DARIDOREXANT (ACT-541468)

STATISTICAL ANALYSIS PLAN

FOR CLINICAL STUDY REPORT

ID-078A401

Version 2

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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LIST OF ABBREVIATIONS AND ACRONYMS

AE	Adverse event
AESI	Adverse event of special interest
ATC	Anatomical Therapeutic Chemical
CI	Confidence interval
C-SSRS©	Columbia Suicide Severity Rating Scale©
eCRF	Electronic case report form
eDiary	Electronic diary
EOS	End-of-study
EOT	End-of-treatment
EOTP	End-of-treatment period
EQ-5D-3L	European Quality of Life 5 Dimensions 3 Level Version
FAS	Full analysis set
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
IDSIQ	Insomnia Daytime Symptoms and Impacts Questionnaire
IMP	Investigational Medicinal Product
ISI©	Insomnia Severity Index©
LS	Least squares
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed model for repeated measures
PD	Protocol deviation
PGA-S	Patient Global Assessment of Disease Severity
PGI-C	Patient Global Impression of Change
PPS	Per-protocol set
PT	Preferred term
RND	Randomized analysis set
SAE	Serious adverse event
SAF	Safety analysis set

SCR	Screened analysis set
SOC	System organ class
sTST	Subjective total sleep time
TEAE	Treatment-emergent adverse event
TP I	Treatment Period I
TP II	Treatment Period II
V	Visit
VAS	Visual analog scale
WHO	World Health Organization

1 INTRODUCTION

This statistical analysis plan describes the analyses and data presentation for the clinical study report prepared for study ID-078A401 in detail. The analyses will be conducted once all randomized subjects have completed the study and the database has been locked.

Obvious corrections to address minor formatting errors or spelling mistakes may be performed at the time of analysis without amending this and related documentation (e.g., mock shells).

Data will be analyzed by Idorsia and designated contract research organizations supervised by Idorsia using SAS® version 9.4 or higher and R version 3.4.3 or higher.

This statistical analysis plan is based on Version 3 of the protocol of ID-078A401, dated 4 September 2023 [D-23.307, Table 1].

Table 1 Study documents

Document	Date, Version
Clinical Study Protocol	4SEP2023, Version 3
eCRF specifications	14NOV2023, Version 5
Protocol deviation list	14MAY2024, Version 6

eCRF = electronic case report form.

2 STUDY DESIGN AND FLOW

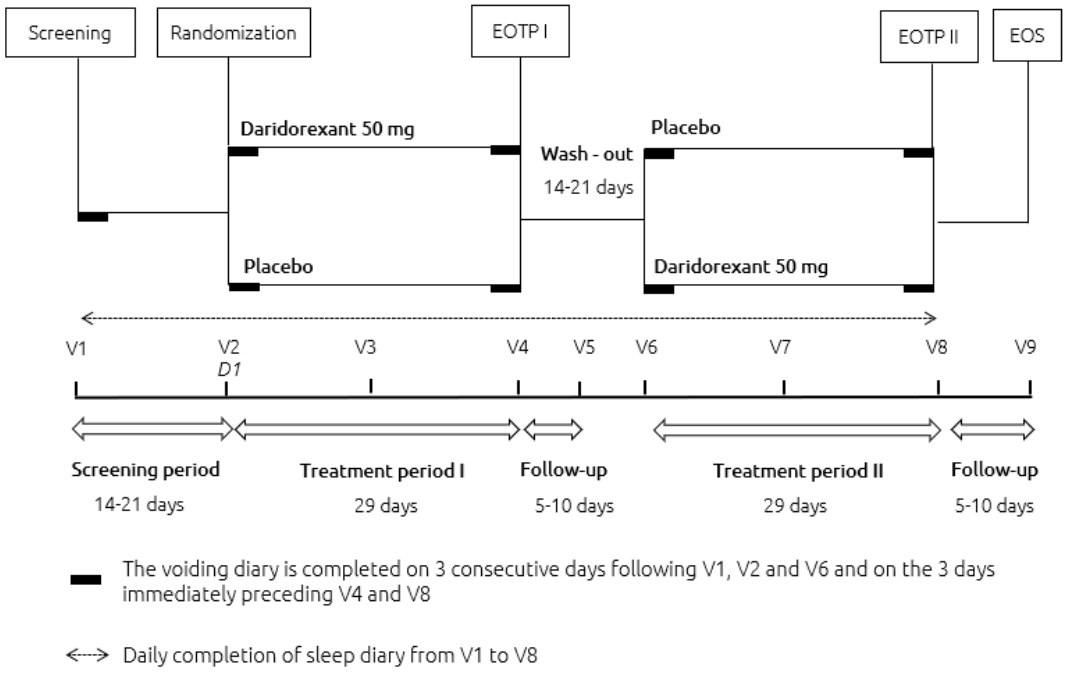
This is a post-approval, multi-center, double-blind, randomized, placebo-controlled, 2-way cross-over study assessing daridorexant at a dosing regimen of 50 mg, once daily, vs placebo over a 4-week treatment period in adult subjects of 55 years and older with insomnia and comorbid nocturia.

Approximately 50 subjects will be randomized in a 1:1 ratio to one of two treatment sequences: daridorexant 50 mg / placebo or placebo / daridorexant 50 mg.

The study will be conducted at approximately 18 sites in the United States, Spain, and Germany.

The study design is shown in Figure 1.

Figure 1 Study design for ID-078A401



D = day; EOS = end-of-study; EOTP = end-of-treatment period; V = visit.

The study comprises the following 5 periods: the screening period, TP I, washout period, TP II, and the safety follow-up period.

The **screening period** starts with the signing of the informed consent form at Visit 1 and ends with Randomization at Visit 2 or with a screening failure. It lasts 14–21 days.

TP I starts with the administration of the first dose of study treatment and ends on the day after the last dose of study treatment (Day 29). The study subjects will be treated for 4 weeks.

The **washout period** starts after completion of the TP I and lasts 14–21 days. During the washout period the subjects will not be treated at all and will be followed up for safety (5–10 days).

TP II starts with the administration of the first dose of the 'other' study treatment and ends on the day after the last dose of study treatment (Day 29). The study subjects will be treated for another 4 weeks.

The **safety follow-up period** starts on the day after the last dose of study treatment in TP II and ends at the EOS visit (5–10 days after EOTP II).

3 OBJECTIVES

The overall objective of this post-approval study is to evaluate the clinical efficacy, safety, and tolerability of daridorexant 50 mg administered once daily, compared to placebo in adult subjects with insomnia and comorbid nocturia over a period of 4 weeks.

3.1 Primary objectives

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

3.2 Secondary objectives

The secondary objective is to assess the efficacy of daridorexant on nocturia variables.

3.3 Safety objectives

The safety objectives will be to assess the safety and tolerability of daridorexant.

4 ANALYSIS SETS

4.1 Definitions of analysis sets

A study subject must have given informed consent before being included in any analysis set.

4.1.1 Screened analysis set

The SCR includes all study subjects who entered Screening and have a subject number.

Summaries based on the SCR set will be presented as one group (i.e., all study subjects), unless otherwise specified.

4.1.2 Randomized analysis set

The RND includes all study subjects from the SCR who were randomized (i.e., assigned to a treatment sequence).

4.1.3 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 intent-to-treat principle,

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

4.1.4 Per-protocol set

The PPS includes all subjects from the FAS without important PDs occurring during the screening/baseline assessments or prior to Week 4 (in both treatment periods, i.e., between

Visit 2 and Visit 4 in TP I, and between Visit 6 and Visit 8 in TP II), which could affect the analysis of the primary endpoint variable.

The following important PDs will lead to exclusion from the PPS:

- At least one key inclusion criterion (except #1) was not met (#3, #4, #5, #6, #7; PD Code: 01A02);
- At least one key exclusion criterion was met (#3, #6, #7, #8, #13; PD Code: 01B01);
- Incorrect blister dispensed to the subject and at least one tablet was taken (PD Code: 02A01);
- Failure to comply with IMP storage/retention requirements impacting the quality of the IMP, reported as 'not to be used' by the Quality Assurance department, and at least one tablet was taken by the subject (PD Code: 02B01);
- At least one IMP compliance value < 80% (PD Code: 02E01);
- Non-compliance with blinding procedure/maintenance with consequences of patient treatment / study arm revealed or easily identifiable (PD Code: 03D01);
- Sleep diary not completed at least 2 days during Screening and Week 4 of each treatment period (PD Code: 03G02);
- Treatment with forbidden medication (PD Code: 04A01).

