Cover page

Official Title:

PROTOCOL ID-078A301 - Multi-center, double-blind, randomized, placebo-controlled, parallel-group, polysomnography study to assess the efficacy and safety of ACT-541468 in adult and elderly subjects with insomnia disorder

ClinicalTrials.gov Identifier:

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Date of document:

30 July 2018

ACT-541468

Insomnia Disorder

Protocol ID-078A301

Multi-center, double-blind, randomized, placebo-controlled, parallel-group, polysomnography study to assess the efficacy and safety of ACT-541468 in adult and elderly subjects with insomnia disorder

Study Phase:	3
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Status and version:	Final Version 4
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Idorsia document number (Doc No.):	D-18.160

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 ORGANIZATIONS 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

ACT-541468

Indication

Insomnia Disorder

Protocol number, study title

ID-078A301

Multi-center, double-blind, randomized, placebo-controlled, parallel-group, polysomnography study to assess the efficacy and safety 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 International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines.

Title	Name	Date	Signature
[redacted]			

INVESTIGATOR SIGNATURE PAGE

Treatment name / number

ACT-541468

Indication

Insomnia Disorder

Protocol number, study title

ID-078A301

Multi-center, double-blind, randomized, placebo-controlled, parallel-group, polysomnography study to assess the efficacy and safety 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.

I am participating in the following sub-study (only for sites in Germany and the USA):

PAtient Preferences StUdy in InSomnia (PAUSe)

Principal Investigator	Country	Site number	Town	Date	Signature

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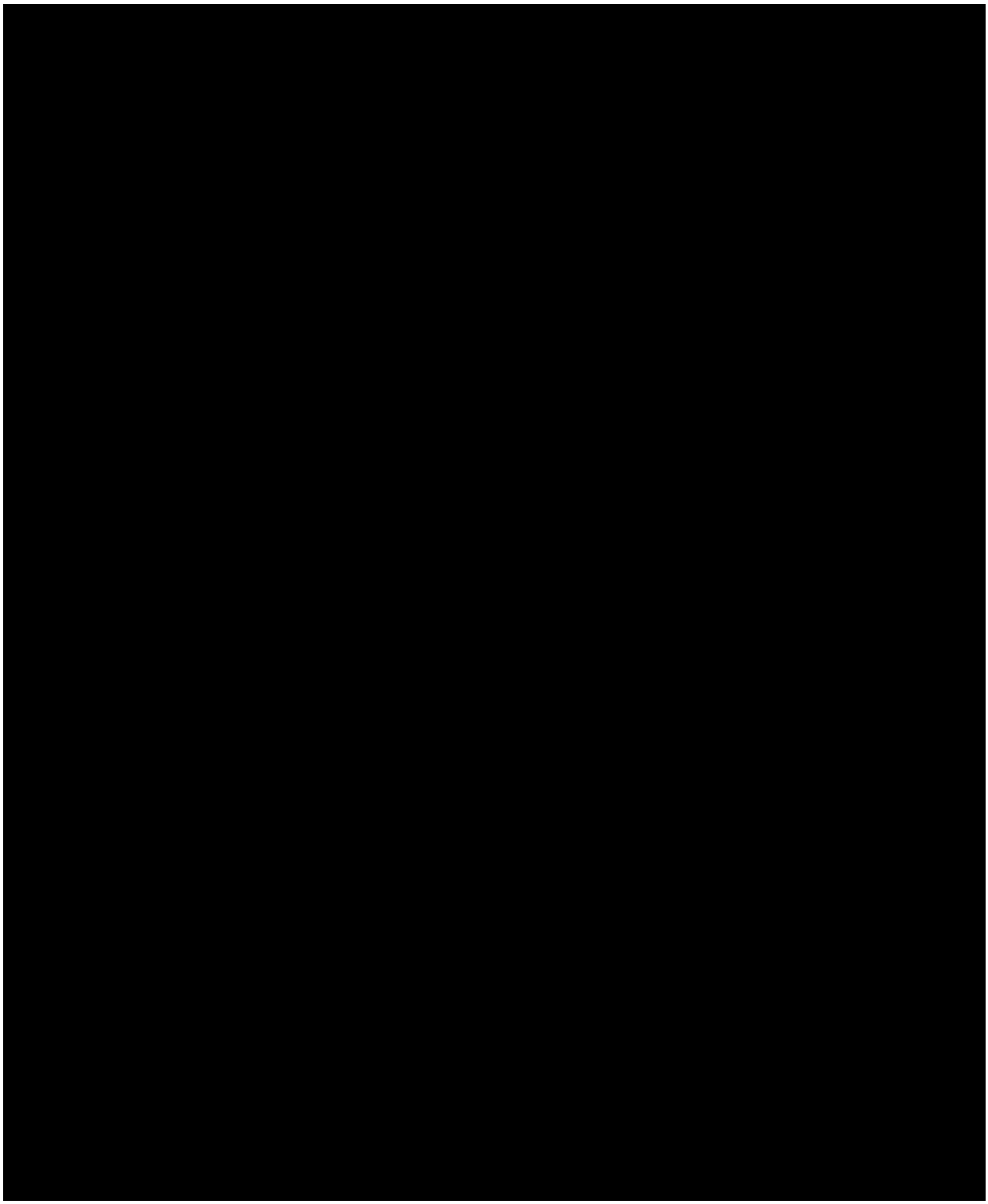
LIST OF ABBREVIATIONS AND ACRONYMS

AE	Adverse event
AESI	Adverse event of special interest
AHI	Apnea/hypopnea index
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AV	Atrioventricular
BMI	Body mass index
BP	Blood pressure
bpm	Beats per minute
BRA	Benefit-risk assessment
BWSQ	Benzodiazepine Withdrawal Symptom Questionnaire
CBT	Cognitive behavioral therapy
CFR	Code of Federal Regulations (US)
CNS	Central nervous system
CR	Controlled-release
CRA	Clinical Research Associate
CRO	Contract Research Organization
CSR	Clinical Study Report
C-SSRS©	Columbia Suicide Severity Rating Scale©
CV%	Coefficient of variation
CYP	Cytochrome P450
DB	Double-blind
DCE	Discrete Choice Experiment
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
E_{max}	Maximum effect
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
GABA	Gamma-aminobutyric acid
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
MAR	Missing at random

MedDRA	Medical Dictionary for Regulatory Activities
MINI©	Mini International Neuropsychiatric Interview©
MMSE©	Mini Mental State Examination©
NOAEL	No-observed-adverse-effect level
PAUSe	PAtient Preferences StUdy in InSomnia
PD	Pharmacodynamic(s)
PGA-S	Patient Global Assessment of Disease Severity
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
PI	Principal Investigator
PK	Pharmacokinetic(s)
PLMAI	Periodic limb movement with arousal index
PPS	Per-Protocol Set
PSG	Polysomnography
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
REM	Rapid eye movement
RSI	Reference Safety Information
RUT	Random utility theory
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard deviation
SDS©	Sheehan Disability Scale©
SIV	Site Initiation Visit
sLSO	Subjective Latency to Sleep Onset

SMAA	Stochastic multicriteria acceptability analysis
SOC	System Organ Class
SpO_2	Blood oxygen saturation level by pulse oximetry
SQ	Sleep quality
sTST	Subjective Total Sleep Time
SUSAR	Suspected unexpected serious adverse reaction
sWASO	Subjective Wake After Sleep Onset
SWS	Slow wave sleep
$t_{½}$	Half-life
TEAE	Treatment-emergent adverse event
TST	Total Sleep Time
ULN	Upper limit of normal
USPI	United States Package Insert
VAS	Visual analog scale(s)
WASO	Wake After Sleep Onset



PROTOCOL SYNOPSIS ID-078A301

TITLE	Multi-center, double-blind, randomized, placebo-controlled, parallel-group, polysomnography study to assess the efficacy and safety of ACT-541468 in adult and elderly subjects with insomnia disorder
OBJECTIVES	**Primary objectives** To evaluate the efficacy of 25 mg and 50 mg ACT-541468 on objective sleep parameters in subjects with insomnia disorder. **Secondary objectives** To evaluate the efficacy of 25 mg and 50 mg ACT-541468 on subjective sleep parameters and next-day functioning in subjects with insomnia disorder. **Safety objectives** To assess the safety and tolerability of ACT-541468 in subjects with insomnia disorder during treatment and upon treatment discontinuation.
DESIGN	Multi-center, double-blind, randomized, placebo-controlled, parallel-group, Phase 3 study.
PHASES	The study comprises the following 3 phases: the screening phase, the treatment phase, and the safety follow-up phase. The screening phase starts with the signature of the informed consent form at Visit 1 and ends at Randomization (Visit 4), provided the subject fulfills all the eligibility criteria. It includes the Screening period and the Run-in period. The screening phase lasts 20 to 31 days. The **Screening period** starts with Visit 1 and ends at Visit 2. During the Screening period, the investigator verifies eligibility criteria and eligible subjects perform a one-night polysomnography (PSG) assessment. The Screening period lasts 7 to 18 days to allow time to perform all required procedures at Visit 1, the PSG assessment and collect the minimum number of eDiary entries (i.e., 7 days) between Visit 1 and Visit 2. The **Run-in period** starts with Visit 2 and ends at Randomization (i.e., Visit 4). At Visit 2 eligible subjects are allocated a single-blinded placebo treatment that is taken daily. During the Run-in period subjects come to the site for Visit 3, which consists of

	2 PSG nights and is performed when the subject has completed the eDiary for at least 7 days and eligibility is confirmed. The Run-in period lasts 13 to 24 days, to allow collection of the minimum number of eDiary entries (i.e., 7 days), perform 2 PSG nights at Visit 3, and receive the eligibility confirmation from the PSG central reader. The **double-blind (DB) treatment phase** lasts 3 months. It starts at Randomization (Visit 4). DB study treatment is taken daily. A safety telephone call is performed at Visit 5 to collect information about adverse events (AEs) and concomitant medications. Sleep parameters of each subject are objectively assessed with 2 consecutive PSG nights at Visit 6 and Visit 8. A safety visit without PSG night will be performed at Visit 7. An eDiary is completed every day during the treatment phase. **End-of-Double-Blind-Treatment (EODBT)** is reached in the second morning of Visit 8. The **safety follow-up phase** starts after EODBT. 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 9. Visit 9 consists of one PSG night on single-blind placebo treatment. Visit 9 is followed by 6 days at home with single-blind placebo treatment. The eDiary is completed every day during the Run-out period. The end of the Run-out period (End-of-Treatment [EOT]) is reached after all visit assessments have been performed at Visit 10. The **Safety follow-up period** starts after EOT and ends 30 days after the last dose of DB study treatment intake for subjects that are not enrolled in the ID-078A303 extension study. Subjects who complete DB study treatment and the Run-out period are eligible to enter the ID-078A303 extension study (if approved by the national health authorities and local Independent Ethics Committees / Institutional Review Boards). For these subjects, the safety follow-up period ends on the date of enrolment into ID-078A303. **End-of-Study (EOS)** for an individual subject is defined as the date of the 30-day follow-up telephone call (Visit 11) or the date of enrolment into the ID-078A303 extension study. If a subject is

	prematurely discontinued from study treatment EOS is performed as planned on Day 115. 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.
PLANNED DURATION	Approximately 18 months from first subject, first visit to last subject, last visit.
SITE(S) / COUNTRY(IES)	The study will be conducted at approximately 75 sites in 10 countries.
SUBJECTS / GROUPS	Approximately 900 subjects will be randomized to either 25 mg or 50 mg ACT-541468, or to placebo, in a 1:1:1 ratio. Treatment allocation will be stratified by age into 2 categories: < 65 and ≥ 65 years. Approximately 40% of subjects will be elderly subjects (≥ 65 years old), of which approximately 5% will be above 75 years old. These percentages will be monitored by the sponsor through the IRT.
INCLUSION CRITERIA	**Criteria assessed at Visit 1:** 1. Signed informed consent prior to any study-mandated procedure. 2. Male or female aged ≥ 18 years. 3. Insomnia disorder according to Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria, as follows: 3.1 The predominant complaint is dissatisfaction with sleep quantity or quality, associated with one (or more) of the following symptoms: • Difficulty initiating sleep. • Difficulty maintaining sleep, characterized by frequent awakenings or problems returning to sleep after awakenings. • Early-morning awakening with inability to return to sleep. 3.2 The sleep disturbance causes clinically significant distress or impairment in social, occupational, educational, academic, behavioral, or other important areas of functioning. 3.3 The sleep difficulty occurs despite adequate opportunity for sleep.

	3.4 The insomnia is not better explained by and does not occur exclusively during the course of another sleep-wake disorder (e.g., narcolepsy, a breathing-related sleep disorder, a circadian rhythm sleep-wake disorder, a parasomnia). 3.5 The insomnia is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication). 3.6 Coexisting mental disorders and medical conditions do not adequately explain the predominant complaint of insomnia. 3.7 Self-reported history of all the following on at least 3 nights per week and for at least 3 months prior to Visit 1: 3.7.1 ≥ 30 min to fall asleep, and 3.7.2 Wake time during sleep ≥ 30 min, and 3.7.3 Subjective Total Sleep Time (sTST) ≤ 6.5 h 4. Insomnia Severity Index© score ≥ 15. 5. Ability to communicate well with the investigator, to understand the study requirements and, as judged by the investigator, to be alert and oriented to person, place, time, and situation. **Criteria assessed at Visit 3** 6. Meeting all the following sleep parameters on at least 3 nights out of 7 nights on the sleep diary completed at home between Visit 2 and Visit 3: 6.1 ≥ 30 min to fall asleep, and 6.2 Wake time during sleep ≥ 30 min, and 6.3 sTST of ≤ 6.5 h 7. Usual bedtime between 21:30 and 00:30 as reported on sleep diary completed between Visit 2 and Visit 3. 8. Regular time in bed between 6 and 9 h as reported on sleep diary completed between Visit 2 and Visit 3. 9. Meeting all the following sleep parameters on the 2 PSG nights at Visit 3: 9.1 Mean Latency to Persistent Sleep (LPS) ≥ 20 min (with neither of the two nights < 15 min), and 9.2 Mean Wake After Sleep Onset (WASO) ≥ 30 min (with neither of the two nights < 20 min), and 9.3 Mean Total Sleep Time (TST) < 420 min

	Criteria assessed at Visit 1, Visit 2, and Visit 4: 10. For women of childbearing potential, the following are required: • Negative serum pregnancy test (Visit 1). • Negative urine pregnancy test (Visit 2, Visit 4). • Agreement to use the contraception scheme as required by the protocol from Screening up to at least 30 days after last DB study treatment intake.
EXCLUSION CRITERIA	**Criteria assessed at Visit 1** 1. Body mass index below 18.5 or above 40.0 kg/m^2. 2. Any lifetime history of sleep-related breathing disorder, including chronic obstructive pulmonary disease and sleep apnea. 3. Cognitive behavioral therapy (CBT) for any indication is allowed only if the CBT started at least 1 month prior to Visit 3 and the subject agrees to continue this CBT throughout the study. 4. Self-reported usual daytime napping ≥ 1 h per day, and ≥ 3 days per week. 5. Acute or unstable psychiatric conditions (including but not restricted to anxiety disorder, major depression, bipolar disorder, schizophrenia, obsessive compulsive disorder, or depression) that are diagnosed by the Mini International Neuropsychiatric Interview© or that require pharmacological treatment for these disorders. N.B.: subjects with a history of major depressive disorder currently without any symptoms and not requiring treatment are eligible. 6. Mini Mental State Examination© score < 25 in subjects ≥ 50 years. 7. Shift work within 2 weeks prior to the screening visit, or planned shift work during the study. 8. Travel across ≥ 3 time zones within 2 weeks prior to the screening visit, or planned travel across ≥ 3 time zones during the study. 9. Unstable medical condition, significant medical disorder or acute illness, ECG, hematology or biochemistry test results within 1 month prior to the screening visit, which, in the opinion of the investigator, could affect the subject's safety or interfere with the study assessments. 10. Treatment with central nervous system-active drugs prohibited by this protocol within 5 half-lives of the respective drug (or

	2 weeks, whichever is longer) prior to Visit 1, including over-the-counter medication and herbal medicines. 11. Diagnosis of alcohol or substance use disorder within 2 years prior to the screening visit or inability to refrain from drinking alcohol for at least 3 consecutive days. 12. Heavy tobacco use (at least one pack of cigarettes a day or inability to refrain from smoking during the night). 13. Caffeine consumption ≥ 600 mg per day or any caffeine consumption after 4 pm. 14. Treatment with another investigational drug within 3 months prior to Visit 1, previous treatment with ACT-541468 or previous randomization in any trial involving ACT-541468. 15. Known hypersensitivity or contraindication to drugs of the same class as the study treatment or to any excipients of the study drug formulation. 16. Not able or willing to stop treatment with moderate or strong cytochrome P450 (CYP)3A4 inhibitors, or treatment with moderate or strong CYP3A4 inducers, within at least 1 week prior to Visit 2. 17. Not able or willing to stop consumption of grapefruit, Seville (bitter) oranges or juices from those fruits within at least 1 week prior to Visit 2. **Criteria assessed at PSG visit between Visit 1 and Visit 2** 18. Periodic limb movement disorder with arousal index (PLMAI) ≥ 15/h (assessed on the 1st PSG night), restless legs syndrome, circadian rhythm disorder, rapid eye movement (REM) behavior disorder, or narcolepsy. 19. Apnea/hypopnea index ≥ 15/h according to American Academy of Sleep Medicine criteria or event associated with blood oxygen saturation level by pulse oximetry (SpO_2) < 80%, as assessed on the 1st PSG night. **Criteria assessed at Visit 1 and Visit 3** 20. Aspartate aminotransferase and/or alanine aminotransferase > 2 × upper limit of normal (ULN) and/or direct bilirubin > 1.5 × ULN. 21. Severe renal impairment: known or defined as estimated creatinine clearance < 30 mL/min/1.73 m^2, according to the 4-variable Modification of Diet in Renal Disease formula.

	22. Hematology or biochemistry test results deviating from the normal range to a clinically relevant extent as per judgment of the investigator. 23. Any of the following conditions related to ECG abnormalities: • A prolonged QT interval corrected with Bazett's formula (QTcB) or QT interval corrected with Fridericia's formula (QTcF) (greater than 450 ms). If QTcB or QTcF is greater than 450 ms on the first ECG, a second ECG recording will be performed after at least 30 min. If QTcB or QTcF is greater than 450 ms on the second ECG, the subject is not eligible. • A history of additional risk factors for torsade de pointes (e.g., heart failure, hypokalemia, family history of long QT syndrome). • ECG with clinically significant atrioventricular (AV) conduction disturbance (e.g., second- or third-degree AV block), sick sinus syndrome, bradycardia (resting pulse < 40 bpm), or accessory bypass tract (e.g., Wolff-Parkinson-White). **Criterion assessed at Visit 1, Visit 2, Visit 3 and Visit 4** 24. Any of the following conditions related to suicidality: • Any suicidal ideation with intent, with or without a plan, at screening, i.e., answering "Yes" to questions 4 or 5 on the suicidal ideation section of the lifetime (Visit 1) and visit (Visit 2, Visit 3, Visit 4) version of the Columbia Suicide Severity Rating Scale© (C-SSRS©). • History of suicide attempt on the suicidal behavioral section of the lifetime version of the C-SSRS© (Visit 1). **Criteria assessed at Visit 1, PSG visit between Visit 1 and Visit 2, Visit 2, Visit 3 and Visit 4** 25. For female subjects: pregnant, lactating or planning to become pregnant during projected duration of the study. 26. Positive urine drug test (for benzodiazepines, barbiturates, cannabinoids, opiates, amphetamines, phencyclidine or cocaine) or presence of alcohol in exhaled breath as detected by breathalyzer test.

STUDY TREATMENTS	**Investigational treatment** ACT-541468 tablets at strengths of 25 mg and 50 mg will be administered orally, once daily in the evening during the DB treatment period. **Placebo** ACT-541468-matching placebo will be administered orally, once daily in the evening during the single-blind run-in period, the DB treatment period and the single-blind run-out period.
ENDPOINTS	**Primary efficacy endpoints** The primary efficacy endpoints of this study are defined as: • the change from baseline to Month 1 in WASO (sleep maintenance) • the change from baseline to Month 3 in WASO • the change from baseline to Month 1 in LPS (sleep onset) • the change from baseline to Month 3 in LPS Baseline is defined as mean of the 2 PSG nights at Visit 3. Month 1 and Month 3 are defined as the mean of the 2 PSG nights at Visit 6 and Visit 8, respectively. LPS (min) is the time from start of recording to the beginning of the first continuous 20 epochs (i.e., 10 min) scored as non-awake, i.e., epochs scored as either sleep stage 1 (S1), sleep stage 2 (S2), sleep stage 3 (slow wave sleep) or REM, as determined by PSG. WASO is the time (min) spent awake after onset of persistent sleep until lights on, as determined by PSG. **Secondary efficacy endpoints** The secondary efficacy endpoints of this study are defined as: • the change from baseline[a] to Month 1[b] in sTST. • the change from baseline[a] to Month 3[c] in sTST. • the change from baseline[a] to Month 1[b] in Insomnia Daytime Symptoms and Impacts Questionnaire (IDSIQ) sleepiness domain score. • the change from baseline[a] to Month 3[c] in IDSIQ sleepiness domain score.

	[a] Baseline is the mean value based on the screening sleep diary / IDSIQ entries performed at home in the 7 days immediately preceding the first PSG at Visit 3. [b] 'Month 1' is the mean value based on the sleep diary / IDSIQ entries performed at home in the 7 days immediately preceding the first PSG at Visit 6. [c] 'Month 3' is the mean value based on the sleep diary / IDSIQ entries performed at home in the 7 days immediately preceding the first PSG at Visit 8. **Safety endpoints** In addition to the standardized collection of AEs, safety data specific to insomnia and its treatment will be assessed as follows: • Withdrawal effects (physical dependence) upon treatment discontinuation will be assessed based on the changes from last assessment on DB treatment (Visit 8, 2nd morning) to run-out period in the Benzodiazepine Withdrawal Symptom Questionnaire (BWSQ) total score (Visit 9 and Visit 10), the occurrence of relevant AEs and marked ECG abnormalities. • Rebound insomnia will be assessed based on objective sleep parameters (WASO, LPS, and TST) at Visit 9 as compared to Visit 3. It will also be assessed using subjective sleep parameters (subjective WASO [sWASO], subjective Latency to Sleep Onset [sLSO], and sTST) from run-out period as compared to baseline. • Next-day residual effects will be assessed based on changes from baseline (Visit 3) to Month 1 and Month 3 in: – Coding sub-test© – Sheehan Disability Scale© (SDS©) – Scores on the visual analog scale (VAS; mm) • Serious adverse events up to 30 days after DB study treatment discontinuation or until enrollment into the extension study. • Treatment-emergent AEs (TEAEs) up to 30 days after DB study treatment discontinuation or until enrollment into the extension study. • AEs leading to premature discontinuation of the DB study treatment. • AEs of special interest (AESIs) after adjudication by an 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 (Visit 3) to Month 1 (Visit 6) and Month 3 (Visit 8) in vital signs (mean of the 2 PSG nights in systolic and diastolic blood pressure [BP] and pulse rate). • Change from baseline (Visit 1) to Month 3 (Visit 8) in body weight. • Marked ECG abnormalities on DB study treatment. • Change from baseline (Visit 3) to Month 3 (Visit 8) and the end of run-out (Visit 10) in ECG variables. • Marked laboratory abnormalities on DB study treatment. • Change from baseline (Visit 3) to Month 1 (Visit 6) and Month 3 (Visit 8) in laboratory variables. • Occurrence of suicidal ideation and/or behavior on DB study treatment based on C-SSRS©.
ASSESSMENTS	Refer to the schedule of assessments in Table 1.
STATISTICAL METHODOLOGY	**Analysis of the primary and secondary efficacy endpoints** The Type I error rate will be controlled for the testing of multiple null hypotheses associated with the two primary endpoints (LPS and WASO) and two other endpoints (sTST and IDSIQ) assessed at 1 and 3 months of treatment, and the two dose levels included in this study, i.e., 25 mg and 50 mg. The eight statistical null hypotheses associated with the primary efficacy endpoints are: <u>Sleep maintenance:</u> • $H1_{WASO}$: Higher Dose – Placebo = 0 for WASO at Month 1 • $H2_{WASO}$: Higher Dose – Placebo = 0 for WASO at Month 3 • $H3_{WASO}$: Lower Dose – Placebo = 0 for WASO at Month 1 • $H4_{WASO}$: Lower Dose – Placebo = 0 for WASO at Month 3 <u>Sleep onset:</u> • $H1_{LPS}$: Higher Dose – Placebo = 0 for LPS at Month 1 • $H2_{LPS}$: Higher Dose – Placebo = 0 for LPS at Month 3

- $H3_{LPS}$: Lower Dose – Placebo = 0 for LPS at Month 1
- $H4_{LPS}$: Lower Dose – Placebo = 0 for LPS at Month 3

The eight statistical null hypotheses associated with the secondary efficacy endpoints are:

Sleep quantity:

- $H1_{sTST}$: Higher Dose – Placebo = 0 for sTST at Month 1
- $H2_{sTST}$: Higher Dose – Placebo = 0 for sTST at Month 3
- $H3_{sTST}$: Lower Dose – Placebo = 0 for sTST at Month 1
- $H4_{sTST}$: Lower Dose – Placebo = 0 for sTST at Month 3

Next-day performance:

- $H1_{IDSIQ}$: Higher Dose – Placebo = 0 for IDSIQ sleepiness domain score at Month 1
- $H2_{IDSIQ}$: Higher Dose – Placebo = 0 for IDSIQ sleepiness domain score at Month 3
- $H3_{IDSIQ}$: Lower Dose – Placebo = 0 for IDSIQ sleepiness domain score at Month 1
- $H4_{IDSIQ}$: Lower Dose – Placebo = 0 for IDSIQ sleepiness domain score at Month 3

where 'Higher Dose', 'Lower Dose', and 'Placebo' represent the mean change from baseline for the given endpoint (WASO, LPS, sTST or IDSIQ sleepiness domain score) and time point (Month 1 or Month 3) for the 50 mg, 25 mg, and placebo treatment group, respectively.

