Cover page

Official Title:

PROTOCOL ID-078A303 - Multi-center, double-blind, parallel-group, randomized, placebo-controlled, three doses, 40-week extension to studies ID-078A301 and ID-078A302 to assess the long-term safety and tolerability of ACT-541468 in adult and elderly subjects with insomnia disorder

ClinicalTrials.gov Identifier:

NCT03679884

Date of document:

17 February 2020

Daridorexant (ACT-541468)

Insomnia Disorder

Protocol ID-078A303

Multi-center, double-blind, parallel-group, randomized, placebo-controlled, three doses, 40-week extension to studies ID-078A301 and ID-078A302 to assess the long-term safety and tolerability of ACT-541468 in adult and elderly subjects with insomnia disorder

Study Phase:	3
EudraCT Number:	2017-004644-38
Status and version:	Final Version 3
Date:	17 February 2020
Document type	Global protocol
Idorsia document number (Doc No.):	D-20.025

SPONSOR CONTACT DETAILS

Sponsor	Idorsia Pharmaceuticals Ltd Hegenheimermattweg 91 CH-4123 Allschwil Switzerland ☎ +41 58 844 00 00
Clinical Trial Physician	Contact details of the Clinical Trial Physician can be found in the Investigator Site File
Medical Emergency Hotline Toll phone number	Site-specific toll telephone numbers and toll-free numbers for the Medical Emergency Hotline can be found in the Investigator Site File

CONTRACT RESEARCH ORGANIZATION INFORMATION

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

SIGNATURE PAGE FOR IDORSIA PHARMACEUTICALS LTD

Hereinafter called Idorsia

Treatment name / number

Daridorexant (ACT-541468)

Indication

Insomnia disorder

Protocol number, study title

ID-078A303

Multi-center, double-blind, parallel-group, randomized, placebo-controlled, three doses, 40-week extension to studies ID-078A301 and ID-078A302 to assess the long-term safety and tolerability of ACT-541468 in adult and elderly subjects with insomnia disorder

I approve the terms and conditions relating to this study as defined in this protocol. I confirm that the information contained in this protocol is consistent with the current risk-benefit evaluation of ACT-541468, and with the ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki and the ICH GCP guidelines.

Title	Name	Date	Signature
[redacted]			

INVESTIGATOR SIGNATURE PAGE

Treatment name / number

Daridorexant (ACT-541468)

Indication

Insomnia disorder

Protocol number, study title

ID-078A303

Multi-center, double-blind, parallel-group, randomized, placebo-controlled, three doses, 40-week extension to studies ID-078A301 and ID-078A302 to assess the long-term safety and tolerability of ACT-541468 in adult and elderly subjects with insomnia disorder

I agree to the terms and conditions relating to this study as defined in this protocol, the case report form, 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 study 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. I confirm herewith that the sponsor is allowed to enter and utilize my professional contact details and function in an electronic database for internal purposes and for submission to health authorities worldwide.

Principal Investigator	Country	Site number	Town	Date	Signature

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

LIST OF ABBREVIATIONS AND ACRONYMS

AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BP	Blood pressure
bpm	Beats per minute
BWSQ	Benzodiazepine Withdrawal Symptom Questionnaire
CBT	Cognitive behavioral therapy
CFR	Code of Federal Regulations (US)
CNS	Central nervous system
CRA	Clinical Research Associate
CRO	Contract Research Organization
CSR	Clinical study report
C-SSRS©	Columbia Suicide Severity Rating Scale©
CYP	Cytochrome P450
DB	Double-blind
DoA	Delegation of Authority
DORA	Dual orexin receptor antagonist
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
ECG	Electrocardiogram/graphy
eCRF	Electronic case report form
EDS	Excessive daytime sleepiness
EMA	European Medicines Agency
EODBT	End of Double-Blind Treatment
EOS	End-of-Study
EOT	End-of-Treatment
ESS©	Epworth Sleepiness Scale©
FAS	Full Analysis Set
FDA	Food and Drug Administration

GCP	Good Clinical Practice
HR	Heart rate
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
IDSIQ	Insomnia Daytime Symptoms and Impacts Questionnaire
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISAC	Independent Statistical Analysis Center
ISB	Independent Safety Board
ISF	Investigator Site File
ISI©	Insomnia Severity Index©
LPS	Latency to Persistent Sleep
MedDRA	Medical Dictionary for Regulatory Activities
PGA-S	Patient Global Assessment of Disease Severity
PGI-C	Patient Global Impression of Change
PI	Principal Investigator
PK	Pharmacokinetic
PT	Preferred term
QS	Quality System
QTc	Corrected QT interval
QTcB	QT interval corrected with Bazett's formula
QTcF	QT interval corrected with Fridericia's formula
RSI	Reference safety information
SAE	Serious adverse event
SDS©	Sheehan Disability Scale©
SIV	Site Initiation Visit
sLSO	Subjective Latency to Sleep Onset
SOC	System organ class

sTST	Subjective Total Sleep Time
SUSAR	Suspected unexpected serious adverse reaction
sWASO	Subjective Wake After Sleep Onset
TEAE	Treatment-emergent adverse event
USPI	United States Package Insert
VAS	Visual analog scale(s)
WASO	Wake After Sleep Onset

SUBSTANTIAL GLOBAL AMENDMENT 2

Amendment rationale

This amendment applies to global protocol ID-078A303 Version 2 dated 4 July 2018. The resulting amended global protocol is Version 3 dated 17 February 2020.

The main protocol change is related to the inclusion of an interim analysis for safety and efficacy to support global regulatory filings. The interim analysis will be conducted when all subjects who did not prematurely discontinue study treatment have reached Visit 3, to ensure at least 6 months of double-blind study treatment (confirmatory and extension studies). At this time, approximately 260 subjects will have been treated with daridorexant for 12 months.

The submission of an NDA/MAA for daridorexant based on interim data from this study will potentially allow earlier access to daridorexant for patients with insomnia.

A second interim analysis may be performed to fulfill the FDA requirement to submit updated safety data from ongoing studies 120 days after NDA submission, in case the study has not been completed by that time.

The study will run until its completion (i.e., EOS for the last subject) to fulfill its primary objective and all data generated will be analyzed and reported in the final clinical study report, which will be available for regulatory authorities. Therefore, subjects enrolled later will equally benefit from the study.

To maintain the integrity of the study after the interim analysis, participating subjects as well as investigators will remain blinded for the entire duration of the study. The sponsor personnel involved in data collection and medical monitoring of the study will also remain blinded until the end of the study.

In addition to the protocol modifications required to support the interim analysis, the sponsor has made the following changes:

- Clarification regarding the allowed methods of contraception: a formal documentation of a subject's vasectomy or tubal occlusion/ligation is not necessary. The information can be obtained during the medical interview of the subject by the investigator.
- Clarification regarding the definition and reporting of overdose, misuse, abuse and treatment error as an adverse event.
- Clarification regarding the telephone calls to be performed monthly by the investigator/delegate.
- Clarification that subgroup analyses will be conducted.

- Clarification regarding the reporting/transfer of ongoing medical history, adverse events, and concomitant therapies from the pivotal studies into the extension study database.
- Clarification regarding some exploratory and safety endpoints.

Furthermore, minor editorial changes have been made and typographical errors have been corrected.

Changes to the protocol

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.

Amended protocol sections

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

3.1	Study design
3.2	Study design rationale
4.5.2	Acceptable methods of contraception
5.1.4.1	Double-blind treatment period
5.1.5.1	Unblinding for interim analyses
5.2.2	Reporting of previous/concomitant therapy in the eCRF
6.1	Safety endpoints
6.2	Exploratory endpoints
7.1.3	Telephone calls between visits
Table 1	Table of assessments
7.2.4.1	Type of laboratory
9.1.1	Definition of adverse events
10.3.3	Subgroup analyses
10.4	Interim analysis
11.3	Database management and quality control

Summary of previous amendments

Amendment	Date	Main reason(s)
1	4 July 2018	Address the comment received on 26 June 2018 during the Voluntary Harmonization Procedure (VHP) review of this Clinical Trial Application (CTA) in the EU.

PROTOCOL SYNOPSIS ID-078A303

TITLE	Multi-center, double-blind, parallel-group, randomized, placebo-controlled, three doses, 40-week extension to studies ID-078A301 and ID-078A302 to assess the long-term safety and tolerability of ACT-541468 in adult and elderly subjects with insomnia disorder.
OBJECTIVE	To assess the long-term safety and tolerability of 10, 25 and 50 mg ACT-541468.
DESIGN	Multi-center, double-blind, parallel-group, randomized, three-dose, 40-week extension to studies ID-078A301 and ID-078A302, Phase 3 study.
PHASES	The study starts at Visit 1, with the signature of the informed consent. The subject will receive the allocated treatment, provided all the eligibility criteria are met. ID-078A303 Visit 1 can be performed on the same day as the run-out, i.e., End-of-Treatment (EOT) of ID-078A301 or ID-078A302 studies, after all run-out assessments have been completed, or as an independent visit within a maximum of 7 days after EOT. The study comprises a treatment phase and a safety follow-up phase: The **double-blind (DB) treatment phase** lasts 40 weeks, starting when the treatment is allocated. DB study treatment is taken daily. A safety telephone call is performed at Visit 2 (Day 7 to Day 14) to collect information about adverse events (AEs) and concomitant medications. Safety parameters of each subject are assessed at Visit 3 (Week 14), Visit 4 (Week 27) and at Visit 5 (Week 40). The sleep diary and Insomnia Daytime Symptoms and Impacts Questionnaire (IDSIQ) are completed at home daily during the last week of each consecutive 4-week DB study treatment period. Reminder telephone calls are scheduled within one week (preferably 2 days) before the week of questionnaire completion to increase the subject's compliance with the diary.

	During these telephone calls, the investigator/delegate is also encouraged to collect the results of the urine pregnancy tests performed at home. Alternatively, another telephone call can be set up to collect these data. End of Double-Blind Treatment (EODBT) is reached at Visit 5. The **safety follow-up phase** starts after EODBT and ends 30 days after last dose of DB study treatment. It consists of a single-blind placebo run-out period of 7 days and a safety follow-up period. The run-out period starts in the evening of Visit 5 (EODBT) with the intake of one dose of single-blind placebo treatment and ends after a total of 7 days of single-blind placebo intake (Visit 6). EOT is reached at Visit 6. The safety follow-up period starts after the run-out period and ends 30 days after last dose of DB study treatment. **End-of-Study** for an individual subject is defined as the date of the 30-day follow-up telephone call (Visit 7). The study duration for a single subject is expected to be approximately 45 weeks.
PLANNED DURATION	Approximately 24 months from first subject, first visit to last subject, last visit.
SITE(S) / COUNTRY(IES)	The study will be implemented at each site taking part in the ID-078A301 and ID-078A302 studies (approximately 150 centers in 17 countries), depending on health authority / Independent Ethics Committee / Institutional Review Board approval.
SUBJECTS / GROUPS / STUDY TREATMENTS	Subjects assigned to the placebo arm in ID-078A301 or ID-078A302 studies will be randomized to receive either placebo or 25 mg ACT-541468 in a 1:1 ratio in the extension study. Treatment allocation will be stratified by age into 2 categories: < 65 and ≥ 65 years (the age entered at the screening visit in the ID-078A301 or ID-078A302 studies will be taken into consideration for the ID-078A303 randomization of these subjects). Subjects assigned to the ACT-541468 arms

	in the ID-078A301 or ID-078A302 studies will continue on the same dose (10, 25, or 50 mg) in the extension study. It is anticipated that approximately 1260 subjects will take part in the extension study. However, participation will be offered to all eligible subjects.
INCLUSION CRITERIA	For all the following criteria, time points in brackets refer to the visits when the criterion must be assessed. 1. Signed informed consent prior to any study-mandated procedure (Visit 1). 2. Having completed the DB study treatment and run-out period of ID-078A301 or ID-078A302 (Visit 1). 3. For woman of childbearing potential, the following is required: • Negative urine pregnancy test (EOT of ID-078A301 or ID-078A302 studies). • Agreement to use the contraception scheme as required by the protocol from Visit 1 up to at least 30 days after EODBT.
EXCLUSION CRITERIA	For all the following criteria, timepoints in brackets refer to the visits when the criterion must be assessed. 1. Unstable medical condition, significant medical disorder or acute illness, or ECG, Columbia Suicide Severity Rating Scale© (C-SSRS©), hematology or biochemistry test results in ID-078A301 and ID-078A302, which, in the opinion of the investigator, could affect the subject's safety or interfere with the study assessments (Visit 1). 2. For female subjects: lactating or planning to become pregnant over the duration of the study (Visit 1). 3. Positive urine drug test (for benzodiazepines, barbiturates, cannabinoids, opiates, amphetamines, or cocaine) (Visit 1).
STUDY TREATMENTS	**Investigational treatment** ACT-541468 supplied as identical film-coated tablets at strengths of 10 mg, 25 mg and 50 mg will be administered orally, once daily at bedtime during the DB treatment period.

	Placebo ACT-541468-matching placebo will be administered orally, once daily at bedtime during the DB treatment period and the single-blind run-out period.
ENDPOINTS	To evaluate long-term safety and efficacy of ACT-541468, data from ID-078A301 and ID-078A302 will be included for subjects entering this extension study. For subjects who received placebo in ID-078A301 or ID-078A302 that are randomized to 25 mg ACT-541468 in this extension study, baseline refers to assessments taken before start of ACT-541468 intake. For all other subjects, and unless stated otherwise, baseline refers to assessments performed before start of DB study treatment of study ID-078A301 or ID-078A302. **Safety endpoints:** • Serious adverse events (SAEs) up to 30 days after DB study treatment discontinuation. • Treatment-emergent AEs (TEAEs) up to 30 days after DB study treatment discontinuation. • AEs leading to premature discontinuation of the DB study treatment. • AEs of special interest (AESIs) after adjudication by Independent Safety Board (ISB): – narcolepsy-like symptoms (i.e., excessive daytime sleepiness [EDS], cataplexy and complex sleep behavior events including hallucinations / sleep paralysis). – suicide/self-injury. • Change from baseline to Visit 3, Visit 4, Visit 5 and Visit 6 in Epworth Sleepiness Scale© total score. • Change from baseline to Visit 3, Visit 4 and Visit 5 in vital signs (systolic and diastolic blood pressure [BP], and pulse rate). • Change from baseline to Visit 5 in body weight. • Marked ECG abnormalities on DB study treatment.

	• Change from baseline to Visit 3, Visit 4, Visit 5 and Visit 6 in ECG parameters. • Marked laboratory abnormalities on DB study treatment. • Change from baseline to Visit 3, Visit 4, Visit 5 and Visit 6 in laboratory parameters. • Occurrence of suicidal ideation and/or behavior on DB study treatment and during the treatment withdrawal period based on C-SSRS©. • Withdrawal effects (physical dependence) upon treatment discontinuation will be assessed based on the changes from last assessment on DB treatment (Visit 5) to end of the run-out period (Visit 6) in the Benzodiazepine Withdrawal Symptom Questionnaire (BWSQ) total score, the occurrence of relevant AEs and marked ECG abnormalities. • Rebound insomnia will be assessed based on change from baseline to the run-out period in subjective Total Sleep Time (sTST). • Next-day residual effect will be assessed based on change from baseline to Visit 3, Visit 4 and Visit 5 in Sheehan Disability Scale© (SDS©) and change from baseline over time in morning sleepiness score on the sleep diary visual analog scale (VAS; mm). VAS scores are the subjects' rating of their morning sleepiness (from 'the way you feel this morning'), daytime alertness (from 'your daytime alertness today') and daytime ability to function (from 'your daily ability to function today'). **Exploratory efficacy endpoints:** • Change from baseline over time in sTST. sTST is the total sleep time, as reported in item 9 of the sleep diary. • Change from baseline over time in sLSO. sLSO is the self-reported time to fall asleep, as reported in item 5 of the sleep diary. • Change from baseline over time in subjective sleep maintenance (sWASO). sWASO is the self-reported time spent awake after sleep onset as reported in item 7 of the sleep diary.

