Daridorexant (ACT-541468)

Insomnia and comorbid nocturia

Global Protocol ID-078A401

A multi-center, double-blind, randomized, placebo-controlled, 2-way cross-over post approval study to investigate the efficacy of daridorexant in subjects with insomnia and comorbid nocturia

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Medical Emergency Hotline Toll Telephone Number	Site-specific toll telephone numbers and toll-free telephone numbers for the Medical Emergency Hotline can be found in the Investigator Site File

CONTRACT RESEARCH ORGANIZATION INFORMATION

Some key study activities are delegated to Contract Research Organizations. A list of site-specific contact details can be found in the Investigator Site File.

SIGNATURE PAGE FOR IDORSIA PHARMACEUTICALS LTD

Hereinafter called Idorsia

Compound name / number

Daridorexant (ACT-541468)

Indication

Insomnia and comorbid nocturia

Protocol number, study title

ID-078A401

A multi-center, double-blind, randomized, placebo-controlled, 2-way cross-over post approval study to investigate the efficacy of daridorexant in subjects with insomnia and comorbid nocturia

Name (Title)	Date	Signature
PPD MSc	_____	PPD _____
PPD MD, PhD PPD	_____	PPD _____
PPD MSc PPD	_____	PPD _____

INVESTIGATOR SIGNATURE PAGE

Compound name / number

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I agree to the terms and conditions relating to this study as defined in this protocol and any other protocol-related documents. I fully understand that any changes instituted by the investigator(s) without previous agreement with the sponsor would constitute a protocol deviation, including any ancillary studies or procedures performed on subjects (other than those procedures necessary for the well-being of the subjects).

I agree to conduct this study in accordance with the Declaration of Helsinki principles, ICH GCP guidelines, and applicable regulations and laws.

Principal Investigator	**Location (Site number)**	**Date**	**Signature**

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LIST OF ABBREVIATIONS AND ACRONYMS

AE	Adverse event
AESI	Adverse event of special interest
BFLUTS-SF	Bristol Female Lower Urinary Tract Symptoms Short Form
CBT(-I)	Cognitive behavioral therapy (for insomnia)
CNS	Central nervous system
CRA	Clinical Research Associate
CRO	Contract Research Organization
C-SSRS©	Columbia Suicide Severity Rating Scale©
CYP	Cytochrome P450
DBP	Diastolic blood pressure
DDI	Drug-drug interaction
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
eCRF	Electronic case report form
eDiary	Electronic diary
EMA	European Medicines Agency
EOS	End-of-Study
EOTP	End-of-Treatment Period
EQ-5D-3L	European Quality of Life 5 Dimensions 3 Level Version
EU	European Union
F	Forbidden
FAS	Full analysis set
FDA	Food and Drug Administration (US)
GCP	Good Clinical Practice
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
ICIQ	International Consultation on Incontinence Questionnaire
ICIQ-FLUTS	ICIQ female lower urinary tract symptoms
ICIQ-MLUTS	ICIQ male lower urinary tract symptoms
ICIQ-NQoL	ICIQ Nocturia Quality of Life

ICSmaleSF	International Continence Society male Short Form
IDMC	Independent Data Monitoring Committee
IDSIQ	Insomnia Daytime Symptoms and Impacts Questionnaire
IEC	Independent ethics committee
IMP	Investigational Medicinal Product
IRB	Institutional review board
IRT	Interactive Response Technology
ISF	Investigator Site File
ISI©	Insomnia Severity Index©
LS Mean	Least squares mean
LUTS	Lower urinary tract symptoms
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed model for repeated measures
NRS	Numeric Rating Scale
OX_1	Orexin-1
OX_2	Orexin-2
PEOT	Premature End-of-Treatment
PGA-S	Patient Global Assessment of Disease Severity
PGI-C	Patient Global Impression of Change
PPS	Per-protocol set
PRO	Patient-reported outcome
R	Restricted
REM	Rapid eye movement
RND	Randomized analysis set
SAE	Serious adverse event
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SCR	Screened analysis set
SD	Standard deviation
SDQ	Sleep Diary Questionnaire
SmPC	Summary of Product Characteristics

SOC	System Organ Class
sTST	Subjective total sleep time
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event
UNS	Unscheduled visit
US	United States
VAS	Visual analog scale

SUBSTANTIAL GLOBAL AMENDMENT 2

Amendment rationale

This amendment applies to global protocol ID-078A401 Version 2, dated 5 April 2023. The resulting amended global protocol is Version 3 dated, 4 September 2023.

The main reason for this global amendment is to provide clear instructions to the investigator for the immediate discontinuation of study treatment upon the occurrence of complex sleep behaviors. This protocol amendment is based on post-marketing reports from the US and EU of patients treated with daridorexant who experienced complex sleep behaviors. The amendment aims at minimizing the risk for subjects in this study.

In addition, Appendices 12 to 14 related to the treatment satisfaction and treatment period preference questionnaires, and the narrative text about the impact of insomnia and nocturia on daily life according to the patient have been included. These have been incorporated solely for completeness and do not represent new assessments within this study. Furthermore, minor editorial changes have also been made and typographical errors corrected.

Amended protocol sections

Two versions of the amended protocol will be prepared: 1) a clean version and 2) a Word comparison document showing deletions and insertions in comparison to the previous protocol version.

The main sections of the protocol affected by this global amendment are listed below. Where applicable, the same changes have also been made to the corresponding sections of the protocol synopsis [Section 1.1]:

5.9.1	Study treatment interruption and premature discontinuation of study treatment
Appendix 12	Treatment satisfaction questionnaire
Appendix 13	Treatment period preference questionnaire
Appendix 14	Narrative

Summary of previous amendments

Amendment	Date	Main reason(s)
EU.A	31 Jan 2023	Clarification on eligibility and study interruption/discontinuation criteria
USA.A	22 Feb 2023	Clarification on eligibility criteria and introduction of AESIs
1	5 Apr 2023	Summarizing local protocols into global protocol

1 PROTOCOL SUMMARY

1.1 Protocol synopsis ID-078A401

TITLE	A multi-center, double-blind, randomized, placebo-controlled, 2-way cross-over post approval study to investigate the efficacy of daridorexant in subjects with insomnia and comorbid nocturia
OBJECTIVES	**Efficacy objectives** The primary objective of this study is to assess the efficacy of daridorexant on insomnia in subjects with insomnia and comorbid nocturia. The following variables will be evaluated: a) Quantitative measure of subjective total sleep time (sTST) by the Sleep Diary Questionnaire (SDQ). b) Overall rating of the insomnia severity by the Insomnia Severity Index© (ISI©). c) Other SDQ-derived variables: (i) quality of sleep visual analog scale (VAS), (ii) depth of sleep VAS, (iii) daytime alertness VAS, (iv) daily ability to function VAS, and (v) number of awakenings. The secondary objective is to assess the efficacy of daridorexant on nocturia. There is no data for daridorexant in subjects with insomnia and comorbid nocturia. The following variables will be evaluated: a) Voiding diary-derived assessments: (i) time to the first nocturnal void, (ii) each voiding volume (nighttime and daytime) including total volume, (iii) number of nocturnal voids. b) Lower urinary tract symptoms (LUTS) sub-score using the International Consultation on Incontinence Questionnaire (ICIQ) -MLUTS and -FLUTS for male and female subjects, respectively. c) Quality of life relative to nocturia, assessed by ICIQ Nocturia Quality of Life (ICIQ-NQoL).

	Other objectives will focus on subject's overall assessment ratings of their condition and symptoms including: a) Patient Global Assessment of Disease Severity and Patient Global Impression of Change for insomnia and for nocturia. b) Quality of life using the European Quality of Life 5 Dimensions 3 Level Version (EQ-5D-3L). c) Overall assessment of subjective treatment satisfaction by numeric rating scale. d) Subject preference for treatment. In addition to efficacy and safety, the following exploratory efficacy endpoints will be studied: a) The sensitivity of the Insomnia Daytime Symptoms and Impacts Questionnaire to detect clinical changes in this study population, b) The use of narratives to report subject's perception of treatment effect. **Safety objectives** The safety objectives will be to assess the safety and tolerability of daridorexant based on: a) Adverse event (AE) reporting b) Occurrence of suicidal ideation, suicidal behavior, and/or self-injurious behavior with/without suicidal intent based on the Columbia Suicide Severity Rating Scale© (C-SSRS©) c) Morning sleepiness as determined by morning sleepiness VAS.
DESIGN	Multi-center, double-blind, randomized, placebo-controlled, 2-way cross-over, post-approval study. The study consists of 2 treatment periods (I and II) of 29 days each, separated by a 14–21 day washout period.
ENDPOINTS	**Primary efficacy endpoint** • Change from baseline to Week 4 in sTST in each treatment period

	Baseline is the mean value based on the screening sleep diary for sTST, which must be performed on each of the 7 days preceding Randomization. Week 4 is the mean value based on the sleep diary entries for sTST performed on study days 23–29 of each period. **Other efficacy endpoints** Other endpoints are listed in the main body of the protocol. **Safety endpoints** Safety monitoring will include: • Occurrence of treatment-emergent AEs up to 5 days after End-of-Treatment Period I (EOTP I) and/or End-of-Treatment Period II (EOTP II). • Occurrence of treatment-emergent AESIs up to 5 days after EOTP I and/or EOTP II. • Occurrence of treatment-emergent serious AEs up to 5 days after EOTP I and/or EOTP II. • Occurrence of treatment-emergent AEs leading to premature discontinuation of the study and/or treatment. • Change from baseline to EOTP I and EOTP II in vital signs (systolic blood pressure, diastolic blood pressure, and pulse rate). • Change from baseline to EOTP I and EOTP II in morning sleepiness as determined by the scores on the VAS in the morning. • Occurrence of suicidal ideation, suicidal behavior, and/or self-injurious behavior with / without suicidal intent based on the C-SSRS© at Visit 1, Visit 4, Visit 5, Visit 8, and Visit 9.
PERIODS	**Screening period:** Starts with the full signature of the informed consent form (ICF) at Visit 1 and lasts 14–21 days. All baseline assessments as well as eligibility checks will be done during this period. **Treatment period (Periods I and II):** Randomization will take place on Day 1 (Visit 2) after confirmation that all eligibility criteria have been met, prior to the first study drug

	administration of Treatment Period I. The double-blind cross-over phase will consist of 2 treatment periods of 29 days ± 2 days each that are separated by a washout period of 14–21 days. EOTP I and EOTP II is reached on the morning after the last treatment intake in the evening of the respective treatment period. Each subject will be randomized in a 1:1 ratio to one of the two treatment sequences defined as: • Treatment A: 50 mg daridorexant followed by treatment B: Placebo • Treatment B: Placebo followed by treatment A: 50 mg daridorexant **Follow-up and washout period:** The follow-up period to detect any safety events related to the cessation of study treatment starts after completion of the EOTP I and EOTP II visit of each treatment period (I and II) and lasts for 5–10 days. For Period I the washout period and follow-up period overlap for 5–10 days, followed by an additional 9–16 days of washout, before entering Treatment Period II. The End-of-Study (EOS) visit will be completed by phone.
PLANNED DURATION	The global end-of-study is defined as completion of the last subject's EOS phone call. The study is expected to last approximately 15 months.
SITES / COUNTRIES	The study will be conducted at approximately 20 sites in 3 countries.
SUBJECTS / GROUPS	Approximately 50 subjects aged ≥ 55 years will be randomized (i.e., enrolled) in a 1:1 ratio to either sequence. No stratification will be applied.
INCLUSION CRITERIA	1. Signed and dated ICF prior to any study-mandated procedure. 2. Male or female subjects ≥ 55 years old at the time of signing the ICF. 3. Insomnia complaints for at least 3 months prior to Visit 1

	4. ISI© score ≥ 13 at Visit 1. *Note: An ISI© score of ≥ 13 is considered appropriate as it represents a score suggesting subthreshold to moderate insomnia. The wide range of ISI© scores between the different insomnia categories indicates that the scores are to be considered as a guidance only. In this study, a score of at least 13 is adequate to detect clinically relevant insomnia.* 5. Diagnosis of nocturia as per International Continence Society: • Waking to pass urine during the main sleep period. • The first nocturia episode must be preceded by sleep. Subsequent nocturia episodes must be followed by the intention of getting back to sleep. 6. Nocturia severity: on average ≥ 3 nocturnal voidings per night reported by the subjects for at least 1 month prior to Visit 1. *Note: ≥ 2 voidings per night have been reported to be clinically relevant. The threshold set in this study is to capture a more severe population that is bothered by their frequent nocturia episodes.* 7. Average ≥ 2.6 nocturia episodes reported on the bladder diary per night over a period of 3 consecutive nights following Visit 1. None of the 3 nights can have less than 2 voidings. *Note: Given the night-to-night variability that can be observed in the number of nocturia episodes, this threshold allows to include a population that suffers from clinically relevant nocturia episodes.* 8. Ability to communicate well with the investigator, to understand the study requirements, and judged by the investigator to be alert and oriented to person, place, time, and situation.

EXCLUSION CRITERIA	1. Woman of childbearing potential, pregnant, or planning to become pregnant. *Note: A woman is considered of childbearing potential, i.e., fertile, following menarches and until becoming post-menopausal unless permanently sterile.* 2. Planned travel across ≥ 3 time zones during study. *Note: It is expected that by changing time zones subject's sleep will be impaired.* 3. Any of the following conditions related to suicidality: • Any suicidal ideation with intent, with or without a plan, at Screening, i.e., answering "Yes" to questions 4 or 5 on the suicidal ideation section of the lifetime (screening visit) version of the C-SSRS©. • History of suicide attempt on the suicidal behavioral section of the lifetime version of the C-SSRS© (screening visit). *Note: As with many hypnotics, suicidal thoughts and actions may occur especially in those with a history of them. For that purpose, these subjects will be excluded from the study* 4. Regular caffeine consumption after 4 pm. *Note: Caffeine consumption may interfere with sleep and nocturia assessments.* 5. Unable to refrain from smoking during the night. *Note: Heavy smoking may interfere with sleep and nocturia assessments.* 6. Known and documented diagnosis of narcolepsy, periodic limb movement disorder, moderate to severe obstructive sleep apnea, restless legs syndrome, circadian rhythm sleep-wake disorder, or rapid eye movement (REM) sleep behavior disorder. *Note: Daridorexant is contraindicated in narcoleptic subjects. The occurrence of other sleep disorders may interfere with the efficacy and safety assessments.* 7. Known and documented diagnosis of Type 1 diabetes mellitus, uncontrolled Type 2 diabetes mellitus, central

	or nephrogenic diabetes insipidus, and primary/secondary polydipsia within the last 6 months prior to Visit 1. *Note: Conditions that manifest with the symptoms of large intake of fluids may suggest the presence of other underlying diseases that need appropriate medical attention. The investigator must certify the absence of these conditions.* 8. Known and documented nocturia linked to urinary tract infection, neoplasms of bladder, prostate or urethral cancer, bladder or urethral calculi, or neurogenic voiding dysfunction within the last 6 months prior to Visit 1. *Note: These conditions are known to cause nocturia for a limited time period and/or are not expected to remain stable during the duration of the study and may interfere with the efficacy and safety assessments. The investigator must certify the absence of these conditions.* 9. Any signs or symptoms of active, ongoing infection judged to be clinically relevant by the investigator. *Note: Investigators should not screen subjects if an ongoing infectious disease is suspected.* 10. Known and documented diagnosis of severe compromised respiratory function (e.g., chronic obstructive pulmonary disease). *Note: See the Summary of Product Characteristics (SmPC) or the Investigator's Brochure (IB).* 11. Known and documented moderate to severe hepatic impairment. *Note: Daridorexant is not recommended in subjects with severe hepatic impairment, while subjects with moderate hepatic impairment require a dose adjustment which is not allowed in this study. In accordance with the EU SmPC or IB, the investigator must certify the absence of these conditions and may refer to local laboratory testing.* 12. Known hypersensitivity to the investigational treatment, any of its excipients or drugs of the same class.

	13. Treatment with forbidden medications including moderate or strong Cytochrome P450 (CYP) 3A4 inhibitors and inducers within 2 weeks or 5 half-lives (whichever is longer) prior to Visit 2. *Note: As per daridorexant label, 50 mg daridorexant must not be taken if co-administered with moderate to strong CYP3A4 inducers or inhibitors. This includes other medication that could interfere with the efficacy or safety assessment. See the SmPC or IB. Background treatment of nocturia is allowed if started prior to entering the study, is considered to remain stable during the study and does not meet the criteria for forbidden medication.* 14. Treatment with another investigational treatment or participation in another clinical trial up to 3 months prior to Visit 2. 15. Any known factor or disease that might interfere with treatment compliance, study conduct, or interpretation of the results, such as drug or alcohol dependence or psychiatric disease. 16. Known concomitant life-threatening disease with a life expectancy < 12 months. *Note: The cross-over study design is only applicable for chronic and stable diseases that are expected to be comparable during the different study periods.* 17. Ongoing cognitive behavioral therapy for insomnia at Visit 1 or planned start during the study.
STUDY TREATMENTS	**Investigational treatment and matching placebo description** Daridorexant is available as oral film-coated tablets at a strength of 50 mg. Daridorexant-matching placebo is provided as identically looking oral tablets, formulated with the same inactive ingredients (excipients) as the active tablets.

	After randomization, daridorexant or matching placebo will be taken orally, once daily in the evening within approximately 30 min before going to bed. Missed doses must not be replaced and the subject must continue with the regular treatment on the next evening
STATISTICAL METHODOLOGY	**Analysis sets** ***Randomized analysis set (RND)*** The RND includes all subjects who have been assigned to double-blind study treatment. ***Full analysis set (FAS)*** The FAS includes all subjects from the RND who received at least one dose of double-blind study treatment. To adhere to the intention-to-treat principle: • Subjects will be evaluated according to their assigned study treatment, which may differ from the treatment they have received. • Unless otherwise stated, all available data will be included in analyses. The FAS will be used for analyses of the primary endpoint and all exploratory efficacy endpoints. ***Per-protocol set (PPS)*** The PPS includes all subjects from the FAS without important protocol deviations, occurring prior to Week 4, which could affect the analysis of the primary endpoint variable. The precise reasons for excluding subjects from the PPS will be fully defined and documented in the statistical analysis plan before breaking the randomization blind. ***Safety set*** The Safety set will include all subjects who received at least one dose of double-blind study treatment. Subjects will be analyzed based on the treatment received (in each period). The Safety set will be used for the analysis of safety

	endpoints (including previous and concomitant medications, and study treatment exposure). **Description of statistical analyses** All available data for each subject will be used in all statistical analyses, unless otherwise specified. **Analysis of the primary estimand based on the primary efficacy endpoint** The primary efficacy endpoint of this study is defined as the change from Baseline to Week 4 in sTST. The primary estimand follows a 'treatment policy' strategy for intercurrent events. Baseline is the mean value based on the screening sleep diary for sTST, performed on the 7 days preceding Randomization. Week 4 is the mean value based on the sleep diary entries for sTST performed on study days 23–29 for each period. Data after the EOTP I/II visits will not be included in the analysis, as subjects are expected to be on double-blind treatment up to that point. Changes from baseline to post-baseline visits in sTST will be analyzed using a mixed model for repeated measures (MMRM) with change from baseline in sTST as response, treatment group (daridorexant 50 mg; placebo), period (Period I; Period II), and week within period (Week 1, Week 2, Week 3, Week 4) as factors, baseline sTST assessment as covariate, and the interaction of treatment group × week. Each weekly average for Weeks 1–3 will be included in the MMRM and computed following the same approach as for Week 4. To evaluate the efficacy hypotheses, the difference in least squares mean change from baseline between daridorexant 50 mg and placebo at Week 4 will be estimated from the MMRM. An unstructured covariance matrix will be used to account for the correlation between repeated measurements from the same subject.

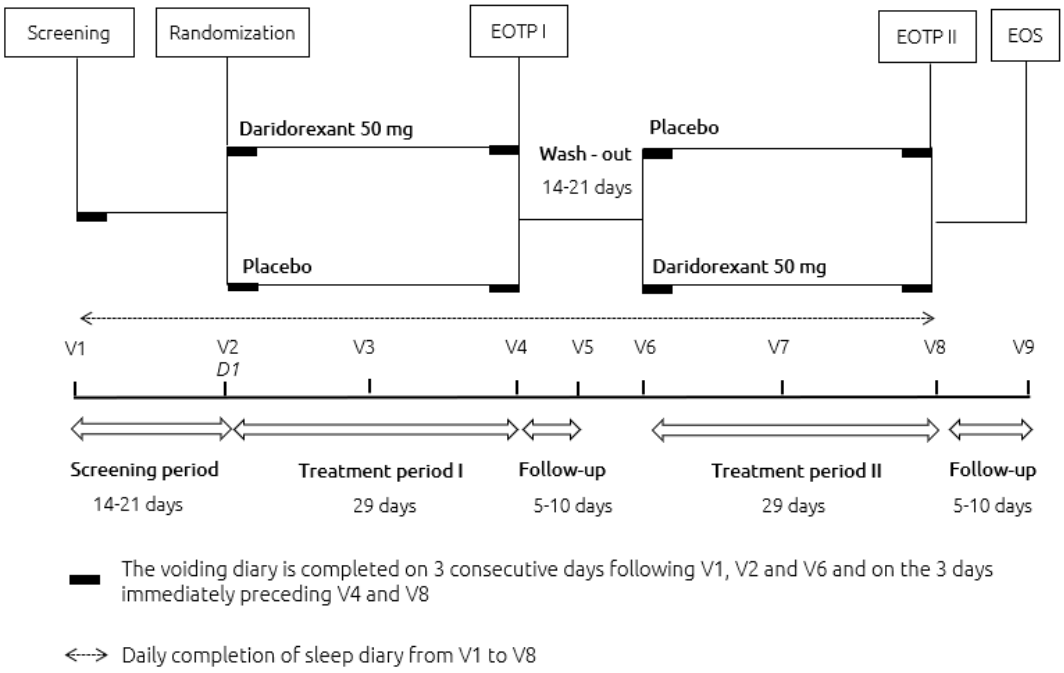
	Hypotheses for the primary endpoint are defined as follows: • H_0: Mean of the within-subject changes in sTST from baseline to Week 4 between daridorexant 50 mg and placebo = 0 • H_1: Mean of the within-subject changes in sTST from baseline to Week 4 between daridorexant 50 mg and placebo ≠ 0 **Sample size estimation** The assumptions for the sample size calculations were determined using data from studies ID-078A202 and ID-078A301 for the treatment groups daridorexant 50 mg and placebo. Data of sTST changes from baseline and the corresponding standard deviations (SDs) were derived based on simulations using sTST data at Baseline and at Month 1 from the ID-078A301 study for the age group ≥ 55 years. Subsets of 50 subjects were randomly selected from both the daridorexant 50 mg and placebo groups and compared via t-tests for independent samples, with means and SDs averaged across 1000 iterations. The simulations resulted in a mean difference of the change from baseline to Month 1 in sTST of 26 min for daridorexant 50 mg and placebo, with SDs of 42.5 min for placebo and 50.5 min for daridorexant 50 mg. Correlations between daridorexant 50 mg and placebo for sTST data were derived based on the cross-over study ID-078A202 (based on subjects aged ≥ 65 years). The Pearson correlation coefficient was estimated at 0.58. Combining all the information above resulted in an SD of the difference in the change of sTST from baseline to Month 1 of 44 min (based on the variance/covariance formula). Based on a two-sided type I error of 0.05, an estimated within-subject mean difference of the change from baseline to Month 1 in sTST between daridorexant 50 mg and placebo of 26 min and an associated SD of 44 min, a total sample size of 50 subjects, in this cross-over setting, provides at least 90% power, based on a two-sided paired

	t-test. A smaller within-subject mean difference between daridorexant 50 mg and placebo of 20 min would still result in a power of at least 80%.

1.2 Schema

The overall study design is depicted in Figure 1.

Figure 1 Study design



D = Day; EOS = End-of-Study; EOTP = End-of-Treatment Period; V = Visit.

1.3 Schedule of activities

The visit schedule and protocol-mandated activities are performed according to the schedule of activities [Table 1] and are described in Section 7 and Sections 3.2 and 3.3.