Study subjects will be evaluated according to the treatment they have been assigned to. If only one of the two treatment periods of a subject is affected by one of the above PDs, the subject still will be completely excluded from the analysis as the deviation also might have an impact on the second treatment period (e.g., forbidden medication with a long half-life or similar).

4.1.5 Safety analysis set

The SAF 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).

4.2 Analysis

The number of study subjects in each analysis set defined above will be tabulated by treatment sequence (daridorexant 50 mg / placebo or placebo / daridorexant 50 mg) and overall. Any study subject excluded, along with the reason(s) for exclusion from the PPS, will be summarized and listed.

4.3 Usage of the analysis sets

The analyses of the primary endpoint and all other efficacy endpoints will be performed using the FAS.

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

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

The SCR is used to provide the same summaries for the screen failures.

Subject disposition will be described based on the SCR.

Study subjects' data will be listed using the SCR, unless otherwise specified.

Of note, there are no baseline disease characteristics collected in this study other than baseline values of efficacy and safety variables.

Table 2 Usage of analysis datasets

Analysis	SCR	RND	FAS	PPS	SAF
Subject disposition	X				
Demographics / Baseline Characteristics		X*	X*		
Previous and concomitant medication					X
Study drug exposure					X
Efficacy analysis			X	X	
Safety and tolerability analyses					X

FAS = full analysis set; PPS = per-protocol analysis set; RND = randomized analysis set; SAF = safety analysis set; SCR = screened analysis set.
* Regulatory request for both RND and FAS.

5 SUBJECT VARIABLES AND ANALYSES

Due to the cross-over design, each subject will contribute to both treatment columns if the summary tables or figures are presented by treatment.

5.1 Subject disposition

5.1.1 Screen failures

Screen failures will be summarized based on the SCR and will include:

- Number (%) of study subjects who did not successfully complete the screening period (based on 'Was the subject randomized?' recorded as 'No' on the 'Randomization' page).
- Primary reason for screen failure (based on reason entered on the 'Randomization' page).

The eligibility criteria not met will be summarized. All reasons for screen failures will be listed.

Of note, no re-screening is allowed in the study.

5.1.2 Study disposition

Study subject disposition will be summarized based on the SCR, presented by treatment sequence and overall, and will include:

- Number of study subjects screened (only for overall column).
- Number (%) of study subjects randomized (based on non-missing randomization number).
- Number (%) of study subjects who received study treatment during the TP I (based on non-missing 'Treatment start date' for TP I on the 'Study Treatment Log' page). Percentage will be based on randomized subjects.
- Number (%) of study subjects who received study treatment during the TP II (based on non-missing 'Treatment start date' for TP II on the 'Study Treatment Log' page). Percentage will be based on randomized subjects.
- Number (%) of study subjects who completed TP I (based on 'Reason for treatment stop' entered as 'Completion as per protocol' for TP I on the 'Study Treatment Log' page). Percentage will be based on study subjects who received study treatment (in TP I).
- Number (%) of study subjects who completed the TP II (based on 'Reason for treatment stop' entered as 'Completion as per protocol' for TP II on the 'Study Treatment Log' page). Percentage will be based on study subjects who received study treatment (in TP II).
- Number (%) of study subjects completing the study (based on 'Did the subject complete the study?' recorded as 'Yes' on the 'End of Study Status' page). Percentage will be based on randomized subjects.
- Number (%) of study subjects completing the washout-period, i.e., subjects being treated in TP I and TP II.

5.1.3 Study and study treatment completion/discontinuation

The following summary will be based on the SAF and presented by treatment and overall:

- Number (%) of study subjects who prematurely discontinued study treatment (based on 'Reason for treatment stop' entered as 'Discontinuation' on the 'Study Treatment Log' page).
- Primary reason for premature study treatment discontinuation (based on 'Discontinuation, Reason' entered on the 'Study Treatment Log' page).

The treatment discontinuation table will also be presented by treatment period and treatment based on the SAF.

The following summary will be based on the RND and FAS, and presented by treatment and overall:

- Number (%) of study subjects who prematurely discontinued from the study (based on non-missing reason for stopping study entered on the 'End of Study Status' page).
- Primary reason for premature discontinuation from the study (based on 'Study stopped due to' entered on the 'End of Study Status' page).

The study discontinuation table will also be presented by study period and treatment (TP I, washout-period, TP II, safety follow-up period).

All reasons for premature study treatment discontinuation and study discontinuation will be listed based on the RND.

5.1.4 Study enrollment

The number (%) of screened and randomized study subjects will be displayed by site based on the SCR.

The randomization scheme and codes will be listed for randomized study subjects only based on the RND.

5.2 Protocol deviations

The RND will be used for the summary of PDs. All PDs and important PDs will be summarized in separate tables as per pre-specified category (i.e., selection criteria, IMP, study conduct/procedure, forbidden medication, withdrawal criteria and other).

A study subject with multiple occurrences of a PD is counted only once per PD category.

The PD outputs will be summarized by treatment sequence and overall.

A listing of PDs will be provided using the SCR.

5.3 Subject characteristics

Unless noted otherwise, summaries and listings described in this section will be based on the RND.

Summaries will be provided by treatment sequence and overall. Data will be listed individually by study subject.

5.3.1 Demographics

Demographic data at Screening, including age, sex, race, and ethnicity, will be summarized (by treatment sequence and overall) based on the RND and FAS, and listed.

The same summary will also be provided for screen failures based on the SCR.

5.3.2 Baseline disease characteristics

The baseline disease characteristics table will contain a summary of sTST, ISI© score, the ISI© score in categories (≤ 14, 15–21, ≥ 22) and the summary of the average number of nocturnal voidings at baseline, as derived by Minze Health [Bladt 2022]. Baseline disease characteristics will be summarized based on the RND and FAS.

Baseline disease characteristics data will be listed based on the RND.

5.3.3 Medical history and concomitant diseases at Screening

Relevant medical history and current medical conditions will be coded using MedDRA.

Any disease or diagnosis is defined as previous if 'Ongoing at informed consent' is answered as 'No'; all other diseases/diagnoses are considered as study concomitant (where answer is 'Yes').

Medical history and current (ongoing) medical conditions will be summarized separately and listed (based on the RND). Summaries will be presented for each treatment sequence and overall, by primary SOC and PT. Medical history will be sorted by SOC and PT within each SOC by descending frequency based on all treatment sequences combined.

The MedDRA version used for reporting will be specified in the footnote of the applicable output.

5.3.4 Previous and concomitant therapy

Previous and concomitant therapies will be coded using the WHO Drug Global reference dictionary that employs the WHO ATC classification system. The WHO Drug Global version used for reporting will be specified in the footnote of the applicable output.

Previous therapies are any treatments for which the end date is prior to the start of study treatment. A previous therapy is to be recorded in the 'Previous/Concomitant Medication' page if discontinued less than 30 days prior to signing of the informed consent form.

Study treatment-concomitant therapies are any treatments that are either ongoing at the start of study treatment or initiated on or after the start of TP I. The use of all treatment-concomitant therapies (including contraceptives and traditional and alternative medicines, e.g., plant-, animal-, or mineral-based medicines) is to be recorded in the 'Previous/Concomitant Medication' page.

Number (%) of study subjects having taken at least one previous or concomitant therapy will be summarized by ATC classification level 4 (or next highest available level) and individual preferred name within each ATC classification based on the SAF. Previous and concomitant therapy will be sorted by ATC class and preferred name within each ATC class by descending frequency based on all treatment sequences combined.

Summary tables will be provided for previous and study treatment-concomitant therapies separately (by treatment sequence and overall). All concomitant therapies will be listed using the SAF and those related to an AE will be flagged.

5.4 Study treatment exposure and compliance

Summaries and listings described in this section will be based on the SAF.

