Study Protocol AC-078A202

Multi-center, Double-blind, Randomized, Placebo-controlled, 5-period, 5-treatment Crossover, Polysomnography Dose-response Study to Assess the Efficacy and Safety of ACT-541468 in Elderly Subjects With Insomnia Disorder.

ClinicalTrials.gov Identifier NCT02841709

The study was sponsored was sponsored by Actelion Pharmaceuticals Ltd.
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ACT-541468

Insomnia Disorder

Protocol AC-078A202

Multi-center, double-blind, randomized, placebo-controlled, 5-period, 5-treatment crossover, polysomnography dose-response study to assess the efficacy and safety of ACT-541468 in elderly subjects with insomnia disorder

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SPONSOR CONTACT DETAILS

Sponsor	ACTELION Pharmaceuticals Ltd Gewerbestrasse 16 CH-4123 Allschwil Switzerland [redacted]
Clinical Trial Physician	Contact details of the Clinical Trial Physician can be found in the Investigator Site File
Medical Emergency Hotline	Site-specific toll telephone numbers and toll-free numbers for the Medical Emergency Hotline can be found in the Investigator Site File

ACTELION CONTRIBUTORS TO THE PROTOCOL

Clinical Trial Scientist	[redacted]
Clinical Trial Statistician	[redacted]
Clinical Trial Physician	[redacted]
Clinical Trial Pharmacologist	[redacted]
Drug Safety Physician	[redacted]

CONTRACT RESEARCH ORGANIZATIONS INFORMATION

CENTRAL LABORATORY	[redacted]
CENTRAL RANDOMIZATION	
ePRO	
ECG core lab	
PSG core lab	

A list of site-specific contact details for Contract Research Organizations (CROs) can be found in the Investigator Site File.

SIGNATURE PAGE FOR ACTELION PHARMACEUTICALS LTD

Hereinafter called Actelion

Treatment name / number

ACT-541468

Indication

Insomnia Disorder

Protocol number, study title

AC-078A202

Multi-center, double-blind, randomized, placebo-controlled, 5-period, 5-treatment crossover, polysomnography dose-response study to assess the efficacy and safety of ACT-541468 in elderly subjects with insomnia disorder.

I approve the design of this study.

Title	Name	Date	Signature
Clinical Trial Physician	[redacted]		
Clinical Trial Statistician			

INVESTIGATOR SIGNATURE PAGE

Treatment name / number

ACT-541468

Indication

Insomnia Disorder

Protocol number, study title

AC-078A202

Multi-center, double-blind, randomized, placebo-controlled, 5-period, 5-treatment crossover, polysomnography dose-response study to assess the efficacy and safety of ACT-541468 in elderly subjects with insomnia disorder.

I agree to the terms and conditions relating to this study as defined in this protocol, the electronic Case Report Form (eCRF), 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 wellbeing of the subjects).

I agree to conduct this study in accordance with the Declaration of Helsinki principles, International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines, and applicable regulations and laws. I will obtain approval by an independent ethics committee or institutional review board (IEC/IRB) prior to study start and signed informed consent from all subjects included in this study. If an amendment to the protocol is necessary, I will obtain approval by an IEC/IRB and ensure approval by regulatory authorities has been obtained before the implementation of changes described in the amendment, and I will re-consent the subjects (if applicable). I will allow direct access to source documents and study facilities to sponsor representative(s), particularly Clinical Research Associate(s) (CRA[s]) and auditor(s), and agree to inspection by regulatory authorities or IEC/IRB representative(s). I will ensure that the study treatment(s) supplied by the sponsor is/are being used only as described in this protocol. I will ensure that all subjects have understood the nature, objectives, benefits, implications, risks and inconveniences for participating in this study. During the conduct of the study, I will constantly monitor the risk/benefit balance for an individual subject. 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.

	Country	Site number	Town	Date	Signature
Principal Investigator					

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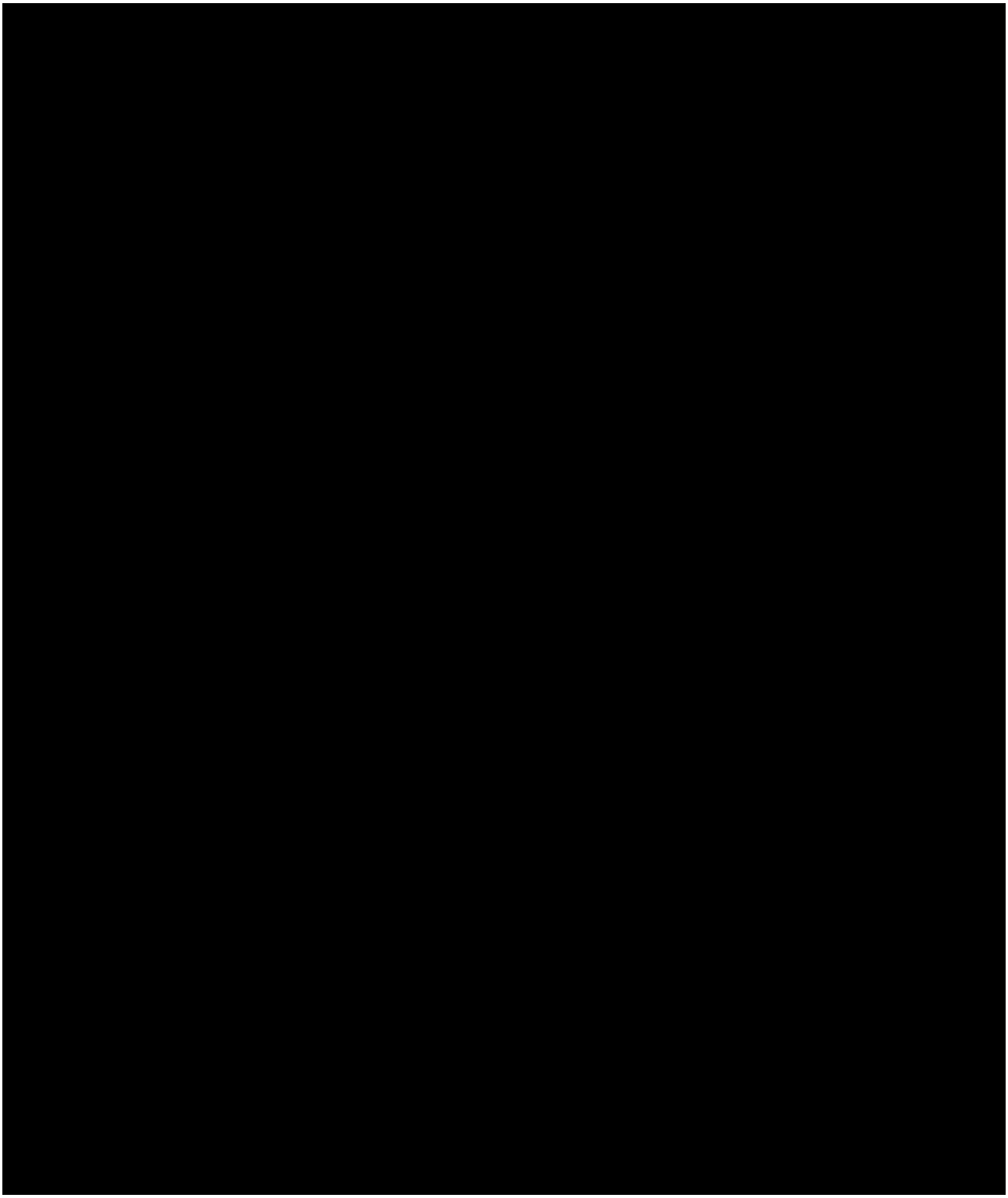
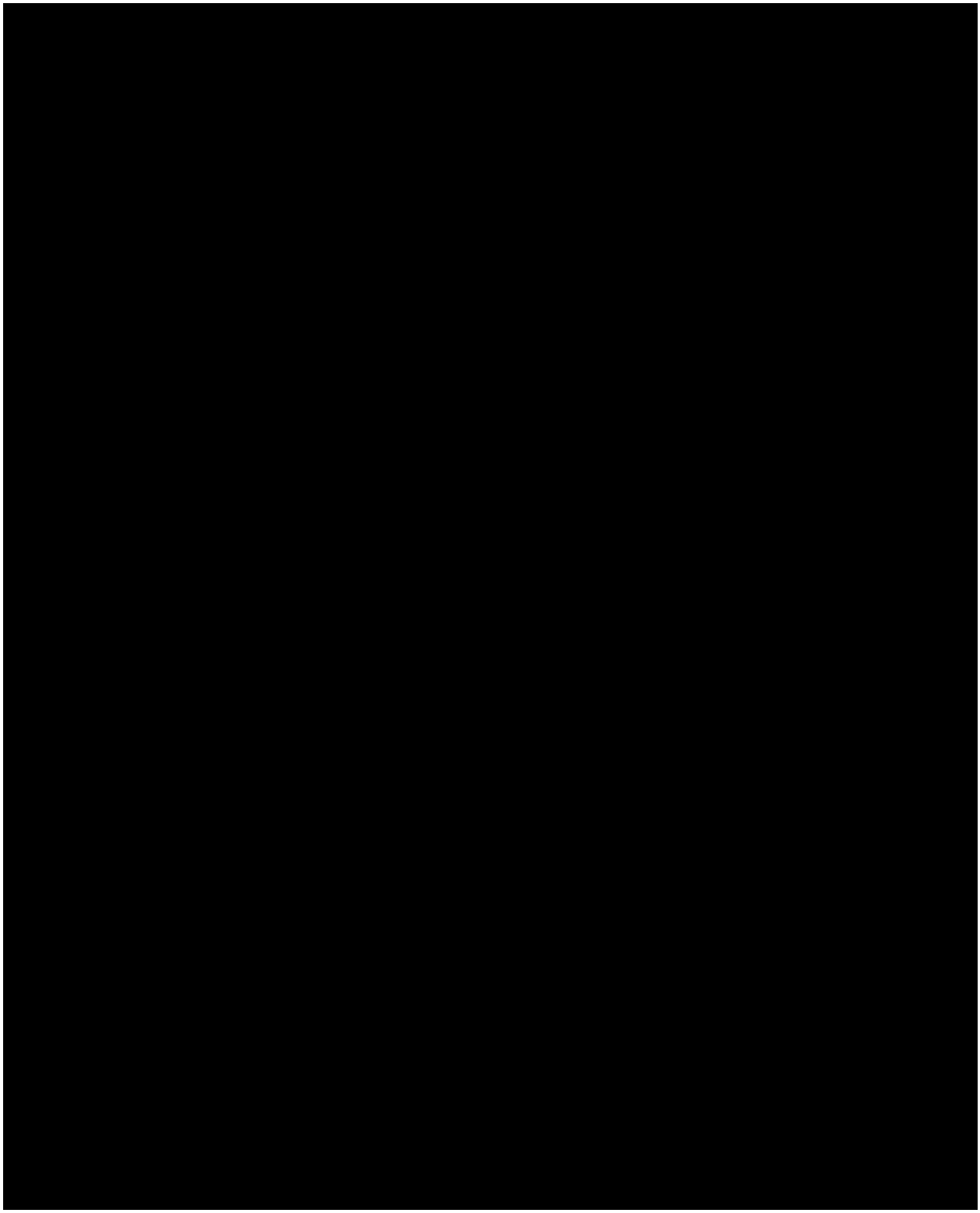
AASM	American Academy of Sleep Medicine
AE	Adverse event
AHI	Apnea/hypopnea index
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve
$AUC_{0-\infty}$	Area under the plasma concentration-time curve from zero to infinity
BCRP	Breast Cancer Resistance Protein
BMI	Body mass index
BP	Blood pressure
bpm	Beats per minute
CBT	Cognitive behavioral therapy
C_{max}	Maximum plasma concentration
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
CYP	Cytochrome P450
DDI	Drug-drug interaction
DoA	Delegation of Authority
DORA	Dual orexin receptor antagonist
DSM	Diagnostic and Statistical Manual of Mental Disorders
DSST©	Digit Symbol Substitution Test
ECG	Electrocardiogram
eCRF	Case Report Form (eCRF, electronic CRF)
EMA	European Medicines Agency
E_{max}	Effect maximum
EOS	End of Study

EOT	End of Treatment
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
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
KSS	Karolinska Sleepiness Scale
LPS	Latency to persistent sleep
MCP-Mod	Multiple Comparison Procedure – Modeling
MCT	Multiple contrast test
MedDRA™	Medical Dictionary for Regulatory Activities
mFAS	Modified Full Analysis Set
NOAEL	No-observed-adverse-effect level
NOEL	No-observed-effect level
OTC	Over-the-counter
PD	Pharmacodynamics
P-gP	P-glycoprotein 1
PI	Principal investigator
PK	Pharmacokinetics
PLMAI	Periodic limb movement with arousal index
PPS	Per-protocol Set
PRO	Patient-Reported Outcome

PSG	Polysomnography
QS	Quality System
QT_C	Corrected QT interval
REM	Rapid eye movement
RSI	Reference safety information
SAD	Single-ascending dose
SAE	Serious adverse event
SAP	Statistical analysis plan
SDS©	Sheehan Disability Scale
SE	Sleep efficiency
SIV	Site initiation visit
sLSO	Subjective latency to sleep onset
sNA	Self-reported number of awakenings
SOC	System organ class
SOP	Standard operating procedure
SpO_2	Oxygen saturation by pulse oximetry
SQ	Sleep Quality
SS	Safety Set
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
t_{max}	Time to reach maximum plasma concentration
TST	Total sleep time
ULN	Upper limit of the normal range
USPI	US package insert
V	Visit
VAS	Visual analog scales
VHP	Voluntary Harmonization Procedure
WASO	Wake after sleep onset





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PROTOCOL SYNOPSIS AC-078A202

TITLE	Multi-center, double-blind, randomized, placebo-controlled, 5-period, 5-treatment crossover, polysomnography dose-response study to assess the efficacy and safety of ACT-541468 in elderly subjects with insomnia disorder.
OBJECTIVES	**Primary objective** The primary objective of the study is to evaluate the dose response of ACT-541468 on the change of wake after sleep onset (WASO) assessed by polysomnography (PSG) on the first two days of each treatment period. **Secondary objective** The secondary objective of the study is to evaluate the dose response of ACT-541468 on latency to persistent sleep (LPS) on the first two days of each treatment period. **Other objectives** Other objectives are described in Section 2.3.
DESIGN	Multi-center, double-blind, randomized, placebo-controlled, 5-period, 5-treatment crossover, polysomnography dose-response Phase 2 study in elderly subjects with insomnia disorder.
PHASES	The **screening phase** lasts a minimum of 14 days and a maximum of 28 days. It starts with the signature of the Informed Consent Form and ends with subject randomization. It includes the screening period (from Day –28 to Day –7) and the run-in period (from Day –14 to Day –1). The **screening period** starts with Visit (V) 1, which occurs between Day –28 and Day –14. V1 is followed by the completion of the screening sleep diary for at least 7 consecutive days at home and until V2. The **run-in period** occurs between Day –14 and Day –1 and starts with V2. V2 consists of two consecutive PSG nights on single-blind placebo treatment occurring between Day –14 and Day –6. V2 is followed by 5 to 12 days at home with no treatment.

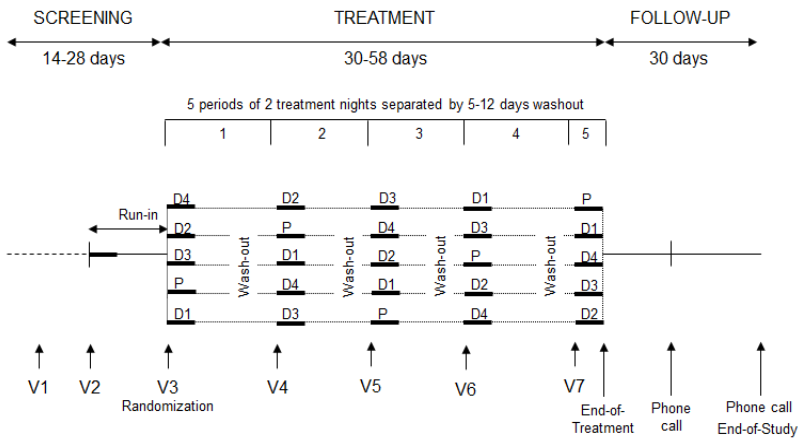
The double-blind **treatment phase** starts with the first dose of double-blind study treatment in the first evening of the Randomization visit (V3) and ends in the second morning of V7. It consists of five **treatment periods**, each consisting of two consecutive PSG nights on the assigned study treatment followed by a 5- to 12-day washout.

The **End of Treatment (EOT)** is reached in the second morning of V7, after the last dose of double-blind treatment and after all morning assessments have been performed.

The **safety follow-up phase** starts after EOT and lasts at least 30 days (i.e., until the second follow-up telephone call). A first telephone call is done 5 days (+7 days) after EOT to collect treatment-emergent adverse events (TEAEs) from last study treatment dose.

The **End of Study** (EOS) for a single subject is defined as the date of the 30-day follow-up telephone call. 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 overall duration of participation in the study of a subject is expected to be approximately 16 weeks (see diagram below).



V = visit; ▬ polysomnographic (PSG) nights; D = dose; P = placebo.

PLANNED DURATION	Approximately 9 months from first subject first visit to last subject last visit.
SITE(S) / COUNTRY(IES)	Approximately 10 sites in two countries (US, Germany).
SUBJECTS/SEQUENCES	Approximately 50 subjects will be centrally randomized to five different sequences of five study treatments according to a Latin square design.
INCLUSION CRITERIA	1. Signed informed consent prior to any study-mandated procedure (V1). 2. Male or female aged ≥ 65 years (V1). 3. Body mass index (BMI): 18.5 ≤ BMI (kg/m^2) < 32.0 (V1). 4. Insomnia disorder according to Diagnostic and Statistical Manual of Mental Disorders-5 criteria (V1). 5. Self-reported history of all of the following on at least 3 nights per week and for at least 3 months prior to V1: • ≥ 30 minutes to fall asleep • Wake time during sleep ≥ 30 minutes • Total sleep time (TST) of ≤ 6.5 h 6. Insomnia Severity Index (ISI©) score greater than or equal to 15 (V1). 7. Willing to comply with all aspects of the study protocol (V1). 8. Ability to communicate well with the investigator, to understand the study requirements and judged by the investigator to be alert and oriented to person, place, time and situation (V1). 9. Meeting the following sleep parameters on at least 3 nights out of 7 consecutive nights on the sleep diary completed at home between V1 and V2 (to be checked at V2): • ≥ 30 minutes to fall asleep • Wake time during sleep ≥ 30 minutes • TST of ≤ 6.5 h

	10. Usual bedtime between 21:30 and 00:30 as reported on the sleep diary completed at home between V1 and V2 (to be checked at V2). 11. Regular time in bed between 6 and 9 hours as reported on the sleep diary completed at home between V1 and V2 (to be checked at V2). 12. Meeting the following sleep parameters on the two PSG nights (V2): • Mean LPS ≥ 20 minutes (with neither of the two nights < 15 minutes), and • Mean WASO ≥ 30 minutes (with neither of the two nights < 20 minutes), and • Mean TST < 420 minutes.
EXCLUSION CRITERIA	1. Any current sleep disorder(s) other than insomnia, or any lifetime history of related breathing disorder, periodic limb movement disorder, restless legs syndrome, circadian rhythm disorder, rapid eye movement (REM) behavior disorder, or narcolepsy (V1). 2. Self-reported usual daytime napping ≥ 1 hour per day, and on ≥ 3 days per week (V1). 3. Caffeine consumption ≥ 600 mg per day (V1) [see Appendix 3]. 4. Shift work within 2 weeks prior to the screening visit, or planned shift work during study (V1). 5. Travel ≥ three time zones within 1 week prior to the screening visit, or planned travel ≥ three time zones during study (V1). 6. Hematology or biochemistry test results deviating from the normal range to a clinically relevant extent as per judgment of the investigator (V1, V2) 7. Aspartate aminotransferase and/or alanine aminotransferase > 2 × the upper limit of normal (ULN) and/or direct bilirubin > 1.5 × ULN (V1, V2).

	8. Severe renal impairment: known or defined as estimated creatinine clearance < 30 mL/min, according to the 4-variable Modification of Diet in Renal Disease formula (V1, V2). 9. Unstable medical condition, significant medical disorder or acute illness within 1 month prior to the screening visit that in the opinion of the investigator could affect the subject's safety or interfere with the study assessments (V1). 10. Systolic blood pressure (BP) > 150 mmHg and diastolic BP > 90 mmHg (V1,V2). 11. Resting pulse rate < 50 or ≥ 100 beats per minute (V1, V2). 12. Any of the following conditions related to corrected QT (QTc) intervals (V1,V2): • A prolonged QTc interval (QTc greater than 450 ms). In case of QTc greater than 450 msec on the first electrocardiogram (ECG), a second ECG recording will be performed after at least 30 minutes on the same day. If QTc 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). 13. 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 screening / baseline version of the Columbia-Suicide Severity Rating Scale (C-SSRS©;V1, V2). • Lifetime history of suicide attempt (V1). 14. Any known factor or disease that might interfere with treatment compliance, study conduct or interpretation of the results such as history of non-compliance to medical

	regimen, psychiatric disease, neurological disorders which may impact sleep, motor performance, or cognition, including Parkinson disease, predementia, dementia, other neurodegenerative disorders, and stroke, (V1). 15. Treatment with another investigational drug within 1 month prior to V1. 16. Known hypersensitivity or contraindication to drugs of the same class of the study treatment or to any excipients of the study drug formulation (V1). 17. Treatment with prohibited central nervous system (CNS)- active drugs [as defined in Appendix 4] for 5 half-lives of the respective drug (but at least 2 weeks) prior to V1 and until 24 hours after EOT, including over-the-counter (OTC) medication and herbal medicines. 18. Cognitive behavioral therapy (CBT) within one month prior to V1. 19. Treatment with moderate to strong cytochrome P450 (CYP) 3A4 inhibitors, CYP3A4 inducers, sensitive CYP3A4 substrates, P-glycoprotein 1 (P-gP) substrates, Breast Cancer Resistance Protein (BCRP) substrates and CYP2B6 substrates [as defined in Appendix 4] within 1 week prior to V1 until 24 h after EOT. 20. Consumption of grapefruit and grapefruit juice within 1 week prior to V1. 21. Diagnosis of alcohol or drug abuse or dependence within 2 years prior to the screening visit or inability to refrain from drinking alcohol for at least 3 consecutive days (V1). 22. Positive drug test (for benzodiazepines, barbiturates, cannabinoids, opiates, amphetamines, or cocaine) or presence of alcohol in exhaled breath as detected by breathalyzer test (V1,V2). 23. Heavy tobacco use (≥ 10 cigarettes per day) and/or inability to refrain from smoking for at least 14 hours during the night (V1).