	• Change from baseline over time in IDSIQ scores (i.e., total score; alert/cognition, mood and sleepiness domain scores). • Change from baseline over time in sleep quality based on scores on the sleep diary VAS (mm). VAS scores are the subjects' rating of 'the quality of your sleep last night' and 'the depth of your sleep last night', daytime alertness and daytime ability to function questions. • Change from baseline to Visit 3, Visit 4 and Visit 5 in Insomnia Severity Index© (ISI©) scores. The number (%) of subjects with ≥ 6-point decrease in ISI© Total score from baseline to Visit 3, Visit 4 and Visit 5 will be tabulated. • Change from baseline over time in mean number of self-reported awakenings. • Change from baseline over time in Patient Global Assessment of Disease Severity scores (daytime symptoms). • Change from baseline over time in Patient Global Impression of Change scores (daytime symptoms).
ASSESSMENTS	Refer to the schedule of assessments in Table 1.
STATISTICAL METHODOLOGY	To evaluate long-term safety and efficacy of ACT-541468, baseline data from ID-078A301 and ID-078A302 will be included for subjects entering this extension study. For subjects who received placebo in ID-078A301 or ID-078A302 that are randomized to 25 mg ACT-541468 in this extension study, baseline refers to assessments taken before start of ACT-541468 intake. For all other subjects, and unless stated otherwise, baseline refers to assessments performed before start of DB study treatment of study ID-078A301 or ID-078A302. **Analysis of safety endpoints** Analysis of safety endpoints will be performed using the Safety Set, unless noted otherwise. ***Adverse events*** AEs will be coded using MedDRA. The number (%) of subjects experiencing a TEAE (including SAEs, AESIs after

	adjudication by the ISB, and AEs leading to premature discontinuation of the DB study treatment) will be summarized by system organ class (SOC) and/or preferred term (PT), and maximum intensity. A subject with multiple intensities reported for an AE will be summarized under the maximum intensity recorded for the event. A subject with multiple occurrences of an AE is counted only once in the AE category (e.g., SOC, PT). ***Laboratory data*** Laboratory analyses will be based on data received from the central laboratory. Observed values and changes from baseline to Visit 3, Visit 4, Visit 5 and Visit 6 in both hematology and blood chemistry laboratory parameters will be summarized. The number (%) of subjects having a marked laboratory abnormality during DB study treatment will be tabulated. ***Vital signs and body weight*** Observed values and changes from baseline to Visit 3, Visit 4 and Visit 5 in vital signs (systolic and diastolic BP, and pulse rate) will be summarized. Observed values and changes from baseline to Visit 5 in body weight will be summarized. ***Electrocardiograms*** Observed values and changes from baseline to Visit 3, Visit 4, Visit 5 and Visit 6 for each ECG parameter (QTcB, QTcF, heart rate, PR, QRS) will be summarized. The number (%) of subjects having a marked ECG abnormality during DB study treatment will be tabulated. ***Withdrawal symptoms*** The Treatment Withdrawal Set will be used to assess the potential for withdrawal symptoms. The BWSQ total score will be summarized using descriptive statistics for the observed values and changes from the last assessment on treatment (Visit 5) to the end of the run-out period (Visit 6). In addition, withdrawal symptoms after DB study treatment withdrawal will be assessed through the incidence of AEs and marked ECG abnormalities occurring during the treatment withdrawal period. The number (%) of subjects having,

	separately, an AE and a marked ECG abnormality during the treatment withdrawal period will be tabulated. ***Rebound insomnia*** The Treatment Withdrawal Set will be used to assess the potential for rebound insomnia. Changes from baseline to the treatment withdrawal period (Visit 6, Week 41) in sTST will be summarized using descriptive statistics. ***Next-day residual effect*** Observed values and changes from baseline to Visit 3, Visit 4 and Visit 5 in SDS©, and sleep diary VAS scores (mm) assessing morning sleepiness (from 'the way you feel this morning'), daytime alertness (from 'your daytime alertness today') and daytime ability to function (from 'your daily ability to function today'), will be summarized. ***C-SSRS©*** Number (%) of subjects with suicidal ideation, suicidal behavior, and/or self-injurious behavior without suicidal intent based on the C-SSRS© during DB treatment and during the treatment withdrawal period will be tabulated. Shifts from baseline showing any changes in suicidal ideation and suicidal behavior during DB treatment and during the treatment withdrawal period will also be provided. Subjects will be summarized under the worst of the following three categories, shown here in the order from best to worst: 1) No suicidal ideation or behavior, 2) Suicidal ideation only, and 3) Suicidal ideation and behavior. **Epworth Sleepiness Scale©** The change from baseline to Visit 3, Visit 4, Visit 5 and end of the run-out period Visit 6 in ESS© total score will be summarized. Observed values will also be summarized. **Analysis of exploratory efficacy endpoints** Analysis of the efficacy endpoints will be performed using the FAS. A longitudinal data analysis method (i.e., linear mixed effects model) will be used for the analysis of change from baseline in

	sTST, sWASO, sLSO and IDSIQ scores (i.e., Total score; alert/cognition, mood, and sleepiness domain scores), separately. All available data, regardless of occurrence of intercurrent events (e.g., study treatment discontinuation, the use of prohibited medication), will be included in the model. The analysis model will adjust for the baseline value of the relevant response variable, age group (< 65; ≥ 65 years), treatment (10 mg; 25 mg; 50 mg; placebo), visit (Month 6; Month 9; Month 12), and the interaction of treatment by visit, and baseline by visit. An unstructured covariance matrix shared across treatment groups will be used to model the correlation among repeated measurements. A restricted maximum likelihood approach 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]. Appropriate contrasts will be used to test the treatment differences of interest (e.g., the difference in least squares mean change from baseline of 10 mg vs placebo, 25 mg vs placebo and 50 mg vs placebo at Month 6). Baseline is the mean value based on the screening sleep diary / IDSIQ entries performed at home in the 7 days immediately preceding the first polysomnography at Visit 3 of the ID-078A301 or ID-078A302 study. Month 6 is the mean value based on the sleep diary / IDSIQ entries performed at home over the 7 days in Week 12 of the extension study; Month 9 and Month 12 is defined similarly. Observed values and changes from baseline over time in sTST, sWASO, sLSO and IDSIQ scores (i.e., total score; alert/cognition, mood and sleepiness domain scores) will be summarized. Summary statistics will be provided for other efficacy endpoints using number (%) of subjects for categorical variables and descriptive statistics (e.g., mean, standard deviation, median, min., max.) for continuous variables.

	Interim analyses An interim analysis is planned to support global regulatory filings. The interim analysis will be conducted when all subjects who did not prematurely discontinue study treatment have reached Visit 3. A second interim analysis may be performed to fulfill the FDA requirement to submit updated safety data from ongoing studies 120 days after NDA submission, if the study has not been completed by that time. The interim analyses will include all safety and efficacy data. To maintain the integrity of the study after the interim analysis, participating subjects as well as investigators will remain fully blinded for the entire duration of the study. The sponsor personnel involved in data collection and medical monitoring of the study will also remain blinded until the end of the study. No adjustment for multiple testing is required as no formal interim analysis will be performed for determining whether to stop (or modify) the study (i.e., no hypothesis testing will be conducted ad interim).
STUDY COMMITTEES	An Independent Data Monitoring Committee (IDMC) will have overall responsibility for safeguarding the interests of subjects, by monitoring safety and efficacy data obtained in the study, and making appropriate recommendations based on the reported data. This will ensure that the study is being conducted to the highest scientific and ethical standards. The IDMC will be fully operational prior to the enrollment of the first subject into the study. The composition and operation of the IDMC is described in the IDMC charter. The IDMC will not be involved in any of the interim analyses described. An ISB will review and adjudicate in a blinded manner AESIs, i.e., narcolepsy-like symptoms (EDS, cataplexy and complex sleep behavior events including hallucinations / sleep paralysis), or suicide/self-injury. The composition and operation of the ISB is described in the ISB charter.

PROTOCOL

1 BACKGROUND

1.1 Insomnia disorder

1.1.1 Definition

The definition of insomnia disorder used in the protocol is the one described in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) [APA 2013]:

"Insomnia disorder is a predominant complaint of dissatisfaction with sleep quantity or quality, associated with difficulty initiating or maintaining sleep, or early morning awakening. Furthermore, the sleep disturbance is associated with significant social or functional distress or impairment. Sleep difficulty occurs at least 3 nights per week and is present for at least 3 months, and occurs despite adequate opportunity for sleep. The insomnia (a) is not better explained by, and does not occur exclusively during, the course of another sleep-wake disorder, (b) is not attributable to the physiological effect of a substance, and (c) is not explained by co-existing mental disorders or medical conditions."

1.1.2 Epidemiology

Insomnia is a common problem. Population-based epidemiological studies suggest that 30% or more of the general population complain of sleep disruption and approximately 10% of the general population have complaints of sleep disruption with associated symptoms of distress or daytime functional impairment consistent with the diagnosis of insomnia disorder [NIH 2005, Roth 2007].

1.1.3 Treatment

The current standards of care encompass non-pharmacological therapies and pharmacotherapy [Schutte-Rodin 2008].

Non-pharmacological (psychological and behavioral) standard-of-care therapies for insomnia include a variety of treatment methods, such as cognitive behavioral therapy (CBT), stimulus control, and relaxation training [Schutte-Rodin 2008]. Sleep hygiene therapy is often added to these treatment modalities.

Prescription sleep medications (hypnotics) indicated for the treatment of insomnia include benzodiazepines, non-benzodiazepine benzodiazepine receptor agonists, melatonin agonists, and, in some regions, the orexin receptor antagonist suvorexant and low-dose doxepin.

Suvorexant is an oral dual orexin receptor antagonist (DORA) that was approved in the USA, Japan, and Australia for the treatment of insomnia characterized by difficulties with

sleep onset and/or sleep maintenance. Suvorexant is contraindicated in patients with narcolepsy. Next-day effects, including impaired driving performance, have been reported at 20 mg [Belsomra® USPI]. Next-day residual effects might be related to the long half-life ($t_{½}$ = 12 hours) of suvorexant [Citrome 2014]. Rebound insomnia or withdrawal signs upon drug discontinuation were not observed in clinical trials [Herring 2016].

Use of sleep medications increases with age and is highest in the elderly [Ohayon 2002, Ohayon 2010]. Despite the increased risk of falls, non-benzodiazepine benzodiazepine receptor agonists and generic antidepressants are among the most prescribed classes of medications for elderly patients with insomnia in the US.

1.1.4 Unmet medical need

CBT is generally the recommended first-line treatment for insomnia disorder [Schutte-Rodin 2008]. However, this may not be the ideal course of 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 is highly challenging [Pigeon 2007, Schutte-Rodin 2008].

Insomnia disorder is a chronic disease and currently available treatments are limited to short-term use with the exception of eszopiclone and suvorexant (in the US). Caution and dose reduction are also often advised in the elderly.

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.

Overall, there is a need for a long-term pharmacological treatment for insomnia disorder that addresses the most prominent and pressing symptoms of insomnia without negatively impacting next-day functioning.

1.2 Study treatment: ACT-541468

1.2.1 The orexin system

The orexin system is involved in the regulation of sleep and arousal by the central nervous system (CNS) and is currently being targeted in the development of new therapies for sleep disorders.

1.2.2 ACT-541468 properties

ACT-541468 is a new potent and selective DORA that blocks the actions of the orexin neuropeptides at both orexin-1 and orexin-2 receptors. ACT-541468 shows similar potency on human, rat, and dog orexin receptors. ACT-541468 is not teratogenic, not genotoxic, not phototoxic, and showed no embryo-fetal toxicity. The nonclinical safety data and the resulting safety margins are considered adequate to support the safe use of ACT-541468 at doses of 10, 25, and 50 mg in clinical studies with a duration of up to 12 months.

The human clinical experience with ACT-541468 consists of 11 completed Phase 1 studies and two completed Phase 2 studies. The Phase 2 program consisted of two Phase 2 studies. AC-078A201 was conducted in 360 adults (18 to 65 years old) treated for 1 month with one dose of double-blind (DB) study treatment and AC-078A202 was conducted in 58 elderly subjects (≥ 65 years old) treated for 2 days with each dose of DB study treatment. Both studies demonstrated a dose-response effect on the change from baseline to Days 1&2 in mean Wake After Sleep Onset (WASO).

More detailed information can be found in the ID-078A301 and ID-078A302 protocols as well as in the Investigator's Brochure (IB) [Daridorexant IB].

1.3 Purpose and rationale of the study

1.3.1 Purpose of the study

The main purpose of this Phase 3 extension study is to confirm that at least one dose of ACT-541468 is, in the long-term, well tolerated in subjects with insomnia disorder.

1.3.2 Rationale for the study

The orexin system is involved in the regulation of sleep and arousal. In two Phase 2 studies in subjects with insomnia disorder, ACT-541468 has shown objective and subjective improvements in sleep onset and sleep maintenance.

The dose levels of 10, 25, and 50 mg of ACT-541468 planned for this study were all investigated in Phase 2. The 10 mg dose is considered the minimal effective dose, providing clinical benefit in some patients, primarily on Latency to Persistent Sleep (LPS), in both adult and elderly subjects. The 25 mg and 50 mg doses provided a better effect on objective sleep parameters, and resulted in statistically significant reductions in mean WASO and in mean LPS at Days 1&2 compared with baseline, in both patient populations. These three doses were well tolerated and no significant safety findings emerged.

The ID-078A303 study will be an extension of the two confirmatory ACT-541468 studies (i.e., ID-078A301 and ID-078A302) in adult and elderly subjects with insomnia disorder. This Phase 3 extension study aims to assess the long-term safety of ACT-541468 as required by ICH-E1 [ICH 1994], i.e., at least 300 subjects exposed to any dose of

ACT-541468 for 26 weeks and at least 100 subjects exposed for 52 weeks, combining the time of treatment of the confirmatory and extension studies.

1.4 Summary of known and potential risks and benefits

1.4.1 Benefits and risks of the study treatments

Based on the mechanism of action of ACT-541468, nonclinical data, and data collected in Phase 1 and 2 studies in adult and elderly subjects, a shortened latency to sleep onset and a positive effect on sleep maintenance are anticipated. It is expected that the efficacy will be maintained long-term and some subjects may benefit from prolonged treatment of their insomnia.

One year long-term treatment with ACT-541468 is not expected to induce additional risks compared with what was observed in Phase 2, as it has been demonstrated in previous Phase 1 studies that ACT-541468 does not accumulate in any organs.

The most frequently observed treatment-emergent adverse events (TEAEs) reported in the conducted Phase 2 studies involving 418 subjects, out of which 297 were exposed to ACT-541468, included headache, somnolence, fatigue, and dizziness. Isolated cases of excessive daytime sleepiness (EDS) were observed.

Considering the mode of action of DORAs and the known adverse reactions associated with the use of sleep medications, adverse events of special interest (AESIs) include:

- Narcolepsy-like symptoms (i.e., EDS, cataplexy and complex sleep behavior events including hallucinations/sleep paralysis).
- Suicide/self-injury.

These AESIs will be reviewed and adjudicated in a timely manner by the Independent Safety Board (ISB).

The results of the AC-078-103 study have shown that ACT-541468 metabolism is mainly dependent on cytochrome P450 (CYP)3A4; co-administration of ACT-541468 and strong or moderate CYP3A4 inhibitors or inducers must be avoided [see Appendix 3].

ACT-541468 did not impair male or female fertility, was not teratogenic, and showed no embryo-fetal toxicity in animals. However, as the developmental and reproductive toxicology program of ACT-541468 is not yet fully complete, ACT-541468 must only be given to women of childbearing potential when the absence of pregnancy has been verified and a reliable method of contraception is practiced. Women of childbearing potential are required to use contraception during the whole study and for 30 days after discontinuation of ACT-541468.

[redacted]

Insomnia is not considered a life-threatening disease with irreversible morbidity if not treated immediately. It is hence considered acceptable and ethical to include a placebo-treated arm in a long-term trial of subjects with insomnia [ICH 2000]. Subjects are aware of the probability of being assigned to the placebo arm and of the therapeutic alternatives. However, to minimize the long-term exposure to placebo, patients who have been assigned to placebo in the confirmatory studies ID-078A301 and ID-078A302 will be randomized to either placebo or 25 mg ACT-541468 in ID-078A303.

Subjects are encouraged to take the study drug as long as possible. However, if needed, withdrawal from study treatment and the use of standard-of-care will be accepted. In that case, subjects are encouraged to remain in the study until its completion to limit the amount of missing data and ensure the accuracy of the study results. The sponsor will continuously monitor missing treatment data, treatment discontinuation and withdrawal from the study.

1.4.2 Safety and risk-minimization measures taken in the present study

Next-day residual effects will be evaluated with the Sheehan Disability Scale© (SDS©), and a visual analog scale (VAS) assessing sleepiness. Suicidality will be assessed using the Columbia Suicide Severity Rating Scale© (C-SSRS©) at Visit 1, Visit 3, Visit 4, Visit 5 and Visit 6.

As half of the subjects that were receiving placebo in the confirmatory studies will be randomized to 25 mg ACT-541468, and thus to a new treatment, in this study, a telephone call will be performed approximately 2 weeks after Visit 1 to collect adverse events (AEs) and concomitant medication. This will be done for all subjects, to maintain the blinding.

Hematology and clinical chemistry laboratory variables will be monitored in the study.

Two committees will be set up for the study:

- An ISB will review and adjudicate all AESIs listed in Section 1.4.1 in a blinded manner.
- An Independent Data Monitoring Committee (IDMC) will monitor safety and efficacy data in an unblinded manner. This committee will make appropriate recommendations

regarding continuation of the trial or potential modification to the sponsor to ensure data integrity and the safety of the subjects.

A charter will provide a well-defined and structured process for each committee to operate effectively.

It is the investigator's responsibility to monitor the risk-benefit 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 participation in the study if, on balance, he/she believes that continuation would be detrimental to the subject's well-being.

In conclusion, based on available data on ACT-541468 and the risk-minimization measures mandated by the protocol, the anticipated risk-benefit assessment supports the conduct of this 40-week treatment extension study in adult and elderly subjects with insomnia disorder.

2 STUDY OBJECTIVES

2.1 Primary objective

The objective of this extension study is to assess the long-term safety and tolerability of 10, 25 and 50 mg ACT-541468.

2.2 Exploratory objective

To evaluate the efficacy of 10 mg, 25 mg and 50 mg ACT-541468 on subjective sleep parameters (using an ad hoc sleep diary) and next-day functioning (using the dedicated Insomnia Daytime Symptoms and Impacts Questionnaire [IDSIQ]) in subjects with insomnia disorder during long-term treatment.

3 OVERALL STUDY DESIGN AND PLAN

3.1 Study design

Subjects who complete DB study treatment and the run-out period of the confirmatory studies ID-078A301 and ID-078A302, and who are willing to participate, will be eligible to enter the ID-078A303 extension study.

Subjects assigned to the placebo arm in the ID-078A301 or ID-078A302 studies will be randomized to receive either placebo or 25 mg ACT-541468 in a 1:1 ratio in the extension study. Treatment allocation will be stratified by age into 2 categories: < 65 and ≥ 65 years (the age entered at the screening visit in the ID-078A301 or ID-078A302 studies will be taken into consideration for the ID-078A303 randomization of these subjects). Subjects assigned to one of the ACT-541468 arms in the ID-078A301 or ID-078A302 studies will receive the same dose in the extension study.

An interim analysis will be conducted when all subjects that did not prematurely discontinue study treatment have reached Visit 3, to ensure 6 months of cumulative double-blind treatment (confirmatory and extension).

Subjects treated with placebo during the confirmatory studies and randomized to ACT-541468 25 mg are excluded from the conditions mentioned above as they will not all display 6-month data.