Table 1 Schedule of activities

PERIODS	Name	SCREENING PERIOD	TREATMENT PERIOD I			Washout		TREATMENT PERIOD II				FOLLOW-UP
	Duration	14–21 days	29 ± 2 days			14–21 days		29 ± 2 days				5–10 days
VISITS	Number	1	2	3	4*/ EOTP I	5	-	6	7	8*/ EOTP II	PEOT**	9/EOS
	Name	Screening Visit	Randomization	Phone call	End of treatment Period I	Safety Follow-up Phone call			Phone call	End of treatment Period II	Premature End-of-Treatment	Phone call
	Time window	Day −14 to Day −1	Day 1	Day 14 ± 2 days	Day 29 ± 2 days	5 - 10 days after EOTP visit		Day 1	Day 14 ± 2 days	Day 29 ± 2 days	1 - 5 days after last study treatment intake	5 - 10 days after EOTP visit
Informed consent		X										
Contact IRT		X	X		X			X		X	X[3]	
Demographics		X										
Eligibility		X	X[2]									
Medical history		X										
Previous/concomitant therapy		X	X[2]	X[4]	X	X[4]		X	X[4]	X	X[3]	X[4]
Vital signs (BP, PR)		X			X					X	X[3]	
C-SSRS©		X			X	X[4]				X	X[3]	X[4]
Sleep diary including VAS[6]		←	—	—	—	—		—	—	—	→	
ISI©		X		X[4]	X				X[4]	X		
IDSIQ[8]		←	—	—	—	—		—	—	—	→	
Voiding Diary[7]		X	X		X			X		X		
PGA-S[5]		X	←	—	→			←	—	→		
PGI-C daytime symptoms [5]			←	—	→			←	—	→		
PGI-C nighttime symptoms[5]			←	—	→			←	—	→		
PGA-S (daily life)		X			X					X		

PERIODS	Name	SCREENING PERIOD	TREATMENT PERIOD I			Washout		TREATMENT PERIOD II				FOLLOW-UP
	Duration	14–21 days	29 ± 2 days			14–21 days		29 ± 2 days				5–10 days
VISITS	Number	1	2	3	4*/ EOTP I	5	-	6	7	8*/ EOTP II	PEOT**	9/EOS
	Name	Screening Visit	Randomization	Phone call	End of treatment Period I	Safety Follow-up Phone call			Phone call	End of treatment Period II	Premature End-of-Treatment	Phone call
	Time window	Day −14 to Day −1	Day 1	Day 14 ± 2 days	Day 29 ± 2 days	5 - 10 days after EOTP visit		Day 1	Day 14 ± 2 days	Day 29 ± 2 days	1 - 5 days after last study treatment intake	5 - 10 days after EOTP visit
PGI-C (daily life)					X					X		
Nocturia Quality of Life (ICIQ-NQoL)		X			X					X		
ICIQ-MLUTS/FLUTS[9]		X			X					X		
EQ-5D-3L		X		X	X				X	X		
Treatment satisfaction					X					X	X[3]	
Treatment period preference										X	X[3]	
Narrative		X			X					X	X[3]	
Study treatment dispensing/return			X		X			X		X	X[3]	
Study drug intake			←	—	→			←	—	→		
Treatment accountability					X					X	X[3]	
SAEs/AEs[1]		←										→

[1] All AEs and SAEs that occur after signing the ICF and up to 5–10 days after study treatment discontinuation must be reported [see also Section 8.1 and 8.2].
[2] Must be done before randomizing the subject.
[3] Only applicable for subjects who prematurely discontinued study treatment. All subjects withdrawn from study treatment will be encouraged to follow planned study procedures (e.g., visits, diary and questionnaire completion until planned EOS visit) provided that the subject's consent for this limited participation in the study has not been withdrawn.
[4]Will be completed by phone call.
[5]PGA-S and PGI-C (daytime symptoms and nighttime symptoms questionnaires) will be completed at home once a week between Visit 2 and Visit 8. The patient global scales are completed on the same days.
[6]The hand-held device is handed out to the subject and completed at home daily from Visit 1 to Visit 8.

[7]The voiding diary must be completed by the subjects for 3 consecutive days and nights after the Visit 1, Visit 2 and Visit 6 as well as for 3 consecutive days and nights immediately preceding Visit 4 and Visit 8, respectively [see Table 2]. The investigator should plan the completion of the diary according to the visit schedule.
[8]The IDSIQ will be administered from Visit 1 to Visit 8 and completed daily.
[9]The ICIQ-MLUTS will only be given to male subjects, while females will receive the ICIQ-FLUTS.
*The site will contact the subject to remind him/her to complete the voiding diary for 3 consecutive days preceding the EOTP visit.
** The subject will be asked to return for a PEOT visit within 5 days of last intake of study treatment and thereafter to attend the following visits up to the respective EOTP visit.

AE = adverse event; BP = blood pressure; C-SSRS© = Columbia Suicide Severity Rating Scale©; EOS = End-of-Study; EOTP = End-of-Treatment Period; EQ-5D-3L = European Quality of Life 5 Dimensions 3 Level Version; ICF = informed consent form; ICIQ-MLUTS/FLUTS = International Consultation on Incontinence Questionnaire (male/female) lower urinary tract symptoms; IDSIQ = Insomnia Daytime Symptoms and Impacts Questionnaire; IRT = Interactive Response Technology; ISI© = Insomnia Severity Index©; PEOT = Premature End-of-Treatment; PGA-S = Patient Global Assessment of Disease Severity; PGI-C = Patient Global Impression of Change; PR = pulse rate; SAE = serious adverse event; VAS = visual analog scale.

Table 2 Recommended schedule for completion of Minze Diary Pod during the Screening Period

Visit 1 Screening Visit Day −14	Day −13	Day −12	D -11	Day −10	Day −9	Day −8	Day −7	Day −6	Day −5	Day −4	Day −3	Day −2	Day −1
	X	X	X										

Schedule for completion of Minze Diary Pod for Visits 2, 4, 6 and 8

Visit 2 / Visit 6 Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Visit 3 / Visit 7 Day 14	Day 15	Day 16	Day 17	Day 18	Day 19	Day 20	Day 21	Day 22	Day 23	Day 24	Day 25	Day 26	Day 27	Day 28	Visit 4 / Visit 8 Day 29
	X	X	X																						X	X	X	

2 INTRODUCTION

2.1 Insomnia and comorbid nocturia

2.1.1 Definition

Insomnia and nocturia show an increased prevalence with age, and both conditions show similar impairments of daytime functioning (excessive daytime sleepiness, fatigue, concentration deficits) and an increased risk of falls and injuries.

Insomnia is often assessed using the ISI©, which uses a 5-point Likert scale to assess the severity of sleep onset, sleep maintenance and early morning awakening problems, sleep dissatisfaction, as well as the interference with daytime functioning and quality of life. Using the ISI© total score, insomnia can be grouped into 4 categories: 0–7, 8–14, 15–21, and 22–28 for no clinically significant insomnia, subthreshold insomnia, moderate insomnia, and severe insomnia, respectively.

Nocturia is defined by the International Continence Society as waking at least once nightly to void, where the first void must be preceded by sleep and all subsequent voidings must be followed by the intention of getting back to sleep [Van Kerrebroeck 2002].

Patients suffering from nocturia are confronted with nocturnal awakenings that may result in severe sleep disruption including difficulties maintaining sleep, as well as difficulties falling back asleep after getting up for voiding. This condition not only affects sleep at night but continues to negatively impact the daytime functioning of affected patients by causing excessive daytime sleepiness and reducing productivity [Ohayon 2008, Miller 2016]. In fact, nocturia has been identified as an independent predictor of insomnia where increasing number of voiding episodes have been associated with worsened sleep disruptions and reduced quality of life [Asplund 1992, Yu 2006, Bliwise 2009].

2.1.2 Current treatment strategies

Despite the high prevalence of sleep disruptions in patients suffering from nocturia, only a limited number of studies have investigated the effect of sleeping agents and these studies are limited by low sample sizes and lack of placebo arms. Nevertheless, these studies suggest that treatment of the sleep disorder in patients with nocturia may improve both conditions. The combination of tamsulosin and zolpidem reduced nocturia episodes better than tamsulosin alone, and at the same time improved sleep disturbances [Miwa 2011]. Nocturia may be improved by lifestyle and behavioral modification such as reducing caffeine intake, reducing fluid intake before bedtime, and restriction of alcohol intake. If behavioral modifications do not adequately improve the condition, pharmacological treatments of underlying causes focus on improving nocturnal bladder storage capacity and increasing the volume at which bladder activity is elicited and/or aim at decreasing urine production at night. It should not be forgotten that the multifactorial nature of nocturia

usually requires the tailored treatment of the underlying cause. Therefore, a variety of pharmacological therapies are used in clinical practice, including; muscarinic receptor antagonists, β_3-adrenoceptor antagonists (mirabegron), α1-adrenoreceptor antagonists, 5α-reductase inhibitors, phosphodiesterase type 5 inhibitors, and various natural products. In nocturia associated with nocturnal polyuria (increased urine production), treatment with an antidiuretic, such as desmopressin acetate is warranted to counteract the insufficient secretion of arginine vasopressin during the night, therefore inducing antidiuresis. Diuretics, alone or in combination with desmopressin, can also be used in the treatment of nocturia with the rationale of reducing salt and water load in the body prior to bedtime (e.g., given 6 h before sleep) [Reynard 1998, Fu 2011, Oelke 2017, Weiss 2019].

Non-pharmacological CBT-I is generally the recommended first-line treatment for insomnia [Schutte-Rodin 2008]. However, this may not be the ideal treatment for all patients. Many patients with insomnia are not interested in CBT, and when they are, access to CBT may be limited by the lack of therapists with adequate training and experience, and the fact that CBT is time-consuming, costly, and its reimbursement challenging [Pigeon 2007, Schutte-Rodin 2008]. Furthermore, pharmacological treatments that address sleep onset problems alone do not provide relief to people with sleep maintenance difficulties, and treatments indicated for those with sleep maintenance problems may be associated with risks of cognitive impairment, postural instability, or next-day residual sedation that may impair driving [Neubauer 2014]. Moreover, the use of benzodiazepines and benzodiazepine receptor agonists is associated with an increased risk of falling [McCall 2004] leading to hip and femur fractures, increased disability, and use of healthcare resources. This suggests that current pharmacological interventions have a significant potential to impair motor and cognitive functions and are of specific safety concern to the nocturia population experiencing multiple awakenings during the night. Additionally, current treatment options for insomnia have failed to show an improvement on daytime functioning, despite the importance of daytime symptoms to patients with insomnia. This is especially relevant to nocturia as these patients often report daytime sleepiness [Shao 2016]. Daridorexant may close this gap by offering a safe and effective solution to patients with frequent nighttime awakenings.

Therefore, there is a need for a pharmacological treatment with favorable benefit/risk profile supported by an adequate, controlled clinical study in subjects with insomnia with associated nocturia and different underlying medical conditions.

2.2 Daridorexant

Daridorexant is a potent and selective orexin receptor antagonist that blocks the actions of the orexin neuropeptides at both OX_1 and OX_2 receptors. The orexin system is involved in the regulation of sleep and arousal and is targeted in the development of new therapies for sleep disorders in adult and elderly subjects. Daridorexant has been approved in the US,

EU, United Kingdom, Iceland, Norway, Switzerland, and Liechtenstein for the treatment of adult patients with insomnia.

The human clinical experience with daridorexant to date consists of:

- Twenty completed Phase 1 studies [Daridorexant IB].
- Two completed Phase 2 studies in subjects with insomnia disorder in 360 adults and 58 elderly subjects, respectively [Dauvilliers 2020, Zammit 2020].
- Three completed Phase 3 studies in adult and elderly subjects with insomnia disorder. ID-078A301 and ID-078A302 were conducted in 930 and 924 subjects, respectively [Mignot 2022]. ID-078A303 consisted of a common extension to both pivotal studies in which 804 subjects were included.

For additional information please refer to the IB [Daridorexant IB] or the EU SmPC [QUVIVIQ™ SmPC][1].

2.3 Study rationale

Daridorexant at a dose of 50 mg has been proven safe and efficacious in the treatment of adult and elderly subjects with insomnia disorder [Daridorexant IB], showing benefits in improving sleep onset and sleep maintenance, as well as daytime functioning, with the latter two being the most frequent complaints observed in patients suffering from insomnia and having associated nocturia. In addition, daridorexant was shown to be devoid of morning or even daytime somnolence effects, as compared to placebo. This leads to the assumption that daridorexant may be ideal in targeting some of the key symptoms observed in subjects with insomnia and comorbid nocturia.

The potential effect of daridorexant on nocturia will be assessed for the first time in this study. A few studies in older adults reported that behavioral treatments and gamma-aminobutyric acid receptor agonists for sleep disruptions resulted in better clinical outcomes in these patients, by improving both their sleep and nocturia symptomatology and their quality of life [Miwa 2011, Tyagi 2014]. The hypothesis is that nocturia may be partly a consequence of sleep disruption; the urge to urinate may become evident in these patients due to prolonged awakening during the night; thus, an effective treatment for insomnia could also improve nocturia. In the same vein, some literature suggests that sleep disorders play an important role in the severity of nocturia [Konishi 2021]. However, nocturia may also be the cause of poor sleep [Bliwise 2009].

[1] QUVIVIQ is a trademark of Idorsia Pharmaceuticals Ltd which is registered in a number of countries.

2.4 Benefit/risk assessment

2.4.1 Clinical trial

With the participation in this clinical trial subjects will receive an approved treatment that has been proven safe and efficacious for the treatment of insomnia, thus potentially providing a benefit for both their sleep problems and the impairment of their daytime activities. Furthermore, subjects enrolled in this study will contribute to the research into and understanding of the link between insomnia and frequent nocturia. Importantly, with the implemented cross-over design, all subjects will be exposed to an active treatment (i.e., 50 mg daridorexant) at one point in the study, which will translate into a potential benefit for all participants. On the other hand, in the cross-over design, it is critically important that subjects are willing to remain in the study for its entire duration to limit the amount of missing data and ensure a fair comparison between the new treatment and placebo through objective and subjective endpoints. As with every clinical study, the clinical efficacy and safety in this specific population, despite the well-established profile of daridorexant in insomnia, remain unknown. It is therefore the responsibility of the investigator to ensure that the subjects are informed about the benefits and risks of participating in this study during the informed consent process, as well as the importance of their commitment to remain in the study until their EOS visit.

2.4.2 Daridorexant

Based on the mechanism of action of daridorexant, nonclinical data, and results from the Phase 1, 2, and 3 studies in adults and elderly subjects, an increased total sleep time, a decrease in wakening after sleep onset, a shortened latency to sleep onset as well as improved daytime functioning are anticipated without rebound effects / withdrawal symptoms upon treatment cessation.

Daridorexant metabolism is mainly dependent on CYP3A4, therefore, co-administration of moderate and strong CYP3A4 inducers or inhibitors must be avoided.

Additional information can be found in the IB [Daridorexant IB] or in the EU SmPC [QUVIVIQ™ SmPC].

2.4.3 Safety and risk-minimization included in this study

The most frequent TEAEs for daridorexant (reported in at least 2% of subjects treated with daridorexant with a ≥ 1% difference to subjects receiving placebo during the adult Phase 3 program) were headache, somnolence, fatigue, dizziness, and nausea.

Risk of suicidality will be assessed at Visit 1, Visit 4, Visit 5, Visit 8, Visit 9 and PEOT using the C-SSRS©. At Screening (Visit 1), the C-SSRS© will inquire about the subject's lifetime state, and all other visits will refer to the time elapsed since the previous visit. Participants who demonstrate any suicidal ideation, suicidal behavior, and/or self-injurious

behavior without suicidal intent at any time during the study must be referred to the investigator for follow-up evaluation.

The risk of falls is known to be increased in elderly subjects compared to younger adults, regardless of treatment. Falls may happen when subjects wake up and go to the bathroom. However, in the Phase 3 clinical trials, daridorexant was not associated with an increase of falls compared to placebo, including at a dose of 50 mg daridorexant in the elderly population. Subjects will be informed of the potential risk of fall, and this risk will be carefully monitored by the investigator and by the sponsor.

It is the investigator / authorized delegate's responsibility to monitor the benefit/risk ratio of study treatment administration, as well as the degree of distress caused by study procedures on an individual subject level, and to discontinue study treatment or the study if, on balance, he/she believes that continuation would be detrimental to the subject's well-being.

3 STUDY OBJECTIVES AND ENDPOINTS

3.1 Objectives

The overall objective of this study is to explore the clinical efficacy of daridorexant and to further evaluate its safety and tolerability in subjects with insomnia and comorbid nocturia.

Based on the mode of action of daridorexant and the knowledge acquired during its development, it is reasonable to identify the following objectives to be explored in this study:

Efficacy objectives

The primary objective of this study is to assess the efficacy of daridorexant on insomnia in subjects with insomnia and comorbid nocturia. The following variables will be evaluated:

a) Quantitative measure of sTST by the SDQ.
b) Overall rating of the insomnia severity by the ISI© with a recall period of 2 weeks.
c) Other SDQ-derived variables: (i) quality of sleep VAS, (ii) depth of sleep VAS, (iii) daytime alertness VAS, (iv) daily ability to function VAS, and (v) number of awakenings.

The secondary objective is to assess the efficacy of daridorexant on nocturia. There is no data for daridorexant in subjects with insomnia and comorbid nocturia. The following variables will be evaluated:

a) Voiding diary derived assessments: (i) time to the first nocturnal void, (ii) each voiding volume (nighttime and daytime) including total volume, (iii) number of nocturnal voids.

b) Lower urinary tract symptoms sub-score using the ICIQ-MLUTS and -FLUTS for male and female subjects, respectively.
c) Quality of life relative to nocturia assessed by ICIQ-NQoL.

Other objectives will focus on patient's overall assessment ratings of their condition and symptoms including:

a) PGA-S and PGI-C for insomnia and for nocturia.
b) Quality of life using the EQ-5D-3L.
c) Overall assessment of subjective treatment satisfaction by NRS.
d) Subject preference for treatment.

In addition to efficacy and safety this study the following exploratory efficacy endpoints will be studied a) the sensitivity of the IDSIQ to detect clinical changes in this study population, and b) the use of narratives to report subject's perception of treatment effect.

Safety objectives

The safety objectives will be to assess the safety and tolerability of daridorexant based on:

a) AE reporting.
b) Occurrence of suicidal ideation, suicidal behavior and/or self-injurious behavior with/without suicidal intent based on the C-SSRS©.
c) Morning sleepiness as determined by morning sleepiness VAS.

3.2 Efficacy assessments and time points

3.2.1 SDQ [Appendix 2]

The sleep diary includes a morning and evening questionnaire and four VASs related to the efficacy assessments (and a fifth VAS to collect morning sleepiness, described below in the safety assessment Section 3.3.2). The morning and evening questionnaires collect information on self-reported sleep characteristics (e.g., sTST and other sleep quantitative characteristics), napping, bedtime, and timing of study treatment intake. The VAS collects information on quality of sleep, depth of sleep, daytime alertness, and daytime ability to function by asking the subjects to report their feelings by placing a mark on a VAS. Self-reported quality of sleep and depth of sleep are assessed in the morning whereas self-reported daytime alertness and daytime ability to function are assessed in the evening.

The sleep diary will be uploaded into an electronic hand-held device and given to the subjects at Visit 1. Sleep diaries will be available in the subject's language and must be completed daily from Visit 1 until Visit 8 and at PEOT.

For further information about the set-up and the use of the sleep diary on the hand-held device, refer to the investigator site electronic Clinical Outcome Assessment study information guide.

For assessments that derive from the SDQ, baseline is defined as the average of the 7 days immediately preceding Visit 2. The endpoints will be assessed at Week 1, Week 2, Week 3, and Week 4 using averages of 7 days.

3.2.2 IDSIQ [Appendix 3]

The IDSIQ is programmed on the electronic hand-held device and must be completed every day in the evening before the evening sleep diary by the subject from Visit 1 until Visit 8 and at PEOT. It will be completed by the subjects on the hand-held device.

The IDSIQ is structured in 3 domains (i.e., alertness/cognition; negative mood; tiredness/sleepiness) and contains overall 14 items, each based on an 11-point NRS, with a recall period of "today". The psychometric validation of the IDSIQ instrument was performed in study ID-078A203 [Hudgens 2021].

Baseline is defined as the average of the 7 days immediately preceding Visit 2. The endpoints will be assessed at Week 1, Week 2, Week 3, and Week 4 using averages of 7 days.

3.2.3 ISI© [Appendix 4]

The ISI© assesses the severity of a subject's insomnia by scoring the severity of sleep onset and sleep maintenance difficulties and any insomnia-related interference with daytime functioning. The assessment is on a 5-point scale (0–4), where the composite score is obtained by summing the 7 rated dimensions measuring the subject's perception of his or her insomnia. A score of 15–21 indicates a moderate level of insomnia and a score of 22–28 indicates severe insomnia. An ISI© total score < 10 indicates that the subject's subjectively rated insomnia symptoms, daytime impairment, and quality of life have improved to the minimal-to-none range [Morin 1993, Scharf 2007]. The ISI© will be completed by the subject on the electronic device at Visit 1, Visit 3, Visit 4, Visit 7, and Visit 8. The ISI© questionnaire used in this study uses a recall period of 2 weeks.

Baseline is defined as the ISI© score at Visit 1. The ISI© score will be assessed based on the entries on Visit 3 and Visit 7 (Week 2) as well as Visit 4 and Visit 8 (Week 4).

3.2.4 PGA-S (daytime symptoms) [Appendix 5]

The PGA-S (daytime symptoms) is a question concerning the overall severity of daytime symptoms (e.g., sleepiness) and impacts (e.g., effort to perform daily activities) that the subject may have experienced due to their *insomnia* over the 7 days preceding the PGA-S.

It will be completed by the subjects on the electronic device at Visit 1 and weekly during both treatment periods.

3.2.5 PGI-C (daytime symptoms) [Appendix 5]

The PGI-C (daytime symptoms) is a question concerning the change in overall severity of daytime symptoms (e.g., sleepiness) and impacts (e.g., effort to perform daily activities) that the subject may have experienced due to their *insomnia* over the 7 days preceding the PGI-C daytime symptoms compared to the week before he/she started treatment. It will be completed weekly by the subjects on the electronic device during both treatment periods.

3.2.6 PGI-C (nighttime symptoms) [Appendix 5]

The PGI-C (nighttime symptoms) is a question concerning the change in the subject's insomnia symptoms at night (e.g., trouble falling asleep, total time asleep, time to fall back asleep or number of times they wake up) over the past week (7 nights) preceding the PGI-C nighttime symptoms compared to the week before the subject started treatment. It will be completed weekly by the subjects on the electronic device during both treatment periods.

3.2.7 PGA-S (daily life) [Appendix 5]

The PGA-S (daytime symptoms) is a question concerning the overall impacts on the daily life (e.g., effort to perform daily activities) that the subject may have experienced due to their *insomnia and their nocturia* over the 4 weeks preceding the PGA-S. It will be completed by the subjects on the electronic device at Visit 1, Visit 4, and Visit 8.

3.2.8 PGI-C (daily life) [Appendix 5]

The PGI-C is a question concerning the change in overall severity of the daily life symptoms that the subject may have experienced due to their insomnia and their nocturia over a period of 4 weeks. It will be completed by the subjects on the electronic device at Visit 4 and Visit 8.

3.2.9 Minze Diary Pod

The Minze Diary Pod consists of a voiding pod and a voiding diary and uses a derivation from the ICIQ bladder diary which is a 3-day diary that allows subjects to record urinary frequency, volume voided, urgency and fluid intake (amount and type) [Bright 2014]. The voiding pod will automatically transfer the voiding information (i.e., volume and timepoints) to the voiding diary and the subjects must provide additional information. The Minze Diary Pod must be completed during the day, and it must preferably be started in the morning meaning that the completion starts only in the morning after Visit 1 to assess eligibility. Furthermore, the Minze Diary Pod must be completed the morning after Visit 2 and Visit 6 and lasts 3 days; the Minze Diary Pod must also be completed for 3 full days immediately preceding Visit 4 and Visit 8.

For assessments derived from the voiding diary, baseline is defined as the average of the 3 consecutive nights following Visit 1. The endpoints are collected on 3 consecutive days and nights immediately following Visit 2 and Visit 6 (defined as Week 1), and 3 days immediately preceding the end of each treatment at Visit 4 and Visit 8 (defined as Week 4), respectively.

3.2.10 EQ-5D-3L [Appendix 6]

The EQ-5D-3L is an instrument that assesses quality of life, irrespective of the disease. The 5 Dimensions include: mobility, self-care, usual activities, pain/discomfort, anxiety/depression. "None, some, extreme" are the 3 modalities for each dimension. Depending on the box checked by the subject a number is assigned to each dimension resulting into a 5-digit number combination (e.g., a completely healthy subject would have a score of 11111).

Additionally, the EQ VAS records the subject's self-rated health ranging from "best imaginable health state" to "worst imaginable health state".

