Index
ISO	International Organization for Standardization
LC-MS/MS	Liquid chromatography-tandem mass spectrometry
LDH	Lactate dehydrogenase
LPS	Latency to persistent Sleep – the number of minutes from lights off to the first 10 consecutive minutes of non-wakefulness)

MDR	Medical Device Regulation
MedDRA	Medical Dictionary for Regulatory Affairs
mmHg	Millimeter of mercury
MMRM	Mixed model with repeated measures
MRI	Magnetic resonance imaging
MRCP	Magnetic resonance cholangiopancreatography
N/A	Not applicable
NK / NK-1 / NK-3	Neurokinin / neurokinin 1 / neurokinin 3
NOAC	New oral anticoagulants
OATP	Organic-anion-transporting polypeptide
PD	Pharmacodynamic(s)
PET	Positron emission tomography
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
P-gp	P-glycoprotein
PK	Pharmacokinetic(s)
PLMAI	Periodic Limb Movement disorders with Arousal Index
PopPK	Population pharmacokinetics
PROMIS SD SF 8b	Patient-Reported Outcomes Measurement Information System Sleep Disturbance Short Form 8b
PSG	Polysomnography
PT	Prothrombin time
QTL(s)	Quality tolerance limit(s)
RNA	Ribonucleic acid
SAE(s)	Serious adverse event(s)
SAP	Statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus -2
SAS	Statistical analysis software
SCR-1/ SCR-2,	Screening Visit 1 / screening Visit 2
SD	Sleep Diary
SDLL	Source Data Location List
SE	Sleep Efficiency – ratio between the total time a participant is asleep (TST) to the total time spent in bed. Presented as a percentage
SoA	Schedule of activities
SUSAR	Suspected unexpected serious adverse reaction(s)
T1/T2/T3	Treatment Visit 1/ Treatment Visit 2/ Treatment Visit 3
TBL	Total bilirubin
TEAE(s)	Treatment-emergent adverse event(s)
TMF	Trial master file
TST	Total Sleep Time – total number of minutes the participant is asleep
ULN	Upper limit of normal
US	United States
VMS	Vasomotor symptoms
WASO	Wakefulness after sleep onset – total number of minutes that a participant is awake after having initially fallen asleep
WOCBP	Woman of childbearing potential

Definition of terms:

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

1. Protocol Summary

1.1 Synopsis

Protocol Title: A randomized, parallel-group treatment, Phase 2, double-blind pilot study to investigate the efficacy and safety of elinzanetant compared with placebo for treatment of sleep disturbances associated with menopause.

Short Title: A pilot study to assess the effects of elinzanetant on sleep disturbances associated with menopause.

Regulatory Agency Identifier Number(s):

EU-CT number: 2023-504955-28-00

Envisaged indication: Sleep disturbances associated with menopause

Rationale: This is a Phase 2 study to assess the efficacy and safety of elinzanetant for the treatment of sleep disturbances related to menopause.

Objectives, Endpoints and Estimands:

Objectives	Endpoints
Primary	
• To explore the efficacy of elinzanetant on sleep disturbances associated with menopause as determined by PSG	**Primary endpoint** • Change from baseline in WASO at Week 4 as measured by PSG **Secondary endpoints** • Change from baseline in WASO at Week 12 as measured by PSG • Change from baseline in SE at Week 4 as measured by PSG • Change from baseline in SE at Week 12 as measured by PSG
Secondary	
• To explore the efficacy of elinzanetant on sleep disturbance associated with menopause as determined by patient-reported outcomes	• Change from baseline in PROMIS SD SF 8b total score at Week 4 • Change from baseline in PROMIS SD SF 8b total score at Week 12 • Change from baseline in ISI total score at Week 4 • Change from baseline in ISI total score at Week 12
• To evaluate the safety of elinzanetant for the treatment of sleep disturbances associated with menopause	• TEAEs • Abnormal laboratory parameters

The full list of exploratory endpoints will be presented in the SAP.
ISI = Insomnia Severity Index, PROMIS SD SF 8b = Patient-Reported Outcomes Measurement Information System Sleep Disturbance Short Form 8b, PSG = Polysomnography, SAP = statistical analysis plan, SE = Sleep Efficiency, TEAE = Treatment-emergent adverse event, WASO = Wakefulness after sleep onset.

Estimands

The primary clinical question of interest for the primary objective is:

What is the difference in mean change from baseline in WASO as measured by PSG at Week 4 comparing elinzanetant to placebo in women with sleep disturbances associated with menopause assuming no study treatment interruption and discontinuation and no use of prohibited concomitant medications impacting sleep?

The attributes of the main estimand for the primary endpoint are as follows:

- Population: Women aged 40–65 with sleep disturbance associated with the menopause, further defined by the key inclusion/exclusion criteria.
- Variable: Change from baseline in WASO measured by PSG at Week 4.
- Treatment: Elinzanetant 120 mg or placebo.
- ICEs and strategies: Important ICEs to consider are listed in Table 1–1.

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

ICEs	Proposed Strategy	Data Handling Method	Interpretation
Temporary study treatment interruption	Hypothetical	Discard data collected after the ICE	The treatment effect that would be if participants complied with treatment
Premature discontinuation of study treatment	Hypothetical	Discard data collected after the ICE	The treatment effect that would be if participants did not discontinue the randomized treatment
Intake of prohibited concomitant medication having impact on efficacy	Hypothetical	Discard data collected after the ICE	The treatment effect that would be if participants did not take prohibited concomitant medications impacting sleep

ICE = Intercurrent event.

- Population level summary: Mean change from baseline in WASO measured by PSG at Week 4

Overall Design Synopsis:

This is a multi-center, multi-country, double-blind, randomized, parallel-group, placebo-controlled, pilot intervention study in women with sleep disturbances associated with menopause.

Short Summary:

The purpose of this study is to assess efficacy and safety of elinzanetant on sleep disturbances associated with menopause. Study details include:

The study duration will be about 23 weeks (plus potential washout period).

The treatment duration will be approximately 12 weeks.

The visit frequency will be once every 1–2 weeks during the screening period (depending on the scheduling of PSG) and once every 4–5 weeks during the intervention and follow-up periods.

Number of Participants:

Approximately 223 participants will be screened to achieve 78 participants to be randomized in a 1:1 ratio to investigational intervention. This will result in an estimated 70 participants (35 per study intervention) evaluable for the primary efficacy analysis.

Study Arms and Duration:

All participants will receive either 120 mg of elinzanetant or matching placebo orally once daily prior to going to sleep:

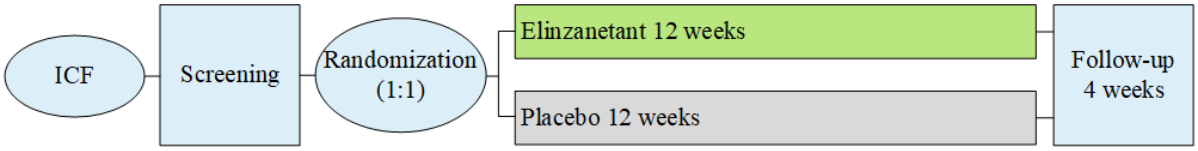
- Elinzanetant 120 mg for 12 weeks
- Placebo for 12 weeks

Treatment may be prolonged by up to 1 week to allow for scheduling of the sleep laboratory assessment at EoT.

Data Monitoring/Other Committee: No

1.2 Schema

Figure 1–1: Study Schema



ICF = signing of informed consent form.

1.3 Schedule of Activities (SoA)

SoA is presented in Table 1–2.

Table 1–2: Schedule of Activities

Period	Screening period [a]			Intervention period			FU period
Visit name	**SCR-1**	**SCR-2**	**BL**	**T1**	**T2**	**T3/ EoT [b,c]**	**FU**
In person (IP) or phone visit	**IP**	**IP**	**IP**	**IP**	**☎**	**IP**	**☎**
Visit week	**Please see footnote a**			**4**	**8**	**12**	**16**
Visit day	**-42 to -24 [a]**	**-10 [a]**	**1 [a]**	**29**	**57**	**85**	**113**
Allowed window in days	**Please see footnote a**			**+7**	**+7**	**+7**	**+7**
Baseline characteristics							
Informed consent	●						
Demography	●						
Medical history (includes substance usage)	●						
Check for prohibited medication washout (Section 10.7)	●	●	●				
Screening and randomization							
Inclusion and exclusion criteria	●	● [d]	●				
IRT Screening	●						
IRT Screen fail (if applicable)	●	●	● [e]				
IRT Randomization			●				
Study medication and study exit							
Study medication dispensing/training			●				
Study medication			Starts on Visit Day 1 evening ---------->				
Study medication collection (if applicable)						●	
Study intervention compliance			Starts after the first dose of study medication ---------->				
IRT for EoT						●	
Participant feedback survey (optional)						●	
Safety / laboratory							
Complete physical examination including height and weight	●						
Vital signs	●			●		●	
Blood samples (safety)	●			●		●	
Urine pregnancy test (if applicable, Section 8.3.4)	●						
Urinalysis	●					●	
Blood sample (PK)				● [f]		● [f]	

Table 1–2: Schedule of Activities

Period	Screening period [a]			Intervention period			FU period
Visit name	**SCR-1**	**SCR-2**	**BL**	**T1**	**T2**	**T3/ EoT [b,c]**	**FU**
In person (IP) or phone visit	**IP**	**IP**	**IP**	**IP**	**☎**	**IP**	**☎**
Visit week	**Please see footnote a**			**4**	**8**	**12**	**16**
Visit day	**-42 to -24 [a]**	**-10 [a]**	**1 [a]**	**29**	**57**	**85**	**113**
Allowed window in days	**Please see footnote a**			**+7**	**+7**	**+7**	**+7**
Symptom-based physical examination				●		●	
AE (Section 8.4.1)	Procedure-related AEs only		Starts after the first dose of study medication ---------->				
Prior and concomitant medication	---------->						
Digital health technology tools							
PSG [g] + Sleepiz One+ (2 consecutive nights)		●		●		●	
Sleepiz One+ device dispensation and training		●					
Sleepiz One+ (at home)		---------->					
Sleepiz One+ device collection						●	
eDiary and eCOA instruments							
Dispensation and training of participant's handheld device	●						
eC-SSRS	●			●		●	
SD (daily)	---------->						
HFDD (twice daily)	---------->						
PROMIS SD SF 8b [h]	●		---------->				
ISI	●		●	●		●	
GAD-7			●	●		●	
PGI-S [i]		---------->					
PGI-C [j]			Starts 1 weeks after BL ---------->				
Study medication intake documentation			Starts after the first dose of study medication ---------->				
Collection of handheld device						●	

AE = adverse event, BL = baseline, eCOA = Electronic clinical outcome assessments, EoT = End of Treatment, ePRO = Electronic patient-reported outcome, FU = follow-up, IP = In person, IRT = Interactive response technology, PK = pharmacokinetics, PSG = polysomnography, SCR = screening, SoA = Schedule of activities, T = treatment.
Questionnaires: eC-SSRS = Electronic Columbia-Suicide Severity Rating Scale, GAD-7 = Generalized Anxiety Disorder Scale -7, HFDD = Hot Flash Daily Diary, ISI = Insomnia Severity Index, PGI-C = Patient Global Impression of Change, PGI-S = Patient Global Impression of Severity, PROMIS SD SF 8b = Patient-reported Outcomes Measurement Information System Sleep Disturbance Short Form 8b, SD = Sleep Diary.

a All screening evaluations should typically be completed within 4–6 weeks with at least 14 days between SCR-1 and SCR-2 and at least 7 days at home after SCR-2 and before BL. The time required for scheduling for PSG and central reading of PSG needs to be considered for visit planning.
b All EoT assessments (except for the safety and PK sample) are performed in the morning after the second night in the PSG lab.
c If a participant discontinues prematurely from treatment, an EoT visit will be performed as soon as possible; it will comprise all assessments scheduled for the EoT visit. The EoT visit will be followed after 4 weeks by the FU visit. The handheld device will be collected at the last scheduled IP visit.
d Eligibility check on inclusion criterion 3 (HFDD) should be assessed prior to PSG.
e Including consultation about results obtained from screening procedures.
f PK sample is collected on the second day in the PSG lab together with the safety lab sample.
g All PSGs scheduled for T1 and T3 need to be performed under treatment, i.e., the second PSG night at EoT needs to be performed at the latest during the night after the last capsule has been taken.
h The PROMIS SD SF 8b will be collected at SCR-1 and weekly from BL until EoT.
i The PGI-S will be collected weekly from SCR-2 until EoT.
j The PGI-C will be collected weekly following the PGI-S from 1 week after BL until EoT.