Each null hypothesis will be tested against the alternative hypothesis: that ACT-541468 improves WASO/LPS/sTST/ IDSIQ sleepiness domain score at the given dose (25 or 50 mg) and time point (Month 1 or Month 3) compared to placebo.

The order of testing and the alpha level applied to each null hypothesis will be based on the Bonferroni-based gatekeeping procedure [Bretz 2009], which will control the study-wise Type I error at a two-sided 5% significance level. To account for the concurrent evaluation (multiple comparison) of two distinct endpoint categories (i.e., sleep maintenance and sleep onset), a Bonferroni correction is applied. Both endpoint categories will be tested at half

	of the two-sided 5% significance level. This supports the sponsor's intention to make a superiority claim versus placebo for efficacy in either sleep maintenance and/or sleep onset. The remaining hypotheses will be tested following the gatekeeping strategy moving from Month 1 to Month 3 for higher dose ACT-541468 vs placebo and then from Month 1 to Month 3 for lower dose ACT-541468 vs placebo. The pre-specified proportion of alpha that will be distributed once a given null hypothesis (node) is rejected is shown on the arrow in the directed graph. If a certain null hypothesis cannot be rejected, the alpha level used for that test is absorbed at that node and not distributed further. The main analysis 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 WASO, LPS, sTST, and IDSIQ 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. **Analysis of the safety endpoints** *Adverse events:* The number (%) of subjects experiencing a TEAE (including serious adverse events, AESIs after adjudication by the ISB, and AEs leading to premature discontinuation of the DB study treatment) will be summarized by System Organ Class and/or Preferred Term, and maximum intensity. *Laboratory data:* Observed values and changes from baseline to Month 1 and Month 3 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 weight:* Observed values and changes from baseline to Month 1 and Month 3 in vital signs (mean of the two PSG nights in systolic and diastolic BP and pulse rate) and observed values and changes from baseline to Month 3 in body weight will be summarized. *Electrocardiograms:* Observed values and changes from baseline to Month 3 for each ECG parameter (QTcB, QTcF, heart rate, PR, QRS)

	will be summarized. The number (%) of subjects with a marked ECG abnormality during DB study treatment will be tabulated. *Withdrawal symptoms:* The BWSQ total score will be summarized using descriptive statistics for the observed values and changes from the last assessment on DB treatment (Visit 8, 2nd morning) to the beginning and the end of the treatment withdrawal period (in the morning at Visit 9 and at Visit 10, respectively). The number (%) of subjects having, separately, an AE and a marked ECG abnormality during the treatment withdrawal period will be tabulated. *Insomnia rebound effect:* The changes from baseline to the treatment withdrawal period (Visit 9, run-out) in objective sleep parameters (WASO, LPS, and TST) will be summarized using descriptive statistics. The changes from baseline (mean value based on the screening sleep diary entries performed at home in the 7 days immediately preceding the first PSG at Visit 3) to the treatment withdrawal period (after PSG night at Visit 9) in subjective sleep parameters (sWASO, sLSO, and sTST) will be summarized using descriptive statistics. *Next-day residual effects:* Observed values and changes from baseline to Month 1 and Month 3 in Coding sub-test©, SDS©, and VAS scores (mm) assessing morning sleepiness, daytime alertness, and daytime ability to function, 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 will be tabulated. Shifts from baseline showing any changes in suicidal ideation and suicidal behavior during DB treatment will also be provided.
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. 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.
SUB-STUDY	A sub-study will be performed to collect patient preferences data. The Discrete Choice Experiment methodology aims to collect preferences for selected treatment outcomes in a subgroup of at least 360 subjects in USA and Germany that are part of the approximately 900 subjects enrolled in the ID-078A301 study, using the questionnaire for the PAtient Preferences StUdy in InSomnia (PAUSe) developed by Idorsia.
STUDY EXTENSION	Subjects who completed the study until EOT will have the possibility to participate in the extension study ID-078A303. The 9-month ID-078A303 study will be available at each site and subjects will be treated for up to 12 months overall (i.e., including the treatment period of the confirmatory trial).

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) it 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]. Insomnia symptoms (difficulties initiating sleep, early-morning awakenings, and dissatisfaction with sleep) increase with age. Factors associated with aging and not with age *per se*, such as depressed mood, respiratory symptoms, poor perceived health and physical disability are associated with the decrease in ability to sleep [Ohayon 2001].

Insomnia disorder results in difficulty falling asleep or difficulty maintaining sleep, characterized by multiple or long awakenings during the sleep period, or early-morning awakenings. Difficulty maintaining sleep is the most common problem among patients with insomnia, occurring in approximately two-thirds of them [Neubauer 2014]. Studies have shown that the most common symptoms are combined difficulties to both fall and to stay asleep [Hohagen 1994]. Elderly patients are more likely to suffer from chronic insomnia characterized by difficulty maintaining sleep, rather than difficulty initiating sleep [McCall 2004].

Insomnia is associated with impairment in cognitive functioning, daytime fatigue, increased accident risk, and difficulties in interpersonal relationships [Balter 1991, Ancoli-Israel 1999, Rosenthal 1993, Zammit 1999, Fortier-Brochu 2014]. Insomnia

increases utilization of medical care [Simon 1997, Léger 2002, McCall 2004], has been correlated with chronic health issues and perceptions of poor health [Balter 1991, Ancoli-Israel 1999, Rosenthal 1993, Zammit 1999, Fortier-Brochu 2014], and in elderly subjects may also precipitate falls [McCall 2004]. Numerous studies have shown an association between insomnia and psychiatric disorders, specifically depression, anxiety, and other significant mental health conditions [Ford 1989, Benca 2004].

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, the orexin receptor antagonist suvorexant, and low-dose doxepin.

Benzodiazepines are a class of medications that bind to multiple gamma-aminobutyric acid (GABA) type A receptor subtypes [Lieberman 2007]. Drugs in this class, which includes flurazepam, temazepam, trialozam, estazolam, and quazepam, were previously commonly prescribed for insomnia. While the efficacy of these medications has been well documented, their usefulness is limited by adverse effects such as daytime sedation (e.g., morning or next-day hangover), cognitive impairment (including anterograde amnesia), motor dyscoordination, abuse liability, and dependence [Holbrook 2000, Buscemi 2007]. Benzodiazepines also alter sleep architecture: they prolong stage 2 sleep and may slightly reduce the relative amount of rapid eye movement (REM) sleep [Treat Guidel Med Lett 2009]. Their use has been associated with tolerance development and rebound insomnia upon withdrawal of medication [Kales 1978, Petursson 1981].

Non-benzodiazepine benzodiazepine receptor agonists have a more targeted action on one or more GABA type A receptor subtypes, but the availability of these treatments highly varies across regions. Zolpidem, zolpidem controlled-release (CR) and zaleplon show affinity for the alpha-1 receptor subtype, while eszopiclone shows affinity for the alpha-2 and -3 receptor subtypes [Nutt 2006]. All of these drugs reduce latency to sleep onset, but zolpidem CR and eszopiclone have also been shown to reduce Wake After Sleep Onset (WASO), reflecting an improvement in sleep maintenance [Ambien® USPI, Lunesta® USPI]. Although they have less impact on sleep architecture, possibly by virtue of their receptor selectivity, the drugs in this group have similar adverse effects as the benzodiazepines. In 2007 the US Food and Drug Administration (FDA) requested that all

manufacturers of hypnotic drug products strengthen their product labeling to include stronger language related to potential risks. These risks include severe allergic reactions (i.e., anaphylaxis) and complex sleep-related behaviors, which may include sleep-driving [FDA 2007].

Newer hypnotics that do not act at the GABA receptor have been developed. The melatonin receptor agonist ramelteon is approved for insomnia in the US and in Japan, but not in Europe. Ramelteon reduces sleep latency and increases Total Sleep Time (TST), but has no effect on WASO [Kuriyama 2014], making it an inappropriate treatment for people with sleep maintenance problems [Simpson 2008]. Ramelteon is devoid of next-day residual effects, withdrawal or rebound insomnia and does not appear to be associated with abuse liability.

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 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.

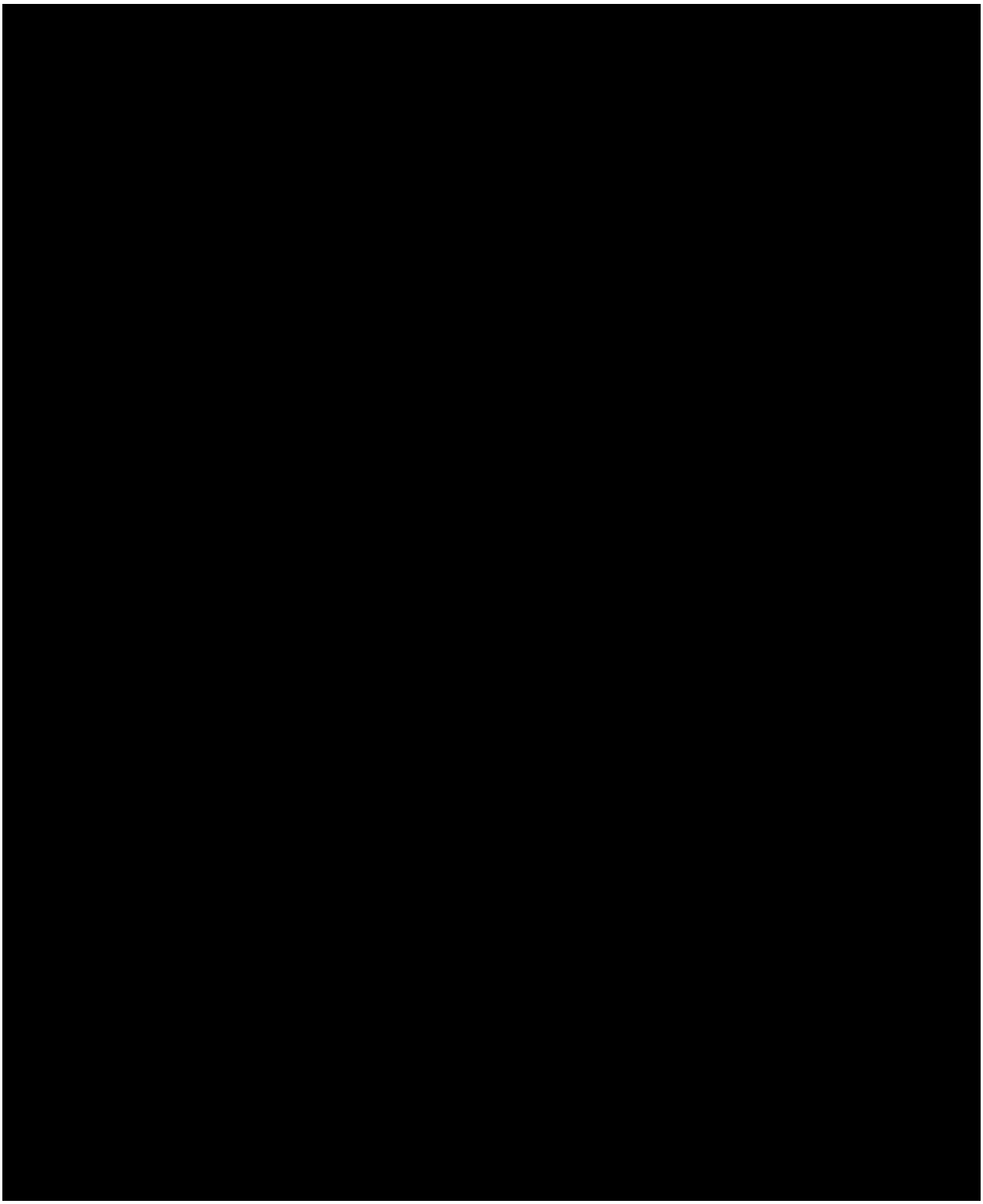
1.2 Study treatment: ACT-541468

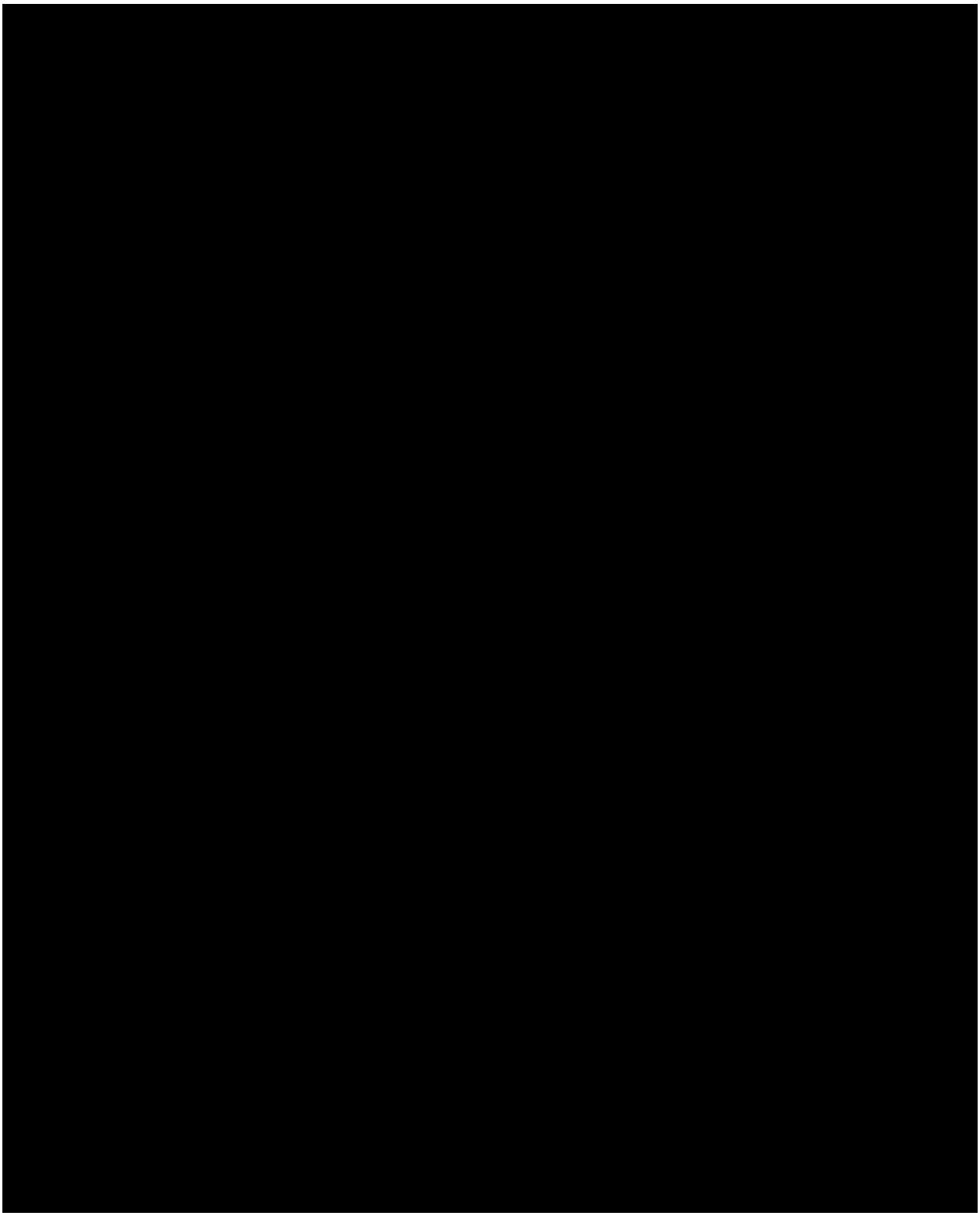
1.2.1 The orexin system

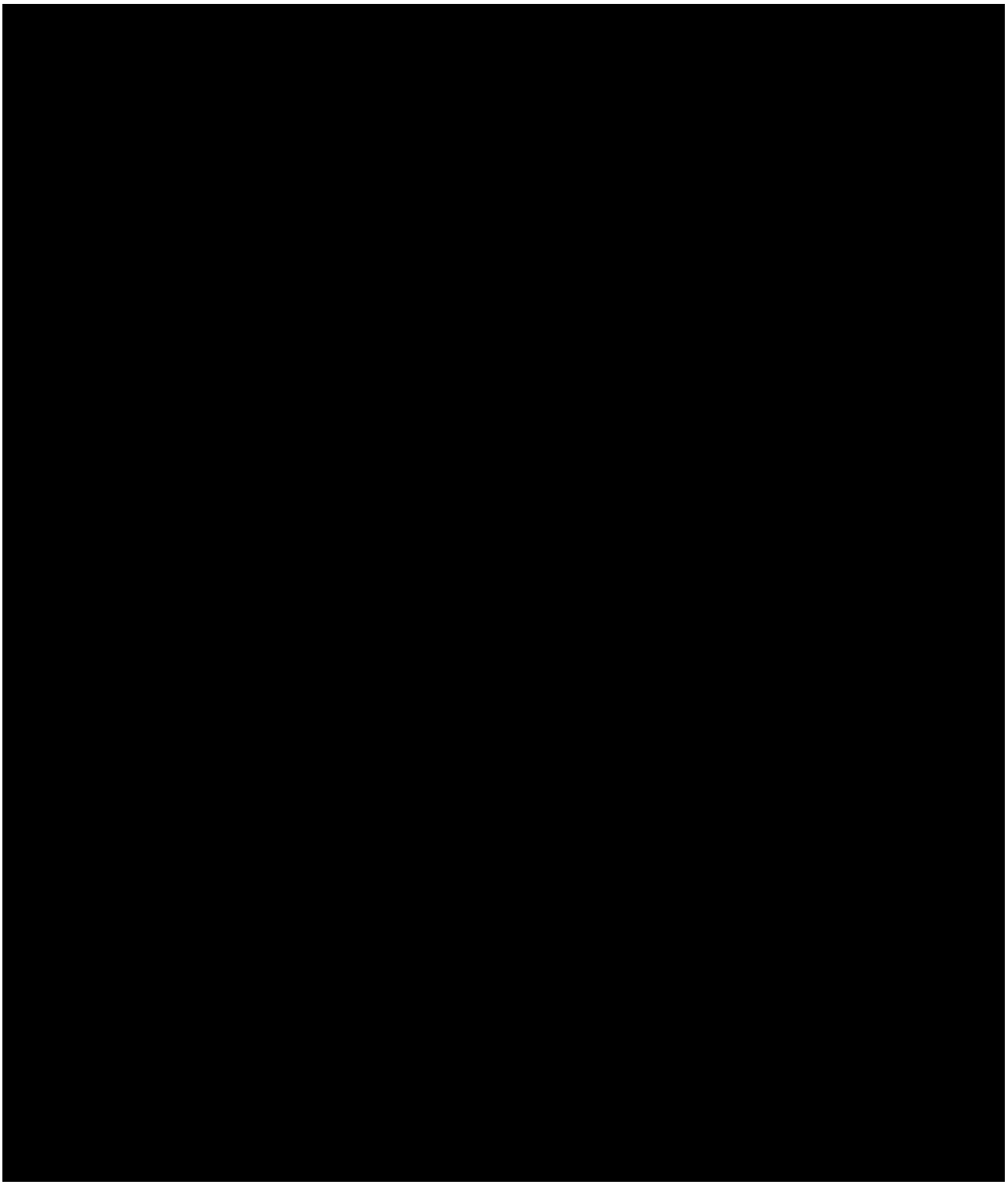
The orexin system is involved in the regulation of sleep and arousal by the central nervous system (CNS) and is currently being targeted in the development of new therapies for sleep disorders.

The neuropeptides orexin-A and orexin-B are synthesized in the lateral hypothalamic areas [de Lecea 1998] and activate the orexin-1 and orexin-2 receptors [Kilduff 2000]. Nerve fibers from orexin neurons make projections to the basal forebrain, corticolimbic structures, and brainstem, particularly to those regions related to waking and regulation of sleep [Hagan 1999, Sakurai 2007]. Infusing exogenous orexins into cerebral ventricles in rats leads to enhanced behavioral activity, arousal, delayed onset of sleep, and maintenance of cortical activation [Hagan 1999, Samson 2010]. Orexin-producing neurons are active during wakefulness and fall quiet during sleep [Sakurai 2007]. Orexin-A levels in the cerebrospinal fluid of several species fluctuate according to circadian rhythms, being highest during active wake periods [Zeitzer 2003, Desarnaud 2004].

The absence of orexins is implicated in the genesis of narcolepsy, due to findings of low cerebral spinal fluid orexin levels in most patients with unequivocal narcolepsy with cataplexy [Mignot 2002] and near-complete destruction of orexin neurons in post-mortem brains of patients with narcolepsy-cataplexy [Thannickal 2000], coupled with the observation of behavioral phenotypes consistent with narcolepsy in multiple animal models of orexin deficiency or dysfunction [Lin 1999].







1.3 Purpose and rationale of the study

1.3.1 Purpose of the study

The main purpose of this Phase 3 study is to confirm that at least one dose of ACT-541468 is well tolerated and efficacious in promoting sleep onset and/or sleep maintenance 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 25 and 50 mg of ACT-541468 planned for this study were both investigated in Phase 2 studies, which demonstrated statistically significant reductions in

mean WASO and in mean LPS at Days 1&2 as compared to baseline, in both adult and elderly subjects. These two doses were well tolerated and no significant safety findings emerged. This Phase 3 study aims to confirm the results obtained in Phase 2 on the selected doses and to assess additional long-term efficacy and safety benefits in patients.

1.4 Summary of known and potential risks and benefits

1.4.1 ACT-541468

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. According to the safety assessments from Phase 2 studies, the occurrence of next-day residual effects, withdrawal symptoms, and rebound insomnia is assessed as unlikely.

The most frequently observed TEAEs reported in the conducted Phase 2 studies involving 418 subjects, out of which 297 were exposed to ACT-541468, include headache, somnolence, fatigue, and dizziness. Isolated cases of EDS were observed.

Considering the mode of action of DORAs and the common adverse reactions associated with the use of sleep medications, AESIs include:

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

The results of the AC-078-103 study have shown that ACT-541468 metabolism is mainly dependent on CYP3A4; co-administration of ACT-541468 and strong or moderate CYP3A4 inhibitors or inducers must be avoided.

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]

[redacted]

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

To evaluate next-day residual effects, the subjects will undergo neurological examination based on the evaluation of gait, the Tandem Walking Test, and the Romberg Test on each of the mornings following drug administration in sleep centers. Next-day residual effects will also be evaluated with the Coding sub-test©, the SDS©, and a visual analog scale (VAS) assessing sleepiness.

Suicidality will be assessed using the C-SSRS© at Visit 1, Visit 2, Visit 3, Visit 4, Visit 6, Visit 7, Visit 8, Visit 9 and Visit 10.

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

Two committees will be set up for the study. An Independent Data Monitoring Committee (IDMC) charter and an ISB charter will provide a well-defined and structured process for each committee to operate effectively.

- An ISB will review and adjudicate in a blinded manner all AESIs, i.e., narcolepsy-like symptoms (EDS, cataplexy and complex sleep behavior events including hallucinations/sleep paralysis), or suicide/self-injury.
- An IDMC will monitor efficacy and safety data in an unblinded manner. This committee will make appropriate recommendations to ensure safety of the subjects.

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 to 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 expected risk-benefit assessment supports the conduct of this 12-week treatment study in adult and elderly subjects with insomnia disorder.