The EQ-5D has no recall period, instead it represents a snapshot of how the subject feels on the day it is completed. It will be completed by the subjects on an electronic device at Visit 1, Visit 3, Visit 4, Visit 7, and Visit 8.

Baseline is defined as the EQ-5D-3L score at Visit 1. The EQ-5D-3L score will be assessed based on the entries on Visit 3 and Visit 7 (Week 2) as well as Visit 4 and Visit 8 (Week 4).

3.2.11 ICIQ-NQoL [Appendix 7]

The ICIQ-NQoL is an adaptation of the NQoL [Abraham 2004] for use within the ICIQ structure. It is a subject-completed questionnaire covering daytime and nighttime impact of nocturia in men and women and consists of 13 items. The recall period is 4 weeks. The overall score is calculated by summing the first 12 items (ranging from 0 to 4), resulting in an overall score that ranges from 0–48 where greater scores indicate a decrease in quality of life. It will be completed by the subjects on the electronic device at Visit 1, Visit 4, and Visit 8.

Baseline is defined as the ICIQ-NQoL score at Visit 1. Week 4 is defined as the ICIQ-NQoL score assessed at the end of each treatment period at Visit 4 and Visit 8, respectively.

3.2.12 ICIQ-MLUTS [Appendix 8]

The ICIQ-MLUTS is a questionnaire that evaluates lower urinary tract symptoms in males. It is a patient-completed questionnaire that includes 13 items and is derived from the ICSmaleSF questionnaire [Donovan 2000]. The questionnaire is split into two subscales ranging from 0–20 for voiding symptoms and 0–24 for incontinence symptoms, where

higher numbers indicate a higher burden. It will be completed by the subjects on the electronic device at Visit 1, Visit 4, and Visit 8.

Baseline is defined as the ICIQ-MLUTS sub-scores at Visit 1. Week 4 is defined as the lower urinary tract symptoms sub-scores assessed at the end of each treatment period at Visit 4 and Visit 8, respectively.

3.2.13 ICIQ-FLUTS [Appendix 9]

The ICIQ-FLUTS is a questionnaire that evaluates lower urinary tract symptoms in females. It is a patient completed questionnaire that includes 12 items and is derived from the BFLUTS-SF questionnaire [Brookes 2004]. The questionnaire is split into three subscales ranging from 0–16 for filling symptoms, 0–12 for voiding symptoms, and 0–20 for incontinence symptoms, where higher numbers indicate a higher burden. It will be completed by the subjects on the electronic device at Visit 1, Visit 4, and Visit 8.

Baseline is defined as the ICIQ-FLUTS sub-scores at Visit 1. Week 4 is defined as the lower urinary tract symptoms sub-scores assessed at the end of each treatment period at Visit 4 and Visit 8, respectively.

3.2.14 Treatment satisfaction [Appendix 12]

The NRS collects information on the treatment satisfaction during the clinical trial by asking the subjects to mark the number that best describes the overall satisfaction.

Self-reported treatment satisfaction is assessed in the morning of Visit 4,Visit 8 and PEOT on the electronic device.

3.2.15 Treatment period preference [Appendix 13]

The subjects will be asked at Visit 8 and PEOT to select which treatment period (Period I or II) was preferred and complete it on the electronic device.

3.2.16 Narrative [Appendix 14]

The subjects will complete a free text question on the electronic device at Visit 1, Visit 4, Visit 8 and PEOT. They will also be asked to write a short text about their overall feeling.

At Visit 1 the narrative question will refer to the time before being on treatment, while at Visits 4, 8 and PEOT the narrative will refer to the time while on treatment.

3.3 Safety assessments

Unless otherwise specified, the date of each assessment will be collected in the eCRF.

The definitions, reporting and follow-up of AEs, SAEs, and pregnancies are described in Section 8.

3.3.1 Vital signs

SBP, DBP and pulse rate will be measured and recorded in the eCRF. The date and actual time of vital sign measurements will be entered in the eCRF.

Blood pressure and pulse measurements will be assessed with the subject in a supine or sitting position using an automated device. Manual techniques will be used only if an automated device is not available.

The subject should be allowed to rest for at least 5 min in a quiet setting without distractions (e.g., television, cell phones), and to use the same position (supine or sitting) and same arm throughout the study for an individual subject.

Vital signs will be collected at Visit 1, Visit 4, Visit 8 and PEOT.

3.3.2 VAS [Appendix 2]

The VAS collects information on morning sleepiness by asking the subjects to report their feelings by placing a mark on a VAS and is part of the SDQ. It is collected every morning on the electronic device from Visit 1 to Visit 8 and at PEOT.

3.3.3 Clinical laboratory assessments

Exceptional circumstances that may require recording of local laboratory results include the possible need for clarification of certain exclusion criteria or hospitalization of the subject due to a medical emergency. Local laboratory results must be reported in the eCRF.

The following documents will be collected from the local laboratory: normal ranges, laboratory certification, and curriculum vitae of laboratory director.

3.3.4 C-SSRS© [Appendix 10]

The C-SSRS© is an instrument that reports the presence and severity of both suicidal ideation and behaviors [Posner 2007]. Suicidal ideation is classified on a 5-item scale:

1. Wish to be dead
2. Non-specific active suicidal thoughts
3. Active suicidal ideation with any methods (not plan) without intent to act
4. Active suicidal ideation with some intent to act, without specific plan
5. Active suicidal ideation with specific plan and intent

The C-SSRS© also captures information about the intensity of ideation, specifically the frequency, duration, controllability, deterrents, and reasons for the most severe types of ideation. In addition, the C-SSRS© captures information using yes/no question and answers on suicidal behaviors, specifically actual, interrupted, and aborted attempts; preparatory acts or behaviors; and if suicidal behaviors were present during the assessment period.

More than one classification can be selected provided they represent separate episodes. For actual attempts only, the actual or potential lethality is classified for the initial, most lethal, and most recent attempts.

At Visit 1 (Screening) the C-SSRS© will be completed for the subject lifetime history of suicidal ideation and behaviors. At all other visits (Visit 4, Visit 5, Visit 8, Visit 9 and PEOT), the C-SSRS© will be completed for suicidal ideation and behaviors since the previous visit.

The investigator, a delegated physician, or a nurse trained according to local requirements and local clinical practice will complete this questionnaire with the subject on an electronic device and assess the findings.

Participants who answer "yes" to items 1, 2, 3, 4, or 5 on the C-SSRS© assessment at any post-randomization visit must undergo further evaluation by the investigator to assess the risk. Study treatment will be interrupted in such participants until after the investigator confirms suitability of the participant to remain under treatment. This evaluation and decision should also be clearly recorded in the source documents.

3.4 Endpoints

It is anticipated that the collection of the voiding volume will interfere with sleep-related endpoints, therefore a staggered approach for the endpoint assessments is pursued. The details are described below and apply for each treatment period.

Information on the endpoints and their relation to the objectives is shown in Table 3.

Further details on the endpoints are described in the SAP.

Table 3 Endpoints and objectives

Objectives	Endpoints in period I and period II
To assess the efficacy of daridorexant on insomnia in subjects with insomnia and comorbid nocturia	**Primary endpoint:** • Change from baseline to Week 4 in sTST **Other insomnia related endpoints:** • Changes from baseline to Week 1, Week 2, and Week 3 in sTST • Changes from baseline to Week 2 and Week 4 in ISI© total score • Changes from baseline to Week 1, Week 2, Week 3, and Week 4 in quality and depth of sleep as determined by scores on the VAS (mm) in the morning • Changes from baseline to Week 1, Week 2, Week 3, and Week 4 in the daytime alertness and daily ability to function as determined by scores on the VAS (mm) in the evening • Changes from baseline to Week 1, Week 2, Week 3, and Week 4 in mean number of self-reported awakenings based on the sleep diary
To assess the efficacy of daridorexant on nocturia	**Nocturia related:** • Changes from baseline to Week 1 and Week 4 in number of nocturnal voids assessed using a voiding diary • Changes from baseline to Week 1 and Week 4 in the time to the first nocturnal void assessed using the voiding diary • Changes from baseline to Week 1 and Week 4 in the volume of the first nocturnal void assessed using the voiding diary • Changes from baseline to Week 1 and Week 4 in the total nighttime voiding volume assessed using the voiding diary • Change from baseline to Week 1 and Week 4 in number of daytime voids assessed using a voiding diary • Changes from baseline to Week 1 and Week 4 in the total daytime voiding volume assessed using the voiding diary • Change from baseline to Week 4 in ICIQ-NQoL • Change from baseline to Week 4 in lower urinary tract symptoms sub-score using the ICIQ-MLUTS and FLUTS for male and female subjects, respectively
To assess the overall patient's ratings of their condition and symptoms	• Changes from baseline to Week 1, Week 2, Week 3, and Week 4 in Patient Global Assessment of Disease Severity (daytime symptoms)

Objectives	Endpoints in period I and period II
	• Changes from baseline to Week 1, Week 2, Week 3, and Week 4 in Patient Global Impression of Change (daytime and nighttime symptoms) • Change from baseline to Week 4 in Patient Global Assessment of Disease Severity (daily life) • Change from baseline to Week 4 in Patient Global Impression of Change (daily life) • Change from baseline to Week 2 and Week 4 in EQ-5D-3L score • Treatment satisfaction at Week 4 assessed via NRS • Treatment period preference at Visit 8 (EOTP II)
To explore a) the sensitivity of the IDSIQ to detect clinical changes in this study population and b) the use of narratives to report subject's perception of treatment effect	• The change from baseline to Week 1, Week 2, Week 3, and Week 4 in all IDSIQ domains • The subjects will be asked to complete a narrative at the end of each treatment period. More details on the analysis will be provided in the SAP.
To assess the safety and tolerability of daridorexant	**Safety endpoints** Safety monitoring will include: • Occurrence of TEAEs up to 5 days after EOTP I and/or EOTP II. • Occurrence of treatment emergent AESIs up to 5 days after EOTP I and/or EOTP II. • Occurrence of treatment-emergent serious adverse events up to 5 days after EOTP I and/or EOTP II. • Occurrence of TEAEs leading to premature discontinuation of the study and/or treatment. • Change from baseline to EOTP I and EOTP II in vital signs (systolic blood pressure, diastolic blood pressure, and pulse rate). • Change from baseline to EOTP I and EOTP II in morning sleepiness as determined by the scores on the VAS in the morning. • Occurrence of suicidal ideation, suicidal behavior, and/or self-injurious behavior with / without suicidal intent based on the C-SSRS© at Visit 1, Visit 4, Visit 5, Visit 8, and Visit 9.

AE = adverse event; AESI = adverse event of special interest; C-SSRS© = Columbia Suicide Severity Rating Scale©; EOTP = End-of-Treatment Period; EQ-5D-3L = European Quality of Life 5 Dimensions 3 Level Version; ICIQ-(M/F)LUTS = International Consultation on Incontinence Questionnaire – (male/female) lower urinary tract symptoms; ICIQ-NQoL = International Consultation on Incontinence Questionnaire – Nocturia Quality of Life; IDSIQ = Insomnia Daytime Symptoms and Impacts Questionnaire; ISI© = Insomnia Severity Index©; NRS = Numeric Rating Scale; SAP = statistical analysis plan; (s)TST = (subjective) total sleep time; TEAE = treatment-emergent adverse event(s); VAS = visual analog scale.

3.5 Appropriateness of endpoints

This study is a post-approval study and aims to investigate the effect of daridorexant on managing insomnia as well as frequent nocturnal voids (nocturia). The chosen endpoints in this study have not been adequately statistically powered except for sTST, however it is anticipated that the study is large enough to detect efficacy and safety signals of daridorexant on nocturia and sleep variables.

This study will assess sleep-related endpoints such as sTST, which has been selected as a primary endpoint as it is a clinically meaningful subjective endpoint that has already showed good response during the first weeks of treatment in both pivotal Phase 3 studies of daridorexant, although in a different subject population (insomniacs diagnosed through DSM-5 criteria, without nocturia). By measuring an improvement in sTST, the study will capture the effect of daridorexant on both wake periods at the beginning and end of the night. Nocturia by definition causes disruption of sleep continuity, and the need to void occurs throughout the entire night; in fact, the number of voidings has been significantly associated with the number of hours of sleep per night [Coyne 2003]. Moreover, these subjects have been diagnosed with insomnia and will likely experience sleep problems throughout the full night. Therefore, sTST is the variable that correlates best with both conditions.

Furthermore, to assess the potential effects of daridorexant on nocturia, this study will also measure nocturia-related variables such as the number and volume of voidings, as well as the nocturia quality of life questionnaire. As even ≥ 2 voidings during the night are considered clinically meaningful [Kim 2016], it is expected that a reduction in the number of voidings will directly result in a clinical benefit in these subjects. Additionally, with the nocturia quality of life questionnaire, the change in nocturia symptoms can be quantified into an impact on the subject's life.

Finally, this study will also assess the sensitivity to change of the IDSIQ, thus providing further information on the applicability of this instrument in the population in this study.

Accounting for the safety data that were collected in the entire daridorexant clinical program, the proposed safety endpoints are considered adequate as they capture all relevant safety aspects related to the use of an orexin receptor antagonist. In the Phase 3 studies the occurrence of narcolepsy-like events was low and there was no pattern to the occurrence of falls. Therefore, the proposed safety endpoints allow for an adequate characterization of safety following administration with daridorexant in subjects with insomnia and comorbid nocturia.

4 STUDY DESIGN AND PLAN

4.1 Study design

This is a multi-center, double-blind, randomized, placebo-controlled, 2-way cross-over post-approval study.

Approximately 50 subjects aged ≥ 55 years will be randomized (i.e., enrolled) in a 1:1 ratio to either sequence for 1 month. No stratification will be applied. The study will be conducted at approximately 20 sites in 3 countries.

4.1.1 Study periods for an individual subject

Screening period: Starts with the full signature of the ICF at Visit 1 and lasts 14–21 days. All baseline assessments and eligibility checks will be done during this period.

Treatment period (Periods I and II): Randomization will take place on Day 1 (Visit 2) after confirmation that all eligibility criteria have been met, prior to the first study drug administration of Treatment Period I. The double-blind cross-over phase will consist of 2 treatment periods of 29 days ± 2 days each that are separated by a washout period of 14–21 days. EOTP I and EOTP II is reached on the morning after last treatment intake in the evening of the respective treatment period. Each subject will be randomized in a 1:1 ratio to one of the treatment sequences defined as:

- Treatment A: 50 mg daridorexant, followed by Treatment B: placebo
- Treatment B: Placebo, followed by Treatment A: 50 mg daridorexant

Follow-up and Washout period:

The follow-up period, to detect any safety events related to the cessation of study treatment, starts after completion of the EOTP I and EOTP II visit of each treatment period (I and II) and lasts for 5–10 days.

For period I, the first 5–10 days of the washout period overlap with the follow-up period and are followed by an additional 9–16 days of washout, for a total of 14–21 days washout period before entering treatment period II.

A subject's participation in the study ends with the completion of the EOS phone call 5–10 days after EOTP II (Visit 9) of Period II [Table 1].

The visit schedule and protocol-mandated procedures are performed according to the schedule of activities [Table 1] and are described in Section 3.2, 3.3, and 7.2.

The overall study design is depicted in Figure 1.

4.2 Study duration and global end-of-study definition

The study starts with the recruitment of the first subject. A subject is considered recruited when the subject's ICF has been fully signed.

The study primary completion date is the date of the last subject's Visit 8 morning visit, when the last assessment for the primary efficacy endpoint is collected.

The duration of individual subject's participation in the study will be approximately 3.5 months.

The global end-of-study is defined as completion of the last subject's EOS phone call. The study is expected to last approximately 15 months.

Study results will be submitted within 1 year of the primary completion date of the study.

4.3 Study design rationale

The randomized, placebo-controlled, 2-way cross-over study setting is considered adequate to prevent and account for bias in the endpoints that are assessed, as every subject will act as their own control, resulting in reduced variability and, therefore, also in a smaller sample size. Furthermore, a cross-over design is adequate to assess chronic conditions like insomnia and nocturia as it is not expected that the disease status changes over the duration of study. To avoid the risk of carry-over, a washout period of 14–21 days is implemented between the two treatment periods to allow variables to return to baseline conditions. This is considered adequate given the half-life of 8 h of daridorexant.

This study is a post-approval investigation to study efficacy and safety in subjects with insomnia and comorbid nocturia. In line with the EMA guideline on medicinal products for the treatment of insomnia [EMA 2011], the FDA guideline for the clinical evaluation of hypnotic drugs [FDA 1977] as well as the entire clinical developmental program of daridorexant, this study includes a placebo group to allow proper characterization of the efficacy and safety results of daridorexant. The use of a placebo group for a period of 1 month in this population is considered medically acceptable.

Data from the Phase 2 and Phase 3 studies support the duration of the treatment period of 29 days ± 2 days to assess subjective changes in day- and nighttime variables in subjects with insomnia. No placebo run-out is included in the trial, as the Phase 3 studies did not indicate any withdrawal symptoms and/or rebound effect, which is anticipated to be similar in this population. Potential AEs related to the cessation of the study drug will be assessed during the 5–10 day follow-up period.

4.4 Study committee(s)

No Independent Safety Board or IDMC will be appointed for this study, given the established safety profile of daridorexant, the small size, the anticipated recruitment time and the short duration of the study.

5 STUDY POPULATION

5.1 Subject population description

This study will enroll male and female subjects aged ≥ 55 years with insomnia and comorbid nocturia.

5.2 Inclusion criteria

Subjects must meet all the following inclusion criteria:

1. Signed and dated ICF prior to any study-mandated procedure.
2. Male or female subjects ≥ 55 years old at the time of signing the ICF.
3. Insomnia complaints for at least 3 months prior to Visit 1.
4. ISI© score ≥ 13 at Visit 1.

   Note: An ISI© score of ≥ 13 is considered appropriate as it represents a score suggesting subthreshold to moderate insomnia. The wide range of ISI© scores between the different insomnia categories indicate that the scores are to be considered as a guidance only. In this study, a score of at least 13 is adequate to detect clinically relevant insomnia [Morin 2011].
5. Diagnosis of nocturia as per International Continence Society:
   - Waking to pass urine during the main sleep period.
   - The first nocturia episode must be preceded by sleep. Subsequent nocturia episodes must be followed by the intention of getting back to sleep.
6. Nocturia severity: on average ≥ 3 nocturnal voidings per night reported by the subjects for at least 1 month prior to Visit 1.

   Note: ≥ 2 voidings per night have been reported to be clinically relevant. The threshold set in this study is to capture a more severe population that is bothered by their frequent nocturia episodes.
7. Average ≥ 2.6 nocturia episodes reported on the bladder diary per night over a period of 3 consecutive nights following Visit 1. None of the 3 nights can have less than 2 voidings.

   Note: Given the night-to-night variability that can be observed in the number of nocturia episodes, this threshold enables inclusion of a population that suffers from clinically relevant nocturia episodes.

8. Ability to communicate well with the investigator, to understand the study requirements, and judged by the investigator to be alert and oriented to person, place, time, and situation.

5.3 Exclusion criteria

Subjects must not meet any of the following exclusion criteria:

1. Woman of childbearing potential, pregnant or planning to become pregnant.

   Note: A woman is considered of childbearing potential, i.e., fertile, following menarches and until becoming post-menopausal unless permanently sterile.
2. Planned travel across ≥ 3 time zones during study.

   Note: It is expected that by changing time zones subject's sleep will be impaired.
3. Any of the following conditions related to suicidality:
   - Any suicidal ideation with intent, with or without a plan, at Screening, i.e., answering "Yes" to questions 4 or 5 on the suicidal ideation section of the lifetime (screening visit) version of the C-SSRS©.
   - History of suicide attempt on the suicidal behavioral section of the lifetime version of the C-SSRS© (screening visit).

     Note: As with many hypnotics, suicidal thoughts and actions may occur especially in those with a history of them. For that purpose, these subjects will be excluded from the study.
4. Regular caffeine consumption after 4 pm.

   Note: Caffeine consumption may interfere with sleep and nocturia assessments.
5. Unable to refrain from smoking during the night.

   Note: Heavy smoking may interfere with sleep and nocturia assessments.
6. Known and documented diagnosis of narcolepsy, periodic limb movement disorder, moderate to severe obstructive sleep apnea, restless legs syndrome, circadian rhythm sleep-wake disorder, or REM sleep behavior disorder.

   Note: Daridorexant is contraindicated in narcoleptic subjects. The occurrence of other sleep disorders may interfere with the efficacy and safety assessments.
7. Known and documented diagnosis of Type 1 diabetes mellitus, uncontrolled Type 2 diabetes mellitus, central or nephrogenic diabetes insipidus, and primary/secondary polydipsia within the last 6 months prior to Visit 1.

   Note: Conditions that manifest with the symptoms of large intake of fluids may suggest the presence of other underlying diseases that need appropriate medical attention. The investigator must certify the absence of these conditions.

8. Known and documented nocturia linked to urinary tract infection, neoplasms of bladder, prostate or urethral cancer, bladder or urethral calculi, or neurogenic voiding dysfunction within the last 6 months prior to Visit 1.

   Note: These conditions are known to cause nocturia for a limited time period and/or are not expected to remain stable during the duration of the study and may interfere with the efficacy and safety assessments. The investigator must certify the absence of these conditions.

9. Any signs or symptoms of active, ongoing infection judged to be clinically relevant by the investigator.

   Note: Investigators should not screen subjects if an ongoing infectious disease is suspected.

10. Known and documented diagnosis of severe compromised respiratory function (e.g., chronic obstructive pulmonary disease).

    Note: See the SmPC or the IB.

11. Known and documented moderate to severe hepatic impairment.

    Note: Daridorexant is not recommended in subjects with severe hepatic impairment, while subjects with moderate hepatic impairment require a dose adjustment which is not allowed in this study. In accordance with the EU SmPC or IB, the investigator must certify the absence of these conditions and may refer to local laboratory testing.

12. Known hypersensitivity to the investigational treatment, any of its excipients or drugs of the same class.

13. Treatment with forbidden medications including moderate or strong CYP3A4 inhibitors and inducers within 2 weeks or 5 half-lives (whichever is longer) prior to Visit 2.

    Note: As per daridorexant label, 50 mg daridorexant must not be taken if co-administered with moderate to strong CYP3A4 inducers or inhibitors. This includes other medication that could interfere with the efficacy or safety assessments. See the SmPC or IB. Background treatment of nocturia is allowed if started at least 1 month prior to entering the study, is considered to remain stable during the study and does not meet the criteria for forbidden medication.

14. Treatment with another investigational treatment or participation in another clinical trial up to 3 months prior to Visit 2.

15. Any known factor or disease that might interfere with treatment compliance, study conduct, or interpretation of the results, such as drug or alcohol dependence or psychiatric disease.

16. Known concomitant life-threatening disease with a life expectancy < 12 months.

Note: The cross-over study design is only applicable for chronic and stable diseases that are expected to be comparable during the different study periods.

17. Ongoing CBT-I at Visit 1 or planned start during the study.

5.4 Rationale for the selection of the study population

Sleep disruptions in adults with frequent nocturia complaints are very common. One survey identified that going to the bathroom was the most frequent cause for waking up at night in adults and it increased with age [Ohayon 2008]. The severity of the nocturia defined by the number of awakenings for voiding has been shown to correlate with the severity of sleep disruption as well as with impaired quality of life in patients [Drake 2005]. While nocturia is a multifactorial condition that can have several origins, it is usually split into three categories:

1. Nocturnal polyuria:

These patients have a large production of urine during sleep, usually related to alterations in biological master clock regulations, large liquid intake before bedtime, diurnal perturbations of antidiuretic hormone, and increased atrial natriuretic peptide release with increasing age [Van Kerrebroeck 2002].

2. Bladder storage problems:

These symptoms are of neurogenic or myogenic origins. The storage problems can have several causes, e.g., by detrusor overactivity caused by secondary conditions such as benign prostatic hyperplasia, bladder hypersensitivity, or urogenital aging.

3. Nocturia due to global polyuria:

This population will not be included in this study, as these subjects usually have other severe underlying conditions that would make participation in this trial unfeasible. For example, subjects with severe global polyuria require large fluid intake, including at night, which would directly influence the defined study outcomes. However, subjects on stable treatment for type 2 diabetes mellitus for at least 3 months will be allowed to participate if study criteria are met.

While pharmacological interventions exist to relieve nocturia complaints, the comorbid sleep disruption is usually left untreated even though its treatment has been associated with improvement in the overall clinical outcome for these subjects. This indicates that sleep disruptions may not necessarily be a consequence of nocturia, but also the cause for the nocturnal voidings. There is a high unmet medical need to identify effective and safe treatments that target the frequent sleep complaints in this population.