2. Introduction

2.1 Study Rationale

This is a Phase 2 study to assess the efficacy and safety of elinzanetant for the treatment of sleep disturbances related to menopause.

2.2 Background

Menopause is a stage of natural aging that marks the end of a woman's reproductive period and is characterized by various physiological changes. Among menopausal symptoms, sleep disturbances are one of the most debilitating symptoms that occur during menopause. Nighttime awakenings due to vasomotor symptoms (also known as night-sweats or hot flashes) are one instigator of sleep disturbances, however sleep disturbances associated with menopause are not completely explained by nocturnal vasomotor symptoms and likely has a multifactorial basis (Baker et al. 2018a, Woods et al. 2016). The effect of hormone treatment on sleep disturbances in this group of women is small (Guthrie et al. 2018) indicating that additional biological mechanisms beyond reduced estrogen receptor signaling and nighttime awakening due to VMS may contribute to sleep disturbances during the menopausal period.

Clinical studies using objective measurement methods have identified increases in night time awakenings and WASO as key aspects of sleep disturbance in peri-/postmenopausal women, but have not found differences in total sleep time or hyperarousal compared with younger women (Baker et al. 2018b, Coborn et al. 2022, Pengo et al. 2018).

A small double-blind, randomized cross-over study in healthy male volunteers confirmed the involvement of Substance P in sleep disturbances. After intravenous infusion of Substance P both polysomnography and subjective rating scales indicated a significant decrease of sleep quantity and quality (Lieb et al. 2002). Antagonizing Substance P activity with a NK-1 receptor antagonist is therefore expected to show an improvement in sleep. A much larger study has shown that vestipitant, a NK-1 receptor antagonist improves WASO in 161 male and female patients with primary insomnia (Ratti et al. 2013).

There are currently no approved treatments that are specifically targeted towards sleep disturbances associated with menopause. The current clinical practice guidelines recommend cognitive behavioral therapy for insomnia (CBT-I), HT, antidepressants, or sleep medications (Riemann et al. 2017, Sateia et al. 2017, Silvestri et al. 2019).

Elinzanetant (formerly NT-814[1]) is a dual neurokinin (NK)-1,3 receptor antagonist and is in development for the treatment of moderate to severe vasomotor symptoms. SWITCH-1 (814-PM-02), a Phase 2b study, showed statistically significant and clinically meaningful improvements on elinzanetant 120 mg and 160 mg once daily compared to placebo in global Pittsburgh Sleep Quality Index (PSQI) and total ISI (Simon et al. 2023).

If benefits of elinzanetant on sleep are confirmed in further studies, it is anticipated that elinzanetant will be a relevant improvement for women with sleep disturbances associated with menopause.

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

2.3 Benefit/Risk Assessment

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

2.3.1 Risk Assessment

Table 2–1: Risk assessment

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

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

Table 2–1: Risk assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	originated from ongoing (blinded) Phase 3 studies did not reveal any new or relevant safety concern.	
Skeletal muscle toxicity	The reactions were observed in a repeat dose study in rats at high doses but not in subsequent longer-term studies in rat and cynomolgus monkey. These findings are considered unlikely to be relevant safety findings but will continue to be monitored in clinical studies. Clinical data originated from Phase 2 and ongoing (blinded) Phase 3 studies did not reveal any new or relevant safety concern.	Continuous AE monitoring together with evaluation of related laboratory parameters (CK, AST, LDH) at specific time points will ensure proper evaluation of the risk during the study.
Phototoxicity	Preclinical safety finding. The *in vitro* 3T3 Neutral Red Uptake phototoxicity assay showed a potentially phototoxic effect. However, this test has a high rate of false-positives and poor positive predictive value. One participant in the SWITCH-1 study who received 160 mg of elinzanetant reported a mild skin reaction that was potentially consistent with photosensitivity. The event resolved after 15 days despite continued treatment with elinzanetant. No particular precautions to avoid sunlight had been taken. Clinical data originated from ongoing (blinded) Phase 3 studies did not reveal any new or relevant safety concern.	Investigators and participants will be advised of the potential for skin sensitivity and to be vigilant to any possible reactions. Measures are to be taken to avoid strong sunlight should such reactions occur.
Increase in liver enzymes	Two participants were withdrawn from the SWITCH-1 study because of increased liver enzymes, although both were subsequently found to be noncompliant with the elinzanetant treatment. There was one further participant participating in the Phase 1 study (814-1- 05) who was found to have increased transaminases. The participant had abnormal GGT at screening and fatty liver.	Defined exclusion criteria. Regular monitoring of liver parameters during the study. Defined strategy for close observation and defined stopping criteria for participants with increased liver parameters during the study.

Table 2–1: Risk assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	Clinical data originated from ongoing (blinded) Phase 3 studies did not reveal any new or relevant safety concern.	
Arrhythmias	A possible signal with respect to an increased incidence of arrhythmias was identified in Phase 1 studies in healthy male volunteers but has not been substantiated in subsequent studies. Clinical data originated from ongoing (blinded) Phase 3 studies did not reveal any new or relevant safety concern.	Continuous AE monitoring.
Effects on reproductive function	There was no evidence of developmental or reproductive toxicity in embryo-fetal toxicity studies at doses up to 100 mg/kg/day in rats or up to 140 mg/kg/day in rabbits representing about 11- or 1-times the human exposure in rats or rabbits, respectively. In a female rat fertility and early embryonic development study, increased percentage of pre-implantation and post-implantation embryo loss, reduced litter size and lower fetal body weights were seen at the dose of 100 mg/kg/day, which exceeds human exposure at the anticipated therapeutic dose of 120 mg/day by a factor of 11. The dose free of findings represents 3-times the human exposure. Elinzanetant reduced plasma estradiol, progesterone and luteinizing hormone in premenopausal females. These effects were correlated in one of the studies with delayed or irregular menses.	Defined inclusion criterion negative urine pregnancy test at screening. Women going through the menopausal period have a low chance of getting pregnant, therefore participants are informed of the effects on reproductive function.

Table 2–1: Risk assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Procedures		
No relevant risks are expected related to the study procedures	All study procedures are routine medical procedures in this participant population.	All study procedures will be conducted by appropriately trained staff.
Other		
Non-effective treatment for participants who are randomized to placebo.	Participants who are randomized to placebo will not receive active treatment for the total duration of the study.	Participants are not expected to suffer undue medical consequences from absence of treatment.

AE = Adverse event, AST = Aspartate aminotransferase, CK = Creatine kinase, CYP3A4 = Cytochrome P450 isoenzyme 3A4, GGT = Gamma glutamyl transferase, LDH = Lactate dehydrogenase.

2.3.2 Benefit Assessment

There are currently no approved treatments that are specifically targeted towards sleep disturbances associated with menopause although sleep disturbances are one of the most common and debilitating symptoms experienced by women in the menopausal period. The dual mechanism of elinzanetant acting congruently on the 2 main symptoms of menopause, VMS and sleep disturbances can be a significant addition to the treatment options available to healthcare professionals and patients.

Based on the mode of action, preclinical, and clinical data it is expected that treatment with elinzanetant will provide relevant clinical benefits to menopausal women with sleep disturbances. These benefits may include, but are not limited to:

Reduction of wakefulness after sleep onset

Improvements in sleep efficiency

Improvements in sleep quality

Participants who are randomized to placebo are still expected to have some benefit from participation in the study as they will receive a thorough medical evaluation.

2.3.3 Overall Benefit: Risk Conclusion

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

3. Objectives, Endpoints, and Estimands

Objectives and endpoints are listed in Table 3–1.

Table 3–1: Objectives and endpoints

Objectives	Endpoints
Primary	
• To explore the efficacy of elinzanetant on sleep disturbances associated with menopause as determined by PSG	**Primary endpoint** • Change from baseline in WASO at Week 4 as measured by PSG **Secondary endpoints** • Change from baseline in WASO at Week 12 as measured by PSG • Change from baseline in SE at Week 4 as measured by PSG • Change from baseline in SE at Week 12 as measured by PSG
Secondary	
• To explore the efficacy of elinzanetant on sleep disturbance associated with menopause as determined by patient-reported outcomes	• Change from baseline in PROMIS SD SF 8b total score at Week 4 • Change from baseline in PROMIS SD SF 8b total score at Week 12 • Change from baseline in ISI total score at Week 4 • Change from baseline in ISI total score at Week 12
• To evaluate the safety of elinzanetant for the treatment of sleep disturbances associated with menopause	• TEAEs • Abnormal laboratory parameters
Exploratory	
• To explore the relationship between HF and sleep disturbances as determined by PSG	• Frequency of HFs over time • WASO as measured by PSG over time
• To explore the efficacy of elinzanetant on the frequency of anxiety symptoms	• Change from baseline in GAD-7 total score over time
• To evaluate the efficacy of elinzanetant on the PGI-S and PGI-C	• Actual values of the PGI-C individual item scores over time • Change from baseline in PGI-S individual item scores over time
Other pre-specified	
• To evaluate variability in exposure in relation to the efficacy and safety for elinzanetant	• Systemic exposure of elinzanetant in plasma via sparse PK sampling
• To further investigate the study intervention and similar compounds (e.g., mode-of-action-related effects, safety) and to further investigate pathomechanisms deemed relevant to sleep disturbances associated with menopause.	• Various biomarkers (e.g., diagnostic, safety, pharmacodynamic, monitoring, or potentially predictive biomarkers)
• To investigate the efficacy of elinzanetant on sleep disturbance associated with menopause determined by Sleepiz One+	• Parameters captured remotely and continuously at home by Sleepiz One+ including e.g. WASO, TST, SE

The full list of exploratory endpoints will be presented in the SAP.
GAD-7 = General Anxiety Disorder-7, HF = Hot Flash, ISI = Insomnia Severity Index, PGI-C = Patient Global Impression of Change, PGI-S = Patient Global Impression of Severity, PK = Pharmacokinetics, PROMIS SD SF 8b = Patient-Reported Outcomes Measurement Information System Sleep Disturbance Short Form 8b, PSG = Polysomnography, SAP = Statistical analysis plan, SE = Sleep Efficiency, TEAE = Treatment-emergent adverse event, TST = Total Sleep Time,

WASO = Wakefulness after sleep onset.