<table>
<tr><td></td><td>24. Apnea/hypopnea index ≥ 15/h on the first PSG screening night according to the American Academy of Sleep Medicine (AASM) criteria (V2).

25. Apnea or hypopnea event (according to AASM criteria) associated with oxygen saturation by pulse oximetry < 80%, on the first PSG screening night (V2).

26. Periodic limb movement with arousal index ≥ 15/h on the first PSG screening night (V2).</td></tr>
<tr><td>STUDY TREATMENTS</td><td>Investigational treatment
ACT-541468 capsules will be administered orally, once daily in the first two evenings of the assigned treatment period. ACT-541468 doses will include: 5 mg, 10 mg, 25 mg and 50 mg. Available dose strengths of ACT-541468 are 5 mg, 10 mg and 25 mg.

Placebo
Placebo capsules matching ACT-541468 will also be administered orally, once daily in the first two evenings of the assigned treatment period and in addition at V2.

Number of capsules taken according to treatment dose
<table>
<tr><th>Dose strength (mg) / Treatment dose (mg)</th><th>Placebo (0)</th><th>5</th><th>10</th><th>25</th></tr>
<tr><td>Placebo (0)</td><td>2</td><td>0</td><td>0</td><td>0</td></tr>
<tr><td>5</td><td>1</td><td>1</td><td>0</td><td>0</td></tr>
<tr><td>10</td><td>1</td><td>0</td><td>1</td><td>0</td></tr>
<tr><td>25</td><td>1</td><td>0</td><td>0</td><td>1</td></tr>
<tr><td>50</td><td>0</td><td>0</td><td>0</td><td>2</td></tr>
</table></td></tr>
<tr><td>CONCOMITANT THERAPY (MEDICATION, DIET, ACTIVITIES)</td><td>The following therapies are forbidden during the study:

• Treatment with another investigational drug until the end of the safety follow-up phase.
• Prohibited CNS-active medications, including OTC and herbal medicines, until 24 hours after EOT [see Appendix 4].
• Treatment with moderate to strong CYP3A4 inhibitors, CYP3A4 inducers, sensitive CYP3A4 substrates (i.e., have</td></tr>
</table>

	low bioavailability due to a marked first-pass effect), P-gP substrates, BCRP substrates, and CYP2B6 substrates [see Appendix 4] until 24 hours after EOT. • CBT and other psychological therapies, excluding common advice related to sleep hygiene, until 24 hours after EOT. The following activities and diet are forbidden during the study: • Consumption of grapefruit and grapefruit juice until 24 hours after EOT. • Consumption of food within 2 hours prior to study treatment intake. • Caffeine consumption [more details in Appendix 3] – > 600 mg/day – after 14:00 on the days of PSG nights • Alcohol consumption [more details in Appendix 2]: – > 2 drinks a day – within 24 hours prior to PSG night and during all PSG visits • Heavy tobacco use (≥ 10 cigarettes per day) and smoking during PSG assessment at night. At home, it is recommended not to smoke or to use other tobacco products including oral snuff tobacco from 10 pm to 8 am.
ENDPOINTS	**Primary efficacy endpoint(s)** The primary efficacy endpoint of this study is defined as the change of WASO from Baseline[1] to Days 1 and 2[2] as determined by PSG. WASO is the time (minutes) spent awake after onset of persistent sleep (see definition of LPS below) until lights on as determined by PSG. Total time in bed is fixed at 480 minutes (8 hours) during the PSG nights. The first screening PSG recording starts (lights off) within ± 30 minutes of usual bedtime (determined by sleep diary between V1 and V2); this time is then considered as the

[1] 'Baseline' is the mean of the two PSG nights during run-in period (V2).

[2] 'Days 1 and 2' are the mean of the corresponding two PSG treatment nights for a given treatment period.

	habitual bedtime and held constant ± 5 min throughout the study. PSG is recorded for 960 epochs of 30 seconds (8 hours) from lights off until lights on. PSG recording is centrally scored by independent assessors. **Secondary efficacy endpoints** The secondary efficacy endpoint of this study is defined as the change from Baseline[1] to Days 1 and 2[2] in mean LPS. LPS is the time (minutes) from start of recording to the beginning of the first continuous 20 epochs (i.e., 10 minutes) scored as non-wake, 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. **Other efficacy endpoints** Other efficacy endpoints are described in Section 6.1.3. **Safety endpoints** • TEAEs[3] up to 5 days after study treatment discontinuation. • Serious adverse events (SAEs) up to 30 days after study treatment discontinuation. • Adverse events (AEs) leading to premature discontinuation of the double-blind study treatment. • AEs of special interest starting or worsening after the first dose of the first treatment period until EOS (and after adjudication by the ISB): – Narcolepsy-like events (e.g., excessive daytime sleepiness, cataplexy) – Complex sleep behavior events. – Suicidal thoughts and/or behaviors. • Change from Baseline (mean of the first and second morning values after the two PSG nights at V2, run-in period) to Days 1 and 2[4] of each period in vital signs (systolic and diastolic BP, pulse rate and body

[3] A TEAE is any AE temporally associated with the use of study treatment from Day 1 until 5 days after last study drug intake in each treatment period and until 5 days after study treatment discontinuation whether or not considered by the investigator as related to study treatment.

[4] Days 1 and 2 refers to the mean of the first and second morning values after the two PSG nights of a treatment period.

	temperature). • Change from Baseline (V1) to the second morning after the PSG nights at V7 in body weight. • Treatment-emergent ECG abnormalities from V3 until EOT. • Change from Baseline (V2, second morning) to the second morning after the PSG nights at V3, V4, V5, V6 and V7 in ECG parameters. • Marked laboratory abnormalities on double-blind study treatment. • Change from Baseline (V2, second morning) to the second morning after the PSG nights at V3, V4, V5, V6 and V7 in laboratory variables. • Change from Baseline (mean of the two PSG nights at V2, run-in period) to Days 1 and 2^4 of each treatment period in: – Digit Symbol Substitution Test© performed in the morning, 30–60 minutes after lights on. – Sheehan Disability Scale© performed in the morning, 30–60 minutes after lights on. – Karolinska Sleepiness Scale performed in the morning, 30–60 minutes after lights on. • Incidence of most severe suicidal ideation and suicidal behavior according to the C-SSRS© for each treatment group. **Pharmacokinetic endpoints** Concentration of ACT-541468 (and possibly several of its metabolites) approximately 9–10 hours post-dose at V3, V4, V5, V6 and V7.
ASSESSMENTS	Refer to the schedule of assessments in Table 3.
STATISTICAL METHODOLOGY	**Analysis Sets** *Screened Analysis Set* The Screened Analysis Set includes all subjects who are screened and have a subject identification number. *Randomized Analysis Set* The Randomized Analysis Set includes all subjects who have been assigned to a study treatment.

	Full Analysis Set The Full Analysis Set (FAS) includes all subjects from the Randomized Analysis Set who received any dose of study treatment. *Modified FAS* The modified FAS (mFAS) includes all patients from the FAS and who have at least one WASO assessment at Baseline and at least one at Days 1 and 2 of any given treatment period. *Per-protocol Analysis Set* The Per-protocol Analysis Set comprises all subjects from the mFAS, who have two consecutive WASO values at both Baseline and Days 1 and 2 of each treatment period, and who complied with the protocol sufficiently to allow relevant assessment of treatment effects. *Safety Set* The Safety Set (SS) includes all randomized subjects who received at least one dose of study treatment. Subjects will be evaluated according to the actual dose they received, which may differ from the randomly assigned dose. *PK Analysis Set* The PK Analysis Set includes all subjects in the SS who have at least one PK sample collected after initiation of study drug. **Methods** The study is intended to select the dose that allows a clinically meaningful reduction of WASO compared to placebo. **Primary efficacy analysis** The primary statistical analysis will be performed on the mFAS. The study is using the generalized Multiple Comparison Procedure – Modeling (MCP-Mod) approach [Bretz 2005, Pinheiro 2006, Pinheiro 2014], which combines a multiple-comparison procedure to assess the efficacy of the drug versus placebo and a modeling step to further identify the dose that is most likely to provide the expected level of efficacy (based on the primary efficacy endpoint). The generalized approach is appropriate for this study design where

	each patient receives different doses in a sequence. A univariate dose-response relationship is modeled based on the mean change from baseline in WASO at each dose. The following pre-defined dose-response models are considered: one linear, and three E_{max} models. The analysis will be performed using the R-package *DoseFinding*. A dose-response relationship is demonstrated if at least one of the four multiple contrast tests has an adjusted p-value < 0.05. The best fitting model based on Akaike's Information Criterion will be used to estimate the target dose, defined as the dose that achieves a placebo-corrected mean reduction from baseline of at least 15 minutes with a 95% confidence interval excluding 0. The primary endpoint will be summarized by dose using the mean, median, standard deviation, standard error, quartiles, minimum, maximum and 95% confidence limits of mean. **Secondary efficacy analysis** Similarly, an MCP-Mod-based analysis will be conducted on the secondary endpoint. Treatment effects on the secondary efficacy endpoint will also be assessed using a mixed model similar as for the primary analysis **Safety analysis** Safety analyses will be performed on the SS. Observations (e.g. AEs, laboratory data) occurring within a treatment period (from the time of dosing to the time immediately prior to the next dose) will be assigned to the dose taken in that period. *Adverse events:* AEs and SAEs in subjects who were screened but not part of the SS will be listed. The number and percentage of subjects experiencing TEAEs and SAEs will be tabulated by dose and by: • MedDRA™ system organ class (SOC) in alphabetical order and individual preferred term within each SOC, in descending order of incidence in the highest dose group. • Frequency of subjects with events coded with the same preferred term, in descending order of incidence in the

	highest dose group. TEAEs, AEs of special interest and SAEs will be tabulated as described above by severity and relationship to study treatment. AEs leading to premature discontinuation of the study treatment and AEs with outcome death will be summarized as described above. AEs and SAEs with onset between screening and first day of double-blind study treatment will also be summarized. Listings will be provided for all reported AEs, including SAEs. In addition, separate listings will be provided for SAEs, for AEs leading to premature discontinuation of study treatment, and for AEs with outcome death. *Laboratory variables:* Descriptive summary statistics by dose will be provided for observed values and absolute changes from baseline, in both hematology and blood chemistry laboratory tests. All central laboratory data will be taken into account regardless of whether they correspond to scheduled or unscheduled assessments. Local laboratory results will only be listed and not included in the safety analysis. Marked laboratory abnormalities will be summarized for each laboratory variable by dose providing their incidence and frequency. The number and percentage of subjects with treatment-emergent laboratory abnormalities will be tabulated by dose. **Other endpoints analysis** Treatment effects on other endpoints will be evaluated and described in detail in the statistical analysis plan.
STUDY COMMITTEES	An Independent Data Monitoring Committee (IDMC) will monitor safety and efficacy data in an unblinded manner and make appropriate recommendations to ensure safety of the subjects, thus ensuring that the study is being conducted with 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 AEs of special interest, i.e., narcolepsy-like events (e.g., excessive daytime sleepiness, cataplexy), complex sleep behavior events and suicidal thoughts and/or behaviors. The composition and operation of the ISB is described in the ISB charter.

PROTOCOL

1 BACKGROUND

1.1 Insomnia disorder

1.1.1 Definition

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

"Insomnia disorder is a 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 in the elderly population. Population-based epidemiological studies suggest that insomnia symptoms (difficulties initiating sleep, early morning awakenings, and dissatisfaction with sleep) increase with age [Ohayon 2001]. However, the decrease in ability to sleep is associated with factors associated with aging, such as depressed mood, respiratory symptoms, poor perceived health and physical disability, not with *age per se*. A stagnation or decline in insomnia disorder diagnosis in age groups ≥ 65 years is seen, as the negative consequences of insomnia symptoms on functioning and well-being are likely less endorsed in the elderly than in adults [Ancoli-Israel 2009, Ohayon 2009]. Prevalence of insomnia disorder in elderly populations ≥ 65 years based on DSM-IV criteria in Europe was estimated at approximately 8% [Ohayon 2010, Ohayon 2002, Schlack 2013]. Insomnia in the elderly is twice as common Lopez-Torres Hidalgo 2012].

Changes in sleep architecture, such as slow-wave sleep decreases, as well changes in sleep parameters such as increase in sleep onset latency and decreases in sleep maintenance and efficiency have been described in elderly people. Those changes are associated with age, occur in middle age and stabilize from 60 years onwards. Only sleep efficiency continues to decline with age [Ohayon 2004].

The co-morbidities associated with insomnia in the elderly have been examined in a number of studies [Ohayon 2005, Dam 2008, Blackwell 2006]. Elderly individuals with insomnia symptoms have poor physical and mental health, as well as an increased risk of

mortality, at least in older women. Disrupted sleep in the elderly results in reduced physical performance and impairment in cognitive functioning. Insomnia in elderly subjects may also precipitate falls and be an important factor for nursing-home placement due to associated injuries [McCall 2004]. After adjustment for many confounders, including the use of antidepressant or benzodiazepine, there is a 30–40% increased risk of subsequent falls with short sleep duration and poor sleep efficiency.

1.1.3 Treatments

The current standards of care encompass pharmacotherapy and non-pharmacological therapies [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. 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 it may be limited by the lack of therapists with adequate training and experience [Pigeon 2007, Schutte-Rodin 2008]. Pharmacological options may be warranted.

Prescription of sleep medications (hypnotics) 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 gamma-aminobutyric acid (GABA) type A receptor subtypes [Lieberman 2007]. Drugs in this class, which include 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 incoordination, 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. Zolpidem, zolpidem controlled-release (CR), and zaleplon show affinity for the alpha 1 receptor sub-type, while eszopiclone shows affinity for the alpha 2 and 3 receptor sub-types [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 benzodiazepines. For example, 15% of subjects experienced anterograde amnesia after zolpidem administration, and in approximately 50% of those patients, it occurred within 30 minutes [Praplan-Pahud 1990]. Zolpidem and other drugs in this group also are known to impair postural stability as much as benzodiazepines and may increase the risk of falling [Mets 2010]. This represents a safety concern for older people who use hypnotics [Agostini 2004]; about 1% of falls result in hip fractures that lead to restricted mobility for 60%, increased functional dependence for 25%, and death within 6 months for 25 % of the patients [Avidan 2005]. In addition to these concerns, 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 and complex sleep-related behaviors [FDA 2007].

Newer hypnotics that do not act at the GABA receptor have been developed. The melatonin 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 subjects 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.

Low-dose doxepin (3 mg and 6 mg tablets) is indicated for insomnia characterized by difficulty with sleep maintenance. This drug appears to act through selective histamine-1 receptor blockade [Scharf 2008].

Suvorexant is an oral dual orexin receptor antagonist (DORA) that was approved by the FDA (2014) 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]. Concerns related to driving safety led the FDA to approve suvorexant at a maximum dose of 20 mg per night [Vermeeren 2015], a lower dose than anticipated based on efficacy data with up to 40 mg. 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].

Generally, use of sleep medications among all subjects increases with age and is highest in the elderly [Ohayon 2002, Ohayon 2010]. In Germany, 7.4% of women and 5% of men in the age group of 60–79 years reported consumption of sleep medications at least once per week [Schlack 2013]. In Italy, the prevalence of sleep medication use in the

elderly is approximately twice higher than in Germany, and half of the subjects using sleep medications report daily use [Ohayon 2002]. Benzodiazepines indicated for anxiety or sleep disorders as well as zolpidem and zopiclone were the most common sleep medications accounting for about three-quarters of all self-reported sleep medications in those countries [Ohayon 2002, Ohayon 2010]. In the US, the use of sleep medications increases with age. Up to 7% in people aged 80 years and more report to use prescription sleep medications in the 30 days prior to a survey [Chong 2013].

Use of benzodiazepines and zolpidem has been correlated with an increased risk of falling and a higher serum concentration of benzodiazepines or zolpidem has been noted in those who fall compared with those who do not fall [McCall 2004]. Despite the increased risk for falls, benzodiazepines and generic antidepressants (such as trazodone) are among the most popular classes of medications prescribed for elderly patients in the US. An analysis of inappropriate (risk > benefit) psychotropic prescribing determined that antidepressant agents, anti-anxiety drugs, and sedative-hypnotics were the drug classes most frequently prescribed to ambulatory elderly patients [Mort 2000]

1.1.4 Unmet medical need

There are effective treatments for insomnia in the elderly [Schutte-Rodin 2008]. However, currently available treatments are limited to short-term use with the exception of eszopiclone (in the US), and caution and dose reduction are 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, next-day residual sedation and increased risk of falls [Neubauer 2014]. This represents an important unmet medical need. Moreover, the use of benzodiazepines and benzodiazepine receptor agonists has been also correlated with an increased risk of falling [McCall 2004] leading to hip and femur fractures, to increased disability and use of healthcare resources. There is also a need for a pharmacological treatment for insomnia disorder that addresses the most prominent and pressing symptoms of insomnia without negatively impacting next-day functioning. ACT-541468 is a DORA that has been investigated so far in nonclinical and early-phase clinical studies. Results of nonclinical and early-phase clinical studies [Section 1.2.2] warrant the evaluation of ACT-541468 as a sleep medication in order to investigate its efficacy and safety in insomnia as well as its potential lack of next-day impairment or significant abuse liability.