5.4.1 Exposure

The duration of study treatment (including categories: ≤ 1, > 1–2, > 2–3, > 3– 4, > 4 weeks) will be summarized based on the SAF, by treatment and overall.

The duration of treatment (in days) is defined as the difference between the treatment end date and the treatment start date plus one day. This calculation ignores periods of treatment interruption.

Due to the cross-over design, the duration of the washout period will also be summarized based on the SAF (only for those subjects who were treated in both treatment periods). The washout period is defined as:

- Washout-period (in days) = Treatment start date of TP II – Treatment end date of TP I + 1 day.

The duration of treatment along with the reason for treatment discontinuation will be listed by treatment sequence and period based on the SAF. The duration of the washout period will also be listed based on the SAF.

5.4.2 Compliance with study treatment

Study treatment compliance will be assessed through study treatment dispensing and accountability.

The following formula will be used to calculate compliance for the treatment period:

- Study treatment compliance (%) = [(Number of capsules dispensed – Number of capsules returned[a]) / (Treatment duration – Total duration of treatment interruptions)] × 100.

Treatment duration and total duration of treatment interruptions are calculated using the dedicated eCRF page ‘Study Treatment Log’.

[a] If a study subject did not return his/her bottle (e.g., it is lost), compliance will not be calculated, and compliance will be set to missing.

Treatment duration is calculated as:

- Treatment duration (days) = Date of last drug intake of study treatment – Date of first drug intake of study treatment + 1 day.

Total duration of treatment interruption (days) is the sum of all the treatment interruptions' durations, calculated as:

- Treatment interruption duration = Date restarted study treatment – End date of study treatment due to an interruption – 1 day.

For example, if a study subject stopped his/her treatment on 19MAR2022 and started again on 23MAR2022, as the treatment is taken on the start and end dates, the calculation will be 23MAR2022 – 19MAR2022 – 1 day = 3 days of interruption. Should the study subject interrupt the treatment again for 7 days, the total duration of interruptions will be 10 days.

Study treatment compliance (including categories 0%, > 0%–< 50%, 50%–< 80%, 80%–< 100%, 100%, > 100%), treatment interruptions (Yes/No), and duration of treatment interruptions will be summarized based on the SAF. The summary table will be repeated by treatment period based on the SAF.

The number (%) of study subjects who have treatment interruptions, and the corresponding reasons will be tabulated based on the SAF.

Study treatment compliance, dispensing and accountability data will be listed based on the SAF.

6 EFFICACY VARIABLES AND ANALYSES

The analyses of efficacy endpoints will be performed using the FAS. Efficacy data described below will be listed using the FAS.

As there were no secondary endpoints defined in the protocol, only the primary endpoint and other efficacy endpoints will be analyzed.

6.1 Primary endpoint analysis

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

6.1.1 Primary efficacy endpoint

The primary efficacy endpoint of this study is defined as the change from baseline to Week 4 (of both treatment periods) in sTST.

In each treatment period, the change from baseline[a] to Week 4[b] in sTST is calculated as follows:

- Change from baseline = Mean value at Week 4[b] – Mean value at baseline[a].

Changes from baseline in sTST for Weeks 1–3 will 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.

For subjects discontinuing a treatment period prematurely (TP I or TP II), all data up to Day 29 will be included to derive the weekly averages (if data is available up to that point). In the event that subjects have extended treatment periods > 4 weeks, only data up to Day 29 will be included in the derivation of the weekly averages.

6.1.2 Overall testing strategy

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

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 2-sided 0.05 significance level.

A preview of the main analyses is given in Table 3 using the estimand terminology [ICH 2019]. Estimands are defined by five attributes: treatment condition of interest, target population, endpoint, strategy for addressing intercurrent events (i.e., premature discontinuation of treatment), and population-level summary.

The primary estimand is based on the primary endpoint: the difference in means between the two treatments in the change from baseline to Week 4 in sTST, regardless of treatment discontinuation. 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

[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.

same period. The other four attributes are given in the table below. The primary estimand follows a 'treatment policy' strategy.

The secondary estimand is also based on the primary endpoint. Intercurrent events are defined as premature treatment discontinuations. Details are provided in Table 3. The secondary estimand follows a 'hypothetical' strategy.

Table 3 Estimands for the primary objective

Estimand	Target population	Endpoint	Strategy for addressing intercurrent events	Population-level summary
Primary estimand	Subjects with insomnia associated to nocturia	Change from baseline to Week 4 in sTST	Treatment policy strategy, i.e., endpoint data after premature treatment discontinuation are used.	Treatment effect expressed as difference of LS Mean changes from baseline to Week 4 (daridorexant minus placebo; from MMRM)
Secondary estimand	Subjects with insomnia associated to nocturia	Change from baseline to Week 4 in sTST	Hypothetical strategy, i.e., endpoint data after premature treatment discontinuation 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.

6.1.3 Statistical model

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

An unstructured covariance matrix will be used to account for the correlation between repeated measurements from the same subject. This approach relies on the missing at random assumption. A restricted maximum likelihood approach in combination with the Newton Raphson Algorithm will be used to derive (unbiased) estimates of variance components. The Kenward-Roger approximation will be used to compute the denominator degrees of freedom and adjust standard errors [Kenward 1997]. If the analysis fails to converge, the following structures will be tested in the subsequent order until model-convergence is achieved: heterogeneous Toeplitz, Toeplitz, autoregressive, and compound symmetry.

To evaluate the efficacy hypotheses, appropriate contrasts will be used to test the treatment differences of interest (i.e., the difference in LS Mean change from baseline to Week 4 between daridorexant 50 mg and placebo).

The LS Mean for each treatment per time point will be displayed along with its associated standard error and 95% CI. For the daridorexant comparison with placebo, the placebo-adjusted LS Mean will be displayed along with the associated standard error, 95% CI and unadjusted 2-sided p-value. The null hypothesis will be rejected if the 95% CI for this difference excludes 0.

6.1.4 Handling of missing data

Section 6.1.1 explains how the primary efficacy endpoint is derived in the event of partially missing data.

The primary endpoint analysis 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 [Mignot 2022]. Even though this does not fully follow the intent-to-treat principle, the approach seems justified as limited dropouts are expected (< 3%) due to the short duration of each treatment period (4 weeks) and the known safety and efficacy profile of daridorexant. Every effort will be made to keep all subjects in the study, even in the event of premature treatment discontinuation, to collect all the relevant data for analysis of the primary endpoint. Data collected after premature treatment discontinuation will be included in the primary analysis (following a 'treatment policy' strategy).

6.1.5 Descriptive statistics

The primary efficacy endpoint (based on data used for the primary estimand) and its observed values (i.e., weekly averages of sTST) will be summarized over time by treatment using descriptive statistics.

A plot of the mean change from baseline over time for sTST will be provided by treatment (based on data used for the primary estimand).

The incidence and pattern of missing values will be explored to assess the appropriateness of the statistical analysis and the possible impact on the results (for the data used for the primary estimand). The incidence of missing data and the observed missing data patterns for the primary endpoint at baseline and each timepoint (Weeks 1, 2, 3, and 4) will be presented for each treatment. The missing data patterns will be sorted from completely missing to completely observed in the order of the first occurrence of missing data.

In addition, descriptive statistics will be provided by week and treatment, summarizing the number of available days that contribute to the weekly averages for sTST (for the data of the primary estimand). The analysis will be repeated by treatment period.

Based on the exploration of the observed missing data patterns, further sensitivity analyses in addition to those described below might be performed.

6.1.6 Sensitivity analyses

6.1.6.1 Per-protocol set

The analyses of the primary endpoint will be repeated on the PPS (based on the same MMRM and data used for the primary estimand).

6.1.6.2 Analysis not considering the days of urine collection

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 the days with urine collection from the weekly averages (based on data of the primary estimand).

For this analysis, 'Baseline' is defined as the mean value based on the screening sleep diary entries for sTST, completed for the 7 days preceding Randomization, except for the nights where urine was collected. 'Week 4' is defined as the mean value based on sleep diary entries for sTST completed for 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 (including baseline mean). Otherwise, the mean value will be considered missing for that week.

6.1.7 Supplementary analyses

No supplementary analyses are planned for this study.