5.5 Contraception requirements for women of childbearing potential

No contraceptive methods are needed for female subjects participating in this clinical study as women of childbearing potential will not be included.

5.6 Contraception for male subjects with a partner who is of childbearing potential

No contraceptive methods are needed for male subjects participating in this clinical study.

5.7 Dietary aspects and physical activity restrictions

During the study, subjects will be instructed about the following restrictions:

- No alcohol consumption within 3 hours before going to bed.
- Avoiding intake of large quantities of fluid before going to bed that will likely result in the need to void.
- No caffeine consumption after 4 pm (this includes also different types of tea such as black or green tea, coffee, caffeinated gums, caffeine tablets).
- No heavy tobacco use leading to inability to refrain from smoking during the night.
- No driving or engaging in activities that require operating vehicles or dangerous machinery within 7 hours following study treatment intake.
- No travelling across ≥ 3 times zones or planned travel across ≥ 3 times zones at any time during the study.
- No daytime naps during the study.

5.8 Screen failures and re-screening

Screen failures are defined as subjects recruited in the clinical study (i.e., ICF fully signed) who are not subsequently randomized in the study. Minimum information includes demography (i.e., age, sex, race, and ethnicity) screen failure details (e.g., eligibility criteria not met, withdrawal of consent), medical history, any SAEs, as well as concomitant medications related to the treatment or occurrence of the SAEs.

It is not permitted to re-screen subjects in this study, however procedures or assessments conducted as part of the subject's routine clinical management (e.g., laboratory sample) and obtained before signing the ICF may be used for screening or baseline purposes [Section 7.1.1]. This includes repeating assessments in the event of exceptional circumstances (e.g., technical issues).

5.9 Criteria for withdrawal and retention of subjects

A subject has the right to prematurely discontinue study treatment at any time, by withdrawal from study treatment only or by withdrawal from study treatment **and** any

further participation in the study (i.e., premature withdrawal from the study). It is recommended that the investigator / authorized delegate makes a reasonable effort to maintain subjects on treatment, as medically appropriate, and follow the schedule of visits, as data robustness depends on such compliance. Should a subject stop treatment or withdraw from the study, the investigator / authorized delegate should ascertain the reason(s), while fully respecting the subject's rights.

Subjects who prematurely discontinue study treatment / the study for any reason will not be replaced, given the low discontinuation rate observed in the clinical program of daridorexant.

5.9.1 Study treatment interruption and premature discontinuation of study treatment

The decision to prematurely discontinue study treatment may be made by the subject, the investigator / authorized delegate, or the sponsor personnel.

The investigator / authorized delegate has the option of temporarily interrupting or prematurely discontinuing study treatment for a given subject in response to an AE, a diagnostic or therapeutic procedure, a laboratory abnormality, or for administrative reasons. If study treatment is interrupted by the subject for any reason, he/she must inform the investigator / authorized delegate as soon as possible. All study treatment interruptions must be recorded in the eCRF.

The investigator / authorized delegate must permanently discontinue study treatment for a given subject if, on balance, he/she believes that continued administration would be contrary to the best interests of the subject.

Study-specific criteria for temporary interruption and permanent discontinuation of study treatment are described in Sections 5.9.1.1, 5.9.1.2, 5.9.1.3 and 5.9.1.4.

The main reason for permanent discontinuation of study treatment (e.g., due to pre-specified study treatment discontinuation criteria, an AE, lack of efficacy, study termination) must be documented in the eCRF.

A subject who prematurely discontinues study treatment is **NOT** considered withdrawn from the study. The subject will be asked to return for a PEOT visit within 5 days of last intake of study treatment and thereafter to attend the following visits up to the respective EOTP visit as defined in the schedule of activities [Table 1] and in Section 7.2. After the EOTP visit has been completed, the subject will perform the Safety Follow-up Phone call 5 to 10 days later which will be considered an EOS visit. All subjects withdrawn from study treatment will be encouraged to follow planned study procedures (e.g., visits, diary, and questionnaire completion [Table 1]) until planned EOS provided that the subject's

consent for this limited participation in the study has not been withdrawn. This will reduce the amount of missing data which is important from a study integrity perspective.

5.9.1.1 Pregnancy / pregnancy plans

If a subject becomes pregnant while on study treatment, study treatment **must** be permanently discontinued. The investigator / authorized delegate must counsel the subject and discuss the risks of continuing with the pregnancy and the possible effects on the fetus. For reporting of pregnancies, refer to Section 8.3.1.

5.9.1.2 C-SSRS©

Subjects who answer "yes" to items 1, 2, 3, 4, or 5 on the C-SSRS© assessment at any post-randomization visit must undergo further evaluation by the investigator to assess the risk. If a positive answer is provided during the first treatment period, the investigator must interrupt study treatment and confirm the suitability of the subject to remain under treatment. This evaluation and decision must be clearly recorded in the source documents.

5.9.1.3 Concomitant use of forbidden medications

Subjects must not take forbidden medications during the study. However, if the subject is treated with a forbidden medication [Appendix 11], study treatment must be discontinued. See Section 5.9.1 for the handling of subjects that have prematurely discontinued study treatment.

5.9.1.4 Occurrence of complex sleep behaviors while on study treatment

Complex sleep behaviors include sleepwalking, sleep driving, sleep-talking or engaging in other activities while not fully awake (e.g., preparing and eating food, making phone calls, having sex). Subjects who experience a complex sleep behavior event during the study must discontinue study treatment immediately.

5.9.2 Withdrawal from the study

Subjects may voluntarily withdraw from the study without justification for any reason at any time. Subjects are considered withdrawn if they state an intention to withdraw further participation in all components of the study (i.e., withdrawal of consent), die, or are lost to follow-up [see Section 5.9.3]. If a subject withdraws consent for further study participation, no further data will be collected in the eCRF from the date of withdrawal onward. The investigator / authorized delegate may withdraw a subject from the study (without regard to the subject's consent) if, on balance, he/she believes that continued participation in the study would be contrary to the best interests of the subject. Withdrawal from the study may also result from a decision by the sponsor for any reason, including early termination or suspension of the study [see Section 10.10]. Enrolled subjects who prematurely discontinue from the study for any reason will not be replaced.

If, for whatever reason (except death or loss-to-follow-up), a subject is withdrawn from the study, the investigator / authorized delegate should make best efforts to schedule a last appointment / phone call to assess the safety and well-being of the subject, collect unused study treatment and discuss follow-up medical care. Data obtained during this last appointment / phone call will be recorded in the subject's medical records, but it will not be collected in the eCRF.

The main reason for premature withdrawal from the study must be documented in the eCRF.

The investigator must provide follow-up medical care for all subjects who are prematurely withdrawn from the study, or must refer them for appropriate ongoing care, as described in Section 6.3.

5.9.3 Lost to follow-up

A subject will be considered as lost to follow-up if he/she repeatedly fails to return for scheduled visits and the site is unable to contact him/her.

The site must take preventive measures to avoid a subject being lost to follow-up (e.g., document different ways of contact such as phone number, home address, email address, person to be contacted if the subject cannot be reached).

The following actions must be taken if a subject fails to return to the site for a scheduled study visit:

- The site staff must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain if the subject wishes to and/or should continue in the study.
- If the subject cannot be reached, the site must make a reasonable effort to contact the subject and document all attempts in the subject's medical chart. Reasonable efforts include where possible 3 phone calls to the last available phone number and 1 registered/certified letter to the subject's last known mailing address or local equivalent methods.
- If the subject is still unreachable after all contact attempts listed above, he/she will be considered to be lost to follow-up.

The date of last contact with the subject will be collected in the eCRF.

5.9.4 Retention of subjects

To avoid missing data caused by subjects dropping out of the study, the investigator / authorized delegate must inform subjects on the study duration and train subjects on upcoming procedures upfront, as part of the information to subjects prior to signing

consent. It is not advisable to consider subjects for screening if there is any suspicion that the subject may not be inclined to remain in the study for its entire duration, although subjects remain free to withdraw anytime as per text in Section 5.9.2. The benefit/ risk assessment as provided in Section 2.4 must be discussed and the doctor-patient relationship should be strengthened to reduce drop-out rates. If the study participant's usual physician is not the investigator, if the subject consents the investigator should make sure that the subject's usual physician, for example the general practitioner, is aware of the subject's participation in the study. It is important to note that the retention measures should be in line with ICH GCP, meaning that the subject's safety and wellbeing prevail over interests of science and society.

6 TREATMENTS

6.1 Study treatment

6.1.1 IMP and matching placebo description

Daridorexant is available as oral film-coated tablets at a strength of 50 mg.

Placebo matching daridorexant is provided as identical-looking oral tablets, formulated with the same inactive ingredients (excipients) as the active tablets.

6.1.2 Study treatment dosing and administration

At Visit 1, after the ICF has been signed, the investigator / authorized delegate will contact the IRT system to get a subject number allocated to the subject.

At Visit 2, the investigator / authorized delegate contacts the IRT system to assign the treatment wallet number.

After randomization, daridorexant or matching placebo will be taken orally, once daily in the evening within approximately 30 min before going to bed.

Missed doses must not be replaced and the subject must continue with the regular treatment the next evening.

6.1.2.1 Study treatment dose adjustments

Study treatment dose adjustments are not permitted.

6.1.3 Justification for dose

The 50 mg dose is the dose with the best risk-benefit ratio as assessed during the entire clinical developmental program and represents the dose that also showed a significant improvement in the daytime functioning in subjects with insomnia disorder in the pivotal Phase 3 program. Daytime functioning is also documented to be impaired in subjects suffering from frequent nighttime voidings.

6.1.4 Treatment assignment

Approximately 50 subjects aged ≥ 55 years will be randomized (i.e., enrolled) in a 1:1 ratio to either sequence. No stratification will be applied.

After verifying that the subject meets all inclusion criteria and that none of the exclusion criteria are violated, the investigator / authorized delegate contacts the IRT system at Visit 2 to randomize the subject. The IRT system assigns the treatment kit number to the subject, which matches the treatment arm assigned by the randomization list to the randomization number.

The IRT system is handled by an external independent vendor who will generate the randomization list.

6.1.5 Blinding

6.1.5.1 Double-blind treatment period

This study will be performed in a double-blind fashion. The investigator, site study personnel, subjects, sponsor personnel, CRAs, and vendor/CRO personnel responsible for the conduct of the study will remain blinded to the study treatment allocation until study database lock.

To ensure adequate supply of study treatment, the IRT vendor personnel responsible for clinical study distribution and the sponsor individuals contributing to clinical supply distribution will need to be unblinded at subject level and depot level, respectively. These persons will be clearly identified, their unblinding status will be documented in the trial master file and controlled as per sponsor/CRO procedures.

Until the time of unblinding for final data analysis, the randomization list is kept strictly confidential, and accessible only to authorized persons, e.g., Quality Assurance, dedicated members of the Pharmaceutical Development department who are not involved in the conduct of the study.

The investigational treatment and its matching placebo are indistinguishable, and all treatment kits will be packaged in the same way.

6.1.6 Unblinding

6.1.6.1 Unblinding for final analyses

Full randomization information will be made available for data analysis only after database lock, in accordance with the sponsor and/or the CRO's Quality System documents.

6.1.6.2 Unblinding for IDMC

Not applicable.

6.1.6.3 Unblinding for interim analyses

Not applicable.

6.1.6.4 Unblinding for SUSARs

If a SUSAR [see definition in Section 8.2.3] occurs for a subject, the sponsor's Global Drug Safety department will perform unblinding of the treatment assignment for that subject in order to meet regulatory requirements.

Unblinded information will only be accessible to sponsor personnel who need to be involved in the safety reporting to the regulatory authorities and/or IECs/IRBs, and to the sponsor's Global Drug Safety personnel performing ongoing safety evaluations during the clinical study.

6.1.6.5 Emergency procedure for unblinding

The identity of the study treatment may be revealed only if the subject experiences a medical event, the management of which would require knowledge of the blinded treatment assignment. In this case, the investigator / authorized delegate can receive the unblinded treatment assignment through the IRT.

In these situations, the decision to unblind resides solely with the investigator and must be clearly justified and explained. Whenever possible, and if it does not interfere with (or does not delay) any decision in the best interest of the subject, the investigator is invited to discuss the intended unblinding with the sponsor personnel. In all cases, the sponsor personnel must be informed as soon as possible before or after the unblinding.

Once unblinding has occurred, the knowledge of the blinded treatment assignment must stay restricted at the site level except if an SAE has occurred and must be reported to Global Drug Safety, then the treatment assignment must be provided on the SAE Form.

A subject may stay on study treatment after unblinding if considered appropriate by the medical judgment of the investigator.

The circumstances leading to unblinding must be documented in the hospital charts, the ISF, and in the IRT system.

6.1.7 Study treatment handling/preparation/storage/accountability

Manufacture, labeling, packaging, and supply of study treatment will be conducted according to Good Manufacturing Practice.

All study treatment supplies are to be used only in accordance with this protocol, and not for any other purpose.

6.1.7.1 Study treatment packaging and labeling

Study treatment is provided as film-coated tablets and supplied in blister packs.

Study treatment is labeled to comply with the applicable laws and regulations of the countries in which the study sites are located.

6.1.7.2 Study treatment distribution and storage at the site

Study treatment supplies must be kept in an appropriate, secure area and stored according to the conditions specified on the IMP label and according to local requirements.

6.1.7.3 Study treatment dispensing

The subjects will receive sufficient study treatment to cover the period up to the next scheduled visit. Subjects are asked to return all used, partially used, and unused study treatment blister packs at each visit. Should the treatment blister packs dispensed at a scheduled visit be lost or damaged, a replacement kit can be requested via the IRT system.

The protocol-mandated study treatment dispensing procedures may not be altered without prior written approval from the sponsor. In exceptional circumstances (e.g., if the subject is unable to return to the site due to a medical emergency / hospitalization at another hospital / long distance to travel / pandemic restriction), unscheduled dispensing and delivery of study treatment may occur outside of a scheduled visit. If the study treatment needs to be shipped to the subject, the site staff must first contact the sponsor representative to check whether the dispensing and delivery process is in accordance with the sponsor / CRO's Quality System documents as well as any local or national regulatory requirements.

An accurate record of the date and amount of study treatment dispensed to each subject must be available for inspection at any time.

6.1.7.4 Study treatment accountability

The inventory of study treatment dispensed to and returned by the subject (i.e., study treatment accountability) must be performed by site personnel on the day of the visit and before dispensing further study treatment. The inventory is to be recorded by site personnel in the site documentation and in the eCRF. The study treatment accountability log in the eCRF will include at least the following information for each study treatment unit (i.e., blister) dispensed to the subject:

- Dispensed blisters
- Date dispensed and number of tablets dispensed
- Date returned and number of tablets returned

All study treatment supplies, including partially used or empty blisters must be retained at the site.

If the subject forgets to bring the remaining study treatment to a study visit, he/she must be instructed to not take any tablets from the remaining study treatment blister and to return it at the next visit in person or by shipping it to the site, if allowed by local regulations.

6.1.7.5 Study treatment return and destruction

On an ongoing basis and/or when the study ends, the CRA will collect used and unused treatment kits, which will be sent to the warehouse, where the sponsor / depot personnel or a deputy will check treatment reconciliation.

In certain circumstances (e.g., local hospital procedures), used and unused study treatment containers may be destroyed at the site. In general, this can only be done once study treatment accountability is finalized and has been checked by the sponsor personnel representative, and written permission for destruction has been obtained from the sponsor. Exceptions might occur if a local process requests immediate destruction of the study treatment. Such local study treatment destruction processes must be provided and approved by the sponsor.

6.1.8 Study treatment compliance

Study treatment compliance with the prescribed study treatment dose regimen is based on study treatment accountability. Study treatment compliance will be calculated by site personnel at Visit 4 and Visit 8 using the formula below:

Compliance = [(number of tablets dispensed – number of tablets returned) / Total number of tablets that should have been taken during the period*] × 100

*The period is defined as the number of days during which study treatment should have been taken according to the actual visit dates.

A compliance of between 80–100% is expected during the treatment period. Any values deviating from this range will be considered protocol deviations and will be reported by the CRA in the Clinical Trial Management System.

The investigator / authorized delegate must discuss the non-compliance with the subject to clarify the reasons and to take appropriate actions to avoid re-occurrence. This discussion and its outcome must be documented in the source documents.

Subjects also report their daily study treatment intake in the eDiary every morning, however these entries will not be considered to assess compliance.

6.2 Previous and concomitant medications / non-pharmacological therapy

6.2.1 Allowed concomitant therapy

Therapies necessary for the subject's well-being and not categorized as prohibited medications can be used in this study.

Use of non-sedating antihistamines is allowed no more than twice per week. Use of inhaled corticosteroids is allowed. Use of narcotics or muscle relaxants to treat pain is allowed if the use of alternative medications, such as non-steroidal anti-inflammatory drugs is not sufficient to manage the pain. Use of nocturia-related treatments is allowed if they are treating the underlying condition, considered to remain stable during the study and are not listed as forbidden [Appendix 11].

Subjects can receive vaccinations with any available vaccine as per local guidelines, provided the vaccination conditions set forth by the respective manufacturer (consistent with the respective prescribing information/package insert) are observed. Prior to any vaccination the investigator must be informed by the study participant of such a plan. Receipt of the vaccine, and details thereof, should be recorded in the subject's medical charts and in the eCRF under concomitant medications.

General reporting of AEs should continue to be implemented as described in Section 8.2 and reports of AEs for approved vaccines should be submitted as appropriate.

6.2.2 Forbidden concomitant therapy

Concomitant therapies must not be discontinued, instead subjects must be considered ineligible both due to their condition and the need for these therapies.

The following concomitant therapies are forbidden:

- Treatment with another investigational product within 3 months prior to Visit 2 until EOS.
- CNS-active medications including over-the-counter medications, herbal medicines or other sleep medications within 2 weeks or 5 half-lives (whichever is longer) prior to Visit 2 until 24 hours after study treatment discontinuation.
- Treatment with moderate or strong CYP3A4 inhibitors/inducers within 2 weeks or 5 half-lives (whichever is longer) prior to Visit 2 until 24 hours after study treatment discontinuation.

A non-exclusive list of forbidden medications is available in Appendix 11.

6.3 Medical care of subjects after study completion / withdrawal from study

After the subject's study completion or premature withdrawal from the study, whichever applies, the investigator / authorized delegate will explain to subjects what treatment /

medical care is necessary and available according to local medical practice and applicable guidelines.

7 VISIT SCHEDULE AND STUDY ASSESSMENTS AND PROCEDURES

7.1 General information

The study visits and their respective time windows are listed in the schedule of activities [Table 1]. All assessments pertaining to a visit must be performed on the same day.

7.1.1 Screening

The subjects who agree to be part of the study and the investigator / authorized delegate must both sign the ICF prior to participation in the study. The ICF must be fully signed [see Section 10.2 for informed consent procedure] on the day of Screening.

If the first study-specific procedures or assessments are performed on the day that the ICF is signed, it must be clear from the source documents that informed consent was obtained prior to any study-specific procedures being performed (i.e., time of signature must be available).

Procedures or assessments conducted as part of the subject's routine clinical management (e.g., laboratory sample) and obtained before signing the ICF may be used for screening or baseline purposes, provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the schedule of activities [Table 1].

After the ICF has been fully signed, the investigator / authorized delegate contacts the IRT system to get a subject identification number allocated to the subject.

7.1.2 Unscheduled visits

Unscheduled visits may be performed at any time during the study and will be recorded in the eCRF. Depending on the reason for the unscheduled visit (e.g., AE), appropriate assessments will be performed based on the judgment of the investigator and the results will be recorded in the eCRF. After an unscheduled visit, the regular scheduled study visits must continue according to the schedule of activities [Table 1].

7.1.3 Study completion

A subject who completes both treatment periods and the safety follow-up period is considered to have completed the study. A subject who prematurely discontinues the study due to pre-defined criteria [see Section 5.9.1] or is withdrawn from the study because of study closure or early termination or suspension of the study [see Section 10.10] is considered as an early discontinuation. In the event of a pandemic or epidemic disease, the process for this study is described in Appendix 1.

7.2 Study assessments and procedures

All study assessments performed during study visits (scheduled or unscheduled) are done by the investigator / authorized delegate and are recorded in the eCRF, unless otherwise specified. Under exceptional circumstances (e.g., technical issues) an assessment can be repeated.

All PROs collected daily (e.g., evening/morning diary) or during a site visit will be recorded on the handheld device or on the site tablet.

- *Assessments during the visit include:*
  - Vital signs (Visit 1, Visit 4,Visit 8 and PEOT)
  - Recording of concomitant medications (All visits)
  - AEs and SAEs (All visits)
  - C-SSRS© (Visit 1, Visit 4, Visit 5, Visit 8, Visit 9 and PEOT)
  - ISI© (Visit 1, Visit 3, Visit 4, Visit 7, and Visit 8)
  - EQ-5D-3L (Visit 1, Visit 3, Visit 4, Visit 7, and Visit 8)
  - ICIQ-NQoL (Visit 1, Visit 4, and Visit 8)
  - ICIQ-MLUTS or ICIQ-FLUTS (Visit 1, Visit 4, and Visit 8)
  - Treatment satisfaction (Visit 4,Visit 8 and PEOT)
  - Treatment period preference (Visit 8 and PEOT)
  - Narrative (Visit 1, Visit 4, Visit 8 and PEOT)

If the investigator/institution retains the services of any individual or party to perform trial-related duties and functions, the investigator/institution must ensure this individual or party is qualified to perform those trial-related duties and functions and must implement procedures to ensure the integrity of the trial-related duties and functions performed and any data generated. The investigator / authorized delegate must inform the sponsor before using these services. The supervision of any external facilities remains the responsibility of the investigator.

Calibration certificates / evidence of equipment maintenance for the below-listed equipment used to perform study assessments must be available prior to the recruitment of the first subject. Calibration certificates / evidence of equipment maintenance of other equipment must be available as per local requirements:

- Temperature measurement devices for study treatment storage area.

7.2.1 Demographics / baseline characteristics

Demographic and baseline characteristic data to be collected in the eCRF for all subjects include: age, sex, race, and ethnicity (if allowed in the country). Relevant medical history

and/or current medical conditions based on the investigator / authorized delegate's judgment (e.g., chronic and ongoing acute conditions, serious past conditions) present before and/or at the time of signing informed consent will be recorded in the eCRF. Where possible, diagnoses and not symptoms will be recorded.

Insomnia severity will be assessed with the ISI©. Subjects will need to have a score of at least 13 at Visit 1.

The number of voidings per night will be captured using a voiding diary and will be applied in the first 3 days following Visit 1. Subjects will have to report on average ≥ 2.6 voidings during the night to be eligible.

The reason for not being of childbearing potential will be recorded in the eCRF.

7.2.2 Reporting of previous/concomitant medications / non-pharmacological therapy / auxiliary medicinal products and methods of birth control in the eCRF

A concomitant medication / non-pharmacological therapy is any treatment that is either ongoing at the start of study treatment or is initiated during the treatment period.

A previous medication / non-pharmacological therapy is any treatment for which the end date is prior to the start of study treatment.

The use of all concomitant medications / non-pharmacological therapies (including traditional and alternative medicines, e.g., plant-, animal-, or mineral-based medicines) will be recorded in the eCRF. Previous medications / non-pharmacological therapies must be recorded in the eCRF if discontinued within 30 days prior to signing of the informed consent.

Subjects will be asked to list any sleep medications that have been taken up to 1 year prior to the study.

8 SAFETY DEFINITIONS AND REPORTING REQUIREMENTS

8.1 Safety definitions

An AE is any untoward medical occurrence, i.e., any unfavorable and unintended sign, including an abnormal laboratory finding, symptom, or disease that occurs in a subject during the study, whether or not considered by the investigator / authorized delegate as related to study treatment.

AEs include:

- Exacerbation of a pre-existing disease if considered medically relevant.

- Exacerbation of a pre-existing disease except for efficacy endpoints and associated symptoms.
- Increase in frequency or intensity of a pre-existing episodic disease or medical condition.
- Disease or medical condition detected or diagnosed during the study, even though it may have been present prior to the start of the study.
- Continuous persistent disease or symptoms present at study start that worsen after the start of the study.
- Abnormal change on physical examination or ECG findings, if they represent a clinically significant finding that was not known at study start or worsened during the study as per investigator medical assessment.
- Laboratory test abnormalities if they represent a clinically significant finding (symptomatic or not) which was not known at study start or worsened during the study as per investigator judgment, led to dose reduction, interruption or permanent discontinuation of study treatment.

8.1.1 Definition of adverse events of special interest

AESIs are defined as:

- Events of falls

If the subject reports an event of fall at any time during the study, the investigator will be asked to complete the form in the eCRF that collects further information (e.g., time of event, external causes).