1.2 Study treatment: ACT-541468

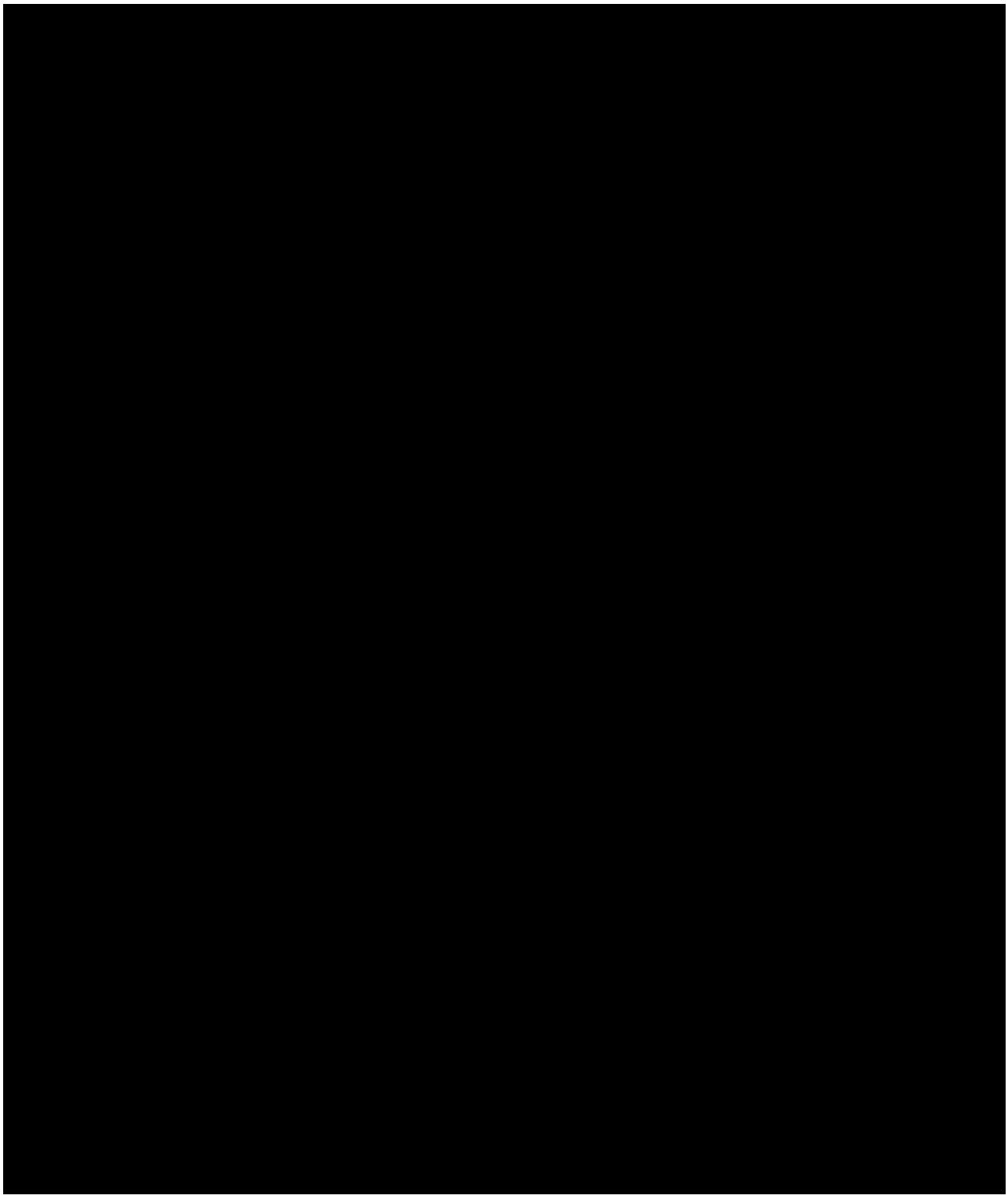
1.2.1 The orexin system

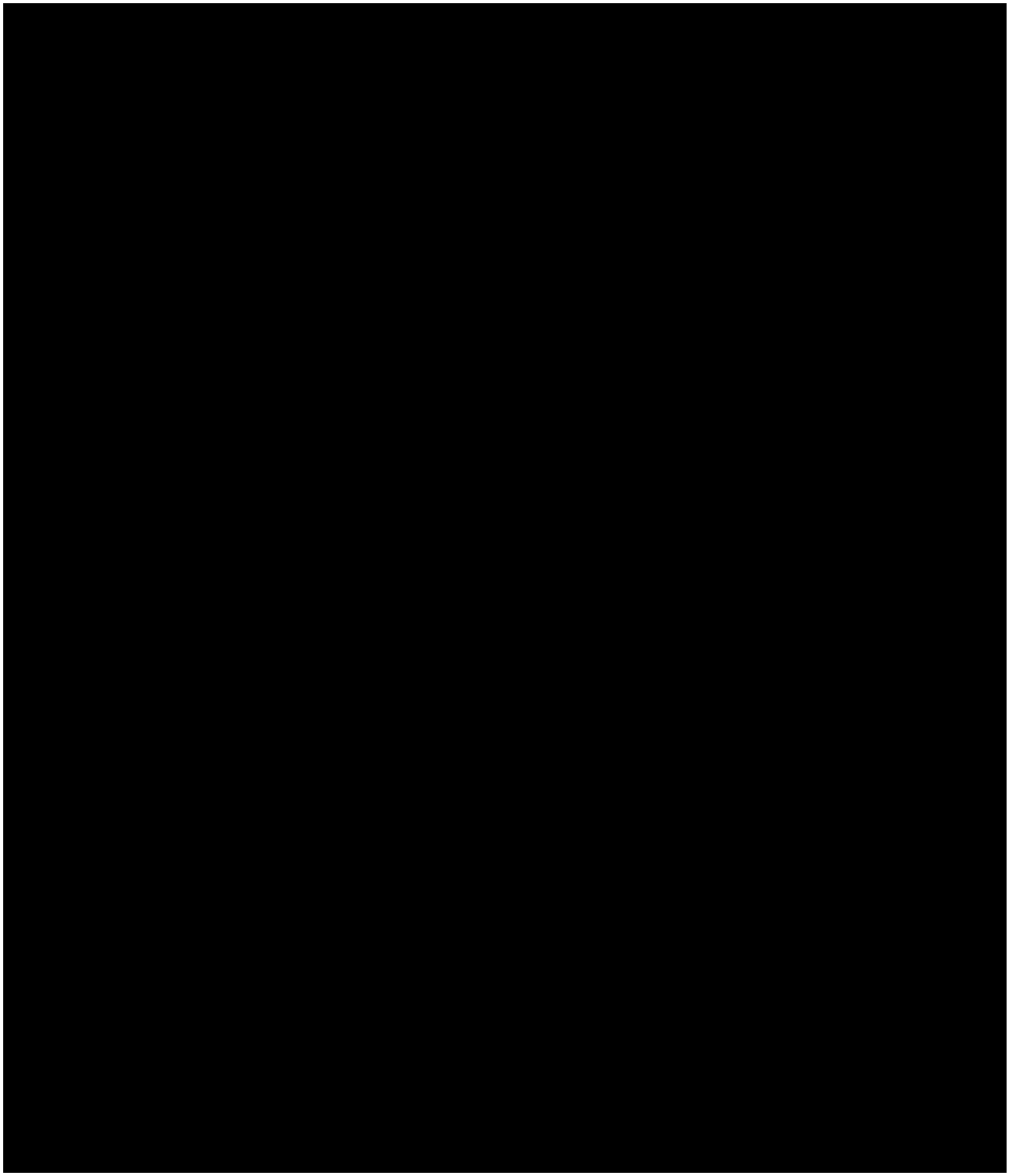
The orexin system is involved in the regulation of sleep and arousal by the central nervous system (CNS) and is currently being targeted in the development of new therapies for sleep disorders.

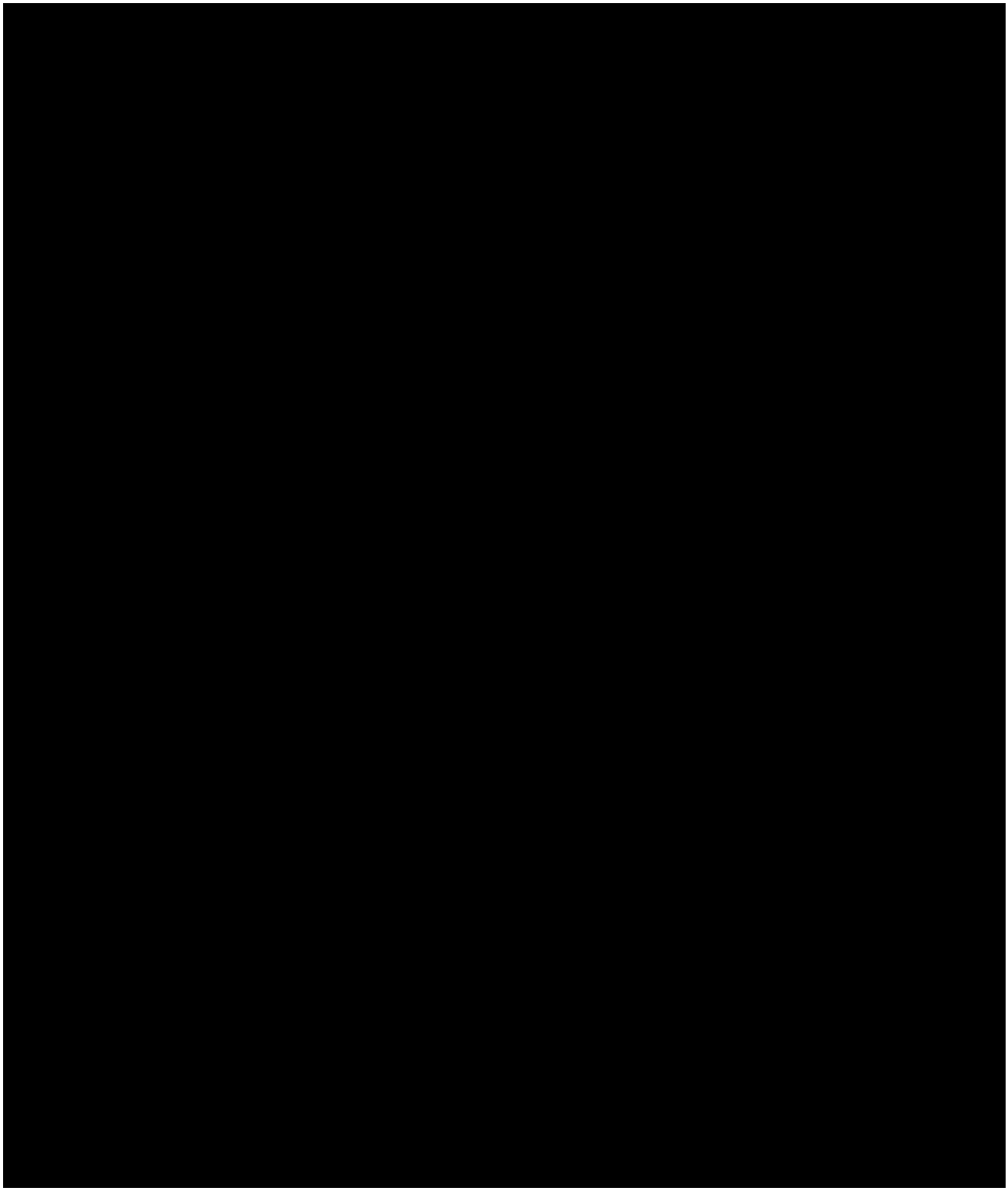
The neuropeptides orexin-A and orexin-B are synthesized in the lateral hypothalamic areas [de Lecea 1998] and activate the orexin-1 and orexin-2 receptors [Kilduff 2000]. Nerve fibers from orexin neurons make projections to the basal forebrain, corticolimbic structures, and brainstem, particularly to 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].

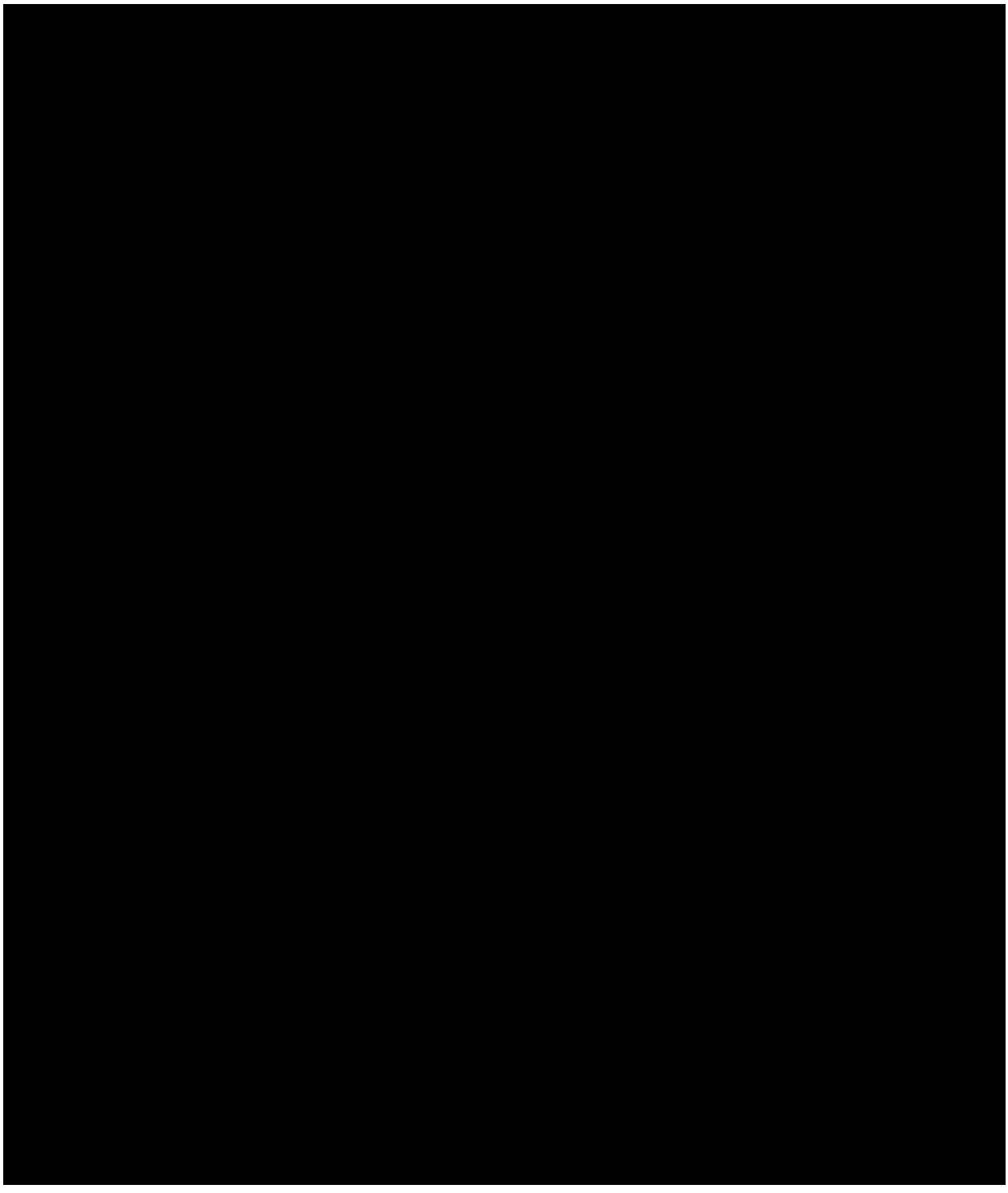
Orexins may be implicated in the genesis of narcolepsy, due to findings of low cerebral spinal fluid orexin levels in most patients with unequivocal narcolepsy [Mignot 2002] and near-complete atrophy of orexin neurons in post-mortem brains of patients with narcolepsy [Thannickal 2000], coupled with the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

One DORA, suvorexant, has shown efficacy in subjects with insomnia, and is approved notably in the US. For a description of the effects of suvorexant, refer to Section 1.1.3.









[redacted]

1.3 Purpose and rationale of the study

1.3.1 Purpose of the study

The main purpose of this dose-response study is to define the ACT-541468 dose(s) that will show a favorable efficacy and safety profile and to assess the safety and tolerability of the compound in elderly subjects with insomnia disorder.

The dose to be studied in future clinical trials will be established based on the change in objectively assessed WASO and safety data, such as next-day residual effect from baseline versus placebo.

1.3.2 Rationale for study

ACT-541468 is a DORA. The orexin system is involved in the regulation of sleep and arousal.

DORAs are efficacious in the treatment of insomnia disorder. Suvorexant, an oral DORA, demonstrated efficacy and was approved by the FDA in 2014 for the treatment of insomnia characterized by difficulties with sleep onset and/or sleep maintenance in adults and elderly [Citrome 2014]. Another DORA, almorexant, demonstrated objective and subjective improvements in sleep maintenance and TST compared with placebo in two studies in subjects with primary insomnia.

Elderly people exhibit a different sleep pattern than younger adults and the sensitivity of elderly and younger adults to the PD properties of a compound may differ. European guidelines therefore advise that the efficacy and the safe dose (range) of a drug must be defined in elderly, and they recommend a specific dose-finding study in elderly subjects [EMA 2011]. This dose-finding study in the elderly will be performed in addition to a dose-finding study in adult subjects.

The dose levels of 5, 10, 25, and 50 mg of ACT-541468 planned for this study were all investigated in Phase 1 studies, with clear sleep-promoting effects starting at 25 mg in healthy adult subjects. In healthy elderly subjects who received a single morning dose of 15 mg, effects lasting > 12 h were observed on saccadic peak velocity, the most sensitive PD parameter. All other PD variables showed no effect at 15 mg. No effects on the VAS Bond & Lader subjective alertness were observed at 5, 15 and 25 mg in healthy elderly subjects.

The highest dose tested after evening administration in healthy elderly subjects was 25 mg for 7 days and was well tolerated with no more AEs reported by the elderly subjects than by the healthy young adults at similar doses. After morning administration in healthy young adults, single doses up to 200 mg and doses up to 75 mg for 5 days were well tolerated. The $t_{½}$ is longer in healthy elderly than in healthy young adults. However, the study drug will be administered for periods of 2 days in a sleep center and subjects will be discharged from the center after a neurological examination. With these risk-minimization measures, the good tolerability of ACT-541468 at higher doses than 50 mg in healthy young adults, the lower percentage of AEs reported by elderly subjects than by young adults after multiple 25 mg doses, and consistent CNS-depressant effects observed starting only from 25 mg in young and elderly subjects, a dose of 50 mg administered in a sleep center can be tested in elderly subjects with insomnia disorder to assess the high end of the dose-response relationship.

The ACT-541468 mechanism of action, the results of nonclinical studies and Phase 1 studies in healthy young and elderly adults and the limitations of the existing sleep medications justify the need for evaluating ACT-541468 in insomnia disorder and identifying the compound's efficacious and safe doses in elderly with insomnia.

1.4 Summary of known and potential risks and benefits

1.4.1 ACT-541468

Based on the mechanism of action of ACT-541468, and current nonclinical data and data collected in Phase 1 studies in healthy adult and elderly subjects, a fast effect on sleep induction and a sustained effect on sleep maintenance are anticipated. Suvorexant, a compound with a similar mechanism of action, has been demonstrated to be efficacious in the treatment of insomnia without evidence of physical dependence or withdrawal symptoms after discontinuation of suvorexant.

ACT-541468 crosses the blood–brain barrier and decreases wakefulness in rats and dogs, is associated with a short sleep latency, and increases sleep efficacy following oral administration. In particular, it shows a shorter latency to non-REM sleep and better sleep efficacy than suvorexant in rats and shorter duration of sleep in dogs. REM and non-REM sleep are prolonged proportionately in rats and dogs, thus decreasing wakefulness while preserving natural sleep architecture.

This study will be the first study with the compound in elderly subjects with insomnia disorder. In humans, clear and consistent CNS-depressant effects were observed at the morning dose of 25 mg in healthy young adults and elderly subjects. An effect was also seen on the most sensitive PD parameter, saccadic peak velocity, after morning single dose administration of 15 mg ACT-541468 in healthy elderly subjects. There were no relevant differences between PD effects measured on Day 1 and Day 5. In the

Phase 1 studies, no next-day residual effects were observed after multiple evening dose administration both in healthy young and elderly subjects at 25 mg.

The most frequently observed adverse drug reactions reported in the conducted studies involving approximately 110 healthy subjects exposed to ACT-541468 include headache, somnolence, fatigue and dizziness. Elderly subjects reported fewer AEs than young adults in Phase 1 studies at the equivalent dose.

The results of the ACT-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 must be avoided.

Considering both the mode of action of DORA and common adverse reactions associated with the use of sleep medications, potential risks include:

- Induction of next-day somnolence, which is associated with increased risk of impaired alertness and motor coordination.
- Narcolepsy-like events.
- Complex sleep-related behaviors, including night-time sleep driving and other complex behaviors while out of bed and not fully awake.
- Suicidal thoughts and/or behavior.

[redacted]

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

Next-day sleepiness may potentially occur with ACT-541468. On each of the mornings following drug administration in sleep centers, the subjects will undergo neurological examinations based on the evaluation of gait, the Tandem Walking Test and the Romberg Test. Based on the results of the neurological examination, the investigator will discuss with the subjects and decide whether it is safe for the subject to leave the study centers.

As required by current guidelines, the Columbia Suicide Severity Rating Scale (C-SSRS©) will be completed by the subjects on each morning after the polysomnography (PSG) nights at visit (V) 2 to V7 to assess suicidality prior to randomization and during the double-blind treatment phase.

Liver variables and other laboratory variables will be monitored in the study at each study visit.

Due to lack of data about interaction of ACT-541468 with food, the study treatment will be administered at least 2 hours after a meal.

Elderly subjects enrolled in this study will receive the study treatment only at the sleep centers and will not be discharged from the sleep centers with the study treatment.

Two committees will be set up for the study:

- An Independent Safety Board (ISB) will review and adjudicate in a blinded manner all AEs of special interest, i.e., narcolepsy-like events (e.g., excessive daytime sleepiness, cataplexy), complex sleep behavior events and suicidal thoughts and/or behaviors.
- An Independent Data Monitoring Committee (IDMC) will monitor safety and efficacy data in an unblinded manner and 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 the study if, on balance, he/she believes that continuation would be detrimental to the subjects' well-being.

In conclusion, based on available data on the study drug ACT-541468 and the risk-minimization measures mandated by the protocol, the expected benefit-risk assessment supports the conduct of this study in elderly subjects with insomnia. The short duration of the study (five periods of 2 consecutive days' exposure to study treatment separated by a wash-out of 5–12 days), and the careful follow-up of subjects mandated by the protocol minimize inconvenience and risk.

2 STUDY OBJECTIVES

2.1 Primary objective

The primary objective of the study is to evaluate the dose response of ACT-541468 on the change of WASO assessed by PSG on the first two days of each treatment period.

2.2 Secondary objective

The secondary objective of the study is to evaluate the dose response of ACT-541468 on latency to persistent sleep (LPS) on the first two days of each treatment period.

2.3 Other objectives

To explore the effect of ACT-541468 on other sleep parameters at each treatment period. Sleep parameters will include various objective and subjective measures [see Appendix 10].

To assess the safety and tolerability of oral administration ACT-541468 in elderly subjects with insomnia disorder.

To explore the relationship between exposure (concentration of ACT-541468 approximately 9–10 h post-dose at second morning of V3, V4, V5, V6, and V7) and safety.

3 OVERALL STUDY DESIGN AND PLAN

3.1 Study design

This is a multi-center, double-blind, randomized, placebo-controlled, five-period, five-treatment crossover, PSG dose-response Phase 2 study in elderly subjects with insomnia disorder.

In order to have approximately 50 subjects randomized, approximately 120 subjects will be screened (estimated screen failure rate is up to 60%). Subjects will be randomized 1:1:1:1:1 to five different sequences of five study treatments according to a Latin square design [see Table 1]. The five study treatments are oral fixed doses of AC-541468 5 mg (D1), 10 mg (D2), 25 mg (D3) and 50 mg (D4), and placebo (P).

Table 1 Latin square design sequences

		Periods				
		1	**2**	**3**	**4**	**5**
Sequence	**1**	Dose 4	Dose 2	Dose 3	Dose 1	Placebo
	2	Dose 2	Placebo	Dose 4	Dose 3	Dose 1
	3	Dose 3	Dose 1	Dose 2	Placebo	Dose 4
	4	Placebo	Dose 4	Dose 1	Dose 2	Dose 3
	5	Dose 1	Dose 3	Placebo	Dose 4	Dose 2

The study will be conducted in approximately 10 sites in two countries (US and Germany).

Subjects who prematurely discontinue the study will not be replaced. Estimated dropout rate for the study is around 10%.

No interim analysis is planned during the conduct of the study. Subjects who complete the study or prematurely discontinue the study will be treated with standard of care according to investigator's opinion.

3.1.1 Study phases

3.1.1.1 Screening phase

The **screening phase** lasts a minimum of 14 days and a maximum of 28 days. It starts with the signature of the Informed Consent Form (ICF) and ends with subject randomization. It includes the screening period (from Day –28 to Day –7) and the run-in period (from Day –14 to Day –1).

The **screening period** starts with V1, which occurs between Day –28 and Day –14 and is followed by the completion of the screening sleep diary for at least 7 consecutive days at home and until V2.

The **run-in period** occurs between Day –14 and Day –1 and starts with V2. V2 consists of two consecutive PSG nights on single-blind placebo treatment occurring between Day –14 and Day –6. V2 is followed by 5 to 12 days at home with no treatment.

3.1.1.2 Double-blind treatment phase

The double-blind **treatment phase** starts with the first dose of study treatment in the first evening of the Randomization visit (V3) and ends in the second morning of V7. It consists of five **treatment periods**, each consisting of two consecutive PSG nights on the assigned study treatment followed by a 5- to 12-day washout.

The **End of Treatment (EOT)** is reached in the second morning of V7, after the last dose of double-blind treatment and after all morning assessments have been performed.

The **safety Follow-up phase** starts after the EOT and lasts at least 30 days (i.e., until the second follow-up telephone call). A first telephone call is done 5 days (+ 7 days) after EOT to collect TEAEs from the last study treatment dose.