6.1.8 Subgroup analyses

Subgroup analyses of the primary endpoint will be conducted by sex and country (based on the MMRM of the primary estimand and using data of the primary estimand).

6.2 Secondary endpoint analysis

Not applicable.

6.3 Analysis of other efficacy variables

The following other efficacy endpoints will be analyzed for this study:

Insomnia-related endpoints:

- Change from baseline up to Week 2 and Week 4 of the insomnia severity by the ISI©;
- Change from baseline to Week 1, 2, 3, and 4 in quality of sleep VAS, depth of sleep VAS, daytime alertness VAS, daily ability to function VAS;
- Change from baseline to Week 1, 2, 3, and 4 in the mean number of self-reported awakenings (based on the sleep diary);

Nocturia-related endpoints:

- Change from baseline to Week 1 and Week 4 in number of nocturnal voids assessed using a voiding diary;
- Change from baseline to Week 1 and Week 4 in the time to the first nocturnal void assessed using the voiding diary;
- Change from baseline to Week 1 and Week 4 in the volume of the first nocturnal void assessed using the voiding diary;
- Change 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;
- Change from baseline to Week 1 and Week 4 in the total daytime voiding volume assessed using the voiding diary;

Quality of life and treatment preference endpoints:

- 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;
- Change from baseline to Week 4 in quality of life relative to nocturia assessed by ICIQ-NQoL;
- Change from baseline to Week 1, Week 2, Week 3, Week 4 in PGA-S and PGI-C for insomnia and for nocturia;
- Change from baseline to Week 2 and Week 4 in quality of life using the EQ-5D-3L;
- Assessment of subjective treatment satisfaction at Week 4 by Numeric Rating Scale;
- Subject preference for treatment;
- Change from baseline to Week 1, Week 2, Week 3, Week 4 in IDSIQ scores (total; alert/cognition; sleepiness; mood).

Analyses of the other endpoints are described below.

6.3.1 Analysis of insomnia-related endpoints (ISI©, VAS, number of awakenings)

All endpoints will be summarized based on the FAS.

6.3.1.1 Insomnia Severity Index©

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. The ISI© will be completed by the subject on the eDiary at Visit 1 (baseline), Visit 3 (Week 2, Period 1), Visit 4 (Week 4, Period 1), Visit 7 (Week 2, Period 2), and Visit 8 (Week 4, Period 2).

The change from baseline to Week 2 and Week 4 will be summarized by treatment. Observed values will also be summarized. Changes from baseline to Week 2 and Week 4 will also be analyzed based on an MMRM, as described in Section 6.1.3.

In addition, the proportion of subjects with an ISI© decrease from baseline of greater than or equal to 6 will be summarized, as well as the proportion of subjects with ISI© values of 7 or less at Week 2 and Week 4, by treatment.

6.3.1.2 Visual analog scale

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. Sleep diaries must be completed daily from Visit 1 to Visit 8.

6.3.1.2.1 Variables

Baseline VAS is defined as the mean value based on the sleep diary entries completed for the 7 days immediately preceding the randomization visit.

For Week 1, the VAS scores are averaged across Days 2–8, for Week 2 across Days 9–16, for Week 3 across Days 17–22, and for Week 4 across Days 23–29 (in both treatment periods). 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.

6.3.1.2.2 Analysis

The change from baseline to Week 1–Week 4 in VAS scores will be summarized by treatment. Observed values will also be summarized by treatment. Changes from baseline to Week 1–Week 4 will also be analyzed based on an MMRM, as described in Section 6.1.3.

6.3.1.3 Number of awakenings

The number of awakenings is collected daily via a Sleep Diary Questionnaire.

The change from baseline to Week 1–Week 4 in number of awakenings will be summarized by treatment. Observed values will also be summarized by treatment.

Definitions of the weekly averages are the same as described in Section 6.3.1.2.

6.3.2 Analysis of nocturia-related endpoints (time to first nocturnal void; voiding volume; number of nocturnal voids)

The Minze Diary Pod [Bladt 2022] 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 (i.e., urgency, and amount and type of fluid intake). The Minze Diary Pod must be completed during the day, and it must be started in the morning, i.e., completion only starts on the first morning after Visit 1, Visit 2, and Visit 6 and lasts for 3 days; the Minze Diary Pod must also be completed for 3 full days immediately preceding Visit 4 and Visit 8. The Minze Diary Pod collects all data for the endpoints time to the first nocturnal void, change in voiding volume (nighttime and daytime) including total voiding volume, and change in number of nocturnal voids.

For all analyses below, 'pod voids' as well as 'manual voids' will be used. Only data from completed cycles will be included in the analysis. Bedtime and waketime were collected by Minze Health. Bedtime is defined as the 'exact time the subject went to sleep', and waketime is defined as the 'exact time the subject woke in the morning', according to Minze Health specifications.

6.3.2.1 Time to the first nocturnal void

6.3.2.1.1 Variable

The variable derivation follows the approach as used by Minze Health.

The time to first nocturnal void (hours) is derived for each voiding night ('Cycle') separately as follows:

- Time to first nocturnal void (in hours) = Time of first nocturnal void (after bedtime and before waketime) – Bedtime.

Potentially, a date is required for computation of the variable if the bedtime is prior to midnight and the first void is after midnight. In the event of missing information on bedtime and/or waketime, the variable is set to missing and the data will not be included in the analyses defined below.

After derivation of the time to first nocturnal void per night (in hours), the average time to first void will also be computed across the 3 voiding nights (by visit). In the event of missing nights or nights without voids, the average will be computed based on the nights with available data.

In the event of no voiding during any of the 3 consecutive nights, the censoring time is defined as follows:

- Censoring time (in hours) = Maximum (Waketime – Bedtime) during voiding cycle 1, 2 or 3 (by visit).

6.3.2.1.1.1 Minimum and maximum time to first void

The minimum and maximum time to first void will be analyzed to establish a range during which subjects are having their first void of the night.

To assess the minimum time to first void across all 3 voiding nights, variables will be derived as follows:

- Minimum time to first nocturnal void (in hours) = Minimum (Time of first nocturnal void – Bedtime) during cycles 1, 2 or 3 (by visit).

The derivation of the variable will be repeated for the maximum time to first void:

- Maximum time to first nocturnal void (in hours) = Maximum (Time of first nocturnal void – Bedtime) during cycles 1,2 or 3 (by visit).

The same derivations apply in the event of missing voiding nights, and censoring is also defined in the same way [see Section 6.3.2.1.1].

6.3.2.1.2 Analysis

All analyses will be conducted based on the FAS.

6.3.2.1.2.1 Kaplan-Meier analysis

Kaplan-Meier summary tables and plots will be constructed separately for Week 1 and Week 4 by treatment. The number of subjects with events and censored observations will be presented by treatment and visit.

Kaplan-Meier plots at baseline will be constructed by sequence and overall.

No inferential statistics will be provided due to the dependence of the observations in this cross-over design.

The average time to first void and the changes from baseline will be summarized via descriptive statistics by treatment and visit.

6.3.2.2 Within-subject comparison of time to the first nocturnal void

6.3.2.2.1 Variable

The time to first nocturnal void is derived as described in Section 6.3.2.1.1 (for Week 1 and Week 4). As each subject receives both treatments, a within-subject comparison of the time to first nocturnal void is performed, separately at Week 1 and Week 4, i.e., the 'preferences' (= longer average duration to first nocturnal void across 3 cycles) are summarized in a 2 × 2 contingency table, as shown in Table 4. If a subject is missing data in one or both treatment periods, this subject's information is considered as missing and will not be included in the analysis. In the event of censored data, i.e., subjects that have no single void in 3 cycles, the preference will be assigned to the period where the subject was censored.

Table 4 Contingency table of preferences

	Treatment preference		
Treatment group	TP I	TP II	Total
Daridorexant 50 mg	x	y	x + y
Placebo	z	a	z + a
Total	x + z	y + a	x + y + z + a

TP I/II = treatment period I/II

From this table it can be derived that (x + y) subjects prefer daridorexant 50 mg, whereas (z + a) subjects prefer placebo. The differences across periods can be observed in the total row (x + z for TP I; y + a for TP II).