A second interim analysis, focusing on safety, may need to be conducted to fulfill the FDA requirement to submit updated safety data from ongoing studies 120 days after NDA submission, if the study has not been completed by that time.

It is expected that approximately 1260 subjects (i.e., ~70% of the total subjects in the combined confirmatory studies) having completed the confirmatory studies will enter the extension study. ID-078A303 will be offered at every site participating in ID-078A301 and ID-078A302 (approximately 150 centers in 17 countries), and to every eligible subject.

3.1.1 Study periods

The study starts at Visit 1, with the signature of the informed consent. The subject will receive the allocated treatment, provided all the eligibility criteria are met. ID-078A303 Visit 1 can be performed on the same day as End-of-Treatment (EOT) of ID-078A301 or ID-078A302 studies, after all run-out assessments have been completed, or as an independent visit within a maximum of 7 days after EOT.

The study comprises a treatment phase and a safety follow-up phase [see Figure 1].

3.1.1.1 Treatment phase

The **DB treatment phase** lasts 40 weeks, starting when the treatment is allocated. DB study treatment is taken daily.

A safety telephone call is performed at Visit 2 (Day 7 to Day 14) to collect information about AEs and concomitant medications. Safety parameters of each subject are assessed at Visit 3 (Week 14), Visit 4 (Week 27) and Visit 5 (Week 40). The sleep diary and IDSIQ are completed at home daily during the last week of each consecutive 4-week DB study treatment period. Reminder telephone calls are scheduled within one week (preferably 2 days) before the week of questionnaire completion to increase the subject's compliance with the diary. During these telephone calls, the investigator/delegate is also encouraged to collect the results of the urine pregnancy tests performed at home. Alternatively, another telephone call can be set up to collect these data. EODBT is reached at Visit 5.

3.1.1.2 Safety follow-up phase

The **safety follow-up phase** starts after the End of Double-Blind Treatment (EODBT) and ends 30 days after last dose of DB study treatment. It consists of a single-blind placebo run-out period of 7 days and a safety follow-up period.

The **run-out period** starts in the evening of Visit 5 with the intake of one dose of single-blind placebo treatment and ends after a total of 7 days of single-blind placebo intake (Visit 6). **EOT** is reached at Visit 6.

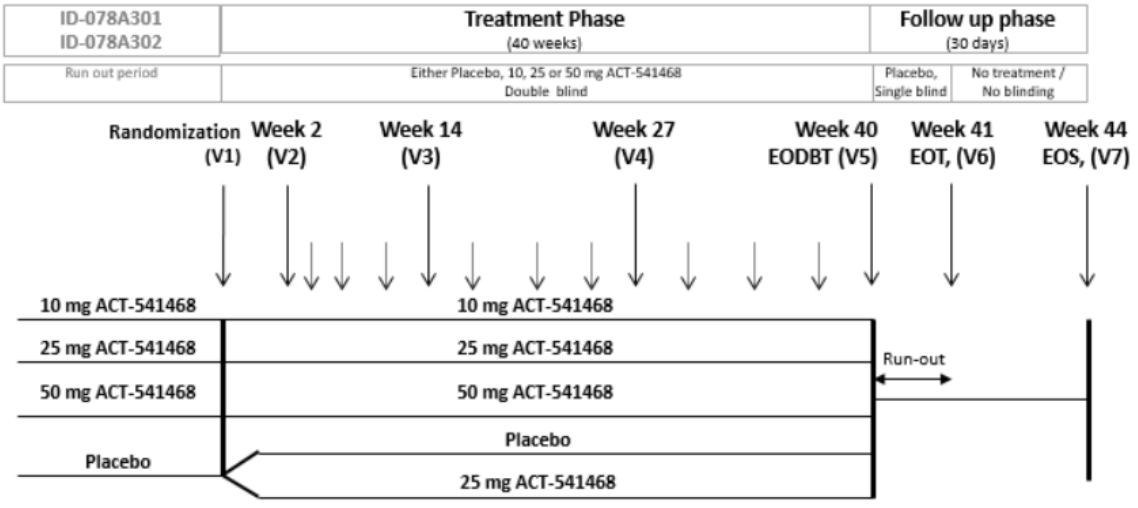
The **safety follow-up period** starts after the run-out period and ends 30 days after last dose of DB study treatment.

End-of-Study (**EOS**) for an individual subject is defined as the date of the 30-day follow-up telephone call (Visit 7). If a subject is prematurely discontinued from study treatment, EOS is performed as planned on Day 309. If a subject withdraws consent and does not wish to participate in the study any longer, EOS is the date of consent withdrawal for this subject. If a subject is declared lost to follow-up, EOS is the date of last successful contact for this subject.

The visit schedule and protocol-mandated procedures will be performed according to the visit and assessment schedule [Table 1] and are described in Section 7.

The overall study design is depicted in Figure 1.

Figure 1 Study design



⋯⋯> Monthly telephone call
EODBT = End of Double-Blind Treatment; EOS = End-of-Study; EOT = End-of-Treatment.
* Subjects randomly assigned to the ACT-541468 arms in the confirmatory studies will receive the same dose in the extension study.
** Subjects randomly assigned to the placebo arm in the confirmatory studies will be randomized to receive either placebo or 25 mg ACT-541468 in a 1:1 ratio in the extension study.

3.1.2 Study duration

The study starts with the signature of the Informed Consent Form (ICF) at Visit 1 for the first subject enrolled and ends with the EOS of the last subject. The anticipated total study time is approximately 24 months.

Each subject will be treated for approximately 40 weeks in study ID-078A303, and will therefore receive 12 months of cumulative treatment combining ID-078A301/ID-078A302 and the extension study. For an individual subject, the study is completed with the EOS visit (Visit 7; safety follow-up telephone call at the end of follow-up) and the maximum duration of participation in the study of this subject is expected to be approximately 45 weeks.

3.2 Study design rationale

In accordance with the EMA guideline on medicinal products for the treatment of insomnia [EMA 2011] and the FDA guideline for the clinical evaluation of hypnotic drugs [FDA 1977], the inclusion of a placebo arm in this extension study allows a better discrimination between the background rate of AEs and that of AEs potentially attributable to the study drug.

A parallel-group design is an appropriate design to assess the continuous exposure to ACT-541468 in the wake of studies ID-078A301 and ID-078A302, and is accepted by health authorities [EMA 2011, FDA 1977].

The treatment allocation ratio will allow the collection of maximum information on safety and efficacy of the medium dose of ACT-541468, the 25 mg dose. The number of subjects allocated to ACT-541468 10 mg and 50 mg is also adequate to ensure an appropriate characterization of the safety profile of those doses over a 52-week period. In addition, study ID-078A303 provides an appropriate investigation of the sustained effect of ACT-541468 on both sleep parameters and next-day performance at the three dose levels studied.

A blinded placebo run-out period of 7 days allows the assessment of withdrawal symptoms after a long-term treatment period as it covers more than 5 half-lives of either 10, 25, or 50 mg ACT-541468. The duration of the run-out period is also compliant with FDA guidance [FDA 1977] stating that a minimum of 3 nights of placebo withdrawal is necessary to assess withdrawal effects. To assess withdrawal effects AEs and ECG abnormalities will be collected during the 7-day run-out period and subjects will complete the Benzodiazepine Withdrawal Symptom Questionnaire (BWSQ) at Visit 6. The completion of the sleep diary from at least 3 days following treatment discontinuation will allow the assessment of rebound insomnia based on subjective parameters. Thus, this 7-day run-out period allows potential long-term withdrawal effects to be captured, as well as potential shorter-term rebound symptoms.

Importantly, the study will provide long-term efficacy data as required by the EMA guideline on medicinal products for the treatment of insomnia [EMA 2011]. The study will assess the maintenance of the treatment effect over time beyond the 3 months of the confirmatory trials: efficacy will be assessed by subjective endpoints describing sleep parameters (subject's diary) and next-day functioning (IDSIQ) for 26 weeks (6 months) and up to 52 weeks of overall treatment, combining the time of treatment of the confirmatory and extension studies. Enrolled subjects will have to fill in the two questionnaires during the last 7 days of each consecutive 4-week DB study treatment period. This is to collect relevant subjective data without adding too much burden for the subjects.

An interim analysis will be performed after completion of the pivotal studies and when all subjects have performed Visit 3. One additional interim analysis may be performed as required by health authorities (FDA) if the study is still ongoing, to provide additional safety information.

After the planned interim analysis, sites and subjects will remain blinded to the treatment allocation while the study continues to collect data on the entire population for 52 weeks.

This approach allows an early analysis of the efficacy and safety data after 6 months of exposure of the entire study population collected in a blinded way. These data will support the initial filing with health authorities for ACT-541468 without triggering early termination of the study. Therefore, subjects enrolled later will equally benefit from the study along with ACT-541468 being potentially available earlier on the market for the patients.

To maintain the integrity of the study, the sponsor personnel involved in the data collection and medical monitoring of the study will not be involved in the interim analysis and will remain blinded until the completion of the study without having access to the results of the interim analysis [see Section 5.1.4.1].

3.3 Study committees

An IDMC will have overall responsibility for safeguarding the interests of subjects, by monitoring safety and efficacy data obtained in the study and making appropriate recommendations to the sponsor based on the reported data. This will ensure that the study is being conducted to the highest scientific and ethical standards and will protect the safety and well-being of the subjects. The IDMC will be fully operational prior to the enrollment of the first subject into the study. The composition and operation of the IDMC is described in the IDMC charter. The IDMC will not be involved in any interim analysis.

An ISB will review and adjudicate in a blinded manner AESIs, i.e., narcolepsy-like symptoms (i.e., EDS, cataplexy and complex sleep behavior events including

hallucinations / sleep paralysis), or suicide/self-injury. The composition and operation of the ISB is described in the ISB charter.

4 SUBJECT POPULATION

4.1 Subject population description

This study will enroll adult and elderly (≥ 18 years), male and female subjects with insomnia disorder according to the DSM-5 definition, having completed the DB study treatment and run-out period of the confirmatory studies ID-078A301 or ID-078A302. For more details on inclusion and exclusion criteria, see Sections 4.3 and 4.4.

4.2 Rationale for the selection of the study population

Adult (18–64 years) and elderly (≥ 65 years) subjects with insomnia as defined by DSM-5 who have completed the ID-078A301 or ID-078A302 study will be included, unless presenting a significant medical condition which in the opinion of the investigator could affect the subject's safety or interfere with the study assessments. This will allow the collection of long-term safety and tolerability information across a broad population.

4.3 Inclusion criteria

For all the following criteria, time points in brackets refer to the visits when the criterion must be assessed.

1. Signed informed consent prior to any study-mandated procedure (Visit 1).
2. Completion of the DB study treatment and run-out period of ID-078A301 or ID-078A302 (Visit 1).
3. For woman of childbearing potential, the following is required:
   - Negative urine pregnancy test (EOT of ID-078A301 or ID-078A302 studies).
   - Agreement to use the contraception scheme as required by the protocol from Visit 1 up to at least 30 days after EODBT.

4.4 Exclusion criteria

For all the following criteria, time points in brackets refer to the visits when the criterion must be assessed.

1. Unstable medical condition, significant medical disorder or acute illness, or ECG, C-SSRS©, hematology or biochemistry test results in ID-078A301 or ID-078A302 study, which, in the opinion of the investigator, could affect the subject's safety or interfere with the study assessments (Visit 1).
2. For female subjects: lactating or planning to become pregnant during the study (Visit 1).

3. Positive urine drug test (for benzodiazepines, barbiturates, cannabinoids, opiates, amphetamines, or cocaine) (Visit 1).

4.5 Criteria for women of childbearing potential

4.5.1 Definition of childbearing potential

A woman is considered to be of childbearing potential unless she meets at least one of the following criteria:

- Previous bilateral salpingectomy, bilateral salpingo-oophorectomy or hysterectomy.
- Postmenopausal (defined as 12 consecutive months with no menses without an alternative medical cause [ICH M3 definition]).
- Premature ovarian failure (confirmed by a specialist), XY genotype, Turner syndrome, uterine agenesis.

The reason for not being of childbearing potential will be recorded in the electronic case report form (eCRF).

4.5.2 Acceptable methods of contraception

For women of childbearing potential [see definition in Section 4.5.1], any of the following acceptable birth control methods are required:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - oral
  - intravaginal
  - transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation:
  - oral
  - injectable
  - implantable
- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion (tubal occlusion / ligation at least 6 weeks prior to screening; information can be obtained via the medical interview of the subject).
- Vasectomized partner with documented post-vasectomy confirmation of the absence of sperm in the ejaculate (information can be obtained via the medical interview of the subject).

- Sexual abstinence from intercourse with a male partner only if it is in line with the preferred lifestyle of the subject and if locally accepted as a reliable method of contraception.

Rhythm methods, the use of a female condom, cervical cap, diaphragm or the partner's use of a condom are not considered acceptable methods of contraception for this study.

The method of birth control used must be recorded in the hospital charts.

To ensure compliance, the study personnel must remind women of childbearing potential at each visit to use the methods of contraception defined for this study. The reminders must be documented in the hospital chart.

5 TREATMENTS

5.1 Study treatment

The study drugs are ACT-541468 and ACT-541468-matching placebo.

5.1.1 Investigational treatment and matching placebo: Description and rationale

ACT-541468 or matching placebo will be administered during the treatment period as tablets, orally, once daily at bedtime. ACT-541468-matching placebo will be administered as well during the run-out period.

ACT-541468 is supplied by Idorsia as identical film-coated tablets at strengths of 10 mg, 25 mg and 50 mg. The rationale for the selection of these ACT-541468 doses is described in Section 1.3.2. The ACT-541468-matching placebo is supplied by Idorsia as identical tablets, formulated with the same inactive ingredients (excipients).

5.1.2 Study treatment administration

The tablet must not be broken or crushed. The date and time of treatment intake will be recorded in the sleep diary by the subject daily during the last week of each consecutive 4-week DB study treatment period (the first 4-week treatment period starts at Day 1 after randomization of the subject at Visit 1) during the DB treatment phase and daily during the run-out period.

If one or more doses have been missed, the next dose must be taken in the evening of the following day.

The last dose of study treatment will be taken the evening before Visit 6.

5.1.3 Treatment assignment

Subjects assigned to the placebo arm in the ID-078A301 and ID-078A302 studies will be randomized to receive either placebo or 25 mg ACT-541468 in a 1:1 ratio in the extension study. Treatment allocation will be stratified by age into 2 categories: < 65 and ≥ 65 years

(the age entered at the screening visit in the ID-078A301 or ID-078A302 studies will be taken into consideration for the ID-078A303 randomization of these subjects). Subjects assigned to the ACT-541468 arms in the ID-078A301 and ID-078A302 studies will receive the same dose in the extension study.

At Visit 1, after the ICF has been signed and after having verified that the subject meets all inclusion criteria and none of the exclusion criteria, the investigator/delegate contacts the Interactive Response Technology (IRT) to obtain the treatment kit numbers assigned to the subject. The IRT assigns the treatment kit number, which matches the treatment arm assigned per the randomization list. Subject number assigned in the confirmatory studies will be identical in the extension study.

At Visit 3, Visit 4 and Visit 5, the investigator/delegate contacts the IRT and the treatment kit, which matches the treatment arm assigned per the randomization list, will be dispensed to the subject. During the run-out period, subjects will receive single-blind placebo treatment.

The randomization list is generated by an independent Contract Research Organization (CRO) and kept strictly confidential.

5.1.4 Blinding

5.1.4.1 Double-blind treatment period

From Randomization (Visit 1) until EODBT, the study will be performed in a DB fashion. The subjects, the investigator and site personnel, and the monitors will remain blinded to the study treatment until the end of the ID-078A303 extension study.

Idorsia personnel responsible for clinical study supply distribution will monitor the depot stock levels in collaboration with the study team based on recruitment data and site activation. Site stocks will be maintained according to the settings in the IRT system.

Until the time of unblinding for ID-078A303 final data analysis, the randomization lists of studies ID-078A301 and ID-078A302 (and thus, also ID-078A303) are kept strictly confidential, and accessible to the IRT vendor, the sponsor authorized persons (i.e., dedicated persons from Quality Assurance, Systems and Compliance personnel, as well as from the Bioanalytical Laboratory group) the Independent Statistical Analysis Center (ISAC), and the IDMC. None of those people are involved in the conduct of the three studies.

In order to maintain the blinding of the study, a different team will be responsible for the conduct of the extension study. In particular, the sponsor staff that had access to the randomization lists from the ID-078A301 and ID-078A302 studies or after the interim

analysis will not be involved in the conduct of the extension study until its final database closure. The process will be duly documented in Idorsia Quality System (QS) documents.

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

5.1.4.2 Run-out period

During the run-out period, placebo treatment will be administered in a single-blind fashion. The subjects will remain blinded to the study treatment until EOT. Subjects must not be informed about the change in treatment at the beginning of the run-out period.

The investigators and study personnel, the monitors, Idorsia personnel, and CROs involved in the conduct of the study will be unblinded to the treatment provided during the run-out period.

5.1.5 Unblinding

5.1.5.1 Sponsor unblinding for interim and final analyses

Randomization information will be made available for interim analysis after interim database closure, in accordance with Idorsia QS documents.

The randomization list will not be shared with investigators and site personnel until the end of the study and the final analysis to maintain the blind.

Sponsor personnel involved in data collection and medical monitoring of the study before and after interim analysis will also remain blinded, in accordance with Idorsia QS documents (i.e., Blinding Management Plan).

5.1.5.2 Unblinding for IDMC review

An ISAC, not otherwise involved in the design, conduct and analysis of the study, will have access to the randomization code in order to prepare unblinded reports for IDMC review meetings during the course of the trial. The randomization code will be made available to the ISAC in accordance with Idorsia's QS documents.

5.1.5.3 Unblinding for suspected unexpected serious adverse reactions

If a suspected unexpected serious adverse reaction (SUSAR) occurs for a subject participating in the study, Idorsia Global Drug Safety will request the unblinding of the treatment assignment. The treatment assignment will not be communicated to site personnel or to the Idorsia Clinical Trial Team. Unblinded SUSAR information will be provided to respective health authorities and Independent Ethics Committees / Institutional Review Boards (IECs/IRBs) only. SUSARs will be reported to investigators in a blinded fashion.