2 STUDY OBJECTIVES

The main objectives of this study are to assess efficacy and safety of ACT-541468 in subjects with insomnia disorder. Efficacy will be evaluated on sleep onset and sleep maintenance.

2.1 Primary objective

To evaluate the efficacy of 25 mg and 50 mg ACT-541468 on objective sleep parameters in subjects with insomnia disorder.

2.2 Secondary objectives

To evaluate the efficacy of 25 mg and 50 mg ACT-541468 on subjective sleep parameters and next-day functioning in subjects with insomnia disorder.

2.3 Safety objectives

To assess the safety and tolerability of ACT-541468 in subjects with insomnia disorder during treatment and upon treatment discontinuation.

3 OVERALL STUDY DESIGN AND PLAN

3.1 Study design

This is a 3-month, multi-center, double-blind, randomized, placebo-controlled, parallel-group, Phase 3 study to assess the efficacy and safety of two doses (25 mg and 50 mg) of ACT-541468 in subjects with insomnia disorder.

Approximately 900 subjects will be randomized to either 25 mg or 50 mg of ACT-541468, or to placebo, in a 1:1:1 ratio. Treatment allocation will be stratified by age into 2 categories: < 65 and ≥ 65 years. Approximately 40% of subjects will be elderly subjects (≥ 65 years old), of which approximately 5% will be above 75 years old. These percentages will be monitored by the sponsor through the Interactive Response Technology (IRT) system.

The study will be conducted at approximately 75 sites in 10 countries.

In addition, a sub-study to collect data on the subject's preferences will be performed, aiming to enroll at least 360 subjects both from the USA and Germany who are part of the approximately 900 subjects enrolled in the ID-078A301 study. That means that the study recruitment will end when approximately 900 subjects have been randomized in the ID-078A301 study.

3.1.1 Study periods

The study comprises the following 3 phases: the screening phase, the treatment phase, and the safety follow-up phase [see Figure 1].

3.1.1.1 Screening phase

The screening phase starts with the signature of the informed consent form (ICF) at Visit 1 and ends at Randomization at Visit 4, provided the subject fulfills all eligibility criteria. It includes the Screening period and the Run-in period. The screening phase lasts 20 to 31 days.

The **Screening period** starts with Visit 1 and ends with Visit 2. During the screening period, the investigator verifies the eligibility criteria and eligible subjects perform a one-night PSG assessment. The Screening period lasts 7 to 18 days to allow time to perform

all required procedures at Visit 1, the PSG assessment and collect the minimum number of eDiary entries (i.e., 7 days) between Visit 1 and Visit 2.

The **Run-in period** starts with Visit 2 and ends at Randomization (i.e., Visit 4). At Visit 2 eligible subjects are allocated a single-blinded placebo treatment that is taken daily. During the Run-in period subjects come to the site for Visit 3, which consists of 2 PSG nights and is performed when the subject has completed the eDiary for at least 7 days and eligibility is confirmed. The Run-in period lasts 13 to 24 days, to allow collection of the minimum number of eDiary entries (i.e., 7 days), perform 2 PSG nights at Visit 3, and receive the eligibility confirmation from the PSG central reader.

3.1.1.2 Treatment phase

The **DB treatment phase** lasts 3 months. It starts at Randomization (Visit 4). DB study treatment is taken daily. A safety telephone call is performed at Visit 5 to collect information about AEs and concomitant medications. Sleep parameters of each subject are objectively assessed with 2 consecutive PSG nights at Visit 6 and Visit 8. A safety visit without PSG night will be performed at Visit 7. An eDiary is completed every day during the treatment phase.

End-of-Double-Blind-Treatment (EODBT) is reached in the second morning of Visit 8.

3.1.1.3 Safety follow-up phase

The **safety follow-up phase** starts after EODBT. 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 9. Visit 9 consists of one PSG night on single-blind placebo treatment. Visit 9 is followed by 6 days at home with single-blind placebo treatment. The eDiary is completed every day during the Run-out period. The end of the Run-out period (End-of-Treatment [EOT]) is reached after all visit assessments have been performed at Visit 10.

The **Safety follow-up period** starts after EOT and ends 30 days after last dose of DB study treatment intake for subjects that are not enrolled in the ID-078A303 extension study.

Subjects who complete DB study treatment and the Run-out period are eligible to enter the ID-078A303 extension study (if approved by the national health authorities and local Independent Ethics Committees / Institutional Review Boards [IECs/IRBs]). For these subjects, the Safety follow-up period ends at the date of enrolment into ID-078A303.

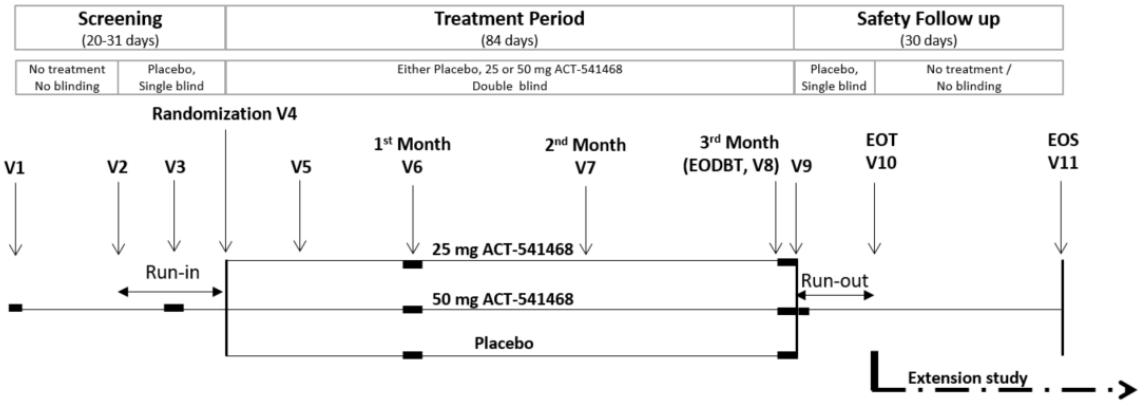
End-of-Study (EOS) for an individual subject is defined as the date of the 30-day follow-up telephone call (Visit 11, Day 115) or the date of enrollment into the ID-078A303 extension study. If a subject is prematurely discontinued from study treatment, EOS is performed as planned on Day 115. If a subject 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 are performed according to the table of assessments [Table 1] and are described in Section 7.

The overall study design is depicted in [Figure 1].

Figure 1 Study design



V = Visit; ▬ = polysomnography nights; EODBT = End-of-Double-Blind-Treatment; EOS = End-of-Study; EOT = End-of-Treatment.

3.1.2 Study duration

The study starts with the signature of the ICF at Visit 1 for the first subject enrolled and ends with the EOS of the last subject. Anticipated total study time is approximately 18 months.

Each subject will be treated for approximately 3 months. For an individual subject who does not decide to continue in the extension study, the study is completed with the EOS visit (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 5 months.

Subjects who completed the study until EOT are eligible to participate in the extension study ID-078A303. After the completion of the Run-out period, the 9-month ID-078A303 extension study will be available at each site, depending on health authority / IEC / IRB approval, and subjects will be treated for up to 12 months overall (i.e., including the treatment period of the confirmatory trial). For the subjects who decide to participate in the extension study, ID-078A301 is completed with the enrollment into ID-078A303.

3.1.3 Sub-study – Patient Preferences

A sub-study will be performed to collect patient preferences data.

The Discrete Choice Experiment (DCE) methodology aims to collect preferences for selected treatment outcomes in a subgroup of at least 360 subjects in USA and Germany using the questionnaire for the PAtient Preferences StUdy in InSomnia (PAUSe) developed by Idorsia.

The questionnaire will present subjects with the following treatment outcomes:

- Time to fall asleep
- Total time asleep
- Next day impairment
- Dizziness/grogginess during the daytime
- Abnormal thinking and behavioral changes
- Falls in the night
- Dependence

The design of the DCE questionnaire was carried out in steps 1–3 below:

1. Qualitative pilot (n = 24), where a mobile ethnography platform was used over a period of 10 days to collect patient experiences with insomnia in interactive sessions. This was followed by face-to-face interviews with patients to further discuss themes that emerged during the 10 days of interactive sessions (completed).
2. Qualitative pilot (n = 24), where face-to-face interviews were conducted to ensure that the DCE outcomes and levels are associated with patients' experiences with (and expectations for) insomnia, and that the proposed survey accurately describes these outcomes in an easily understandable manner (completed).
3. Quantitative pilot (n = 200), where an online survey was conducted to elicit preferences from patients, using the PAUSe questionnaire. The data from the quantitative pilot will be used to update the priors of the Bayesian model and finalize the design of the sub-study.

This sub-study has the following objectives: 1) To describe the stated preferences of insomnia disorder subjects within a clinical trial by applying the DCE technique; 2) To describe the impact of treatment on the preferences of insomnia subjects; 3) To describe the relationship between demographic, disease characteristics, previous medical history and elicited preferences among insomnia subjects.

In addition, the results of the sub-study may contribute to the construction of a patient-oriented benefit-risk assessment model.

3.2 Study design rationale

3.2.1 Core study

This is a multi-center, double-blind, randomized, placebo-controlled, parallel-group study.

In accordance with the European Medicines Agency (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 study includes a placebo as a comparator to support the evaluation of the efficacy of each dose of ACT-541468. Moreover, it is an acceptable approach for a non-life-threatening condition.

A parallel-group design is a well-established study design to assess efficacy and safety in medical conditions, recommended by health authorities [EMA 2011, FDA 1977].

The subjects will receive either a 50 or 25 mg daily dose of ACT-541468, or placebo DB study treatment. The doses to be tested for this study are based on a comprehensive set of data from Phase 1 and Phase 2 studies. A lower dose (10 mg), identified as the minimum effective dose in Phase 2, will be tested along with the 25 mg dose in another separate Phase 3 study (i.e., ID-078A302). All three doses selected for this program have a favorable benefit-risk profile based on data collected so far during Phase 1 and Phase 2 studies in adults and elderly subjects. This will allow appropriate investigation of the sustained effect of ACT-541468 on sleep parameters and next-day performance as well as an optimized characterization of the safety profile of ACT-541468 over a 3-month period, allowing full characterization of the benefit/risk ratio.

The goal of the placebo run-in period is to increase the proportion of subjects in the clinical trial who will benefit due to taking active treatment, partly by reducing the placebo effect that will occur during the DB phase of the study and also aims to ensure sufficient stability of the subjects' insomnia disorder and may reduce the impact of regression toward the mean.

A run-out of 7 days is appropriate to assess withdrawal symptoms as it covers more than 5 half-lives of ACT-541468. The duration of the run-out period is also compliant with the FDA guidance [FDA 1977], stating that a minimum of 3 nights of placebo withdrawal is necessary to assess withdrawal effects. To assess withdrawal symptoms, AEs and ECG abnormalities will be collected during the 7-day run-out period and subjects will complete the Benzodiazapine Withdrawal Symptom Questionnaire (BWSQ) at Visit 9 and Visit 10.

One PSG night is planned after the first day of treatment discontinuation and the sleep diary completed in the 3 days following treatment discontinuation will allow assessment of rebound insomnia on objective and subjective parameters, respectively. Thus, this 7-day run-out period allows to capture long-term withdrawal effects, as well as shorter-term potential rebound symptoms.

3.2.2 Patient preferences sub-study

Measuring patient preferences as an input to healthcare decisions has its foundations in two fields related to behavioral decision making, namely 'decision theory' and 'decision analysis'. Research by Pauker et al. demonstrated that it was feasible to use decision analysis to understand individual treatment choices which were complicated by multiple uncertainties and personal values [Pauker 1981]. Increased understanding of individual values and preferences is critical for a number of reasons. Firstly, it enables the development of patient-specific recommendations and reliable decision aids, which are helpful both for patients and for doctors in advising patients and their carers or families. Secondly, understanding of patients' preferences is the basis for shared decision-making, which in turn encourages patient compliance and health outcomes [Bowling 2001]. Lastly, understanding of preferences for health outcomes allows the design of transparent health policies, and informs resource allocation in healthcare, as these preferences can inform the judgment of cost-effectiveness of different treatments, for different patients [Coyle 2001]. DCEs are a form of stated preference method used by economists to explore how people make trade-offs between an intervention's outcomes. They involve participants responding to a number of survey questions, in which they choose between alternative interventions, each described by a level of performance against the outcomes that influence choices. DCE has its microeconomic foundation in random utility theory (RUT), assuming that products can be valued in terms of their constituent outcomes and that respondents act in a utility maximizing manner, making choices contingent upon the outcome levels described in the exercise [Clark 2014, Tervonen 2017]. Consequently, the choice data can be analyzed using econometric methods compatible with RUT, which estimate how participants' utility is influenced by changes in intervention outcomes. DCEs are frequently used in healthcare to address a wide range of health policy-related concerns, including identifying the trade-offs patients make when choosing between treatments, which can in turn be used to determine the probability that patients would prefer one treatment or another [Bridges 2011, Clark 2014].

3.3 Study committees

An IDMC has 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, thus ensuring that the study is being conducted to the highest scientific and ethical standards. The IDMC will be fully operational prior to enrollment of the first subject into the study. The composition and operation of the IDMC is described in the IDMC charter.

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.

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 Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5). For more details on inclusion and exclusion criteria, see Sections 4.3 and 4.4.

Insufficient sleep quantity is defined in this study by self-reported history of ≥ 30 min to fall asleep, of wake time during sleep ≥ 30 min and of subjective TST (sTST) ≤ 6.5 h during the night. Those 3 self-reported parameters must be present on at least 3 nights per week for at least 3 months prior to the screening visit and on the sleep diary sleep data collected during the period between Visit 2 and Visit 3. They will also be validated by objective PSG-based criteria collected from the Visit 3 PSG nights spent in a sleep laboratory during the run-in. Poor Sleep Quality (SQ) is defined as an Insomnia Severity Index© (ISI©) score ≥ 15 at screening.

4.2 Rationale for the selection of the study population

In this study, adult (18–64 years) and elderly (≥ 65 years) subjects with insomnia as defined by DSM-5 will be included [see definition in Section 1.1.1], unless subject's insomnia is associated with major comorbidities, especially comorbid neurological, affective or psychiatric disorders (e.g., severe or uncontrolled depression, anxiety or dementia) that may interfere with the efficacy and safety in the trial.

Elderly people exhibit a different sleep pattern to younger adults [Ohayon 2004] and the sensitivity of elderly and younger adults to the PD properties of a compound may therefore differ in the long term. Thus, randomization will be stratified by age in both pivotal studies to ensure that tested doses are given to a proportion of elderly subjects (i.e., 40% with age ≥ 65 years) and to ensure balance of the treatment groups within strata is achieved.

Concomitant pharmacological treatments for insomnia or concomitant CNS-related medications are not allowed in the study. This approach will favor optimizing the evaluation of the safety and efficacy profile of ACT-541468 by avoiding any potential confounding effects due to background co-medications.

4.3 Inclusion criteria

For inclusion in the study, all of the following inclusion criteria must be fulfilled. It is not permitted to waive any of the criteria for any subject.

Criteria assessed at Visit 1

1. Signed informed consent prior to any study-mandated procedure.
2. Male or female aged ≥ 18 years.

3. Insomnia disorder according to DSM-5 criteria as follows:
    3.1 The predominant complaint is dissatisfaction with sleep quantity or quality, associated with one (or more) of the following symptoms:
        - Difficulty initiating sleep.
        - Difficulty maintaining sleep, characterized by frequent awakenings or problems returning to sleep after awakenings.
        - Early-morning awakening with inability to return to sleep.
    3.2 The sleep disturbance causes clinically significant distress or impairment in social, occupational, educational, academic, behavioral, or other important areas of functioning.
    3.3 The sleep difficulty occurs despite adequate opportunity for sleep.
    3.4 The insomnia is not better explained by and does not occur exclusively during the course of another sleep-wake disorder (e.g., narcolepsy, a breathing-related sleep disorder, a circadian rhythm sleep-wake disorder, a parasomnia).
    3.5 The insomnia is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication).
    3.6 Coexisting mental disorders and medical conditions do not adequately explain the predominant complaint of insomnia.
    3.7 Self-reported history of all the following on at least 3 nights per week and for at least 3 months prior to Visit 1:
        3.7.1 ≥ 30 min to fall asleep, and
        3.7.2 Wake time during sleep ≥ 30 min, and
        3.7.3 sTST ≤ 6.5 h
4. ISI© score ≥ 15.
5. Ability to communicate well with the investigator, to understand the study requirements and judged by the investigator to be alert and oriented to person, place, time, and situation.

Criteria assessed at Visit 3

6. Meeting all the following sleep parameters on at least 3 nights out of 7 nights on the sleep diary completed at home between Visit 2 and Visit 3:
    6.1 ≥ 30 min to fall asleep, and
    6.2 Wake time during sleep ≥ 30 min, and
    6.3 sTST of ≤ 6.5 h
7. Usual bedtime between 21:30 and 00:30, as reported on sleep diary completed between Visit 2 and Visit 3.
8. Regular time in bed between 6 and 9 h, as reported on sleep diary completed between Visit 2 and Visit 3.
9. Meeting all the following sleep parameters on the 2 PSG nights at Visit 3:
    9.1 Mean LPS ≥ 20 min (with none of the two nights < 15 min), and

9.2 Mean WASO ≥ 30 min (with none of the two nights < 20 min), and
9.3 Mean TST < 420 min

Criterion assessed at Visit 1, Visit 2, and Visit 4

10. For women of childbearing potential, the following is required:
    - Negative serum pregnancy test (Visit 1).
    - Negative urine pregnancy test (Visit 2, Visit 4).
    - Agreement to use the contraception scheme as required by the protocol from Screening up to at least 30 days after last study treatment intake.

4.4 Exclusion criteria

Criteria assessed at Visit 1

1. Body mass index (BMI) below 18.5 or above 40.0 kg/m^2.
2. Any lifetime history of sleep-related breathing disorder, including chronic obstructive pulmonary disease and sleep apnea.
3. Cognitive behavioral therapy (CBT) for any indication is allowed only if the CBT started at least 1 month prior to Visit 3 and the subject agrees to continue this CBT throughout the study.
4. Self-reported usual daytime napping ≥ 1 hour per day, and ≥ 3 days per week.
5. Acute or unstable psychiatric conditions (including but not restricted to anxiety disorder, major depression, bipolar disorder, schizophrenia, obsessive compulsive disorder or depression) that are diagnosed by the Mini International Neuropsychiatric Interview© (MINI©) or that require pharmacological treatment for these disorders. N.B.: subjects with a history of major depressive disorder currently without any symptoms and not requiring treatment are eligible.
6. Mini Mental State Examination© (MMSE©) score < 25 in subjects ≥ 50 years.
7. Shift work within 2 weeks prior to the screening visit, or planned shift work during the study.
8. Travel across ≥ 3 time zones within 2 weeks prior to the screening visit, or planned travel across ≥ 3 time zones during study.
9. Unstable medical condition, significant medical disorder or acute illness, ECG, hematology or biochemistry test results within 1 month prior to the screening visit, which, in the opinion of the investigator, could affect the subject's safety or interfere with the study assessments.
10. Treatment with CNS-active drugs prohibited by this protocol for 5 half-lives of the respective drug (or 2 weeks, whichever is longer) prior to Visit 1, including over-the-counter medication and herbal medicines.

11. Diagnosis of alcohol or substance use disorder within 2 years prior to the screening visit or inability to refrain from drinking alcohol for at least 3 consecutive days.
12. Heavy tobacco use (at least one pack of cigarettes a day or inability to refrain from smoking during the night).
13. Caffeine consumption ≥ 600 mg per day or any caffeine consumption after 4 pm.
14. Treatment with another investigational drug within 3 months prior to Visit 1, previous treatment with ACT-541468 or previous randomization in any trial involving ACT-541468.
15. Known hypersensitivity or contraindication to drugs of the same class as the study treatment or to any excipients of the study drug formulation.
16. Not able or willing to stop treatment with moderate or strong CYP3A4 inhibitors, or treatment with moderate or strong CYP3A4 inducers, within at least 1 week prior to Visit 2.
17. Not able or willing to stop consumption of grapefruit, Seville (bitter) oranges or juices from those fruits within at least 1 week prior to Visit 2.

Criteria assessed at PSG visit between Visit 1 and Visit 2

18. Periodic limb movement disorder with arousal index (PLMAI) ≥ 15/h (assessed on the 1st PSG night), restless legs syndrome, circadian rhythm disorder, REM behavior disorder, or narcolepsy.
19. Apnea/hypopnea index (AHI) ≥ 15/h according to American Academy of Sleep Medicine criteria or event associated with blood oxygen saturation level by pulse oximetry (SpO_2) < 80%, as assessed on the 1st PSG night.

Criteria assessed at Visit 1 and Visit 3

20. AST and/or ALT > 2 × ULN and/or direct bilirubin > 1.5 × ULN.
21. Severe renal impairment: known or defined as estimated creatinine clearance < 30 mL/min/1.73m^2, according to the 4-variable Modification of Diet in Renal Disease formula.
22. Hematology or biochemistry test results deviating from the normal range to a clinically relevant extent as per judgment of the investigator.
23. Any of the following conditions related to ECG abnormalities:
    - A prolonged QT interval corrected with Bazett's formula (QTcB) or QT interval corrected with Fridericia's formula (QTcF) (greater than 450 ms). If QTcB or QTcF is greater than 450 ms on the first ECG, a second ECG recording will be performed after at least 30 min. If QTcB or QTcF is greater than 450 ms on the second ECG, the subject is not eligible.

- A history of additional risk factors for torsade de pointes (e.g., heart failure, hypokalemia, family history of long QT syndrome).
- ECG with clinically significant atrioventricular (AV) conduction disturbance (e.g., second- or third-degree AV block), sick sinus syndrome, bradycardia (resting pulse < 40 bpm), or accessory bypass tract (e.g., Wolff-Parkinson-White).

Criterion assessed at Visit 1, Visit 2, Visit 3 and Visit 4

24. Any of the following conditions related to suicidality:
    - Any suicidal ideation with intent, with or without a plan, at screening, i.e., answering "Yes" to questions 4 or 5 on the suicidal ideation section of the lifetime (Visit 1) and visit (Visit 2, Visit 3, Visit 4) version of the C-SSRS©.
    - History of suicide attempt on the suicidal behavioral section of the lifetime version of the C-SSRS© (Visit 1).

Criteria assessed at Visit 1, PSG visit between Visit 1 and Visit 2, Visit 2, Visit 3 and Visit 4

25. For female subjects: pregnant, lactating or planning to become pregnant during projected duration of the study.
26. Positive urine drug test (for benzodiazepines, barbiturates, cannabinoids, opiates, amphetamines, phencyclidine or cocaine) or presence of alcohol in exhaled breath as detected by breathalyzer test.

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
- Vasectomized male partner with documented post-vasectomy confirmation of the absence of sperm in the ejaculate.
- Bilateral tubal occlusion (tubal occlusion / ligation at least 6 weeks prior to screening).
- Sexual abstinence from intercourse with a male partner only when this 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 as tablets, orally, once daily in the evening during the DB treatment period. ACT-541468-matching placebo will be administered as well during the run-in and the run-out period. At home, the study treatment

will be taken at bedtime to mimic real life drug intake habits and at the site visits, the study treatment will be administered at least 2 h after the last meal and approximately 30 min before lights off to avoid a potential delay in ACT-541468 effects when administered with food which might bias objective endpoints.

ACT-541468 is supplied by Idorsia as film-coated tablets at strengths of 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 when taken at home and by the site personnel in the patient's chart and the eCRF during the PSG nights. At Visit 2, the date of single-blind placebo treatment dispensing will also be recorded in the patient's chart and the eCRF.

5.1.2.1 Study treatment administration at site visits and at home

During the PSG visits at the site, 1 tablet of study treatment will be taken at least 2 h after the last meal and approximately 30 min (± 5 min) before lights off, in the evening of each PSG night.

At home, the tablet will be taken at bedtime.

5.1.2.2 Missed doses

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

5.1.3 Treatment assignment

Each of the study sites will be assigned a unique site number and every subject will receive a unique subject number which identifies the subject throughout the study.

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

During the run-in and run-out periods, subjects will receive single-blind placebo treatment. At Visit 2 and Visit 9, the investigator/delegate contacts the IRT system to assign the treatment wallet number.

On the day of randomization (Visit 4), after having verified that the subject meets all inclusion criteria and none of the exclusion criteria, the investigator/delegate contacts the IRT to randomize the subject. The IRT assigns the treatment wallet number, which matches the treatment arm assigned per the randomization list.

Subjects will be randomized in a 1:1:1 ratio to 25 or 50 mg of ACT-541468, or placebo, respectively (i.e., approximately 300 subjects per arm). Treatment allocation will be stratified by age into 2 categories: < 65 and ≥ 65 years.