- Events of incontinence episodes

Worsening or new onset of urinary incontinence will be documented by the study sites including patient's demographic information, medical history, current medications, voiding diary information, and time of occurrence of the incontinence episode if available.

8.1.2 Definition of serious adverse events

An SAE is defined by the ICH guidelines as any AE fulfilling at least 1 of the following criteria:

- Fatal.
- Life-threatening: Refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death had it been more severe.
- Requiring in-patient hospitalization (i.e., the AE required admission to hospital) or prolongation of existing hospitalization.

- Resulting in persistent or significant disability or incapacity.
- Congenital anomaly or birth defect.
- Medically significant: Refers to important medical events that may not immediately result in death, be life-threatening, or require hospitalization but may be considered to be SAEs based upon appropriate medical judgment, as they may jeopardize the subject, and/or may require medical or surgical intervention to prevent 1 of the outcomes listed in the definitions above.

The following reasons for hospitalization are not considered as SAEs:

- Hospitalization for cosmetic elective surgery, or social and/or convenience reasons.
- Hospitalization for pre-planned (i.e., planned prior to signing the ICF) surgery or standard monitoring of a pre-existing disease or medical condition that did not worsen, e.g., hospitalization for coronary angiography in a subject with stable angina pectoris.

8.1.3 Intensity of adverse events

The intensity of AEs is graded on a three-point scale — mild, moderate, severe — as follows:

- Mild

The event may be noticeable to the subject. It does not usually influence daily activities, and normally does not require intervention.

- Moderate

The event may make the subject uncomfortable. Performance of daily activities may be influenced, and intervention may be needed.

- Severe

The event may cause noticeable discomfort and usually interferes with daily activities. The subject may not be able to continue in the study, and treatment or intervention is usually needed.

A mild, moderate, or severe AE may or may not be serious [see Section 8.1.2]. These terms are used to describe the intensity of a specific event. Medical judgment should be used on a case-by-case basis.

8.1.4 Relationship to study treatment

Each AE/SAE must be assessed by the investigator / authorized delegate as to whether or not there is a reasonable possibility of causal relationship to the study treatment and reported as either related or unrelated.

8.1.5 Relationship to study design or protocol-mandated procedure

An AE/SAE is defined as related to the study design or protocol-mandated procedure if it appears to have a reasonable possibility of a causal relationship to either the study design or to a protocol-mandated procedure.

The determination of the likelihood that a protocol-mandated procedure caused the AE/SAE will be provided by the investigator / authorized delegate.

8.1.6 Definition of study treatment overdose, misuse, and abuse

An overdose is defined as the administration of a study treatment dose (per intake or cumulatively) which is above the instructions provided in the protocol. When applying this definition, clinical judgement should always be applied (e.g., just because a subject returned less tablets than anticipated number is not an overdose as per definition).

The sponsor does not recommend specific treatment for an overdose. The subject should be monitored to detect any potential AE linked to the overdose

Study treatment misuse is defined as any **intentional and inappropriate use** of the study treatment which is different from the instruction provided in the protocol.

Study treatment abuse is defined as any **intentional and excessive use** of the study treatment, with harmful physical or psychological effects.

In the event of a study treatment overdose, abuse or misuse, the investigator / authorized delegate must contact the sponsor and closely monitor the subject for any AEs/SAEs as well as complete an additional form in the eCRF.

8.2 Reporting procedures

8.2.1 Reporting adverse events

The occurrence of an AE may come to the attention of study personnel during study visits, phone calls, narrative texts or interviews with subjects presenting for medical care.

At each study visit (scheduled or unscheduled), the investigator / authorized delegate will inquire about the occurrence of AEs since the last visit.

All AEs with an onset date after signing the ICF and up to 5 days after study treatment discontinuation must be recorded in the eCRF.

The AE should be reported as a final diagnosis (if possible) rather than a list of symptoms.

Information to be collected on an AE form in the eCRF includes date of onset, action taken with the study treatment, outcome of AE, date of resolution (if applicable), and

investigator / authorized delegate's assessment of intensity as well as relationship to study treatment, study design or protocol-mandated procedures.

Information on worsening of intensity will be collected on a new AE form. If the AE lessens in intensity, no change in the severity is required to be reported.

AEs still ongoing after study treatment discontinuation must be followed up until resolution, until they are no longer considered clinically relevant, or until stabilization.

8.2.2 Reporting serious adverse events

All SAEs must be reported by the investigator / authorized delegate to the sponsor's Global Drug Safety department within 24 hours of site staff first becoming aware of the event.

All SAEs occurring after signing the ICF up to 5 days after study treatment discontinuation must be recorded on an SAE form, regardless of the investigator-/delegate-attributed causal relationship with study treatment or study-mandated procedures.

The SAE forms must be sent to the sponsor's Global Drug Safety department (see contact details on the SAE form). The investigator / authorized delegate must complete the SAE form in English and must assess the event's causal relationship to the study treatment.

Any relevant information from source documents regarding the SAE, e.g., hospital notes or discharge summaries, etc., must be summarized on the SAE form.

Follow-up information about a previously reported SAE must be promptly reported. The sponsor's Global Drug Safety personnel may contact the investigator / authorized delegate to obtain further information.

If the subject is hospitalized in a hospital other than that of the study site, it is the investigator / authorized delegate's responsibility to obtain all SAE-relevant information and documentation.

New SAEs occurring after the follow-up period must be reported to the sponsor's Global Drug Safety department within 24 hours of site staff first awareness/knowledge of the event, **only** if considered by the investigator / authorized delegate to be causally related to previous exposure to the study treatment.

SAEs still ongoing after study treatment discontinuation must be followed up until resolution, stabilization, or until the event outcome is provided.

8.2.3 Reporting procedure for SUSARs

For patients included in the trial in the US, the expectedness of an SAE is determined by the sponsor according to the reference safety information section provided in the IB. For patients included in the trial in Europe, the expectedness of an SAE is determined by the

sponsor according to the list of adverse reactions detailed in section 4.8 of the EU SmPC. Any SAE that is assessed as related and unexpected against the reference safety information is considered a SUSAR.

Any SUSAR must be reported by the sponsor/CRO to relevant health authorities, and investigators. Submission to central/local IECs/IRBs will be done as per their requirements.

8.3 Pregnancy

Although women of childbearing potential are excluded from this study, a pregnancy could still occur. If a woman becomes pregnant while on study treatment, study treatment must be discontinued. The investigator / authorized delegate must counsel the subject and discuss the risks of continuing with the pregnancy and the possible effects on the fetus.

8.3.1 Reporting of pregnancy

Any pregnancy occurring in a female subject after signing the ICF, the start of study treatment administration and up to 30 days after study treatment discontinuation must be reported to the sponsor's Global Drug Safety department within 24 hours of site staff first becoming aware of the event.

All pregnancies must be reported on the sponsor Pregnancy form, which is sent to the sponsor's Global Drug Safety department (see contact details provided on the Pregnancy form) and the eCRF.

The investigator / authorized delegate must complete the Pregnancy form in English.

8.3.2 Follow-up of pregnancy

Any pregnancies must be followed up to their conclusion and the outcome must be reported to the sponsor's Global Drug Safety department.

Any AE associated with the pregnancy of a female subject occurring during the AE reporting time must be reported on separate AE forms in the eCRF as described in Section 8.2.1.

Any SAE occurring during the pregnancy must be reported on an SAE form as described in Section 8.2.2.

9 STATISTICAL METHODS

All statistical analyses will be conducted by the sponsor or a CRO designated by the sponsor.

A SAP will provide full details of the analyses, data displays, and algorithms to be used for data derivations.

9.1 Analysis sets

9.1.1 Screened analysis set

The SCR includes all subjects for whom informed consent to participate in the study was obtained [see Section 10.2] and have a subject identification number.

9.1.2 Randomized analysis set

The RND includes all subjects who have been assigned to double-blind study treatment.

9.1.3 Full analysis set

The FAS includes all subjects from the RND who received at least one dose of double-blind study treatment.

To adhere to the intention-to-treat principle:

- Subjects will be evaluated according to their assigned study treatment, which may differ from the treatment they have received.
- Unless otherwise stated, all available data will be included in analyses.

9.1.4 Per-protocol set

The PPS includes all subjects from the FAS without important protocol deviations, occurring prior to Week 4, which could affect the analysis of the primary endpoint variable.

The precise reasons for excluding subjects from the PPS will be fully defined and documented in the SAP before breaking the randomization blind.

9.1.5 Safety set

The Safety set will include all subjects who received at least one dose of double-blind study treatment. Subjects will be analyzed based on the treatment received (in each period).

9.1.6 Other analysis sets

Other analysis datasets might be defined in the SAP, e.g., sub-study sets or subgroups of interest.

9.1.7 Usage of the analysis sets

The analyses of the primary endpoint and all exploratory efficacy endpoints will be performed using the FAS. Baseline and disease characteristics will be analyzed on the FAS as well.

The analyses of the primary endpoint will be repeated based on the PPS.

The Safety set will be used for the analysis of safety endpoints (including previous and concomitant medications, and study treatment exposure).

Subject data will be listed using the SCR, unless otherwise specified.

9.2 Description of statistical analyses

All available data for each subject, regardless of intercurrent events, will be used in all statistical analyses, unless otherwise specified.

All efficacy analyses will be based on the FAS, unless otherwise specified.

9.2.1 Overall testing strategy

The primary efficacy endpoint of this study is defined as the change from Baseline to Week 4 in sTST.

Hypotheses are defined as follows:

- H_0: Mean of the within-subject changes in sTST from baseline to Week 4 between daridorexant 50 mg and placebo = 0
- H_1: Mean of the within-subject changes in sTST from baseline to Week 4 between daridorexant 50 mg and placebo ≠ 0

The null hypothesis will be tested at a two-sided alpha of 0.05.

9.2.2 Analysis of the primary efficacy endpoint

The primary endpoint will be analyzed based on an MMRM. Some sensitivity analyses will also be performed for the primary endpoint. These analyses will not form part of the testing strategy.

No secondary endpoints are defined for this study.

9.2.2.1 Estimands

Estimands are defined by five attributes: treatment condition of interest, target population, endpoint, strategy for addressing intercurrent events (i.e., premature discontinuation of treatment or use of other, forbidden, medication), and population-level summary.

The primary estimand is based on the primary endpoint. For the primary estimand the treatment condition is daridorexant 50 mg once daily for up to 4 weeks, whereas the alternative condition is placebo once daily for the same period. The other four attributes are given in Table 4.

The secondary estimand is based on the primary endpoint as well. Intercurrent events considered are premature treatment discontinuations. Details are provided in Table 4.

Table 4 Estimand for the primary objective

Estimand	Target Population	Endpoint	Strategy for addressing intercurrent events	Population-level summary
Primary Estimand	Study subjects with insomnia and nocturia	Change from Baseline to Week 4 in sTST	Treatment policy, i.e., endpoint data after intercurrent events are used.	Treatment effect expressed as difference of LS Mean changes from Baseline to Week 4 (daridorexant minus placebo; from MMRM)
Secondary Estimand	Study subjects with insomnia and nocturia	Change from Baseline to Week 4 in sTST	Hypothetical, i.e., endpoint data collected after intercurrent events are not used.	Treatment effect expressed as difference of LS Mean changes from Baseline to Week 4 (daridorexant minus placebo; from MMRM)

LS Mean = least squares mean; MMRM = mixed model for repeated measures; sTST = subjective total sleep time.

9.2.2.2 Variable definition (sTST)

The change from Baseline[a] to Week 4[b] in sTST is calculated as follows:

Change from Baseline = Averaged value at Week 4 – Averaged value at Baseline.

[a] Baseline is the mean value based on the screening sleep diary for sTST, performed on the 7 days preceding Randomization.

[b] 'Week 4' is the mean value based on the sleep diary entries for sTST performed on study days 23–29 for each period. Data after the EOTP I/II visits will not be included in the analysis, as subjects are expected to be on double-blind treatment up to that point.

As sTST for Weeks 1–3 will also be included in the MMRM, definitions for the changes from baseline will be identical. For Week 1, sTST is averaged across days 2–8, for Week 2 across days 9–15, and for Week 3 across days 16–22.

Subjects must have at least 2 days of data during each week to calculate a weekly mean. Otherwise, the mean value will be considered missing for that week.

9.2.2.3 Analysis of primary estimand (primary efficacy analysis)

Changes from baseline to post-baseline visits in sTST will be analyzed using an MMRM with change from baseline in sTST as response, treatment group (daridorexant 50 mg; placebo), period (Period I; Period II), and week within period (Week 1; Week 2; Week 3; Week 4) as factors, baseline sTST assessment as covariate, and the interaction of treatment group × week.

To evaluate the efficacy hypotheses, the difference in LS mean change from baseline between daridorexant 50 mg and placebo at Week 4 will be estimated from the MMRM. An unstructured covariance matrix will be used to account for the correlation between repeated measurements from the same subject. In the event of convergence issues of the MMRM, the primary estimand will be estimated as described in the SAP. This approach relies on the Missing at Random assumption.

9.2.2.4 Handling of missing data and intercurrent events

Section 9.2.2.1 explains how the primary efficacy endpoint is derived in the event of partially missing data.

The analyses of the primary endpoint will only include subjects with a valid baseline and at least one of the four weekly assessments for sTST, following the same approach as in the Phase 3 program. The approach is justified, as very limited dropouts are expected (< 3%) due to the short duration of the treatment period (4 weeks). Every effort will be made to keep all subjects in the study, even in the event of premature treatment discontinuations, to collect all the relevant data for the analysis of the primary endpoint. Data collected after premature discontinuation of treatment will be included in the analysis (following the treatment policy strategy for the primary estimand).

The analysis of the primary endpoint will also be performed *excluding* data collected after premature discontinuation of treatment (following the hypothetical strategy for the secondary estimand).

9.2.2.5 Sensitivity analyses

As the collection of urine during pre-defined study nights might have an impact on the primary outcome sTST, a sensitivity analysis will be performed removing those days from the weekly averages.

For this analysis, ‘Baseline’ is defined as the mean value based on the screening sleep diary for sTST, recorded on the 7 days preceding Randomization, except for the nights where urine was collected. ‘Week 4’ is defined as the mean value based on the sleep diary entries for sTST recorded on study days 23–29 for each period, except for the nights where urine was collected. As sTST for Weeks 1–3 will also be included in the MMRM, definitions for the changes from baseline will be identical. Subjects must have at least 2 days of data

during each week to calculate a weekly mean. Otherwise, the mean value will be considered missing for that week.

9.2.2.6 Supportive analyses

The analyses of the primary endpoint will be repeated on the PPS (based on the same MMRM).

No supplementary analyses are currently foreseen in the protocol. Additional analyses may be added to the SAP at a later time point.

9.2.2.7 Subgroup analyses

No subgroup analyses are planned for this study because of the small study size. Some potential subgroup analyses might be added at a later stage and will be defined in the SAP.

9.2.3 Analysis of the secondary efficacy endpoints

No secondary efficacy endpoints are defined in this study.

9.2.4 Analysis of other efficacy endpoints

The analyses of all other exploratory efficacy outcomes will be described in detail in the SAP. Exploratory variables may also be analyzed by subgroup. Exploratory efficacy endpoints will be analyzed at each relevant time point listed in the schedule of activities [Table 1] along with any data from unscheduled visits as appropriate.

9.2.5 Analysis of safety outcomes

The Safety set will be used to perform all safety analyses. Safety analyses will be conducted by period.

If not otherwise stated, only treatment-emergent safety data will be considered in tables and figures. All safety data will be included in listings, with flags for safety data not considered to be treatment emergent.

9.2.5.1 Adverse events

9.2.5.1.1 Treatment-emergent AEs and SAEs

TEAEs and SAEs will be tabulated by study treatment, SOC, and preferred terms within each SOC: the number and percentage of subjects who experienced at least 1 (S)AE, at least 1 (S)AE within each SOC, and at least 1 (S)AE within each preferred term will be displayed. (S)AEs will also be summarized by decreasing frequency of preferred term. (S)AEs will also be tabulated by maximum intensity and by relationship to study treatment.

AEs and SAEs are considered treatment-emergent AEs and SAEs if they occur up to 5 days after DB study treatment discontinuation.

9.2.5.1.2 AEs leading to premature discontinuation of study treatment

AEs leading to premature discontinuation of study treatment will be summarized in a similar manner as those described in Section 9.2.5.1.1.

9.2.5.2 Vital signs

Descriptive summary statistics by visit and study treatment will be provided for observed treatment-emergent values and absolute changes from baseline in pulse rate, systolic and diastolic blood pressure.

9.2.6 Analyses of other outcomes

A full description of all other safety analyses will be provided in the SAP.

9.3 Interim analyses

No interim analysis is planned for this study.

9.4 Sample size

The assumptions for the sample size calculations were determined using data from studies ID-078A202 and ID-078A301 for the treatment groups daridorexant 50 mg and placebo.

Data of sTST changes from baseline and the corresponding SDs were derived based on simulations using sTST data at Baseline and at Month 1 from the ID-078A301 study for the age group ≥ 55 years. Subsets of 50 subjects were randomly selected from both the daridorexant 50 mg and placebo groups and compared via t-tests for independent samples, with means and SDs averaged across 1000 iterations. The simulations resulted in a mean difference of the change from baseline to Month 1 in sTST of 26 min for daridorexant 50 mg and placebo, with SDs of 42.5 min for placebo and 50.5 min for daridorexant 50 mg.

Correlations between daridorexant 50 mg and placebo for sTST data were derived based on the cross-over study ID-078A202 (for subjects aged ≥ 65 years). The Pearson correlation coefficient was estimated at 0.58. Combining all the information above resulted in an SD of the difference in the change of sTST from baseline to Month 1 of 44 min (based on the variance/covariance formula).

Based on a two-sided type I error of 0.05, an estimated within subject mean difference of the change from baseline to Month 1 in sTST between daridorexant 50 mg and placebo of 26 min and an associated SD of 44 min, a total sample size of 50 subjects, in this cross-over setting, provides at least 90% power, based on a two-sided paired t-test. A smaller within subject mean difference between daridorexant 50 mg and placebo of 20 min still results in power of at least 80%.

9.4.1 Power considerations for the endpoint change from baseline to Week 4 in number of nocturnal voids assessed using a voiding diary

Sample size calculations/considerations for the endpoint change from baseline to Week 4 in number of nocturnal voids assessed using a voiding diary were performed based on two-sided paired t-tests for different scenarios:

1. Assuming a within-subject mean difference between daridorexant 50 mg and placebo in the number of nocturnal voids of 0.30 (averaged across 3 consecutive nights) after 4 weeks of treatment, and assuming an SD of the within-subject difference of 0.7, leads to approximately 80% power, based on 50 subjects and a type I error of 0.05, using a two-sided paired t-test.

2. Increasing the SD of the within-subject difference between daridorexant 50 mg and placebo to 1.0, would require a within-subject mean difference in the number of nocturnal voids of 0.45 to reach 80% power for the same number of subjects.

3. Increasing the SD of the within-subject difference between daridorexant 50 mg and placebo to 1.2, would require a within-subject mean difference in the number of nocturnal voids of 0.55 to reach 80% power for the same number of subjects.

Assumptions for the sample size calculations were derived based on Key Opinion Leader feedback and based on data from previous nocturia studies with a study duration of up to 4 weeks [Ferring 2015, Ferring 2012, Miwa 2011].

10 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1 Regulatory and ethical considerations

The sponsor personnel and the investigator(s) will ensure that the study is conducted in full compliance with ICH GCP guidelines, the principles of the Declaration of Helsinki, the protocol and with the laws and regulations of the country in which the study is conducted.

The investigator and/or sponsor/CRO will submit this protocol and any related document(s) provided to the subject (such as the ICF) to an IEC/IRB and to the health authority (as applicable). Approval from both the IEC/IRB and the health authority must be obtained before starting the study and must be documented in a dated letter to the investigator and/or sponsor/CRO, clearly identifying the study, the documents reviewed, and the date of approval.

Modifications made to the protocol or the ICF after receipt of the approval must also be submitted as amendments by the investigator / authorized delegate and/or sponsor/CRO to the IEC/IRB and to the health authority in accordance with local procedures and regulations.

10.2 Informed consent process

It is the responsibility of the investigator / authorized delegate to obtain informed consent according to ICH GCP and Declaration of Helsinki guidelines and local regulations from each individual participating in this study. The investigator / authorized delegate must explain to subjects that they are completely free to refuse to enter the study, or to voluntarily withdraw from the study at any time for any reason without having to provide any justification. Special attention must be paid to the information needs of specific subject populations and of individual subjects, as well as to the methods used to deliver the information. Adequate time must be given for the subject to consider his or her decision to participate in the study and it must be verified that the subject has understood the information (e.g., by asking the subject to explain what is going to happen).

If a revised version of the ICF is approved by health authorities (if applicable) and IRBs/IECs:

- Newly recruited subjects must provide consent using the most current version of the ICF(s).
- Subjects who are already participating in the study (e.g., already recruited) must be re-consented using the most current version of the ICF(s) if necessary (e.g., additional study procedure, new safety information) and/or requested (e.g., as per IRB/IEC requirements).

A copy of the signed and dated ICF is given to the subject; the original is filed in the site documentation. The informed consent process must be fully documented in the subject's medical records. This must include at a minimum the study reference, the subject identification number, the date and, if applicable, time when the subject was first introduced to the study, the language in which the study has been explained, the date and, if applicable, time of consent, who participated in the consent discussion, who consented the subject, and any additional persons present during the consent process (e.g., subject's family member[s]), and the information that a copy of the signed ICF was given to the subject.

If the site intends to recruit subjects who are considered vulnerable (e.g., subject cannot read or write, does not speak or understand the ICF language), additional measures must be implemented to ensure the subject's rights are respected and the consent obtained is legally valid. The sponsor, the regulatory authorities (if applicable), and the IEC/IRB must be informed prior to the recruitment. The consent process (e.g., involvement of an impartial witness) must be fully described, submitted to, and approved by the IEC/IRB, according to procedures and before subjects are recruited.

10.3 Data protection and privacy

Subject data confidentiality and privacy are strictly held in trust by the investigators, their staff and the sponsor or delegate.

The investigator / authorized delegate must ensure that data confidentiality is maintained. On eCRFs or other documents (e.g., documents attached to SAE forms / Pregnancy forms) submitted to the sponsor and any vendors or CROs, subjects must be identified only by number and never by their name or initials, hospital numbers, or any other personal identifier. The investigator / authorized delegate must keep a subject identification code list at the site. Documents identifying the subjects (e.g., signed ICFs) must not be sent to the sponsor or any vendors or CROs, and must be kept in strict confidence by the investigator / authorized delegate.

In the electronic device, there will be no possibility to enter any personal identifier and the subject will only be identified by the study site and subject identification number. Each time the subject makes an entry in the electronic device, he/she will be required to enter his/her own confidential password.

The subjects must be informed that their personal study-related data will be used by the sponsor in accordance with the applicable data protection law.

The subjects must be informed that their medical records may be inspected by the sponsor or sponsor's delegate, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.4 Indemnification, compensation, and refund of expenses to subjects and investigators

The sponsor provides insurance to indemnify (with both legal and financial coverage) the investigator/site against claims arising from the study, except for claims that arise from malpractice and/or negligence.

The indemnification of the subjects in the event of study-related injuries will comply with applicable regulations.

Subjects will be reimbursed for study-related expenses (e.g., travel costs, meals, accommodation), and may be offered financial compensation for their participation in the study only to the extent permitted by applicable local law.

10.5 Essential documents and retention of documents

The investigator / authorized delegate must maintain adequate records necessary for the reconstruction and evaluation of the study. Several attributes are considered of universal importance to source data and the records that hold those data. These include that the data

and records are accurate, legible, contemporaneous, original (or a certified copy), attributable, complete, consistent, enduring, and available when needed.

These records are to be classified into 2 different categories of document: ISF and subjects' source documents.

These records must be kept by the investigator/site for as long as is necessary to comply with the sponsor's requirements (i.e., as specified in the clinical study agreement), ICH GCP and national and/or international regulations, whichever is the longest period. If the investigator/site cannot guarantee this archiving requirement at the site for any or all of the documents, special arrangements, respecting the data confidentiality, must be made between the investigator/site and the sponsor to store these documents off site, so that they can be retrieved in the event of a regulatory inspection. Study documents must not be destroyed without prior written approval from the sponsor. If the site needs to transfer the study records to another location and/or if the site facility can no longer store the study records, the investigator/site must immediately inform the sponsor.