5.1.5.4 Emergency procedure for unblinding

The investigator, study personnel and Idorsia personnel must remain blinded to the subject's treatment assignment as defined in Section 5.1.4. 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 can receive the unblinded treatment assignment through the IRT. In these situations, the decision to unblind resides solely with the investigator. Whenever possible, and if it does not interfere with (or does not delay) any decision in the best interests of the subject, the investigator is invited to discuss the intended unblinding with Idorsia personnel.

The occurrence of any emergency unblinding during the study must be clearly justified and explained by the investigator. In all cases, Idorsia personnel must be informed of the unblinding decision as soon as possible before or after the unblinding.

The circumstances leading to unblinding must be documented in the Investigator Site File (ISF).

5.1.6 Study treatment supply

Manufacture, labeling, packaging, and supply of study treatment will be conducted according to Good Manufacturing Practice, GCP, and any local or national regulatory requirements.

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

5.1.6.1 Study treatment packaging and labeling

Study treatment (including placebo during the run-out period) is provided as tablets and supplied in wallets containing 35 tablets.

Study treatment is labeled to comply with the applicable laws and regulations of the countries in which the study sites are located. The treatment wallets will display the study number on the front label to ensure only the ID-078A303 study treatment wallets are provided to the subjects.

5.1.6.2 Study treatment distribution and storage

Study treatment supplies must be kept in an appropriate, secure area and stored according to the conditions specified on the label (i.e., 8–25 °C). Temperature measurement devices for study treatment storage area are required.

5.1.6.3 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 wallets at each visit. If a treatment wallet is lost or damaged, a replacement wallet can be requested through the Treatment Replacement module of the IRT system. The protocol-mandated study treatment dispensing procedures may not be altered without prior written approval from Idorsia. In exceptional circumstances (e.g., if the subject lost the study treatment between two visits, or if the subject is unable to return to the site due to a medical emergency / hospitalization at another hospital), unscheduled dispensing and delivery of study treatment may occur outside of a scheduled visit. An accurate record of the date and amount of study treatment dispensed to each subject must be available for inspection at any time.

5.1.6.4 Study treatment return and destruction

The protocol-mandated study treatment return procedures may not be altered without prior written approval from Idorsia. On an ongoing basis and/or on termination of the study, the Clinical Research Associate (CRA) will collect used and unused treatment wallets, which will be sent to the warehouse, where Idorsia personnel or a deputy will check treatment reconciliation. In certain circumstances, used and unused study treatment containers may be destroyed at the site once study treatment accountability is finalized and has been checked by Idorsia personnel or the deputy, and written permission for destruction has been obtained from Idorsia.

5.1.7 Study treatment accountability and compliance with study treatment

5.1.7.1 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 at each visit and before dispensing further study treatment. It is to be recorded by site personnel on the study treatment dispensing and accountability log and in the eCRF, and checked by the CRA during site visits and at the end of the study. The study treatment accountability log in the eCRF will include at least the following information for each study treatment unit (i.e., wallet) dispensed to the subject:

- Dispensed subject wallet number.
- Date and number of tablets dispensed.
- Date and number of tablets returned.

All study treatment supplies, including partially used or empty wallets must be retained at the site for review by the CRA.

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 wallet and to return it at the next visit.

5.1.7.2 Study treatment compliance

Study treatment compliance is based on study treatment accountability. Study treatment compliance for the treatment period (Visit 1 to EODBT) and the run-out period will be separately calculated for each of these periods by site personnel using the formula below:

Compliance = [(number of tablets dispensed – number of tablets returned) / total number of tablets that needs to be taken during the period*] × 100

* The period is defined as number of days during which study treatment should be taken as per actual visit dates.

During the treatment period (Day 1 to EODBT), compliance is expected to be at least 70%. Compliance values below this will be considered as a protocol deviation which will be reported in the Clinical Trial Management System by the CRA. The investigator 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.

5.1.8 Study treatment dose adjustments and interruptions

Study treatment dose adjustments are not permitted.

Study treatment may be temporarily interrupted in response to an AE, a diagnostic or therapeutic procedure, a laboratory abnormality, or for administrative reasons. Study-specific criteria for interruption of study treatment are described in Section 5.1.10.

If study treatment is interrupted by the subject for any reason, he/she must immediately inform the investigator.

Interruptions of study treatment must be kept as short as possible.

Study treatment interruptions must be recorded in the eCRF.

5.1.9 Premature discontinuation of study treatment

Maintenance of subjects in the study is important from a study integrity perspective. It is recommended to advise the subject to remain in the study even if he/she wishes to be withdrawn from study treatment. This will decrease the amount of missing data and increase the reliability of the study results. Measures in place to increase subject retention in the study are described in Section 5.1.11.

The decision to prematurely discontinue study treatment may be made by the subject, the investigator, or Idorsia personnel. The main reason for discontinuation must be documented in the eCRF and in the subject's medical charts (e.g., AE, lack of efficacy).

A subject has the right to prematurely discontinue study treatment at any time, without any justification, by withdrawal from study treatment only or by withdrawal from any further participation in the study (i.e., premature withdrawal from the study [see Section 8.2]). Although a subject is not obliged to give his/her reason for prematurely withdrawing from the treatment or the study, it is recommended that the investigator makes a reasonable effort to ascertain the reason(s), while fully respecting the subject's rights.

The investigator must 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 discontinuation of study treatment are described in Section 5.1.10.

A subject who prematurely discontinues study treatment is not considered to be withdrawn from the study and will be followed up until the planned EOS (Day 309), provided that the subject's consent for this limited participation in the study has not been withdrawn. The subject is recommended to return for safety assessments [see Table 1] within one week of his/her last study treatment intake and to agree to follow planned study procedures (e.g., visits, sleep diary and questionnaire completion) until EOS. In this case, the run-out period (including Visit 6) will not be performed, and subjects will directly enter the follow-up period after Visit 5 (considered as EOT in the event of premature discontinuation). The telephone call will be performed as planned 30 days (+7 days) later, at Visit 7. This will decrease the amount of missing data, helping to maintain study integrity. Subjects who prematurely discontinue study treatment or the study for any reason will not be replaced.

A subject who prematurely discontinues study treatment and withdraws consent to participate in any further study assessments is considered to be withdrawn from the study and no further assessment will be collected after informed consent withdrawal.

Subjects who die or are lost to follow-up are also considered to be withdrawn from the study. Withdrawal from the study and follow-up medical care of subjects withdrawn from the study are described in Sections 8.2 and 8.4, respectively.

5.1.10 Study-specific criteria for interruption / premature discontinuation of study treatment

At each visit, if there are signs of any AEs, the investigator must evaluate whether continuing treatment at home is compatible with the subject's lifestyle and does not affect the subject's safety. The investigator has the responsibility to decide whether it is safe for the subject to continue treatment in the study.

If a subject becomes pregnant while on study drug, study drug must be permanently discontinued. The investigator must counsel the subject and discuss the risks of continuing with the pregnancy and the possible effects on the fetus.

Female subjects participating in the study and wishing to become pregnant during the study must discontinue study drug and continue contraception for at least 1 month.

5.1.11 Study-specific measures for subject retention

Subjects withdrawn from study treatment are encouraged to remain in the study until its completion.

In order to ensure a high level of compliance with the study procedures, subjects that are under DB treatment and subjects that prematurely discontinued will be called within one week (preferably 2 days) before each 4-week DB study treatment period during which the completion of the sleep diary, IDSIQ, Patient Global Assessment of Disease Severity (PGA-S) and Patient Global Impression of Change (PGI-C) is required. The investigator will call the subject to remind him/her to complete the different questionnaires on the hand-held device as instructed, check there is no issue with the study treatment (if applicable) and remind the subject to keep the appointments at the sleep center. An alert email is sent to the investigator to remind him/her to call the subjects.

A reminder is also programmed on the hand-held device the day before the completion must be started and every day during the completion period.

Investigators are encouraged to discuss with the subjects the importance of remaining in the study for data accuracy purposes and scientific relevance of the study results.

5.2 Previous and concomitant therapy

5.2.1 Definitions

A previous therapy is any treatment for which the end date is prior to signing ICF.

A therapy that is study-concomitant is any treatment that is ongoing or initiated after signing of informed consent, or initiated up to EOS.

A therapy that is study treatment-concomitant is any treatment that is either ongoing at the start of study treatment or is initiated during the treatment period until 1 day after the last dose of DB treatment.

5.2.2 Reporting of previous/concomitant therapy in the eCRF

The use of all study-concomitant therapy (including contraceptives and traditional and alternative medicines, e.g., plant-, animal-, or mineral-based medicines) will be recorded in the eCRF.

Previous/concomitant therapy recorded in the ID-078A301 or ID-078A302 study and still ongoing at enrollment in the ID-078A303 study will be automatically transferred on a specific eCRF page into the ID-078A303 database. Concomitant therapies initiated in the extension study will be recorded in the ID-078A303 eCRF. The generic name, start/end dates of administration (as well as whether it was ongoing at EOS), route, dose, and indication will be recorded in the eCRF.

5.2.3 Allowed concomitant therapy

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

5.2.4 Forbidden concomitant therapy

Subjects must not be withdrawn from medically necessary therapies in order to participate in the study. The following concomitant therapies are forbidden during this study and a complete list of forbidden medications is provided in Appendix 3:

- Treatment with another investigational drug until EOS.
- Study-prohibited CNS-active medications at least 1 week prior to Visit 1 and until 24 hours after EOT.
- Treatment with moderate or strong CYP3A4 inhibitors or moderate to strong CYP3A4 inducers at least 1 week prior to Visit 1 until 24 hours after EOT.

5.2.5 Forbidden concomitant diet and activities

The following activities and diet are forbidden during the study:

- Consumption of grapefruit, Seville (bitter) oranges and juices from those fruits from 1 week prior to Visit 1 until 24 hours after the end of the run-out period.
- Caffeine consumption > 600 mg caffeine/day.
- Alcohol consumption > 2 drinks a day.
- Heavy tobacco use (at least one pack of cigarettes per day or inability to refrain from smoking during the night).
- Driving or engaging in activities that require operating vehicles or dangerous machinery within 8 hours after study treatment intake.

The investigator should also advise the subject about the risks of taking the study drug prior to traveling across several time zones or working night shifts. The appropriate safety measures for these specific cases will also be explained.

6 STUDY ENDPOINTS

To evaluate long-term safety and efficacy of ACT-541468, data from ID-078A301 and ID-078A302 for subjects entering this extension study will be included.

For subjects who received placebo in ID-078A301 or ID-078A302 that are randomized to 25 mg ACT-541468 in this extension study, baseline refers to assessments taken before start of ACT-541468 intake. For all other subjects, and unless stated otherwise, baseline refers to assessments performed before start of DB study treatment of study ID-078A301 or ID-078A302.

6.1 Safety endpoints

- Serious adverse events (SAEs) up to 30 days after study DB treatment discontinuation.
- TEAEs up to 30 days after DB study treatment discontinuation.
- AEs leading to premature discontinuation of the DB study treatment.
- AESIs after adjudication by ISB:
  - Narcolepsy-like symptoms (i.e., EDS, cataplexy and complex sleep behavior events including hallucinations / sleep paralysis).
  - Suicide/self-injury.
- Change from baseline to Visit 3, Visit 4, Visit 5 and Visit 6 in Epworth Sleepiness Scale (ESS)© total score.
- Change from baseline to Visit 3, Visit 4 and Visit 5 in vital signs (systolic and diastolic blood pressure [BP], and pulse rate).
- Change from baseline to Visit 5 in body weight.
- Marked ECG abnormalities on DB study treatment.
- Change from baseline to Visit 3, Visit 4, Visit 5 and Visit 6 in ECG parameters.
- Marked laboratory abnormalities on DB study treatment.
- Change from baseline to Visit 3, Visit 4, Visit 5 and Visit 6 in laboratory parameters.
- Occurrence of suicidal ideation and/or behavior on DB study treatment and during the treatment withdrawal period based on C-SSRS©.
- Withdrawal effects (physical dependence) upon treatment discontinuation will be assessed based on the changes from last assessment on DB treatment (Visit 5) to end of the run-out period (Visit 6) in the BWSQ total score, the occurrence of relevant AEs and marked ECG abnormalities.
- Rebound insomnia will be assessed based on change from baseline to the run-out period in subjective Total Sleep Time (sTST).

- Next-day residual effects will be assessed based on change from baseline to Visit 3, Visit 4 and Visit 5 in SDS© and change from baseline over time in morning sleepiness score on the sleep diary VAS (mm). VAS scores are the subjects' rating of their morning sleepiness (from 'the way you feel this morning'), daytime alertness (from 'your daytime alertness today') and daytime ability to function (from 'your daily ability to function today').

6.2 Exploratory efficacy endpoints

- Change from baseline over time in sTST. sTST is the total sleep time as reported in item 9 of the sleep diary.
- Change from baseline over time in sLSO. sLSO is the self-reported time to fall asleep as reported in item 5 of the sleep diary.
- Change from baseline over time in subjective sleep maintenance (sWASO). sWASO is the self-reported time spent awake after sleep onset as reported in item 7 of the sleep diary.
- Change from baseline over time in IDSIQ scores (i.e., total score; alert/cognition, mood and sleepiness domain scores).
- Change from baseline over time in sleep quality based on scores on the sleep diary VAS (mm). VAS scores are the subjects' ratings of 'the quality of your sleep last night', 'the depth of your sleep last night', daytime alertness and daytime ability to function questions.
- Change from baseline to Visit 3, Visit 4 and Visit 5 in Insomnia Severity Index© (ISI©) scores.

  The number (%) of subjects with ≥ 6-point decrease in ISI© Total score from baseline to Visit 3, Visit 4 and Visit 5 will be tabulated.
- Change from baseline over time in mean number of self-reported awakenings.
- Change from baseline over time in PGA-S scores (daytime symptoms).
- Change from baseline over time in PGI-C scores (daytime symptoms).

7 VISIT SCHEDULE AND STUDY ASSESSMENTS

7.1 Study visits

The study visits are listed in Table 1. For all visits during the DB treatment phase, the subjects must be seen on the designated day and within a ± 7 days visit window in comparison with randomization.

7.1.1 Visit 1

At Visit 1, subjects will discuss and sign the ICF, and will undergo eligibility assessments based on the results from the tests performed at EODBT and EOT in the ID-078A301 and

ID-078A302 studies. Visit 1 can be performed either at the same time as EOT of the ID-078A301 or ID-078A302 study, after all assessments related to EOT are done, or as an independent visit within a maximum of 7 days after EOT. Treatment allocation will occur at Visit 1, provided the subject is eligible. The DB study treatment is to be started in the evening of Visit 1.

It is the responsibility of the investigator/delegate (the latter may or may not be a physician, according to local legal requirements, in the EU it must be a physician) to obtain written informed consent from each subject participating in this study after adequate face-to-face explanation of the objectives, methods, and potential risks of the study. The subjects who agree to participate in the study and the investigator/delegate must sign the ICF prior to performing any study-related assessment or procedure.

It is not permitted to re-screen subjects.

7.1.2 Unscheduled visits

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

Pharmacokinetic (PK) samples can be collected at the discretion of the investigator in the event of emergence of an AE (e.g., EDS).

The date and the time of blood sample collection will be entered in the eCRF as an unscheduled visit. The date and time of the last study treatment dosing before blood draw will be entered as well. The site personnel will ship the plasma samples to the central laboratory. The central laboratory will ship the samples to Idorsia Drug Metabolism and Pharmacokinetics department for PK sample analysis.

Alcohol tests can be performed at the discretion of the investigator at any time in the event of suspicion of exaggerated alcohol consumption (i.e., above the accepted threshold defined in Appendix 1).

Details about the collection, sampling, storage, and shipment procedures can be found in the laboratory manual.

7.1.3 Telephone calls between visits.

Questionnaires are to be completed at home during the last week of each consecutive 4-week DB treatment period.

The investigator/delegate will call the subject within 1 week (preferably 2 days) before each 4-week DB study treatment period to remind him/her to switch on / charge the hand-held device and complete the questionnaires. During these telephone calls, the investigator/delegate is also encouraged to collect the results of the urine pregnancy tests performed at home and information regarding potential AEs. Alternatively, another telephone call can be set up to collect these data.