Estimands

The primary clinical question of interest for the primary objective is:

What is the difference in mean change from baseline in WASO as measured by PSG at Week 4 comparing elinzanetant to placebo in women with sleep disturbances associated with menopause assuming no study treatment interruption and discontinuation and no use of prohibited concomitant medications impacting sleep?

The attributes of the main estimand for the primary endpoint are as follows:

- Population: Women aged 40–65 with sleep disturbance associated with the menopause, further defined by the key inclusion/exclusion criteria.
- Variable: Change from baseline in WASO measured by PSG at Week 4.
- Treatment: Elinzanetant 120 mg or placebo.
- ICEs and strategies: Important ICEs to consider are listed in Table 3–2.

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

ICEs	Proposed Strategy	Data Handling Method	Interpretation
Temporary study treatment interruption	Hypothetical	Discard data collected after the ICE	The treatment effect that would be if participants complied with treatment
Premature discontinuation of study treatment	Hypothetical	Discard data collected after the ICE	The treatment effect that would be if participants did not discontinue the randomized treatment
Intake of prohibited concomitant medication having impact on efficacy	Hypothetical	Discard data collected after the ICE	The treatment effect that would be if participants did not take prohibited concomitant medications impacting sleep

ICE = Intercurrent event.

- Population level summary: Mean change from baseline in WASO measured by PSG at Week 4.

4. Study Design

4.1 Overall Design

This is a multi-center, multi-country, double-blind, randomized, parallel-group, placebo-controlled, pilot intervention study in women with sleep disturbances associated with the menopause.

Screening: After giving informed consent, participants will be withdrawn from prohibited concomitant medications (see Section 10.7) at SCR-1 visit if needed. Screening period consists of 3 visits.

Randomization: At the end of the screening period (BL visit), the participants will be randomized into elinzanetant and placebo arms in a 1:1 ratio. Randomization will be stratified by the average weekly frequency of moderate to severe HFs (including night-time HFs) over the 14 days prior to the respective eligibility check (<35 moderate to severe HFs per week, ≥35–<50 moderate to severe HFs per week, ≥50 moderate to severe HFs per week).

Intervention period: Intervention period will last about 12 weeks:

- 120 mg (2x 60 mg soft gel capsules) of elinzanetant or matching placebo orally once daily for 12 weeks

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

The study includes 3 stationary visits in a sleep laboratory. Each of these visits encompasses 2 consecutive nights. This results in a total of 6 nights in the sleep laboratory.

4.2 Scientific Rationale for Study Design

A double-blind placebo-controlled design is considered necessary to differentiate drug effects from the natural course of disease, the effects of study participation, and background safety findings. A meta-analysis on the effect of placebo on PSG parameters in participants with primary insomnia showed that a placebo response of up to 63% can be expected (Winkler and Rief 2015). Therefore, comparison to placebo is relevant to describe the true treatment effect of elinzanetant.

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

A treatment duration of 12 weeks is considered adequate to describe the difference regarding the primary variable between active treatment and placebo (see Section 9 for details) and to obtain information on the maintenance of treatment and placebo effect.

PSG is considered the current standard method to obtain objectively measured sleep related parameters. Therefore this method is used to assess the primary and several secondary endpoints. Use of the Sleepiz One+ home sleep monitor will be used to obtain continuous sleep related parameters throughout the entire observational period of the elinzanetant Phase 2 study at home. For more information regarding Sleepiz One+ device please see Section 6.1.1 and Section 8.2.1.2.

4.3 Justification for Dose

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

The 120 mg once daily dose was effective on a range of measures in the SWITCH-1 study that included post-menopausal women and was more effective in improving sleep quality than the 2 lower doses studied (40 mg and 80 mg once daily). There was no relevant additional benefit from a higher dose (160 mg once daily).

The plasma concentrations achieved with the 120 mg dose are associated with full occupancy of central NK-1 receptors throughout a dose interval at steady state as demonstrated in a human PET study. Although it is not possible to assess NK-3 receptor occupancy directly, as a suitable NK-3 PET ligand does not exist, the achieved concentrations are also very likely to fully occupy central NK-3 receptors during the dose interval.

This is the first study in the clinical development program that focuses primarily on sleep disturbances associated with menopause. The same product, same dose and dosing regimen that was assessed to be effective for the VMS indication in Phase 2 studies and is currently being tested in Phase 3 studies for the VMS indication will be used to assess safety and efficacy of elinzanetant for the treatment of sleep disturbances associated with menopause.

The rationale for assessing the same dose for this second indication is based on the intention to achieve complete occupancy on both receptors and the observed effects on sleep parameters in SWITCH-1 which follow as similar dose response pattern as the effects on VMS.

For details, refer to the IB.

4.4 End-of-Study Definition

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

The primary completion date is the date when the last participant completes Week 4 visit of the intervention period.

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

5. Study Population

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

5.1 Inclusion Criteria

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

Age

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

Type of Participant and Disease Characteristics

2. Being in the post-menopausal period, defined as: serum FSH levels >40 mIU/mL and a serum estradiol concentration of <30 pg/mL at screening,

   AND

   Hysterectomy performed at least 6 weeks prior to screening.

3. Experiencing VMS associated with menopause, defined as:

   Participant has completed HFDD for at least 11 days during the 2 weeks prior to the respective eligibility check, and during this period participant has recorded a weekly average of at least 20 moderate or severe HF (including night-time HF).

4. The participant's self-reported sleep history includes ongoing sleep disturbances associated with menopause characterized by waking up at night and/or poor quality of sleep.
5. The participant's self-reported ongoing sleep disturbances cause distress or impairment in social, occupational, or other important areas of functioning.
6. WASO of 30 minutes or more (mean of 2 screening PSGs with neither of the 2 nights <20 min).
7. The participant's self-reported time in bed between 6 and 9 hours.
8. The participant's self-reported bedtime is usually between 21.00 and 24.00 hours and it does not vary by more than ±2 hours.
9. Negative urine pregnancy test at screening.
10. BMI between 18 and 38 kg/m^2 at screening.

Informed Consent

11. Capable of giving signed informed consent as described in Section 10.1.3 which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

Additional criteria

12. Normal breast cancer screening result available prior to start of treatment in line with the method and frequency recommended in the respective country. The time elapsed since the last screening examination should be sufficiently short that no further routine screening examination needs to be scheduled during the course of the study. [2]
13. In individuals with a cervix: normal cervical cancer screening result available prior to start of treatment in line with the method and frequency recommended in the respective country. The time elapsed since the last screening examination should be sufficiently short that no further routine screening examination needs to be scheduled during the course of the study.

[2] E.g., for US: Normal breast cancer screening result must be documented no more than 9 months prior to start of treatment.

5.2 Exclusion Criteria

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

Medical Conditions

1. Medical history, or baseline PSG assessment, includes a diagnosis of a sleep disorder other than sleep disturbances associated with the menopause (e.g., sleep apnea, restless leg syndrome, circadian rhythm sleep disorder).[3]
2. Clinically significant abnormalities that interfere with the study goals, in the opinion of the investigator, based on the medical history, physical examination, vital signs, clinical laboratory tests[4], eC-SSRS, and other assessments completed during screening.
3. Current or history (except complete remission for 5 years or more) of any malignancy (except basal and squamous cell skin tumors).
4. Renal impairment greater than moderate (i.e. estimated glomerular filtration rate <30 mL/min/1.73 m^2) at screening.
5. Abnormal liver parameters (presence of at least one of the following criteria):
    - AST >2 x ULN
    - ALT >2 x ULN
    - AP >2 x ULN
    - TBL >ULN unless explained by Gilbert's syndrome
    - INR >ULN unless explained by, e.g., intake of anticoagulants[5]
    - Diagnosis of hepatitis B infection, i.e., Hbs-antigen positive at screening
    - Diagnosis of hepatitis C infection, i.e., hepatitis C antibodies and HCV-RNA positive at screening.

Prior/Concomitant Therapy

6. Has used and is unwilling to wash-out use of any of the prohibited concomitant medications, as specified in Sections 6.9 and 10.7.
7. Inability to comply with the use of prohibited medications as described in Sections 6.9.1 and 10.7.
8. Current cognitive behavioral therapy for sleep disorders.

Prior/Concurrent Clinical Study Experience

9. Concurrent (or within 2 months prior to signing of ICF) participation in a clinical study with an investigational medicinal product (including medical devices) with the exception for participants who completed another elinzanetant study.

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[3] Details are provided in the PSG manual.

[4] Single re-test allowed.

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

Other Exclusion Criteria

10. Shift work within 2 weeks prior to the SCR-2 visit, or planned shift work during the study.
11. AHI >15 on the first PSG screening night.
12. PLMAI >15 on the first PSG screening night.
13. Travel across ≥3 time zones within 2 weeks prior to the SCR-2 visit, or planned travel across ≥3 time zones during study.
14. Regular napping i.e. >3 naps per week each with duration of >30 minutes.
15. At screening a suicidal ideation in the past 6 months (as indicated by "Yes" on item 4 or item 5 of the suicidal ideation section of the eC-SSRS) or suicidal behavior in the past 6 months (indicated by "Yes" on any item of the suicidal behavior section of the eC-SSRS).
16. Clinically relevant drug or alcohol abuse within 12 months of signing of informed consent.
17. Use of substances that in the opinion of the investigator contribute to the participant's sleep disturbances (e.g. caffeine, alcohol, cannabis and its derivatives).
18. Dependent on the investigator, the contract research organisation(s) or Sponsor for education or employment (e.g. family members, employees, people who receive grants/education).
19. Known hypersensitivity to elinzanetant or any of the excipients in the formulation.
20. Inability to comply with the study procedures for any reason, including the following examples: language comprehension, psychiatric illness, general inability to get to the study site or ePRO completion.

Additional criteria

21. Current diagnosis of the following pre-malignant conditions: cervical dysplasia; breast atypia including atypical ductal hyperplasia, atypical lobular hyperplasia, lobular carcinoma in situ; cirrhosis of the liver; and nodular hepatic lesions.

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

During their stay in the study center for the PSGs, participants may consume food and beverages provided or allowed by the study center.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study medication. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, date of informed consent, date of last visit, screen failure details, and eligibility criteria based on completed procedures. Screening PROs (PROMIS, ISI, HFDD and SD) and screening lab PSG data (if available) will also be

collected on screen failures to identify sleep PROs that predict sleep disturbances associated with the menopause.

Re-screening is allowed only once. Re-screening can be performed in the following cases, whichever occurs first:

- If the inclusion/exclusion criteria, including related footnotes, preventing participant's initial attempt to participate have been changed via a protocol amendment, OR
- In case of abnormal or implausible results, which may be caused by intercurrent diseases, short-term treatable conditions, other temporary health disorders (e.g. acute infection, laboratory changes), or circumstances affecting safety and/or efficacy evaluation (e.g. technical issues affecting central/local laboratory analyses or the assessment at the sleep laboratory) the investigator may decide to repeat the respective screening parameter(s).

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

For re-screening, the participant must sign a new ICF and will be assigned a new participant number.

5.5 Criteria for Temporarily Delaying Randomization

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

A delayed assessment or report of procedures required for assessment of eligibility would constitute a reason for postponing randomization.

Under these circumstances, the screening period may be extended until these conditions have resolved or the delayed assessment is available. In case the screening period is extended to more than 8 weeks, a new blood sample has to be taken and urinalysis as well as a urine pregnancy test need to be performed for assessment of eligibility.

6. Study Intervention(s) and Concomitant Therapy

Study interventions are all pre-specified, investigational and non-investigational medicinal products, medical devices and other interventions (e.g., surgical and behavioral) intended to be administered to the study participants during the study conduct.