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

5.1.4 Blinding

5.1.4.1 Run-in and run-out periods

During run-in and run-out periods, placebo treatment will be administered in a single-blind fashion. The subjects will remain blinded to the study treatment until the end of the ID-078A303 extension study. Subjects must not be informed about the change in treatment at the end of run-in and at the beginning of run-out. The investigator 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-in/run-out periods.

5.1.4.2 Double-blind treatment period

From Randomization 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 final data analysis, the randomization list is kept strictly confidential, and accessible only to the IRT vendor and sponsor authorized persons (e.g., Quality assurance, Systems and compliance personnel, Bioanalytical Laboratory group) the Independent Statistical Analysis Center (ISAC) and the IDMC, who are not involved in the conduct of the study.

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

To minimize the possibility of systematic unblinding, the results of PK data will not be communicated to the investigator and site study personnel, the subjects and Clinical Research Associates (CRAs) until the end of the ID-078A303 extension study. Results will be transferred by the sponsor Bioanalytical Laboratory group (for the PK data) to the sponsor and CRO personnel involved in the conduct of the study only after database lock.

5.1.5 Unblinding

5.1.5.1 Unblinding for final analyses

Randomization information will be made available for data analysis only after database lock, in accordance with Idorsia Quality System (QS) documents.

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 the sponsor'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 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. 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 interest of the subject, the investigator is invited to discuss the intended unblinding with Idorsia personnel.

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

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

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 run-in and run-out period) is provided as tablets and supplied in wallets. All pack types are childproof 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.

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 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. Subjects also report their compliance in the eDiary every morning. Study treatment compliance for the Run-in period, the DB treatment period (Day 1 to EODBT) and the Run-out period will be separately calculated for each of these periods by site personnel using the below formula and entered in the eCRF:

$$\text{Compliance} = [(\text{number of tablets dispensed} - \text{number of tablets returned}) / \text{total number of tablets that needs to be taken during the period}^{*}] \times 100$$

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

During the DB 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, she/he 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

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 as withdrawn from the study and will be followed up until the planned EOS (Day 115), 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 DB study treatment intake (N.B., next day residual assessments will only be performed if the subjects can be assessed within 24 h of last DB study drug intake). All subjects withdrawn from study treatment are encouraged to follow planned study procedures (e.g., visits, sleep diary and questionnaire completion) until EOS. In this case, the run-out period (including Visit 9 and Visit 10) will not be performed, and subjects will directly enter the follow-up period after Visit 8 (considered as EOT in the event of premature discontinuation). The phone call will be performed as planned 30 days (+ 7 days) later, at Visit 11. This will decrease the amount of missing data which is important from a study integrity perspective. 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 as 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 as 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.

5.2 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 DB study treatment or is initiated during the DB 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 therapy must be recorded in the eCRF if discontinued less than 30 days prior to signing of the ICF. The generic name, start/end dates of administration (as well as whether it was ongoing at start of treatment and/or EOS), route, dose, and indication will be recorded in the eCRF.

5.2.3 Allowed concomitant therapy

CBT consists of a combination of cognitive therapy, behavioral, and educational interventions and is ideally delivered by a specially trained physician or a qualified psychotherapist. Given the shortage of certified sleep therapists, access to CBT is limited, particularly in Europe [Pigeon 2010, Schutte-Rodin 2008]. CBT for any indication is only

allowed if the treatment started at least 1 month prior to Visit 3 and the subject agrees to continue this CBT throughout the study. Details about subject's CBT or reason why CBT was not considered by the subject must be recorded in the eCRF. Initiation of CBT during the course of the study is not allowed.

Therapies considered necessary for the subject's well-being and not categorized as prohibited concomitant medications can be used in this study. However, initiation of new medication is to be discouraged and concomitant medication will preferably not be changed during the study. Non-sedating antihistamines (cetirizine, loratadine, desloratadine, fexofenadine and levocabastine) may be used a maximum of twice weekly for allergic symptoms. Inhaled or nasal corticosteroids are permitted.

5.2.4 Forbidden concomitant therapy

Subjects must not be withdrawn from medically necessary therapies in order to participate in the study. They must rather be considered as non-eligible to the study, both due to their medical condition and due to their requirement for these therapies. Several forbidden therapies are associated with excluded medical disorders (e.g., cardiovascular disease, Parkinson's disease, stroke).

The following concomitant therapies are forbidden during the study:

- Treatment with another investigational drug until EOS.
- Study-prohibited CNS-active medications from for 5 half-lives of the respective drug (but at least 2 weeks) prior to Visit 1 and until 24 hours after EOT [see Appendix 3].
- Treatment with moderate or strong CYP3A4 inhibitors, or moderate or strong CYP3A4 inducers until 24 hours after EOT [see Appendix 3].

5.2.5 Forbidden concomitant diet and activities

The following activities and diet are forbidden during the study:

- Consumption of grapefruit, Seville (bitter) oranges or juices from those fruits from 1 week prior to Visit 2 until 24 h after the end of run-out period.
- Caffeine consumption ≥ 600 mg caffeine/day or consumption of any caffeine after 4 pm (after 2 pm on PSG nights) [see Appendix 2].
- Alcohol consumption [see Appendix 1]
  - > 2 drinks a day
  - less than 3 hours before going to bed on non-PSG nights
  - within 24 hours prior to PSG night and during all PSG visits
- Heavy tobacco use (at least one pack of cigarettes a 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 following study treatment intake for adult and elderly subjects.

6 STUDY ENDPOINTS

The ID-078A301 trial is designed to assess safety and efficacy of ACT-541468 on objective and subjective endpoints.

6.1 Primary efficacy endpoints

The primary efficacy endpoints of this study are defined as:

- the change from baseline to Month 1 in WASO (sleep maintenance)
- the change from baseline to Month 3 in WASO
- the change from baseline to Month 1 in LPS (sleep onset)
- the change from baseline to Month 3 in LPS

Baseline is defined as the mean of the 2 PSG nights at Visit 3. Month 1 and Month 3 are defined as the mean of the 2 PSG nights at Visit 6 and Visit 8, respectively.

LPS (min) is the time from start of recording to the beginning of the first continuous 20 epochs (i.e., 10 min) scored as non-awake, i.e., epochs scored as either sleep stage 1 (S1), sleep stage 2 (S2), sleep stage 3 (slow wave sleep [SWS]) or REM, as determined by PSG.

WASO is the time (min) spent awake after onset of persistent sleep until lights on, as determined by PSG.

6.2 Secondary endpoints

The secondary efficacy endpoints of this study are defined as:

- the change from baseline[a] to Month 1[b] in sTST
- the change from baseline[a] to Month 3[c] in sTST
- the change from baseline[a] to Month 1[b] in Insomnia Daytime Symptoms and Impacts Questionnaire (IDSIQ) sleepiness domain score
- the change from baseline[a] to Month 3[c] in IDSIQ sleepiness domain score

[a] Baseline is the mean value based on the screening sleep diary / IDSIQ entries performed at home in the 7 days immediately preceding the first PSG at Visit 3.

[b] 'Month 1' is the mean value based on the sleep diary / IDSIQ entries performed at home in the 7 days immediately preceding the first PSG at Visit 6.

[c] 'Month 3' is the mean value based on the sleep diary / IDSIQ entries performed at home in the 7 days immediately preceding the first PSG at Visit 8.

6.3 Other efficacy endpoints

- Change from baseline (mean of the 2 PSG nights at Visit 3) to Month 1 (mean of the 2 PSG nights at Visit 6) and Month 3 (mean of the 2 PSG nights at Visit 8) in TST.
- Change from baseline[a] to Month 1[b] and Month 3[c] in subjective WASO (sWASO).
- Change from baseline[a] to Month 1[b] and Month 3[c] in subjective Latency to Sleep Onset (sLSO).
- Change from baseline[a] to Month 1[b] and Month 3[c] in IDSIQ scores (i.e., Total score; alert/cognition and mood domain scores).

[a] Baseline is the mean value based on the screening sleep diary / IDSIQ entries performed at home in the 7 days immediately preceding the first PSG at Visit 3.

[b] 'Month 1' is the mean value based on the sleep diary / IDSIQ entries performed at home in the 7 days immediately preceding the first PSG at Visit 6.

[c] 'Month 3' is the mean value based on the sleep diary / IDSIQ entries performed at home in the 7 days immediately preceding the first PSG at Visit 8.

6.4 Exploratory endpoints

For each variable, multiple aspects will be considered in the analysis, in particular changes from baseline at different time points.

- WASO over time (by hour of the night and by quarter of the night) on each PSG night.
- Change from baseline (Visit 3) to Month 1 and Month 3 in SQ. SQ is the sleep quality as determined by scores on the VAS (mm) in the morning.
- Change from baseline (Visit 3) to Month 1 and Month 3 in duration of TST in each sleep stage (S1, S2, SWS and REM).
- Change from baseline (Visit 3) to Month 1 and Month 3 in sleep architecture assessed as percentage of TST in each sleep stage (S1, S2, SWS, and REM) over the whole night, and for each quarter of the night.
- Change from baseline (Visit 3) to Month 1 and Month 3 in mean numbers of shifts from S2, SWS or REM to S1 or awake.
- Change from baseline (Visit 3) to Month 1 and Month 3 in ISI© scores.
- Change from baseline (Visit 3) to Month 1 and Month 3 in mean number of awakenings (defined as the number of awakenings between first epoch and last epoch not scored

wake) as measured by PSG (will be summarized for the whole night, for each quarter of the night, and for each hour of the night).

- Change from baseline (Visit 3) to Month 1 and Month 3 in mean number of self-reported awakenings.
- Change from baseline (Visit 3) to Month 1 and Month 3 in sWASO.
- Change from baseline (Visit 3) to Month 1 and Month 3 in Sleep Efficiency (defined as 100 × ([TST / time in bed]).
- Change from baseline (Visit 1) to Month 1 and Month 3 in Patient Global Assessment of Disease Severity (PGA-S) scores (daytime symptoms).
- Change from baseline (Visit 3) to Month 1 and Month 3 in Patient Global Impression of Change (PGI-C) scores (daytime symptoms).
- Change from baseline (Visit 3) to Month 1 and Month 3 in PGI-C scores (night-time symptoms).
- Change from baseline (Visit 3) to Month 1 and Month 3 in Patient Global Impression of Severity (PGI-S) scores (night-time symptoms).

6.5 Safety endpoints

In addition to the standardized collection of AEs, safety data specific to insomnia and its treatment will be assessed as follows:

- Withdrawal effects (physical dependence) upon treatment discontinuation will be assessed based on the changes from last assessment on DB treatment (Visit 8, 2nd morning) to run-out period in the BWSQ total score (Visit 9 and Visit 10), the occurrence of relevant AEs and marked ECG abnormalities.
- Rebound insomnia will be assessed based on objective sleep parameters (WASO, LPS and TST) at Visit 9 as compared to Visit 3. It will also be assessed using subjective sleep parameters (sWASO, sLSO and sTST) from run-out period as compared to baseline.
- Next-day residual effect will be assessed based on changes from baseline (Visit 3) to Month 1 and Month 3 in:
  - Coding sub-test©
  - SDS©
  - Scores on the VAS (mm)
- SAEs up to 30 days after DB study treatment discontinuation or until enrollment into the extension study.
- TEAEs up to 30 days after DB study treatment discontinuation or until enrollment into the extension study.

- AEs leading to premature discontinuation of the DB study treatment.
- AEs of special interest 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 (Visit 3) to Month 1 (Visit 6) and Month 3 (Visit 8) in vital signs (mean of the 2 PSG nights in systolic and diastolic blood pressure [BP] and pulse rate).
- Change from baseline (Visit 1) to Month 3 (Visit 8) in body weight.
- Marked ECG abnormalities on DB study treatment.
- Change from baseline (Visit 3) to Month 3 (Visit 8) and the end of the run-out period (Visit 10) in ECG parameters.
- Marked laboratory abnormalities on DB study treatment.
- Change from baseline (Visit 3) to Month 1 (Visit 6) and Month 3 (Visit 8) in laboratory parameters.
- Occurrence of suicidal ideation and/or behavior on DB study treatment based on C-SSRS©.

6.6 Pharmacokinetic endpoints

ACT-541468 plasma concentrations 9–10 h post-dose (morning after the second PSG night at Visit 6 and Visit 8) or in the event of excessive sleepiness based on the investigator's opinion.

6.7 Patient preferences exploratory endpoints

The preferences resulting from the choice sets collected in the third section of the PAUSe questionnaire will be used to derive the following endpoints:

- Partial value of each treatment outcome at Visit 4 and Visit 8.
- Partial value function and weights for each treatment outcome at Visit 4 and Visit 8.
- Total value score for each treatment at Visit 4 and Visit 8.
- Change in total value score for each treatment from Visit 4 to Visit 8.
- Probability that patients would prefer a treatment at Visit 4 and Visit 8.
- Change in probability that patients would prefer a treatment from Visit 4 to Visit 8.

7 VISIT SCHEDULE AND STUDY ASSESSMENTS

7.1 Study visits

The study visits are listed in Table 1. Screening will last 20 to 31 days. For all visits during the DB treatment phase, the subjects must be seen on the designated day and within a ± 2

days visit window in comparison with randomization (Visit 4). A follow-up safety telephone call must be performed 30 days (+ 7 days) after last DB study treatment intake if the subject is not enrolled in the ID-078A303 extension study.

7.1.1 Screening

At Visit 1 subjects will discuss and sign the ICF, and will undergo initial eligibility assessments. The date on which the ICF is signed corresponds to the date of the screening visit (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.

Subjects who are in the screening phase when the enrollment target has been met may still be randomized.

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 ECGs and laboratory assessments, and changes 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].

Table 1 Visit and assessment schedule

	SCREENING PHASE (20–31 days)								TREATMENT PHASE (82–86 days)											FU PHASE (30–37 days)			
	Screening period (7–18 days)			**Run-in period (13–24 days)**					**Double-blind treatment (84 days ± 2 days[13])**											**Run-out period (7 days + 2 days)**			**FU period (23 days + 7 days)[17]**
Visit	**1**			**2**	**3**				**4[16]**	**5 (phone call)**	**6**				**7**	**8**				**9**		**10**	**11 (phone call)**
Target Study Days					**1st night**		**2nd night**		**1**	**7 to 14**	**1st night [13] 27/28**		**2nd night 28/29**		**55**	**1st night [13] 83/84**		**2nd night 84/85**		**85/86**		**92 (+ 2 days)**	**115 (+ 7 days)**
Evening(PM) / Morning (AM)		**PM**	**AM**		**PM**	**AM**	**PM**	**AM**			**PM**	**AM**	**PM**	**AM**		**PM**	**AM**	**PM**	**AM**	**PM**	**AM**		
Informed consent	X																						
Inclusion and exclusion criteria	X	X	X	X	X	X	X	X	X														
Demographics	X																						
Medical history	X																						X
Concomitant therapy	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[6]	X	X	X	X
Physical examination, body weight and height [9]	X																		X[6]				
Vital signs	X		X	X		X		X	X			X		X	X		X		X[6]		X	X	
12-lead ECG	X							X											X[6]			X	
Hematology, blood chemistry	X							X						X	X				X[6]				
Pregnancy test [1]	X			X					X		X				X				X[6]			X	
Urine drug screen	X	X		X	X		X		X		X		X		X	X		X		X		X	
Alcohol test	X	X		X	X		X		X		X		X			X		X		X		X	
PK sampling														X					X				
PSG		X[4]			X		X				X		X			X		X		X			
ISI©	X							X						X					X[6]				
IDSIQ	◄	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	
Sleep diary (incl. VAS)[2]	◄	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	
Neurological exam[8]			X			X		X				X		X			X		X		X		
C-SSRS© [7]	X			X				X	X					X	X				X[6]		X	X	
Coding sub-test© [7]						X		X				X		X			X		X[15]		X		
ESS©	X			X				X						X					X			X	
SDS© [7]						X		X				X		X			X		X[6]		X		
BWSQ[7]								X						X					X[6]		X	X	
MINI©	X																						

	SCREENING PHASE (20–31 days)								TREATMENT PHASE (82–86 days)												FU PHASE (30–37 days)			
	Screening period (7–18 days)			**Run-in period (13–24 days)**					**Double-blind treatment (84 days ± 2 days[13])**												**Run-out period (7 days + 2 days)**			**FU period (23 days + 7 days)[17]**
Visit	**1**			**2**	**3**				**4[16]**	**5 (phone call)**	**6**				**7**	**8**				**9**		**10**	**11 (phone call)**
Target Study Days					**1st night**		**2nd night**		**1**	**7 to 14**	**1st night [13] 27/28**		**2nd night 28/29**		**55**	**1st night [13] 83/84**		**2nd night 84/85**		**85/86**		**92 (+ 2 days)**	**115 (+ 7 days)**
Evening(PM) / Morning (AM)		**PM**	**AM**		**PM**	**AM**	**PM**	**AM**			**PM**	**AM**	**PM**	**AM**		**PM**	**AM**	**PM**	**AM**	**PM**	**AM**		
MMSE©[10]	X																						
PGA-S[11]	X			X	X				◄	- - - - -	- - - - -	- - - - -	- - - - -	- - - - -	- - - - -	- - - - -	- - - - -	- - - - -	►			X	
PGI-C[11] daytime symptoms					X				◄	- - - - -	- - - - -	- - - - -	- - - - -	- - - - -	- - - - -	- - - - -	- - - - -	- - - - -	►			X	
PGI-C[11] night-time symptoms						X			◄	- - - - -	- - - - -	- - - - -	- - - - -	- - - - -	- - - - -	- - - - -	- - - - -	- - - - -	►			X	
PGI-S[11]	X			X		X			◄	- - - - -	- - - - -	- - - - -	- - - - -	- - - - -	- - - - -	- - - - -	- - - - -	- - - - -	►			X	
Patient Preferences[14]									X										X				
Contact IRT	X			X					X		X				X					X			
Randomization[12]									X														
Dispense IMP wallet(s)				X					X		X				X					X			
Study drug intake[3]				◄	- - - - -	- - - - -	- - - - -	- - - - -	- - - - -	- - - - -	- - - - -	- - - - -	- - - - -	- - - - -	- - - - -	- - - - -	- - - - -	- - - - -	- - - - -	- - - - -	- - - - -	►	
SAEs and AEs [5]	◄	- - - - -	- - - - -	- - - - -	- - - - -	- - - - -	- - - - -	- - - - -	- - - - -	- - - - -	- - - - -	- - - - -	- - - - -	- - - - -	- - - - -	- - - - -	- - - - -	- - - - -	- - - - -	- - - - -	- - - - -	- - - - -	►

1. For women of childbearing potential, serum test at V1 and V8 and urine test at V2, V4, V6, V7, V10. **2.** The hand-held device is handed out to the subject and completed at home daily from V1 to V10. **3.** Daily placebo single-blind treatment during run-in and run-out periods, and daily double-blind study treatment during treatment phase. **4.** The 1st PSG can be performed any nights between V1 and V2. It includes assessment of AHI, PLMAI, SpO_2. **5.** SAE and AE reporting and follow-up: all SAEs and AEs from signed ICF up to EOS. **6.** In the event of permanent study treatment discontinuation, safety assessments of V8 are recommended to be performed within 7 days of last DB study drug intake. If the subject remains in the study, he or she will perform study visits and assessments as planned until EOS (Day 115), without the run-out period (including Visit 9 and Visit 10). **7.** Approximately 30 to 60 minutes after PSG lights on. **8.** Performed approximately 1 hour after lights on. **9.** Height only at V1. **10.** For elderly subjects only. **11.** PGA-S, PGI-S and PGI-C (daytime symptoms and night-time symptoms questionnaires) will be completed at home once a week between V4 and EODBT. **12.** Randomization will take place after all the V4 assessments have been performed and provided the subject fulfills all the eligibility criteria. **13.** A time window of ± 2 days is allowed at each visit vs randomization visit (V4). **14.** Patient preferences sub-study (PAUSe) available for sites in Germany and in the USA only. **15**. In the event of permanent study treatment discontinuation, next day residual assessment of V8 will only be performed if the subjects can be assessed within 24 h of last DB study drug intake. **16**. Three working days are required between V3 and V4 to obtain eligibility confirmation regarding objective sleep parameters. **17**. If Run-out period exceeded by 2 days, then the follow-up period can only be exceeded by a maximum of 5 days.

AE = adverse event; AHI = apnea/hypopnea index; BWSQ = Benzodiazepine Withdrawal Symptom Questionnaire; C-SSRS© = Columbia Suicide Severity Rating Scale; ECG = electrocardiogram; EODBT = End-of-Double-Blind-Treatment; EOS = End-of-Study; ESS© = Epworth Sleepiness Scale©; FU = Follow-up; ICF = Informed Consent Form; IDSIQ = Insomnia Daytime Symptoms and Impacts Questionnaire; IMP = Investigational Medicinal Product; IRT = Interactive Response Technology; ISI© = Insomnia Severity Index©; MINI© = Mini International Neuropsychiatric Interview©; MMSE© = Mini Mental State Examination©; PAUSe = PAtient Preferences StUdy in InSomnia; PGA-S = Patient Global Assessment of Disease Severity; PGI-C = Patient Global Impression of Change (daytime symptoms and night-time symptoms); PGI-S = Patient Global Impression of Severity; PK = pharmacokinetic; PLMAI = periodic limb movement with arousal index; PSG = polysomnography; SAE = serious adverse event; SDS© = Sheehan Disability Scale©; SpO_2 = oxygen saturation by pulse oximetry; V = Visit; VAS = visual analog scale(s).

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.

The following order of assessments is recommended:

- In the evening before a PSG night:
  - Urine drug screen and alcohol test
  - IDSIQ
  - Evening questionnaire in sleep diary (including VAS)
  - PGA-S daytime symptoms (in the first evening at Visits 3, 6 and 8)
  - PGI-C daytime symptoms (in the first evening at Visits 3, 6 and 8)
  - Recording of concomitant medications
  - AEs and SAEs
  - Study drug intake (30 minutes before lights off)
- In the morning after a PSG night (subject fasted):
  - Blood samples (hematology and blood chemistry, only second morning at Visits 3, 6 and 8; PK, only second morning at Visits 6 and 8.
- In the morning after a PSG night and after completion of normal morning routine (e.g., using the bathroom, eating breakfast):
  - Vital signs
  - C-SSRS© (only second morning at Visits 3, 6 and 8)
  - Coding sub-test©
  - ISI© (only second morning at Visits 3, 6 and 8)
  - ESS©
  - SDS©
  - BWSQ (only second morning at Visits 3, 6, 8 and 9)
  - Morning questionnaire in sleep diary (including VAS)
  - PGI-S night-time symptoms (in the first morning at Visits 3, 6 and 8)
  - PGI-C night-time symptoms (in the first morning at Visits 3, 6 and 8)
  - Recording of concomitant medications
  - AEs and SAEs
  - Neurological examination
  - 12-lead ECG (only second morning at Visits 3and 8)
  - Patient preferences questionnaire PAUSe (only second morning at Visit 8)

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

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

If the Principal Investigator (PI) delegates any study procedure/assessment for a subject, to an external facility, he/she must inform Idorsia 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 PI.

Calibration certificates / evidence of equipment maintenance for the below-listed equipment used to perform study assessments must be available prior to the screening 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.
- Polysomnographic device.

Use of hand-held and tablet devices

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

Subjects will be required to complete the following questionnaires on a tablet at site: Patient preferences questionnaire (PAUSe).

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

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 to be collected in the eCRF for all subjects include: age, sex, race and ethnicity. Relevant medical history / current medical conditions (e.g., chronic and ongoing acute conditions, serious past conditions) present before signing informed consent will be recorded on the medical history page. Where possible, diagnoses and not symptoms will be recorded.

Characteristics of insomnia will be captured on a specific Diagnosis eCRF page.

Subject's information regarding CBT will be captured on a specific Medical History eCRF page.

For subjects who failed screening, the following data will be collected in the eCRF if available:

- Demographics (i.e., age, sex, race and ethnicity)
- Informed consent date
- Reason for screening failure
- AEs.

7.2.2 Efficacy assessments

7.2.2.1 Polysomnography

PSG data will be used to assess objective sleep parameters (WASO and LPS) as well as data on sleep architecture (sleep stages).

PSG recordings must be performed by technologists who are familiar with the recording techniques described in the investigator site operations manual for the acquisition, processing, scoring, archiving, and transfer of digital PSG data (provided by the central scoring CRO). The quality of PSG recordings is monitored and quality-controlled on an ongoing basis. Technologists must be able to follow the procedures in this manual in order to produce technically acceptable tracings. Technologists are not required to be registered PSG technologists. Technologists must receive study-specific training prior to their participation in the study. Documentation of technologists' prior experience and training, and study-specific training will be maintained at each clinical trial site. The sites and scorers that participate in this study must be certified by the CRO. The center conditions must allow an undisturbed environment and PSG recordings must be conducted in a sleep laboratory environment that meets the guidelines for sleep disorder centers [aasmnet.org].