6.3.2.2.2 Analysis

The contingency table is analyzed separately at Week 1 and Week 4 based on the FAS via a 2-sided sign test for matched pairs. A binomial distribution will be used to compute the p-values (2-sided), which will be presented in the table.

6.3.2.3 Changes from baseline to Week 1 and Week 4 in the volume of the first nocturnal void

The first nocturnal voiding volume is defined as the volume of the first nocturnal void collected after bedtime and before waketime.

The first voiding volume per night will be averaged across voiding nights. The mean first voiding volume and corresponding change from baseline will be summarized descriptively by visit and treatment.

6.3.2.4 Change from baseline in total voiding volume (nighttime and daytime)

Three analyses will be conducted for the change from baseline in total nocturnal voiding volume:

1. Nocturnal voiding volume as derived by Minze Health (derived data are provided by Minze Health).
2. Derived nocturnal voiding volume, defined as cumulative voiding volume between bedtime and waketime.
3. Derived nocturnal voiding volume, defined as cumulative voiding volume between bedtime and waketime, excluding nights with a total voiding volume of 0.

The rationale for the conducted analyses is the partially incorrect labelling of day, night and morning voids in the Minze Health database and nights without any voids. For nights

without any voids, it is unclear whether the data were not collected or if the patient did not void at all.

Analyses for the nocturnal voiding volume **plus** the morning volume will be conducted as well, but only based on data as derived by Minze Health.

6.3.2.4.1 Variable

For analysis 2, the total nocturnal voiding volume will be derived as cumulative voiding volume between bedtime and waketime.

For analysis 3, the total nocturnal voiding volume will be derived as cumulative voiding volume between bedtime and wake time. Nights with 0 total nocturnal voiding volume will be set as missing.

6.3.2.4.2 Analysis

The total voiding volume per night will be averaged across voiding nights with available data (for baseline, Week 1, and Week 4 assessments). The mean total voiding volume and corresponding changes from baseline will be summarized descriptively by visit and treatment (based on all 3 approaches as described above). In addition, the total night voiding volume **plus** the morning volume will be summarized descriptively by visit and treatment (based on data derived by Minze Health).

Analyses will be repeated for the morning voiding volume and the total daytime voiding volume based on the data provided by Minze Health.

6.3.2.5 Change in number of nocturnal and daytime voids

Three analyses will be conducted for the number of nocturnal voids:

1. Number of nocturnal voids as derived by Minze Health (derived data are provided by Minze Health).
2. Derived number of nocturnal voids, defined as the number of nocturnal voids between bedtime and waketime.
3. Derived number of nocturnal voids, defined as the number of nocturnal voids between bedtime and waketime, excluding nights with 0 number of voids.

The rationale for the analysis is the same as described in Section 6.3.2.4.

6.3.2.5.1 Variable

For analysis 2, the number of nocturnal voids will be derived as the number of nocturnal voids between bedtime and waketime.

For analysis 3, the number of nocturnal voids will be derived as the number of nocturnal voids between bedtime and waketime. Nights with 0 voids will be set as missing.

Changes from baseline in the total number of nocturnal voids will be computed using averages across the 3 voiding nights ('Cycles') at baseline, Week 1, and Week 4 (based on available data in the corresponding treatment period).

6.3.2.5.2 Analysis

Changes from baseline to post-baseline visits in the number of nocturnal voids will be analyzed using an MMRM with treatment (daridorexant 50 mg; placebo), week within period (Week 1; Week 4), and period (TP I; TP II) as factors, baseline number of nocturnal voids as covariate, and the interaction of treatment and week. The MMRM will be applied to all 3 approaches, as described above.

An unstructured covariance matrix will be used to account for the correlation between repeated measurements from the same subject. A restricted maximum likelihood approach in combination with the Newton Raphson Algorithm will be used to derive (unbiased) estimates of variance components. The Kenward-Roger approximation will be used to compute the denominator degrees of freedom and adjust standard errors [Kenward 1997]. If the analysis fails to converge, the following structures will be tested in the subsequent order until model-convergence is achieved: heterogeneous Toeplitz, Toeplitz, autoregressive, and compound symmetry.

To evaluate the efficacy hypotheses, appropriate contrasts will be used to test the treatment differences of interest (i.e., the difference in LS Mean change from baseline to Week 4 between daridorexant 50 mg and placebo).

The LS Mean for each treatment per time point will be displayed with the associated standard errors and 95% CIs. For the comparison of daridorexant with placebo, the placebo-adjusted LS Mean will be displayed with the associated standard error, 95% CI and unadjusted 2-sided p-value.

The changes from baseline in the total number of nocturnal voids will be plotted over time (averaged across the 3 nights) by treatment (based on all 3 approaches).

The number of nocturnal voids and the change in the number of nocturnal voids will be analyzed descriptively, averaged across the 3 voiding nights, by treatment and visit (based on all 3 approaches).

Descriptive analyses will be repeated for the number of daytime voids, based on the data provided by Minze Health, by treatment and visit.

6.3.3 Quality of life and treatment preference endpoints

All analyses will be conducted based on the FAS.

6.3.3.1 ICIQ-MLUTS and ICIQ-FLUTS

The ICIQ-MLUTS is a questionnaire that evaluates lower urinary tract symptoms in males. It is a patient-completed questionnaire that includes 13 items. It 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 eDiary at Visit 1, Visit 4, and Visit 8.

The ICIQ-FLUTS is a questionnaire that evaluates lower urinary tract symptoms in females. It is a patient-completed questionnaire that includes 12 items. It is split into 3 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 eDiary at Visit 1, Visit 4, and Visit 8.

6.3.3.1.1 Variable

For the ICIQ-MLUTS voiding symptoms score, the items of questions 2a–6a will be summed. For the ICIQ-MLUTS incontinence symptoms score, the items of questions 7a–12a will be summed. Answers to questions 2b–12b will not be analyzed.

For the ICIQ-FLUTS filling symptoms score, the items of questions 2a–5a will be summed. For the ICIQ-FLUTS voiding symptoms score, the items of questions 6a–8a will be summed. For the ICIQ-FLUTS incontinence symptoms score, the items of questions 9a–13a will be summed. Answers to questions 2b–13b will not be analyzed.

Changes from baseline (Visit 1) will be calculated for each sub-score, separately for men and women.

6.3.3.1.2 Analysis

The change from baseline to Week 4 for all sub-scores of ICIQ-MLUTS and ICIQ-FLUTS will be summarized by treatment and sex. Observed values will also be summarized.

6.3.3.2 ICIQ-NQoL

The ICIQ-NQoL 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 0–4), resulting in an overall score that ranges from 0–48, where greater scores indicate a greater decrease in quality of life. It will be completed by the subjects on the eDiary at Visit 1, Visit 4, and Visit 8.

6.3.3.2.1 Variable

All items of questions 3–14 will be summed for one overall score. Changes from baseline will be calculated.

6.3.3.2.2 Analysis

The change from baseline to Week 4 for the overall ICIQ-NQoL score will be summarized by treatment. Observed values will also be summarized.

6.3.3.3 EQ-5D-3L

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, and anxiety/depression. 'None', 'some', and '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). It will be completed by the subjects at Visit 1, Visit 3, Visit 4, Visit 7, and Visit 8.

6.3.3.3.1 Variable

As the study is mainly conducted in the Unites States, the derivation of the scores for EQ-5D-3L follows the publication by Shaw et al. [Shaw 2005]

Each of the 5-digit number combinations is assigned a score, e.g., for combination 11111 a score of 1.000 is assigned, while for combination 12332 a score of 0.302 is assigned. The assignments of all scores are summarized in Appendix 13.4.

6.3.3.3.2 Analysis

The change from baseline to Week 2 and Week 4 for the overall EQ-5D-3L score will be summarized by treatment. Observed values will also be summarized.

6.3.3.4 PGA-S and PGI-C endpoints

6.3.3.4.1 PGA-S endpoints

The PGA-S (daytime symptoms) is indicative of the overall severity of daytime symptoms (e.g., sleepiness) and impact (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. The PGA-S (daytime symptoms) is a 1-item, 6-point scale that ranges from 'None' to 'Very severe'. It will be completed by the subjects on the eDiary at Visit 1 and weekly during both treatment periods.