Table 1 Visit and assessment schedule

		TREATMENT PHASE[11]					FU PHASE	
		DB treatment period (40 weeks ± 7 days)					Run-out period (7 days + 2 days)	FU period (23 days + 7 days)
VISITS	Number	1	2 (telephone call)	3	4	5[6]	6	7 (telephone call)
	Time	Day 1 (+ 7 days from ID-078A301 or ID-078A302 EOT)	Day 7 to Day 14	Week 14 (Day 98 ± 7 days)	Week 27 (Day 189 ± 7 days)	Week 40 (Day 280 ± 7 days)	Week 41 (Day 287 + 2 days)	Week 44 (Day 309 + 7 days)
Informed Consent[1]		X						
Randomization[2]		X						
Inclusion & Exclusion Criteria		X[5]						
Demographics[12]		X						
Medical History[13]		X						
Concomitant Medications		X	X	X	X	X[6]	X	
Physical examination, height and body weight[3]		X[5]		X	X	X[6]		
Vital signs		X[5]		X	X	X[6]	X	
12-lead ECG		X[5]		X	X	X[6]	X	
Hematology, blood Chemistry		X[5]		X	X	X[6]	X	
Pregnancy test[4]		X[5]		X	X	X[6]	X	
Urine Drug Screen		X[5]		X	X	X	X	
ISI©		X		X	X	X		
C-SSRS©		X[5]		X	X	X[6]	X	
Rebound insomnia							X	
BWSQ						X[6]	X	
ESS©		X[5]		X	X	X	X	
SDS©		X		X	X	X[6]	X	
IDSIQ[7]		←	—	—	—	—	→	
PGA-S[7]		←	—	—	—	→	X	
PGI-C[7]		←	—	—	—	→	X	

		TREATMENT PHASE[11]					FU PHASE	
		DB treatment period (40 weeks ± 7 days)					Run-out period (7 days + 2 days)	FU period (23 days + 7 days)
VISITS	Number	1	2 (telephone call)	3	4	5[6]	6	7 (telephone call)
	Time	Day 1 (+ 7 days from ID-078A301 or ID-078A302 EOT)	Day 7 to Day 14	Week 14 (Day 98 ± 7 days)	Week 27 (Day 189 ± 7 days)	Week 40 (Day 280 ± 7 days)	Week 41 (Day 287 + 2 days)	Week 44 (Day 309 + 7 days)
Contact IRT		X		X	X	X		
Dispense IMP kits		X		X	X	X		
Sleep diary[8] (incl. VAS)		←	—	—	—	—	→	
Study Drug Intake[9]		←	—	—	—	—	→	
SAE and AEs[10]		←	—	—	—	—	—	→

1: Signature of informed consent can occur at the same time as EOT of ID-078A301 or ID-078A302 studies after all EOT assessments are done, or within a maximum of 7 days from EOT; **2**: Randomization takes place at Visit 1 provided the subject fulfills all the eligibility criteria. **3**: Height only at Visit 1 and body weight only at Visit 1 and Visit 5. At Visit 1, height values are taken from ID-078A301 or ID-078A302 Visit 1 and weight values are taken from ID-078A301 or ID-078A302 EODBT. **4**: For women of childbearing potential, urine pregnancy tests will be performed at Visits 3, 4, and 6 and a serum pregnancy test will be performed at Visit 5. At Visit 1, results from the urine pregnancy test performed at EOT in ID-078A301 or ID-078A302 will be used to assess the eligibility of the subject. In addition, 2 urine pregnancy tests will be provided to WOCBP at Visit 1, Visit 3 and Visit 4, to be performed monthly at home. The investigator/delegate will call the subject to collect the results of the pregnancy test. **5**: Eligibility criteria will be assessed based on the latest test results available, i.e., EODBT (hematology and biochemistry, physical examination, body weight, ECG) and EOT (vital signs, pregnancy test) of the confirmatory studies. If Visit 1 happens on the same day as EOT, eligibility criteria for suicidality, sleepiness, drug consumption will be assessed based on EOT assessments (C-SSRS©, ESS© and urine drug screen respectively). If Visit 1 happens within 7 days after EOT, the C-SSRS©, ESS© and urine drug screen assessments must be performed again at the time of Visit 1. **6**: In the event of permanent discontinuation, safety assessments of Visit 5 are recommended to be performed within 7 days of last study drug intake and will be reported as an unscheduled visit in the eCRF. **7**: To be completed at home (daily for the IDSIQ and sleep diary and once for the PGI-S and PGA-C) during the last week of each consecutive 4-week DB treatment period and daily (for the sleep diary and IDSIQ) during the run-out period. The investigator/delegate will call the subject within 1 week (preferably 2 days) before each 4-week DB study treatment period to remind him/her to switch on/charge the hand-held device and complete the questionnaires. During these telephone calls, the investigator/delegate is also encouraged to collect the results of the urine pregnancy tests performed at home. Alternatively, another telephone call can be set up to collect these data. **8**: The following parameters are obtained through the sleep diary completion (daily during the last week of each consecutive 4-week period during the treatment period and the run-out period) at home: subjective Latency to Sleep Onset, subjective Wake After Sleep Onset, subjective Total Sleep Time, sleep quality as determined by scores on the VAS, wake time during sleep, self-reported frequency of awakenings, sleep efficiency, next-day performance. **9**: Daily DB study treatment during treatment phase and daily placebo single-blind treatment during run-out period. **10**: SAE and AE reporting and follow-up: all SAEs and all AEs from signed ICF up to 30 days after last dose of DB study treatment. **11**: During the treatment period, the investigator/delegate will call the subject within one week (preferably 2 days) before the hand-held device completion period (i.e., Week 4, Week 8, Week 12, Week 16, Week 20, Week 24, Week 28, Week 32 and Week 36) to ensure proper data entry and maximize subject's retention in the study. **12**: No demographics information will be collected, the investigator/delegate only needs to confirm the subject's age that was entered at Visit 1 in the ID-078A301 or ID-078A302 study in the IRT system. **13**: Only medical history still ongoing from ID-078A301 or ID-078A302 will be automatically transferred into the ID-078A303 study database.

AE = adverse event; BWSQ= Benzodiazepine Withdrawal Symptom Questionnaire; C-SSRS© = Columbia Suicide Severity Rating Scale©; DB = double-blind; ECG = electrocardiogram; EODBT = End of Double-Blind Treatment; EOT = End-of-Treatment; ESS© = Epworth Sleepiness Scale©; ICF = Informed Consent Form; IDSIQ = Insomnia Daytime Symptoms and Impacts Questionnaire; IMP = Investigational Medicinal Product; IRT = Interactive Response Technology; ISI© = Insomnia Severity Index©; PGA-S = Patient Global Assessment of Disease Severity; PGI-C = Patient Global Impression of Change; SAE = serious adverse event; SDS© = Sheehan Disability Scale©;VAS = visual analog scale(s); WOCBP = women of childbearing potential.

7.2 Study assessments

The mandatory study assessments are listed in Table 1.

All study assessments are performed by qualified study personnel (medical, nursing, or specialist technical personnel), and are recorded in the medical history and eCRF, unless otherwise specified. Study assessments performed during unscheduled visits will also be recorded in the eCRF.

Visit 1 of ID-078A303 can be performed at the same time as EOT of the ID-078A301 or ID-078A302 studies. Eligibility criteria will be assessed based on the latest test results available, i.e.,

- EODBT (hematology and biochemistry, physical examination, body weight, ECG) and EOT (vital signs, pregnancy test, urine drug screen, C-SSRS©, ESS©) of the ID-078A301 or ID-078A302 studies if Visit 1 happens on the same day as EOT.
- EODBT (hematology and biochemistry, physical examination, body weight, ECG) and EOT (vital signs, pregnancy test) of the ID-078A301 or ID-078A302 studies if Visit 1 happens another day than EOT. In this case, the C-SSRS©, the ESS© and the urine drug screen must be performed again at the time of Visit 1.

The following assessments will be analyzed by an external provider (results will be transferred to Idorsia and integrated into the clinical database and to the investigators):

- Laboratory parameters.
- ECG parameters.
- Questionnaires completed using a hand-held device (listed below).

If the investigator delegates any study procedure/assessment for a subject to an external facility, he/she must inform Idorsia and specify to whom these tasks are delegated. The set-up and oversight must be agreed upon with Idorsia. 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 enrolment of the first subject. Calibration certificates of other equipment must be available as per local requirements:

- Temperature measurement devices for study treatment and sample storage area.

Use of hand-held and tablet devices

Subjects will be required to complete the following questionnaires on a hand-held device: ESS©, ISI©, SDS©, BWSQ, IDSIQ, sleep diary (including VAS), PGA-S and PGI-C.

Investigators, a delegated physician, a specialist nurse or a nurse practitioner, trained according to local requirements and local clinical practice, will be required to complete the following questionnaires on a tablet at site: C-SSRS©.

In addition to the telephone call, a reminder will be sent on each hand-held device the day before questionnaire completion is required and every day during the completion period.

Sites will be properly trained on the accurate use of the hand-held and tablet devices by the sponsor or an external CRO and are then expected to train their subjects on how to appropriately complete the questionnaires. Data collected from the hand-held devices will be electronically transferred to Idorsia by the CRO.

For further details, refer to the tablet and hand-held devices manual.

7.2.1 Demographics

Demographic data will not be collected again in the eCRF for the extension study. The investigator/delegate only needs to confirm the subject's age that was entered at Visit 1 in ID-078A301 or ID-078A302 study in the IRT system.

For subjects who are not eligible, the following data will be recorded in the eCRF if available:

- Informed consent date
- Reason for non-eligibility
- AEs

7.2.2 Safety assessments

The definitions, reporting and follow-up of AEs, SAEs and pregnancies are described in Section 9.

7.2.2.1 Body weight and height

Body weight will be measured at EODBT (Visit 5) and will be recorded in the eCRF.

Height will not be measured again and values will be taken from Visit 1 in the ID-078A301 or ID-078A302 studies.

7.2.2.2 Physical examination

Physical examination will be performed at Visit 3, Visit 4 and EODBT visit (Visit 5) according to site standard medical practice for subjects with insomnia disorders.

Other exams will be performed if indicated, based on medical history and/or symptoms.

Information for all physical examinations must be included in the source documentation at the study site. The observations will not be directly reported in the eCRF. Clinically

significant physical examination findings made after signing of informed consent that meet the definition of an AE [Section 9.1.1] must be recorded on the AE form of the eCRF.

7.2.2.3 Vital signs

Systolic and diastolic BP and pulse rate will be measured non-invasively at Visit 3, Visit 4, Visit 5 and Visit 6.

Vital sign measurements will be collected in the eCRF.

7.2.2.4 Sheehan Disability Scale©

The SDS© consists of 3 questions on impairment of work, social life, and family life / home responsibilities [see Appendix 5; Sheehan 1999]. The SDS© is a self-administered questionnaire on the hand-held device. It will be completed at Visit 1, Visit 3, Visit 4, Visit 5 and Visit 6.

7.2.2.5 Columbia Suicide Severity Rating Scale©

The C-SSRS© is an instrument that reports the presence and severity of both suicidal ideation and behaviors [Posner 2007].

The C-SSRS© will be completed at Visit 3, Visit 4, Visit 5 and Visit 6.

At Visit 1, if this visit does not happen on the same day as EOT of the ID-078A301 and ID-078A302 studies, the C-SSRS© will be completed for suicidal ideation and behaviors since the last visit in the confirmatory studies ID-078A301 and ID-078A302 (i.e., EOT). Otherwise, the C-SSRS© does not need to be repeated at Visit 1. At all other visits, the C-SSRS© will be completed for suicidal ideation and behaviors since the previous visit.

At each visit, the investigator, a delegated physician, a specialist nurse or a nurse practitioner, trained according to local requirements and local clinical practice will complete this questionnaire with the subject on a tablet and assess the findings.

7.2.2.6 Benzodiazepine Withdrawal Symptom Questionnaire

The BWSQ assesses the main symptoms which might be experienced by subjects during withdrawal from benzodiazepines [see Appendix 6; Tyrer 1990]. The questionnaire will be self-administered using the hand-held device at Visit 5 and Visit 6.

7.2.2.7 Epworth Sleepiness Scale©

The ESS© is a validated questionnaire designed to provide a subjective measure of daytime sleepiness [Johns 1991]. The ESS© [see Appendix 10] will be self-administered at Visit 3, Visit 4, Visit 5 and Visit 6 on a hand-held device to assess daytime sleepiness. The assessment must also be performed at Visit 1 if this visit is not performed on the same day as EOT of the ID-078A301 and ID-078A302 studies. All clinically significant findings must be recorded as AEs in the eCRF.

7.2.2.8 ECG assessment

A standard 12-lead ECG is to be performed at Visit 3, Visit 4, Visit 5 and Visit 6.

A 12-lead ECG will be recorded at rest with the subject in the supine position. Data records will be sent to the evaluation center for central reading.

Details will be provided in the 12-lead ECG laboratory manual.

The following parameters will be evaluated: PQ or PR (ms), QRS (ms), QT (ms), heart rate (HR; bpm), and rhythm. QTc (ms) will be calculated according to:

- Bazett's formula: $QTcB = QT / (RR)^{1/2}$
  and
- Fridericia's formula: $QTcF = QT / (RR)^{1/3}$, where $RR = 60 / HR$

Clinically significant findings detected after signing of ICF which meet the definition of an AE must be recorded in the eCRF.

ECG data collected by the CRO will be electronically transferred to Idorsia.

7.2.3 Efficacy assessments

7.2.3.1 Sleep diary

The sleep diary will be uploaded onto an electronic hand-held device (also called eDiary) and will be kept by the subject from the confirmatory studies to the extension study. Sleep diaries will be available in the subject's language, and must be completed daily throughout the last week of each consecutive 4-week period during the treatment period and daily during the run-out period.

The self-administered sleep diary includes a morning and evening questionnaire, and VAS.

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 (provided by the external service provider).

7.2.3.1.1 Morning and evening questionnaire

These questions collect information on self-reported sleep characteristics (sleep induction and maintenance), habitual napping, bedtime, and timing of study treatment intake.

For further details, see Appendix 7.

7.2.3.1.2 Visual analog scales

The VAS collect information on quality of sleep, depth of sleep, morning sleepiness, daytime alertness, and daytime ability to function by asking the subjects to report their feelings by placing a mark on a visual analog scale.

Self-reported quality of sleep, depth of sleep and morning sleepiness are assessed in the morning. Self-reported daytime alertness and daytime ability to function are assessed in the evening.

For further details, see Appendix 7.

7.2.3.2 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 [see Appendix 4]. The ISI© will be completed by the subject on the hand-held device at Visit 1, Visit 3, Visit 4 and Visit 5.

7.2.3.3 Patient Global Assessment of Disease Severity

The PGA-S 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 his/her insomnia over the 7 days preceding the PGA-S completion. It is a self-administered question programmed on the hand-held device, and is to be completed once during the last week of each consecutive 4-week period during the DB treatment period and at Visit 6.

For further details, see Appendix 8.

7.2.3.4 Patient Global Impression of Change

The PGI-C 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 his/her insomnia over the 7 days preceding the PGI-C compared to the week before he/she started treatment. The PGI-C is a self-administered question on the hand-held device, and is to be completed once during the last week of each consecutive 4-week period during the DB treatment period and at Visit 6.

For further details, see Appendix 8.

7.2.3.5 Insomnia Daytime Symptoms and Impacts Questionnaire

The IDSIQ is programmed on the electronic hand-held device in the subject's language, and must be completed daily by the subject throughout the last week of each consecutive 4-week period during the DB treatment period and the run-out period starting from Visit 1, without study staff input or interference.

For further details, see Appendix 9.

7.2.4 Laboratory assessments

7.2.4.1 Type of laboratory

A central laboratory (see central laboratory manual for contact details) will be used for all protocol-mandated laboratory tests, including re-tests due to laboratory abnormalities and laboratory tests performed at unscheduled visits.

Local laboratory results of the parameters described in Section 7.2.4.2 will only be collected in exceptional circumstances (e.g., hospitalization of the subject due to a medical emergency). The local laboratory results (with the corresponding normal ranges) must be recorded in the eCRF.

If a central laboratory sample is lost or cannot be analyzed at Visit 3, Visit 4 and Visit 5 for whatever reason, it is recommended to the investigator to collect an additional sample as soon as possible for repeat analysis.

Central laboratory reports will be sent to the investigator. In the event of specific (pre-defined) laboratory abnormalities, the central laboratory will alert Idorsia personnel and the concerned site personnel.

All laboratory reports must be reviewed, signed, and dated by the investigator or delegate within 10 working days of receipt and filed with the source documentation. The investigator/delegate must indicate on the laboratory report whether abnormal values are considered clinically significant or not. Any clinically significant laboratory abnormalities detected after signing of ICF must be reported as an AE or SAE as appropriate [see Section 9], and must be followed up until the value returns to within the normal range or is stable, or until the change is no longer clinically significant.

Details about the collection, sampling, storage, shipment procedures, and reporting of results and abnormal findings can be found in the laboratory manual. Blood samples will be drawn at Visit 3, Visit 4, Visit 5 and Visit 6.

7.2.4.2 Laboratory tests

Hematology

- Hemoglobin
- Hematocrit
- Erythrocytes
- Reticulocytes
- Leukocytes with differential counts
- Platelets

Clinical chemistry

- ALT
- AST
- Alkaline phosphatase
- Creatine kinase
- Total and direct bilirubin
- Gamma-glutamyl transferase
- Creatinine and creatinine clearance
- Blood urea nitrogen
- Uric acid
- Glucose
- Cholesterol, triglycerides
- Sodium, potassium, chloride, calcium
- Albumin
- Thyroid hormones, i.e., triiodothyronine (total and free) and thyroxine (total and free), and thyroid-stimulating hormone.

Pregnancy test

Results from the urine pregnancy test performed at EOT of the ID-078A301 or ID-078A302 studies will be taken into account to check the eligibility of the subject at Visit 1. If Visit 1 does not happen on the same day as EOT, a urine pregnancy test must be performed again. If pregnancy is suspected during the study, a serum pregnancy test must be performed immediately.

A serum pregnancy test for women of childbearing potential will be performed at EODBT (Visit 5). A urine pregnancy test will be performed at Visit 3, Visit 4 and Visit 6. In addition, 2 urine pregnancy tests will be provided to women of childbearing potential at Visit 1, Visit 3 and Visit 4. These tests will have to be performed monthly at home. The investigator/delegate will call the subject to ask about the result of the test. This call can be performed at the same time as the reminder phone call for completion of the eDiary or separately, as appropriate. Results of the pregnancy tests performed at home will be recorded in the eCRF.

Other tests

The urine drug screening kits (testing for presence of benzodiazepines, barbiturates, cannabinoids, opiates, amphetamines, phencyclidine or cocaine) and the breathalyzer for alcohol detection in the exhaled breath will be provided by the central laboratory. Urine drug screen is performed at Visit 3, Visit 4, Visit 5 and Visit 6 and must also be performed at Visit 1 if this visit is not performed on the same day as EOT of the ID-078A301 or ID-078A302 studies. Alcohol tests can be performed at the discretion of the investigator at any time in the event of suspicion of exaggerated alcohol consumption (i.e., above the accepted

threshold defined in Appendix 1). Should any technical issue arise with the breathalyzer, alcohol saliva tests will be provided to be used as back-up.

Study drug is administered as described in Section 5.1.2 only if the results of the pregnancy tests and other tests are negative.