During the Screening period, a PSG night will be performed if the subject meets all inclusion criteria and none of the exclusion criteria checked so far, and assesses AHI, PLMAI, and SpO_2. At Visit 3, the first PSG recording starts (lights off) within ± 30 min of

usual bedtime (determined by sleep diary between Visit 2 and Visit 3); this time is then considered as the habitual bedtime and held constant (± 15 min) throughout the study. Study medication is administered 30 min (± 5 min) before the recording starts. The PSG recording is stopped after 480 min when 960 epochs of 30 seconds have been recorded. PSGs will be performed as per the visit and assessment schedule [Table 1].

During the PSG recording, the subject is requested to stay in bed and remains connected to the recording equipment. However, if the subject needs to go to the bathroom, he/she may do so and will be disconnected for this short time from the recording device. Alternatively, urine flasks or bedpans may be provided. The subject must be re-connected as quickly as possible. The time during which the subject is disconnected will be scored as time awake. The subject is not permitted to perform any cognitive activity (such as reading, listening to radio, etc.), and is recommended not to have a watch or access to any clock. The lights remain switched off until the 480 min of recording are finished. After recording is stopped, the lights are turned on and the subject is awakened and asked to perform the morning assessments.

The centers are required to transfer PSG data to the CRO responsible for central scoring, after the Visit 3 PSG visit and after Visit 6, Visit 8 and Visit 9 PSG visits. During the screening phase, PSG data obviously not fitting eligibility criteria at the first PSG and at Visit 3 according to site scoring (more than 10% deviation from protocol range) are not required to be sent for central scoring. If anything prevents any PSG night being scored, the center must contact the monitor for instructions. After Visit 3, the CRO will score the PSG data obtained at the first PSG and at Visit 3 immediately upon receipt and the center will receive the complete Eligibility Assessment (AHI, PLMAI, and the presence of any apnea/hypopnea or event associated with $SpO_2 < 80\%$ as assessed at Visit 1, and WASO, LPS and TST as assessed at Visit 3) within 3 business days following file receipt by the CRO. These PSG data are evaluated and scored centrally by an independent scorer (expert from central reading CRO, not otherwise involved in the study). Based on this information, the investigator assesses the subject's potential eligibility.

Results of all PSG nights (1st PSG, Visit 3, Visit 6, Visit 8, and Visit 9) for the randomized subjects are sent to Idorsia from the central scoring CRO. The following sleep variables assessed by PSG include but are not limited to: WASO, LPS, TST, sleep stages S1 (also called N1), S2 (N2), SWS (N3), REM (R), and Wake time during sleep (W). The definitions of the sleep variables are given in the scoring procedures of the central scoring CRO manual.

The sponsor reserves the right to request the sites to provide PSG data from the 1st PSG night of screened failed subjects to further characterize the patient population. In such case, the sites will be informed in due time.

For more detailed information, refer to the investigator site operations manual for the acquisition, processing, scoring, archiving, and transfer of digital PSG data (provided by central scoring CRO).

7.2.2.2 Sleep diary

The sleep diary (also called eDiary) will be uploaded into an electronic hand-held device and given to the subjects at Visit 1. Sleep diaries will be available in the subject's language, and must be completed daily from Visit 1 at screening and until Visit 10.

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 CRF Health).

7.2.2.2.1 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.

The subject's answer to the sleep diary question "What time did you get into bed?" is expected to be in the time window of 21:30 to 00:30 for at least 50% of the nights between Visit 2 and Visit 3. The median of the values falling into the time window of 21:30 to 00:30 is defined as the usual bedtime and will be used to set the habitual bedtime. The subject's regular time in bed (i.e., time calculated from "What time did you get into bed?" until "What time did you get out of bed for the day?") is expected to be in the time window of 6 to 9 h, for at least 50% of the nights between Visit 2 and Visit 3.

For further details, see Appendix 8.

7.2.2.2.2 Visual analog scales

The VAS collects 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 8.

7.2.2.3 Insomnia Severity Index©

The ISI© assesses the severity of a patient's insomnia by scoring the severity of sleep onset and sleep maintenance difficulties and any insomnia-related interference with daytime

functioning [see Appendix 5]. The assessment is on a 5-point scale (0–4), where the composite score is obtained by summing the 7 rated dimensions measuring the subject's perception of his or her insomnia. A score of 15–21 indicates a moderate level of insomnia and a score of 22–28 indicates severe insomnia. An ISI© total score < 10 indicates that the subject's subjectively-rated insomnia symptoms, daytime impairment, and quality of life have improved to the minimal-to-none range [Morin 1993, Scharf 2007]. The ISI© will be completed by the subject on the hand-held device at Visit 1, Visit 3, Visit 6, and Visit 8.

7.2.2.4 Patient Global Assessment of Disease Severity (daytime symptoms)

The PGA-S (daytime symptoms) is a question concerning the overall severity of daytime symptoms (e.g., sleepiness) and impacts (e.g., effort to perform daily activities) that the subject may have experienced due to his/her insomnia over the 7 days preceding the PGA-S. It is a self-administered question programmed on the hand-held device and is to be completed at Visit 1, Visit 2, Visit 3 1st evening, Visit 6 1st evening, Visit 8 1st evening, Visit 10, and weekly in the evening at home from Visit 4 until EODBT.

For further details, see Appendix 9.

7.2.2.5 Patient Global Impression of Change (daytime symptoms)

The PGI-C (daytime symptoms) is a question concerning the change in overall severity of daytime symptoms (e.g., sleepiness) and impacts (e.g., effort to perform daily activities) that the subject may have experienced due to his/her insomnia over the 7 days preceding the PGI-C daytime symptoms compared to the week before he/she started treatment. The PGI-C daytime symptoms is a self-administered question on the hand-held device and is to be completed at Visit 3 1st evening, Visit 6 1st evening, Visit 8 1st evening, Visit 10, and weekly in the evening at home from Visit 4 until EODBT.

For further details, see Appendix 9.

7.2.2.6 Patient Global Impression of Change (night-time symptoms)

The PGI-C (night-time symptoms) is a question concerning the change in the subject's insomnia symptoms at night (e.g., trouble falling asleep, total time asleep, or number of times they wake up) over the past week (7 nights) preceding the PGI-C night-time symptoms compared to the week before the subject started treatment. The PGI-C night-time symptoms is a self-administered question on the hand-held device and is to be completed at Visit 3 1st morning, Visit 6 1st morning, Visit 8 1st morning, Visit 10, and weekly in the morning at home from Visit 4 until EODBT.

For further details, see Appendix 10.

7.2.2.7 Patient Global Impression of Severity (night-time symptoms)

The PGI-S is a question concerning the overall severity of the subject's night-time symptoms (e.g., trouble falling asleep, total time asleep, or number of times they wake up) that the subject may have experienced due to his/her insomnia over the past week (7 nights) preceding the PGI-S. It is a self-administered question programmed on the hand-held device and is to be completed at Visit 1, Visit 2, Visit 3 1st morning, Visit 6 1st morning, Visit 8 1st morning, Visit 10 and weekly in the morning at home from Visit 4 until EODBT.

For further details, please see Appendix 10.

7.2.2.8 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 every day in the evening before the evening sleep diary by the subject without study staff input or interference from Screening (Visit 1) until EOT (Visit 10).

The IDSIQ is structured in 3 domains (i.e., alertness/cognition; negative mood; tiredness/sleepiness) and contains overall 14 items, each based on an 11-point numeric rating scale. This tool is based on an existing instrument, the Daytime Insomnia Symptom Scale [Buysse 2007]. The psychometric validation of the IDSIQ instrument was performed in study ID-078A203.

For further details, see Appendix 11.

7.2.3 Safety assessments

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

7.2.3.1 Weight and height

Height will be measured at Screening only (Visit 1) and recorded in the eCRF.

Body weight will be measured at Screening (Visit 1) and EODBT visit (Visit 8), and recorded in the eCRF. BMI will be calculated at Visit 1 according to the BMI formula (weight in kg/m^2) and displayed automatically upon entry of weight and height in the eCRF.

7.2.3.2 Physical examination

Physical examination will be performed at Screening (Visit 1) and EODBT visit (Visit 8) 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 findings that are present prior to signing of ICF must be recorded on the Medical History eCRF form. 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.

7.2.3.3 Vital signs

Systolic and diastolic BP and pulse rate will be measured non-invasively at each study visit from Screening (Visit 1) to EOT (Visit 10).

Vital signs measurements will be collected in the eCRF.

7.2.3.4 Coding sub-test©

The Coding sub-test©, formerly known as Digit Symbol Substitution Test, is a measure of attention, perceptual speed, motor speed, visual scanning and memory.

On a sheet of paper, the subject is given 120 seconds to complete as many substitutions as possible, entering a symbol in numbered boxes according to a key shown on the top of the sheet (9 symbols).

The Coding sub-test© is performed at Visit 3, Visit 6, Visit 8 and Visit 9. The number of correct substitutions is recorded as the total Coding sub-test© score and collected in the eCRF.

For further details, see Appendix 4.

7.2.3.5 Sheehan Disability Scale©

The SDS© consists of 3 questions on impairment of work, social life, and family life / home responsibilities [see Appendix 6; Sheehan 1996]. The SDS© is a self-administered questionnaire on the hand-held device performed at Visit 3, Visit 6, Visit 8 and Visit 9.

7.2.3.6 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]. Suicidal ideation is classified on a 5-item scale:

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

The C-SSRS© also captures information about the intensity of ideation, specifically the frequency, duration, controllability, deterrents, and reasons for the most severe types of ideation. In addition, the C-SSRS© captures information using yes/no question and answers on suicidal behaviors, specifically actual, interrupted, and aborted attempts; preparatory acts or behaviors; and if suicidal behaviors were present during the assessment period. More than one classification can be selected provided they represent separate episodes. For actual attempts only, the actual or potential lethality is classified for the initial, most lethal, and most recent attempts. The C-SSRS© will be completed at all study visits except Visit 5 and Visit 11 (i.e., telephone calls). At Visit 1 (Screening) the C-SSRS© will be completed for the subject lifetime history of suicidal ideation and behaviors. At all other visits, the C-SSRS© will be completed for 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.

7.2.3.7 Benzodiazepine Withdrawal Symptom Questionnaire

The BWSQ assesses the main symptoms which might be experienced by subjects during withdrawal from benzodiazepines [see Appendix 7; Tyrer 1990]. The questionnaire consists of 20 items. The symptoms will be rated from 0 (No), 1 (Yes-moderate) to 2 (Yes-severe). The questionnaire will be self-administered using the hand-held device at Visit 3, Visit 6, Visit 8, Visit 9 and Visit 10.

7.2.3.8 Mini International Neuropsychiatric Interview©

The MINI© is a psychiatric examination [Sheehan 1999] and will identify subjects with exclusionary psychiatric conditions. The MINI© will be administered at Screening (Visit 1) by the investigator, a delegated physician, a specialist nurse or a nurse practitioner, trained according to local requirements and local clinical practice. The MINI© Version 7.0.2 will be administered on paper to ascertain the psychiatric diagnoses, and any clinically relevant psychiatric conditions will be reported in the eCRF.

7.2.3.9 Mini Mental State Examination©

The MMSE© is a simplified, scored form of the cognitive mental status examination [see Appendix 13; Folstein 1975]. The MMSE© assesses orientation, attention, immediate and short-term recall, language, and the ability to follow simple verbal and written commands. The MMSE© will be administered at Screening (Visit 1) for subjects ≥ 50 years at the site on a tablet by the investigator, a delegated physician, a specialist nurse or a nurse practitioner, trained according to local requirements and local clinical practice. A subject with a score between 25 and 30 will be eligible and a subject with a score below 25 has greater cognitive impairment and will be excluded.

7.2.3.10 Neurological examinations

At 1st PSG night, Visit 3, Visit 6, Visit 8, and Visit 9, a set of examinations must be performed approximately 1 hour after lights on [see Section 7.2]. The neurological examinations will be done by the investigator, a delegated physician, a specialist nurse or a nurse practitioner, trained according to local requirements and local clinical practice. The following examinations will be performed to detect a possible next-day residual effect:

- Gait
- Tandem walking
- Romberg test

In the event of clinically significant findings, the set of examinations must be repeated approximately every 30 min. until the subject is considered safe to leave the center and the investigator must ensure appropriate safety follow-up of the subject. All clinically significant findings must be recorded as AEs in the eCRF.

Neurological examinations are recorded on the eCRF.

7.2.3.11 Epworth Sleepiness Scale©

The ESS© is a validated questionnaire designed to provide a subjective measure of daytime sleepiness [Johns 1991]. The ESS© [see Appendix 12] will be self-administered at site visits (Visit 1, Visit 2, Visit 3, Visit 6, Visit 8, and Visit 10) on a hand-held device to assess daytime sleepiness. All clinically significant findings must be recorded as AEs in the eCRF.

7.2.3.12 ECG assessment

A standard 12-lead ECG is to be performed at Visit 1, in the second morning of Visit 3, Visit 8 and at Visit 10.

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 $RR = 60 / HR$

If the central review of the ECG detects a prolonged QTcB and/or QTcF interval greater than 450 ms for a subject at screening (Visit 1 or Visit 3), the ECG must be repeated (at least 30 min after first ECG). If the central review confirms that the repeated ECG shows

a QTcB and/or QTcF interval greater than 450 ms, the subject cannot be enrolled into the study.

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.

7.2.4 Patient preferences questionnaire

The DCE methodology requires the presentation of several possible comparative scenarios, (i.e., Treatment A and Treatment B) showing specific treatment outcomes (benefits and risks). After each treatment scenario, subjects will be asked to make choices about the type of treatment they would be willing to take. The patient preferences questionnaire is programmed on the tablet site device in the subject's language (i.e., US English for USA and German for Germany), and if subjects consent to participate to this sub-study, must be completed at Randomization (Visit 4) and at EODBT visit (Visit 8, 2nd morning).

For further details, see Appendix 14.

7.2.5 Laboratory assessments

7.2.5.1 Type of laboratory

A central laboratory (see central laboratory manual for contact details) will be used for all protocol-mandated laboratory tests until EOS, including follow-up tests due to abnormal laboratory findings and laboratory tests performed at unscheduled visits.

Local laboratory results of the parameters described in Section 7.2.5.2 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 for whatever reason, it is recommended to the investigator to collect an additional sample as soon as possible for repeat analysis.

No repeat test is allowed if the subject does not meet the eligibility criteria.

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. Clinically significant laboratory findings present before signing of the ICF must be recorded on the Medical History page of the eCRF. 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 under fasted condition (i.e., before breakfast) at Visit 3, Visit 6, Visit 7 and Visit 8.

7.2.5.2 Laboratory tests

Hematology

- Hemoglobin
- Hematocrit
- Erythrocytes
- Reticulocyte
- 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
A serum pregnancy test for women of childbearing potential will be performed at Screening (Visit 1) and on the second morning of Visit 8. A urine pregnancy test will be performed on Visit 2, Visit 4, on the first evening of Visit 6, Visit 7 and at run-out (Visit 10). If pregnancy is suspected during the study, a serum pregnancy test must be performed immediately.

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. 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 only if the results of the pregnancy tests and other tests are negative.

7.2.6 Pharmacokinetic assessments

PK samples will be collected in the morning after the second PSG night, after lights on, approximately 9–10 h post-dose (i.e., 30–90 min after lights on) at Visit 6 and Visit 8 or in the event of excessive sleepiness based on the investigator's opinion.

The date and the time of blood sample collection will be entered in the eCRF. The date and time of the last study treatment dosing before blood draw will be entered in the eCRF. 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, who are in charge of the PK sample analysis.

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

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. Subjects who completed the study until the end of the run-out period will have the possibility to participate in the extension study ID-078A303 and will complete the safety follow-up phase at the end of the extension.

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.

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, 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 the 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

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 (i.e., emerging from DB study treatment initiation until up to 30 days after DB study treatment discontinuation or until enrollment into 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 interruption or permanent discontinuation of study treatment.

Overdose, misuse, abuse of the study treatment and study treatment errors will be reported as an AE.

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 or until enrollment into 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.

Any increases in intensity of an AE during the study will be reported in 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

The investigator will ask the subject to report all AEs at each study visit, including the telephone calls.

All AEs with an onset date after signing of informed consent and up to EOS for subjects that are not enrolled in ID-078A303 extension study must be recorded on AE pages of the eCRF.

All AEs with an onset date after signing of informed consent, and up to enrollment in the ID-078A303 (i.e., ID-078A301 EOT) for subjects that are participating in the extension study, must be recorded on AE pages of the ID-078A301 eCRF.

9.1.5 Follow-up of adverse events

AEs still ongoing more than 30 days after EOS for subjects that are not enrolled in the ID-078A303 extension study 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 by Idorsia.

For subjects enrolled in ID-078A303, AEs that are ongoing at ID-078A301 EOT will be followed up in the extension study and reported in the ID-078A303 eCRF on a dedicated page.

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.

All SAEs with an onset date after signing of informed consent and up to enrollment in ID-078A303 (i.e., ID-078A301 EOT) for subjects that are participating in the extension study must be recorded on AE pages of the ID-078A301 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 EOS 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.

For subjects enrolled in ID-078A303, SAEs that are ongoing at ID-078A301 EOT will be followed up in the extension study and reported in the ID-078A303 eCRF on a dedicated page.

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 [ACT-541468 IB]. Any SAE that is assessed as related and unexpected against the RSI of the ACT-541468 IB [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 for all randomized subjects and the outcome must be reported to Idorsia Global Drug Safety.

Any AE associated with the pregnancy occurring during the follow-up period after DB 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 are monitoring safety data [see Section 3.3].

10 STATISTICAL METHODS

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

A Statistical Analysis Plan (SAP) 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 Screened Analysis Set

The Screened Analysis Set includes all subjects who entered screening and have a subject identification number.

10.1.2 Full Analysis Set

The Full Analysis Set (FAS) includes all subjects assigned to a DB study treatment. In order to adhere to the intention-to-treat principle as much as possible:

- Subjects are evaluated according to the treatment and strata they have been assigned to, which may differ from the treatment they have received;
- All available data are included.

10.1.3 Per-Protocol Set

The Per-Protocol Set (PPS) comprises all subjects from the FAS who complied with the protocol sufficiently to be likely to exhibit the treatment effects. Criteria for sufficient compliance include exposure to treatment, availability of measurements, and absence of major protocol deviations that have an impact on the treatment effect. The full list of criteria will be finalized before unblinding treatment codes.

10.1.4 Safety Set

The Safety Set includes all subjects who received at least one dose of DB study treatment. Subjects will be evaluated according to the actual treatment they received, which may differ from the randomly assigned treatment.

10.1.5 Treatment Withdrawal Set

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

10.1.6 Pharmacokinetic Analysis Set

The Pharmacokinetic Analysis Set (PK Set) includes all subjects in the Safety Set who have at least 1 PK sample collected after initiation of DB study treatment. Subjects receiving placebo will be excluded from the PK set.

10.1.7 Patient Preferences Analysis Set

The Patient Preferences Analysis Set includes all subjects in the Safety Set who have answered at least one patient preferences questionnaire after initiation of study treatment.

10.1.8 Usage of the analysis sets

The analyses of efficacy endpoints including baseline and disease characteristics will be performed using the FAS, and the PPS for certain sensitivity analyses.

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

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

The Treatment Withdrawal Set will be used for the analysis of endpoints used to assess withdrawal symptoms (e.g., BWSQ total score) and rebound insomnia (e.g., objective and subjective sleep parameters: WASO, LPS, TST, sWASO, sLSO, and sTST).

The analysis of ACT-541468 plasma concentrations 9–10 h post-dose will be performed using the PK Set.

The Patient Preferences Analysis Set will be used for the analysis of endpoints to assess patient preferences.

10.2 Variables

Detailed description 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 the primary and secondary efficacy variables

10.3.1.1 Overall testing strategy

The Type I error rate will be controlled for the testing of multiple null hypotheses associated with the primary and secondary endpoints assessed at 1 and 3 months of treatment and the two dose levels included in this study, i.e., 25 mg and 50 mg.

The eight statistical null hypotheses associated with the primary efficacy endpoints are:

Sleep maintenance:

- $H1_{WASO}$: Higher Dose – Placebo = 0 for WASO at Month 1
- $H2_{WASO}$: Higher Dose – Placebo = 0 for WASO at Month 3
- $H3_{WASO}$: Lower Dose – Placebo = 0 for WASO at Month 1
- $H4_{WASO}$: Lower Dose – Placebo = 0 for WASO at Month 3

Sleep onset:

- $H1_{LPS}$: Higher Dose – Placebo = 0 for LPS at Month 1
- $H2_{LPS}$: Higher Dose – Placebo = 0 for LPS at Month 3
- $H3_{LPS}$: Lower Dose – Placebo = 0 for LPS at Month 1
- $H4_{LPS}$: Lower Dose – Placebo = 0 for LPS at Month 3

The eight statistical null hypotheses associated with the secondary efficacy endpoints are:

Sleep quantity:

- $H1_{sTST}$: Higher Dose – Placebo = 0 for sTST at Month 1
- $H2_{sTST}$: Higher Dose – Placebo = 0 for sTST at Month 3

- $H3_{sTST}$: Lower Dose – Placebo = 0 for sTST at Month 1
- $H4_{sTST}$: Lower Dose – Placebo = 0 for sTST at Month 3

Next day performance:

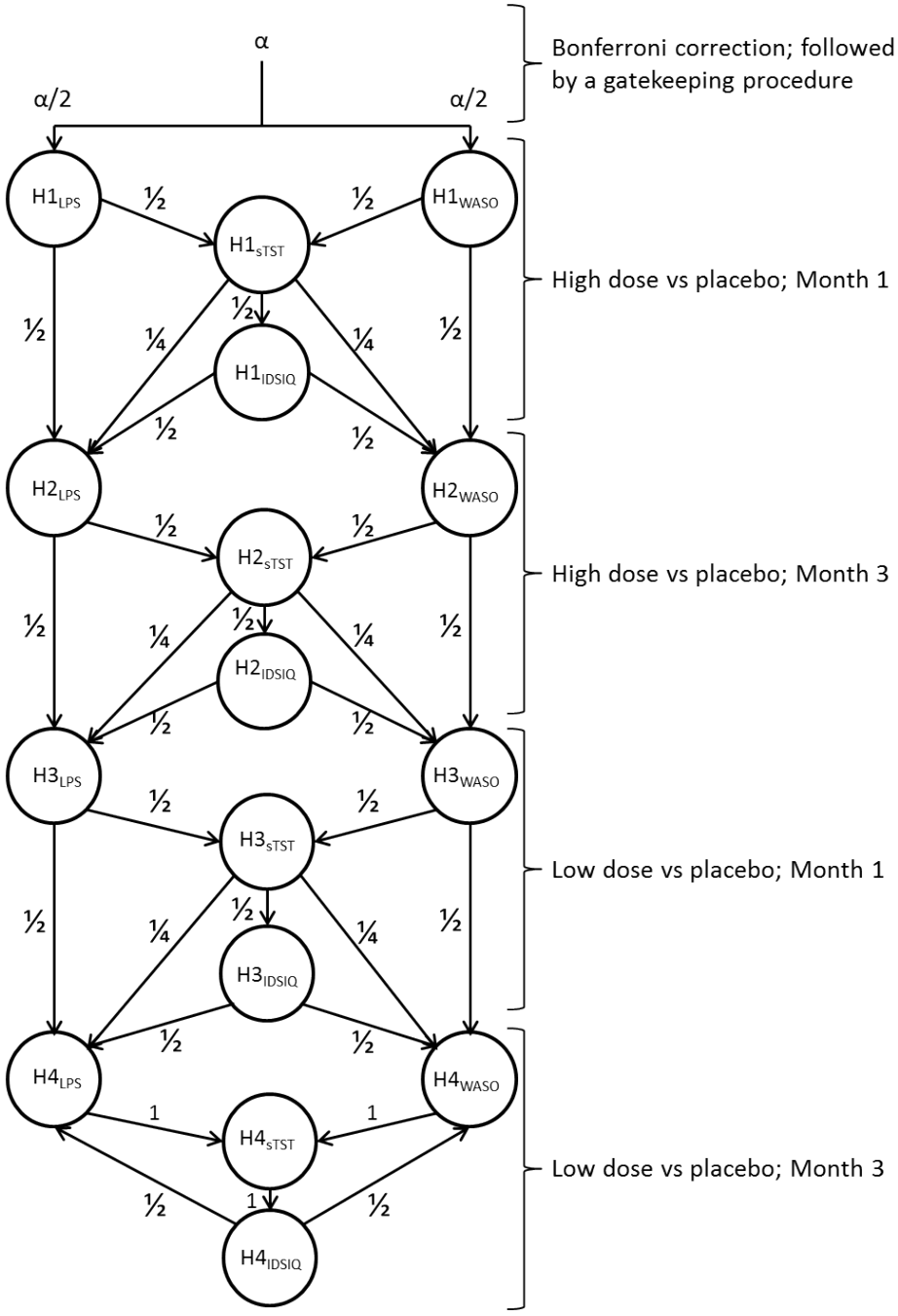
- $H1_{IDSIQ}$: Higher Dose – Placebo = 0 for IDSIQ sleepiness domain score at Month 1
- $H2_{IDSIQ}$: Higher Dose – Placebo = 0 for IDSIQ sleepiness domain score at Month 3
- $H3_{IDSIQ}$: Lower Dose – Placebo = 0 for IDSIQ sleepiness domain score at Month 1
- $H4_{IDSIQ}$: Lower Dose – Placebo = 0 for IDSIQ sleepiness domain score at Month 3

where 'Higher Dose', 'Lower Dose', and 'Placebo' represent the mean change from baseline for the given endpoint (WASO, LPS, sTST or IDSIQ sleepiness domain score) and time point (Month 1 or Month 3) for the 50 mg, 25 mg and placebo treatment group, respectively.