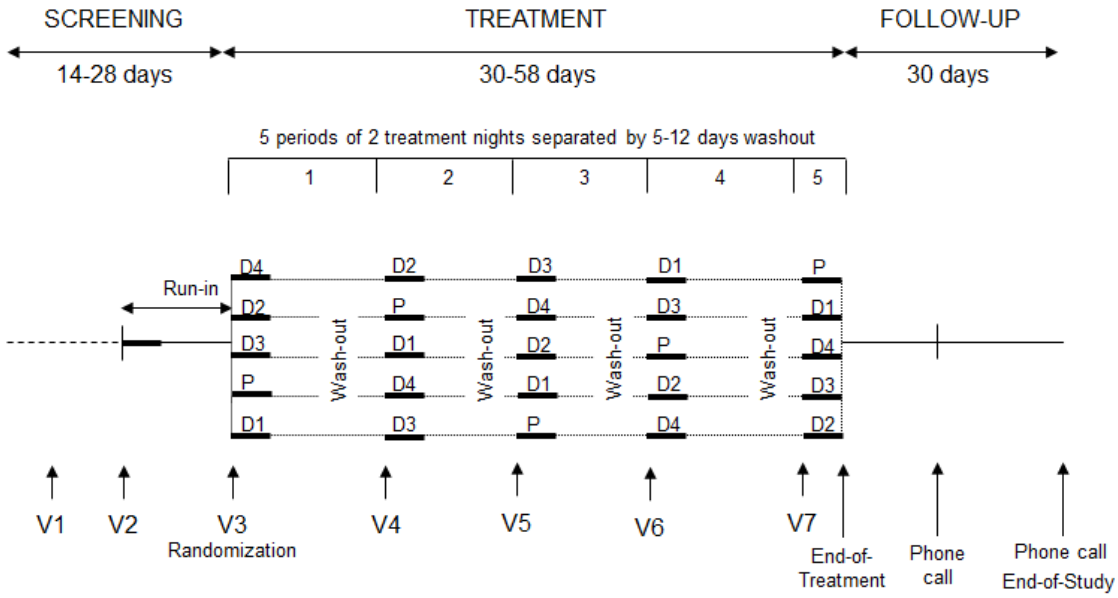
The **End of Study** (EOS) for a single subject is defined as the date of the 30-day follow-up telephone call. If a subject withdraws consent and does not wish to participate in the study any longer, EOS is the date of consent withdrawal for this subject. If a subject is declared lost to follow-up [see also Section 8.2], EOS is the date of last successful contact for this subject.

Unscheduled visits are allowed to take place anytime during the study, in which case study-related information will be collected.

The visit schedule and protocol-mandated procedures will be performed according to the table of assessments [Table 3] and are described in Section 7.

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

Figure 1 Study design



V = visit; ▬ polysomnographic (PSG) nights; D = dose; P = placebo.

3.1.2 Study duration

The study starts with the first act of recruitment (i.e., ICF signed) and ends with the last visit of the last subject.

The double-blind treatment phase for each subject lasts 30 to 58 days. The assigned treatment will be administered during the first two days of the five treatment periods. For an individual subject, the study is completed with EOS (30-day safety follow-up telephone call). The duration of participation in the study of a subject is expected to be approximately 74 to 116 days.

3.2 Study design rationale

This is a multi-center, double-blind, randomized, placebo-controlled, five-period, five-treatment crossover, PSG dose-response study.

The study is double-blind and randomized to prevent any possible bias in the parameters, assessment or analysis.

The effects of each dose of ACT-541468 will be compared to those of placebo for every subject. This allows for conclusions as to the level of relevance and significance of any effect detected.

A crossover design was chosen due to the nature of the disease under investigation (i.e., chronic and stable), the short treatment duration (2 days for each dose), and the possibility to have a long wash-out period (5–12 days) compared to the $t_{½}$ (9.9 h) of ACT-541468 in elderly subjects. Furthermore, recruitment is anticipated to be challenging in the elderly population, and for this design, the sample size required in comparison with a parallel-group design is much smaller [ICH 1998]. As a balanced complete block design, the five-sequence Latin square crossover design minimizes the influence of confounding covariates because each patient serves as his or her own control (i.e., each subject will receive each of the four different doses of ACT-541468 and placebo). Any potential order (or learning) effect occurring over time will be averaged across all doses since each dose of ACT-541468 and placebo is given in each treatment period.

Subjects screened at V1 will complete a run-in period to confirm final eligibility and to perform baseline assessments of parameters, as well as to exclude subjects with major short-term fluctuation of their conditions.

ACT-541468 is expected to be effective from the first day of dose intake. PSG assessments during 2 consecutive nights are considered sufficient to evaluate acute ACT-541468 effects on sleep parameters in elderly subjects. Since no accumulation of ACT-541468 was observed [see Section 1.2.2.2], there is no need to expose subjects longer to reach study drug steady state. It is expected that the effect on sleep parameters observed after 2 days' treatment in elderly will evolve over time in a similar way to what is seen in adults treated over longer time [Herring 2016]. Effects over longer time in the elderly will therefore be extrapolated based on results of the dose-finding study in adults.

3.3 Site staff and their roles: polysomnography technologists

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 Clinilabs, NY). 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. Adequate training for the PSG procedures will be conducted by the contract research organization (CRO; i.e., Clinilabs).

Documentation of technologists' prior experience and training, and study-specific training, will be maintained at each clinical trials site.

3.4 Study committees

An IDMC has overall responsibility for safeguarding the interests of subjects by monitoring, in an unblinded manner, 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 with 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, AEs of special interest, i.e., narcolepsy-like events (e.g., excessive daytime sleepiness, cataplexy), complex sleep-behavior events and suicidal thoughts and/or behaviors. 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 elderly male and female subjects aged ≥ 65 years with insomnia disorder. For more details on inclusion and exclusion criteria, please see Section 4.3 and Section 4.4.

Vulnerable subjects are non-eligible since the research can be carried out in a non-vulnerable group of subjects and no particular benefit has been anticipated for vulnerable subjects that would be different from that in general population.

Insufficient sleep quantity is operationalized in this study by a self-reported history of ≥ 30 minutes to fall asleep and ≥ 30 minutes wake time during sleep, as well as by a TST ≤ 6.5 hours during the night. Those three 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 data collected for at least 7 consecutive days at home and until V2. They will also be validated by objective PSG-based criteria collected from 2 consecutive nights spent in a sleep laboratory during the run-in period. Poor sleep quality (SQ) is quantified by an Insomnia Severity Index (ISI©) score ≥ 15 at screening.

4.2 Rationale for the selection of the study population.

The study will recruit elderly subjects (≥ 65 years). The selective inclusion of elderly subjects is justified by the differences in SQ patterns and architecture between elderly and adults. A separate dose-finding study will be performed in 300 adult subjects.

Gender has been described in the literature as one of the intrinsic factors influencing response to sleep medications, and the administration of the same dose of study drug might results in different drug exposure level in females and male subjects [FDA 2013]. Therefore, both male and female will be included in this study.

Since this study is the first trial of ACT-541468 conducted in elderly subjects with insomnia disorders, concomitant treatments for insomnia (pharmacological or not) or concomitant medications active in the CNS are not allowed in the study to avoid confounding effects on safety and efficacy of the study treatments.

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 (V1 and V2 in brackets refer to the visits when the criteria must be assessed):

1. Signed informed consent prior to any study-mandated procedure (V1).
2. Male or female aged ≥ 65 years (V1).
3. Body mass index (BMI): 18.5 ≤ BMI (kg/m2) < 32.0 (V1).
4. Insomnia disorder according to DSM-5 criteria (V1).
5. Self-reported history of all of the following on at least 3 nights per week and for at least 3 months prior to V1:
    - 5.1 ≥ 30 minutes to fall asleep
    - 5.2 Wake time during sleep ≥ 30 minutes
    - 5.3 TST of ≤ 6.5 h
6. ISI© score ≥ 15 (V1).
7. Willing to comply with all aspects of the study protocol (V1).
8. Ability to communicate well with the investigator, to understand the study requirements and judged by the investigator to be alert and orientated to person, place, time and situation (V1).
9. Meeting the following sleep parameters on at least 3 nights out of 7 consecutive nights on the sleep diary completed at home between V1 and V2 (to be checked at V2):
    - 9.1 ≥ 30 minutes to fall asleep
    - 9.2 Wake time during sleep ≥ 30 minutes
    - 9.3 TST of ≤ 6.5 hours
10. Usual bedtime between 21:30 and 00:30 as reported on the sleep diary completed at home between V1 and V2 (to be checked at V2).
11. Regular time in bed between 6 and 9 hours as reported on the sleep diary completed at home between V1 and V2 (to be checked at V2).
12. Meeting the following sleep parameters on the two PSG nights (V2):
    - 12.1 Mean LPS ≥ 20 minutes (with neither of the two nights < 15 minutes), and
    - 12.2 Mean WASO ≥ 30 minutes (with neither of the two nights < 20 minutes), and
    - 12.3 Mean TST < 420 minutes

4.4 Exclusion criteria

Subjects must not fulfill any of the following exclusion criteria. It is not permitted to waive any of the criteria for any subject (V1 and V2 in brackets refer to the visits when the criteria must be assessed):

1. Any current sleep disorder(s) other than insomnia, or any lifetime history of related breathing disorder, periodic limb movement disorder, restless legs syndrome, circadian rhythm disorder, REM behavior disorder, or narcolepsy (V1).
2. Self-reported usual daytime napping ≥ 1 hour per day, and on ≥ 3 days per week (V1).
3. Caffeine consumption ≥ 600 mg per day (V1) [see Appendix 3].
4. Shift work within 2 weeks prior to the screening visit, or planned shift work during study (V1).
5. Travel ≥ three time zones within 1 week prior to the screening visit, or planned travel ≥ three time zones during study (V1).
6. Hematology or biochemistry test results deviating from the normal range to a clinically relevant extent as per judgment of the investigator (V1, V2)
7. AST and/or ALT > 2 × the ULN and/or direct bilirubin > 1.5 × ULN (V1, V2).
8. Severe renal impairment: known or defined as estimated creatinine clearance < 30 mL/min, according to the 4-variable Modification of Diet in Renal Disease formula (V1, V2)
9. Unstable medical condition, significant medical disorder or acute illness within 1 month prior to the screening visit that in the opinion of the investigator could affect the subject's safety or interfere with the study assessments (V1).
10. Systolic blood pressure (BP) > 150 mmHg and diastolic BP > 90 mmHg (V1,V2).
11. Resting pulse rate < 50 or ≥ 100 beats per minute (V1, V2).
12. Any of the following conditions related to corrected QT (QTc) intervals (V1,V2):
    - 11.1 A prolonged QTc interval (QTc greater than 450 ms). In case of QTc greater than 450 msec on the first ECG, a second ECG recording will be performed after at least 30 minutes on the same day. If QTc is greater than 450 ms on the second ECG, the subject is not eligible.
    - 11.2 A history of additional risk factors for torsade de pointes (e.g., heart failure, hypokalemia, family history of long QT syndrome).
13. Any of the following conditions related to suicidality:
    - 12.1 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 screening / Baseline version of the C-SSRS© (V1, V2).
    - 12.2 Lifetime history of suicide attempt (V1).
14. Any known factor or disease that might interfere with treatment compliance, study conduct or interpretation of the results such as history of non-compliance to medical

regimen, psychiatric disease, or neurological disorders which may impact sleep, motor performance, or cognition, including Parkinson disease, predementia, dementia, other neurodegenerative disorders, and stroke (V1).

15. Treatment with another investigational drug within 1 month prior to V1.
16. Known hypersensitivity or contraindication to drugs of the same class of the study treatment or to any excipients of the study drug formulation (V1).
17. Treatment with prohibited CNS active drugs [as defined in Appendix 4] for 5 half-lives of the respective drug (but at least 2 weeks) prior to V1 and until 24 hours after EOT, including over-the-counter (OTC) medication and herbal medicines.
18. CBT within one month prior to V1.
19. Treatment with moderate to strong CYP3A4 inhibitors, CYP3A4 inducers, sensitive CYP3A4 substrates, P-glycoprotein 1 (P-gP) substrates, Breast Cancer Resistance Protein (BCRP) substrates, and CYP2B6 substrates [as defined in Appendix 4] within 1 week prior to V1 until 24 h after EOT.
20. Consumption of grapefruit and grapefruit juice within 1 week prior to V1.
21. Diagnosis of alcohol or drug abuse or dependence within 2 years prior to the screening visit or inability to refrain from drinking alcohol for at least 3 consecutive days (V1).
22. Positive drug test (for benzodiazepines, barbiturates, cannabinoids, opiates, amphetamines, or cocaine) or presence of alcohol in exhaled breath as detected by a breathalyzer test (V1,V2).
23. Heavy tobacco use (≥ 10 cigarettes per day), and/ or inability to refrain from smoking for at least 14 hours during the night (V1).
24. Apnea/hypopnea index (AHI) ≥ 15/h on the first PSG screening night according to the American Academy of Sleep Medicine (AASM) criteria [Meoli 2001, CMS 2008] (V2).
25. Apnea or hypopnea event (according to AASM criteria [Meoli 2001, CMS 2008]) associated with oxygen saturation by pulse oximetry (SpO_2) < 80% on the first PSG screening night (V2).
26. Periodic limb movement with arousal index (PLMAI) ≥ 15/h on the first PSG screening night (V2).

5 TREATMENTS

5.1 Study treatment

The study drugs are ACT-541468 and ACT-541468-matching placebo. Single-blind placebo will be administered at V2. Double-blind study treatment will be administered at V3, V4, V5, V6 and V7.

5.1.1 Investigational treatment and matching placebo: description and rationale

ACT-541468 capsules will be administered orally, once daily in the first two evenings of the assigned treatment period. ACT-541468 doses will include: 5 mg, 10 mg, 25 mg and 50 mg. Rationale for the selection of these ACT-541468 doses is described in Section 1.3.2.Placebo capsules matching ACT-541468 will also be administered orally, once daily in the first two evenings of the assigned treatment period and in addition at V2.

ACT-541468 is supplied by Actelion as the hydrochloride salt, in hard gelatin capsules at the strengths of 5, 10 and 25 mg. The ACT-541468-matching placebo is supplied by Actelion as identical capsules, formulated with the inactive ingredients (excipients) but without the active ingredient.

5.1.2 Study treatment administration during the different study phases

In the absence of data evaluating food effects on ACT-541468 administration, the study treatment is recommended to be taken at least 2 hours after an evening meal (including V2). Each capsule will be swallowed whole. The date and time of treatment intake will be recorded by the site staff in the electronic Case Report Form (eCRF).

5.1.2.1 Screening phase

At V1, after signing the ICF and preferably prior to any study-mandated procedures, the subject will be given the option to perform a swallow test with two placebo capsules if he/she expresses any concern regarding her/his ability to swallow the study treatment. The test is to be done under the supervision of the site personnel and documented in the charts.

At V2, in the evening of each of the two PSG nights, 2 capsules of ACT-541468-matching placebo will be taken at the site. The capsules will be taken approximately 30 minutes before lights off (= habitual bedtime ± 5 minutes).

5.1.2.2 Double-blind treatment phase

During the double-blind treatment phase (i.e., at V3, V4, V5, V6 and V7), ACT-541468 and/or ACT-541468-matching placebo will be taken approximately 30 minutes before lights off (= habitual bedtime ± 5 minutes) in the evening of each of the PSG nights, as shown in Table 2.

Table 2 Number of capsules taken according to treatment dose

Treatment dose (mg) \ Dose strength (mg)	Placebo (0)	5	10	25
Placebo (0)	2	0	0	0
5	1	1	0	0
10	1	0	1	0
25	1	0	0	1
50	0	0	0	2

For dose levels 5, 10 and 25 mg only one capsule of ACT-541468 is required, while for the 50 mg dose, two capsules of 25 mg will be administered. Therefore, to keep the blind, a placebo capsule matching ACT-541468 will be administered concomitantly with one capsule of ACT-541468 for the 5, 10 and 25 mg doses.

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 V1 after the ICF has been fully signed, the investigator/delegate will contact the Interactive Response Technology system (IRT) to get a subject number allocated to the subject.

At V2, subjects will receive single-blind placebo matching ACT-541468 treatment.

At V3, after having verified that the subject meets all inclusion criteria and none of the exclusion criteria, the investigator/delegate contacts the IRT system to randomize the subject. The IRT system assigns a randomization number to the subject and assigns the treatment site kit number, which matches the treatment sequence assigned by the randomization list to the randomization number.

The randomization list is generated by an independent CRO (ALMAC Clinical Technologies – see contact details on page 3 and in the IRT manual) and kept strictly confidential.

5.1.4 Blinding

5.1.4.1 Screening phase

At V2, placebo matching ACT-541468 will be administered in a single-blind fashion. The subjects will remain blinded to the study treatment at least until study closure. The investigator and study staff, the monitors, Actelion staff, and CROs involved in the conduct of the study will be unblinded to treatment.

5.1.4.2 Double-blind treatment phase

From V3 until V7, the study will be performed in a double-blind fashion. The subjects, investigator and study staff, monitors, Actelion staff, and CROs involved in the conduct of the study will remain blinded to the study treatment until study closure. The Clinical Trial Supplies Manager will monitor the depot stock levels in collaboration with the study team data on recruitment 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 authorized persons who are not involved in the conduct of the study.

5.1.5 Unblinding

5.1.5.1 Unblinding for final analyses

Full randomization information will be made available for data analysis only after database closure in accordance with Actelion Quality System (QS) documents.

5.1.5.2 Unblinding for IDMC review

An independent statistical analysis center (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 review by the IDMC (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 standard operating procedures (SOPs).

5.1.5.3 Unblinding for suspected unexpected serious adverse reaction

If a suspected unexpected serious adverse reaction (SUSAR) occurs for a subject participating in the study, Actelion Global Drug Safety will request the unblinding of the treatment assignment. The randomization code will not be communicated to the site staff or to the Actelion study team. Unblinded SUSAR information will be provided to respective health authorities and institutional review boards (IRBs) / independent ethics committee (IECs) only. SUSARs will be reported to investigators in a blinded fashion.

5.1.5.4 Emergency procedure for unblinding

The investigator, study staff and sponsor staff must remain blinded to the subject's study 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 randomization code for study treatment allocation through the IRT. In these situations, the decision to unblind resides solely with the investigator. Whenever it is 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 Actelion staff.

The occurrence of any unblinding during the study must be clearly justified and explained by the investigator. In all cases, Actelion must be informed 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, Good Clinical 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

Swallow test and V2:

Study treatment is supplied as a site kit and provided in childproof bottles containing 36 capsules.

V3 to V7:

Study treatment is supplied as a site kit and provided in a wallet containing the 20 capsules required for treatment of one subject over the five treatment periods.

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. Temperature measurement devices for study treatment storage area are required.

5.1.6.3 Study treatment dispensing

The study treatment will be kept at study site for administration by the site staff and will not be dispensed to the subjects when they leave the site. The protocol-mandated study treatment dispensing procedures must not be altered without prior written approval from Actelion. 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 Actelion. On an ongoing basis and/or on termination of the study, the Clinical Research Associate (CRA) will collect used and unused site kits, which will be sent to the warehouse, where Actelion staff 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 Actelion staff or the deputy and written permission for destruction has been obtained from Actelion.

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 the subject (i.e., study treatment accountability) must be performed by site staff at each visit and before dispensing further study treatment. It is to be recorded by site staff 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 dispensed to the subject:

At V2 (run-in):
- Bottle number
- Number of capsules dispensed
  Double-blind treatment phase
- Dispensed site kit number
- Date and Number of capsules administered.

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

5.1.7.2 Study treatment periods compliance

Study treatment compliance is based on study treatment accountability. Study treatment compliance for each of the five treatment periods will be calculated by the site staff using the below formula and entered in the eCRF.

> Compliance = [number of capsules administered / total number of capsules that must have been taken during the period*] × 100
>
> *The number of capsules for a treatment period equals 4.

Compliance during each treatment period is expected to be 100%. Compliance values outside of this number will be considered as a protocol deviation, which will be reported in the eCRF 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 dose interruptions must be recorded in the eCRF.

5.1.9 Premature discontinuation of double-blind study treatment

The decision to prematurely discontinue study treatment may be made by the subject, the investigator or Actelion. The main reason and whether discontinuation of study treatment is the decision of the subject (e.g., tolerability- or efficacy-related), the investigator (e.g., due to pre-specified study treatment discontinuation criteria, an AE or lack of efficacy), or Actelion (e.g., study terminated) must be documented in the eCRF and in the subject medical charts.

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 he/she believes that continued administration would be contrary to the best interests of the subject.

A subject must be discontinued from the study in case of:

- ALT $\geq 3 \times$ the ULN and total Bilirubin $> 2 \times$ the ULN on the morning laboratory test following the second drug intake of each treatment period,

or

- ALT and / or AST $> 5 \times$ the ULN on the morning laboratory test following the second drug intake of each treatment period.

A subject who prematurely discontinues study treatment is NOT considered as withdrawn from the study and will be followed up until EOS provided that the subject consents to this limited participation in the study.

Subjects who prematurely discontinue treatment during a treatment period at the center will undergo the morning assessments after the last study drug intake. All subjects who prematurely discontinue study treatment will be asked to agree to be called for the safety

follow-up (one telephone call 5 days [+ 7 days] after the last intake of study treatment, and a second telephone call at least 30 days after the last intake of study treatment).

A subject who prematurely discontinues study treatment and withdraws consent to participate in any further study assessments is considered as withdrawn from the study. 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 is described in Sections 8.2 and 8.4, respectively.

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 of informed consent.

A therapy that is study concomitant is any treatment that is ongoing or initiated after signing of informed consent, or initiated up to 30 days after study treatment discontinuation.

A therapy that is study treatment concomitant is any treatment that is either ongoing at the start of double-blind study treatment or is initiated during the double-blind treatment phase until 1 day after the last dose of double-blind study treatment (V7).

5.2.2 Reporting of previous/concomitant therapy in the eCRF

The use of all study-concomitant therapy (including 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 informed consent.

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

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 medications is to be discouraged and concomitant medications are preferably not to be changed during the course of the study.

5.2.4 Forbidden concomitant therapy

Patients 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, stroke).