8 STUDY COMPLETION AND POST STUDY TREATMENT / MEDICAL CARE

8.1 Study completion as per protocol

A subject who completes the study treatment phase and the safety follow-up phase is considered to have completed the study as per protocol.

8.2 Premature withdrawal from study

Subjects may voluntarily withdraw from the study without justification for any reason at any time. Subjects are considered withdrawn from study 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. If a subject withdraws consent, no further data will be collected in the eCRF from the date of withdrawal onward. Withdrawal from the study may also result from a decision by Idorsia for any reason, including premature termination or suspension of the study.

Investigators are encouraged to explain the importance of remaining in the study to the subjects withdrawn from study treatment. The occurrence of missing data due to a subject's withdrawal from the study treatment must be minimal, to ensure accuracy of the results. Study-specific measures are in place to maximize subject's compliance with the study treatment and procedures [see Section 5.1.11].

Subjects are considered as lost to follow-up if all reasonable attempts by the investigator to communicate with the individual failed. The site must take preventive measures to avoid a subject being lost to follow-up (e.g., document different ways of contact such as telephone number, home address, email address, person to be contacted if the subject cannot be reached). If the subject cannot be reached, the site must make a reasonable effort to contact the subject, document all attempts, and enter the loss of follow-up information into the eCRF. The following methods must be used: at least three telephone calls must be placed to the last available telephone number and one registered letter must be sent by post to the last available home address. Additional methods may be acceptable if they are compliant with local rules/regulations (e.g., a visit by site personnel to the subject's home), respecting the subject's right to privacy. If the subject is still unreachable after all contact attempts listed above, he/she will be considered to be lost to follow-up.

If premature withdrawal occurs for any reason, the reason (if known) for premature withdrawal from the study (e.g., withdrawal by subject, AE, lost to follow-up, death) must be recorded in the eCRF.

If, for whatever reason (except death or loss to follow-up), a subject is withdrawn from the study, the investigator should make efforts to schedule a last appointment / telephone 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 / telephone call will be recorded in the subjects' medical records but it will not be collected 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 8.4.

8.3 Premature termination or suspension of the study

Idorsia 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 prematurely suspended or terminated, Idorsia 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 prematurely terminated for any reason, the investigator – in agreement with Idorsia – must promptly inform all enrolled subjects and ensure their appropriate treatment and follow-up, as described in Section 8.4. Idorsia may inform the investigator of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the subjects' interests.

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

If the IEC/IRB suspends or terminates its approval / favorable opinion of the study, the investigator must promptly notify Idorsia personnel and provide a detailed written explanation of the termination or suspension.

8.4 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/delegate will explain to subjects what treatment / medical care is necessary and available according to local regulations.

9 SAFETY DEFINITIONS AND REPORTING REQUIREMENTS

9.1 Adverse events

9.1.1 Definition of adverse events

The study will deal with AEs, TEAEs, and treatment-emergent AESIs.

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 course of the study, whether or not considered by the investigator as related to study treatment.

A TEAE is any AE temporally associated with the use of study treatment. A TEAE is any AE emerging from randomization in the ID-078A303 study until up to 30 days after DB study treatment discontinuation in the extension study, whether or not considered by the investigator as related to study treatment.

AEs include:

- Exacerbation of a pre-existing disease.
- Increase in frequency or intensity of a pre-existing episodic disease or medical condition.
- Disease or medical condition detected or diagnosed during the course of 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 following the signing of informed consent.
- Abnormal assessments, e.g., change on physical examination, ECG findings, if they represent a clinically significant finding that was not present at study start or worsened during the course of the study.
- Laboratory test abnormalities if they represent a clinically significant finding, symptomatic or not, which was not present at study start or worsened during the course of the study, or led to dose reduction, interruption or permanent discontinuation of study treatment.

An overdose is defined as intake of more than the maximum recommended dose. In the context of this clinical study, it corresponds to the intake of more than one tablet per night and the subject explicitly reports overdose. The verbatim term of the corresponding AE should specify whether the intake was intentional or accidental, the number of nights it occurred, the number of tablets taken at once and the root cause leading to overdose.

Misuse and abuse of the study treatment and study treatment error will be reported as an AE/SAE as determined by the principal investigator. Study treatment abuse is defined as

any **intentional**, **non-therapeutic use** of the study treatment, even once, for the purpose of achieving a desirable psychological or physiological effect.

Study treatment misuse is defined as any **intentional therapeutic use** of the study treatment in an inappropriate way (e.g., taking a tablet during the day). Misuse specifically excludes those events that meet the definition of an abuse event.

Study treatment error is defined as any preventable unintentional error or inappropriate medication use while it is in the control of the subject. The ISB will adjudicate treatment-emergent AESIs which are similar to or indicate:

- Narcolepsy-like symptoms (i.e., EDS, cataplexy and complex sleep behavior events including hallucinations / sleep paralysis).
- Suicide/self-injury.

A treatment-emergent AESI is any AESI emerging from DB study treatment initiation until up to 30 days after DB study treatment discontinuation in the extension study.

9.1.2 Intensity of adverse events

The intensity of clinical AEs is graded on a three-point scale – mild, moderate, severe – and is reported on specific AE pages of the eCRF.

The three categories of intensity are defined 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 9.2.1]. These terms are used to describe the intensity of a specific event. Medical judgment should be used on a case-by-case basis.

Seriousness, rather than intensity assessment, determines the regulatory reporting obligations.

9.1.3 Relationship to study treatment

Each AE must be assessed by the investigator as to whether or not there is a reasonable possibility of causal relationship to the study treatment, and reported as either related or unrelated. The determination of the likelihood that the study treatment caused the AE will be provided by the investigator.

9.1.4 Reporting of adverse events

All AEs with an onset date after signing of informed consent and up to EOS must be recorded on AE pages of the eCRF.

AEs that started during the course of the ID-078A301 or ID-078A302 studies and that are still ongoing at enrollment in the ID-078A303 will be automatically transferred into the AE pages of the ID-078A303 eCRF.

Any increase of intensity will be reported as a new AE in the eCRF. No new AE is required to be reported if there is a decrease of intensity.

9.1.5 Follow-up of adverse events

AEs still ongoing more than 30 days after EODBT must be followed up until they are no longer considered clinically relevant or until stabilization. The follow-up information obtained after the subject's EOS telephone call will not be collected in the eCRF.

9.2 Serious adverse events

9.2.1 Definitions of serious adverse events

An SAE is defined by the ICH guidelines as any AE fulfilling at least one 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 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 when, based upon appropriate medical judgment, they may jeopardize the subject, and may require medical or surgical intervention to prevent one 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 informed consent) 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.

However, complications that occur during hospitalization are AEs or SAEs (e.g., if a complication prolongs hospitalization).

9.2.2 Reporting of serious adverse events

All SAEs occurring after signing of informed consent up to EOS must be reported on AE pages in the eCRF and on an SAE form, regardless of the investigator-attributed causal relationship with study treatment or study-mandated procedures.

SAEs that started during the course of the ID-078A301 or ID-078A302 studies and that are still ongoing at enrollment in the ID-078A303 will be kept open in the eCRF of the ID-078A301 or ID-078A302 studies and reported in the ID-078A303 eCRF.

An SAE is defined as related to protocol-mandated procedures if it appears to have a reasonable possibility of a causal relationship to either the study design or to protocol-mandated procedures (e.g., discontinuation of a subject's previous treatment during a washout period, leading to exacerbation of underlying disease).

9.2.3 Follow-up of serious adverse events

SAEs still ongoing more than 30 days after EODBT must be followed up until resolution or stabilization, or until the event outcome is provided.

The follow-up information obtained after the subject's EOS telephone call must be reported to Idorsia Global Drug Safety, but it is not recorded in the eCRF.

9.2.4 After the 30-day follow-up period

New SAEs occurring after the 30-day follow-up period must be reported to Idorsia Global Drug Safety within 24 hours of the investigator's knowledge of the event, **only** if considered by the investigator to be causally related to previous exposure to the study treatment.

9.2.5 Reporting procedures

All SAEs must be reported by the investigator to Idorsia Global Drug Safety within 24 hours of the investigator's first knowledge of the event.

All SAEs must be recorded on an SAE form, irrespective of the study treatment received by the subject, and whether or not this event is considered by the investigator to be related to study treatment.

The SAE forms must be sent to Idorsia Global Drug Safety (contact details are provided on the SAE form). The investigator 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 also be reported within 24 hours of receiving it. Idorsia Global Drug Safety personnel may contact the investigator to obtain further information.

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

The expectedness of an adverse reaction is determined by Idorsia in the reference safety information (RSI) section provided in the most recent version of the IB for ACT-541468 [Daridorexant IB]. Any SAE that is assessed as related and unexpected against the RSI of the ACT-541468 IB is known as a SUSAR and must be reported by Idorsia to concerned health authorities (including the EudraVigilance database if the study is conducted in Europe), IECs/IRBs and investigators.

9.3 Pregnancy

If a woman becomes pregnant while on study treatment, study treatment must be discontinued. The investigator must counsel the subject and discuss the risks of continuing with the pregnancy and the possible effects on the fetus.

9.3.1 Reporting of pregnancy

Irrespective of the treatment received by the subject, any pregnancy occurring after study start (i.e., signing of informed consent) up to EOS must be reported within 24 hours of the investigator's knowledge of the event.

Pregnancies must be reported on the Idorsia Pregnancy form, which is faxed to Idorsia Global Drug Safety (see contact details provided on the Pregnancy form), and on an AE page in the eCRF.

9.3.2 Follow-up of pregnancy

Pregnancies must be followed up to their conclusion and the outcome must be reported to Idorsia Global Drug Safety for all randomized subjects.

Any AE associated with the pregnancy occurring during the follow-up period after study treatment discontinuation must be reported on separate AE pages in the eCRF. Any SAE occurring during the pregnancy must be reported on an SAE form as described in Section 9.2.5.

9.4 Study safety monitoring

Study safety information (AEs, SAEs, laboratory values, ECGs, vital signs, and study-specific examinations as required) is monitored and reviewed on a continuous basis by the Idorsia Clinical Team (in charge of ensuring subjects' safety as well as data quality). In addition, an IDMC and an ISB will review and adjudicate safety data [see Section 3.3].

10 STATISTICAL METHODS

All statistical analyses will be conducted by Idorsia or by designated CROs supervised by Idorsia.

For subjects who received placebo in ID-078A301 or ID-078A302 who are randomized to 25 mg ACT-541468 in this extension study, baseline refers to assessments performed before randomization or start of ACT-541468 intake. For all other subjects, and unless stated otherwise, baseline refers to assessments performed before start of DB study treatment of study ID-078A301 or ID-078A302.

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

10.1 Analysis sets

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

10.1.1 Enrolled Set

The Enrolled Set includes all subjects who have a subject identification number in the extension study (same as in the confirmatory study).

10.1.2 Full Analysis Set

The Full Analysis Set (FAS) includes all subjects assigned to a study treatment in the extension study. Subjects will be evaluated according to the study treatment they have been assigned.

10.1.3 Safety Set

The Safety Set includes all subjects who received at least one dose of study treatment in the extension study. Subjects will be evaluated according to the actual treatment they received.

10.1.4 Treatment Withdrawal Set

The Treatment Withdrawal Set comprises all subjects from the Safety Set who received single-blind placebo treatment in the run-out period of the extension study.

10.1.5 Usage of the analysis sets

The analyses of efficacy endpoints including baseline and disease characteristics will be performed using the FAS.

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

The Treatment Withdrawal Set will be used for the analysis of endpoints assessing withdrawal symptoms (e.g., BWSQ total score) and rebound insomnia (e.g., sTST).

10.2 Variables

Detailed descriptions of study efficacy and safety variables (endpoints) can be found in Section 6 of this protocol.

10.3 Description of statistical analyses

10.3.1 Analysis of safety endpoints

Analysis of safety endpoints will be performed using the Safety Set, unless noted otherwise.

Adverse events

AEs will be coded using MedDRA. The number (%) of subjects experiencing a TEAE (including SAEs, AESIs after adjudication by the ISB, and AEs leading to premature discontinuation of the DB study treatment) will be summarized by system organ class (SOC) and/or preferred term (PT), and maximum intensity. A subject with multiple intensities reported for an AE will be summarized under the maximum intensity recorded for the event. A subject with multiple occurrences of an AE is counted only once in the AE category (e.g., SOC, PT).

Laboratory data

Laboratory analyses will be based on data received from the central laboratory. Observed values and changes from baseline to Visit 3, Visit 4, Visit 5 and Visit 6 in both hematology and blood chemistry laboratory parameters will be summarized. The number (%) of subjects having a marked laboratory abnormality during DB study treatment will be tabulated.

Vital signs and body weight

Observed values and changes from baseline to Visit 3, Visit 4, Visit 5 and Visit 6 in vital signs (systolic and diastolic BP, and pulse rate) will be summarized. Observed values and changes from baseline to Visit 5 in body weight will be summarized.

Electrocardiograms

Observed values and changes from baseline to Visit 3, Visit 4, Visit 5 and Visit 6 for each ECG parameter (QTcB, QTcF, HR, PR, QRS) will be summarized. The number (%) of subjects with a marked ECG abnormality during DB study treatment will be tabulated.

Withdrawal symptoms

The Treatment Withdrawal Set will be used to assess the potential for withdrawal symptoms.

The BWSQ total score will be summarized using descriptive statistics for the observed values and changes from the last assessment on treatment (Visit 5) to the end of the run-out period (Visit 6).

In addition, withdrawal symptoms after DB study treatment withdrawal will be assessed through the incidence of AEs and marked ECG abnormalities occurring during the treatment withdrawal period. The number (%) of subjects experiencing, separately, an AE and a marked ECG abnormality during the treatment withdrawal period will be tabulated.

Rebound insomnia

The Treatment Withdrawal Set will be used to assess the potential for rebound insomnia.

The changes from the baseline to the treatment withdrawal period (Visit 6, Week 41) in sTST will be summarized using descriptive statistics.

Next-day residual effect

Observed values and changes from baseline to Visit 3, Visit 4 and Visit 5 in SDS©, and sleep diary VAS scores (mm) assessing morning sleepiness (from 'the way you feel this morning'), daytime alertness (from 'your daytime alertness today') and daytime ability to function (from 'your daily ability to function today'), will be summarized.

C-SSRS©

Number (%) of subjects with suicidal ideation, suicidal behavior, and/or self-injurious behavior without suicidal intent based on the C-SSRS© during DB treatment and during the treatment withdrawal period will be tabulated.

Shifts from baseline showing any changes in suicidal ideation and suicidal behavior during DB treatment and during the treatment withdrawal period will also be provided. Subjects

will be summarized under the worst of the following three categories, shown here in the order from best to worst: 1) No suicidal ideation or behavior, 2) Suicidal ideation only, and 3) Suicidal ideation and behavior.

Epworth Sleepiness Scale©

The change from baseline to Visit 3, Visit 4, Visit 5 and end of the run-out period Visit 6 in ESS© total score will be summarized. Observed values will also be summarized.

10.3.2 Analysis of exploratory efficacy endpoints

Analysis of the efficacy endpoints will be performed using the FAS.

A longitudinal data analysis method (i.e., linear mixed effects model) will be used for the analysis of change from baseline in sTST, sWASO, sLSO and IDSIQ scores (i.e., total score; alert/cognition, mood and sleepiness domain scores), separately. All available data, regardless of occurrence of intercurrent events (e.g., study treatment discontinuation, the use of prohibited medication), will be included in the model.

The analysis model will adjust for the baseline value of the relevant response variable, age group (< 65; ≥ 65 years), treatment (10 mg; 25 mg; 50 mg; placebo), visit (Month 6; Month 9; Month 12), and the interaction of treatment by visit, and baseline by visit.

An unstructured covariance matrix shared across treatment groups will be used to model the correlation among repeated measurements. A restricted maximum likelihood approach 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].

Appropriate contrasts will be used to test the treatment differences of interest (e.g., the difference in least squares mean change from baseline between 10 mg vs placebo, 25 mg vs placebo and 50 mg vs placebo at Month 6). Baseline is the mean value based on the screening sleep diary / IDSIQ entries performed at home in the 7 days immediately preceding the first polysomnography at Visit 3 of the confirmatory study. Month 6 is the mean value based on the sleep diary / IDSIQ entries performed at home over the 7 days in Week 12 of the extension study; Month 9 and Month 12 is defined similarly.

Observed values and changes from baseline over time in sTST, sWASO, sLSO and IDSIQ scores (i.e., total score; alert/cognition, mood and sleepiness domain scores) will be summarized.

Summary statistics will be provided for other efficacy endpoints using number (%) of subjects for categorical variables and descriptive statistics (e.g., mean, standard deviation, median, min., max.) for continuous variables.

10.3.3 Subgroup analyses

Subgroup analyses will be conducted to explore the uniformity of the overall treatment effects with regards to efficacy and safety variables, and will be described in the statistical analysis plan.

10.4 Interim analyses

An interim analysis is planned to support global regulatory filings.

The interim analysis will be conducted when all subjects who did not prematurely discontinue study treatment have reached Visit 3. Subjects treated with placebo during the confirmatory studies and randomized to ACT-541468 25 mg are excluded from this condition as they will not all display 6-month data.