Each null hypothesis will be tested against the alternative hypothesis: that ACT-541468 improves WASO / LPS / sTST / IDSIQ sleepiness domain score at the given dose (25 or 50 mg) and time point (Month 1 or Month 3) compared to placebo.

The order of testing and the alpha level applied to each null hypothesis will be based on the Bonferroni-based gatekeeping procedure [Bretz 2009] (shown in Figure 2 below as a directed graph) that will control the study-wise Type I error at a two-sided 5% significance level. To account for the concurrent evaluation (multiple comparison) of two distinct endpoint categories (i.e., sleep maintenance and sleep onset) a Bonferroni correction is applied. Both endpoint categories will be tested at half of the two-sided 5% significance level. This supports the sponsor's intention to make a superiority claim versus placebo for efficacy in either a sleep maintenance and/or sleep onset indication. The remaining hypotheses will be tested following the gatekeeping strategy moving from Month 1 to Month 3 for higher dose ACT-541468 vs placebo and then from Month 1 to Month 3 for lower dose ACT-541468 vs placebo. The pre-specified proportion of alpha that will be distributed once a given null hypothesis (node) is rejected is shown on the arrow in the directed graph. If a certain null hypothesis cannot be rejected, then the alpha level used for that test is absorbed at that node and not distributed further.

Figure 2 Hypothesis testing strategy



10.3.1.2 Hypotheses and statistical model

The main analysis 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 WASO, LPS, sTST, and IDSIQ 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 (either WASO, LPS, sTST or IDSIQ sleepiness domain score), age group (< 65; ≥ 65 years), treatment (higher dose; lower dose; placebo), time point (Month 1; Month 3), and the interaction of treatment by time point, and baseline by time point.

To evaluate the efficacy hypotheses, appropriate contrasts will be used to test the treatment differences of interest (i.e., the difference in Least Squares mean change from baseline between higher dose ACT-541468 vs placebo and lower dose ACT-541468 vs placebo at Month 1 and Month 3). An unstructured covariance matrix will be used to model the correlation among repeated measurements. This approach relies on the missing at random (MAR) assumption.

A term for 'center' is not included in the statistical model due to the low numbers of subjects expected in many centers. Randomization was not stratified by center for the same reason.

10.3.1.3 Handling of missing data

For WASO and LPS values, if one of the two values is missing either for baseline, Month 1 or Month 3, the single value available will be used as the mean for this time point. Otherwise, the mean value will be considered missing for that time point.

For sTST values, subjects must have at least 3 days of data during each week to calculate a weekly mean. Otherwise, the mean value will be considered missing for that week.

For IDSIQ sleepiness domain scores, subjects must have at least 4 days of data during each week to calculate a weekly mean. Otherwise, the mean value will be considered missing for that week.

Note that the above implies implicit imputation: the missing data point(s) is(are) given the same value as the mean of the non-missing data point(s) of that same week or time point.

10.3.1.4 Supportive/sensitivity analyses

The impact of deviations from the MAR assumption underlying the linear mixed effects model as well as the incidence and pattern of missing values will be explored in order to evaluate the possible impact on results and will be described in the SAP.

The analysis performed for the primary and secondary endpoints will be repeated using the PPS in order to assess the effect protocol deviations have on the results.

10.3.2 Analysis of other efficacy variables

Summary statistics will be provided for other efficacy endpoints using either number (%) of subjects for categorical variables or descriptive statistics (e.g., mean, SD, median, min., max.) for continuous variables. Further details will be described in the SAP.

10.3.3 Analysis of the safety variables

Analyses 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 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 Month 1 and Month 3 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 weight

Observed values and changes from baseline to Month 1 and Month 3 in vital signs (mean of the two PSG nights in systolic and diastolic BP, and pulse rate) will be summarized.

Observed values and changes from baseline to Month 3 in body weight will be summarized.

Electrocardiograms

Observed values and changes from baseline to Month 3 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 DB treatment (Visit 8, 2nd morning) to the beginning and the end of the treatment withdrawal period (in the morning at Visit 9 and at Visit 10, respectively).

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.

Insomnia rebound effect

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

The changes from baseline to the treatment withdrawal period (Visit 9, run-out) in objective sleep parameters (WASO, LPS and TST) will be summarized using descriptive statistics.

The changes from baseline (mean value based on the screening sleep diary entries performed at home in the 7 days immediately preceding the first PSG at Visit 3) to the treatment withdrawal period (after PSG night at Visit 9) in subjective sleep parameters (sWASO, sLSO, and sTST) will be summarized using descriptive statistics.

Next-day residual effect

Observed values and changes from baseline to Month 1 and Month 3 in Coding sub-test©, SDS©, and VAS scores (mm) assessing morning sleepiness, daytime alertness and daytime ability to function, 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 will be tabulated.

Shifts from baseline showing any changes in suicidal ideation and suicidal behavior during DB treatment 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.

10.3.4 Analysis of pharmacokinetic variables

PK analyses will be performed using the PK Set.

Descriptive statistics (n, mean, standard deviation, coefficient of variation [CV%], m [number of non-zero concentrations], geometric mean, geometric standard deviation, geometric CV%, median, minimum and maximum) of the ACT-541468 plasma

concentrations collected approximately 9–10 h post-dose (morning after the second PSG night) at Visit 6 and Visit 8 will be provided.

Exposure-safety analysis

The exposure-safety relationship will be explored using $C_{9–10h}$ (plasma concentrations of ACT-541468 in the morning after the second PSG night at Visit 6 and Visit 8) and will be based on the PK Set. Safety parameters considered for this analysis will likely include selected AEs (e.g., somnolence), changes from baseline in Coding sub-test©, SDS©, VAS scores (mm) assessing morning sleepiness, daytime alertness and daytime ability to function, and other parameters as relevant. Further details will be described in the SAP.

10.3.5 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 SAP.

10.3.6 Analysis of the patient preferences variable

Discrete choice data from the PAUSe sub-study will be analyzed using multinomial logit, random parameter logit, latent class and heteroscedastic conditional logit models. Socio-demographic and clinical characteristics, and health literacy and numeracy data will be collected from the study participants, and used as covariates for assessing preference and scale heterogeneity. The results of the DCE may be used to specify the weights and partial value functions in a quantitative benefit-risk assessment (BRA) of insomnia treatments. The BRA will be run both deterministically and probabilistically and will facilitate a stochastic multicriteria acceptability analysis (SMAA). The SMAA will involve running up to 10,000 iterations of the BRA, each time sampling weights and performance inputs from pre-specified distributions. Further details on analysis of the PAUSe sub-study will be provided in a separate SAP.

10.4 Interim analyses

No formal interim analysis will be performed for determining whether to stop (or modify) the study early (i.e., no hypothesis testing will be conducted *ad interim*). Therefore, no adjustment for multiple testing is required. This study includes an IDMC and ISB that will assess the safety of ACT-541468 on a regular basis as per the IDMC and ISB charters, respectively. To support the review of the safety and efficacy data by the IDMC, blinded data will be provided by Idorsia (or designated CRO) for the open sessions, and unblinded data will be provided by the ISAC for the closed sessions.

10.5 Sample size

The assumptions used to calculate sample size are provided in Table 2.

Table 2 Sample size assumptions for primary and secondary endpoints

Endpoint at Month 1 & Month 3	Expected mean difference compared to placebo	SD per treatment group	Effect size (mean/SD)
WASO	15	40	≈ 0.37
LPS	15	40	≈ 0.37
sTST	20	54	≈ 0.37
[redacted]	[redacted]	[redacted]	[redacted]

IDSIQ = Insomnia Daytime Symptoms and Impacts Questionnaire; LPS = Latency to Persistent Sleep; SD = standard deviation; sTST = subjective Total Sleep Time; WASO = Wake After Sleep Onset.

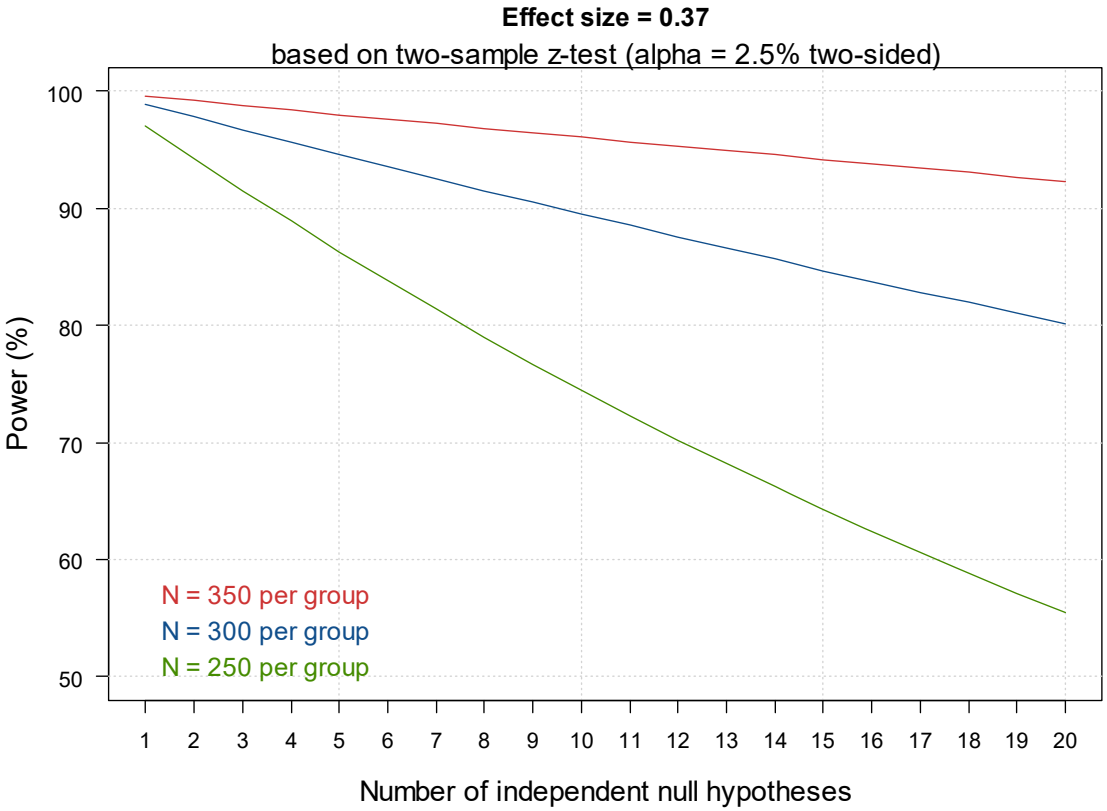
The assumptions for the between-subject SD per treatment group are based on two recently completed Phase 2 studies (AC-078A201, AC-078A202) conducted in adult and elderly populations receiving 5 mg, 10 mg, 25 mg, 50 mg ACT-541468 and/or placebo. The minimal clinically relevant difference compared to placebo in the mean change from baseline to Month 1 and Month 3 in WASO, LPS, and sTST is 15, 15 and 20 min, respectively.

[redacted]

Based on a two-sample z-test, at least 900 subjects randomized to 50 mg ACT-541468, 25 mg ACT-541468, and placebo in a 1:1:1 ratio (i.e., 300 per group) provides 98.9% power to detect an effect size of 0.37 for a single hypothesis test. This accounts for the Bonferroni correction [Section 10.3], where the significance level (alpha) is halved and set to 2.5% two-sided. However, as the number of null hypotheses (endpoints) to test increases, the power decreases, as shown in the figure below [Figure 3]. The power calculation in the figure assumes all null hypotheses are independent (a conservative assumption for power calculations) and the curves for N = 250 per group and N = 350 per group are included for

reference. Consequently, 900 subjects will provide at least 90% power to detect an effect size of 0.37 for testing 9 independent null hypotheses.

Figure 3 Effect of testing multiple null hypotheses on power at a given sample size



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, VAS, ISI©, IDSIQ, PGA-S daytime symptoms, PGI-C daytime and night-time symptoms, PGI-S night-time symptoms, SDS©, BWSQ) and on paper (i.e., Coding sub-test©) as well as the physician-reported global assessment on a tablet at site (i.e., C-SSRS©, MMSE©, PAUSe) and on paper (i.e., MINI©) 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 subject metadata or answers in physician-reported assessments. Site personnel will not be allowed to alter subject-generated data. A data correction form will be completed by the site personnel to request any data changes and sent to the CRO provider that 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 screening/randomization 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. If discrepant data are 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, PSGs and hand-held device data will be processed through a central laboratory / CRO and the results will be electronically sent to Idorsia.

If local laboratory data is obtained, 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 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. Study subjects will be reimbursed for the study-related expenses (e.g., travel costs, meals, hotel), and may be offered financial compensation for their participation in the study only to the extent permitted by applicable local 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 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 25 years 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 document 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 having 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 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 screening 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(s) 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 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 (the PAUSe sub-study results will be reported in a separate 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

[D-15.653] Double-blind, placebo-controlled, randomized, single ascending dose study to investigate the tolerability, safety, pharmacokinetics, pharmacodynamics, absolute bioavailability, mass balance, and metabolism of ACT-541468 in healthy male subjects. Actelion Pharmaceuticals Ltd. Clinical Study Report AC-078-101. 4 March 2016.

[D-16.087] A single-center, open-label, randomized, two-way crossover study to investigate the effect of multiple-dose diltiazem on the pharmacokinetics of a single dose of 25 mg ACT-541468 in healthy male subjects. Actelion Pharmaceuticals Ltd. Clinical Study Report AC-078-103. 28 April 2016.

[D-16.386] Double-blind, placebo-controlled, randomized study to investigate the tolerability, safety, pharmacokinetics, and pharmacodynamics of ACT-541468: Part A: Multiple-ascending doses in healthy young adults after morning administration; Part B: Single-ascending doses in healthy elderly subjects after morning administration; Part C: Repeated doses in both healthy young adults and elderly subjects after evening administration. Actelion Pharmaceuticals Ltd. Clinical Study Report AC-078-102. 7 November 2016.

[D-17.098] A single-center, open-label study to investigate the food effect on the pharmacokinetics of ACT-541468 and the effect of single- and multiple-dose ACT-541468 on the pharmacokinetics of midazolam and its metabolite 1-hydroxymidazolam in healthy male subjects. Idorsia Pharmaceuticals Ltd. Clinical Study Report AC-078-104. 28 November 2017.

[ACT-541468 IB] Investigator's Brochure for ACT-541468 version 5. Idorsia Pharmaceuticals Ltd. January 2018.

[aasmnet.org] American Academy of Sleep Medicine Standards and Guidelines for the Practice of Sleep Medicine, [regularly updated]. Available from: http://www.aasmnet.org

[Ambien® USPI] Ambien® (zolpidem) US Package Insert. United States Food and Drug Administration full prescribing information; https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/019908s038lbl.pdf

[Ancoli-Israel 1999] Ancoli-Israel S, Roth T. Characteristics of insomnia in the United States: results of the 1991 National Sleep Foundation Survey. Sleep. 1999;22 Suppl 2:S354-58.

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

[Balter 1991] Balter MB, Uhlenhuth EHJ. The beneficial and adverse effects of hypnotics. J Clin Psychiatry. 1991;52 Suppl:16-23.

[Belsomra® USPI] Belsomra® (suvorexant) US Package Insert. United States Food and Drug Administration full prescribing information; http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/204569s000lbledt.pdf

[Benca 2004] Benca RM, Ancoli-Israel S, Moldofsky H. Special considerations in insomnia diagnosis and management: depressed, elderly, and chronic pain populations. J Clin Psychiatry. 2004;65 Suppl 8:26-35.

[Bowling 2001] Bowling A, Ebrahim S. Measuring patients' preferences for treatment and perceptions of risk. Quality in Health Care. 2001;10(Supplement 1):i2–i8

[Bretz 2009] Bretz F, Maurer W, Brannath W, Posch M. A graphical approach to sequentially rejective multiple test procedures. Stat Med. 2009;28:586-604.

[Bridges 2011] Bridges JFP, Hauber AB, Marshall D, Lloyd A, Prosser L.A, Regier DA, et al. Conjoint Analysis Applications in Health—a Checklist: A Report of the ISPOR Good Research Practices for Conjoint Analysis Task Force, Value in Health 2011;14,403– 413.

[Buscemi 2007] Buscemi N, Vandermeer B, Friesen C, Bialy L, Tubman M, Ospina M, et al. The efficacy and safety of drug treatments for chronic insomnia in adults: a meta-analysis of RCTs. J Gen Intern Med. 2007;22(9):1335-50.

[Buysse 2007] Buysse DJ, Thompson W, Scott J, Franzen PL, Germain A, Hall M, et al. Daytime symptoms in primary insomnia: a prospective analysis using ecological momentary assessment. Sleep Med. 2007 Apr;8(3):198–208.

[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.

[Clark 2014] Clark MD, Determann D, Petrou S, Moro D, de Bekker-Grob EW. Discrete choice experiments in health economics: a review of the literature. Pharmacoeconomics. 2014;32(9):883-902.

[Coyle 2001] Coyle D, Wells G, Graham I, et al. The impact of risk on preference values: Implications for evaluations of postmenopausal osteoporosis therapy. Value in Health. 2001;4(5):385–91.

[de Lecea 1998] de Lecea L, Kilduff TS, Peyron C, Gao X, Foye PE, Danielson PE, et al. The hypocretins: hypothalamus-specific peptides with neuroexcitatory activity. Proc Natl Acad Sci USA. 1998;95:322–7.

[Desarnaud 2004] Desarnaud F, Murillo-Rodriguez E, Lin L, Xu M, Gerashchenko D, Shiromani SN, et al. The diurnal rhythm of hypocretin in young and old F344 rats. Sleep. 2004;27:851–6.

[EMA 2011] European Medicines Agency guideline on medicinal products for the treatment of insomnia. EMA/CHMP/16274/2009 Rev. 1. 7 February 2011. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2011/02/WC500102351.pdf

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

[FDA 2007] Food and Drug Administration (US) Requests Label Change for All Sleep Disorder Drug Products. Available from: https://www.ptcommunity.com/news/20170421/fda-requests-label-change-all-sleep-disorder-drug-products

[FDA 2017] Food and Drug Administration (US): Assessment of Abuse Potential of Drugs. January 2017; Available from: https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm198650.pdf

[Folstein 1975] Folstein MF, Folstein SE, McHugh PR. “Mini-mental state”: A practical method for grading the cognitive state of patients for the clinician. J. Psychiat. Res. 1975;12:189-98

[Ford 1989] Ford DE, Kamerow DB. Epidemiologic study of sleep disturbances and psychiatric disorders. An opportunity for prevention? JAMA. 1989;262(11): 1479-84.

[Fortier-Brochu 2014] Fortier-Brochu E, Morin CM. Cognitive impairment in individuals with insomnia: clinical significance and correlates. Sleep. 2014;37(11):1787-98.

[Hagan 1999] Hagan JJ, Leslie RA, Patel S, Evans ML, Wattam TA, Holmes S, et al. Orexin A activates locus coeruleus cell firing and increases arousal in the rat. Proc Natl Acad Sci USA. 1999;96:10911–6.

[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.

[Hohagen 1994] Hohagen F, Käppler C, Schramm E, Riemann D, Weyerer S, Berger M. Sleep onset insomnia, sleep maintaining insomnia and insomnia with early morning awakening-temporal stability of subtypes in a longitudinal study on general practice attenders. Sleep. 1994;17(6):551-4.

[Holbrook 2000] Holbrook AM, Crowther R, Lotter A, Cheng C, King D. Meta-analysis of benzodiazepine use in the treatment of insomnia. CMAJ. 2000;162(2):225-33.

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

[Kales 1978] Kales A, Scharf MB, Kales JD. Rebound insomnia: a new clinical syndrome. Science. 1978;201(4360):1039-41.

[Kilduff 2000] Kilduff TS, Peyron C. The hypocretin/orexin ligand-receptor system: implications for sleep and sleep disorders. Trends Neurosci. 2000;23:359–65.

[Kuriyama 2014] Kuriyama A, Honda M, Hayashino Y. Ramelteon for the treatment of insomnia in adults: a systematic review and meta-analysis. Sleep Med. 2014;15(4):385-92.

[Léger 2002] Léger D, Guilleminault C, Bader G, Lévy E, Paillard M. Medical and socio-professional impact of insomnia. Sleep. 2002;25(6):625-9.

[Lieberman 2007] Lieberman JA. Update on the safety considerations in the management of insomnia with hypnotics: incorporating modified-release formulations into primary care. Prim Care Companion J Clin Psychiatry. 2007;9(1):25-31.

[Lin 1999] Lin L, Faraco J, Li R, Kadotani H, Rogers W, Lin X, et al. The sleep disorder canine narcolepsy is caused by a mutation in the hypocretin (orexin) receptor 2 gene. Cell. 1999;98(3):365-76.

[Lunesta® USPI] Lunesta® (eszopiclone) US Package Insert. United States Food and Drug Administration full prescribing information; http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/021476s030lbl.pdf

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

[Mignot 2002] Mignot E, Lammers GJ, Ripley B, Okun M, Nevsimalova S, Overeem S, et al. The role of cerebrospinal fluid hypocretin measurement in the diagnosis of narcolepsy and other hypersomnias. Arch Neurol. 2002;59(10):1553–62.

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

[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.

[Nutt 2006] Nutt D. GABAA receptors: subtypes, regional distribution, and function. J Clin Sleep Med. 2006;2(2):Suppl S7-11.

[Ohayon 2001] Ohayon MM, Zulley J, Guilleminault C, Smirne S, Priest RG. How age and daytime activities are related to insomnia in the general population: consequences for older people. J Am Geriatr Soc. 2001;49(4):360–6.

[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 2004] Ohayon MM, Carskadon MA, Guilleminault C, Vitiello MV. Meta-analysis of quantitative sleep parameters from childhood to old age in healthy individuals: developing normative sleep values across the human lifespan. Sleep. 2004;27(7):1255–73.

[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.

[Pauker 1981] Pauker SG, McNeil BJ. Impact of patient preferences on the selection of therapy. J Chronic Dis. 1981; 34(2–3):77–86

[Petursson 1981] Petursson H, Lader MH. Benzodiazepine dependence. Br J Addict. 1981;76(2):133-45.

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

[Pigeon 2010] Treatment of adult insomnia with cognitive-behavioral therapy. J Clin Psychol. 2010;66(11):1148–60.

[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.

[Rosenthal 1993] Rosenthal L, Roehrs TA, Rosen A, Roth T. Level of sleepiness and total sleep time following various time in bed conditions. Sleep. 1993;16(3): 226-32

[Roth 2007] Roth T. Insomnia: Definition, Prevalence, Etiology, and Consequences. J Clin Sleep Med. 2007;3 Suppl 5:S7-10.

[Sakurai 2007] Sakurai T. The neural circuit of orexin (hypocretin): maintaining sleep and wakefulness. Nat Rev Neurosci. 2007;8:171–81.

[Samson 2010] Samson WK, Bagley SL, Ferguson AV, White MM. Orexin receptor subtype activation and locomotor behaviour in the rat. Acta Physiol (Oxf). 2010;198:313–24.

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

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

[Sheehan 1996] Sheehan DV, Harnett-Sheehan K, Raj BA. The measurement of disability. Int Clin Psychopharmacol 1996;11 Suppl 3:S89-95

[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.

[Simon 1997] Simon GE, VonKorff M. Prevalence, burden, and treatment of insomnia in primary care. Am J Psychiatry. 1997;154(10):1417-23.

[Simpson 2008] Simpson D, Curran MP. Ramelteon: a review of its use in insomnia. Drugs. 2008;68(13):1901-19.