The following therapies are forbidden during the study:

- Treatment with another investigational drug until the end of the safety follow-up phase.
- Prohibited CNS-active medications, including OTC medications and herbal medicines, until 24 hours after EOT [see Appendix 4].
- Treatment with moderate to strong CYP3A4 inhibitors, CYP3A4 inducers, sensitive CYP3A4 substrates (i.e., have low bioavailability due to a marked first-pass effect), P-gP substrates, BCRP substrates and CYP2B6 substrates until 24 hours after EOT [see Appendix 4].
- CBT and other psychological therapies, excluding common advice related to sleep hygiene, until 24 hours after EOT.

5.2.5 Forbidden concomitant diet and activities

The following activities and diet are forbidden during the study:

- Consumption of grapefruit and grapefruit juice until 24 hours after EOT.
- Consumption of food within 2 hours prior to study treatment intake.
- Caffeine consumption [more details in Appendix 3]
  - > 600 mg/day
  - after 14:00 on the days of PSG nights
- Alcohol consumption [more details in Appendix 2]:
  - > 2 drinks a day
  - within 24 hours prior to PSG night and during all PSG visits
- Heavy tobacco use (≥ 10 cigarettes per day) and smoking during PSG assessment at night. At home, it is recommended not to smoke or to use other tobacco products including oral snuff tobacco from 10 pm to 8 am.

6 STUDY ENDPOINTS

6.1 Efficacy endpoints

6.1.1 Primary efficacy endpoint

The primary efficacy endpoint of this study is defined as the change of WASO (min) from Baseline[5] to Days 1 and 2[6] as determined by PSG.

[5] 'Baseline' is the mean of the two PSG nights during run-in period (V2).

[6] 'Days 1 and 2' is the mean of the corresponding two PSG treatment nights for a given treatment period.

WASO is the time (minutes) spent awake after onset of persistent sleep (see definition of LPS in Section 6.1.2) until lights on as determined by PSG. WASO assessed by PSG is a sleep parameter evaluating sleep continuity. It is considered as an adequate endpoint for dose finding studies [EMA 2011].

Total time in bed is fixed at 480 minutes (8 hours) during the PSG nights. The first screening PSG recording starts (lights off) within ± 30 minutes of usual bedtime (determined by sleep diary between V1 and V2); this time is then considered as the habitual bedtime and held constant ± 5 min throughout the study. PSG is recorded for 960 epochs of 30 seconds (8 hours) from lights off until lights on. PSG recording is centrally scored by independent scorers.

6.1.2 Secondary efficacy endpoint

The secondary efficacy endpoint of this study is defined as the change from Baseline[5] to Days 1 and 2[6] in mean LPS.

LPS is the time (minutes) from start of recording to the beginning of the first continuous 20 epochs (i.e., 10 minutes) scored as non-wake, 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.

6.1.3 Other efficacy endpoints

For each variable, multiple aspects will be considered in the analysis, in particular changes from baseline at different time points. Details are provided in Section 10.2.3:

- Subjective WASO (sWASO), WASO overnight
- Subjective LSO (sLSO)
- TST and subjective TST (sTST)
- SQ
- Sleep stage S1, S2, SWS and REM,
- Shifts from S2, SWS or REM to S1 or wake
- Wake time during sleep
- Frequency of awakenings as measured by PSG and self-reported
- Sleep efficiency (SE; defined as 100 × [TST / time in bed])
- Next-day performance

6.2 Safety endpoints

- TEAEs[7] up to 5 days after study treatment discontinuation
- SAEs up to 30 days after study treatment discontinuation
- AEs leading to premature discontinuation of the double-blind study treatment
- AEs of special interest starting or worsening after the first dose of the first treatment period until EOS (and after adjudication by the ISB):
  - Narcolepsy-like events (e.g., excessive daytime sleepiness, cataplexy)
  - Complex sleep behavior events.
  - Suicidal thoughts and/or behaviors.
- Change from Baseline (mean of the two PSG nights at V2, run-in period) to the Days 1 and 2[8] of each period in vital signs (systolic and diastolic BP, pulse rate and body temperature)
- Change from Baseline (V1) to the second morning after the PSG nights at V7 in body weight
- Treatment-emergent ECG abnormalities from V3 until EOT
- Change from Baseline (V2, second morning) to the second morning after the PSG nights at V3, V4, V5, V6 and V7 in ECG parameters
- Marked laboratory abnormalities on double-blind study treatment
- Change from Baseline (V2, second morning) to the second morning after the PSG nights at V3, V4, V5, V6 and V7 in laboratory variables
- Change from Baseline (mean of the two PSG nights at V2, run-in period) to Days 1 and 2[8] of each treatment period in:
  - Digit Symbol Substitution Test (DSST©) performed in the morning, 30–60 minutes after lights on
  - Sheehan Disability Scale (SDS©) performed in the morning, 30–60 minutes after lights on
  - Karolinska Sleepiness Scale (KSS) performed in the morning, 30–60 minutes after lights on
- Incidence of most severe suicidal ideation and suicidal behaviors according to the C-SSRS© for each treatment period.

[7] A TEAE is any AE temporally associated with the use of study treatment from Day 1 until 5 days after last study drug intake in each treatment period and until 5 days after study treatment discontinuation whether or not considered by the investigator as related to study treatment.

[8] Days 1 and 2 is the mean of the first and second morning values after the two PSG nights of a treatment period.

6.3 Pharmacokinetic endpoints

Concentration of ACT-541468 (and possibly several of its metabolites) approximately 9–10 hours post-dose on the second morning at V3, V4, V5, V6 and V7 and in the event of excessive sleepiness also on the first morning at these visits.

7 VISIT SCHEDULE AND STUDY ASSESSMENTS

7.1 Study visits

The study visits are listed in Table 3. For all double-blind treatment phase visits (V3 to V7), the subjects must be seen between 5 and 12 days after the previous visit. Two follow-up safety telephone calls must be performed: one telephone call 5 days (+ 7 days) after the last intake of study treatment, and a second telephone call at least 30 days (+ 7 days) after the last intake of study treatment.

7.1.1 Screening/re-screening

Screening starts with the signature of the ICF. The date on which the first screening assessment is performed corresponds to the date of the screening visit (V1).

It is the responsibility of the investigator/delegate to obtain written informed consent from each subject participating in this study after adequate face-to-face explanation of the objectives, methods and potential hazards of the study. The subjects who agree to participate in the study and the investigator/delegate must sign the ICF prior to 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 permitted to re-screen subjects once, after discussion with Actelion. All screening assessments must then be repeated at the time of re-screening (or as agreed with Actelion).

A swallow test will be proposed to subjects after signing the ICF and before starting any study-mandated procedures. The swallow test will be optional; however, if a subject chooses to perform the swallow test but cannot swallow the study medication, he/she will be considered a screen failure and will be discontinued from the study.

7.1.2 Unscheduled visits

Unscheduled visits may be performed at any time during the study. Depending on the reason for the unscheduled visit (e.g., AE), appropriate assessments will be performed based on the judgment of the investigator. Results of ECG, laboratory assessments and change in concomitant treatment will be recorded in the eCRF. After an unscheduled

visit, the regular scheduled study visits must continue according to the planned visit and assessment schedule [Table 3].

Table 3 Visits and assessments schedule

	NAME	SCREENING PHASE							TREATMENT PHASE (5 treatment periods)										FOLLOW-UP PHASE	
	Duration	14 to 28 days							30 to 58 days										30 days	
VISITS	**Number**	**1**	-	**2**				-	**3, 4, 5, 6**				-	**7**					**Safety FU 1[8]**	**Safety FU 2[8]**
	Name	**Screening Period**		**Run-in period**					**PSG treatment nights of each visit**				**Wash out**	**Last PSG treatment nights / Permanent discontinuation[6]**						
	Time	**Between Day -28 and -14 days**	**At home 7 to 21 days**	**1st night Day -14 to -7**		**2nd night Day -13 to -6**		**Day-12 to Day -1 (At home 5 to 12 Days)**	**1st night**		**2nd night**		**At home 5 to 12 days**	**1st night**		**2nd night**			**5 (+ 7) days after EOT**	**30 (+ 7) days after EOT**
				1st Evening	1st Morning	2nd Evening	2nd Morning		1st Evening	1st Morning	2nd Evening	2nd Morning		1st Evening	1st Morning	2nd Evening	2nd Morning			
Informed consent		X																		
Inclusion and exclusion criteria		X		X					X											
Demographics		X																		
Medical history		X																		
Physical examination		X		X					X					X			X[6]			
Body weight		X															X[6]			
Body height		X																		
Vital signs and Body Temperature		X		X	X		X		X	X		X		X	X		X[6]			
12-lead ECG		X					X					X					X[6]			
Hematology, blood chemistry		X					X		X			X		X			X[6]			
Drug and alcohol tests		X		X		X			X		X			X		X				
PK sampling										X[10]		X			X[10]		X			
PSG				X[4]		X			X		X			X		X				
ISI® score		X																		
Sleep Diary (incl. VAS)		X[2]	X		X	X	X			X	X	X			X	X	X[6]			
Neurological exam[9]					X		X			X		X			X		X[6]			
C-SSRS®[7]		X			X		X			X		X			X		X[6]			
DSST®[7]					X		X			X		X			X		X[6]			
SDS®[7]					X		X			X		X			X		X[6]			
KSS[7]					X		X			X		X			X		X[6]			

Randomization[1]								X										
Study drug intake			X[3]		X[3]			X		X			X		X			
Previous and concomitant medications[11]	X		X	X	X	X		X	X	X	X		X	X	X	X[6]		
SAEs and AEs[5]	X		X	X	X	X		X	X	X	X		X	X	X	X[6]	X	X

1. Before study drug intake. **2.** The hand-held device is handed out to the subject, in order to be completed for at least 7 consecutive days at home until V2 and at the site during visits. **3.** Placebo single-blind treatment. **4.** Includes AHI, PLMAI, SpO_2. **5.** SAEs and AEs reporting and follow-up: all SAEs from signed ICF up to 30 days after double-blind study drug discontinuation. AEs from signed ICF up to 5 days after double-blind study drug discontinuation. **6.** In case of permanent discontinuation, safety assessments of V7 are recommended to be performed within 24 hours of last study drug intake. **7.** Approximately 30–60 minutes after PSG lights on [see Section 7.2 for the order of assessments]. **8.** Telephone call. **9.** Approximately 1 hour after lights on, if failed repeated every 30 minutes until subject safe to leave center [see Section 7.2 for the order of assessments]. **10.** In the event of excessive sleepiness according to investigator opinion one hour after lights on in the morning after the first PSG night, it is recommended to draw a PK sample at this time. **11.** Previous medications will be collected at V1.

AE, adverse event; AHI, Apnea/Hypopnea Index; C-SSRS®, Columbia Suicide Severity Rating Scale; DSST®, Digit Symbol Substitution Test; ECG, electrocardiogram; EOT, End of Treatment; follow-up; KSS, Karolinska Sleepiness Scale; ISI®, Insomnia Severity Index; PK, pharmacokinetic, PLMAI, Periodic Limb Movement Arousal Index; PSG, polysomnography; SAE, serious adverse event; SDS®, Sheehan Disability Scale; SpO_2, oxygen saturation by pulse oximetry; VAS, visual analog scale.

7.2 Study assessments

The mandatory study assessments are listed in Table 3.

All study assessments are performed by qualified study staff (medical, nursing, or specialist technical staff) and are recorded in the 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 PSG night:
  - Physical examination (first evening)
  - Vital signs and body temperature (first evening)
  - Drug and alcohol test
  - Hematology and blood chemistry (first evening at V3, V4, V5, V6 and V7)
  - Evening questionnaire in sleep diary, including VAS (second evening)
  - Recording of concomitant medications
  - AEs and SAEs
  - Study drug intake 30 minutes (± 5 minutes) before lights off
- In the morning after PSG night, after completion of normal morning routine (e.g., using the bathroom, eating breakfast):
  - Physical examination (second morning at V7)
  - Vital signs and body temperature
  - DSST©
  - SDS©
  - KSS
  - C-SSRS©
  - Morning questionnaire in sleep diary (including VAS)
  - Recording of concomitant medications
  - AEs and SAEs
  - Neurological examination*

- Hematology and blood chemistry (second morning)
- PK sampling* (second morning at V3, V4, V5, V6 and V7)
- 12-lead ECG (second morning)

*The neurological examination must be performed approximately 1 hour after lights on and repeated approximately every 30 minutes until it is safe for the subject to leave the center. In the event of excessive sleepiness according to investigator opinion one hour after lights on in the morning after the first PSG night, it is recommended to draw a PK sample at this time.

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

- Lab 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 Actelion to whom these tasks are delegated. The set-up and oversight will be agreed upon with Actelion. 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 storage area
- PSG device

<u>Use of hand-held device</u>
Patients will be required to complete the following questionnaires on a hand-held device: ISI©, SDS©, KSS, C-SSRS©, sleep diary and VAS.

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

For further details refer to the hand-held device 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 in the eCRF. Where possible, diagnoses and not symptoms will be recorded.

7.2.2 Insomnia severity index©

The ISI© assesses the severity of a subject's insomnia by scoring the severity of sleep-onset and sleep maintenance difficulties and any insomnia-related interference with daytime functioning [see Appendix 6]. The assessment is on a 5-point scale (0–4), where the composite score is obtained by summing the seven 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 subjective-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.

Actelion has been granted license agreement for the use of ISI©.

7.2.3 Efficacy assessments

7.2.3.1 Polysomnography

PSG data will be used to assess objective sleep parameters (WASO and LPS) as well as data on sleep architecture (sleep stages). The PSG data are evaluated and scored centrally by an independent scorer (expert from CRO Clinilabs, NY, not otherwise involved in the study). The technical requirements for montage and recording of the PSG are outlined in the PSG manual. The quality of PSG recordings is monitored and quality controlled on an ongoing basis.

All PSG recordings are supervised by qualified technical staff. The site and scorers that participate in this study must be certified by the CRO.

The first screening PSG recording starts (lights off) within ± 30 minutes of usual bedtime (determined by the sleep diary between V1 and V2); this time is then considered as the habitual bedtime and held constant (± 5 minutes) throughout the study. Study medication is administered 30 minutes (± 5 minutes) before the recording starts. The PSG recording is stopped after 480 minutes when 960 epochs of 30 seconds have been recorded. Two consecutive PSG nights will take place at V2, V3, V4, V5, V6 and V7. The first PSG screening night (at V2) also includes AHI, PLMAI, and SpO_2.

The time in bed is fixed at 8 hours. 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 PSG recording, the subject is requested to stay in bed and remain connected to the recording equipment. However, if the subject needs to go to the bathroom, he or 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 activity (such as reading, listening to radio, etc.) and is recommended not to have access to any watch or mobile phone device. The lights remain switched off until the 480 minutes of recording are finished. After recording is stopped, the lights are turned on and the subject is awakened. The subject is then allowed to go to the bathroom and to get dressed. Within 30–60 minutes vital signs are measured and the subject is asked to perform the morning assessments. The presence of any AE or change in concomitant medication will be checked. Based on the results of the neurological examination, the investigator will discuss with the subjects and decide whether it is safe for the subject to leave the study centers.

The centers are required to transfer PSG data to the CRO responsible for central scoring, after each second PSG night. During the run-in period, PSG data obviously not fitting eligibility criteria 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. The CRO will score the PSG data immediately upon receipt and the center will receive the complete eligibility assessment (mean WASO, mean LPS, mean TST, AHI, PLMAI, and the presence of any apnea/hypopnea event associated with $SpO_2 < 80\%$) within 3 business days following the file's receipt by the CRO. Based on this information, the investigator assesses the subject's potential eligibility.

After the last PSG night at Visit 7, results of all the PSG nights for the subject (V2, V3, V4, V5, V6 and V7) are sent by the CRO to Actelion. The following sleep variables will be assessed by PSG: WASO, LPS, TST, sleep stages S1 (called N1 in the scoring procedures of the Clinilabs manual), S2 (N2), SWS (N3) and REM (R), wake time during sleep (W). The definitions of the sleep variables are given in the scoring procedures of the Clinilabs manual.

Incidental findings identified by central reading will be communicated to the PI. If the incidental findings are considered clinically relevant by the PI, they will be reported in the medical history or as an AE, as applicable.

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 Clinilabs, NY)'.

7.2.3.2 Sleep diary

The sleep diary is provided to the subject at V1 as an electronic hand-held device, programmed in the subject's language, and must be completed at home every day for at least 7 consecutive days between V1 and V2. The self-administered sleep diary includes a morning and an evening questionnaire and VAS.

On each morning after the two PSG nights at V2, V3, V4, V5, V6 and V7, the subject will complete the sleep diary morning questionnaire and VAS.

On the second evening before the second PSG night at V2, V3, V4, V5, V6 and V7, the subject will complete the sleep diary evening questionnaire and VAS.

7.2.3.2.1 Morning and evening questionnaires

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

For further details, see Appendix 9.

7.2.3.2.2 Visual analog scale

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

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 9.

7.2.4 Safety assessments

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

7.2.4.1 Weight and height

Height will be measured at V1 only and recorded in the eCRF.

Body weight will be measured at V1 and in the second morning of V7 (recommended within 24 hours after last dose of double-blind study drug intake) and recorded in the eCRF. BMI will be calculated according to the BMI formula (weight in kg/m^2) and displayed automatically upon entry of weight and height in the eCRF.

7.2.4.2 Vital signs

Systolic and diastolic BP, pulse rate and body temperature will be measured non-invasively at each study visit (i.e., V1 as well as first evening and each morning at V2, V3, V4, V5, V6 and V7). Vital signs will be measured with the subject either in a supine or sitting position. It is recommended to allow the subject to rest for at least 5 minutes and to use the same position (supine or sitting) throughout the trial for an individual subject. The right or left arm may be used, but it is recommended to use the same arm throughout the trial.

Vital sign measurement and conditions will be collected in the eCRF.

7.2.4.3 Physical examination

Physical examination is to be performed at V1 and on the second morning of V7 (recommended within 24 hours after last dose of double-blind study drug intake) as well as on the first evening at V2, V3, V4, V5, V6 and V7. It includes the examination of the following body systems:

- Head, ear, nose and throat
- Eyes
- Neck
- Cardiovascular system
- Respiratory system
- Abdomen
- Skin
- Extremities
- Neurological system
- Musculoskeletal system

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 must be recorded according to body system. In the event of an abnormality, the related signs (e.g., systolic murmur) and not the diagnosis (e.g., mitral valve insufficiency) must be recorded in the eCRF. Clinically relevant findings (other than those related to insomnia disorder), including smoking habits that are present prior to signing of informed consent, must be recorded on the Medical History eCRF form. 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.

7.2.4.4 Digit Symbol Substitution Test©

The DSST© is to be performed each morning after a PSG night at V2, V3, V4, V5, V6 and V7. The DSST© 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 centers are provided with eight different test versions that use the same symbols in a different sequence. At each administration, a different test version is assigned among the eight versions, in order to minimize the impact of symbol/coding learning from one test to the subsequent one.

The number of correct substitutions is recorded as the total DSST© score.

Actelion has been granted a license agreement for the use of the DSST©. For further details, see Appendix 5

7.2.4.5 Sheehan Disability Scale©

The SDS© is to be performed each morning after a PSG night at V2, V3, V4, V5, V6 and V7. The SDS© consists of three questions on impairment of work, social life, and family life/home responsibilities [Appendix 7, Sheehan 1996]. The SDS© is a self-administered questionnaire on the hand-held device. Actelion has been granted the license agreement for the use SDS©.

7.2.4.6 Karolinska Sleepiness Scale

The KSS is to be performed each morning after a PSG night at V2, V3, V4, V5, V6 and V7. The KSS will be used to assess next-day alertness [see Appendix 8]. The subject will be asked to mark his/her sleepiness on a 9-point scale. The scale has a range from 1 being 'very alert' to 9 being 'very sleepy, great effort to keep awake, fighting sleep'. The KSS is a self-administered questionnaire on the hand-held device.

7.2.4.7 Columbia Suicide Severity Rating Scale©

The C-SSRS© is to be performed at V1 and on each morning after a PSG night at V2, V3, V4, V5, V6 and V7. The C-SSRS© is an instrument that reports the severity of both suicidal ideation and behavior [Posner 2007]. Suicidal ideation is classified on a 5-item scale:

1. wish to be dead
2. nonspecific 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 behavior, specifically actual, interrupted, and aborted attempts; preparatory acts or behavior; and if suicidal behavior was 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. At V1 (screening) the C-SSRS© will be completed for the subject lifetime history of suicidal ideation and behavior. At all other visits, the C-SSRS© will be completed for ideation and behavior since the previous visit.

At each visit, the investigator will review the responses provided by the subject and assess the findings. The scale will be self-administered using the hand-held device in the presence of an adequately trained staff member.

Actelion has been granted the license agreement for the use of the electronic C-SSRS©.

7.2.4.8 Neurological examinations

In the morning following each PSG night (V2, V3, V4, V5, V6 and V7), 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.

The set of examinations will be repeated approximately every 30 minutes until it is safe for the subject to leave the center [see Section 7.2]. The time when it is considered safe for the subject to leave the center will be recorded in the eCRF.

7.2.4.9 ECG assessment

A standard 12-lead ECG is to be performed, at V1 and in the second morning of V2, V3, V4, V5, V6 and V7.

12-lead ECG will be recorded at rest with the subject in the supine position for a 5-minute period. 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. QT_C (ms) will be calculated according to

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

If the central review of the ECG detects a prolonged QTc interval greater than 450 ms for a subject at screening (V1, V2), ECG must be repeated (at least 30 minutes after first ECG on the same day). If the central review confirms that the repeated ECG shows a QTc interval greater than 450 ms, the subject cannot be enrolled into the study.

Clinically relevant findings made after randomization that meet the definition of an AE must be recorded in the eCRF.

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

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, including re-tests due to laboratory abnormalities and laboratory tests performed at unscheduled visits.

Exceptional circumstances that will require recording of local laboratory results of the parameters described in Section 7.2.5.2 (with corresponding normal ranges), include hospitalization of the subject due to a medical emergency, and missing central laboratory results from a scheduled or unscheduled visit.