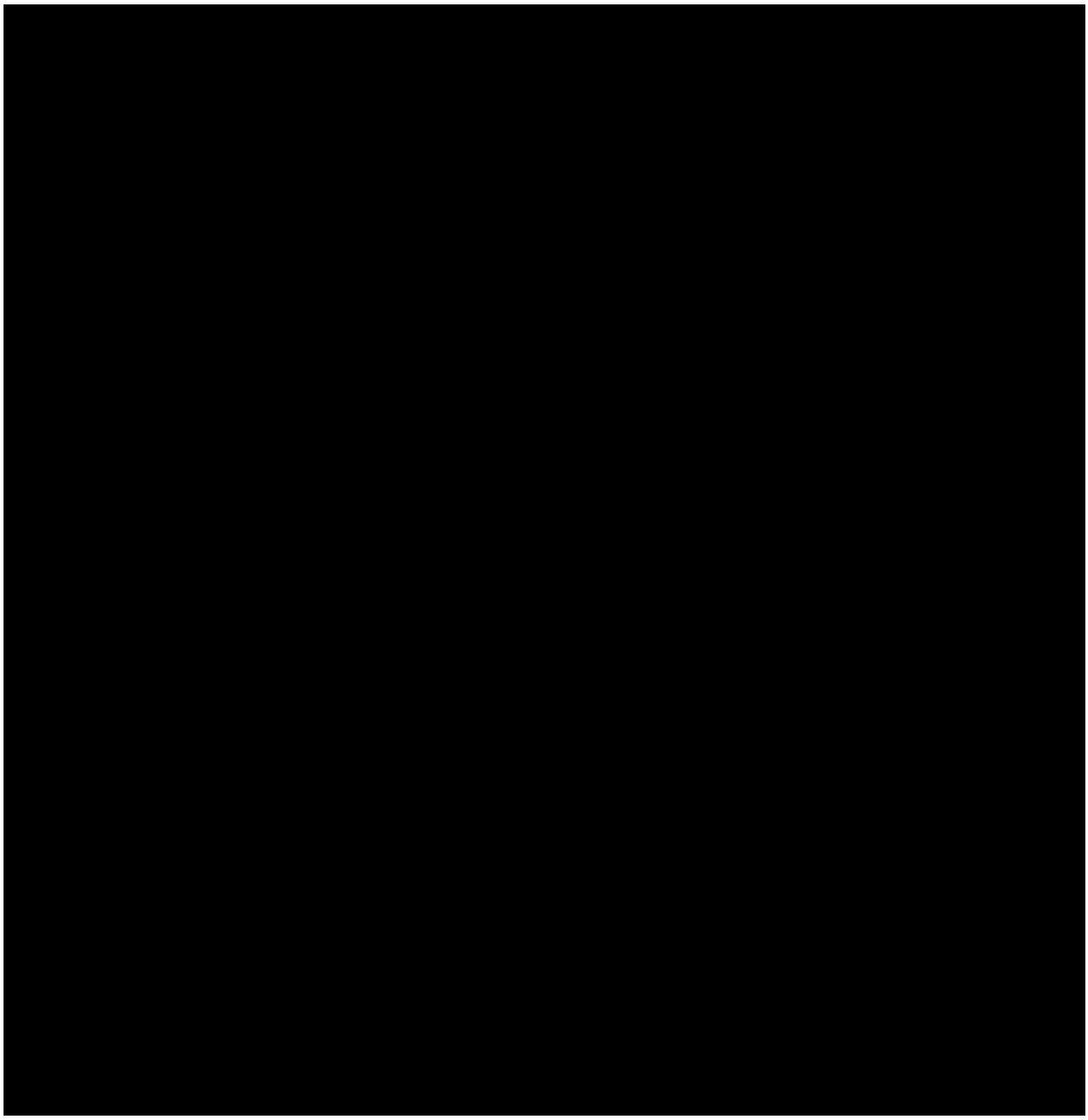
To maintain the integrity of the study after the interim analysis, participating subjects as well as investigators will remain blinded for the entire duration of the study. The sponsor personnel involved in data collection and medical monitoring of the study will also remain blinded until the end of the study.

A second interim analysis may be performed to fulfill the FDA requirement to submit updated safety data from ongoing studies 120 days after NDA submission, if the study has not been completed by that time.

The interim analyses will be based upon a snapshot of the clinical trial database and will include all safety and efficacy data. In addition, a cut-off date will be set and any data generated after the cut-off date will not be included in the interim analysis. For further details, refer to the statistical analysis plan.

Additional descriptions regarding the planned analyses for the interim report will be described in the statistical analysis plan.

No adjustment for multiple testing is required as no formal interim analysis will be performed for determining whether to stop (or modify) the study (i.e., no hypothesis testing will be conducted ad interim).



11 DATA HANDLING

11.1 Data collection

The investigator/delegate is responsible for ensuring the accuracy, completeness and timeliness of the data reported. All source documents are recommended to be completed

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

eCRF data will be reported through electronic data capture (a web-based tool). 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/delegate will approve the data (i.e., confirm the accuracy of the data recorded) using an electronic signature (ref. to US 21 CFR Part 11).

Entries recorded by the subject on the hand-held device (i.e., ESS©, sleep diary (including VAS), ISI©, IDSIQ, PGA-S, PGI-C, SDS©, BWSQ) as well as the physician-reported global assessment on a tablet at site (i.e., C-SSRS©) are considered source data. Site personnel will review and ensure completeness and readability of the subjects' entries. Site personnel will be allowed to instigate correction or deletion of subjects' metadata or answers in physician-reported assessments. Site personnel will not be allowed to alter subject-generated data, unless requested to do so by the subject. A data correction form will be completed by the site personnel to request any data changes and sent to the CRO provider, who will process the changes as per CRO data management procedures.

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

For each subject enrolled, regardless of study treatment initiation, an eCRF must be completed and signed by the investigator/delegate. This also applies to those subjects who fail to complete the study. If a subject withdraws from the study, the reason must be noted on the eCRF.

11.2 Maintenance of data confidentiality

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

11.3 Database management and quality control

eCRFs will be used for all subjects. The investigators will have access to the site eCRF data until the database is locked. Thereafter, they will have read-only access. The eCRF

must be kept current to reflect subject status at any time point during the course of the study.

While entering the data, the investigator/delegate will be instantly alerted to data queries by validated programmed checks. Additional data review will be performed by Idorsia personnel on an ongoing basis to look for unexpected patterns in data and for study monitoring. Should discrepant data be detected, a query specifying the problem and requesting clarification will be issued and visible to the investigator/delegate via the eCRF. All electronic queries visible in the system either require a data correction (when applicable) and a response from the investigator/delegate to clarify the queried data directly in the eCRF, or simply a data correction in the eCRF.

This process will continue until database closure.

The investigator/delegate must, on request, supply Idorsia 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 confidentiality is protected.

Laboratory samples, ECGs and hand-held device data will be processed through a central laboratory / CRO and the results will be electronically sent to Idorsia.

Should local laboratory data be generated, as may be required per protocol in certain instances, it must be entered in the eCRF by the site personnel.

AEs are coded according to the latest version of MedDRA and previous/concomitant therapies are coded using the latest version of WHODrug used by Idorsia.

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 Idorsia QS documents. After database closure, the investigator will receive the eCRFs of the subjects of his/her site (including the audit trail) on electronic media or as a paper copy.

12 PROCEDURES AND GOOD CLINICAL PRACTICE

12.1 Ethics and Good Clinical Practice

Idorsia personnel and the investigators will ensure that the study is conducted in full compliance with ICH GCP guidelines, the principles of the “Declaration of Helsinki”, and with the laws and regulations of the country in which the study is conducted.

12.2 Independent Ethics Committee / Institutional Review Board

The investigator will submit this protocol and any related document(s) provided to the subject (such as the ICF) to an IEC/IRB. Approval from the committee/board must be obtained before starting the study, and must be documented in a dated letter to the investigator, 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 to the IEC/IRB in accordance with local procedures and regulations [see Section 12.6].

A list of members participating in the IEC/IRB meetings must be provided, including the names, qualifications, and functions of these members. If that is not possible, the attempts made to obtain this information along with an explanation as to why it cannot be obtained or disclosed must be documented in the study documentation.

If a member of the study personnel was present during an IEC/IRB meeting, it must be clear that this person did not vote.

12.3 Informed consent

It is the responsibility of the investigator/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/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 shall be paid to the information needs of specific subject populations and of individual subjects, as well as to the methods used to give the information. Adequate time shall be given for the subject to consider his or her decision to participate in the study and it shall be verified that the subject has understood the information (e.g., by asking the subject to explain what is going to happen).

The ICF will be provided in the country local language(s).

Site personnel authorized (according to local regulation) to participate in the consent process and/or to obtain consent from the subject will be listed on the Delegation of Authority (DoA) form supplied by Idorsia. A study physician must always be involved in the consent process. In European countries, the informed consent must be obtained by a physician.

The subject and authorized site personnel listed on the DoA form supplied by Idorsia must sign, personally date, and time (if the first study-mandated procedure is to be performed on

the same day informed consent is obtained) the ICF before any study -related procedures (i.e., any procedures required by the protocol) begin.

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 number, the date and, if applicable, time when the subject was first introduced to the study, the date and, if applicable, time of consent, who participated in the consent discussion, who consented the subject, and any additional person 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.

12.4 Compensation to subjects and investigators

Idorsia provides insurance in order 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 compensation of the subject in the event of study-related injuries will comply with applicable regulations.

12.5 Protocol adherence/compliance

The investigator must conduct the study in compliance with the IEC/IRB 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.

If a protocol deviation occurs, the investigator/delegate will inform Idorsia or its representative in a timely manner. The investigator/delegate must document and explain any deviation from the approved protocol. Deviations considered to be a violation of ICH GCP must be reported to the IEC/IRB and regulatory authorities according to Idorsia or (overruling) local requirements.

All protocol deviations will be reported in the clinical study report (CSR). IECs/IRBs will be provided with listings of protocol deviations as per local requirements.

12.6 Protocol amendments

Any change to the protocol can only be made through a written protocol amendment. An amended protocol must be submitted to the IEC/IRB and regulatory authorities, according to their requirements.

12.7 Essential documents and retention of documents

The investigator/delegate must maintain adequate records necessary for the reconstruction and evaluation of the study. A number of 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 certified copy), attributable, complete, consistent, enduring, and available when needed.

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

These records must be kept by the investigator for as long as is necessary to comply with Idorsia's requirements (i.e., as specified in the clinical study agreement), and national and/or international regulations, whichever would be the longest period. If the investigator 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 and Idorsia to store these documents outside the site so that they can be retrieved in the event of a regulatory inspection. No study documents should be destroyed without prior written approval from Idorsia. Should the investigator wish to assign the study records to another party, or move them to another location, Idorsia must be notified in advance.

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

If the site is using an electronic/computerized system to store subject medical records but it could not be confirmed that the system is validated or if the CRA could not be provided access to the system, 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 coversheet, signed and dated by the investigator/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 and must be filed either with the subject's medical records or with the subject's eCRF.

In order to verify that the process the site uses to prepare certified copies is reliable, the CRA must be able to observe this process and confirm that the comparison of the source documents and the certified copy did not reveal inconsistencies. The CRA does not need to verify this process for all data of all subjects but at least for some of them (e.g., first subject; regular check during the study of critical data like inclusion/exclusion criteria, endpoints for some subjects) as per Idorsia's instructions. If it were not possible for the

CRA to observe this process, it would not be possible to rely on the site's certified copies and therefore the site cannot be selected for the clinical study.

12.8 Monitoring

Prior to study start, a Site Initiation Visit (SIV) will be performed after the required essential study documents are approved by Idorsia. The study treatment will be shipped to the site upon approval of the required essential documents.

The Principal Investigator (PI) must ensure that all site personnel involved in the study are present during the SIV and will dedicate enough time to it. Site Information Technology support should also be available during the SIV.

The SIV must be completed before the site can start the enrollment of study subjects. Following the SIV, a copy of the completed initiation visit report and follow-up letter will be provided to the PI 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. Idorsia monitoring standards require full verification that informed consent has been provided, verification of adherence to the inclusion/exclusion criteria, documentation of SAEs, and the recording of the main efficacy, safety, and tolerability endpoints. Additional checks of the consistency of the source data with the eCRFs will be performed according to the study-specific monitoring guidelines. The frequency of the monitoring visits will be based on subject recruitment rate and critical data-collection times.

The PI must ensure that the eCRF is completed after a subject's visit (site visit or telephone call), 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. If the subject is hospitalized or dies in a hospital other than the study site, the investigator is responsible for contacting that hospital in order to document the SAE, in accordance with local regulations.

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 enroll any subjects, the close-out visit may be performed prior to study database closure at the discretion of Idorsia.

12.9 Investigator Site File

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

The ISF will include a table of contents listing the essential documents. All study-related documentation must be maintained in the ISF.

In some cases, exceptions can be discussed with the CRA regarding the filing of the study documents outside the ISF. It should be clearly documented where each document is filed. This note to file should be present in the specific tab of the document in the ISF.

The ISF must be stored in a secure and access-restricted area during and after the study. It must be kept by the site for as long as needed to comply with any applicable rules and regulations, ICH GCP, as well as instructions from Idorsia. If the site needs to transfer the ISF to another location and/or if site facility can no longer store the ISF, the PI must immediately inform Idorsia.

If the PI will change, or if the site will relocate, the CRA must be notified as soon as possible.

12.10 Audit

Idorsia's Pharmaceutical Development group representatives or delegates 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 Idorsia's requirements (e.g., standard operating procedures) will also be verified. Prior to initiating this audit, the investigator will be contacted by Idorsia 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.

12.11 Inspections

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

Should an inspection be announced by a health authority and/or IEC/IRB, the investigator must immediately inform Idorsia (usually via the CRA) that such a request has been made.

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

12.12 Reporting of study results and publication

Idorsia will post the key elements of this protocol and the summary of results on Idorsia's Clinical Trial Register and, within the required timelines, on publicly accessible databases (e.g., clinicaltrials.gov, EU database), as required by law and regulation.

Study results will be documented in a CSR that will be signed by Idorsia representatives and the Coordinating Investigator.

In accordance with the Good Publication Practices and ethical practice, 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.

Authorship will be determined in accordance with the International Committee of 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 Idorsia and will be determined by mutual agreement.

Any study-related publication written independently by investigators must be submitted to Idorsia for review at least 30 days prior to submission for publication or presentation at a congress. Upon review, Idorsia 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 should permit publication during such a review period.

13 REFERENCES

[Daridorexant IB] Investigator's Brochure for daridorexant, version 7. Idorsia Pharmaceuticals Ltd; January 2020.

[APA 2013] American Psychiatric Association. Diagnostic and statistical manual of mental disorders, Fifth Edition. Arlington, VA: American Psychiatric Publishing; 2013.

[Belsomra® USPI] Belsomra® (suvorexant) US Package Insert. United States Food and Drug Administration full prescribing information. Revised 8/2014. Accessed on 25 April 2018. Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/204569s000lbledt.pdf

[Citrome 2014] Citrome L. Suvorexant for insomnia: a systematic review of the efficacy and safety profile for this newly approved hypnotic - what is the number needed to treat, number needed to harm and likelihood to be helped or harmed? Int J Clin Pract 2014;68(12):1429-41.

[EMA 2011] European Medicines Agency guideline on medicinal products for the treatment of insomnia. EMA/CHMP/16274/2009 Rev. 1. 7 February 2011. Accessed on 25 April 2018. 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): Guidelines for the clinical evaluation of hypnotic drugs. September 1977. Accessed on 25 April 2018. Available from: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071711.pdf

[Herring 2016] Herring WJ, Connor KM, Ivgy-May N, Snyder E, Liu K, Snavely DB, et al. Suvorexant in patients with insomnia: Results from two 3-month randomized controlled clinical trials. Biol Psychiatry 2016;79(2):136-48.

[ICH 1994] ICH Tripartite Guideline. The Extent of Population Exposure to Assess Clinical Safety - E1. Accessed on 4 May 2018. Available from: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E1/Step4/E1_Guideline.pdf

[ICH 2000] ICH Tripartite Guideline. Choice of Control Group and Related Issues in Clinical Trials - E10. Accessed on 4 May 2018. Available from: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E10/Step4/E10_Guideline.pdf

[Johns 1991] Johns MW. A new method for measuring daytime sleepiness: the Epworth Sleepiness Scale. Sleep 1991;14(6):540-5.

[Kenward 1997] Kenward MG, Roger JH. Small sample inference for fixed effects from restricted maximum likelihood. Biometrics 1997;53:983-97.

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

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

[NIH 2005] National Institutes of Health, State-of-the-Science Conference Statement on Manifestations and Management of Chronic Insomnia in Adults. NIH Consensus and State-of-the-Science Statements. 2005 Jun;13-15;22(2):1-30.

[Ohayon 2002] Ohayon MM, Smirne S. Prevalence and consequences of insomnia disorders in the general population of Italy. Sleep Med. 2002;3(2):115–20.

[Ohayon 2010] Ohayon MM, Sagales T. Prevalence of insomnia and sleep characteristics in the general population of Spain. Sleep Med. 2010;11(10):1010–8.

[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.

[Roth 2007] Roth T. Insomnia: Definition, prevalence, etiology, and consequences. J Clin Sleep Med 2007;3 Suppl 5:S7-10.

[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.

[Sheehan 1999] Sheehan D, Janavs J, Baker R, Harnett-Sheehan K, Knapp E, Sheehan M. MINI international neuropsychiatric interview. J Clin Psychiatry 1999:60(18):39-60.

[Tyrer 1990] Tyrer P, Murphy S, Riley P. The Benzodiazepine Withdrawal Symptom Questionnaire. J Affect Disord 1990;19:53-61

14 APPENDICES

Appendix 1 Alcohol restrictions during the study

The subjects will be instructed to limit alcohol to a maximum of 2 drinks per day.

A drink is defined as:

a. A bottle/can of 33 cL / 12 ounces of beer (≈14 grams alcohol)
b. A glass of 10–12 cL / 4 ounces of wine (≈12 grams alcohol)
c. A small glass of 3–4 cL / 1 ounce of liquor (≈9 grams alcohol)

Appendix 2 Caffeine content of common beverages

The content of caffeine in common caffeine beverages is approximately:

a. A standard cup of brewed or restaurant-style coffee contains approximately 150–200 mg caffeine.
b. A can of most caffeinated soda drinks contains approximately 50 mg caffeine.
c. A can of energy drink contains approximately 150–200 mg caffeine.

Appendix 3 Forbidden and restricted concomitant medications

1. Forbidden (F) or restricted (R) concomitant medications due to CNS side effects. The use of CNS-active drugs is forbidden or restricted at least 1 week prior to Visit 1 and until 24 hours after EOT.