6.1 Study Intervention(s) Administered

Table 6–1: Study Interventions

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

Alu = Aluminium; N/A = Not applicable.

Study intervention will be dispensed at the study visits summarized in the SoA and the first dose should be taken at home in the evening on the same day. In general, study treatment will be taken once daily before going to sleep with or without food.

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

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

6.1.1 Medical Devices

During the conduct of this study, the following medical devices will be provided.

- No Sponsor-manufactured medical devices (or devices manufactured for the Sponsor by a third party) will be used in this study.
- Medical devices supplied by the eCOA vendor, on behalf of the Sponsor, for use in this study are:
    a. Sleepiz One+ sleep monitor (also see Section 8.2.1.2)

Sleepiz One+ is an FDA-listed class II medical device under 510k exempt and was EU MDR certified as a class IIa product. Instructions for medical device use and study-specific Handling Instruction are provided in the respective handling instructions and manuals provided separately.

6.2 Preparation, Handling, Storage, and Accountability

1. The investigator or designee must confirm appropriate conditions (e.g. temperature) have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
2. Only participants randomized in the study may receive study intervention and only authorized site staff may supply, prepare or administer study intervention.
3. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

4. The investigator or the head of the institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records). Drug returns, reconciliation and destruction return information will be captured in IRT.
5. Further guidance and information for the final disposition of unused study interventions are provided in Investigator Site File.

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

6.3 Assignment to Study Intervention

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

Participants will be randomly assigned in a 1:1 ratio to receive study intervention. The randomization will be stratified by the average weekly frequency of moderate to severe HFs (including night-time HFs) over the 14 days prior to the respective eligibility check (<35 moderate to severe HFs per week, ≥35–<50 moderate to severe HFs per week, ≥50 moderate to severe HFs per week), to ensure a balanced distribution of baseline HF frequency across the treatment groups. There will not be any limitations to the size of the different groups.

6.4 Blinding

This is a double-blind study in which participants and investigators are blinded to study intervention. Investigators will remain blinded to each participant's assigned study intervention throughout the course of the study. In addition, the centralized reading of PSG-data will also be blinded to study intervention.

Unblinding

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

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

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

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

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

Pharmacometrics staff may be unblinded according to Bayer standard operating procedures. Pharmacokinetic and exposure-response analysis might be performed using population approaches (popPK and popPK/PD, e.g., by non-linear mixed effect modeling). Analysis and report will be done under a separate cover. This evaluation might be started prior to database lock. If this is applicable, appropriate measures will be taken to maintain blinding of the study team, e.g., data will be stored separately, and members of the study team will neither have access to the randomization list nor to individual data.

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

6.5 Study Intervention Compliance

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

A record of the number of capsules dispensed to and administered by each participant must be maintained and reconciled with study intervention and compliance records. An adequate record of receipt, distribution, and return/destruction of all study intervention must be captured on the dispensing log and/or in the IRT. If the participant is unable to continue taking the study intervention as required, she should contact the study site.

Study intervention capsules not returned will be considered to have been taken unless otherwise specified. At the end of the study, any remaining capsules will be collected and returned to the Sponsor, destruction depot or destroyed at the site. Any discrepancies between the returned and expected returned study interventions should be explained.

Study medication intake documenting

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

6.6 Dose Modification

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

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

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

6.8 Treatment of Overdose

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

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

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

In the event of an overdose, the investigator should:

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

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

6.9 Prior and Concomitant Therapy

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

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

The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.9.1 Prohibited concomitant medications

Section 10.7 presents a comprehensive (but not exhaustive) list of prohibited concomitant medications and washout periods (recently approved drugs may not be included in the list as well as the drugs used off-label for treatment of sleep disturbances and should be checked on a case-by-case basis).

Prior use of sleep therapies within 3 months before SCR-2 visit should be recorded in the CRFs. The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.9.2 Other Treatment Considerations

Based on preclinical data, an increase in exposure of drugs that are sensitive substrates of OATP1B1/1B3, P-gp or BCRP during co-administration of elinzanetant due to inhibition of those transporters by elinzanetant could not be excluded. Results from a clinical drug-drug interaction study with the BCRP and OATP1B1/B3 substrate rosuvastatin showed no clinically relevant effect on the pharmacokinetics of rosuvastatin when administered together with elinzanetant. Therefore, medications that are substrates of BCRP and/or OATP1B1/1B3 can be administered together with elinzanetant without restrictions. Results from a clinical drug-drug interaction study with the sensitive P-gp substrate dabigatran etexilate (Study 22081: Open-label, fixed sequence crossover study to determine the effects of a single dose of elinzanetant (BAY 3427080) on the pharmacokinetics of dabigatran etexilate in healthy participants) showed no clinically relevant interaction. Therefore, medications that are substrates of P-gp can be administered together with elinzanetant without restrictions.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

Discontinuation of specific sites or of the study as a whole are detailed in Appendix 1.

7.1 Discontinuation of Study Intervention

It may be necessary for a participant to permanently discontinue study intervention. As a general rule, all procedures scheduled for the EoT visit should be performed at the time of premature discontinuation of study intervention and documented. In case this is considered not medically appropriate for certain procedures (e.g. for invasive procedures if only short time has elapsed since the last scheduled assessment) this should be documented by the investigator. The EoT visit should be followed by FU visit as shown in the SoA.

For withdrawal from study see Section 7.2.

7.1.1 Liver Chemistry Stopping Criteria

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

Based on potentially safety-relevant deviations of liver laboratory values, the action described below need to be taken. Monitoring and follow-up assessments are provided in Section 10.5.

Discontinuation of study intervention

Permanent discontinuation

Permanent discontinuation of treatment should be considered if any of the following occurs:

- ALT or AST ≥3 x ULN
  and any of the following:
  - Total bilirubin (TBL) ≥2 x ULN
  - INR ≥1.5
    (Relevant only if the participant is not on vitamin K antagonists, new oral anticoagulants [NOACs] or heparin)
  - Appearance of fatigue, nausea, vomiting, right upper abdominal quadrant pain or tenderness, fever, rash and/or eosinophilia (>5%)
- ALT or AST ≥5 x ULN for ≥2 weeks
- ALT or AST ≥8 x ULN

Participants permanently withdrawn from study intervention should be considered for withdrawal from study participation (see Section 7.2).

7.1.2 Platelet count Stopping Criteria

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

7.1.3 Temporary Discontinuation

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

Temporary discontinuation is also allowed in the following 2 cases:

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

7.1.4 Rechallenge

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

7.1.4.1 Study Intervention Restart After Liver Stopping Criteria Are Met

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

7.2 Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time at the participant's own request, for any reason (or without providing any reason).

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

For withdrawal from study intervention see Section 7.1

7.3 Lost to Follow Up

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

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

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule, and ascertain whether the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls, and if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, the participant will be considered to have withdrawn from the study.

8. Study Assessments and Procedures

- Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.

- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the timeframe defined in the SoA.
- If cervical cancer screening or breast cancer screening results are not available at the time of signing of ICF, they can be performed locally.
- In the event of a significant study-continuity issue (eg, caused by a pandemic), alternate strategies for participant visits, assessments, medication distribution and monitoring may be implemented by the Sponsor or the investigator, as per local health authority/ethics requirements.
- Laboratory/analyte results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.

8.1 Administrative and Baseline Procedures

Baseline assessments are listed in the SoA (Section 1.3).

8.2 Efficacy Assessments

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

Refer to Section 8.8 for biomarkers supporting assessment of efficacy.

8.2.1 Measures to Evaluate Sleep Quality Using a Device

8.2.1.1 Polysomnography (PSG)

On-site PSG assessments (each including 2 consecutive nights) will be performed in qualified sleep laboratories by qualified staff at timepoints described in the SoA.

Parameters derived from PSG will include but are not limited to:

- WASO
- Number of arousals and awakenings
- LPS
- TST
- SE
- Number of minutes and percentage of time in each hypnogram stage (W, R, N1, N2, N3)

Additional details are provided in the PSG manual.

PSG recordings will be sent for interpretation and scoring to a vendor, where an experienced team will perform blinded, centralized reading and scoring of PSG data. The Sponsor will be

provided with a relevant subset of the data. Centralized PSG interpretation will be governed by a vendor's standard operating procedures (SOPs) charter established prior to study start.

Participant eligibility will be based primarily on the PSG reading as assessed by centralized reading. In case PSG is not evaluable due to technical reasons it may be repeated after discussion with the Sponsor. Participant may fail screening after the first PSG night based on the local PSG assessment only, if AHI and/or PLMAI exclusion criteria is/are met. The PSG manual will be maintained at the site and instructions will be provided to sites in the Study Procedure Manual.

8.2.1.2 Sleepiz One+

At study sites in countries where the Sleepiz One+ system is approved for commercial use and at sites where the Sleepiz One+ system has been IRB/EC approved specifically for use in this clinical study, all participants will be invited to take part in continuous nighttime sleep monitoring. The sleep monitor uses radar principle based on radiofrequency scanning and reflection (in the mm-wavelength range) to collect physiologic data during sleep in a contactless manner. Participants who decline to use the sleep monitor may still be enrolled in the study. Data collected with the sleep monitor will not be available to sites or participants. Sites will receive information regarding test quality and participant adherence.

Parameters derived from Sleepiz One+ will include but are not limited to:

WASO
LPS
TST
SE
Total time in bed
Wake up latency
Wake up count
Out of bed count
AHI
Pulse Rate (Mean, Max, Min, Upper Percentile, Lower Percentile)
Breathing rate (Mean, Max, Min, Upper Percentile, Lower Percentile)

The sleep monitor will be provided to the participants at SCR-2 visit. The sleep monitor will be used by the participant to continuously collect sleep data at home in addition to the nights of PSG assessment. A vendor will host and transmit data of the sleep monitoring device via their system.

Participants will receive an instruction document to ensure correct setup and use of the sleep monitor at home. The sleep monitor user manual will be maintained at the site and instructions will be provided to sites in a Study Procedure Manual.

8.2.2 Electronic Patient-Reported Outcomes (ePROs)

During the study visits, ePROs are to be completed prior to any other procedure. An ePRO is an electronically applied measurement based on a report that comes directly from the participant about the status of the participant's health condition without interpretation of the response by a clinician or anyone else. In this trial ePROs will be used for the assessment of different endpoints. These endpoints will be collected using an electronic participant handheld device during the entire study duration both for entries at home (including days of the study

visits), and at study visits at the study site, as indicated in the SoA. Additionally, data will be collected on tablet computers which will be used by the participants during the study visits at the study sites. Web-based back-up versions may be applied in addition. Participant data obtained via handheld or tablet devices will be managed by a vendor.

ePROs collected on the participant's handheld device

The following ePROs will be collected on a handheld device in the following sequence in accordance with the assessment schedule:

- SD
- HFDD (morning diary)
- PROMIS SD SF 8b
- ISI
- GAD-7
- PGI-S
- PGI-C
- HFDD (evening diary)
- Study medication intake documentation (See Section 6.5)

ePROs collected on a tablet computer at the study sites

The following PROs will be collected on a tablet computer:

- eC-SSRS (See Section 8.3.5)

Time for completion

Time for completion of each item of the different PROs is conservatively estimated to be 30 seconds per individual item. The daily completion time therefore ranges from 6 min when only the SD and the HFDD will be completed to a maximum of 30 min on the days of the study visits when most questionnaires are to be completed.