If one central laboratory sample is lost or cannot be analyzed for whatever reason, the investigator will collect an additional sample as soon as possible for repeat analysis, unless a local laboratory sample was collected within the same time-window and these test results are available.

Central laboratory reports will be sent to the investigator. In case of specific (pre-defined) laboratory abnormalities, the central laboratory will alert Actelion and the concerned site. Alert flags that will trigger such notifications are displayed in Appendix 1.

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 relevant or not. Clinically relevant laboratory findings that are known at the time of signature of informed consent must be recorded on the medical history page of the eCRF. Any clinically relevant laboratory abnormalities detected after signature of informed consent must be reported as an AE or SAE as appropriate [see Section 9] and must be followed until the value returns to within the normal range or is stable, or until the change is no longer clinically relevant.

Details about the collection, sampling, storage, shipment procedures, and reporting of results and abnormal findings can be found in the laboratory manual.

7.2.5.2 Laboratory tests

Hematology

- Hemoglobin (g/L)
- Hematocrit (L/L)
- Erythrocytes (10^9/L)
- Reticulocytes (%)
- Leukocytes with differential counts (10^9/L)
- Platelets (10^9/L)
- Prothrombin time and international normalized ratio

Clinical chemistry

- ALT (U/L)
- AST (U/L)
- Alkaline phosphatase (U/L)
- Creatine kinase (mcg/L)
- Total and direct bilirubin (µmol/L)
- Gamma-glutamyl transferase (U/L)
- Creatinine (µmol/L)
- Blood urea nitrogen (mmol/L)
- Uric acid (µmol/L)
- Glucose (mmol/L)
- Cholesterol, triglycerides (mmol/L)
- Sodium, potassium, chloride, calcium (mmol/L)
- Albumin (g/L)
- Thyroid hormones (triiodothyronine, thyroxine), and thyroid-stimulating hormone

Other tests

The urine drug screening kits (testing for presence of benzodiazepines, barbiturates, cannabinoids, opiates, amphetamines, or cocaine) and the breathalyzer for alcohol detection in the exhaled breath will be provided by the central lab.

Study drug is administered as described in Section 5 only if the results of these 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 hours post-dose at V3, V4, V5, V6 and V7. In the event of excessive sleepiness according to investigator opinion one hour after lights on in the morning after the first PSG night, it is also recommended to draw a PK sample at this time.

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 staff will ship the plasma samples to the central laboratory, who will ship the samples to Actelion preclinical drug metabolism and pharmacokinetics department for the PK analysis.

8 STUDY COMPLETION AND POST-STUDY TREATMENT / MEDICAL CARE

8.1 Study completion as per protocol

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

8.2 Premature withdrawal from study

Subjects may voluntarily withdraw from the study without justification for any reason at any time. Subjects are considered withdrawn 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. The investigator may withdraw a subject from the study (without regard to the subject's consent) if he/she believes that continued participation in the study would be contrary to the best interests of the subject. Withdrawal from the study may also result from a decision by Actelion 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 staff 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, along with who made the decision (subject, investigator, or Actelion staff) must be recorded in the eCRF, if known.

If for whatever reason (except death or loss-to-follow-up) a subject is withdrawn from the study, the investigator must make efforts to schedule a last appointment / telephone call to assess the safety and well-being of the subject, 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

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

If the study is suspended or prematurely terminated for any reason, the investigator – in agreement with Actelion – must promptly inform all enrolled subjects and ensure their appropriate treatment and follow-up, as described in Section 8.4. Actelion 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 of his/her site to the study without prior agreement from Actelion, the investigator must promptly inform Actelion staff 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 a study, the investigator must promptly notify Actelion staff 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(s) / 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 (from Day 1 until 5 days after last study drug intake in each treatment period and until 5 days after study treatment discontinuation) whether or not considered by the investigator as related to study treatment.

AEs include:

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

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

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 a specific AE form of the eCRF.

If the intensity of an AE worsens during study treatment administration, only the worst intensity must be reported on the AE form. If the AE lessens in intensity, no change in the severity is required to be reported.

For AEs ongoing at the start of study treatment, if the intensity worsens after the start of study treatment, new AE data must be reported adding a new log line on the AE form. The onset date reported on the new log line corresponds to the date of worsening in intensity.

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]. These terms are used to describe the intensity of a specific event. Medical judgment must be used on a case-by-case basis.

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

9.1.3 Relationship to study treatment

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

9.1.4 Reporting of adverse events

All AEs with an onset date after signature of informed consent and up to 5 days after study treatment discontinuation must be recorded on the specific AE form of the eCRF.

9.1.5 Follow-up of adverse events

AEs still ongoing more than 30 days after study treatment discontinuation 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 Actelion.

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:

1. Hospitalization for cosmetic elective surgery, or social and/or convenience reasons.
2. 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 30 days after study treatment discontinuation 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.

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 study treatment discontinuation 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 Actelion Global Drug Safety, but it is not recorded in the eCRF.

9.2.4 After the 30-day follow-up period

New SAEs occurring after the 30-day follow-up period must be reported to Actelion 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 the Actelion Global Drug Safety department 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 the Actelion Global Drug Safety department (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. The Actelion Global Drug Safety department 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 Actelion in the reference safety information (RSI) section provided in the most recent version of the IB. Any SAE that is assessed as related and unexpected against the RSI is known as a SUSAR and must be

reported by Actelion to concerned health authorities (including the EudraVigilance database if the study is conducted in Europe), IECs/IRBs and investigators.

9.3 Study safety monitoring

Clinical study safety information (AEs, SAEs, laboratory values, ECGs, vital signs, and project-specific examinations as required) is monitored and reviewed on a continuous basis by the Actelion 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 3.4].

10 STATISTICAL METHODS

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

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

This study is using a Latin square crossover design, hence each subject is to receive each treatment (including placebo). All analyses described in this section are based on the assumption that there is no carry-over effect [see Section 3.2].

In the below section the term Days 1 and 2 refers to the two days or nights of each period, i.e., corresponding to a given dose level.

10.1 Analysis sets

10.1.1 Screened Analysis Set

The Screened Analysis Set includes all subjects who are screened and have a subject identification number.

10.1.2 Randomized Analysis Set

The Randomized Analysis Set includes all subjects who have been assigned to a study treatment.

10.1.3 Full Analysis Set

The Full Analysis Set (FAS) includes all subjects from the randomized analysis set who received any dose of study treatment.

In order to adhere to the intention-to-treat principle:

- subjects will be evaluated according to the study treatment they have been assigned to (which may be different from the study treatment they actually receive),
- all available data are taken into account.

10.1.4 Modified FAS

Modified FAS (mFAS) includes all patients from the FAS and who have at least one WASO assessment at Baseline and at least one at Days 1 and 2 of any given treatment period.

10.1.5 Per-protocol Analysis Set

The Per-Protocol Analysis Set (PPS) comprises all subjects from the mFAS, who have two consecutive WASO values at both Baseline and Days 1 and 2 of each treatment period, and who complied with the protocol sufficiently to allow relevant assessment of treatment effects.

Criteria for sufficient protocol compliance include adequate exposure to treatment and absence of major protocol deviations that have an impact on the treatment effect. The full list of criteria will be detailed in the SAP and, at the latest, before breaking the treatment blind.

10.1.6 Safety Set

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

10.1.7 PK Analysis Set

The PK Analysis Set includes all subjects in the SS who have at least one PK sample collected after initiation of study drug.

10.1.8 Usage of the analysis sets

The primary efficacy analysis will be performed on the mFAS based on dose as randomized. Secondary and exploratory efficacy endpoint analyses will also be performed on the mFAS, while FAS and PPS will be considered for sensitivity analyses.

Safety analyses will be performed on the SS based on actual dose received.

Subject listings will be based on the SS, unless otherwise specified. Subject disposition will be described for the Screened and Randomized Analysis Set.

Table 4 describes the analysis sets used for the analysis of each data set.

Table 4 Usage of analysis datasets

	Screened	Randomized	FAS	mFAS	PPS	SS	PK set
Patient disposition	X	X					
Baseline and disease characteristics		(x)	X	(x)	(x)		(x)
Previous and concomitant medication						X	
Study drug exposure					(x)	X	
Primary efficacy endpoint			(x)	X	(x)		
Secondary and exploratory efficacy endpoints			(x)	X	(x)		
Safety and tolerability						X	
PK data							X

Note: X: main analysis, (x): sensitivity analysis to be conducted only if > 10% difference of set size with set used for main analysis.
FAS = Full Analysis Set; mFAS = modified Full Analysis Set; PK = pharmacokinetic; PPS = Per-protocol Set, SS = Safety Set.

10.2 Variables

The absolute change from baseline to time T is defined as the algebraic difference between the value observed at time T minus the value at baseline.

Unless specified otherwise, the baseline value is defined as the arithmetic mean of the last two values collected during the screening phase prior to randomization.

10.2.1 Primary efficacy variable

Efficacy variables are described in Appendix 10.

The primary efficacy endpoint relates to sleep maintenance and is assessed through the absolute change in minutes of WASO from Baseline[9] to Days 1 and 2[10].

WASO is defined in Section 6.1.1.

[9] 'Baseline' is the mean of the two PSG nights during run-in period (V2).

[10] 'Days 1 and 2' is the mean of the corresponding two PSG treatment nights for a given treatment period.

10.2.1.1 Missing values

No imputation will be performed for missing WASO values. However, if the proportion of missing values is significant (e.g., > 10%), sensitivity analyses will be considered to assess the influence on the primary analysis.

If one of the two values is missing either at Baseline or at Days 1 and 2, the only available value will be used for this time point; however, for the PPS analysis, only assessments with two values at each time point will be considered.

10.2.2 Secondary efficacy variable

The secondary efficacy endpoint relates to sleep initiation and is assessed through the absolute change from Baseline[11] to Days 1 and 2[12] in mean LPS.

LPS is defined in Section 6.1.2.

10.2.2.1 Missing values

Similarly to the primary endpoint, no imputation is to be performed; however, sensitivity analyses will be considered as necessary.

10.2.3 Other exploratory efficacy variables

Other exploratory efficacy endpoints include:

- sWASO, WASO overnight
- sLSO
- TST and sTST
- SQ
- Sleep stage S1, S2, SWS and REM
- Shifts from S2, SWS or REM to S1 or wake
- Wake time during sleep
- Frequency of awakenings as measured by PSG and self-reported
- SE (defined as 100 × (TST / time in bed)
- Next-day performance

For each variable, multiple aspects will be considered in the analysis:

10.2.3.1 Sleep-maintenance endpoint

- WASO overnight (by hour of the night and by quarter of the night).
- sWASO absolute change from Baseline[13] to Days 1 and 2[14].

[11] 'Baseline' is the mean of the two PSG nights during run-in period (V2).

[12] 'Days 1 and 2' is the mean of the corresponding two PSG treatment nights for a given treatment period.

10.2.3.2 Sleep-initiation endpoint

- sLSO absolute change from Baseline[13] to Days 1 and 2[14].

10.2.3.3 Total sleep time endpoint

- TST absolute change from Baseline[11] to Days 1 and 2[12].
- sTST absolute change from Baseline[13] to Days 1 and 2[14].

TST is the amount of actual sleep time (time spent in epochs scored as non-wake), as determined by PSG. sTST is the self-reported time spent asleep, as reported in the sleep diary.

10.2.3.4 SQ

- Change from Baseline[13] to Days 1 and 2[14] in SQ.

SQ is the sleep quality as determined by scores on the VAS.

10.2.3.5 Sleep architecture

- Mean[15] duration and mean percent of TST of each sleep stage (S1, S2, SWS and REM) for the whole night, and for each quarter of the night.
- Mean[15] latency to each sleep stage (S1, S2, SWS, and REM).

10.2.3.6 Sleep continuity

- Mean[15] number and frequency of shifts from S2, SWS or REM to S1 or wake for the whole night.
- Mean[15] wake time during sleep: time spent in epochs scored as wake between LPS and last epoch not scored wake for the whole night.
- Mean[15] frequency of awakenings: number of awakenings between first epoch and last epoch not scored wake for the whole night, by hour of the night and by quarter of the night.
- Change from Baseline[13] to Days 1 and 2[14] in self-reported number of awakenings (sNA).

10.2.3.7 SE

- Change from Baseline[11] to Days 1 and 2[12].

SE is defined as 100 × (TST [minutes] / time in bed [minutes]).

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[13] 'Baseline' is the mean value of the sleep diary entries during run-in period (V2).

[14] 'Days 1 and 2' is the mean value of the corresponding sleep diary entries for a given treatment period.

[15] 'Mean' calculated based on two PSG nights for a given treatment period.

10.2.3.8 Next-day performance

- Change from Baseline[13] to Days 1 and 2[14] in next-day performance assessed by scores on the VAS assessing morning sleepiness, daytime alertness and daytime ability to function.

10.2.4 Safety variables

Safety analysis will be conducted on the SS, and will include all safety data collected up to 30 days after study drug discontinuation.

10.2.4.1 Adverse events

An AE is defined as any event that is recorded on the AE eCRF module regardless of the onset date.

TEAEs for a given treatment group are those with onset date/time ≥ start date/time of double-blind study treatment of each treatment period and ≤ 5 days after end of study treatment of each treatment period, and ≤ 5 days after study treatment discontinuation. AE, including AEs of special interest [see Section 6.2], with onset prior to study treatment dose that worsened during the treatment phase will also be reported as TEAEs.

The handling of missing or incomplete dates/time of AEs and assessments will be described in the SAP.

10.2.4.2 Laboratory data

Laboratory analyses are based on data received from the central laboratory. All transferred central laboratory data are taken into account regardless of whether they correspond to scheduled or unscheduled assessments. Baseline laboratory test refers to the latest laboratory test performed prior to start of double-blind study treatment.

10.2.4.3 ECG

- Treatment-emergent ECG abnormalities from V3 until EOT.
- Change from Baseline (V2, second morning) to the second morning after the PSG nights at V3, V4, V5, V6 and V7 in ECG parameters.

10.2.4.4 Other safety parameters of interest

Change from Baseline (mean of the two PSG nights at V2, run-in period) to Days 1 and 2 (mean of the two PSG treatment nights) of each treatment period in:

- KSS performed in the morning, 30–60 minutes after lights on.
- DSST© performed in the morning, 30–60 minutes after lights on.
- SDS© performed in the morning, 30–60 minutes after lights on.

Incidence of most severe suicidal ideation and suicidal behaviors according to the C-SSRS© for each treatment period.

10.2.4.5 Vital signs

Change from Baseline (mean of the first and second morning values after the two PSG nights at V2, run-in period) to the Days 1 and 2 (mean of the first and second morning values after the two PSG treatment nights) for a given treatment period in vital signs (systolic and diastolic BP, pulse rate and body temperature).

10.2.4.6 Body weight

Change from Baseline (V1) to the second morning after the PSG nights at V7 in body weight.

10.2.5 Other variables

Pharmacokinetic
Plasma concentration of ACT-541468 (~9–10 hours post-dose) at V3, V4, V5, V6 and V7.

10.3 Description of statistical analyses

10.3.1 Overall testing strategy

The study is intended to select the dose that allows a clinically meaningful reduction of WASO compared to placebo.

The analyses described in the following sections assume no carry-over effect [see Section 3.2]. The duration of the washout is considered sufficient for all doses of ACT-541468.

The incidence and pattern of missing values will be explored in order to evaluate the possible impact on the planned analyses.

10.3.2 Analysis of the primary efficacy variable

10.3.2.1 Hypotheses and statistical model

Subjects will be randomized 1:1:1:1:1 to five different sequences of five study treatments according to a Latin square design [see Table 1]. The five study treatments are oral fixed doses of AC-541468 (5, 10, 25, 50 mg) and placebo.

The study is using the generalized Multiple Comparison Procedure – Modeling (MCP-Mod) approach [Bretz 2005, Pinheiro 2006, Pinheiro 2014], which combines a multiple-comparison procedure to assess the efficacy of the drug versus placebo and a modeling step to further identify the dose that is most likely to provide the expected level of efficacy (based on the primary efficacy endpoint).

The generalized approach is appropriate for this study design where each patient receives different doses in a sequence. A univariate dose-response relationship is modeled based on the mean change from baseline in WASO at each dose [see Section 10.3.2.3]. This approach has been qualified by the EMA as "*an efficient statistical methodology for model-based design and analysis of phase II dose finding studies under model uncertainty*" [EMA 2013].

The maximum mean reduction in WASO from baseline to Days 1 and 2 with an ACT-541468 dose is assumed to be 25 minutes (standard deviation = 40 minutes) larger than placebo.

The null hypothesis of an absence of a dose-response relationship for change from baseline in WASO will be tested at a two-sided significance level of 5% against the alternative hypothesis of existence of a dose response.

Dose selection to be used in future clinical trials will be done in consideration of the statistical results and clinically meaningful criteria.

10.3.2.2 Handling of missing data

For any given visit, if one of the two WASO values is missing, the available value will be used as the mean for the given treatment period. If both values are missing, no imputation will be considered. Further imputation rules may be defined in the SAP.

10.3.2.3 Main analysis

The primary statistical analysis will be performed on the mFAS.

The absolute change in WASO will be analyzed using the MCP-Mod approach [Bretz 2005, Pinheiro 2006] using a set of multiple contrast tests (MCTs) to establish the existence of a dose response that is based on a pre-specified set of dose-response models describing the potential dose-response relationship.

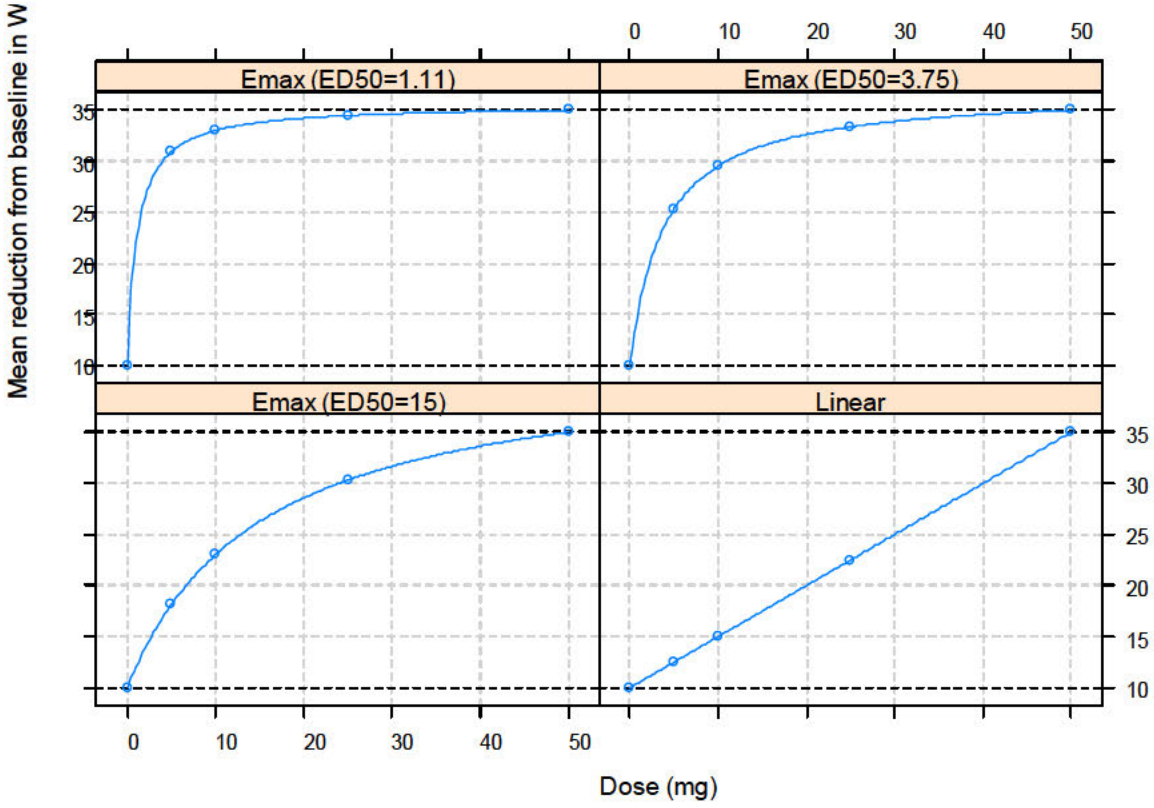
The following pre-defined dose-response models are considered: one linear, and three E_{max} models. Figure 2 shows the candidate dose-response curves for the mean reduction from baseline in WASO.

The analysis will be performed using the R-package *DoseFinding* [Bornkamp 2016]. For each candidate model, a t-statistic is derived based on a linear combination of the mean response estimates per individual dose and using optimal contrast coefficients corresponding to the candidate model. The mean response estimates are the least-squares mean (for change from baseline in WASO) of each dose group estimated by fitting a mixed model adjusted for baseline WASO, with dose group and period as fixed effects, and subject as a random effect. A dose-response relationship is demonstrated if at least one of the four MCTs has an adjusted p-value < 0.05. The best-fitting model based on

Akaike's Information Criterion will be used to estimate the target dose, defined as the dose that achieves a placebo-corrected mean reduction from baseline in WASO of at least 15 minutes with a 95% confidence interval excluding 0.

The primary endpoint will also be summarized by dose using the mean, median, standard deviation, standard error, quartiles, minimum, maximum and 95% confidence limits of the mean.

Figure 2 Candidate dose-response curves



10.3.2.4 Supportive/sensitivity analyses

Sensitivity analyses will be conducted on the PPS if this analysis set differs from the mFAS significantly (e.g., > 10%). Change from Baseline to Days 1 and 2 in mean WASO will also be analyzed using a mixed model with the same factors as above, with possible addition of region, race, gender and age.

10.3.3 Analysis of secondary efficacy variable

Similarly, an MCP-Mod-based analysis will be conducted on the secondary endpoint.

Treatment effects on the secondary efficacy endpoint will also be assessed using a mixed model similar as for the primary analysis.

10.3.4 Analysis of other exploratory efficacy variables

Descriptive statistics will be provided for all the exploratory variables, either as frequency and percentage for categorical variables or using descriptive statistics for continuous variables.

Further exploratory analysis will be conducted to assess the relationship of the changes between the perceived efficacy (subjective measures) and the objective measures from PSG.