Drug Class	Examples	Forbidden / Restricted	Comment
Antihistamines	*Sedating:* e.g., carbinoxamine, triprolidine HCl, acrivastine, azatadine, chlorpheniramine, doxylamine, hydroxyzine, ketotifen, promethazine & timeprazine, diphenhydramine HCl.	F	
Psychotropics	*Stimulants:* e.g., amphetamine derivatives, ephedrine derivatives, modafinil, armodafinil, methylphenidate, aripiprazole, pramipexole, levodopa.	F	
	Antipsychotics, including depot neuroleptics: e.g., quetiapine, olanzapine.	F	
	Anxiolytics: e.g., alprazolam, buspirone, clorazepate, diazepam, flurazepam, lorazepam, midazolam, quazepam, temazepam, triazolam.	F	
	Hypnotics: e.g., ramelteon, suvorexant, zolpidem and OTC.	F	
	Cholinesterase inhibitors: e.g., donepezil, galantamine.	F	
	Mood stabilizers: e.g., carbamazepine, gabapentin, lamotrigine, 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, valerian, passiflora, hypericum.	F	
	Others: e.g., tryptophan, melatonin.	F	
Anticonvulsants	Barbiturates, benzodiazepines, GABA analogs, hydantoins phenyltriazines (e.g., lamotrigine) succinimides (e.g., ethosuximide)	F	
Other	Isotrenitoin	F	
	Systemic glucocorticoids: e.g., dexamethasone, methylprednisone, prednisone.	R	Continuous treatment limited to 1 week. Inhaled corticosteroids are permitted
	Diet pills (prescription and OTC).	F	
	Pseudoephedrine	R	May only be used before 2 pm, and no more than twice a week. Dosage is limited to 30 mg of active ingredient in each tablet. Extended release formulations are forbidden.

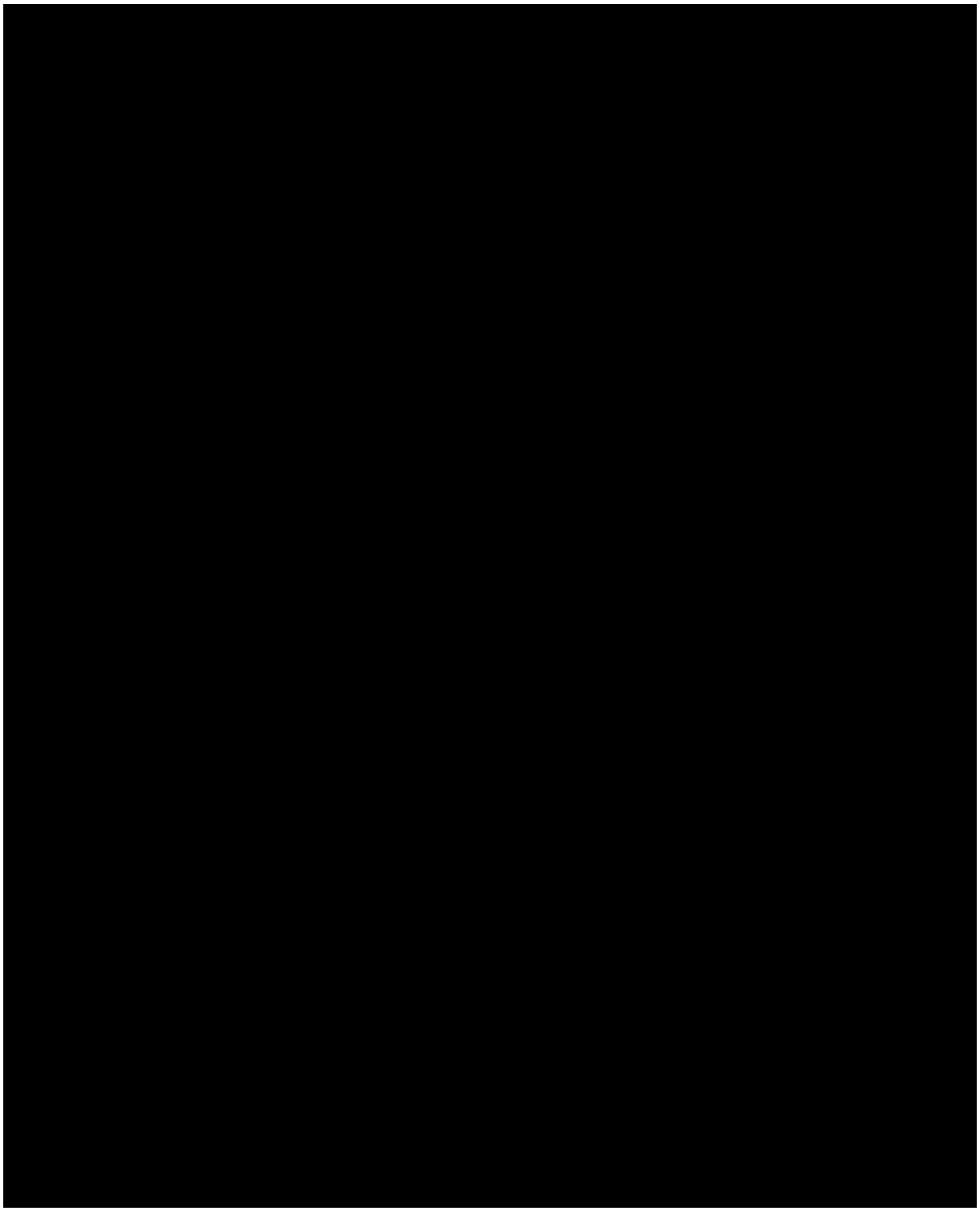
GABA = gamma-aminobutyric acid; NSAID = nonsteroidal anti-inflammatory drug; OTC = over-the-counter.

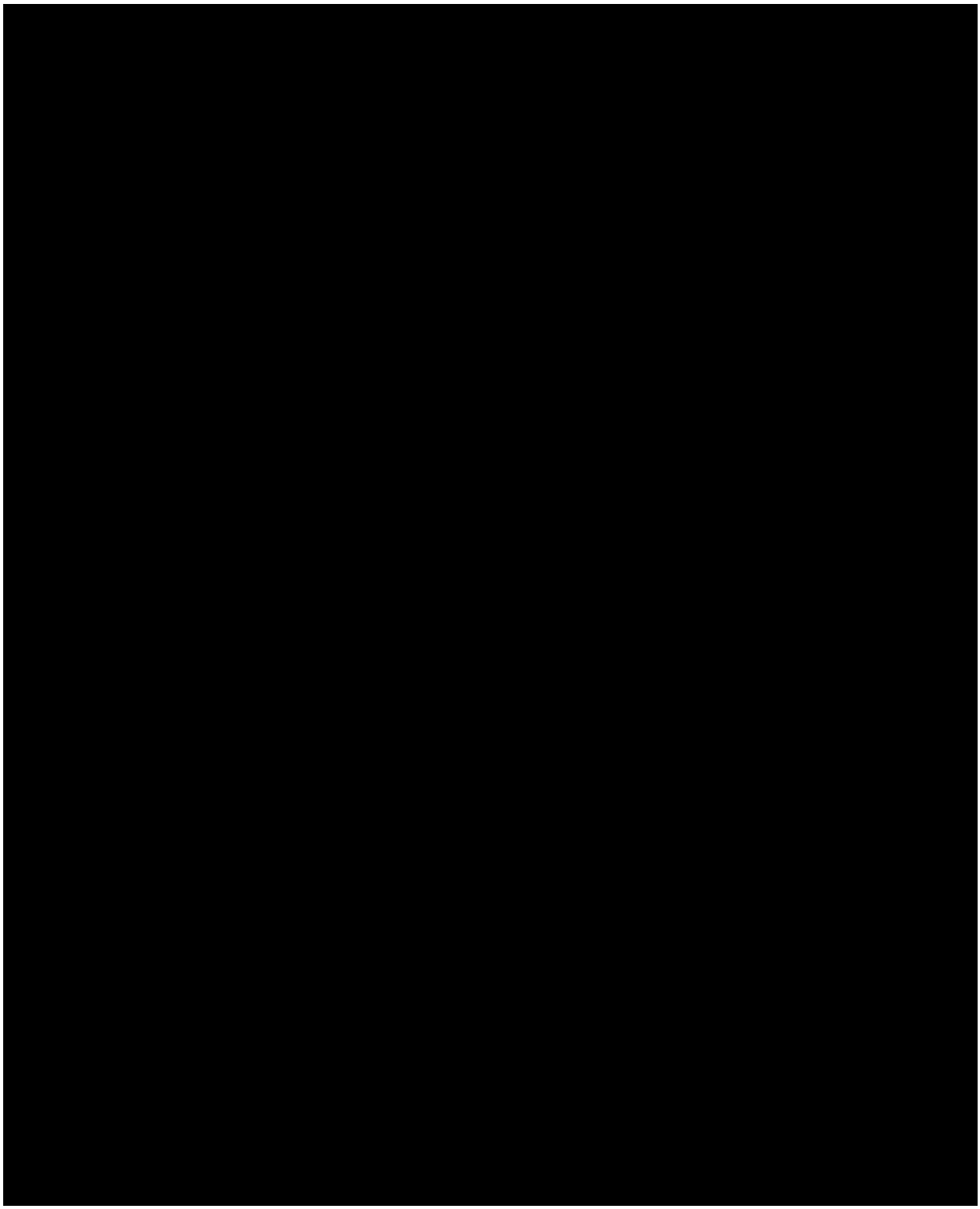
2. Non-exhaustive list of forbidden concomitant medications and diets due to potential drug interactions with CYP3A4 (moderate and strong inhibitors, inducers). Those medications must be discontinued no later than within 1 week prior to Visit 1 and are forbidden until 24 hours after EOT.

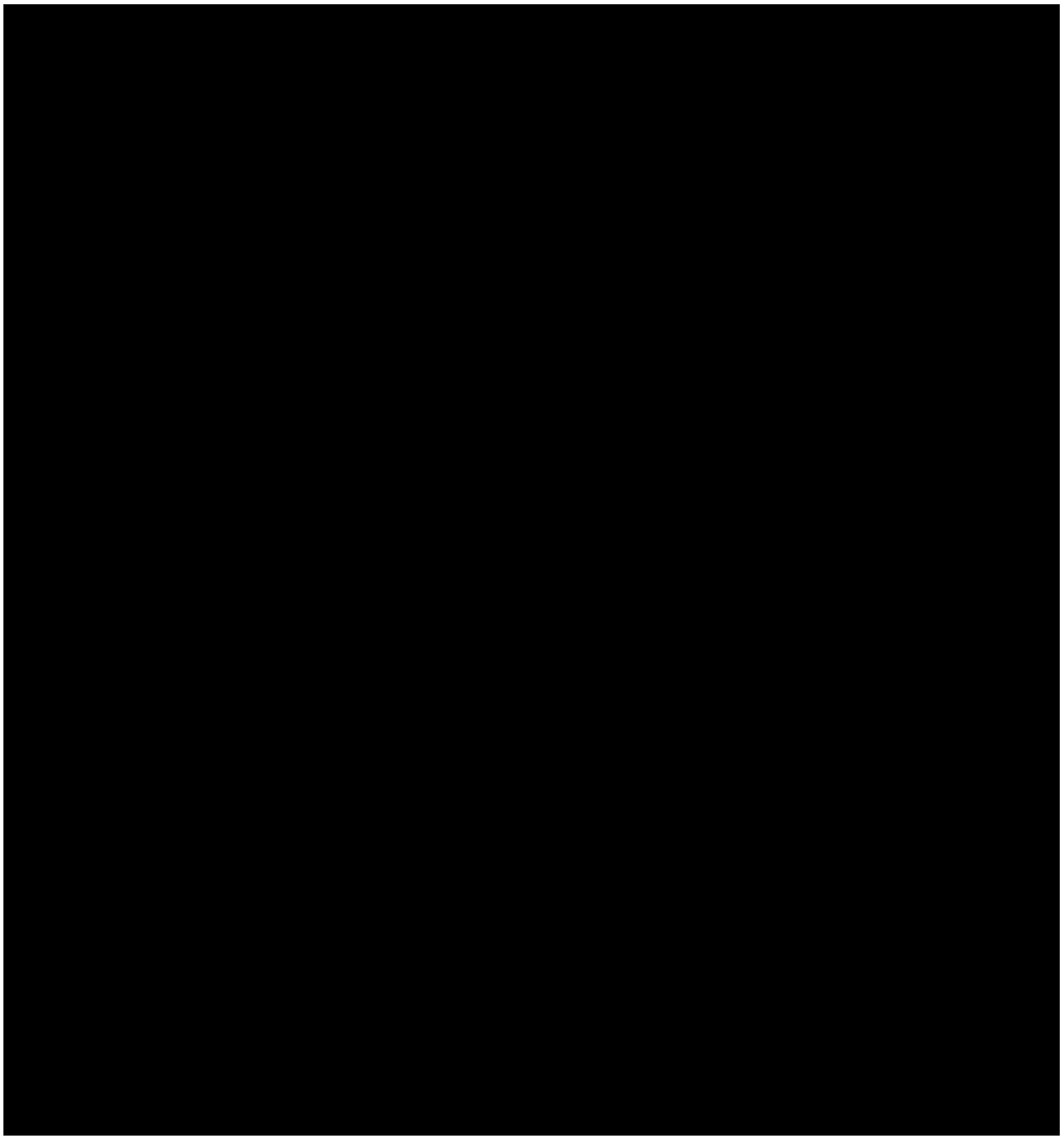
CYP3A4 moderate and strong inhibitors and CYP3A4 moderate and strong inducers:

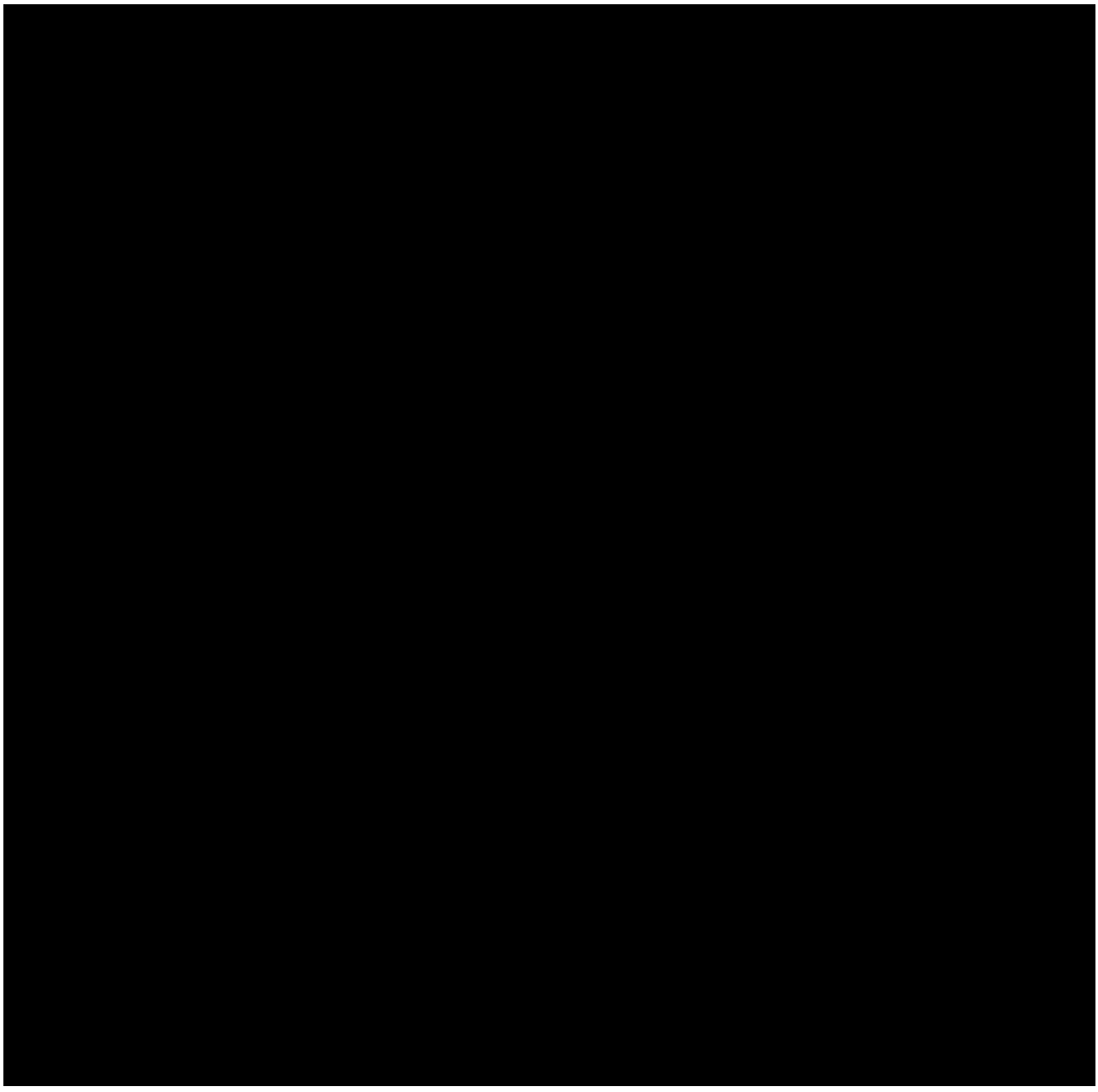
Inhibitors of CYP3A4	Inducers of CYP3A4
HIV antivirals: atazanavir, boceprevir, cobicistat, darunavir, delaviridine, fosamprenavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, telaprevir	HIV antivirals: efavirenz, etravirine
Antibiotics: ciprofloxacin, clarithromycin, erythromycin, norfloxacin, 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	
Grapefruit and grapefruit juice Seville oranges (bitter) and Seville oranges juice	

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









[redacted]

[redacted]

[redacted]