Study protocol AC-078A201

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

ClinicalTrials.gov Identifier NCT02839200

The study was sponsored was sponsored by Actelion Pharmaceuticals Ltd.
Study sponsorship was transferred to Idorsia Pharmaceuticals Ltd in July 2018.

ACT-541468

Insomnia Disorder

Protocol AC-078A201

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Study Phase:	2
EudraCT Number:	2016-000826-21
Status and version:	Final Version 3
Date:	16 December 2016
Document type	Global protocol
Actelion document number (Doc No.):	D-16.648

SPONSOR CONTACT DETAILS

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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

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

COORDINATING INVESTIGATOR

Name / Title	Address
[redacted]	[redacted]

CONTRACT RESEARCH ORGANIZATIONS INFORMATION

CENTRAL LABORATORY	[redacted]
CENTRAL RANDOMIZATION	ALMAC
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ECG CORE LABORATORY	[redacted]
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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-078A201

Multi-center, double-blind, randomized, placebo-controlled, active-reference, parallel-group, polysomnography dose-response study to assess the efficacy and safety of ACT-541468 in adult 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

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AC-078A201

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

I agree to the terms and conditions relating to this study as defined in this protocol, the Case Report Form (CRF), 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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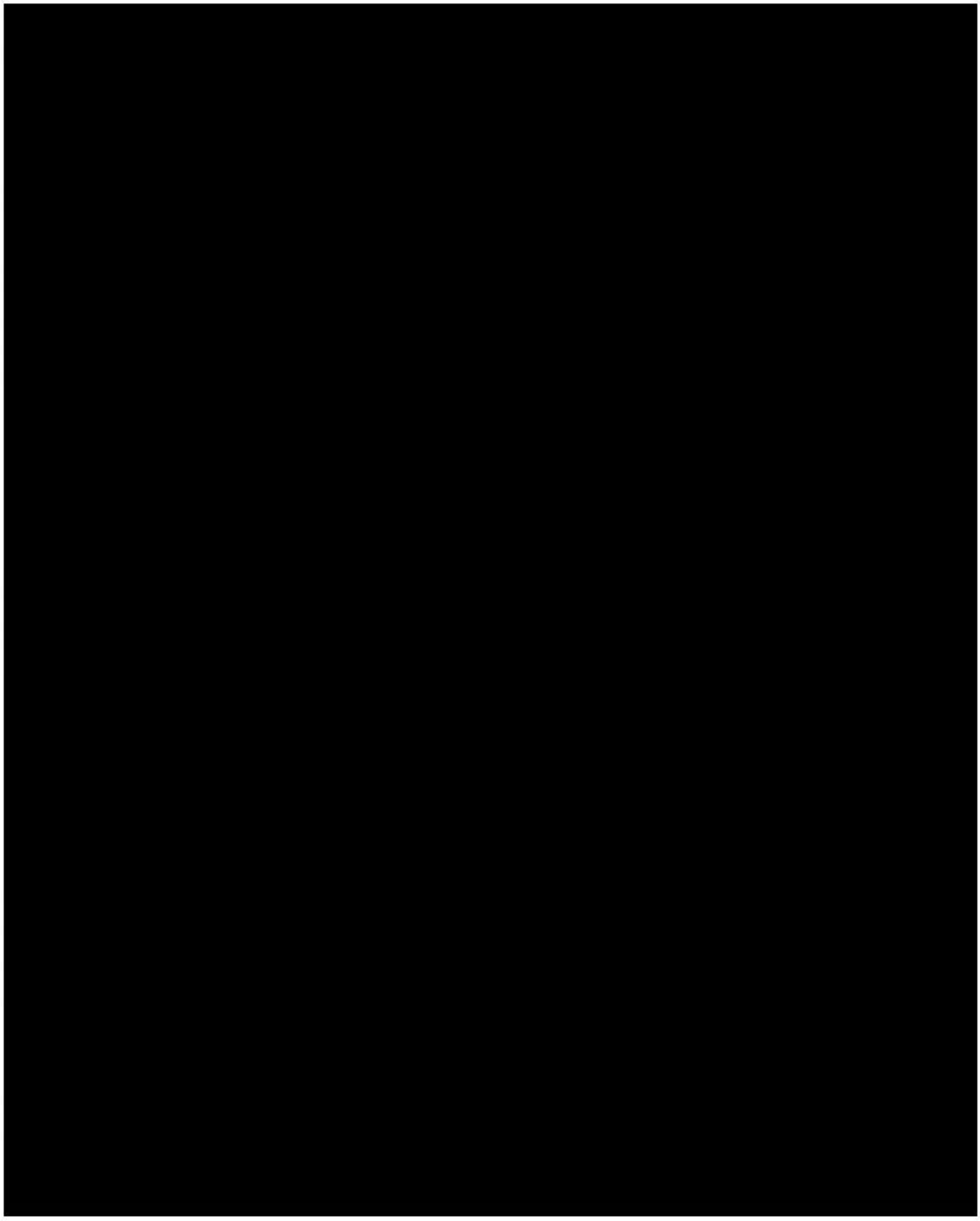
LIST OF ABBREVIATIONS AND ACRONYMS