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

Dispense of the participant's handheld device, data entry and transmission

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

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

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

Training of participants

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

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

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

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

The study site staff will be trained regarding the use of the participant handheld device and the tablet computer at the site, and in resolving technical issues with these devices during the Investigator Meeting and site initiation process. Educational material will be available in the Investigator Site File. The study site staff will provide a standardized technical training on the handling of the participant handheld device and the tablet computer to the participants during SCR-1, and retraining will be performed as needed during the course of the trial. The study site staff will assist the participants in case of any technical queries during the entire study duration.

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

Measures to further prevent missing participants' handheld device entries

In case one entry on the HFDD, the SD or the study medication intake documentation was missed (for HFDD morning diaries and SD in case this was not completed when getting up in the morning; for HFDD evening diaries, and the study medication intake documentation in case this was not completed in the evening when going to bed), retrospective data entry is possible for a pre-defined period of time (provided separately).

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

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

8.2.2.1 Sleep Diary (SD)

Participants' assessments of sleep disturbances will be recorded electronically daily using the Sponsor developed SD. The SD will be completed in the morning after waking up (morning

diary) on the handheld device from visit SCR-1 until EoT as reflected in the SoA. The SD items assess the total sleep time duration by asking for time going to bed, falling asleep and waking up, as well as time spend in bed, number and the duration of awakenings during the night.

8.2.2.2 Hot Flash Daily Diary (HFDD)

Participants' assessments of HF will be recorded electronically twice daily using the Sponsor developed HFDD. The HFDD will be completed in the morning after waking up (morning diary) and each evening at bedtime (evening diary) on the handheld device from visit SCR-1 until EoT as reflected in the SoA. The HFDD items assess the number of mild, moderate, and severe HF experienced during the day and during the night and the severity of sleep disturbances due to HFs experienced during the night.

Mild HF are defined as a "sensation of heat without sweating", moderate HF are defined as a "sensation of heat with sweating, but able to continue activity", and severe HF are defined as a "sensation of heat with sweating, causing cessation (stopping) of activity".

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

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

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

8.2.2.4 Insomnia Severity Index (ISI)

The ISI is a 7 item instrument that quantifies the participant perception of insomnia severity, along with the impact of insomnia on daytime functioning in adults in the last 2 weeks (Bastien et al. 2001). The items refer to: severity of sleep onset, sleep maintenance and early morning wakening problems, satisfaction with sleep pattern, noticeability of sleep problems by others, distress caused by the sleep difficulties and interference of sleep difficulties with daytime functioning. It is scored on a 5 point Likert scale from 0 to 4 depending on the item (0="none", 4="very severe" (Items 1–3); 0="very satisfied", 4="very dissatisfied (Item 4)"; 0="not at all noticeable", 4="very much noticeable" (Item 5); 0="not at all worried", and 4="very much worried" (Item 6); 0="not at all interfering", 4="very much interfering" (Item 7)). The scores for each item are summed to produce the total score (maximum 28).

Total score categories:

0–7 = No clinically significant insomnia

8–14 = Subthreshold insomnia

15–21 = Clinical insomnia (moderate severity)

22–28 = Clinical insomnia (severe)

In this study the ISI will be applied electronically and should be completed as indicated in the SoA.

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

The PGI-S includes 2 items assessing sleep problems using a 5-point response scale (No sleep problems to Very severe for the PGI-S item 1 (severity of sleep problems) and None of the time to nearly all of the time for the PGI-S item 2 (time spent awake after first falling asleep)). The recall period for PGI-S items is "the past week". Each item is scored independently.

The PGI-C includes 2 items assessing change in sleep problems since the participant started taking the study medication. A 5-point response scale is used ranging from e.g. 'much better' to 'much worse' for the PGI-C item 1 (change in severity of sleep problems) and 'much less' to 'much more' for the for the PGI-C item 2 (change in time spent awake). Each item is scored independently.

Both instruments, the PGI-S and the PGI-C are self-invented by the sponsor with the objective to serve as reference measures for a planned psychometric analysis.

In this study the PGI-S and PGI-C will be applied electronically using the handheld device and responded to by the participants at home at timepoints indicated in the SoA.

8.2.2.6 Generalized Anxiety Disorder-7 (GAD-7)

The GAD-7 is a 7 item patient-reported instrument that quantifies the symptom severity in generalized anxiety disorder in the last 2 weeks (Spitzer et al. 2006). Concepts assessed are in particular the frequency of being anxious, worried, having troubles relaxing, being restless, annoyed or irritated and feeling afraid. The items are scored on a 4-point Likert scale from 0 to 3 (0 = "not at all"; 1 = "several days"; 2 = "more than half the days"; 3 = "nearly every day"). The scores for each item are summed to produce the total score (maximum of 21), with higher scores indicating a higher frequency of anxiety symptoms.

Participants with a GAD-7 score ≥10 during the study should be further evaluated by the investigator and referral to a specialist considered.

The investigator will receive an email notification if a GAD-7 of ≥10 is reported.

In this study the GAD-7 will be applied electronically and responded to by the participants at home and during selected in person visits at time points indicated in the SoA.

8.3 Safety Assessments

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

8.3.1 Physical Examinations

- A complete physical examination will be performed at visits indicated in the SoA. It will include, at a minimum, height, weight, and assessments of the Cardiovascular, Respiratory, Gastrointestinal and Neurological systems.
- A symptom-based physical examination will be performed as indicated in the SoA, in a response to new symptoms, or changes in symptoms.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

- Abnormal physical examination findings, including overweight/obesity when BMI >30 kg/m^2, are to be recorded either as medical history or as adverse events.

8.3.2 Vital Signs

- Pulse rate, and systolic and diastolic blood pressure will be assessed.
- Vital signs measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (e.g., television, cell phones).
- Vital signs should be taken before blood collection for laboratory tests.
- Blood pressure and pulse rate measurements will be assessed once in a sitting position with a completely automated device. Manual techniques will be used only if an automated device is not available.
- In case of abnormal results, repeat measurements should be performed to adequately document potential findings, e.g. hypertension.[6]

8.3.3 Clinical Safety Laboratory Tests

- See Section 10.2 for the list of clinical laboratory tests to be performed and the SoA for the timing and frequency.
- The investigator must review the laboratory results, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory results must be retained with source documents.
- Abnormal laboratory findings associated with the underlying disease are not considered clinically significant unless judged by the investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 7 days after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or the medical monitor.
    - If clinically significant values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified, and the Sponsor notified.
    - All protocol-required laboratory tests, as defined in Section 10.2, must be conducted in accordance with the Laboratory manual and the SoA.
    - If laboratory values from non-protocol specified laboratory tests performed at the institution’s local laboratory require a change in participant management or are considered clinically significant by the investigator (e.g., SAE or AE or dose modification), then the results must be recorded.

8.3.4 Pregnancy Testing

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

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[6] Hypertension is defined as systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg over 3 readings on at least 2 different occasions.

8.3.5 Suicidal Ideation and Behavior: Electronic Columbia-Suicide Severity Rating Scale (eC-SSRS)

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

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

See Exclusion Criteria 15 for information on when the participant should not be randomized based on suicidal behavior or ideation.

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

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

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

The definitions of device-related safety events including medical device adverse events (AE), serious adverse events (SAE), and device deficiency can be found in Section 10.6. Device deficiencies are covered in Section 8.4.7.

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

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up all AEs (see Section 7). This includes events reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant’s legally authorized representative).

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

8.4.1 Time Period and Frequency for Collecting AE and SAE Information

(S)AEs will be collected from the start of study intervention until the last follow-up visit at the timepoints specified in the SoA (Section 1.3). (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 ICF.

Any medical occurrences/conditions that begin in the period between signing ICF and the start of study intervention, and which are not related to a protocol-required study procedure, will be recorded as medical history/current medical conditions, not as (S)AEs.

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

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

8.4.2 Method of Detecting AEs and SAEs

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

8.4.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, and AEs of special interest (as defined in Section 8.4.6), will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Section 10.3.

8.4.4 Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, institutional review boards (IRBs)/independent ethics committees (IECs), and investigators.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the Sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.

8.4.5 Pregnancy

In case of a suspected pregnancy, a pregnancy test should be performed. In the unlikely event of a pregnancy the following applies:

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

- If a pregnancy is reported, the investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the pregnancy.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs, and will be reported as such.
- The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the Sponsor.
- Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the Sponsor as described in Section 8.4.1 and Section 8.4.4. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any participant who becomes pregnant while participating in the study will permanently discontinue study intervention.

See Section 10.4 for details on collection of pregnancy information.

8.4.6 Adverse Events of Special Interest

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

- Any condition triggering close liver observation according to Section 10.5.
    - Any increase in liver enzymes meeting the following criteria needs to be reported as an adverse event to the Sponsor within 24 hours of the investigator's awareness for expedited reporting to the health authorities:
        - ALT and/or AST >8x ULN OR
        - ALT and/or AST >3x ULN with total bilirubin >2x ULN
    - The investigator may consider whether the observed increase in liver values would qualify as SAE.
- Post-menopausal bleeding: Any participant experiencing unexplained post-menopausal bleeding after randomization should be referred to a gynecologist and undergo a transvaginal ultrasound with subsequent investigation and management according to the gynecologist's clinical judgment and usual practice.

8.4.7 Medical Device Deficiencies

Medical devices are being provided by or on behalf of the Sponsor for use in this study. To fulfill regulatory reporting obligations worldwide, the investigator is responsible for the detection and documentation of events meeting the definitions of device deficiency that occur during the study with such devices.

The definition of a medical device deficiency can be found in Section 10.6.3.

Device deficiencies associated with a medical device AE/SAE (as defined in Section 10.6) will follow the processes outlined in Section 8.4 of the protocol and shall be documented and reported as a complaint to Bayer and eCOA vendor by the investigator.

Device deficiencies not associated with a medical device AE/SAE will be communicated directly to the eCOA vendor by the study site.

All device deficiencies have to be reported to the device manufacturer by the eCOA vendor according to their manual.

8.5 Pharmacokinetics

Blood samples for measurement of elinzanetant and its principal metabolites in plasma for PK are to be collected at the time points given in the SoA (Section 1.3). PK sample is collected before the second PSG night (together with the safety lab sample) in the PSG lab shortly before intake of the study medication to obtain trough levels. The date and time of the last study medication intake prior to the PK sampling as indicated in the SoA (Section 1.3) and the time of all blood samples are to be documented.

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

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

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

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

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

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

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

Population pharmacokinetic analysis of elinzanetant

Based on the plasma concentrations, the variability in elinzanetant PK will be analyzed using population PK modeling. Optionally, a population PK/PD model could be used to describe the effect of elinzanetant exposure on efficacy and safety. This analysis might start prior to database lock (eg, at the moment that approximately 80% of the expected PK samples have been measured). The final population PK model that will be applied to describe the PK of elinzanetant in the study population may be linked to relevant endpoints or parameters

obtained in this study to investigate the relationship between elinzanetant exposure and response.

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

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

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

8.6 Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7 Genetics

Genetics are not evaluated in this study.

8.8 Biomarkers

In this study biomarkers e.g. related to mode-of-action-related effects or safety and biomarkers deemed relevant to investigate pathomechanims of sleep disturbances associated with menopause may be investigated. These investigations may include e.g., diagnostic, safety, pharmacodynamic, monitoring, or potentially predictive biomarkers.

PK samples (Section 8.5), safety lab samples (Section 10.2 and Section 10.5) and sleep laboratory data (Section 8.2.1) might be used for biomarker studies. For timing see SoA (Section 1.3).

The results of biomarker investigations may be reported separately (e.g. in a biomarker evaluation report).