The PGA-S (daily life) is indicative of the overall impact on daily life (e.g., effort to perform daily activities) that the subject may have experienced due to their *insomnia and nocturia* over the 4 weeks preceding the PGA-S. The PGA-S (daily life) is a 1-item, 5-point scale that ranges from 'Not at all' to 'Extremely'. It will be completed by the subjects on the eDiary at Visit 1, Visit 4, and Visit 8.

6.3.3.4.2 Variable

The PGA-S (daytime symptoms) scales ranges from 1–6, the PGA-S (daily life) ranges from 1–5. Changes from baseline will be calculated.

Time windows will be assigned for both PGA-S assessments due to missing visit labels in the eDiary database. Data were supposed to be collected on Day 8 (Week 1), Day 15 (Week 2), Day 22 (Week 3) and Day 29 (Week 4) after treatment start date for PGA-S (daytime symptoms) and on Day 29 (Week 4) after treatment start date for PGA-S (daily life) in each treatment period.

PGA-S (daytime symptoms) data for Week 1–Week 3 were collected based on a 7-day schedule in the eDiary. A time window of ± 2 days will be assigned to those weeks to select the data (Days 6–10 for Week 1, Days 13–17 for Week 2, and Days 20–24 for Week 3). As the Week 4 data was collected during the hospital visit, the variability of the collection dates is higher. Therefore, a time window of –4 to +7 days will apply for Week 4 (Days 25–36; no overlap with Week 3 data). If two data points were collected within the same time window, the collection date closest to the pre-defined days will be used (Day 8 for Week 1, Day 15 for Week 2, Day 22 for Week 3, and Day 29 for Week 4). Data will be assigned independent of visit labels.

For PGA-S (daily life) a time window of ± 7 days will apply for Week 4. If 2 data points were collected within the same time window, the collection date closest to the pre-defined day will be used (as defined above).

6.3.3.4.3 Analysis

The change from baseline to Week 1–Week 4 for PGA-S (daytime symptoms) and the change from baseline to Week 4 for PGA-S (daily life) will be summarized by treatment. Observed values will also be summarized.

6.3.3.4.4 PGI-C endpoints

The PGI-C (daytime symptoms) is indicative of the change in overall severity of daytime symptoms (e.g., sleepiness) and impact (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. The PGI-C (daytime symptoms) is a 1-item, 7-point scale that ranges from 'Very much better' to 'Very much worse'. It will be completed weekly by the subjects on the eDiary during both treatment periods.

The PGI-C (nighttime symptoms) is indicative of 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 7 nights preceding the PGI-C (nighttime symptoms) compared to the week before the subject started treatment. The PGI-C (nighttime symptoms) is a 1-item, 7-point scale that ranges from 'Very much better' to

'Very much worse'. It will be completed weekly by the subjects on the eDiary during both treatment periods.

The PGI-C (daily life) is indicative of the change in overall severity of daily life symptoms that the subject may have experienced due to their *insomnia and nocturia* over a period of 4 weeks. The PGI-C (daily life) is a 1-item, 5-point scale that ranges from 'Very much better' to 'Very much worse'. It will be completed by the subjects on the eDiary at Visit 4 and Visit 8.

6.3.3.4.5 Variable

The PGI-C (daytime symptoms) scale ranges from 1–7, the PGI-C (nighttime symptoms) ranges from 1–7, and the PGI-C (daily life) ranges from 1–5.

The same time window approach will be used for PGI-C (daytime symptoms) data as described in Section 6.3.3.4.2.

6.3.3.4.6 Analysis

The two PGI-C symptom scores will be summarized by week (Week 1, Week 2, Week 3, and Week 4). The PGI-C (daily life) score will be summarized for Week 4.

6.3.3.5 IDSIQ endpoints

IDSIQ is programmed on the eDiary and must be completed by the subject every day in the evening prior to completing the evening sleep diary. IDSIQ is structured in 3 domains (alert/cognition; mood; sleepiness) and contains 14 items overall, each based on an 11-point Numeric Rating Scale.

6.3.3.5.1 Variable

The different IDSIQ domains are derived as shown in Table 5.

Table 5 Insomnia Daytime Symptoms and Impacts Questionnaire description

Domain	Scoring	Minimum/Maximum Score
Alert/Cognition	Daily: Sum of Item 1*, Item 2*, Item 3, Item 9, Item 10*, Item 14*	Minimum score: 0 Maximum score: 60 Higher score: greater burden of illness
	Weekly Average: Mean of the daily domain score over 7 days	
Mood	Daily: Sum of Item 4, Item 5, Item 6, Item 7	Minimum score: 0 Maximum score: 40 Higher score: greater burden of illness
	Weekly Average: Mean of the daily domain score over 7 days	

Domain	Scoring	Minimum/Maximum Score
Sleepiness	Daily: Sum of Item 8*, Item 11, Item 12, Item 13	Minimum score: 0 Maximum score: 40 Higher score: greater burden of illness
	Weekly Average: Mean of the daily domain score over 7 days	
Total score	Daily: Sum of all domains above	Minimum score: 0 Maximum score: 140 Higher score: greater burden of illness
	Weekly Average: Mean of the daily domain score over 7 days	

* Item 1, Item 2, Item 8, Item 10, and Item 14 scores are reverse-scored prior to summation.

Baseline is the mean value based on the IDSIQ entries performed at home on the 7 days immediately preceding Visit 2.

Week 1–Week 4 are defined as the mean values based on the IDSIQ entries performed during Days 2–8, 9–15, 16–22 and 23–29 in each treatment period, respectively. In order to calculate baseline and Week 1–Week 4 averages, at least two days of data must be available. Otherwise, baseline and weekly averages are considered as missing.

6.3.3.5.2 Analysis

For all IDSIQ scores, weekly averages and corresponding changes from baseline to Week 1–Week 4 will be summarized, by treatment. Changes from baseline to Week 1–Week 4 will also be analyzed for all IDSIQ scores based on an MMRM, as described in Section 6.1.3.

6.3.3.6 Treatment satisfaction

The Numeric Rating Scale collects information regarding treatment satisfaction during the clinical trial by asking the subjects to mark the number that best describes overall satisfaction on a scale from 0 (‘Not at all satisfied’) to 10 (‘Extremely satisfied). Self-reported treatment satisfaction is assessed on the morning of Visit 4 and Visit 8 on the eDiary.

A paired t-test will be applied to the within-subject differences (daridorexant 50 mg vs placebo) to test for differences between the two treatments. The output will contain the mean estimate (including 95% CI) and the associated p-value.

Treatment satisfaction will be summarized descriptively by treatment.

6.3.3.7 Treatment preference

The subjects will be asked at Visit 8 to select which treatment period (TP I or TP II) was preferred and complete it on the eDiary. Subjects that were not treated in TP II will be excluded from analysis.

Treatment preference will be summarized descriptively, overall and by treatment sequence. Odds ratios (including 95% CIs) and associated p-values will be added to the output.

7 SAFETY VARIABLES AND ANALYSES

7.1 Overview of safety analyses

The SAF will be used for tables and listings of safety data, unless otherwise stated.

Unless otherwise noted, only the treatment-emergent safety data will be considered in tables and figures.

All safety data described below will be listed.

7.2 Adverse events

TEAEs are defined as AEs that started or worsened on or after study treatment start date up to the EOT + 5 days (in each treatment period). AEs that start in TP I and continue into TP II will only be presented as TP I AEs, unless there is a worsening in TP II. AEs that start in the washout period (i.e., on day 6 of the washout period up to 1 day prior to start of TP II) and continue into TP II will not be presented for any of the treatment periods.

AEs will be coded using MedDRA. The MedDRA version used for reporting will be specified in the footnote of the applicable output.

The number (%) of study subjects experiencing a TEAE (including SAEs, AESI, and AEs leading to premature discontinuation and/or temporary interruption of study treatment) will be summarized by SOC and/or PT, and/or maximum intensity.

AESIs, defined as AE PTs denoting ‘falls’ and ‘incontinence episodes’ will be summarized separately.

A subject with multiple intensities reported for an AE will be summarized under the maximum intensity recorded for the event.