AASM	American Academy of Sleep Medicine
AE	Adverse event
AHI	Apnea/hypopnea index
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
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
BMI	Body mass index
BP	Blood pressure
bpm	Beats per minute
BCRP	Breast Cancer Resistance Protein
BWSQ	Benzodiazepine Withdrawal Symptom Questionnaire
CBT	Cognitive behavioral therapy
CI	Confidence interval
C_{max}	Maximum observed 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	Electronic Case Report Form
ED_{50}	Effective dose that provides 50% of the maximum effect
EMA	European Medicines Agency
E_{max}	Maximum effect
EODB	End of Double-Blind Treatment
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
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

OX_1	Orexin receptor 1
OX_2	Orexin receptor 2
PD	Pharmacodynamic(s)
P-gP	P-glycoprotein 1
PI	Principal Investigator
PK	Pharmacokinetic(s)
PLMAI	Periodic Limb Movement with Arousal Index
PPS	Per-protocol Set
PSG	Polysomnography
QS	Quality System
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
SmPC	Summary of Product Characteristics
SOC	System organ class
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
TEAE	Treatment-emergent adverse event
TST	Total Sleep Time
ULN	Upper limit of the normal range

USPI	US package insert
V	Visit
VAS	Visual analog scales
WASO	Wake After Sleep Onset



[redacted]

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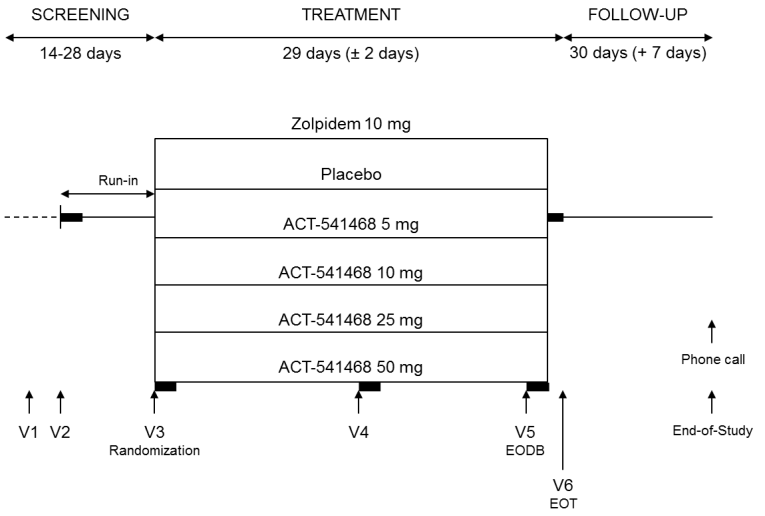
PROTOCOL SYNOPSIS AC-078A201

TITLE	Multi-center, double-blind, randomized, placebo-controlled, active-reference, parallel-group, polysomnography dose-response study to assess the efficacy and safety of ACT-541468 in adult 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; minutes) assessed by polysomnography (PSG) after treatment on Days 1 and 2. **Secondary objectives** The secondary objective of the study is to evaluate the dose response of ACT-541468 on Latency to Persistent Sleep (LPS) on Days 1&2 and subjective Latency to Sleep Onset (sLSO) and subjective WASO (sWASO) at Week 4.
DESIGN	Multi-center, double-blind, randomized, placebo-controlled, active-reference, parallel-group, polysomnography dose-response Phase 2 study.
PHASES	**Screening phase** The **screening phase** lasts a minimum of 14 days and maximum of 28 days. It starts with the signing 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 Visit 1 (V1), 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 until Visit 2 (V2). The **run-in period** occurs between Day –14 and Day –1 and starts with V2. V2 consists of 2 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. A sleep diary must be completed for at least 7 consecutive days from V2 to randomization.