8.9 Immunogenicity Assessments

Not applicable.

8.10 Medical Resource Utilization and Health Economics

Medical resource utilization and health economics parameters are not evaluated in this study.

9. Statistical Considerations

The analysis and reporting will be done on all data from all participants at the time the study ends.

The SAP will be finalized prior to database lock and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a

summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.1 Statistical Hypothesis

The primary objective for the study is to estimate the treatment effect of elinzanetant compared to placebo in the change from baseline in WASO at Week 4 as measured by PSG. No hypotheses are planned to be tested.

9.2 Analysis Sets

For the purposes of analysis, the following analysis sets are defined:

Participant Analysis Set	Description
Full analysis set	• All participants randomly assigned to study treatment.
Safety analysis set	• All participants randomly assigned to study treatment who were exposed to study treatment at least once.

The full analysis set is used to analyze endpoints related to the efficacy objectives and participants will be analyzed according to their randomized study treatment. The Safety Analysis Set is used to analyze the endpoints and assessments related to safety and participants will be analyzed according to the study treatment received.

9.3 Statistical Analyses

9.3.1 General Considerations

The statistical analyses will be performed in SAS and/or ValidR. The versions used will be specified in the SAP.

All variables will be summarized using descriptive statistics as appropriate by study treatment. Continuous variables will be summarized using at least the following descriptive statistics: number of non-missing observations, arithmetic mean, standard deviation, median, minimum and maximum. Categorical data will be summarized with frequency tables with the number of observations and percentages. Confidence intervals will be 2 sided with a confidence level of 90%.

Unless otherwise specified, baseline is defined as the latest available valid measurement at or before the start of study treatment. If the last observation available prior to randomization is the measurement from the screening visit, this would be used as the baseline value.

Important ICEs for this study are defined as:

- Temporary study treatment interruption, defined as:
    a. Week 4 = Treatment taken <80% during weeks 1–4 OR treatment taken on <5/7 days during either Week 3 or 4.
    b. Week 12 = Treatment taken <80% during weeks 1–12 OR treatment taken on <5/7 days during either Week 11 or 12.
- Permanent discontinuation of randomized study treatment
- Intake of prohibited concomitant medications having impact on efficacy

The number of observed ICEs will be summarized by study treatment and overall for each intercurrent event.

9.3.2 Primary Endpoint/Estimand Analysis

9.3.2.1 Definition of Endpoint

The primary endpoint is the change from baseline in WASO at Week 4 as measured by PSG.

Polysomnography assessments will be performed on 2 consecutive nights during screening and at Week 4. The baseline WASO value will be the mean value of the 2 consecutive nights at screening. Similarly, the Week 4 value will be the mean value of the 2 consecutive nights at Week 4.

The change from baseline in WASO to Week 4 will be calculated as below:

Change from baseline = WASO mean value at Week 4 – WASO mean value at baseline

9.3.2.2 Main Analytical Approach

The primary endpoint will be analyzed using a MMRM on the change from baseline values at Week 4 and 12. Baseline value, study treatment, average weekly frequency of moderate-to-severe HFs (stratification factor) and week will be included as covariates in the model as well as the interaction terms baseline-by-week and study treatment-by-week. An unstructured covariance structure will be used. If convergence cannot be attained, alternative structures will be attempted. Additional details will be provided in the SAP. The least square means for each study treatment and the least square means differences comparing elinzanetant with placebo will be estimated with corresponding 90% confidence intervals.

Implementation of Strategies for Intercurrent Event Handling and Data Point Selection

Prior to performing the MMRM model, missing data will be handled in alignment with the estimand strategy for ICEs (described in Section 3).

The hypothetical strategy will be used to handle all of the ICEs in the primary estimand. This strategy will estimate the full efficacy potential of elinzanetant in the ideal situation if participants adhered to randomized study treatment up to Week 4 without taking prohibited concomitant medications impacting sleep. Data collected after the occurrence of any ICE will be discarded, and missing and unobserved data will be modeled using participants from the same study treatment who adhered to study treatment without taking prohibited concomitant medications impacting sleep to Week 4 and have observed data at Week 4.

Details of the imputation model will be provided in the SAP.

9.3.2.3 Sensitivity Analyses

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 all ICEs. This will be done by applying an unfavorable additive shift (referred to as delta adjustment) to the values imputed by the imputation model. Additional details on the tipping point analysis will be provided in the SAP.

9.3.2.4 Supplementary Analyses

A supplementary estimand for the primary endpoint will be estimated. The attributes are the same as the primary estimand (Section 3) except for the handling of the ICEs which will be addressed using the below strategies:

ICEs	Proposed Strategy	Data Handling Method	Interpretation
Temporary study treatment interruption	Treatment Policy	Utilize the available data regardless of the occurrence of ICE	The treatment effect includes the effect of treatment interruptions
Premature discontinuation of study treatment	Hypothetical	Discard data collected after the ICE	The treatment effect that would be if participants who discontinue the randomized treatment remain untreated on randomized treatment
Intake of prohibited concomitant medication having impact on efficacy	Treatment Policy	Utilize the available data regardless of the occurrence of ICE	The treatment effect includes the effect of prohibited concomitant medications impacting sleep

ICE = Intercurrent event.

A treatment policy will be applied to handle the ICE temporary study treatment interruption and intake of prohibited concomitant medication having impact on efficacy. A treatment policy approach for these ICEs are appropriate as this likely reflects the behavior of the target population. According to this strategy, all collected data should be utilized in the analysis irrespective of occurrence of the ICEs. Although all participants are expected to be followed after these ICEs, some missing data may occur which will be handled in line with the estimand strategy.

A hypothetical strategy will be applied to handle the ICE premature discontinuation of study treatment to estimate the treatment effect that would be if participants who prematurely discontinue study treatment remain untreated (do not receive the experimental study treatment until the planned assessment timepoint). This approach reflects what would happen if participants remain in the study after premature discontinuation of study treatment. Missing and unobserved data will be modeled using placebo participants who remain on study treatment to Week 4 and have observed data at Week 4.

Full details of the analysis will be provided in the SAP.

9.3.3 Secondary Endpoints/Estimands Analysis

The secondary endpoints in this study are:

- Change from baseline in WASO at Week 12 as measured by PSG
- Change from baseline in sleep efficiency at Week 4 as measured by PSG
- Change from baseline in sleep efficiency at Week 12 as measured by PSG
- Change from baseline in PROMIS SD SF 8b total score at Week 4
- Change from baseline in PROMIS SD SF 8b total score at Week 12
- Change from baseline in ISI total score at Week 4
- Change from baseline in ISI total score at Week 12

The secondary endpoint change from baseline in WASO at Week 12 as measured by PSG will be derived similarly to the primary endpoint and analyzed using the same model as proposed for the primary efficacy analysis (see Section 9.3.2).

The secondary endpoints on sleep efficiency, PROMIS SD SF 8b and ISI will be analyzed descriptively by study treatment. In addition, the individual items in each patient-reported

outcome will be summarized descriptively. All data will be utilized in the analysis regardless of the occurrence of ICEs. The calculation of the total scores for PROMIS SD SF 8b and ISI will be done according to the respective questionnaire guidelines.

9.3.4 Exploratory Endpoint(s) Analysis

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

9.3.5 Safety Analysis

Analysis on safety data will be performed on the Safety Analysis Set.

TEAEs will be analyzed by descriptive statistics, such as frequency tables. All TEAEs will be tabulated by system organ class and preferred term, as coded by the current version of the MedDRA. Further tables will be provided for serious and/or drug-related TEAEs.

Additional details for the safety analyses will be provided in the SAP.

9.3.6 Other Analysis

Subgroup analyses of the primary endpoint and secondary endpoint change from baseline in WASO at Week 12 as measured by PSG will be provided by the average weekly frequency of moderate to severe HF over the 14 days prior to the respective eligibility check (<35 moderate to severe HFs per week, ≥35–<50 moderate to severe HFs per week, ≥50 moderate to severe HFs per week). Descriptive statistics will be provided and additional subgroups (e.g. region, BMI) will be specified in the SAP.

9.4 Interim Analysis

No interim analysis is planned.

9.5 Sample Size Determination

The primary objective for the study is to estimate the treatment effect of elinzanetant compared to placebo in the change from baseline in WASO to Week 4. Therefore, the sample size is based on precision (i.e. the half width of the confidence interval).

There are no data available on the primary endpoint WASO measured by PSG in women with sleep disturbance associated with the menopause. Therefore, the standard deviation used in the sample size calculation is obtained from a study in patients with insomnia disorder (Mignot et al. 2022). Assuming the pooled standard deviation is 33.2 for the change from baseline in WASO at Week 4, a total sample size of 70 participants (35 per arm) would give a 90% probability that the 2-sided 90% confidence interval will have a half width of 14.7 minutes or less. To account for missing data and possible inflation in variability due to missing data imputation, a total of approximately 78 participants (39 per arm) will be randomized in a 1:1 ratio to both treatments. Approximately 223 participants will be screened to achieve 78 randomized participants.

10. Supporting Documentation and Operational Considerations

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

10.1.1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
    - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and CIOMS international ethical guidelines
    - Applicable ICH GCP guidelines
    - Applicable laws and regulations
- The protocol, protocol amendments, ICF, investigator's brochure, and other relevant documents (e.g., advertisements) must be submitted reviewed and approved in accordance with national legislation and undergo scientific and ethical assessment before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants. Any substantial modification of the protocol will be submitted to the competent authorities as substantial amendments for approval, in accordance with ICH GCP and national and international regulations.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following, as applicable:
    - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
    - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
    - Providing oversight of the conduct of the study at the site and adherence to requirements of ICH guidelines, the IRB/IEC, and all other applicable local regulations

10.1.2 Financial Disclosure

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

10.1.3 Informed Consent Process

- The investigator or the investigator's representative will explain the nature of the study, including the risks and benefits, to the potential participants and answer all questions regarding the study.
- Potential participants must be informed that their participation is voluntary. They will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written

consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participants.

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

10.1.4 Recruitment Strategy

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

10.1.5 Data Protection

- Participants will be assigned a unique identifier by the Sponsor. Any participant records, datasets or biological samples that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- Participants must be informed that their personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.
- Participants must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- The contract between Sponsor and study sites specifies responsibilities of the parties related data protection, including handling of data security breaches and respective communication and cooperation of the parties.
- Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.

10.1.6 Dissemination of Clinical Study Data

Bayer fulfills its commitment to publicly disclose study results through posting the result of the studies on public registries in accordance with applicable law and regulations.

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

In accordance with the current EU regulation, result summaries will be submitted within one year from the end of the studies in adult populations or within 6 months for studies in pediatric population, in **all** participating countries. No preliminary data analysis (eg, on EU data only) will be performed, as this might compromise data integrity and the scientific validity of the study. Bayer commits to sharing upon request from qualified scientific and

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

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

10.1.7 Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRFs unless transmitted to the Sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- Guidance on completion of CRFs will be provided in the CRF Completion Guidelines.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source documents.
- Quality tolerance limits (QTLs) will be predefined in the integrated data review plan to identify systematic issues that can impact participant safety and/or reliability of study results. These pre-defined parameters will be monitored during the study and important deviations from the QTLs and remedial actions taken will be summarized in the Clinical Study Report.
- Monitoring details describing strategy, including definition of study critical data items and processes (e.g., risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plan.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (e.g., contract research organizations).
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.8 Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator’s site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data and its origin can be found in the Source Data Location List (SDLL).

- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The Sponsor or designee will perform monitoring to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- For ePRO and Sleepiz One+ data, the service provider database is the source.