Additional exploratory analysis will be described in full detail in the SAP.

10.3.4.1 Subgroup analyses

Subgroup analyses may be considered and will be described in the SAP.

10.3.5 Analysis of the safety variables

All safety analyses will be performed on the SS, by dose, using descriptive statistics. All safety data will be listed, with flags for quantitative abnormalities.

Observations and assessments (e.g., AEs, laboratory data) occurring within a treatment period (from the time of dosing to the time immediately prior to the next dose) will be assigned to the dose taken in that period.

10.3.5.1 Analysis of safety and tolerability endpoints

Safety and tolerability quantitative endpoints will be summarized using descriptive statistics (mean, standard deviation, median, first and third quartiles, minimum, and maximum) while frequency counts and proportions will be used for categorical data. Unless stated otherwise, percentages will be computed on the number of subjects who received the given dose.

10.3.5.2 Adverse events

AEs and SAEs in subjects who were screened but not part of the SS will be listed.

The number and percentage of subjects experiencing TEAEs and SAEs will be tabulated by dose and by:

- MedDRA™ system organ class (SOC) in alphabetical order and individual preferred term within each SOC, in descending order of incidence in the highest dose group.

- Frequency of subjects with events coded with the same preferred term, in descending order of incidence in the highest dose group.

TEAEs, AEs of special interest and SAEs will be tabulated as described above by severity and relationship to study treatment. AEs leading to premature discontinuation of the study treatment and AEs with outcome death will be summarized as described above.

AEs and SAEs with onset between screening and first day of double-blind study treatment will also be summarized.

Listings will be provided for all reported AEs, including SAEs. In addition, separate listings will be provided for SAEs, for AEs leading to premature discontinuation of study treatment, and for AEs with outcome death.

10.3.5.3 Laboratory variables

Descriptive summary statistics by dose will be provided for observed values and absolute changes from baseline, in both hematology and blood chemistry laboratory tests. All central laboratory data will be taken into account regardless of whether they correspond to scheduled or unscheduled assessments. Marked laboratory abnormalities [Appendix 1] will be summarized for each laboratory variable by dose providing their incidence and frequency.

The number and percentage of subjects with treatment-emergent laboratory abnormalities will be tabulated by dose.

10.3.5.4 ECG

Incidence of clinically abnormal ECG on double-blind study treatment as well as treatment-emergent ECG abnormalities will be tabulated (frequency and percentage) by dose.

On-treatment change in ECG parameters will be described using descriptive statistics.

10.3.5.5 Vital signs

Change will be summarized by dose.

10.3.5.6 Other safety parameters of interest

Change from Baseline (mean of the two PSG nights at V2, run-in period) to Days 1 and 2 (mean of the two PSG treatment nights) in KSS, DSST©, and SDS© will be summarized by dose.

The incidence of most severe suicidal ideation and suicidal behaviors according to the C-SSRS© will be summarized by dose.

All scales analyses will be performed according to their respective manual and interpretation guide.

10.3.5.7 Exposure-safety analysis

The exposure-safety relationship will be explored using $C_{9\text{-}10h}$ (plasma concentration of ACT-541468 the morning of the second PSG night at V3, V4, V5, V6 and V7) and will be based on the PK set. Safety parameters considered for this analysis will include selected AEs (e.g. somnolence), changes from baseline in DSST© and other parameters as relevant.

Further details will be provided in the SAP.

10.3.5.8 Pharmacokinetic

Plasma concentrations of ACT-541468 will be analyzed by descriptive statistics, including arithmetic and geometric means, standard deviation, minimum, maximum, and median.

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 at interim). Therefore, no adjustment for multiple testing is required. This study includes an IDMC and ISB that will assess safety of ACT-541468 on a regular basis as per IDMC and ISB charters, respectively.

Safety and efficacy data supporting the review by IDMC will be provided by Actelion for the part of analyses that are blinded and by an ISAC for the unblinded part.

10.5 Sample size

The following sample-size calculations are based on MCP-Mod methodology [Pinheiro 2006]. Computations were performed in R version 3.1.2 using the *DoseFinding* package.

Assuming the maximum mean reduction in WASO from baseline to Days 1 and 2 with an ACT-541468 dose is 25 minutes (standard deviation = 40 minutes) larger than with placebo, and values from 8% of subjects are not available for analysis, a total sample size of approximately 50 (i.e., 10 subjects per sequence allocated in a 1:1:1:1:1 ratio) provides between 89–92% power (power is 90% when averaged over all candidate models [Figure 2]) to reject the null hypothesis of no dose response at a 5% two-sided significance level, while the alternative hypothesis is that a dose-response relationship exists.

The between-subject standard deviation in WASO across all arms is expected to be no more than 40 minutes. The sample size is conservative, since a correlation of zero (and non-negative) is assumed between assessments across dose within the same subject.

Assuming the maximum mean reduction in WASO is considered to be 20 minutes larger than with placebo, a sample size of 71 subjects (with no dropout) are required. This number decreases to 32 subjects if we consider a maximum reduction of 30 minutes compared to placebo.

This study is powered to detect a dose-response signal given the pre-defined set of candidate dose-response curves shown in Figure 2. The study is not specifically powered to show the superiority of individual doses of ACT-541468 compared to placebo nor to provide a certain precision in estimation of a given target dose.

11 DATA HANDLING

11.1 Data collection

The investigator/delegate is responsible for ensuring the accuracy, completeness and timelines 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 captured via electronic data capture using the Rave system provided by Medidata Solutions, Inc., a web-based tool. The investigator and site staff 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., sleep diary, VAS, ISI©, C-SSRS©, KSS, SDS©) and on paper (i.e., DSST©) are considered source data. Site staff will review and ensure completeness and readability of the subjects' entries.

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) submitted to Actelion and any CROs, subjects must be identified only by number and never by their name or initials, 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 Actelion, 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 closed. 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 Actelion staff 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. The investigator/delegate must, on request, supply Actelion 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 case of health authority queries, it is also necessary to have access to the complete study records, provided that subject confidentiality is protected.

This process will continue until database closure.

Laboratory samples and ECG recordings will be processed through a central laboratory. PSG data will be read by a central reviewer. Patient-reported outcomes (PRO) will be collected on hand-held devices. All the results of the laboratory analyses, ECGs, PSG data and PRO will be electronically sent to Actelion.

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 Medical Dictionary for Regulatory Activities (MedDRA™) used by Actelion.

After the database has been declared complete and accurate, the database will be closed. Any changes to the database after that time may only be made as described in the appropriate Actelion QS documents. After database closure, the investigator will receive the eCRFs of the subjects of his/her site (including all data changes made) on electronic media or as a paper copy.

12 PROCEDURES AND GOOD CLINICAL PRACTICE

12.1 Ethics and Good Clinical Practice

Actelion staff 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 staff 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. In European countries the informed consent must be obtained by a physician. 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 staff authorized 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 Actelion. A study physician must always be involved in the consent process.

The subject and authorized site staff listed on the DoA form supplied by Actelion 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

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

The compensation of the subject in the event of study-related injuries will comply with applicable regulations.

12.5 Protocol adherence/compliance

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

If a protocol deviation occurs, the investigator/delegate will inform Actelion 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 Actelion 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 as long as is necessary to comply with Actelion'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 Actelion to store these documents outside the site, so that they can be retrieved in case of a regulatory inspection. No study document should be destroyed without prior written approval from Actelion. Should the investigator wish to assign the study records to another party, or move them to another location, Actelion 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 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 print-outs 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 Actelion'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 Actelion. The study treatment will be shipped to the site upon approval of the required essential documents.

The PI must ensure that all site staff 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. Actelion 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 staff 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. In case a site does not enroll any subjects, the close-out visit may be performed prior to study database closure at the discretion of Actelion.

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 content 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 Actelion. 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 Actelion.

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

12.10 Audit

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

The investigator and site staff 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 IEC/IRB 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 Actelion (usually via the CRA) that such a request has been made.

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

12.12 Reporting of study results and publication

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

Study results will be documented in a CSR that will be signed by Actelion representatives and the Coordinating Investigator (or PI for single-center studies).

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.

The Trial Coordinating Investigator and the Steering Committee, if any, will have the opportunity to review the analysis of the data and to discuss the interpretation of the study results with Actelion staff prior to submission to a peer-reviewed journal or presentation at a congress.

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 Actelion and will be determined by mutual agreement.

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

Actelion's Policy on Scientific Publications can be found at: http://www.actelion.com/documents/corporate/policies-charters/policy-scientific-publications.pdf.

13 REFERENCES

[aasmnet.org] American Academy of Sleep Medicine (AASM) Standards and Guidelines for the Practice of Sleep Medicine, regularly updated [accessed on 10 June 2016]. Available from: http://www.aasmnet.org.

[ACT-541468 IB] Investigator's Brochure for ACT-541468 dual orexin receptor antagonist version 3. Actelion Pharmaceuticals Ltd May 2016.

[Agostini 2004] Agostini JV, Han L, Tinetti ME. The relationship between number of medications and weight loss or impaired balance in older adults. J Am Geriatr Soc 2004;52(10):1719-1723.

[Ambien® USPI] Ambien® (zolpidem) US Package Insert. United States Food and Drug Administration full prescribing information. Revised 2/2008.

[Ancoli-Israel 2009] Ancoli-Israel S. Sleep and its disorders in aging populations. Sleep Med 2009;10 Suppl 1:S7–11.

[Avidan 2005] Avidan AY, Fries BE, James ML, Szafara KL, Wright GT, Chervin RD. Insomnia and hypnotic use, recorded in the minimum data set, as predictors of falls and hip fractures in Michigan nursing homes. J Am Geriatr Soc 2005;53(6):955-62.

[Belsomra® USPI] Belsomra® (suvorexant) US Package Insert. United States Food and Drug Administration full prescribing information. Revised 8/2014.

[Blackwell 2006] Blackwell T, Yaffe K, Ancoli-Israel S, Schneider JL, Cauley JA, Hillier TA, et al. Poor sleep is associated with impaired cognitive function in older women: the study of osteoporotic fractures. J Gerontol A Biol Sci Med Sci 2006;61(4):405–10.

[Bornkamp 2016] Bornkamp B, Pinheiro J, Bretz F. Documentation of the R Package 'DoseFinding'. 2016, Version 0.9–14.

[Bretz 2005] Bretz F, Pinheiro JC, Branson M. Combining multiple comparisons and modeling techniques in dose-response studies. Biometrics. 2005;61(3):738–48.

[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.

[Carney 2012] Carney CE, Buysse DJ, Ancoli-Israel S, Edinger JD, Krystal AD, Lichstein KL The consensus sleep diary: standardizing prospective sleep self-monitoring. SLEEP 2012;35(2):287–302.

[Chong 2013] Chong Y, Fryar CD, Gu Q. Prescription Sleep Aid Use Among Adults: United States, 2005–2010. NCHS Data Brief 2013;127.

[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.

[CMS 2008] Centers for Medicare and Medicaid Services. National Coverage Determination for Continuous Positive Airway Pressure (CPAP) Therapy for Obstructive Sleep Apnea (OSA). NCD #240.4 2005 [cited in 2008; accessed on 8 June 2016]. Available from: https://www.cms.gov/medicare-coverage-database/indexes/national-and-local-indexes.aspx.

[Dam 2008] Dam TT, Ewing S, Ancoli-Israel S, Ensrud K, Redline S, Stone K. Association between sleep and physical function in older men: the MrOS sleep study. J Am Geriatr Soc 2008;56(9):1665–73.

[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.

[DSM-5 2013] American Psychiatric Association (APA). Diagnostic and Statistical Manual of Mental Disorders (5th edition): Diagnostic criteria for Primary Insomnia, 2013 [accessed on 8 June 2016]. Available from: http://www.psychiatry.org/psychiatrists/practice/dsm/dsm-5.

[EMA 2011] European medicines agency, committee for medicinal products for human use, guideline on medicinal products for the treatment of insomnia; EMA/CHMP/16274/2009 previously (EMEA/16274/2009) Rev. 1 [accessed on 8 June 2016]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2011/02/WC500102351.pdf.

[EMA 2013]. European medicines agency, committee for medicinal products for human use, Qualification Opinion of MCP-Mod as an efficient statistical methodology for model-based design and analysis of Phase II dose finding studies under model uncertainty EMA/CHMP/SAWP/757052/2013 [accessed on 8 June 2016]. Available from:

http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2014/02/WC500161027.pdf.

[FDA 2007] FDA Requests Label Change for All Sleep Disorder Drug Products [accessed on 8 June 2016]. Available from: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2007/ucm108868.htm.

[FDA 2013] FDA Drug Safety Communications. Risk of next morning impairment after use of insomnia drugs; FDA requires lower recommended doses for certain drugs containing zolpidem (Ambien®, Ambien® CR, Edluar, and Zolpimist) [accessed on 8 June 2016]. Available from: http://www.fda.gov/downloads/Drugs/DrugSafety/UCM335007.pdf.

[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.

[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.

[ICH 1998] International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use. Statistical principles for clinical trials E9 [accessed on 8 June 2016]. Available from: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E9/Step4/E9_Guideline.pdf.

[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.

[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.

[Lopez-Torres Hidalgo 2012] Lopez-Torres Hidalgo J, Navarro Bravo B, Parraga Martinez I, Andres Pretel F, Tellez Lapeira J, Boix Gras C. Understanding insomnia in older adults. Int J Geriatr Psychiatry 2012;27(10):1086–93.

[Lunesta® USPI] Lunesta® (eszopiclone) US Package Insert. United States Food and Drug Administration full prescribing information. Revised 5/2014.

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

[Meoli 2001] Meoli AL, Casey KR, Clark RW, Coleman JA Jr, Fayle RW, Troell RJ, et al. Hypopnea in sleep-disordered breathing in adults. Sleep 2001;24(4):469–70.

[Mets 2010] Mets MA, Volkerts ER, Olivier B, Verster JC. Effect of hypnotic drugs on body balance and standing steadiness. Sleep Med Rev 2010;14(4):259–67.

[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.

[Mort 2000] Mort JR, Aparasu RR. Prescribing potentially inappropriate psychotropic medications to the ambulatory elderly. Arch Intern Med 2000;160:2825–31

[Neubauer 2014] Neubauer DN. New and emerging pharmacotherapeutic approaches for insomnia. International Review of Psychiatry 2014;26(2):214–24.

[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 2005] Ohayon MM, Vecchierini MF. Normative sleep data, cognitive function and daily living activities in older adults in the community. Sleep2005;28(8): 981–9.

[Ohayon 2009] Ohayon MM, Reynolds CF. Epidemiological and clinical relevance of insomnia diagnosis algorithms according to the DSM-IV and the International Classification of Sleep Disorders (ICSD). Sleep Med 2009;10(9):952–60.

[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.

[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.

[Pinheiro 2006] Pinheiro J, Bornkamp B, Bretz F. Design and analysis of dose-finding studies combining multiple comparisons and modeling procedures. J Biopharm Stat. 2006;16(5):639–56.

[Pinheiro 2014] Pinheiro J, Bornkamp B, Glimm E, Bretz F. Model-based dose finding under model uncertainty using general parametric models. Statistics in Medicine 2014;33(10):1646–61

[Posner 2007] Posner K. Suicidality issues in clinical trials: Columbia suicidal adverse event identification in FDA safety analyses. Division of Metabolism and Endocrinology Products Advisory Committee Meeting 2007 [accessed on 10 June 2016]. Available from: www.fda.gov/ohrms/dockets/ac/07/slides/2007-4306s1-01-CU-Posner.ppt.

[Praplan-Pahud 1990] Praplan-Pahud J, Forster A, Gamulin Z, Tassonyi E, Sauvanet JP. Preoperative sedation before regional anaesthesia: comparison between zolpidem, midazolam and placebo. Br J Anaesth 1990;64(6):670–4.

[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.

[Scharf 2008] Scharf M, Rogowski R, Hull S, Cohn M, Mayleben D, Feldman N, et al. Efficacy and safety of doxepin 1 mg, 3 mg, and 6 mg in elderly patients with primary insomnia: a randomized, double-blind, placebo-controlled crossover study. J Clin Psychiatry. 2008;69(10):1557–64.

[Schlack 2013] Schlack R, Hapke U, Maske U, Busch M, Cohrs S. Frequency and distribution of sleep problems and insomnia in the adult population in Germany: results of the German Health Interview and Examination Survey for Adults (DEGS1). Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz 2013;56(5-6):740–8.

[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(5):487–504.

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

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

[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(79):23-26.

[Vermeeren 2015] Vermeeren A, Sun H, Vuurman EF, Jongen S, Van Leeuwen CJ, Van Oers AC, et al. On-the-Road Driving Performance the Morning after Bedtime Use of Suvorexant 20 and 40 mg: A Study in Non-Elderly Healthy Volunteers. Sleep 2015;38(11):1803–13.

[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 Marked laboratory abnormalities

Parameters	Sex	Conventional US Reporting of Reference Ranges									SI Reporting Reference Ranges								
		Units	Ref Range Low	Ref Range High	Flag L at	Flag H at	Flag LL at	Flag HH at	Call Alert Low at	Call Alert High at	Units	Ref Range Low	Ref Range High	Flag L at	Flag H at	Flag LL at	Flag HH at	Call Alert Low at	Call Alert High at
Hematology																			
White blood cells	M/F	10^3/uL	4.5	11	4.4	11.1	1.9	22	NA	NA	10^9/L	4.5	11	4.4	11.1	1.9	22	NA	NA
Red blood cells	M	10^6/uL	4.5	5.9	4.49	5.91	NA	NA	NA	NA	10^{12}/L	4.5	5.9	4.49	5.91	NA	NA	NA	NA
Red blood cells	F	10^6/uL	3.8	5.2	3.79	5.21	NA	NA	NA	NA	10^{12}/L	3.8	5.2	3.79	5.21	NA	NA	NA	NA
Hemoglobin	M	g/dL	13	17.5	12.9	17.6	6.9	19	NA	NA	g/L	130	175	129	176	69	190	NA	NA
Hemoglobin	F	g/dL	11.5	16	11.4	16.1	6.9	19	NA	NA	g/L	115	160	114	161	69	190	NA	NA
Hematocrit	M	%	41.6	54.1	41.5	54.2	21	60	21	60	L/L	0.416	0.541	0.415	0.542	0.21	0.6	0.21	0.6
Hematocrit	F	%	36.4	48.9	36.3	49	21	60	21	60	L/L	0.364	0.489	0.363	0.49	0.21	0.6	0.21	0.6
Platelets	M/F	10^3/uL	130	400	129	401	49	1000	NA	NA	10^9/L	130	400	129	401	49	1000	NA	NA
Absolute Neutrophil Count	M/F	10^3/uL	1.8	7.7	1.7	7.8	0.5	15.4	NA	NA	10^9/L	1.8	7.7	1.7	7.8	0.5	15.4	NA	NA
Absolute Lymphocyte Count	M/F	10^3/uL	1	4.8	0.9	4.9	NA	NA	NA	NA	10^9/L	1	4.8	0.9	4.9	NA	NA	NA	NA
Absolute Monocyte Count	M/F	10^3/uL	0.1	0.8	0	0.9	NA	NA	NA	NA	10^9/L	0.1	0.8	0	0.9	NA	NA	NA	NA
Absolute Eosinophil Count	M/F	10^3/uL	0	0.5	NA	0.6	NA	NA	NA	NA	10^9/L	0	0.5	NA	0.6	NA	NA	NA	NA
Absolute Basophil Count	M/F	10^3/uL	0	0.2	NA	0.3	NA	NA	NA	NA	10^9/L	0	0.2	NA	0.3	NA	NA	NA	NA
Percent Neutrophils	M/F	%	40	70	39.9	70.1	NA	NA	NA	NA	%	40	70	39.9	70.1	NA	NA	NA	NA
Percent Lymphocytes	M/F	%	22.2	43.6	22.1	43.7	NA	NA	NA	NA	%	22.2	43.6	22.1	43.7	NA	NA	NA	NA
Percent Monocytes	M/F	%	2	12	1.9	12.1	NA	NA	NA	NA	%	2	12	1.9	12.1	NA	NA	NA	NA
Percent Eosinophils	M/F	%	0	4.5	NA	4.6	NA	NA	NA	NA	%	0	4.5	NA	4.6	NA	NA	NA	NA
Percent Basophils	M/F	%	0	1.8	NA	1.9	NA	NA	NA	NA	%	0	1.8	NA	1.9	NA	NA	NA	NA
Reticulocytes	M/F	%	0.2	2.3	0.1	2.4	NA	NA	NA	NA	%	0.2	2.3	0.1	2.4	NA	NA	NA	NA

Protime	M/F	seconds	9.4	13	9.3	13.1	NA	NA	NA	100.1	seconds	9.4	13	9.3	13.1	NA	NA	NA	100.1
INR	M/F	N/A	0.8	1.2	0.79	1.21	NA	NA	NA	5	N/A	0.8	1.2	0.79	1.21	NA	NA	NA	5

INR = International Normalized Ratio; M/F = male/female; N/A = not applicable.