	Treatment phase The **treatment phase** consists of a double-blind treatment period followed by a run-out period. The **double-blind treatment period** starts with the first dose of double-blind study treatment in the first evening of the Randomization Visit (V3, Day 1). The **End of Double-Blind treatment** is reached in the second morning of V5 (Day 30) after the last dose of double-blind study treatment and after all second morning assessments have been performed. The **run-out period** starts in the evening of Day 30 (V6) with the last dose of study treatment (single-blind placebo). The end of the run-out period corresponds to **End of Treatment** (EOT). EOT is reached after all morning assessments have been performed in the morning of Day 31 (V6). The **safety follow-up phase** starts after EOT (Day 31) and lasts at least 30 days (i.e., until Day 61, follow-up telephone call). **End of Study** (EOS) for a single subject is defined as the date of the 30-day follow-up telephone call (Day 61). 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 12 weeks (see diagram below).

	
PLANNED DURATION	Approximately 11 months from first subject first visit to last subject last visit.
SITES / COUNTRIES	Approximately 38 sites in 6 countries: ESP, GER, HUN, ISR, SWE, USA.
SUBJECTS / GROUPS	Approximately 300 subjects will be centrally randomized in 6 groups in a 1:1:1:1:1:1 ratio stratified by gender; 50 subjects per group.
INCLUSION CRITERIA	1. Signed informed consent prior to any study-mandated procedure (V1). 2. Male or female aged 18–64 years (inclusive) (V1). 3. A woman of childbearing potential must provide: • Negative serum pregnancy test (V1). • Negative urine pregnancy test (V3). • Agreement to undertake pregnancy tests up to 30 days after EOT. • Agreement to use the contraception scheme as described in Section 4.5.2 of the protocol from Screening up to at least 30 days after EOT. 4. Body mass index (BMI): $18.5 \leq$ BMI (kg/m^2) < 32.0 (V1). 5. Insomnia disorder according to DSM-5 criteria (V1). 6. Self-reported history of all of the following on at least 3 nights per week and for at least 3 months prior to V1: • $\geq$ 30 minutes to fall asleep • Wake time during sleep $\geq$ 30 minutes

	• Total sleep time (TST) ≤ 6.5 h 7. Insomnia severity index (ISI©) score ≥ 15 (V1). 8. Willing to comply with all aspects of the study protocol (V1, V2, V3). 9. Ability to communicate well with the investigator and to understand the study requirements and judged by the investigator to be alert and oriented to person, place, time and situation (V1). 10. 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 ≤ 6.5 h 11. Usual bedtime between 21:30 and 00:30 as reported on sleep diary completed between V1 and V2 (to be checked at V2). 12. Regular time in bed between 6 and 9 hours as reported on sleep diary completed between V1 and V2 (to be checked at V2). 13. Meeting the following sleep parameters on the 2 PSG nights (V2): • Mean LPS ≥ 20 min (with neither of the two nights < 15 min), *and* • Mean WASO ≥ 30 min (with neither of the two nights < 20 min), *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 ≥ 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 the study (V1). 5. Travel ≥ 3 time zones within 1 week prior to the screening

	visit, or planned travel ≥ 3 time zones during study (V1). 6. Pregnant, planning to become pregnant or lactating (V1, V3). 7. Hematology or biochemistry test results deviating from the normal range to a clinically relevant extent as per judgment of the investigator (V1, V2). 8. Aspartate aminotransferase and/or alanine aminotransferase > 2 × the upper limit of normal (ULN) and/or direct bilirubin > 1.5 × ULN (V1, V2). 9. 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). 10. Unstable medical condition, significant medical disorder or acute illness, within 1 month prior to the screening visit, which in the opinion of the investigator could affect the subject's safety or interfere with the study assessments (V1). 11. Systolic blood pressure > 150 mmHg and diastolic blood pressure > 90 mmHg (V1, V2). 12. Resting pulse rate < 50 or ≥ 100 bpm (V1, V2). 13. Any of the following conditions related to corrected QT (QTc) interval (V1, V2): • A prolonged QTc interval (QTc greater than 450 ms). If QTc is greater than 450 ms 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. • A history of additional risk factors for torsade de pointes (e.g., heart failure, hypokalemia, family history of long QT syndrome). 14. 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). 15. 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). 16. Treatment with another investigational drug within 1 month prior to V1. 17. Known hypersensitivity or contraindication to drugs of the same class as the study treatment or to any excipients of the study drug formulation, or to zolpidem, including myasthenia gravis (V1). 18. 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 (V6), including over-the-counter (OTC) medication and herbal medicines. 19. Cognitive behavioral therapy (CBT) within one month prior to V1. 20. Treatment with moderate to strong cytochrome P450 (CYP) 3A4 inhibitors, CYP3A inducers, sensitive CYP3A4 substrates, P-gP substrates, BCRP substrates, and CYP2B6 substrates [as defined in Appendix 4] within 1 week prior to V1 until 24 h after EOT. 21. Consumption of grapefruit or grapefruit juice within 1 week prior to V1 until 24 h after EOT. 22. Diagnosis of alcohol or drug abuse or dependence within 2 years prior to V1 or inability to refrain from drinking alcohol for at least 3 consecutive days (V1). 23. 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). 24. Heavy tobacco use (≥ 10 cigarettes per day), and/or inability to refrain from smoking for at least 14 hours during the night (V1). 25. Apnea/hypopnea index ≥ 10/h on the first PSG screening night according to American Academy of Sleep Medicine (AASM) criteria (V2). 26. Apnea or hypopnea event (according to AASM criteria) associated with oxygen saturation by pulse oximetry < 80%, on the first PSG screening night (V2).