Apart from the summaries of occurrences, where each event is counted, a subject with multiple occurrences of an AE is counted only once in the AE category (e.g., SOC, PT). If a single AE worsens on the same treatment, this event will be considered as one occurrence.

AEs will be sorted by descending frequency, first based on daridorexant 50 mg, then based on placebo. After this sorting, SOCs are presented in alphabetical order and PTs are sorted alphabetically within each SOC.

The following AE summary tables will be provided:

- Treatment-emergent AEs;
- TEAEs related to study treatment;

- AEs leading to premature discontinuation of study treatment;
- AEs leading to temporary interruption of study treatment;
- Treatment-emergent SAEs (including occurrences);
- Treatment-emergent SAEs related to study treatment (including occurrences);
- TEAEs with fatal outcome;
- TEAEs related to study treatment with fatal outcome;
- Total number of deaths;
- Treatment-emergent AESIs;
- AEs during the washout period.

All AEs will be listed, with AESIs and SAEs being flagged in the AE listing.

Separate listings will be provided for AEs leading to premature discontinuation of study treatment, AEs leading to temporary interruption of study treatment, SAEs, fatal AEs, and AESIs.

All deaths will be listed, with cause of death, using the SCR.

An AE listing, using the SCR, will also be provided for study subjects who were not randomized (i.e., screen failures) and study subjects who were randomized but did not take study treatment. This listing will therefore include any study subjects who discontinued the study due to an AE but did not receive any study treatment.

Any other summary required for disclosure to the public database will be generated as appropriate.

7.3 Laboratory tests

Local laboratory data will only be listed on the SCR as data is only included in the eCRF in case the investigator decides to collect the local lab data.

7.4 Vital signs, blood pressure and pulse rate

The change from baseline to Week 4 in vital signs (systolic and diastolic blood pressure, and pulse rate) will be summarized based on the FAS by treatment. The observed values at baseline and each scheduled post-baseline visit will also be summarized for the FAS.

7.5 Columbia Suicide Severity Rating Scale©

The C-SSRS© evaluates suicidal ideation and behaviors.

The C-SSRS© outcome categories are provided below. Each category has a binary response (yes/no).

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
6 Preparatory acts or behavior
7 Aborted attempt
8 Interrupted attempt
9 Actual attempt (non-fatal)
10 Completed suicide

Categories 1–5 relate to suicidal ideation and a score of 0 is assigned if no suicidal ideation is present. Categories 6–10 relate to suicidal behavior.

Self-injurious behavior without suicidal intent is also a C-SSRS© outcome (although not suicide-related) and has a binary response (yes/no).

C-SSRS© data are collected at baseline, at Week 4 (in each treatment period), during the safety follow-up periods, and for premature treatment discontinuation.

Based on the C-SSRS©, the number (%) of study subjects with suicidal ideation by category, suicidal behavior by category, suicidal ideation or suicidal behavior, and/or self-injurious behavior without suicidal intent will be tabulated by study phase. The worst C-SSRS© outcomes of Study Phase 1 (TP I; premature treatment discontinuation during TP I; and washout phase) will be derived, as well as the worst C-SSRS© outcomes of study phase 2 (TP II; premature treatment discontinuation during TP II; and safety follow-up phase). Percentages will be based on the number of study subjects with at least one post-baseline C-SSRS© assessment.

Shifts from baseline showing any change in suicidal ideation and suicidal behavior during the two study phases will be provided by treatment. Study subjects will be summarized under the worst of the following 3 categories, shown here in order from best to worst: 1) No suicidal ideation or behavior, 2) Suicidal ideation, and 3) Suicidal behavior (subjects with both suicidal ideation and suicidal behavior are also included in the suicidal behavior category).

7.6 Morning sleepiness (VAS)

Morning sleepiness is analyzed as described in Section 6.3.1.2.

7.7 Analysis of narratives

The analyses of the subject narratives will be conducted based on a separate statistical analysis plan.

8 GENERAL STATISTICAL METHODOLOGY

8.1 General rules for data presentations

Data are listed and summarized as described below.

By-treatment tables will have the following header structure (label and order):

Daridorexant 50 mg *N = xxx*	*Placebo* *N = xxx*

where N indicates the total number of subjects randomized to the respective treatment or treated with the respective treatment within the analysis set.

If the treatment sequence is displayed, the header structure will be:

Daridorexant 50 mg / Placebo *N = xxx*	*Placebo / Daridorexant 50 mg* *N = xxx*

where N indicates the total number of subjects randomized to the respective treatment sequence within the analysis set, unless otherwise specified.

All listings will be sorted by randomized treatment sequence received, subject number (ascending) and, when appropriate, by visit / date of assessment (ascending). Listings related to the SCR will present a treatment label ‘screening failure’ to indicate study subjects who were not randomized and will be listed after the study subjects who were randomized or received study treatment, as relevant.

Unless noted otherwise, the following descriptive statistics will be used to summarize data: number (%) of study subjects for categorical variables; descriptive statistics (number of non-missing values, mean, standard deviation, median, Q1, Q3, minimum, maximum) for continuous variables.

8.2 Handling of missing dates

An incomplete date (day or month missing), or missing concomitant therapy / AE date, will be imputed as described in Table 6. The ‘lower limit’ and ‘upper limit’ refer to the earliest and latest possible dates, respectively.

For example, if concomitant therapy start date / AE onset date is MAR2021 (day missing), the lower limit is 01MAR2021 and the upper limit is 31MAR2021; if concomitant therapy start date / AE onset date is 2021 (day and month missing), the lower limit is 01JAN2021 and the upper limit is 31DEC2021.

Table 6 Imputation rules for an incomplete or missing concomitant therapy or AE date

Field	Incomplete date	Missing date
Concomitant therapy end date / AE resolution date	The upper limit.	No imputation. The therapy / AE is considered as ongoing.
Concomitant therapy start date / AE onset date	The rules below apply in the order presented: 1. If the (imputed) concomitant therapy / AE end date is on or after the start of study treatment, and if the study treatment start falls within the upper and lower limits (inclusive), the study treatment start date of the corresponding treatment period is used.* 2. If the concomitant therapy end date / AE resolution date is missing, and if the study treatment start falls within the upper and lower limits (inclusive), the study treatment start date of the corresponding treatment period is used. # 3. In all the other cases, the lower limit is used.	Whichever is the earlier of the concomitant therapy end date or study treatment start date. If the start date is missing the AE will be assigned to both treatment periods.

* If both treatment start dates (i.e., those for TP I and TP II) are within the lower and upper limit, the concomitant therapy / AE is duplicated and assigned to both treatment periods, i.e., once with treatment 1 start date and once with treatment 2 start date.)
AE = adverse event; TP = treatment period.

The purpose of imputing concomitant therapy / AE dates is only to assign a concomitant therapy / AE to a specific study period for the summary tables. No imputed date is considered in the medical evaluation of an AE or of a causal relationship between a concomitant therapy and an individual AE.

9 INTERIM ANALYSES

No interim analysis will be performed.

10 GENERAL DEFINITIONS AND DERIVATIONS

10.1 Treatment start and end dates

Study treatment start or end date is the earliest or latest date, respectively, of dose intake recorded on the 'Study Treatment Log' page for the corresponding treatment period.

10.2 Study periods

The screening period is defined as the time from the informed consent date until one day before the study treatment start date of TP I, or date of screening failure.

The treatment periods are defined as the time from the day of study treatment start until the day of EOT (Week 4), or, for those who prematurely discontinued study treatment (i.e., those without an EOT date), until the day of study treatment end date.

Provided the subject starts the second treatment, the washout period is defined as the time from one day after the end of TP I until the day before start of TP II.

The safety follow-up period is defined as the time from one day after the end of the last treatment period until end of safety follow-up period / EOS date (for both treatment periods).

10.3 Treatment day and Study day

The Treatment day for an assessment or event will be calculated using the study treatment start date of the corresponding treatment period as reference.

For assessments/events occurring on or after the start date of study treatment, Treatment day will be positive and will be calculated as:

- Treatment day (days) = Date of assessment/event – Start date of study treatment + 1 day

The first day of study treatment is Treatment day 1.