[Tervonen 2017] Tervonen T, Gelhorn H, Sri Bhashyam S, et al. MCDA swing weighting and discrete choice experiments for elicitation of patient benefit-risk preferences: a critical assessment. Pharmacoepidemiol Drug Saf. 2017;1–9.

[Thannickal 2000] Thannickal TC, Moore RY, Nienhuis R, Ramanathan L, Gulyani S, Aldrich M, et al. Reduced number of hypocretin neurons in human narcolepsy. Neuron. 2000;27(3):469–74.

[Treat Guidel Med Lett 2009] Drugs for insomnia. Treat Guidel Med Lett. 2009;7:23-6.

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

[Zammit 1999] Zammit GK, Weiner J, Damato N, Sillup GP, McMillan CA. Quality of life in people with insomnia. Sleep. 1999;22 Suppl 2:S379-85.

[Zeitzer 2003] Zeitzer JM, Buckmaster CL, Parker KJ, Hauck CM, Lyons DM, Mignot E. Circadian and homeostatic regulation of hypocretin in a primate model: implications for the consolidation of wakefulness. J Neurosci. 2003;23:3555–60.

14 APPENDICES

Appendix 1 Alcohol restrictions during the study

The subjects must not drink alcohol for at least 24 hours prior to the start of the PSG assessments, as well as during the PSG assessments including the morning after the second PSG assessment, until they leave the center.

On non-PSG nights, the subjects will be instructed to limit alcohol to a maximum of 2 drinks per day, and to refrain from drinking alcohol at least 3 hours before going to bed.

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 soda drinks (unless decaffeinated 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. To be eligible, subjects must not be treated with CNS-active drugs for 5 half-lives of the respective drug (but at least 2 weeks) prior to Visit 1. The use of CNS-active drugs is forbidden or restricted until 24 hours after EOT (Visit 10).

Drug Class	Examples	Forbidden / Restricted	Comment
Centrally Acting Anticholinergics	e.g., tropatepine, oxybutynin, solifenacin, dimenhydrinate, dextrometorphan.	F	
Antihistamines	*Sedating:* e.g., carbinoxamine, triprolidine HCl, acrivastine, azatadine, chlorpheniramine, doxylamine, hydroxyzine, ketotifen, promethazine & timeprazine, diphenhydramine HCl.	F	
	Non-sedating: e.g., cetirizine, desloratidine, fexofenadine, levocabasteine, loratidine.	R	Non-sedating antihistamines may be used maximum twice weekly for allergic symptoms.
Psychotropics	*Stimulants:* e.g., amphetamine derivatives, ephedrine derivatives, modafinil, armodafinil, methylphenidate, aripiprazole, pramipexole, levodopa.	F	
	Antidepressants: e.g., bupropion, citalopram, doxepin, duloxetine, escitalopram, fluoxetine, fluvoxamine, nefazodone, paroxetine, sertraline, trazodone, amitriptyline, clomipramine, desipramine, imipramine, mirtazapine, nortriptyline, trimipramine, venlafaxine, hydracarbazine, moclobemide, selegiline.	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.		
	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	Warfarin, heparin, ticlopidine	F	
	Isotrenitoin	F	
	Systemic glucocorticoids: e.g., dexamethasone, methylprednisone, prednisone.	F	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.
	Anti-emetics: e.g., domperidone, metoclopramide.	F	

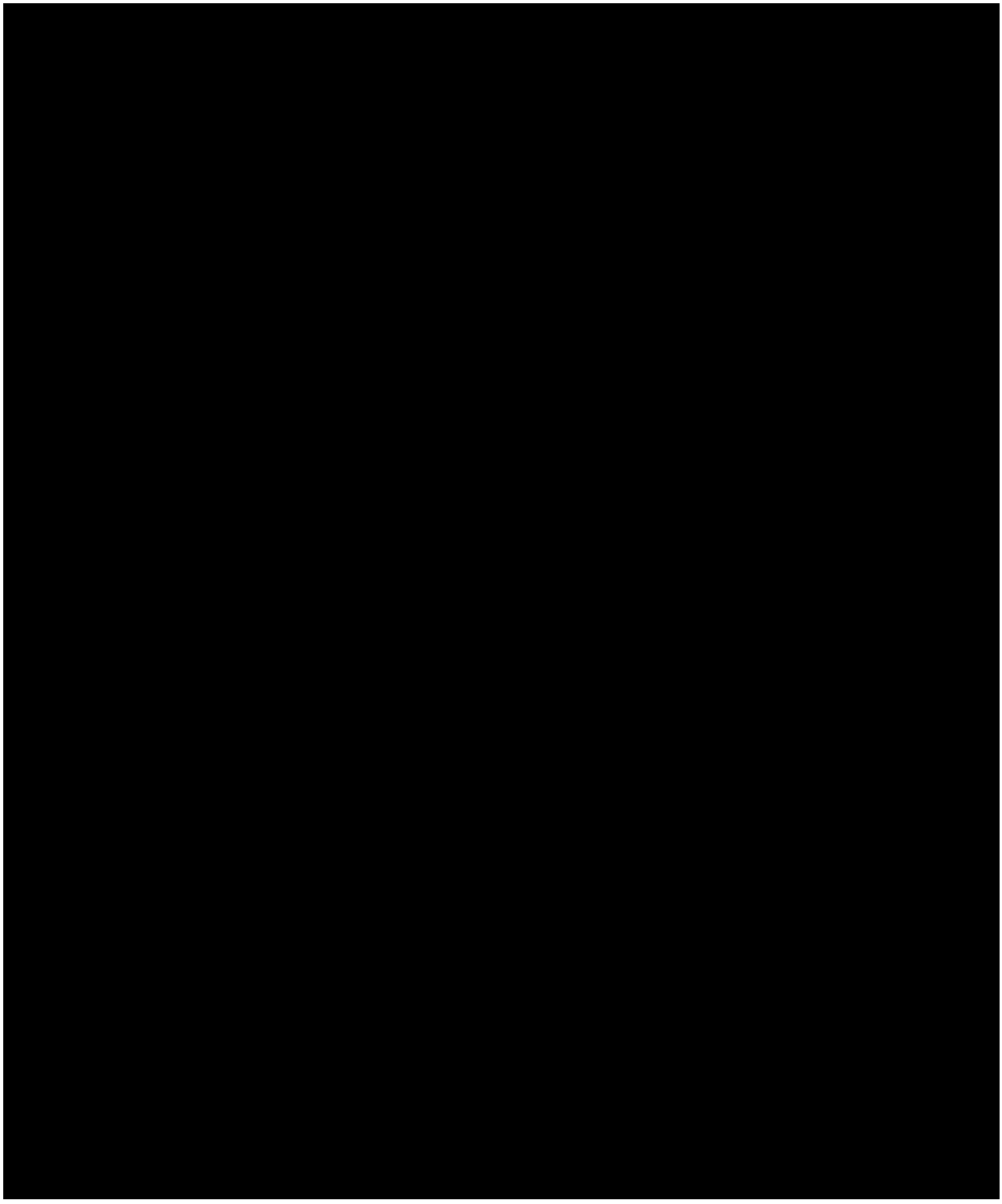
GABA = gamma-aminobutyric acid; NSAID = nonsteroidal anti-inflammatory drug; OTC = over-the-counter.

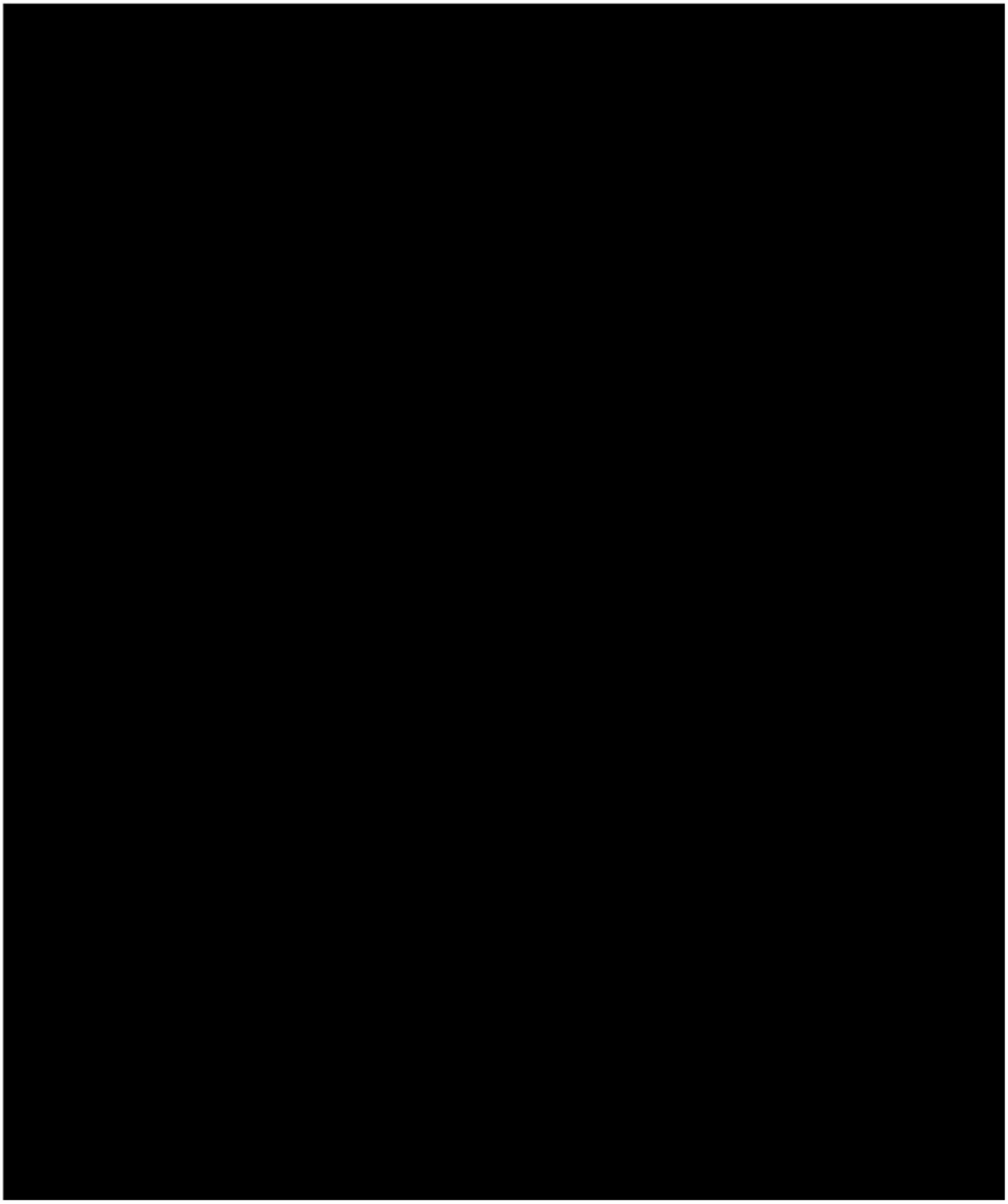
2. Non-exhaustive list of forbidden concomitant medications and diets due to potential drug interactions with CYP3A4 (moderate and strong inhibitors, inducers). Those medications must be discontinued no later than within 1 week prior to Visit 2 and are forbidden until 24 hours after EOT (Visit 10).

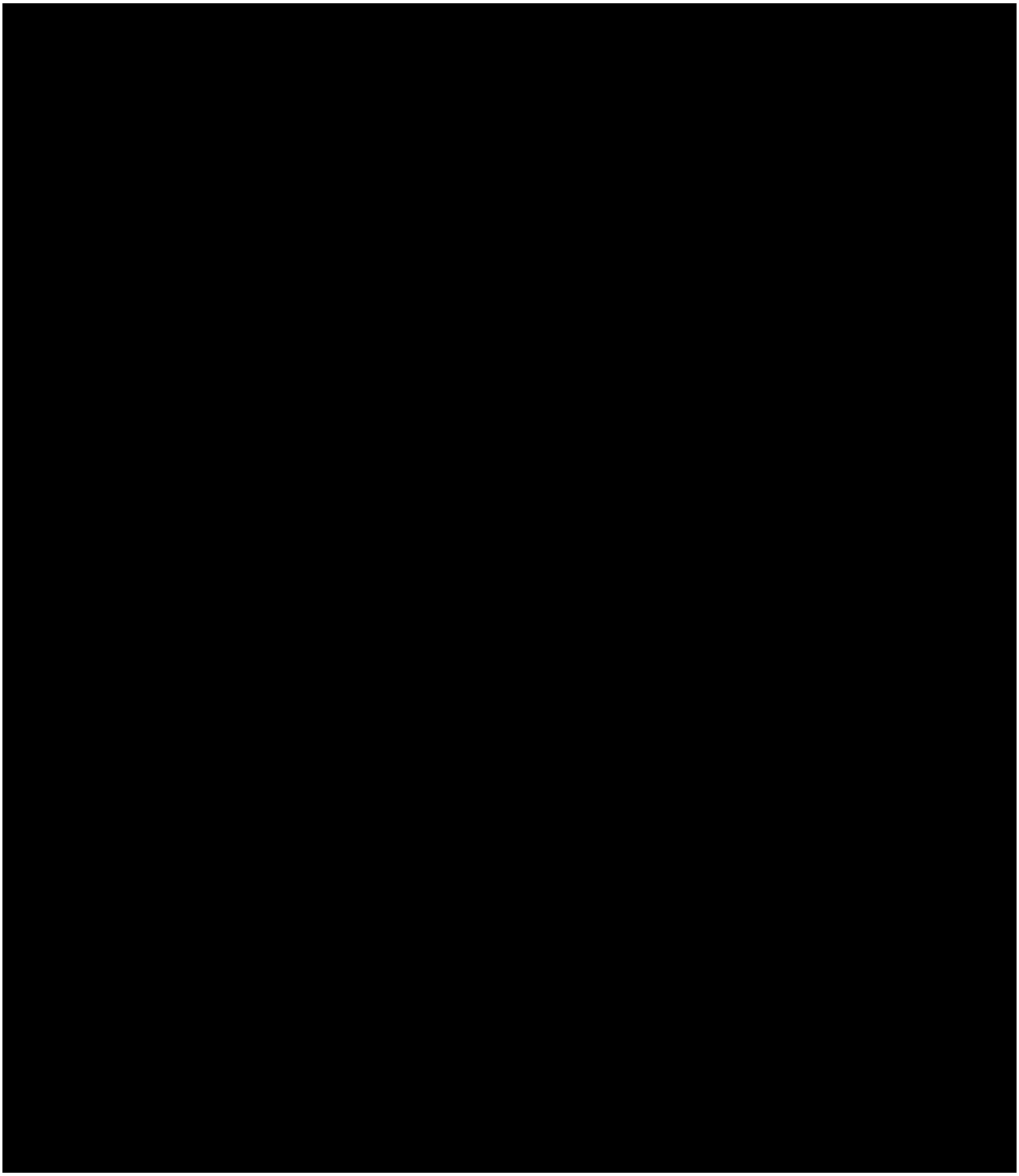
CYP3A4 moderate and strong inhibitors and CYP3A4 moderate and strong inducers:

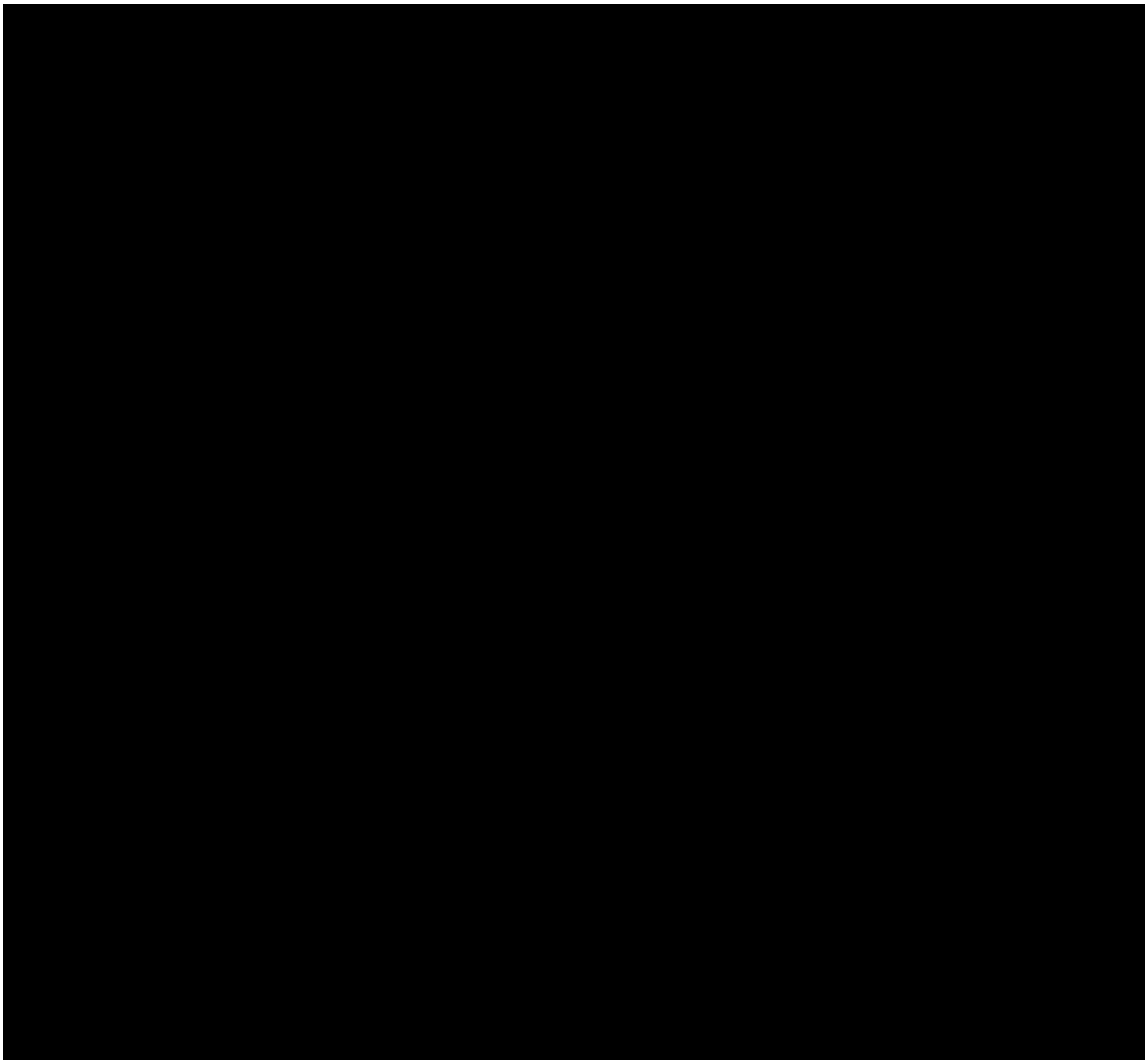
Inhibitors of CYP3A4	Inducers of CYP3A4
HIV antivirals: atazanavir, boceprevir, cobicistat, darunavir, delaviridine, fosamprenavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, telaprevir	HIV antivirals: efavirenz, etravirine
Antibiotics: ciprofloxacin, clarithromycin, erythromycin, norfloxacin, 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	

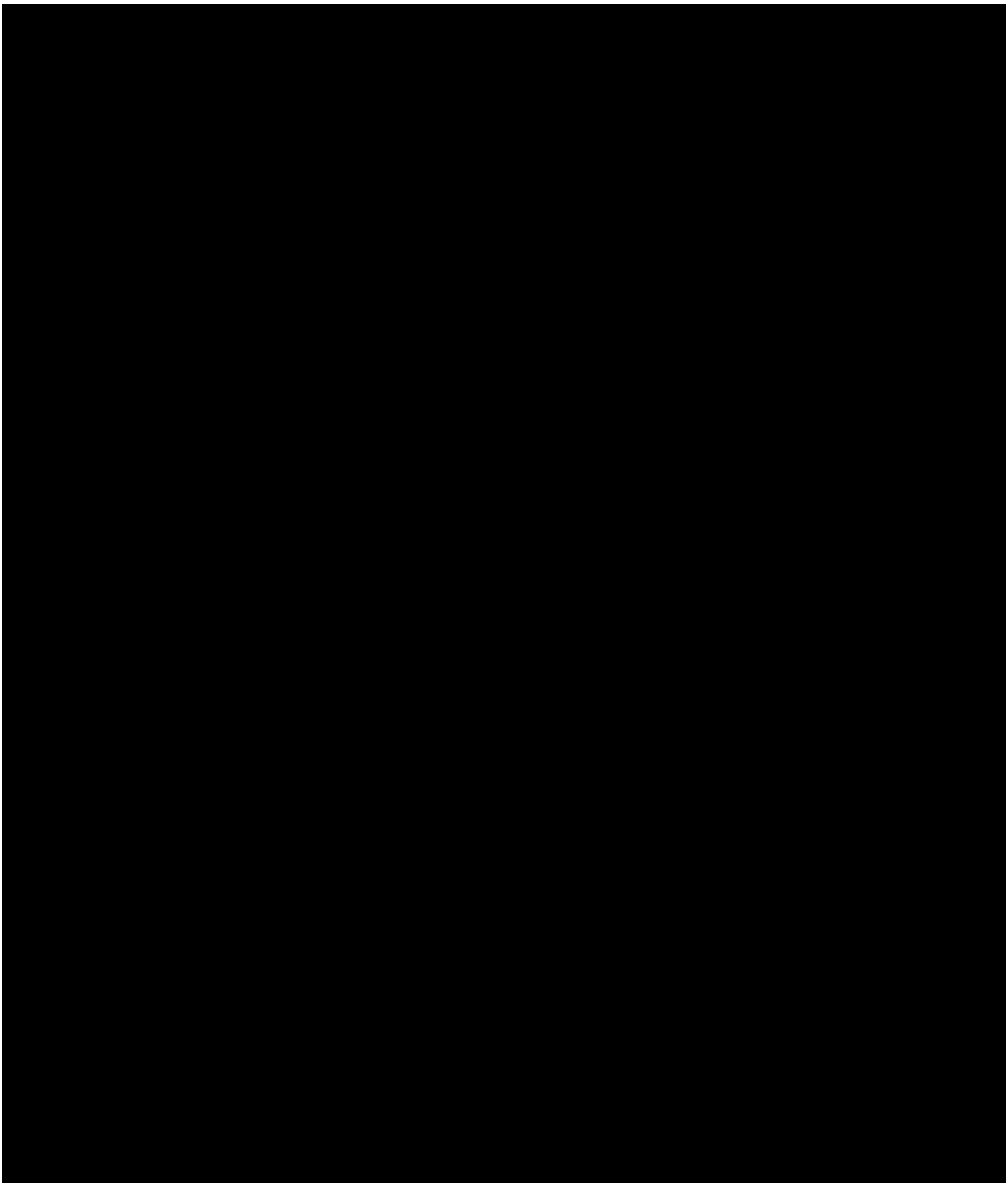
CNS = central nervous system; CYP = cytochrome P450; HIV = human immunodeficiency virus.