Parameters	Sex	Conventional US Reporting of Reference Ranges									SI Reporting Reference Ranges								
		Units	Ref Range Low	Ref Range High	Flag L at	Flag H at	Flag LL at	Flag HH at	Call Alert Low at	Call Alert High at	Units	Ref Range Low	Ref Range High	Flag L at	Flag H at	Flag LL at	Flag HH at	Call Alert Low at	Call Alert High at
Clinical Chemistry																			
Alanine aminotransferase	M	U/L	0	44	NA	45	NA	132	NA	NA	U/L	0	44	NA	45	NA	132	NA	NA
Alanine aminotransferase	F	U/L	0	33	NA	34	NA	99	NA	NA	U/L	0	33	NA	34	NA	99	NA	NA
Albumin	M/F	g/dL	3.5	5.2	3.4	5.3	2.0	7.1	2.0	7.1	g/L	35	52	34	53	20	71	20	71
Alkaline phosphatase	M	U/L	53	129	52	130	NA	440	NA	NA	U/L	53	129	52	130	NA	440	NA	NA
Alkaline phosphatase	F	U/L	42	98	41	99	NA	440	NA	NA	U/L	42	98	41	99	NA	440	NA	NA
Aspartate aminotransferase	M	U/L	14	39	13	40	NA	117	NA	NA	U/L	14	39	13	40	NA	117	NA	NA
Aspartate aminotransferase	F	U/L	14	34	13	35	NA	102	NA	NA	U/L	14	34	13	35	NA	102	NA	NA
Bilirubin, direct	M/F	mg/dL	0.0	0.3	NA	0.4	NA	3.0	NA	NA	umol/L	0.0	5.1	NA	5.2	NA	51.3	NA	NA
Bilirubin, total	M/F	mg/dL	0.3	1.2	0.2	1.3	NA	3.3	NA	NA	umol/L	5.1	20.5	5.0	20.6	NA	56.5	NA	NA
Blood Urea Nitrogen (BUN)	M/F	mg/dL	9	23	8	24	NA	70	NA	NA	mmol/L	3.2	8.2	3.1	8.3	NA	25.0	NA	NA
Calcium	M/F	mg/dL	8.6	10.2	8.5	10.3	6.8	12.0	6.8	14.0	mmol/L	2.15	2.55	2.14	2.56	1.70	3.00	1.70	3.50
Chloride	M/F	mmol/L	99	109	98	110	74	131	NA	NA	mmol/L	99	109	98	110	74	131	NA	NA
Cholesterol, total	M/F	mg/dL	0	199	NA	200	NA	602	NA	NA	mmol/L	0.0	5.2	NA	5.3	NA	15.6	NA	NA
Creatinine	M	mg/dL	0.70	1.30	0.69	1.31	NA	3.00	NA	NA	umol/L	62	115	61	116	NA	265	NA	NA
Creatinine	F	mg/dL	0.50	1.10	0.49	1.11	NA	3.00	NA	NA	umol/L	44	97	43	98	NA	265	NA	NA
Creatine kinase	M	U/L	32	294	31	295	NA	525	NA	NA	U/L	32	294	31	295	NA	525	NA	NA
Creatine kinase	F	U/L	33	211	32	212	NA	525	NA	NA	U/L	33	211	32	212	NA	525	NA	NA
GGT	M	U/L	0	54	NA	55	NA	162	NA	NA	U/L	0	54	NA	55	NA	162	NA	NA
GGT	F	U/L	0	37	NA	38	NA	111	NA	NA	U/L	0	37	NA	38	NA	111	NA	NA
Glucose, Random	M/F	mg/dL	60	140	59	141	40	360	NA	NA	mmol/L	3.3	7.8	3.2	7.9	2.2	20.0	NA	NA
Potassium (K)	M/F	mmol/L	3.5	5.1	3.4	5.2	2.5	6.5	2.5	6.5	mmol/L	3.5	5.1	3.4	5.2	2.5	6.5	2.5	6.5
Sodium (Na)	M/F	mmol/L	136	145	135	146	119	161	NA	NA	mmol/L	136	145	135	146	119	161	NA	NA

Triglycerides	M/F	mg/dL	0	149	NA	150	NA	NA	NA	NA	mmol/L	0.00	1.68	NA	1.69	NA	NA	NA	NA
Uric acid	F	mg/dL	2.3	6.6	2.2	6.7	NA	13.1	NA	NA	umol/L	137	393	136	394	NA	780	NA	NA
TSH	M/F	µIU/mL	0.35	5.50	0.34	5.51	NA	NA	NA	NA	mIU/L	0.35	5.50	0.34	5.51	NA	NA	NA	NA
Triiodothyronine, Free (FT3)	M/F	pg/mL	2.3	4.2	2.2	4.3	NA	NA	NA	NA	pmol/L	3.5	6.5	3.4	6.6	NA	NA	NA	NA
Thyroxine, Total (T4)	M/F	µg/dL	4.5	10.9	4.4	11.0	NA	NA	NA	NA	nmol/L	58	141	57	142	NA	NA	NA	NA

M/F = male/female; NA = not applicable; TSH = thyroid-stimulating hormone.

Appendix 2 Alcohol Restrictions during the study

The subjects must not drink alcohol 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.

A drink is defined as:

- A bottle/can of 33 cl/12 ounces of beer (≈14 grams alcohol)
- A glass of 10–12 cl/4 ounces of wine (≈12 grams alcohol)
- A small glass of 3–4 cl/1 ounce of liquor (≈9 grams alcohol)

Appendix 3 Caffeine content of common beverages

The content of caffeine in common caffeine beverages is approximately:

- A standard cup of brewed or restaurant-style coffee contains approximately 150–200 mg caffeine.
- A can of most soda drinks (unless decaffeinated soda drinks) contains approximately 50 mg caffeine.
- A can of energy drinks contains approximately 150–200 mg caffeine.

Appendix 4 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 V1**. The use of CNS-active drugs is forbidden or restricted until 24 hours after EOT (V7).

Drug Class	Examples	Forbidden / Restricted	Comment
Centrally Acting Anticholinergics and Antihistamines	OTC Histamine1-Antihistamines, e.g.: Diphenhydramine HCl, Carbinoxamine, Dimenhydrinate, Triprolidine HCl Hydroxizine	F	
Antihistamines	Sedating Non-sedating (loratidine, fexofenadine)	F R	Non-sedating antihistamines may be used maximum twice weekly for allergic symptoms.
Psychotropics	Stimulants: Amphetamines Modafinil, armodafinil Methylphenidate	F	
	Antidepressants	F	
	Antipsychotics, including depot neuroleptics	F	
	Anxiolytics, e.g.: Lorazepam Alprazolam Buspirone	F	
	Sleep medications, e.g.: Prescribed zolpidem and other sleep medicines, suvorexant, ramelteon and OTC	F	
	MAOIs	F	
	Melatonin	F	
	Mood stabilizers, e.g.: Lamotrigine Gabapentin Lithium Oxcarbazepine Carbamazepine	F	

	Valproic acid		
	Narcotics	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	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 Johns Wort, valerian	F	
	Tryptophan	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	F	
	Diet Pills (prescription and OTC)	F	
	Pseudoephedrine	R	May only be used before 14.00, and no more than twice a week. Dosage is limited to 30 mg of active ingredient in each tablet. Extended release formulations are forbidden.

GABA = gamma-aminobutyric acid; MAOI = monoamine oxidase inhibitor; 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 and sensitive substrates), with P-gP substrates, with BCRP substrates, and with CYP2B6 substrates.

Those medications must be discontinued no later than **1 week prior to V1** and are forbidden until 24 hours after EOT (V6).

CYP3A4 moderate and strong inhibitors and CYP3A4 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, nevirapine
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, phenytion, St John's Wort
Cardiovascular: amiodarone, diltiazem, dronedarone, mibefradil, verapamil	Cardiovascular: bosentan
	Hypoglycemics: pioglitazone, troglitazone
Aprepitant, conivaptant, cimetidine, imatinib	
Grapefruit and grapefruit juice	

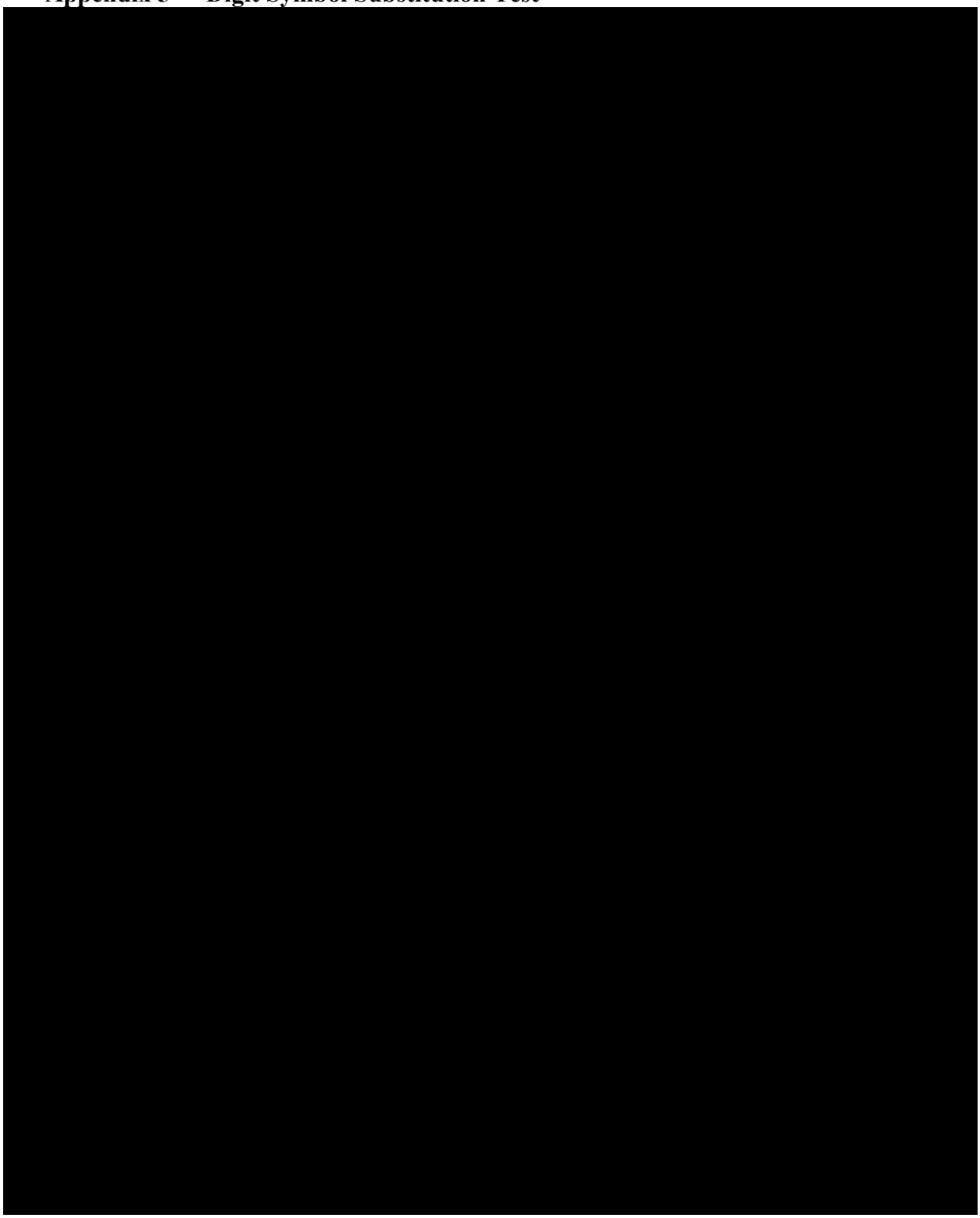
CYP3A4 substrates: alfentanil, apixaban, budesonide, buspirone, cisapride, crizotinib, cyclosporine, darifenacin, dihydroergotamine, domperidone, dronedarone, erlotinib, ergotamine, ethinylestradiol, erythromycin, felodipine, fentanyl, halofantrine, ketamine, lovastatin, lurasidone, maraviroc, midazolam, nifedipine, nisoldipine, oxycodone, quetiapine, saquinavir, sildenafil, simvastatin, sirolimus, tacrolimus, terfenadine, ticagrelor, tipranavir/ritonavir, tolvaptan, triazolam, vardenafil, verapamil.

P-gP substrates: aliskiren, ambrisentan, colchicine, dabigatran etexilate, digoxin, everolimus, fexofenadine, imatinib, lapatinib, maraviroc, nilotinib, posaconazole, ranolazine, saxagliptin, sirolimus, sitagliptin, talinolol, tolvaptan, topotecan.

BCRP substrates: imatinib, irinotecan, lapatinib, methotrexate, mitoxantrone, rosuvastatin, sulfasalazine, topotecan.

CYP2B6 substrates: bupropion, cyclophosphamide, efavirenz, irinotecan, ketamine, promethazine, propofol, selegiline, valproic acid.

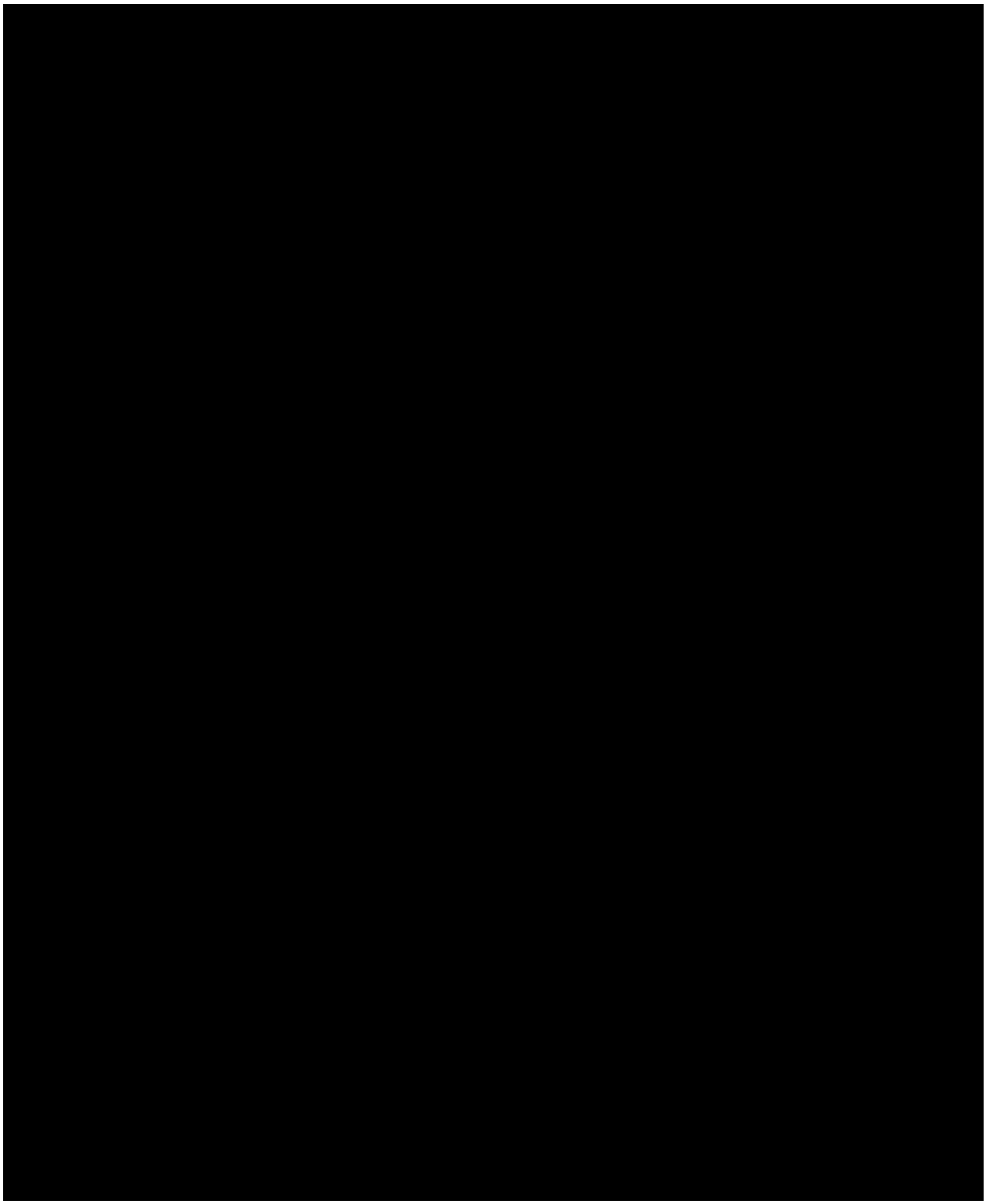
Appendix 5 Digit Symbol Substitution Test©



Appendix 6 Insomnia Severity Index©

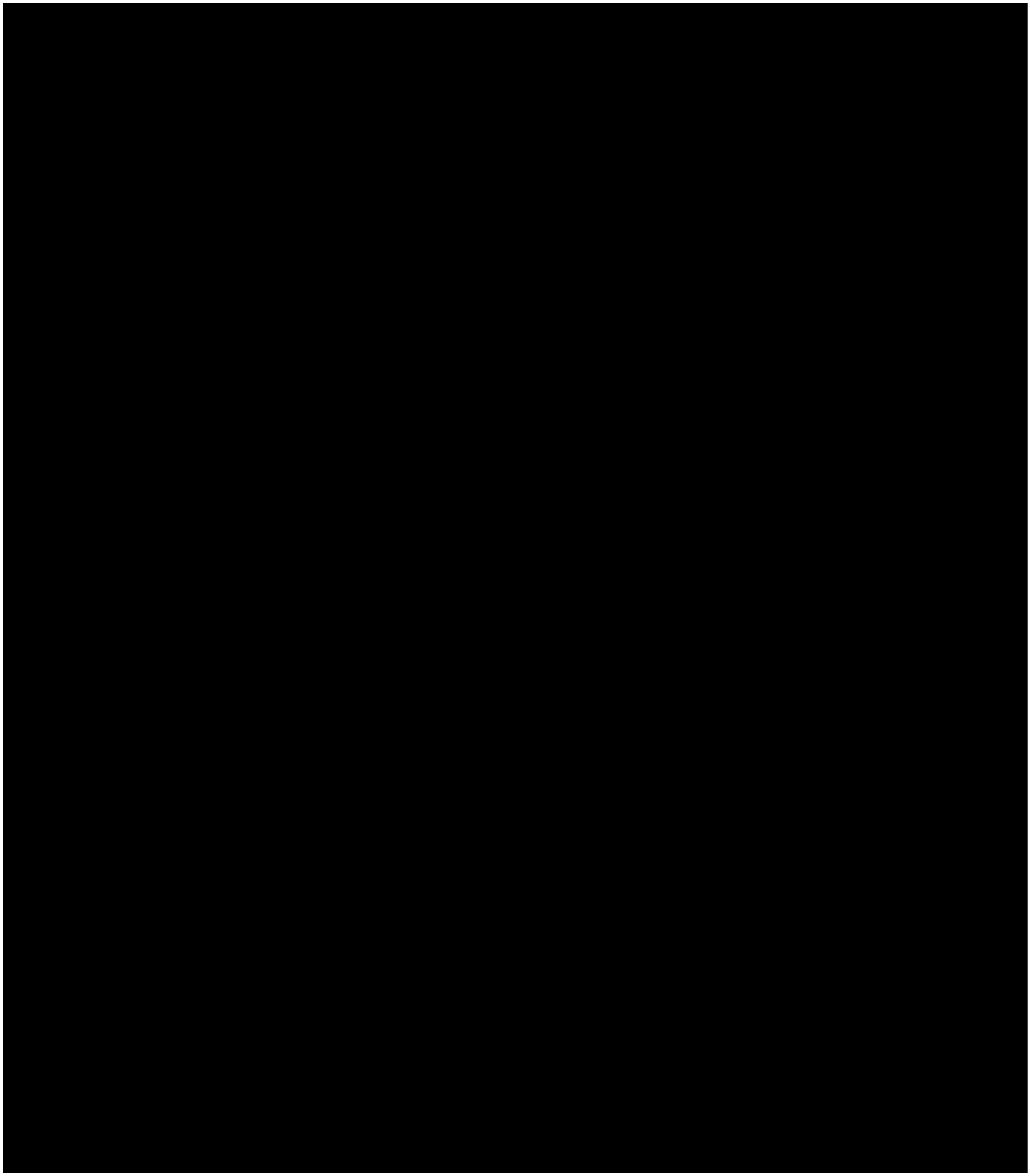
[redacted]

Appendix 7 Sheehan Disability Scale©



Appendix 8 Karolinska Sleepiness Scale

Appendix 9 Sleep diary



Appendix 10 Summary table of efficacy variables

Objectives	**Variables**	**Endpoints**	
Sleep maintenance	WASO	Absolute change from Baseline[a] to Days 1 and 2[b]	Primary
	WASO overnight	Absolute change from Baseline[a] to Days 1 and 2[b] by hour of the night and by quarter of the night	Exploratory
Sleep initiation	LPS	Absolute change from Baseline[a] to Days 1 and 2[b]	Secondary
	sLSO	Absolute change from Baseline[c] to Days 1 and 2[d]	Exploratory
Total sleep time	TST	Absolute change from Baseline[a] to Days 1 and 2[b]	Exploratory
	sTST	Absolute change from Baseline[c] to Days 1 and 2[d]	
Sleep quality	VAS	Absolute change from Baseline[c] to Days 1 and 2[d]	Exploratory
Sleep architecture	Sleep stages duration	Mean[e] duration and mean percent of TST of each sleep stage (S1, S2, SWS and REM) for the whole night, and for each quarter of the night.	Exploratory
	Sleep stages latency	Mean[e] latency to each sleep stage (S1, S2, SWS, and REM).	
Sleep continuity	Shifts between sleep stages	Mean[e] number and frequency of shifts from S2, SWS or REM to S1 or wake for the whole night.	Exploratory
	Wake time during sleep	Mean[e] wake time during sleep: time spent in epochs scored as wake between LPS and last epoch not scored wake for the whole night.	
	Awakenings	Mean[e] frequency of awakenings: number of awakenings between first epoch and last epoch not scored wake for the whole night, by hour of the night and by quarter of the night.	
	sNA	Absolute Change from Baseline[c] to Days 1 and 2[d] in self-reported number of awakenings	
Sleep efficiency	SE	Absolute change from Baseline[a] to Days 1 and 2[b]	Exploratory

Next-day performance	VAS	Absolute change from Baseline[c] to Days 1 and 2[d]	Exploratory

Note: a 'Baseline' is the mean of the two PSG nights during run-in period (V2), b 'Days 1 and 2' is the mean of the corresponding two PSG treatment nights for a given treatment period, c 'Baseline' is the mean value of the sleep diary entries during run-in period (V2), d 'Days 1 and 2' is the mean value of the corresponding sleep diary entries for a given treatment period, e 'Mean' calculated based on two PSG nights value for a given treatment period.

LPS = latency to persistent sleep; PSG = polysomnography; REM = rapid eye movement; SE = sleep efficiency; sLSO = subjective latency to sleep onset; sNA = self-reported number of awakenings; sTST = subjective total sleep time; SWS = slow-wave sleep; TST = total sleep time; VAS = visual analog scale; WASO = wake after sleep onset.