Study day will be calculated as:

- Study day (days) = Date of assessment/event – Start date of study treatment in TP I

For all assessments/events occurring prior to the start date of TP I, Study day will be negative. Study day will be displayed in the data listings as appropriate.

10.4 Baseline

Baseline is the last non-missing assessment performed or value measured before or on the day of the first dose of any study treatment, unless otherwise defined in the specific analysis section.

Study subjects with no data for a given parameter before the first treatment administration will have a missing baseline (and missing change from baseline) for this parameter.

10.5 Change from baseline

The change from baseline is defined as the post-baseline value (any assessment performed after baseline and up to EOS) minus the baseline value. A positive number indicates an increase compared to baseline.

11 CHANGES OR CLARIFICATIONS TO ANALYSES PLANNED IN THE STUDY PROTOCOL

11.1 Changes to the analyses planned in the study protocol

Not applicable.

11.2 Changes in the conduct of the study / data collection

Not applicable.

11.3 Clarifications concerning endpoint definitions and related variables or statistical methods

Analyses for the key voiding endpoints 'Total nocturnal voiding volume' and 'Total number of nocturnal voids' were updated to address potential inconsistencies in the Minze Health voiding data.

Due to issues involving the weekly PGA and PGI endpoint data collection, a time window approach was introduced. Analyses remain the same.

Some minor clarifications were added for C-SSRS© analyses.

Two of the PDs were updated for the definition of the PPS population.

Generally, some minor clarifications were added to the SAP, e.g. outputs repeated on a different population.

The duration of the safety follow-up period was set to 5 days (instead of the 5–10 days specified in the protocol).

11.4 Additional analyses to those planned in the study protocol

Baseline disease characteristics summary tables were added for the RND and FAS.

A table summarizing the duration of the washout period was added.

The study discontinuations summary table will also be produced for the FAS.

Analyses for ISI©, VAS scales and IDSIQ scales will be repeated based on an MMRM for the FAS.

An analysis by treatment period was added for the missing data patterns of the primary endpoint and for the compliance summary table.

Two sensitivity analyses each were added for 'Total nocturnal voiding volume' and 'Total number of nocturnal voids' to account for missing and inconsistent data.

For the time to first nocturnal void, a Kaplan-Meier plot was added for all subjects at baseline.

An analysis was added for the total nocturnal voiding volume plus the morning void volume.

12 REFERENCES

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13 APPENDICES

13.1 Revision history

Version date	Version	Implemented change(s)
5 July 2023	**1**	New
30 May 2024	**2**	Changes as described in Section 11.

13.2 SAS® code for mixed model for repeated measures

This model is used, for example, for the main analyses of the primary endpoint. Assuming the data are in 'long' format (i.e., one row for each subject/visit), example SAS® statements for the primary endpoint analysis are:

```
proc mixed data=data;
        class SUBJID TRT VIS PERIOD;
        model CHG = BASE TRT VIS PERIOD TRT*VIS / ddfm=kr;
        random int / subject=SUBJID;
        repeated VIS / subject=SUBJID*TRT type=un;
        lsmeans TRT*VIS / diff cl;
        estimate 'daridorexant 50 mg vs placebo at Week 4' TRT 1 -1 TRT*VIS 0 0 0 1 0
        0 0 -1 / cl;
run;
```

The dataset '*data'* includes baseline as well as changes (CHG) from baseline to Weeks 1, 2, 3, and 4 (VIS). Furthermore, TRT equals 1 and 2 for daridorexant 50 mg and placebo, respectively, and PERIOD equals 1 and 2 for TP I and TP II.

13.3 SAS® code for Kaplan-Meier analyses

This model is used, for example, for the voiding diary analyses. The duration is the time from bedtime to first void, for example. The status of 0 is assigned to censored patients.

```
proc lifetest data=data;
        time duration*status(0);
        strata treatment;
run;
```

13.4 Reference data for EQ-5D-3L

The 5-digit sequence of the EQ-5D-3L questionnaire will be assigned a score, as presented in Table 7.

Table 7 EQ-5D-3L Coding

Combination	Value
11111	1.000
11211	0.860
21111	0.854
11112	0.844
21211	0.843
11212	0.833
11121	0.827
21112	0.827
12111	0.825
11221	0.816
12211	0.814
21121	0.810
22111	0.808
11122	0.800
12112	0.797
21212	0.794
12121	0.781
21221	0.778
22211	0.775
11222	0.768
12212	0.765
21122	0.761
22112	0.759
12221	0.748
22121	0.742
12122	0.732
21222	0.708
22212	0.705
22221	0.689
12222	0.678
22122	0.672
11311	0.626
21311	0.619
11312	0.609

22222	0.597
11321	0.592
21312	0.592
12311	0.590
21321	0.575
22311	0.573
11322	0.565
12312	0.563
11113	0.550
11213	0.550
12321	0.546
21113	0.543
21213	0.533
13111	0.529
13211	0.529
21322	0.527
22312	0.524
23111	0.522
11123	0.517
12113	0.514
13112	0.512
23211	0.512
22321	0.508
11223	0.506
12213	0.503
13212	0.501
21123	0.499
12322	0.497
22113	0.497
13121	0.496
23112	0.495
13221	0.485
23121	0.478
12123	0.470
13122	0.468
21223	0.467
22213	0.465

11131	0.463
11231	0.463
23212	0.463
21131	0.456
11313	0.452
11132	0.446
23221	0.446
21231	0.446
21313	0.445
31111	0.442
31211	0.442
12223	0.438
22322	0.437
13222	0.436
11232	0.435
22123	0.432
13311	0.431
23122	0.430
21132	0.429
12131	0.427
31112	0.426
23311	0.424
11323	0.418
12231	0.416
12313	0.416
31212	0.415
13312	0.414
22131	0.410
31121	0.409
32111	0.407
21323	0.401
12132	0.400
22313	0.399
31221	0.398
13321	0.397
21232	0.397
23312	0.397

32211	0.396
31122	0.382
23321	0.380
32112	0.379
22223	0.378
22231	0.378
23222	0.376
12323	0.372
13322	0.370
12232	0.368
11331	0.365
32121	0.363
22132	0.361
21331	0.358
13113	0.355
13213	0.354
31222	0.350
23113	0.348
11332	0.348
32212	0.347
31311	0.344
23213	0.337
22323	0.333
23322	0.331
21332	0.331
32221	0.330
12331	0.329
31312	0.327
13123	0.321
32122	0.314
22331	0.312
31321	0.311
13223	0.310
32311	0.308
22232	0.308
23123	0.304
12332	0.302

11133	0.289
11233	0.289
13313	0.286
31322	0.283
21133	0.282
32312	0.281
23313	0.279
23223	0.272
21233	0.271
31113	0.268
13131	0.268
31213	0.268
13231	0.268
32321	0.264
22332	0.263
23131	0.261
32222	0.260
12133	0.253
13323	0.253
13132	0.251
23231	0.250
33111	0.247
33211	0.247
12233	0.242
13232	0.240
22133	0.236
23323	0.235
31123	0.235
23132	0.234
32113	0.232
33112	0.230
31223	0.224
32213	0.222
11333	0.220
33212	0.220
32322	0.216
21333	0.214

33121	0.214
22233	0.204
33221	0.203
23232	0.202
31313	0.199
13331	0.199
23331	0.193
32123	0.188
33122	0.186
12333	0.184
13332	0.182
31131	0.181
31231	0.181
33311	0.178
22333	0.167
31323	0.166
23332	0.165
31132	0.165
32313	0.164
33312	0.162
32223	0.156
33222	0.154
31232	0.154
32131	0.145
33321	0.145
32231	0.135
13133	0.123
13233	0.123
32323	0.120
32132	0.118
33322	0.118
23133	0.117
31331	0.112
23233	0.106
33113	0.102
33213	0.102
31332	0.096

32232	0.086
13333	0.084
23333	0.077
32331	0.077
33123	0.069
33313	0.063
33223	0.058
32332	0.049
31133	0.037
31233	0.036
33323	0.030
33131	0.016
33231	0.015
32133	0.001
33132	-0.001
31333	-0.003
32233	-0.010
33232	-0.012
33331	-0.024
32333	-0.038
33332	-0.040
33133	-0.100
33233	-0.100
33333	-0.109