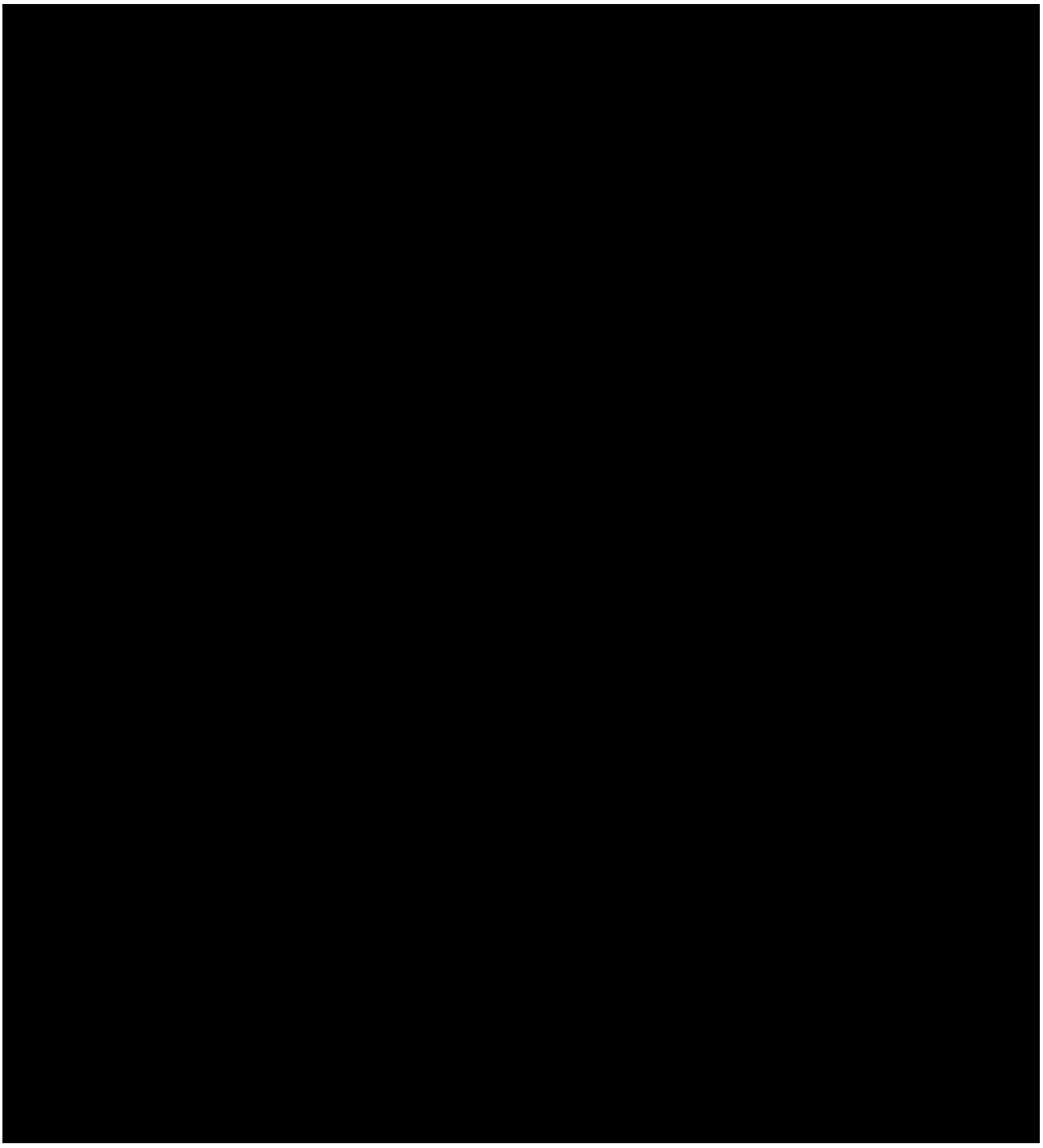


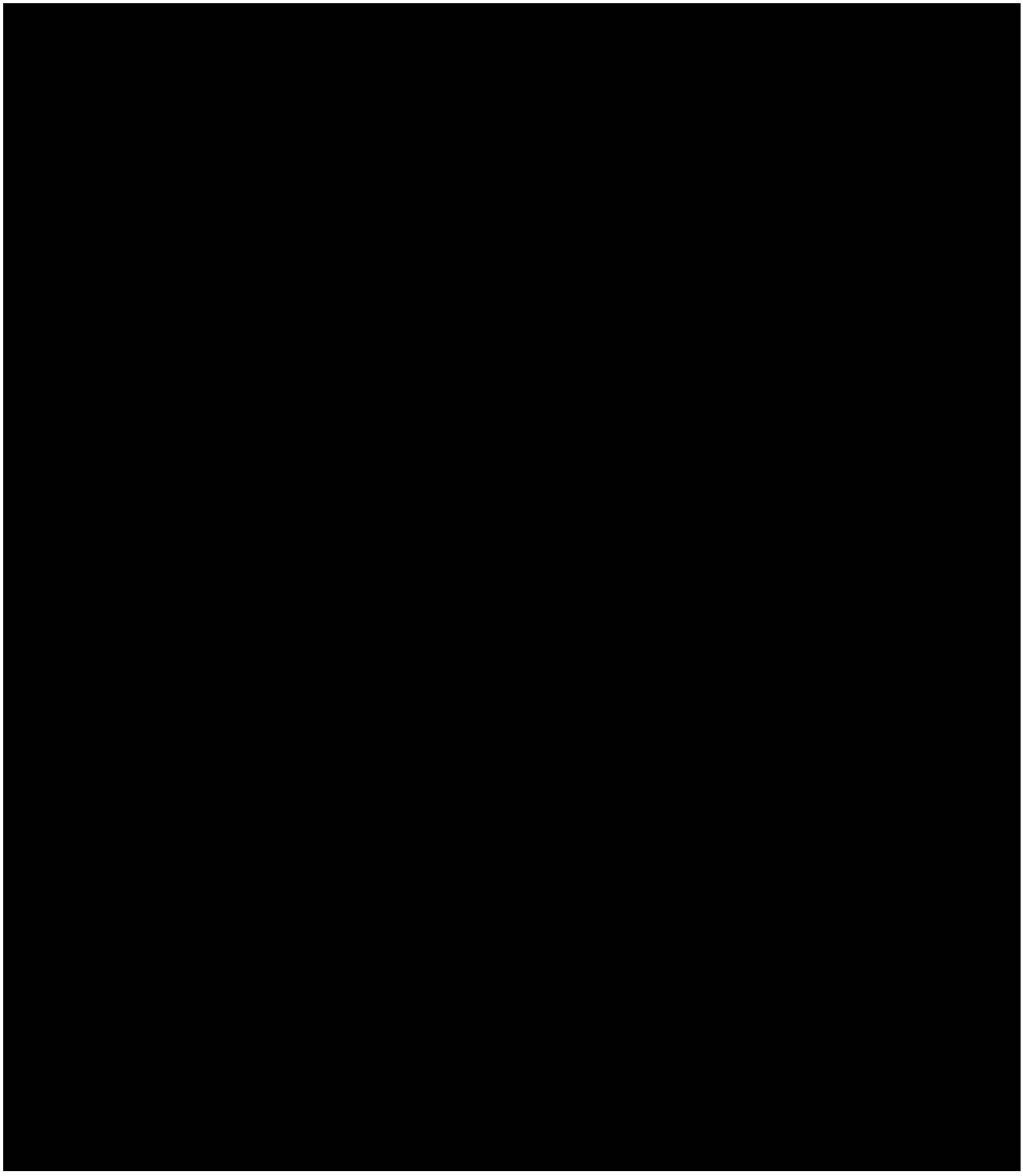


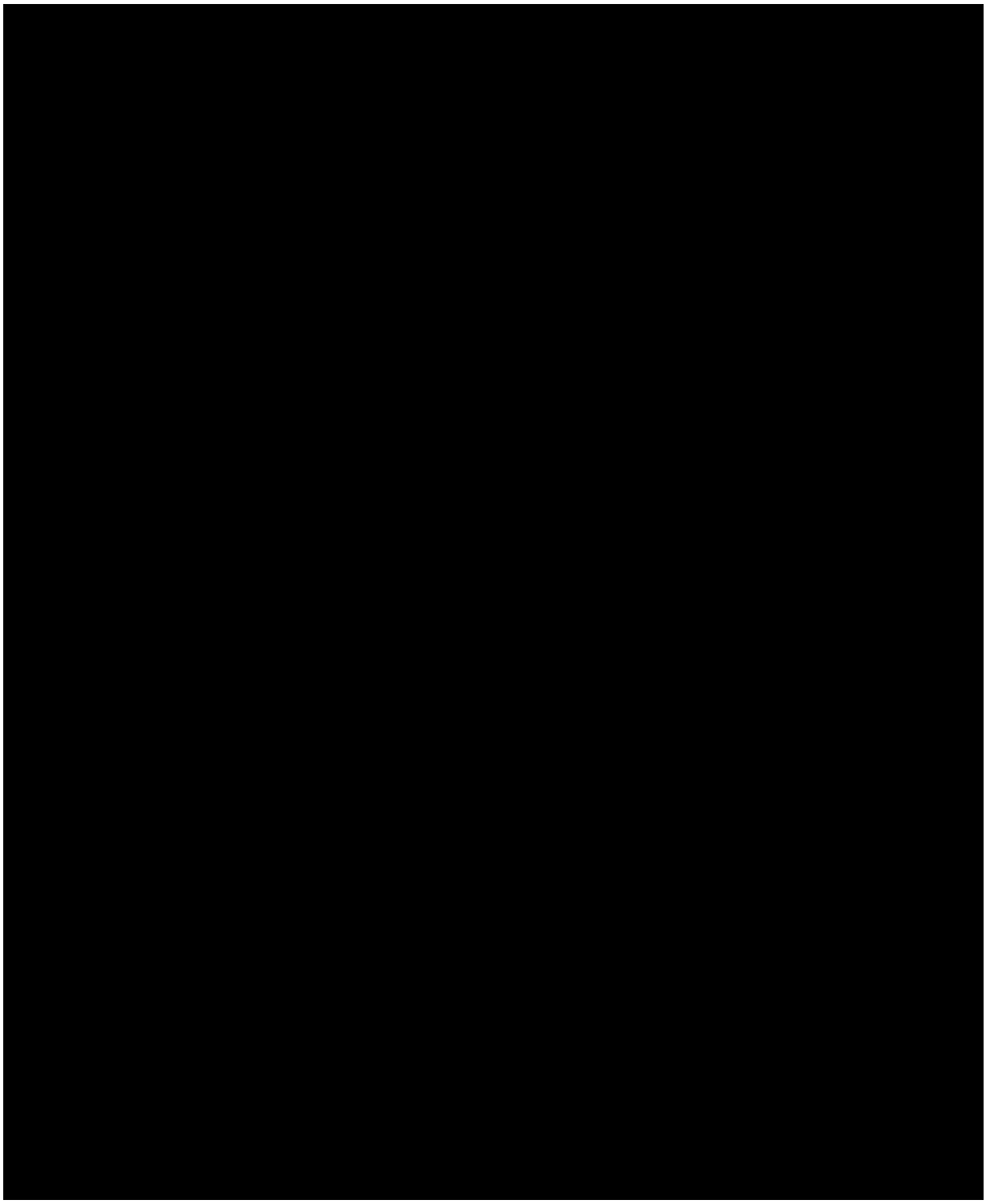


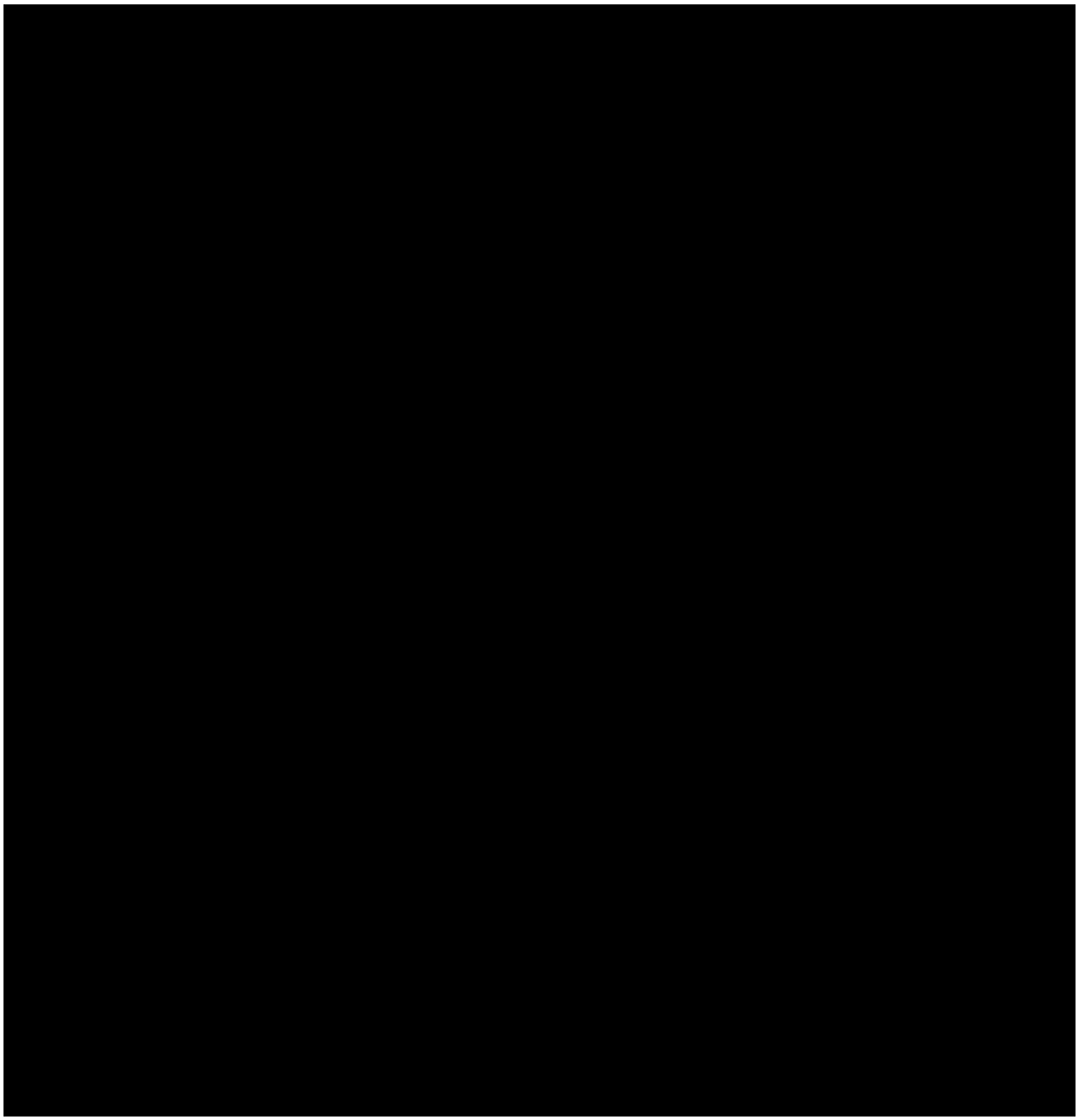


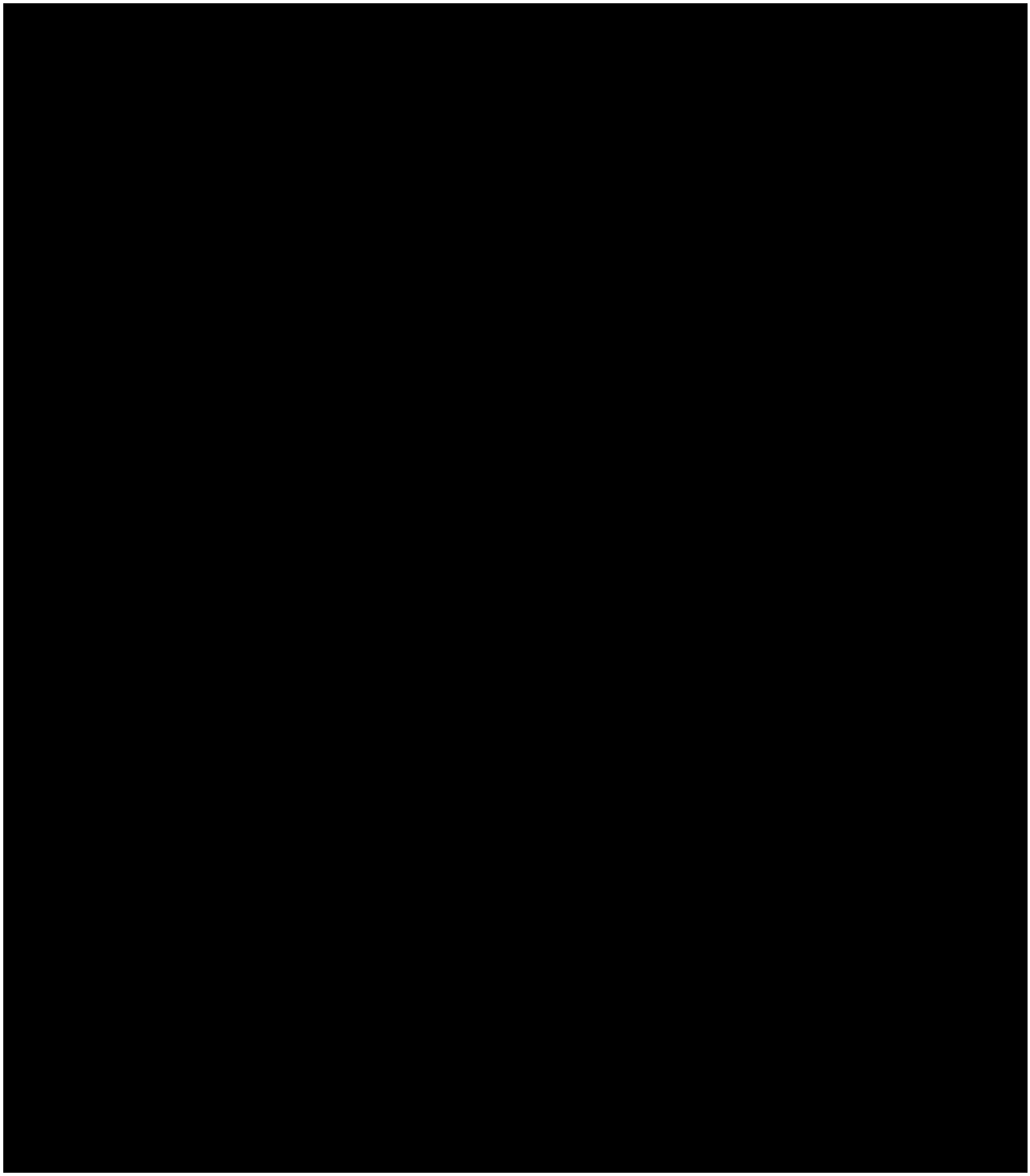


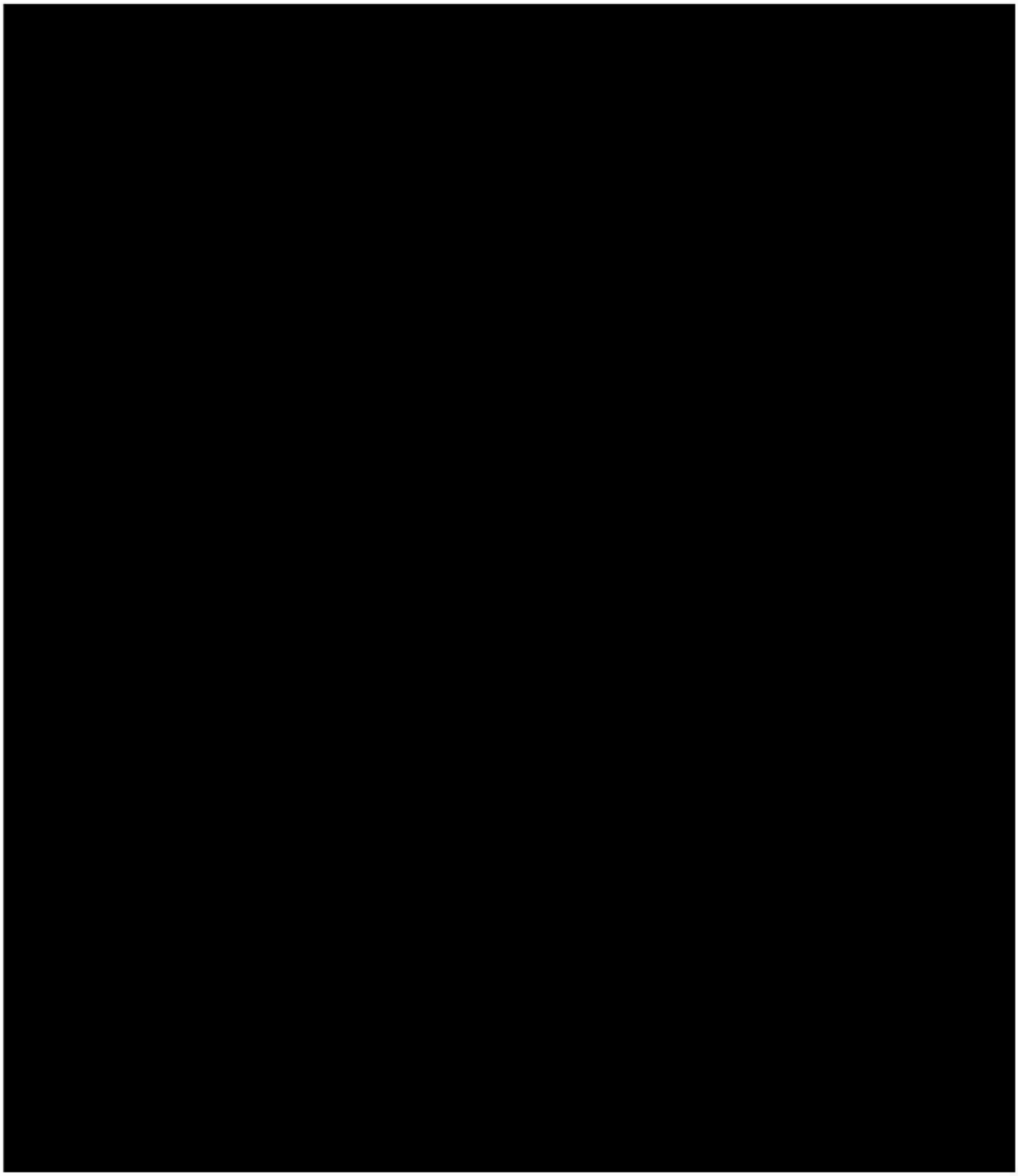


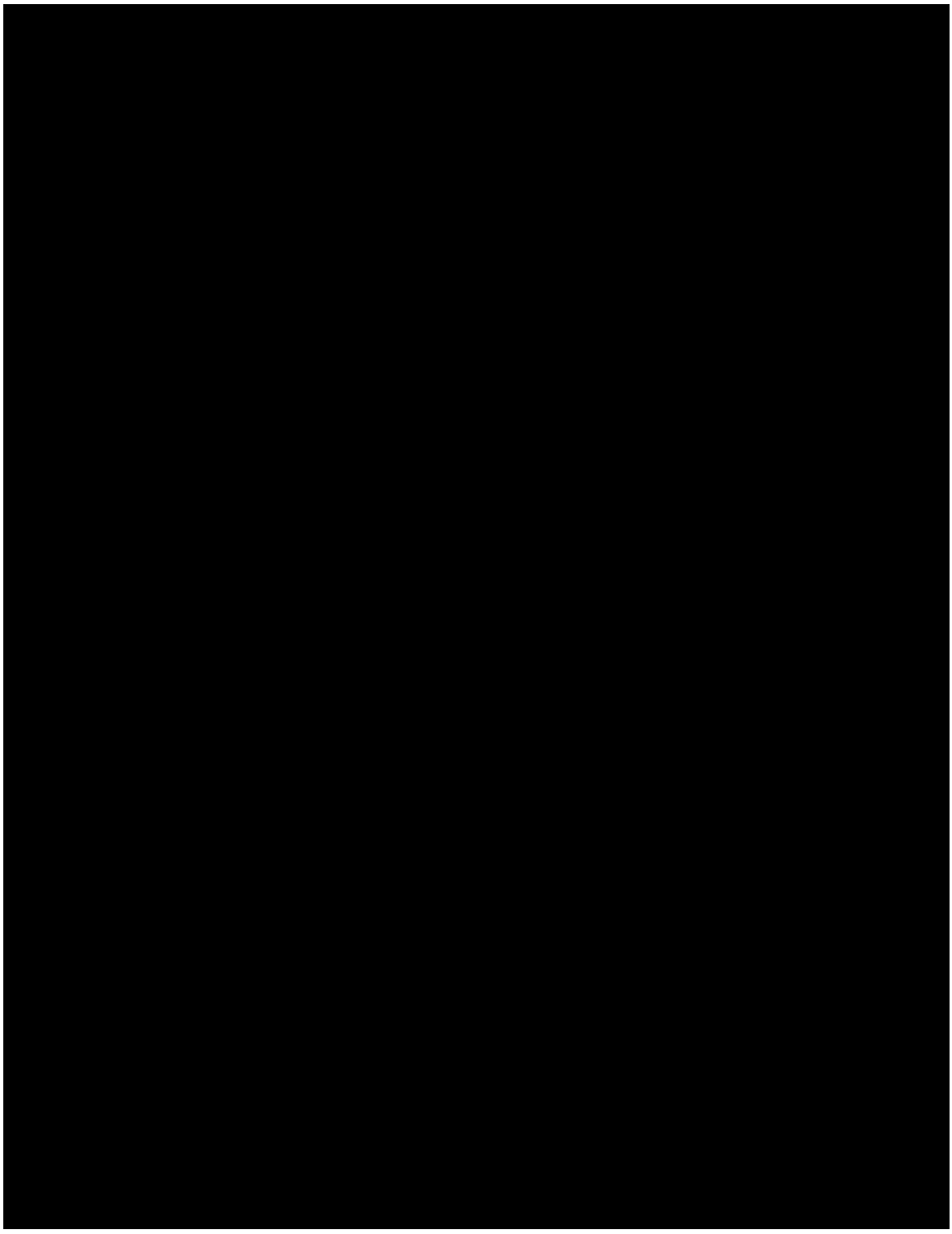












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