10.5.1 Investigator Site File

Each site will maintain an ISF. It will contain all the essential documents that are required to be up-to-date and filed at the site as per ICH GCP section 8.

The ISF must be stored in a secure and access-restricted area during and after the study.

10.5.2 Source documents

All source documents should be completed in a neat and legible manner to ensure accurate interpretation and traceability of the data. Data reported in the eCRF derived from source documents must be consistent with the source documents.

If the site is using electronic/computerized system(s) to store subject medical records, it can be used for the purpose of the clinical study if it is validated (as per 21 CFR Part 11 or equivalent standard) and if the CRA has been provided personal access to subjects' medical records in order to verify consistency between electronic source data and the eCRF during monitoring visits.

If the site is using electronic/computerized system(s) to store subject medical records but it could not be confirmed that the system(s) is/are validated or if the CRA could not be provided access to the system(s), the site is requested to print the complete set of source data needed for verification by the CRA. The printouts must be numbered, stapled together with a cover sheet, signed, and dated by the investigator / authorized delegate to confirm that these certified copies are exact copies containing the same information as the original source data. The printouts will be considered as the official clinical study records. Once printed and certified, the document must not be edited/changed (e.g., manual notes added, clinical value changed) in order not to impact the validity of the certification. If the data

needed to be changed (e.g., correction of a mistake) the change(s) must be done in the electronic/computerized system and a new copy must be printed and certified.

In order to verify that the process the site uses to prepare certified copies is reliable, the CRA periodically requests that a site representative logs into the electronic/computerized system so the CRA could verify the entries in the system against the printouts. The CRA does not need to perform these activities for all subjects but at least for some of them and for key data (e.g., eligibility criteria, primary and key secondary endpoints) as per the sponsor/CRO instructions.

All records on the electronic device will be date and time stamped.

Entries recorded by the subject in the electronic device (i.e., sleep diary including VAS, ISI©, IDSIQ, EQ-5D-3L, PGA-S daytime symptoms, PGI-C daytime and nighttime symptoms, PGA-S daily life, PGI-C daily life, ICIQ-NQoL, ICIQ-MLUTS or ICIQ-FLUTS, treatment satisfaction NRS, treatment preference, and narrative) as well as the physician-reported global assessment (i.e., C-SSRS©) on an electronic device are considered source data.

Entries recorded on paper such as the physician-reported global assessment (i.e., the C-SSRS© in the event the table is not accessible) are considered source data.

10.6 Data handling

10.6.1 Data collection, data transfer procedure, and data access

The investigator / authorized delegate is responsible for ensuring the accuracy, completeness, and timely reporting of subject's data.

Electronic data capture will be used to collect eCRF data. The investigator and site personnel will be trained to enter and edit the data via a secure network, with secure access features (username, password, and identification — an electronic password system). A complete electronic audit trail will be maintained. The investigator / authorized delegate will approve the data (i.e., confirm the accuracy and completeness of the data recorded) using an electronic signature (as per US 21 CFR Part 11).

Subject recruitment and enrollment data will be completed for all subjects (i.e., eligible and non-eligible) through the IRT system and eCRF.

For each subject recruited, regardless of study treatment initiation, an eCRF must be completed and signed by the investigator / authorized delegate. This also applies to those subjects who fail to complete the study.

Site personnel will review and ensure completeness and readability of the subjects' entries. Site personnel can correct electronic subject data in the electronic device. To request any

data changes, a data correction form will be completed by the site personnel and processed according to the CRO procedures.

10.6.2 Database management and quality control

The eCRF must be completed in a timely manner as per eCRF completion guidelines.

While entering the data, the investigator / authorized delegate will be instantly alerted to data queries by validated programmed checks. Additional data review will be performed by the sponsor personnel or delegate on an ongoing basis to look for unexpected patterns in data and for study monitoring. Should discrepant data be detected, a manual query specifying the matter and requesting clarification will be issued and visible to the investigator / authorized delegate via the eCRF. All electronic queries visible in the system either require a data correction (when applicable) and a response from the investigator / authorized delegate to clarify the queried data directly in the eCRF, or simply a data correction in the eCRF. The investigator / authorized delegate must, on request, supply the sponsor with any required background data from the study documentation or clinical records. This is particularly important when errors in data transcription are suspected. In the event of health authority queries, it is also necessary to have access to the complete study records, provided that subject data confidentiality is protected.

This process will continue until database lock.

Electronic questionnaires will be processed through a central vendor and the results of the enrolled subjects will be electronically sent to the sponsor at pre-specified intervals with a final transfer prior to database lock. During the study, the site staff and sponsor representatives can access the data in view-only mode on the central server of the respective vendor [see also Section 10.6.1].

AEs and medical history will be coded with MedDRA. Medications will be coded with the World Health Organization Drug Dictionary.

After the database has been declared complete and accurate, the database will be locked. Any changes to the database after that time may only be made as described in the appropriate sponsor Quality System documents. The sponsor is responsible for ensuring that the investigator / authorized delegate will have permanent access (either “write” access or “read-only” access) to the site eCRF subject data, until receipt of an electronic copy of the site eCRFs (including the audit trail).

10.7 Protocol deviations

A protocol deviation is any change, divergence, or departure from the study design or procedures defined in the protocol.

Prospective approvals of protocol deviations, also known as protocol waivers or exemptions, are not permitted.

The investigator must conduct the study in compliance with the IEC/IRB-approved and/or the regulatory authority-approved version of the protocol and must not implement any deviation/change from the protocol, except when deviation is necessary to eliminate an immediate hazard to the subject.

Protocol deviations must be reported to the IEC/IRB and regulatory authorities according to local requirements.

10.8 Clinical monitoring

Prior to study start at a site, all required approvals must be obtained. A site initiation visit will be performed after the required essential study documents are approved by the sponsor. The study treatment will be shipped to the site upon approval of the required essential documents.

The investigator must ensure that all key site personnel involved in the study are present/available during the site initiation visit and will dedicate sufficient time to it.

The site initiation visit must be completed before the site can start recruiting subjects. Following the site initiation visit, a copy of the completed initiation visit report and follow-up letter will be provided to the investigator and filed in the ISF.

During the study, the CRA will contact and visit the site regularly and must be permitted, on request, to have access to study facilities and all source documents needed to verify adherence to the protocol and the completeness, consistency, and accuracy of the data being entered in the eCRFs and other protocol-related documents. Monitoring activities will be performed according to the study-specific monitoring guidelines. The methodology and the frequency of the monitoring visits will be mainly based on subject recruitment rate and critical data-collection times.

The investigator / authorized delegate must ensure that the eCRF is completed as per the eCRF completion guidelines and that all requested subject files (e.g., ICFs, medical notes/charts, other documentation verifying the activities conducted for the study) are available for review by the CRA. The required site personnel must be available during monitoring visits and allow adequate time to meet with the CRA to discuss study-related issues.

The investigator agrees to cooperate with the CRA to ensure that any issues detected in the course of these monitoring visits are resolved.

A close-out visit will be performed for any initiated site when there are no more active subjects and all follow-up issues have been resolved. If a site does not screen any subjects, the close-out visit may be performed prior to study closure at the discretion of the sponsor.

10.9 Study safety oversight

Study safety information (AEs, SAEs, vital signs, and study-specific examinations, as required) is monitored and reviewed on a continuous basis by the sponsor.

The sponsor may request additional data pertaining to the diagnostic work-up of an AE or SAE (e.g., medical imaging, local laboratory values) for the purpose of monitoring safety. Such additional data may be shared with external experts.

10.10 Early termination or suspension of the study

The sponsor reserves the right to terminate the study at any time globally or locally. Investigators can terminate the participation of their site in the study at any time.

If the study is suspended or early terminated, the sponsor will promptly inform the investigators, the IECs/IRBs, and health authorities, as appropriate, and provide the reasons for the suspension or termination.

If the study is suspended or early terminated for any reason, the investigator — in agreement with the sponsor — must promptly inform all recruited subjects and ensure their appropriate treatment and follow-up, as described in Section 6.3. The sponsor may inform the investigator of additional procedures to be followed to ensure that adequate consideration is given to the protection of the subjects' interests.

In addition, if the investigator suspends or terminates the study without prior agreement from the sponsor, the investigator must promptly inform the sponsor personnel and the IEC/IRB and provide both with a detailed written explanation of the termination or suspension.

10.11 Audit

The sponsor representatives may audit the investigator site during the study or after its completion. The purpose of this visit will be to determine the investigator's adherence to ICH GCP, the protocol, and applicable regulations. Adherence to the sponsor requirements (e.g., SOPs) will also be verified. Prior to initiating this audit, the investigator will be contacted by the sponsor to arrange a time for the audit.

The investigator and site personnel must cooperate with the auditor(s) and allow access to all study documentation (e.g., subject records) and facilities.

10.12 Inspections

Health authorities and/or the IEC/IRB may also conduct an inspection of this study at the site (during the study or after its completion).

Should an inspection be announced by a health authority and/or the IEC/IRB, the investigator must immediately inform the sponsor (usually via the CRA and copying the following mailbox: gcp@idorsia.com) that such a request has been made.

The investigator and site personnel must cooperate with the sponsor to handle the inspection related to sponsor studies. The investigator and site personnel must also cooperate with the inspector(s) to ensure proper performance of the inspection and allow access to all study documentation (e.g., subject records) and study facilities.

10.13 Reporting of study results and publication

The sponsor will register the clinical study in publicly accessible registers (e.g., clinicaltrials.gov) and disclose the results as required by law.

Study results will be documented in a clinical study report that will be signed by the sponsor's representatives and the coordinating investigator.

The sponsor will provide a short summary of this clinical study in lay language to the sites, who are then encouraged to share it with the participants, 12 months following completion of the study.

In accordance with the Good Publication Practices and ethical practice as outlined in internationally recognized guidance documents (e.g., European Medical Writers Association, American Medical Writers Association, International Society for Medical Publication Professionals), the results of the study will be submitted for publication in a peer-reviewed journal. Study results can be submitted for presentation at a congress before submission to a peer-reviewed journal.

The coordinating investigator will have the opportunity to review the analysis of the data and to discuss the interpretation of the study results with the sponsor personnel prior to submission to a peer-reviewed journal or presentation at a congress.

Authorship will be determined in accordance with the International Committee of Medical Journal Editors criteria, and be based on:

- substantial contributions to the conception or design of the study, or the acquisition, analysis, or interpretation of data; and
- drafting of the publication or critical review for important intellectual content; and
- providing final approval of the version to be published; and

- agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

The list of authors of any publication of study results may include representatives of the sponsor and will be determined by mutual agreement.

Any study-related publication written independently by investigators must be submitted to the sponsor for review at least 60 days prior to submission for publication or presentation at a congress. Upon review, the sponsor may provide comments, and may also request alterations and/or deletions for the sole purpose of protecting its confidential information and/or patent rights. Neither the institution nor the investigator is permitted to write a publication during such a review period.

11 REFERENCES

[Daridorexant IB] Investigator's Brochure for daridorexant, version 10. Idorsia Pharmaceuticals Ltd; January 2023.

[Abraham 2004] Abraham L, Hareendran A, Mills IW, Martin ML, Abrams P, Drake MJ, et al. Development and validation of a quality-of-life measure for men with nocturia. Urology. 2004 Mar; 63(3):481-6.

[Asplund 1992] Asplund R, Aberg H. Health of the elderly with regard to sleep and nocturnal micturition. Scand J Prim Health Care. 1992 Jun; 10(2):98-104.

[Bliwise 2009] Bliwise DL, Foley DJ, Vitiello MV, Ansari FP, Ancoli-Israel S, Walsh JK. Nocturia and disturbed sleep in the elderly. Sleep Med. 2009 May; 10(5):540-8.

[Brookes 2004] Brookes ST, Donovan JL, Wright M, Jackson S, Abrams P. A scored form of the Bristol Female Lower Urinary Tract Symptoms questionnaire: data from a randomized controlled trial of surgery for women with stress incontinence. Am J Obstet Gynecol. 2004 Jul;191(1):73-82.

[Bright 2014] Bright E, Cotterill N, Drake M, Abrams P. Developing and validating the International Consultation on Incontinence Questionnaire bladder diary. Eur Urol. 2014 Aug;66(2):294-300.

[Coyne 2003] Coyne KS, Zhou Z, Bhattacharyya SK, Thompson CL, Dhawan R, Versi E. The prevalence of nocturia and its effect on health-related quality of life and sleep in a community sample in the USA. BJU Int. 2003 Dec; 92(9):948-54.

[Dauvilliers 2020] Dauvilliers Y, Zammit G, Fietze I, Mayleben D, Kinter DS, Pain S, et al. Daridorexant, a new dual orexin receptor antagonist to treat insomnia disorder. Ann Neurol. 2020 Mar;87(3):347-56.

[Donovan 2000] Donovan JL, Peters TJ, Abrams P, Brookes ST, de aa Rosette JJ, Schäfer W. Scoring the short form ICSmaleSF questionnaire. International Continence Society. J Urol. 2000 Dec;164(6):1948-55.

[Drake 2005] Drake NL, Flynn MK, Romero AA, Weidner AC, Amundsen CL. Nocturnal polyuria in women with overactive bladder symptoms and nocturia. Am J Obstet Gynecol. 2005 May; 192(5):1682-6.

[EMA 2011] European Medicines Agency. Guideline on medicinal products for the treatment of insomnia. EMA/CHMP/16274/2009 Rev. 1. 17 February 2011 [accessed on 6 April 2022]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2011/02/WC500102351.pdf

[FDA 1977] Food and Drug Administration (US): Guideline for the clinical evaluation of hypnotic drugs. September 1977; Available from: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071711.pdf

[Ferring 2012] Ferring Pharmaceuticals. Comparative Trial to Investigate the Dose-Response of 4 Different Dose Levels of Minirin Melt and Placebo (NOC). ClinicalTrials.gov Study Record, Identifier: NCT01184859. Last update posted: 25 May 2012. Accessed on 12 April 2022. Available from: https://clinicaltrials.gov/ct2/show/NCT01184859

[Ferring 2015] Ferring Pharmaceuticals. Efficacy and Safety of Desmopressin Melt for the Treatment of Nocturia. ClinicalTrials.gov Study Record, Identifier: NCT00477490. Last update posted: 1 November 2015. Accessed on 12 April 2022. Available from: https://clinicaltrials.gov/ct2/show/NCT00477490

[Fu 2011] Fu F-G, Lavery HJ, Wu D-L. Reducing nocturia in the elderly: A randomized placebo-controlled trial of staggered furosemide and desmopressin. Neurourol Urodyn. 2011;30(3):312-16.

[Hudgens 2021] Hudgens S, Phillips-Beyer A, Newton L, Seboek Kinter D, Benes H. Development and Validation of the Insomnia Daytime Symptoms and Impacts Questionnaire (IDSIQ). Patient 2021;14(2):249-68.

[Kim 2016] Kim JW, Moon YT, Kim KD. Nocturia: The circadian voiding disorder. Investig Clin Urol. 2016 May;57(3):165-73.

[Konishi 2021] Konishi S, Hatakeyama S, Imai A, Kumagai M, Okamoto T, Okita K, et al. A longitudinal study of bidirectional relationships between sleep disorder and frequency of nocturia: Results from the Iwaki Health Promotion Project. Urol Int. 2021; 105(3-4):232-9.

[McCall 2004] McCall WV. Sleep in the elderly: Burden, diagnosis, and treatment. Prim Care Companion J Clin Psychiatry. 2004;6(1):9–20.

[Mignot 2022] Mignot E, Mayleben D, Fietze I, Leger D, Zammit G, Bassetti CLA, et al. Safety and efficacy of daridorexant in patients with insomnia disorder: results from two multicentre, randomised, double-blind, placebo-controlled, phase 3 trials. Lancet Neurol. 2022 Feb;21(2):125-39. Erratum in: Lancet Neurol. 2022 Apr 5.

[Miller 2016] Miller PS, Hill H, Andersson FL. Nocturia work productivity and activity impairment compared with other common chronic diseases. Pharmacoeconomics. 2016 Dec; 34(12):1277-97.

[Miwa 2011] Miwa K, Nishino Y, Kikuchi M, Masue T, Moriyama Y, Deguchi T. Efficacy of combination therapy with tamsulosin and zolpidem on nocturia in patients with benign prostatic hyperplasia. Cent European J Urol. 2011; 64(4):232-5.

[Morin 1993] Morin CM, Kowatch RA, Barry T, Walton E. Cognitive-behavior therapy for late-life insomnia. J Consult Clin Psychol. 1993;61(1):137-46.

[Morin 2011] Morin CM, Belleville G, Bélanger L, Ivers H. The Insomnia Severity Index: psychometric indicators to detect insomnia cases and evaluate treatment response. Sleep. 2011 May 1;34(5):601-8.

[Neubauer 2014] Neubauer DN. New and emerging pharmacotherapeutic approaches for insomnia. Int Rev Psychiatry. 2014;26(2):214-24.

[Oelke 2017] Oelke M, De Wachter S, Drake MJ, Giannantoni A, Kirby M, Orme S, et al. A practical approach to the management of nocturia. Int J Clin Pract. 2017 Nov; 71(11).

[Ohayon 2008] Ohayon MM. Nocturnal awakenings and comorbid disorders in the American general population. J Psychiatr Res. 2008 Nov; 43(1):48-54.

[Pigeon 2007] Pigeon WR, Crabtree VM, Scherer MR. The future of behavioral sleep medicine. J Clin Sleep Med. 2007;3(1):73-9.

[Posner 2007] Posner K, Oquendo MA, Gould M, Stanley B, Davies M. Columbia Classification Algorithm of Suicide Assessment (C-CASA): classification of suicidal events in the FDA's pediatric suicidal risk analysis of antidepressants. Am J Psychiatry. 2007 Jul;164(7):1035-43.

[QUVIVIQ™ SmPC] QUVIVIQ™ (daridorexant) 25 mg and 50 mg film-coated tablets. Summary of Product Characteristics. [accessed on 12 July 2022] Available from: https://www.ema.europa.eu/en/documents/product-information/quviviq-epar-product-information_en.pdf

[Reynard 1998] Reynard JM, Cannon A, Yang Q, Abrams P. A novel therapy for nocturnal polyuria: a double-blind randomized trial of frusemide against placebo. Br J Urol. 1998 Feb; 81(2):215-8.

[Scharf 2007] Scharf MB, Black J, Hull S, Landin R, Farber R. Long-term nightly treatment with indiplon in adults with primary insomnia: results of a double-blind, placebo-controlled, 3-month study. Sleep. 2007;30(6):743-52

[Schutte-Rodin 2008] Schutte-Rodin S, Broch L, Buysse D, Dorsey C, Sateia M. Clinical guideline for the evaluation and management of chronic insomnia in adults. J Clin Sleep Med. 2008;4:487–504.

[Shao 2016] Shao IH, Wu CC, Hsu HS, Chang SC, Wang HH, Chuang HC, et al. The effect of nocturia on sleep quality and daytime function in patients with lower urinary tract symptoms: a cross-sectional study. Clin Interv Aging. 2016;11:879-85.

[Tyagi 2014] Tyagi S, Resnick NM, Perera S, Monk TH, Hall MH, Buysse DJ. Behavioral treatment of insomnia: also effective for nocturia. J Am Geriatr Soc. 2014 Jan; 62(1):54-60.

[Van Kerrebroeck 2002] Van Kerrebroeck P, Abrams P, Chaikin D, Donovan J, Fonda D, Jackson S, et al. The standardization of terminology in nocturia: report from the standardization subcommittee of the International Continence Society. BJU Int. 2002 Dec; 90 Suppl 3:11-5.

[Weiss 2019] Weiss JP, Everaert K. Management of nocturia and nocturnal polyuria. Urology. 2019 Nov; 133S:24-33.

[Yu 2006] Yu HJ, Chen FY, Huang PC, Chen TH, Chie WC, Liu CY. Impact of nocturia on symptom-specific quality of life among community-dwelling adults aged 40 years and older. Urology. 2006 Apr; 67(4):713-8.

[Zammit 2020] Zammit G, Dauvilliers Y, Pain S, Kinter DS, Mansour Y, Kunz D. Daridorexant, a new dual orexin receptor antagonist, in elderly subjects with insomnia disorder. Neurology. 2020 May 26;94(21):e2222-e2232

12 APPENDICES

Appendix 1 Assessments in the context of a pandemic or epidemic disease: Recommendations and instructions

Visit 1, Visit 2, Visit 4, Visit 6, and Visit 8 must be performed on site. Should any travel restrictions or quarantine be in place, the EOTP I or EOTP II visit of Period I or II, respectively, can be performed via a phone call or a video call.

The window between two visits can be adapted to accommodate potential restrictions. Any adaptations must be documented in the subject's medical charts.

Flexibility regarding site visits for subjects who can go to sites

If the subject can travel to the investigator's site:

- The investigator should ensure the subject's safety on their way to the site by following local/country regulations (e.g., not using public transportation). Alternatively, taxis or private cars can be used, the cost of which will be reimbursed by the sponsor as per local guidelines.
- The on-site visit assessments should be performed according to the protocol.
- Visit windows can be extended, as long as the subject has enough study treatment. The reason for the delayed scheduled visit must be documented in the subject's medical charts.

Conduct of remote visits for subjects who cannot, are not allowed to, or are not willing to travel to the investigator's site

If the subject cannot, is not allowed to, or is not willing to travel to the investigator's site, the EOTP I or EOTP II visit of Period I or II, respectively, can be replaced by a phone call or video call to keep close contact with subjects. The investigator should notify the IEC/IRB in advance of remote visits if this is a local requirement.

Before the telephone call or video call visit:

The investigator / authorized delegate should ensure the following:

- The date and time that consent was obtained is documented in the subject's medical records.
- Provide details regarding how to return the study material and the remaining study treatment blister kits.

During the telephone call or video call visit:

All efforts should be made to collect the same information as collected during an on-site visit. Efficacy data will be collected, questionnaires and other assessments should be performed, even remotely, if possible. To ensure subjects' safety, the investigator / authorized delegate will conduct an interview to detect any potential AE as described below.

The investigator will interview the subject for:

- Occurrence of any new AEs or worsening of existing ones.
- When asking about the occurrence of AEs, the same process as for a site visit should be followed, i.e., use an open-ended question, such as: "Have you had any significant medical problems since the last study visit?".
- Completion of the C-SSRS© questionnaire, on-site by the investigator.
- Changes in any ongoing medication or start of new medication(s).
- Check compliance with study medication and potential overdose or other medication error(s).

Note: If closer monitoring of any of the above detected findings is required but not possible, depending on the severity of the symptoms observed and the investigator's assessment of the benefit-risk for the study participants in the trial, the investigator may consider discontinuing treatment while trying to maintain the subject in the study.

The phone or video contact must be entered in the eCRF under the EOTP I or EOTP II visit, respectively, and documented in detail (day, time and conversation) in the subject's medical charts. All assessments not performed must be entered as "Not done".

Should any additional phone calls be performed to ensure the subject's safety that are not part of the regular visit plan, the call must be entered as an unscheduled visit ('UNS') in the eCRF and documented in detail (day and reason for the 'UNS') in the subject's medical charts.