10.1.9 Study and Site Start and Closure

Study Start

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

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

Study/Site Termination

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

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

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

For study termination:

Discontinuation of further study intervention development

For site termination:

Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines

Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the investigator

Total number of participants included earlier than expected.

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

10.1.10 Publication Policy

The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2 Appendix 2: Clinical Laboratory Tests

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

Table 10–1: Clinical laboratory tests

Panel	Parameters (by category)
Safety parameter	
Hematology:	Red blood cell count, white blood cell count, hematocrit, hemoglobin, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), %reticulocytes, platelet count and WBC differentials (absolute and relative values)
Clinical chemistry:	Sodium, potassium, glucose, urea (blood urea nitrogen), creatinine (including eGFR*), creatine kinase (CK), albumin, calcium, phosphate, bilirubin (total and direct), alkaline phosphatase** (AP), aspartate transaminase (AST), alanine transaminase (ALT), gamma glutamyl transferase (GGT), total cholesterol, high density lipoprotein (HDL) cholesterol, low density lipoprotein (LDL) cholesterol, triglycerides, magnesium, chloride, total protein, hemoglobin A1c, lactate dehydrogenase (LDH) * The laboratory parameter eGFR will be calculated by the central laboratory based on the CKD-EPI formula. The formula used for calculating eGFR (in mL/min/1.73 m^2) will be the 2009 CKD-EPI equation based on creatinine and including age, sex and race (Levey et al. 2009) ** If alkaline phosphatase is elevated, consider fractionating
Coagulation:	Prothrombin time (Quick), INR, activated partial thromboplastin time (aPTT)
Hormones:	Follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol (E2), progesterone (P), prolactin, thyroid-stimulating hormone (TSH), triiodothyronine (T3), thyroxine (T4), free triiodothyronine (FT3), free thyroxine (FT4), sex hormone-binding globulin (SHBG), total testosterone (tT)
Urine analysis	pH, urobilinogen, blood/hemoglobin, total protein, ketone, bilirubin, nitrite, glucose, leukocytes
Screening/Start of Intervention parameters	
Urine pregnancy test	Highly sensitive beta human chorionic gonadotropin (β-hCG)
Virology	Hepatitis B virus surface antigens and Hepatitis C antibodies, HCV-RNA (HCV-mRNA automatically tested if anti-HCV is positive)
PK	
Pharmacokinetics	Pre-dose PK samples

CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration, eGFR = estimated glomerular filtration rate, HCV = Hepatitis C virus; INR = International normalized ratio; mRNA = Messenger ribonucleic acid; PK = Pharmacokinetics, RNA = ribonucleic acid; WBC = White blood cell count.

Additional laboratory tests to be assessed for close liver observation are described in Table 10–2.

Investigators must document their review of each laboratory safety report.

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

10.3.1 Definition of AE

AE Definition

An AE is any untoward medical occurrence in a clinical study participant, associated with the use of study intervention, whether or not considered related to the study intervention.

NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) associated with the use of study intervention.

Events Meeting the AE Definition

Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease).

Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.

New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.

Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.

Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose *per se* will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

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

Lack of efficacy or failure of expected pharmacological action *per se* will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

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

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

The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition

Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE

Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital)

Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen

10.3.2 Definition of SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets the one or more of the criteria listed:

a. **Results in death**

b. **Is life threatening**

The term *life threatening* in the definition of *serious* refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. **Requires inpatient hospitalization or prolongation of existing hospitalization**

In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. **Results in persistent or significant disability/incapacity**

The term disability means a substantial disruption of a person's ability to conduct normal life functions.

This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. **Is a congenital anomaly/birth defect**

f. **Other situations:**

Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, convulsions, or development of intervention dependency or intervention abuse.

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

AE and SAE Recording

When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.

The investigator will then record all relevant AE/SAE information.

It is not acceptable for the investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the AE/SAE eCRF page.

There may be instances when copies of medical records for certain cases are requested by the Sponsor . In this case, all participant identifiers, with the exception of the

participant number, will be redacted on the copies of the medical records before submission to the Sponsor.

The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

For device deficiencies, it is required that the investigator describes any corrective or remedial actions taken to prevent recurrence of the deficiency.

- A remedial action is any action other than routine maintenance or servicing of a medical device where such action is necessary to prevent recurrence of a device deficiency. This includes any amendment to the device design to prevent recurrence.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to one of the following categories:

Mild: A type of adverse event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.

Moderate: A type of adverse event that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.

Severe: A type of adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

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

Assessment of Causality

The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. The investigator will use clinical judgment to determine the relationship.

A *reasonable possibility* of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.

Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.

For causality assessment, the investigator will also consult the IB and/or product information, for marketed products.

The investigator must review and provide an assessment of causality for each AE/SAE and document this in the medical notes There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the Sponsor. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission** of the SAE data to the Sponsor.

The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare professionals.

If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide the Sponsor with a copy of any postmortem findings including histopathology.

New or updated information will be recorded in the originally submitted documents.

The investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

10.3.4 Reporting of SAEs

SAE Reporting to Sponsor via an Electronic Data Collection Tool

The primary mechanism for reporting an SAE to the Sponsor will be the electronic data collection tool.

If the electronic system is unavailable, then the site will use the paper SAE data transmission (see next section) to report the event within 24 hours.

The site will enter the SAE data into the electronic system as soon as it becomes available.

After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.

If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the local pharmacovigilance contact person by telephone.

Contacts for SAE reporting can be found in the Investigator Site File.

SAE Reporting to the Sponsor via Paper Data Collection Tool

Email transmission of the SAE paper data collection tool is the preferred method to transmit this information to the Sponsor’s Pharmacovigilance department.

Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE data collection tool within the designated reporting timeframes.

Contacts for SAE reporting can be found in the Investigator Site File.

10.4 Appendix 4: Collection of Pregnancy Information

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

Collection of Pregnancy Information:

- The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. The initial pregnancy information will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of learning of a participant's pregnancy.
- The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the Sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
  - While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
  - A spontaneous abortion (occurring at <22 weeks gestational age) or stillbirth (occurring at >22 weeks gestational age) is always considered to be an SAE and will be reported as such.
- Any post-study pregnancy related SAE considered reasonably related to the study intervention by the investigator will be reported to the Sponsor as described in Section 8.4.1 and Section 8.4.4. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any participant who becomes pregnant while participating in the study will permanently discontinue study intervention.

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

10.5.1 Thresholds for liver chemistry

Actions, monitoring and follow-up assessments as outlined in Section 10.5.2 and 10.5.3 are required if any of the following abnormal laboratory results at local or central laboratory are noticed by the investigator:

1. Any of the following (for confirmation, re-test within 48–72 hours is required):
   - Confirmed elevation of ALT or AST ≥3 x ULN after start of study intervention and normal values at baseline
   - Confirmed ALT or AST 2-fold increases above baseline values and elevated liver enzymes before drug exposure
   - Confirmed AP (alkaline phosphatase) value increases to ≥2 x ULN in the absence of bone pathology driving the rise in AP level and irrespective of the level of transaminase (ALT or AST) values

2. ALT or AST ≥3 x ULN and any of the following
   - Total bilirubin (TBL) ≥2 x ULN
   - INR ≥1.5
     (Relevant only if the participant is not on Vitamin K antagonist, new oral anticoagulants (NOACs) or heparin)
   - Appearance of fatigue, nausea, vomiting, right upper abdominal quadrant pain or tenderness, fever, rash and/or eosinophilia (> 5%)

3. ALT or AST ≥5 x ULN for ≥2 weeks

4. ALT or AST ≥8 x ULN

10.5.2 Immediate actions

If any of the criteria specified in Section 10.5.1 is met, the following immediate actions should be initiated:

Discontinuation decision

Criterion 1:	Discontinuation of study intervention should be considered, also in case the participants does not adhere to procedures required for close observation[7]
Criteria 2 to 4:	Discontinuation of study intervention should be decided

Expedited reporting

The investigator has to report the event to the Sponsor on AE/SAE eCRF pages within 24 hours of the investigator`s awareness if the event meets any of the following criteria:

1. Qualifies for an SAE (Section 10.3.2)
   The investigator should consider whether the observed increase in liver values would qualify as SAE
2. Qualifies for an AESI requiring expedited reporting (Section 8.4.6)

[7] In case visits for close observation could not be arranged with a frequency deemed adequate by the investigator, despite of reasonable efforts.

Close observation

The participant needs to be closely observed as described below until the abnormalities of the liver chemistry resolve, stabilize, or return to baseline. The objective is to ensure participant safety and to rule out acute viral or autoimmune hepatitis and other not previously diagnosed liver or biliary tract diseases.

It is critical to initiate close observation immediately upon detection and confirmation of early signals of possible drug-induced liver injury, and not to wait until the next scheduled visit or monitoring interval.

Close observation includes:

1. Repeat liver chemistry tests (ALT, AST, AP and total bilirubin) 2 to 3 times weekly until recovery.
2. Frequency of retesting can decrease to once a week or less if abnormalities stabilize and the participant is asymptomatic.
3. Complete general chemistry forms in liver eCRF (in case local lab is used).
4. Obtain additional tests such as gamma glutamyl transferase (GGT), creatine kinase (CK), lactate dehydrogenase (LDH), prothrombin time (PT), INR, albumin, blood cell count with differentials as appropriate.
5. Take blood for viral- and autoimmune serology, as well as liver-specific tests. Details are provided in Table 10–2.
6. Serum bilirubin fractionation should be performed if total bilirubin is increased.

Specific laboratory tests for close liver observation are specified in Table 10–2. Samples should be analyzed preferably by a central laboratory; if medically indicated to allow immediate clinical actions, an additional local laboratory should be considered. All results, including locally obtained, must be entered into the study database.

If the investigator learns about an AE diagnosed by another treating physician, every effort should be made to obtain all relevant information.

Table 10–2: Laboratory tests for close liver observation

As soon as possible (may be combined with first follow-up sampling) To be repeated in case of abnormalities or if medically indicated	
General chemistry	• Bilirubin total, bilirubin direct, bilirubin indirect, alkaline phosphatase, GGT, AST, ALT, creatine kinase (CK, CPK), LDH, cholesterol total, triglycerides, glucose, hemoglobin A1c, albumin
Coagulation	• Prothrombin time, PT-INR
Hematology	• Hematocrit, hemoglobin, RBC, WBC, Platelets, MCV, neutrophils absolute count; lymphocyte absolute count, monocytes absolute count, eosinophils absolute count, basophils absolute count, neutrophils total (%), lymphocyte (%), monocytes (%), eosinophils (%), basophils (%)
Once only upon start of close liver observation	
Liver-specific chemistry	• Ferritin, total iron, saturation transferrin, ceruloplasmin, alpha-1 antitrypsin, IgG level in blood (Immunoglobulin G)
Virus serology in serum unless otherwise indicated	• Anti-Hepatitis-A-virus antibody IgM • Hepatitis B virus surface antigen (HbsAg) in serum, anti-hepatitis B core antibody (anti-HBc), hepatitis B virus DNA (if HbsAg positive), anti-hepatitis B surface antibody (Anti-Hbs), anti-hepatitis D antibodies (if HbsAg positive) • Anti-hepatitis-C-virus antibody, hepatitis C virus RNA • Anti-hepatitis-E-virus IgG antibody, anti-hepatitis-E-virus IgM antibody, hepatitis E virus RNA (detection per PCR) • Anti-cytomegalovirus (CMV) IgM antibodies • Anti-Epstein-Barr-virus (EBV) IgM antibodies • Herpes simplex IgM (anti-HSV IgM) • HIV1/HIV2 antibody screen
Autoimmune serology in serum unless otherwise indicated	• Antinuclear antibodies (ANA) • Anti-smooth-muscle antibodies (ASMA or smooth muscle antibody) • Anti-mitochondrial autoantibodies (AMA) – only in case of cholestatic pattern • If medically indicated, the following test should be considered: – Anti-LKM-1 antibodies, – Anti-P-ANCA antibodies or perinuclear anti-neutrophil cytoplasmic antibodies, – Anti-C-ANCA antibodies or anti-neutrophil cytoplasmic antibodies, – Anti-F-actin antibody, – Anti-LC1 antibodies or anti-SLA/LP antibodies might be considered in subsequent tests.