Appendix 2 Sleep Diary

Morning questionnaire

1. *Did you take your study medication last night?* Yes / No

2. *If yes, at what time did you take your study medication last night?* _ _ : _ _

3. *What time did you get into bed?* (Write the time that you got into bed. This may not be the time that you began "trying" to fall asleep.) _ _ : _ _

4. *What time did you try to go to sleep?* (record the time that you began "trying" to fall asleep) _ _ : _ _

5. *How long did it take you to fall asleep?* (Beginning at the time you wrote in question 4, how long did it take you to fall asleep.) ___min

6. *How many times did you wake up, not counting your final awakening?* (How many times did you wake up between the time you first fell asleep and your final awakening?) _____times

7. *In total, how long did these awakenings last?* (What was the total time you were awake between the time you first fell asleep and your final awakening. For example, if you woke 3 times for 20 minutes, 35 minutes, and 15 minutes, add them all up: 20+35+15=70 min or 1h10min) ____h ____min

8. *What time was your final awakening?* (Record the last time you woke up in the morning) _ _ : _ _

9. *In total, how long did you sleep last night?* (This should just be your best estimate, based on when you went to bed and woke up, how long it took you to fall asleep, and how long you were awake. You do not need to calculate this by adding and subtracting; just give your best estimate.) ____h ____min

10. *What time did you get out of bed for the day?* (What time did you get out of bed with no further attempt at sleeping? This may be different from your final awakening time (e.g., you may have woken up at 6:35 a.m. but did not get out of bed to start your day until 7:20 a.m.) _ _ : _ _

Evening questionnaire

1. *How many times did you nap or doze?* (A nap is a time you decided to sleep during the day, whether in bed or not in bed. "Dozing" is a time you may have nodded off for a few minutes, without meaning to, such as while watching TV. Count all the times you napped or dozed at any time from when you first got out of bed in the morning until you got into bed again at night.) _____times

2. *In total, how long did you nap or doze?* (Estimate the total amount of time you spent napping or dozing, in hours and minutes. For instance, if you napped twice, once for 30 minutes and once for 60 minutes, and dozed for 10 minutes, you would answer "1 hour 40 minutes.") ____h ____min

Morning VAS of the sleep diary

Rate the quality of your sleep last night by marking clearly and vertically across the line below:

Very poor ├──────────────────────────────────────┤ Very good

Rate the depth of your sleep last night by marking clearly and vertically across the line below:

Very light ├──────────────────────────────────────┤ Very deep

Rate the way you feel this morning by marking clearly and vertically across the line below:

Very sleepy ├──────────────────────────────────────┤ Not at all sleepy

Evening VAS of the sleep diary

Rate your daytime alertness today by marking clearly and vertically across the line below:

Very sleepy ├──────────────────────────────────────┤ Wide awake and alert

Rate your daily ability to function today by marking clearly and vertically across the line below:

Poor ├──────────────────────────────────────┤ Excellent

Appendix 3 Insomnia Daytime Symptoms and Impacts Questionnaire

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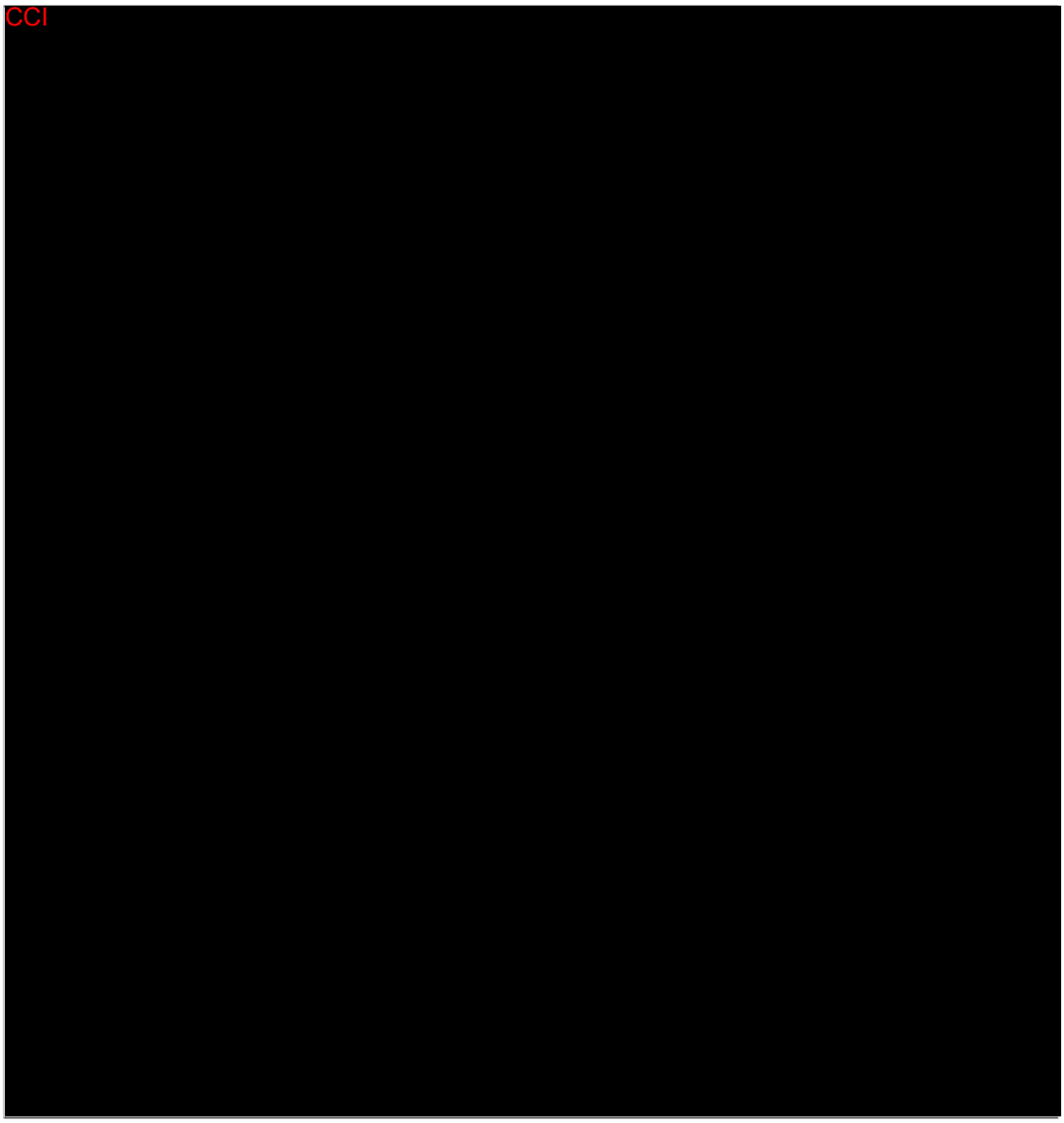
[redacted]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Appendix 4 Insomnia Severity Index®

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Appendix 5 Global Scales

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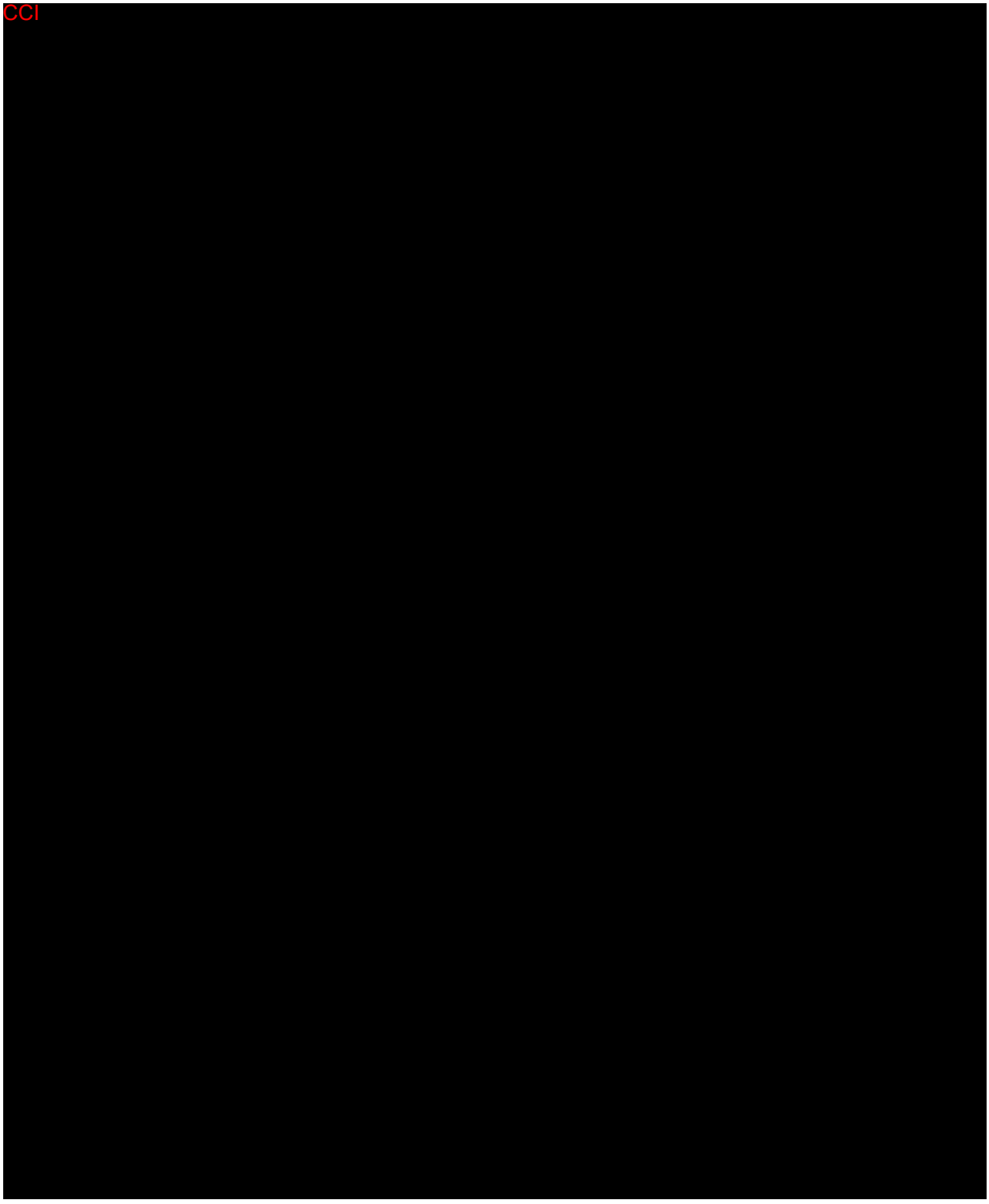

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Appendix 6 EQ-5D-3L

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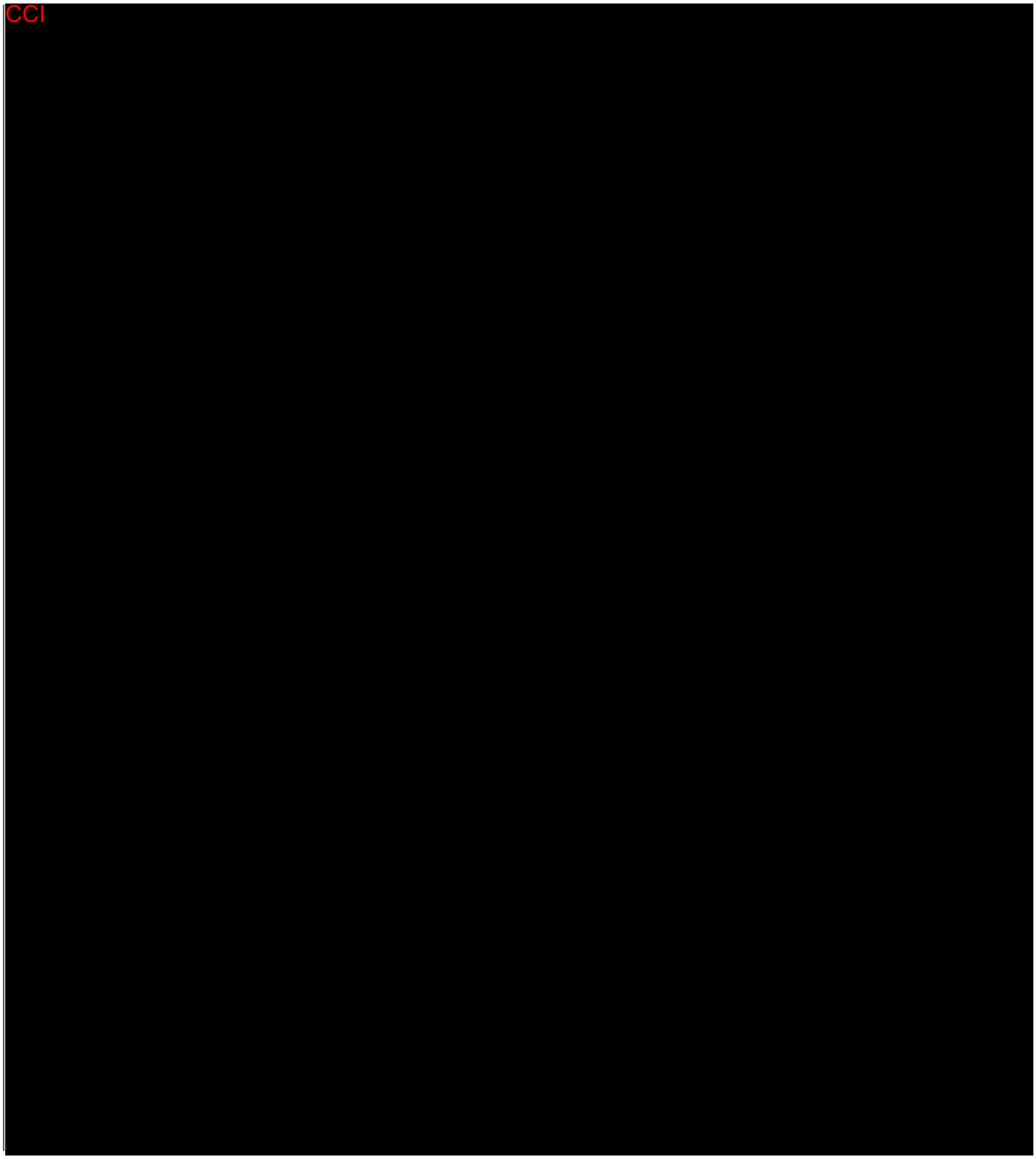

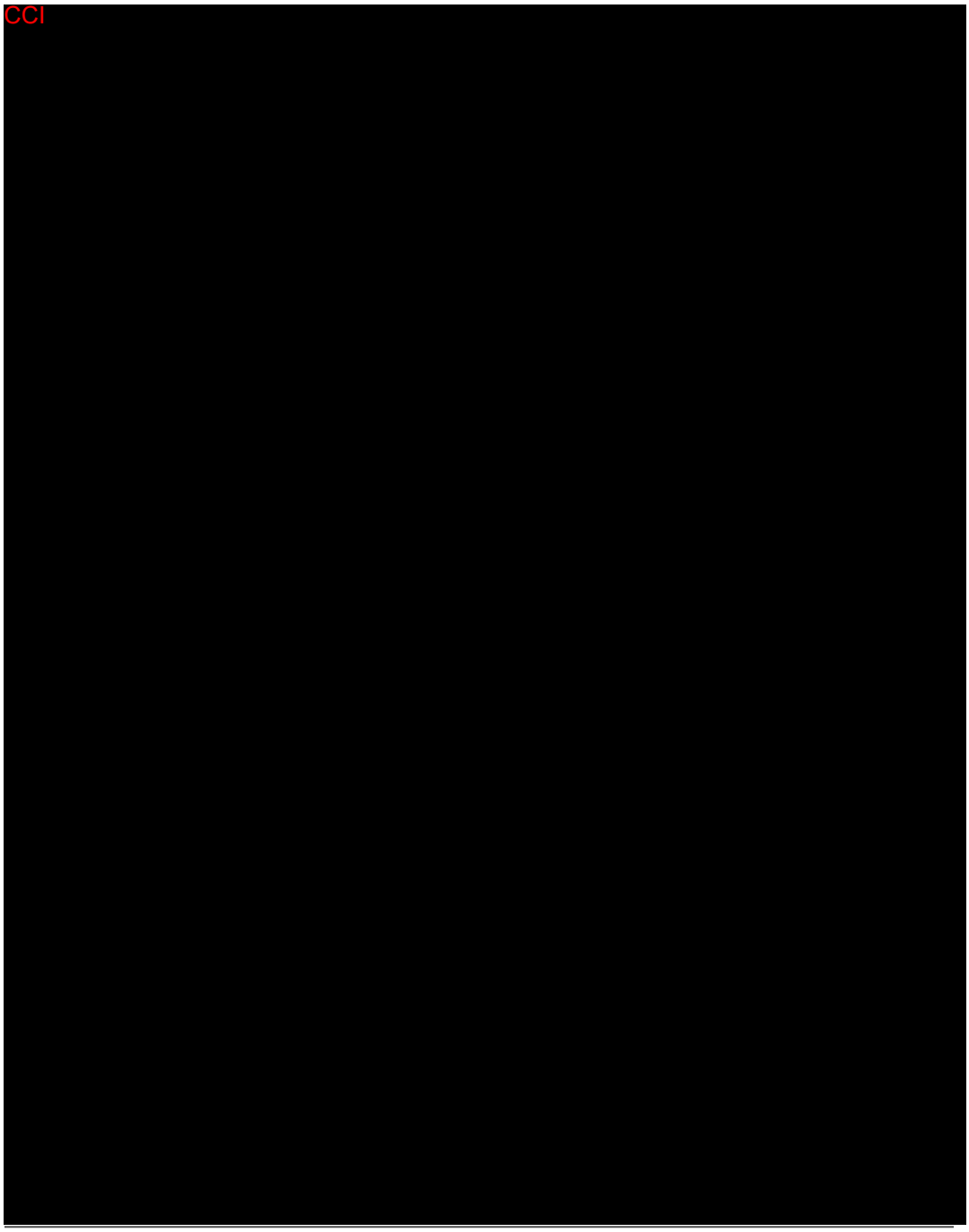
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Appendix 7 ICIQ-NQoL

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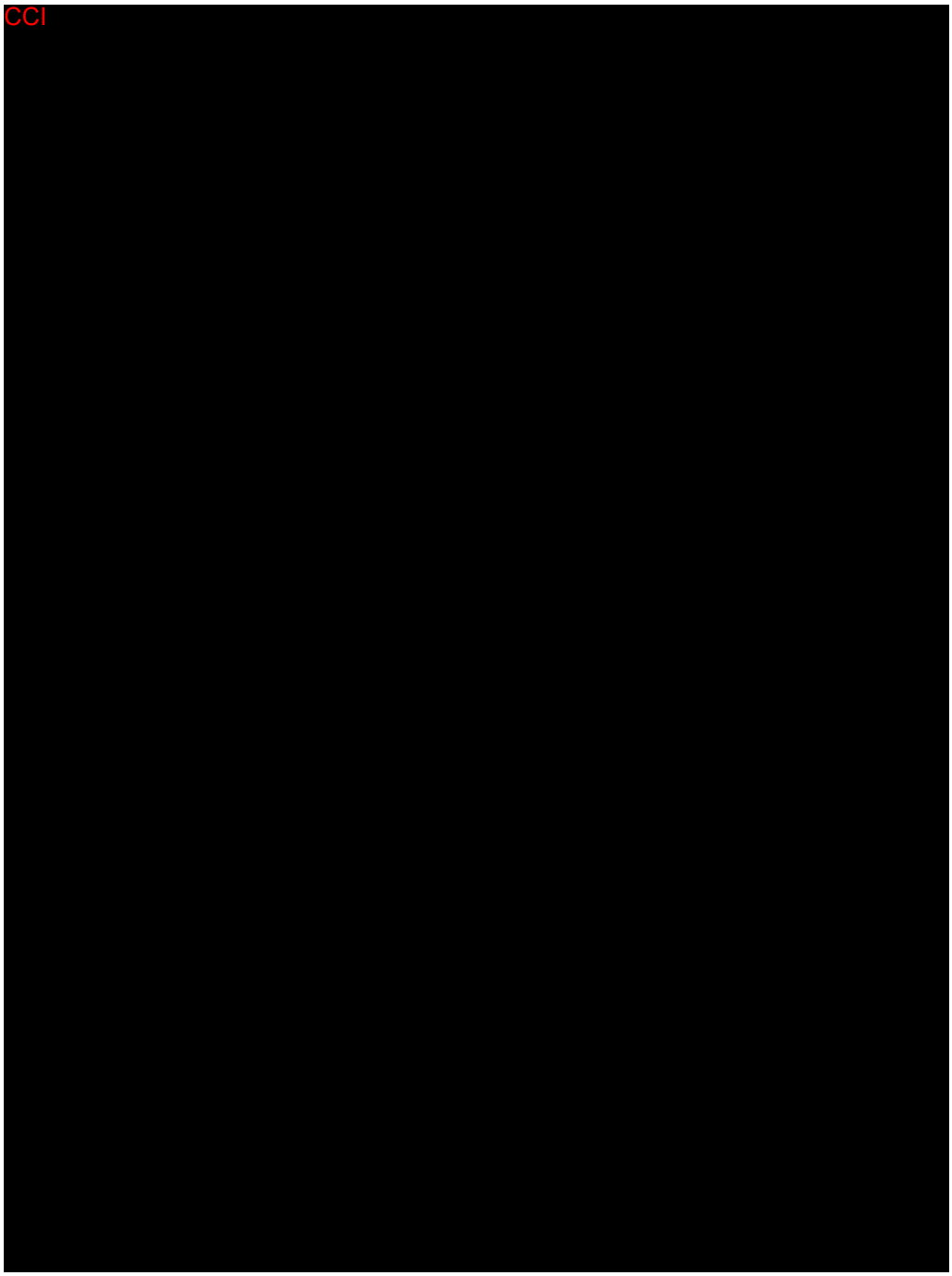

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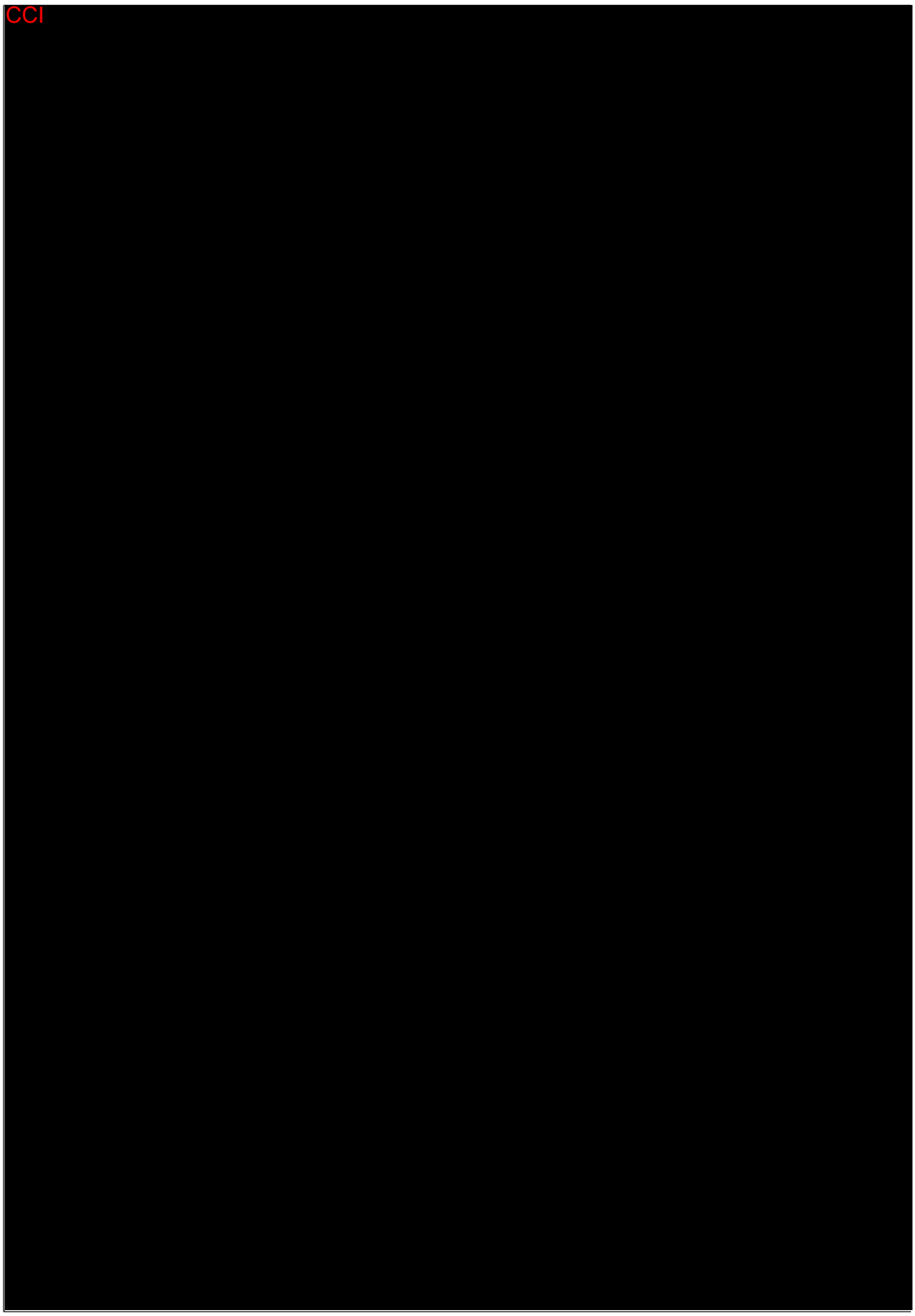
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Appendix 8 ICIQ-MLUTS