ALT = alanine aminotransferase, AST = aspartate aminotransferase, C-ANCA= neutrophil cytoplasmic, CK = creatine kinase, CPK = creatine phosphokinase, DNA = desoxyribonucleic acid, GGT = gamma glutamyl transferase, HIV = human immunodeficiency virus, IgG = immunoglobulin G, IgM = immunoglobulin M, INR = international normalized ratio, LC1 = liver cytosol type 1, LDH = lactate dehydrogenase, LKM-1 = liver kidney microsomal type 1, MCV = Mean corpuscular volume, SLA/LP = soluble liver antigen/liver pancreas, P-ANCA= anti-neutrophil perinuclear antibodies, PCR = polymerase chain reaction, PT = prothrombin time, RBC= red blood cell count, RNA = ribonucleic acid, WBC = white blood cell count.

10.5.3 Follow-up assessments

If any of the criteria specified in Section 10.5.1 is met, the following follow-up assessments should be initiated:

1. Rule out relevant acute intercurrent diseases (e.g. alcoholic hepatitis; fatty liver; hypoxic/ischemic hepatopathy; biliary tract disease or viral hepatitis types A, B, C, D, and E; or autoimmune hepatitis). Details for virus and autoimmune serology are provided in Table 10–2.

   → Report corresponding lab values on the 'Virus serology' and 'Autoimmune serology' eCRF forms

2. Obtain clinical signs and symptoms and a detailed history of prior or concurrent diseases. Special attention is to be paid to new or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or hypersensitivity (such as fever, rash, or eosinophilia).

   → Complete 'Clinical Sings and Symptoms' and 'Pre-existing medical Conditions' eCRF forms

3. Obtain a history of liver-specific risk factors (e.g. specific concomitant drugs including non-prescription medications and herbal and dietary supplement preparations, recreational drug use, exposure to environmental chemical agents, and special diets)

   Fill in 3 different 'Risk Factors' eCRF forms

4. Capture alcohol consumption and recent changes of consumption.

   → Report on 'Substance Use - Alcohol' eCRF form

5. In case of confirmed AP ≥ 2 x ULN in the absence of bone pathologies, liver images (e.g. ultrasound, MRCP, ERCP) are indicated. In all other liver events consider liver imaging (e.g. ultrasound, MRI, CT, MRCP, ERCP, magnetic resonance spectroscopy and/or liver biopsy) – if applicable, report on corresponding 'Hepatic Imaging / Liver Biopsy' eCRF forms

6. Consider gastroenterology or hepatology consultations

10.6 Appendix 6: Medical Device AE, SAE, and Device Deficiencies: Definitions

The definitions and procedures detailed in this appendix are in accordance with ISO 14155 and the European Medical Device Regulation (MDR) 2017/745 for clinical device research (if applicable).

Both the investigator and the Sponsor will comply with all local reporting requirements for medical devices.

The detection and documentation procedures described in this protocol apply to the medical devices supplied by or on behalf of the Sponsor for use in the study. See Section 6.1.1 for the list of medical devices supplied by or on behalf of the Sponsor.

10.6.1 Definition of Medical Device AE

Medical Device AE

A medical device AE is any untoward medical occurrence in a clinical study participant, users, or other persons, temporally associated with the use of study intervention, whether or not considered related to the investigational medical device. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of an investigational medical device. This definition includes events related to the investigational medical device or comparator and events related to the procedures involved except for events in users or other persons, which only include events related to investigational devices.

10.6.2 Definition of Medical Device SAE

A Medical Device SAE is any SAE that:

a. **Led to death**

b. **Led to serious deterioration in the health of the participant, that either resulted in:**

A life-threatening illness or injury. The term *life-threatening* in the definition of *serious* refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

A permanent impairment of a body structure or a body function.

Inpatient or prolonged hospitalization, planned hospitalization for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered an SAE.

Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function.

Chronic disease (MDR 2017/745).

c. **Led to fetal distress, fetal death or a congenital abnormality or birth defect**

d. **Is a suspected transmission of any infectious agent via a medicinal product**

10.6.3 Definition of Device Deficiency

A device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. Device deficiencies include malfunctions, use errors, and inadequacy of the information supplied by the manufacturer.

10.7 Appendix 7: Washout periods for hormonal therapies and prohibited concomitant medications

Tables below present a comprehensive (but not exhaustive) list of prohibited concomitant medications and respective washout periods, as well as a list of medications with limited use during the study. Washout periods are shown in Table 10–3 for hormonal therapies, Table 10–4 for therapies affecting sleep and Table 10–6 for concomitant medications affecting PK. Table 10–5 lists medications that are allowed provided their use is limited during the study. Table 10–7 and Table 10–8 list examples of the most common medication regarded as potent CYP3A4 inhibitors or inducers, or P-gp inhibitors.

Table 10–3: Washout periods for hormonal therapies.

Prohibited from the time shown until after last PSG in the study and last dose of study medication.	
Washout period	**Hormonal therapies**
From 4 weeks prior to SCR-2 visit	Vaginal hormonal products (rings, creams, gels and including DHEA or analogues thereof)
From 4 weeks prior to SCR-2 visit	Transdermal estrogen alone or estrogen/progestin products
From 8 weeks prior to SCR-2 visit	• Oral estrogen and/or progestin therapy • Selective estrogen receptor modulators
From 12 weeks prior to SCR-2 visit	• Progestin implants and estrogen alone injectable drug therapy • Use of adjuvant endocrine therapy (e.g. tamoxifen, aromatase inhibitors, GnRH analogues)
From 24 weeks prior to SCR-2 visit	Estrogen pellet therapy or progestin injectable drug therapy

DHEA = Dehydroepiandrosterone, GnRH = Gonadotropin-releasing hormone,
PSG = polysomnography, SCR = Screening.

Table 10–4: Prohibited concomitant medication potentially confounding efficacy.

Prohibited from the time shown until after last PSG in the study and last dose of study medication.	
Washout period	**Therapies that may affect sleep/wake function**
At least 4 weeks or 5 half-lives (whichever is longer) prior to SCR-2 visit	Chronic use of anxiolytics/hypnotics (defined as a use for ≥4 times per week over a longer period of time than recommended per respective product monograph or treatment guidelines)

At least 2 weeks or 5 half-lives (whichever is longer) prior to SCR-2 visit	• Antidepressant drugs
	• Anticonvulsants
	• Antipsychotics (for depot neuroleptics consider long half-lives)
	• Anxiolytics (benzodiazepines, non-benzodiazepines)
	• Hypnotics
	• Centrally acting anticholinergics
	• Mood stabilizers
	• Muscle relaxants (centrally acting with psychotropic effects)
	• Central Alpha-2 Receptor Agonists
	• Sodium oxybate
	• Sedating antihistamines
	• Melatonin and melatonin receptor agonists
	• Stimulants
	• Adenosine Receptor Antagonist
	• Systemic corticosteroids (inhaled corticosteroids are allowed)
	• Diet pills that contain active substance and/or ingredients that can affect sleep
	• Isotretinoin
	• Any recreational drugs, even if used for medicinal reasons
	• Opioids/narcotics
	• Over-the-counter (OTC) /herbal treatments including:
	  • Supplements with possible psychotropic effect
	  • Extended-release pseudoephedrine
	  • Traditional Chinese medicine used for sleep improvement/disturbances

PSG = polysomnography, SCR = Screening.

Table 10–5: Medication with limited use during the study

During the study	Therapies
Allowed up to twice per week	• Non-sedating antihistamines. See Table 10–6 for non-sedating antihistamines which are prohibited during the study as CYP3A4 substrates.
	• Pseudoephedrine

CYP3A4 = Cytochrome P450 isoenzyme 3A4.

Table 10–6: Prohibited concomitant medication potentially affecting PK.

Prohibited from the time shown until 1 week after the last dose of study medication	
Washout period before SCR-2	**Therapies**
At least 2 weeks or 5 half-lives (whichever is longer) prior to SCR-2 visit: CYP3A4 substrates with a narrow therapeutic range	Alfentanil, astemizole, fentanyl, pimozide, terfenadine
At least 2 weeks or 5 half-lives (whichever is longer) prior to SCR-2 visit: Strong or moderate inhibitors of CYP3A4	Nefazodone, fluvoxamine, tofisopam
At least 2 weeks or 5 half-lives (whichever is longer) prior to SCR-2 visit: Strong or moderate inducers of CYP3A4	Carbamazepine, phenytoin, St. John's wort, phenobarbital, primidone
Washout period before BL	**Therapies**
From 1 week prior to BL visit: CYP3A4 substrates with a narrow therapeutic range	Cisapride, cyclosporine, dihydroergotamine, ergotamine, quinidine, sirolimus, tacrolimus
From 2 weeks prior to BL visit: Strong or moderate inhibitors of CYP3A4	See Table 10–7 for examples of most common moderate and strong CYP3A4 inhibitors
From 4 weeks prior to BL visit: Strong or moderate inducers of CYP3A4	See Table 10–8 for examples of most common moderate and strong CYP3A4 inducers
From 1 week prior to BL visit: P-glycoprotein inhibitors	Azithromycin, conivaptan, cyclosporine, diltiazem, erythromycin, ketoconazole, ranolazine, amiodarone, carvedilol, clarithromycin, dronedarone, itraconazole, lapatinib, propafenone, quinidine

BL = Baseline, CYP3A4 = Cytochrome P450 isoenzyme 3A4, PK = Pharmacokinetics, SCR = Screening.

Table 10–7: Examples of clinical inhibitors for CYP3A4

Strong inhibitors	Moderate inhibitors
boceprevir	aprepitant
clarithromycin	ciprofloxacin
cobicistat	conivaptan
danoprevir and ritonavir	crizotinib
elvitegravir and ritonavir	cyclosporine
grapefruit juice	diltiazem
idelalisib	dronedarone
indinavir and ritonavir	erythromycin
itraconazole	fluconazole
ketoconazole	fluvoxamine
lopinavir and ritonavir	imatinib
nefazodone	tofisopam
nelfinavir	verapamil
paritaprevir and ritonavir and (ombitasvir and/or dasabuvir)	
posaconazole	
ritonavir	
saquinavir and ritonavir	
telaprevir	
tipranavir and ritonavir	
telithromycin	
troleandomycin	
voriconazole	

CYP3A4 = Cytochrome P450 isoenzyme 3A4.
Source: (FDA 2020)

Table 10–8: Examples of clinical inducers for CYP3A4

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

CYP3A4 = Cytochrome P450 isoenzyme 3A4.
Source: (FDA 2020)

10.8 Appendix 8: Country/region-specific Requirements

Not applicable.

10.9 Appendix 9: Protocol Amendment History

10.9.1 Amendment 1 (21 SEP 2023)

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

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