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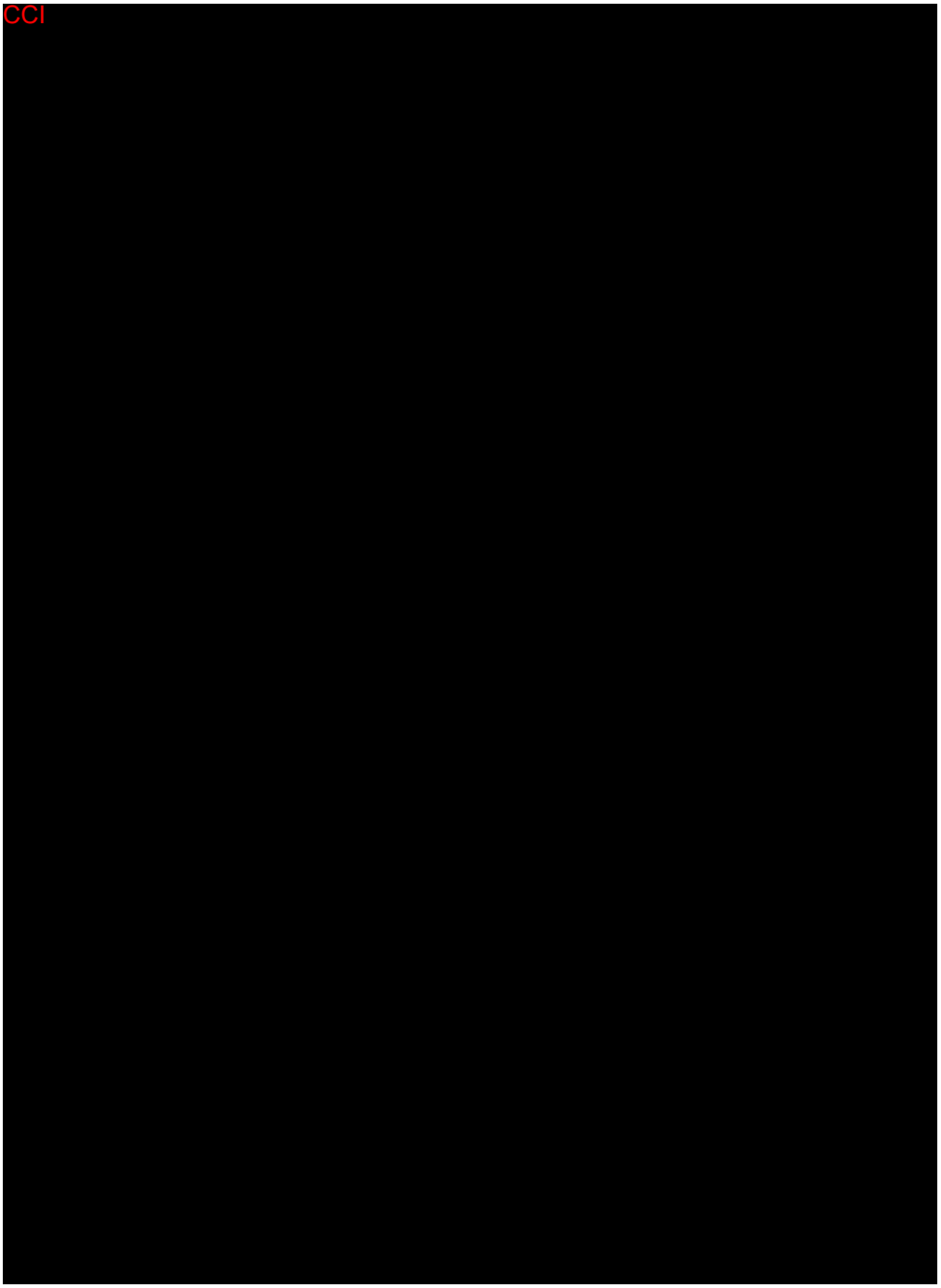

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Appendix 9 ICIQ-FLUTS

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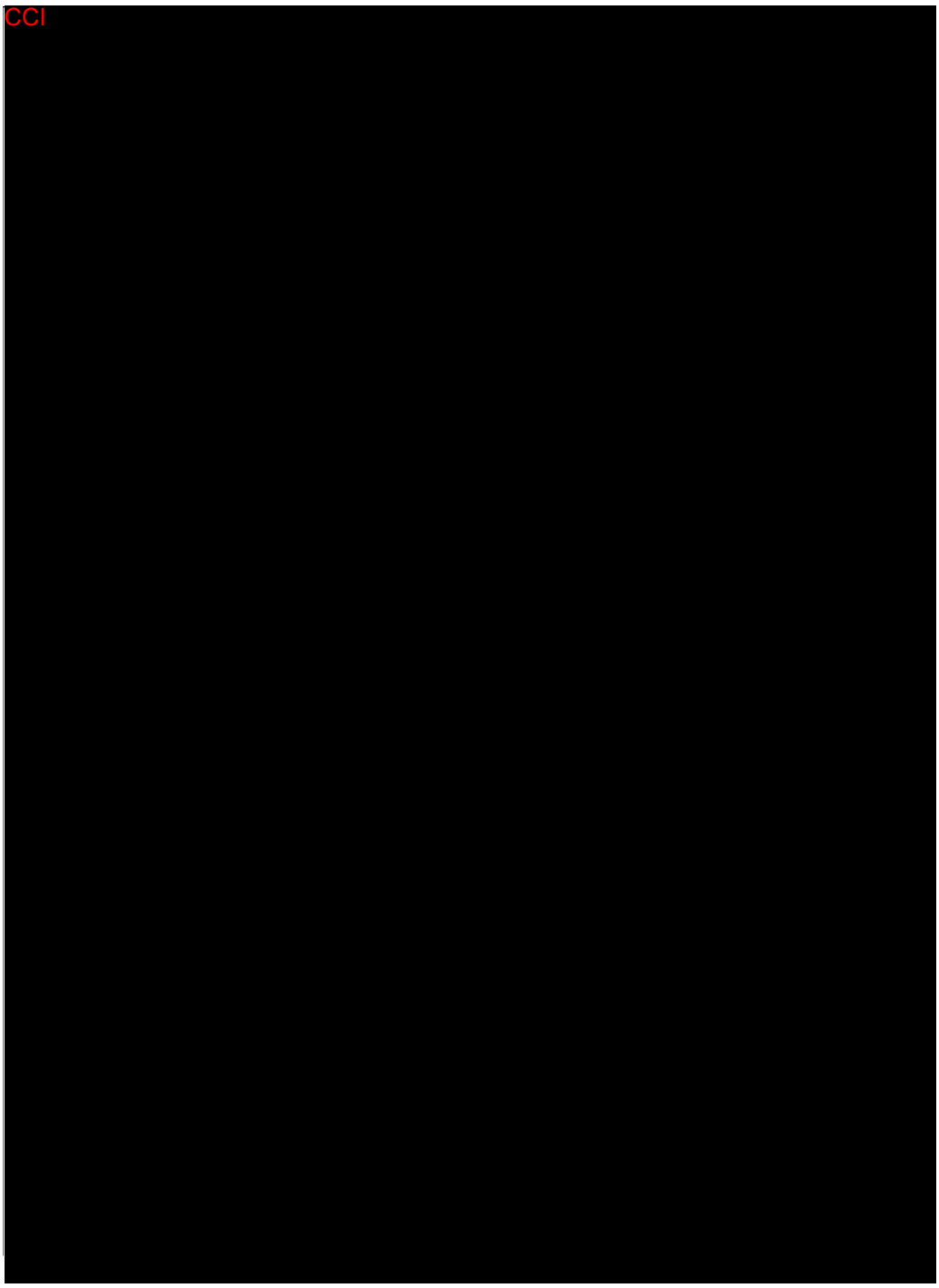

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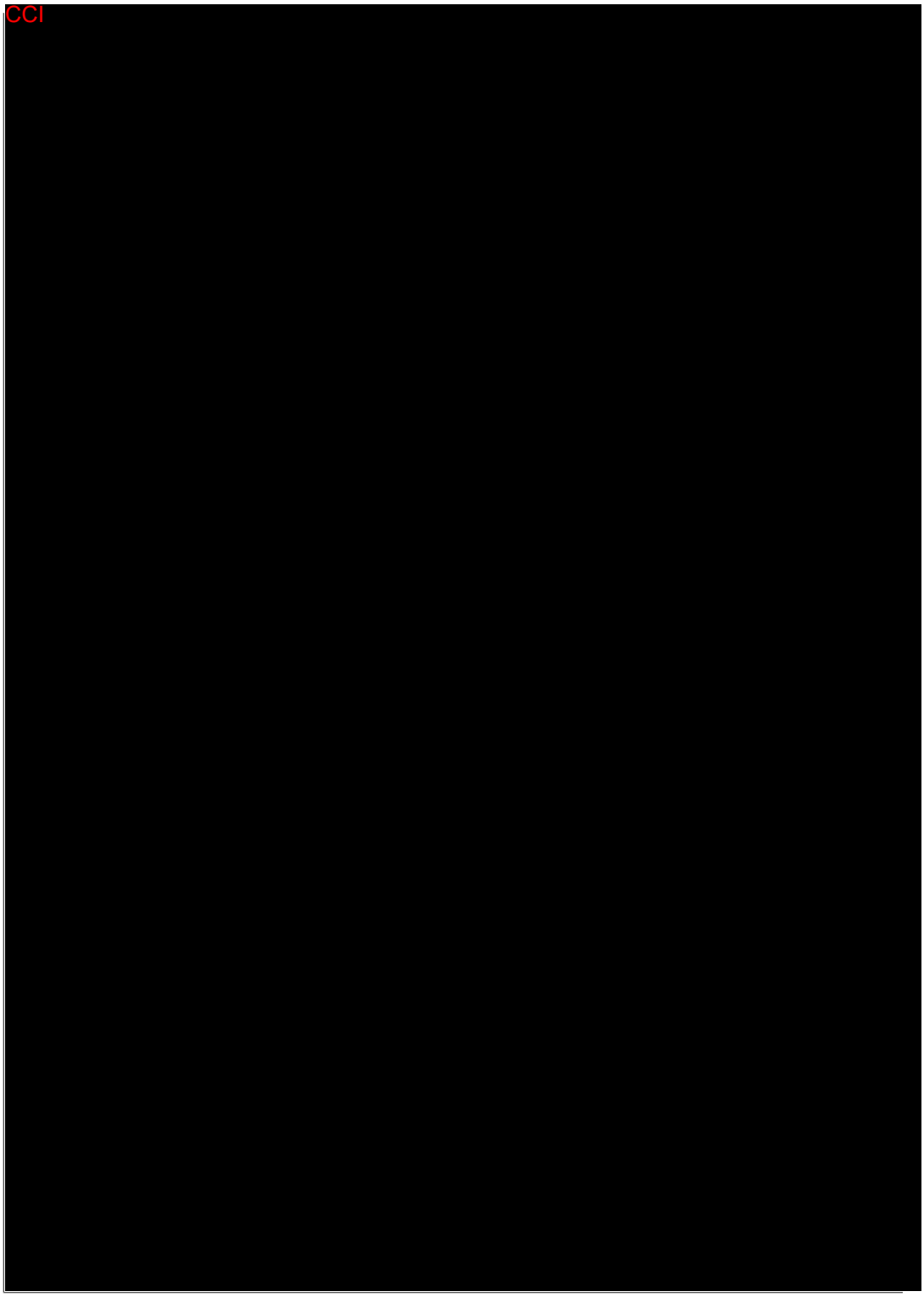
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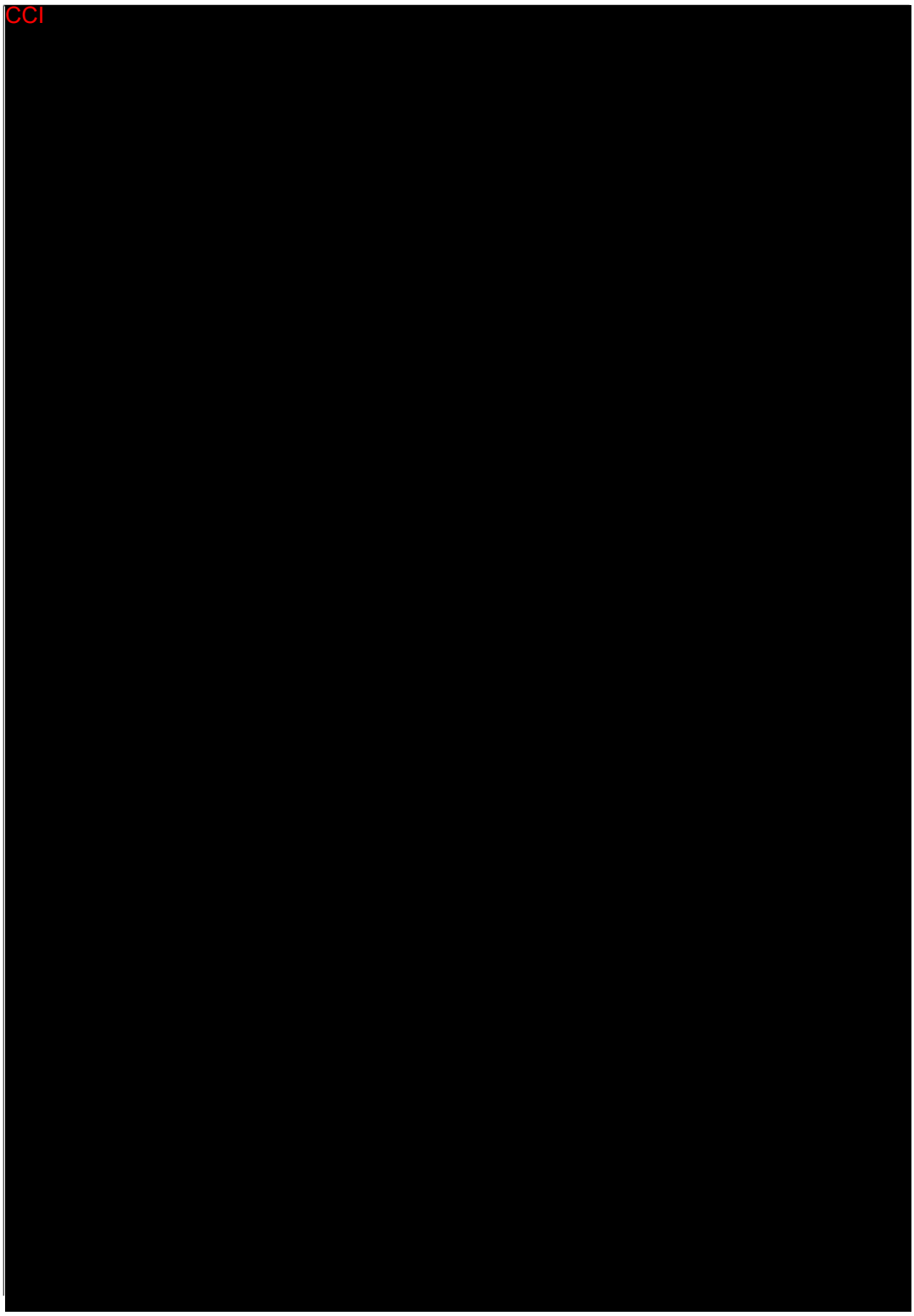
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Appendix 10 Columbia Suicide Severity Rating Scale© (C-SSRS©)

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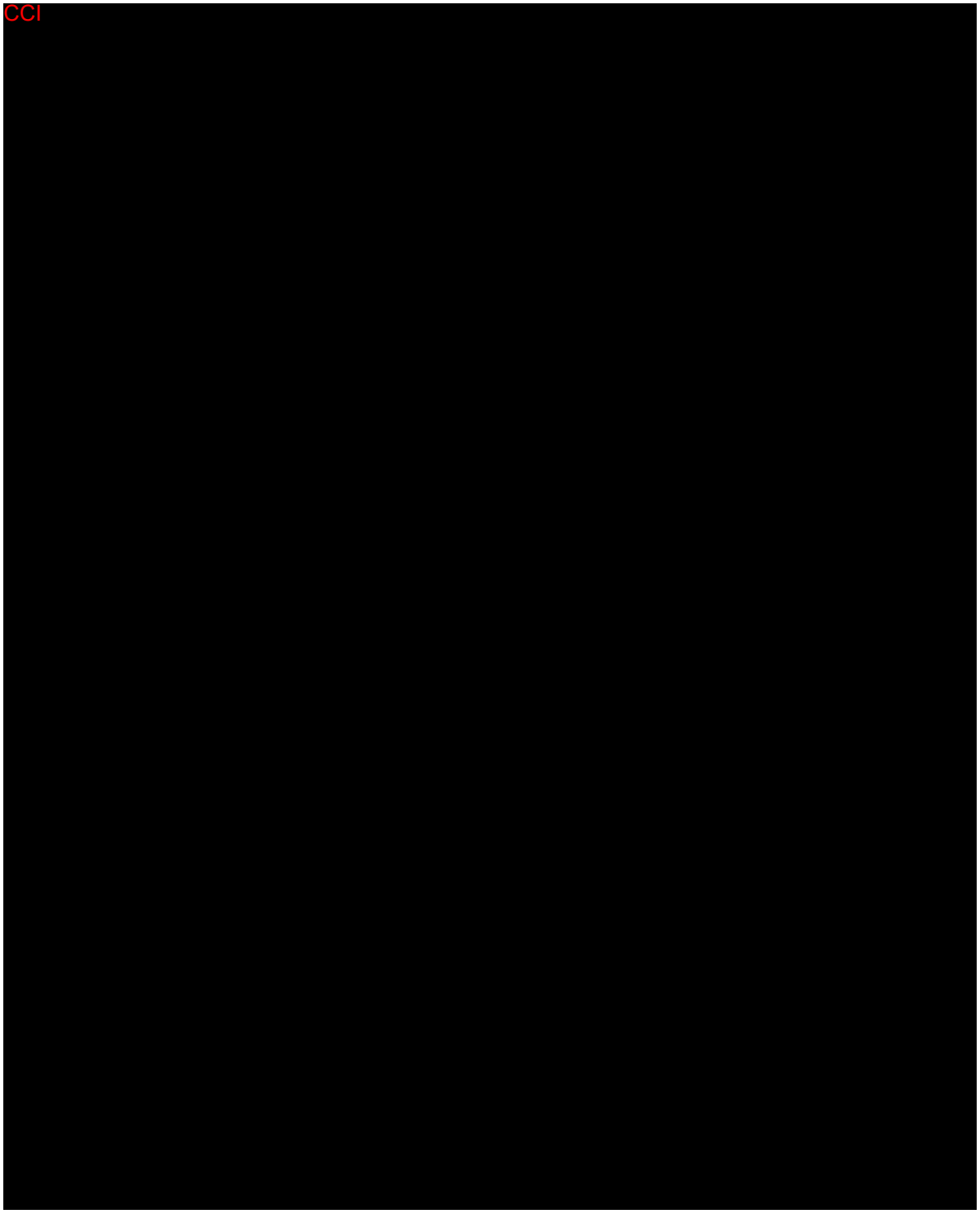

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Appendix 11 Forbidden medications

Forbidden (F) or restricted (R) concomitant medications due to CNS side effects and DDI interactions.

To be eligible, subjects must not be treated with CNS-active drugs for 5 half-lives of the respective drug or 2 weeks prior to Visit 2 (whichever is longer) until 24 hours after study treatment discontinuation.

Drug Class	Examples	Forbidden / Restricted	Comment
Anticholinergics	e.g., oxybutynin, solifenacin	R	The use of anticholinergics are allowed if initiated at least 1 month prior to Visit 1 and planned to remain stable during the study.
Antihistamines	*Sedating:* e.g., carbinoxamine, triprolidine HCl, azatadine, chlorpheniramine, doxylamine, hydroxyzine, ketotifen, promethazine & timeprazine, diphenhydramine HCl, dimenhydrinate	F	
Psychotropics	*Stimulants:* e.g., amphetamine derivatives, ephedrine derivatives, modafinil, armodafinil, methylphenidate, aripiprazole, pramipexole, levodopa, guanfacine, atomoxetine	F	
	Antidepressants: e.g., bupropion, citalopram, doxepin, duloxetine, escitalopram, fluoxetine, fluvoxamine, nefazodone, paroxetine, sertraline, trazodone, amitriptyline, clomipramine, desipramine, imipramine, mirtazapine, nortriptyline, trimipramine, venlafaxine, moclobemide, selegiline	F	
	Antipsychotics, including depot neuroleptics: e.g., quetiapine, olanzapine, haloperidol, loxapine, molindone, thiothixene, fluphenazine, mesoridazine	F	

Drug Class	Examples	Forbidden / Restricted	Comment
	Anxiolytics: e.g., alprazolam, buspirone, clorazepate, diazepam, flurazepam, lorazepam, midazolam, quazepam, temazepam, triazolam	F	
	Hypnotics: e.g., ramelteon, suvorexant, lemborexant, zolpidem	F	
	Cholinesterase inhibitors: e.g., donepezil, galantamine		
	Mood stabilizers, e.g., carbamazepine, gabapentin, lithium, oxcarbazepine, pregabalin, valproic acid, tiagabine	F	
	Opioids/Narcotics: e.g., codeine, oxycodone, heroin, marijuana	R	Use of narcotics for pain relief must be avoided if there are effective alternative medications (such as NSAIDs)
	Centrally acting muscle relaxants with psychotropic effects: e.g., methocarbamol, tetrazepam	R	Use of centrally acting muscle relaxants must be avoided if there are effective alternative medications (such as NSAIDs)
	Herbal preparations with possible psychotropic effects: e.g., St John's Wort	F	
	Others: e.g., tryptophan, melatonin, clonidine, dextromethorphan	F	
Anticonvulsants	Barbiturates, benzodiazepines, GABA analogs, hydantoins phenyltriazines (e.g., lamotrigine) succinimides (e.g., ethosuximide)	F	
Alpha Blockers:	Silodosin, tamsulosin	R	Allowed if initiated at least 1 month prior to Visit 1 and planned to remain stable during the study
5-Alpha-Reductase-Inhibitors	e.g., finasteride, dutasteride	R	5-alpha-reductase-inhibitors are allowed if initiated at least 6 months prior to Visit 1

Drug Class	Examples	Forbidden / Restricted	Comment
			and planned to remain stable during the study
Other	Desmopressin	R	Desmopressin is allowed at therapeutic doses of 25–50 mg, only if initiated at least 6 months prior to Visit 1 and planned to remain stable during the study
	Systemic glucocorticoids: e.g., dexamethasone, methylprednisone, prednisone	F	Inhaled/topical corticosteroids are permitted
	Diet pills (prescription and OTC)	F	
	Pseudoephedrine	R	Use as nasal decongestant is allowed

GABA = gamma-aminobutyric acid; NSAID = non-steroidal anti-inflammatory drug; OTC = over-the-counter.

Non-exhaustive list of forbidden concomitant medications and diets due to potential drug interactions with CYP3A4 (moderate and strong inhibitors, inducers).

Those medications must be discontinued no later than 2 weeks or 5 half-lives (whichever is longer) prior to Visit 2 and are forbidden until 24 hours after study treatment discontinuation.

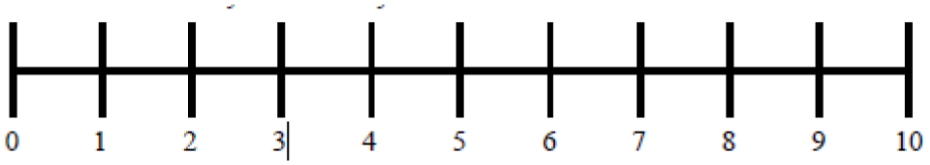
Inhibitors of CYP3A4	Inducers of CYP3A4
HIV antivirals: atazanavir, boceprevir, cobicistat, darunavir, delaviridine, fosamprenavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, telaprevir	HIV antivirals: efavirenz, etravirine
Antibiotics: ciprofloxacin, clarithromycin, erythromycin, norfloxacin, quinupristin, telithromycin, troleandomycin	Antibiotics: nafcillin, rifabutin, rifampin
Antifungal: fluconazole, itraconazole, ketoconazole, posaconazole, voriconazole	
CNS-active: fluvoxamine, nefazodone	CNS-active: carbamazepine, fenobarbital, modafinil, phenytoin, St. John's Wort
Cardiovascular: amiodarone, diltiazem, dronedarone, verapamil	Cardiovascular: bosentan
Aprepitant, conivaptan, cimetidine, imatinib	

CNS = central nervous system; CYP = cytochrome P450; HIV = human immunodeficiency virus.

Appendix 12 Treatment satisfaction questionnaire

Treatment satisfaction:

*"Please mark the number that best describes your overall satisfaction with the study medication **during** the clinical study (Mark one number only)"*



Not
at all Satisfied

Extremely
Satisfied

Appendix 13 Treatment period preference questionnaire

Treatment period preference

- *"Please specify which treatment period you preferred":*
  ☐ Period 1 ☐Period 2

Appendix 14 Narrative

CCI