<table>
<tr><td></td><td>27. Periodic limb movement with arousal index ≥ 10/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 evening during the double-blind 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.

Reference and/or placebo
Two capsules of ACT-541468-matching placebo will be administered orally once daily at V2 and V6.

During the double-blind treatment period, subjects will receive orally once daily two capsules as shown in the table below.
<table>
<tr><th colspan="2">Treatment group</th><th>Number (and dose strength) of ACT-541468 capsules</th><th>Number of ACT-541468-matching placebo capsules</th><th>Number of over-encapsulated zolpidem 10 mg capsules</th><th>Number of over-encapsulated zolpidem-matching placebo capsules</th></tr>
<tr><td rowspan="4">ACT-541468</td><td>5 mg</td><td>1 (5 mg)</td><td>1</td><td>0</td><td>0</td></tr>
<tr><td>10 mg</td><td>1 (10 mg)</td><td>1</td><td>0</td><td>0</td></tr>
<tr><td>25 mg</td><td>1 (25 mg)</td><td>1</td><td>0</td><td>0</td></tr>
<tr><td>50 mg</td><td>2 (25 mg)</td><td>0</td><td>0</td><td>0</td></tr>
<tr><td colspan="2">Placebo</td><td>0</td><td>2</td><td>0</td><td>0</td></tr>
<tr><td colspan="2">Zolpidem</td><td>0</td><td>0</td><td>1</td><td>1</td></tr>
</table></td></tr>
<tr><td>CONCOMITANT THERAPY (MEDICATION, DIET, ACTIVITIES)</td><td>The following concomitant therapies are forbidden during the study:
• Treatment with another investigational drug until end of safety follow-up phase.
• Prohibited CNS-active medications, including OTC medication and herbal medicines, until 24 hours after EOT [see Appendix 4].
• Treatment with moderate to strong CYP3A4 inhibitors,</td></tr>
</table>

	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 [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 caffeine/day – after 4 pm on non-PSG nights – after 2 pm on the days of PSG nights. • Alcohol consumption [for definition of drinks see Appendix 2]: – > 2 drinks a day – less than 3 hours before going to bed on non-PSG nights – within 24 hours prior to PSG night and during all PSG visits. • Heavy tobacco use (≥ 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** The primary efficacy endpoint of this study is WASO, defined as the change of WASO from Baseline[a] to Days 1&2[b] as determined by PSG. WASO (min) is the time 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 min (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. Where: [a] 'Baseline' is the mean of the 2 PSG nights during the run-in period (V2). [b] 'Days 1&2' are the mean of the corresponding 2 PSG treatment nights (V3). **Secondary efficacy endpoints** The secondary efficacy endpoints of this study are sleep initiation endpoints such as LPS and sLSO and a sleep maintenance endpoint such as subjective WASO (sWASO). <u>Sleep-initiation endpoints</u> Change from Baseline[a] to Days 1&2[b] in mean LPS. LPS (min) is the time from start of recording to the beginning of the first continuous 20 epochs (i.e., 10 min) scored as non-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. Change from Baseline[c] to Week 4[d] in mean subjective sLSO. sLSO is the self-reported time to fall asleep, as reported in the sleep diary. <u>Sleep-maintenance endpoint</u> Change from Baseline[c] to Week 4[d] in mean sWASO. sWASO is the self-reported time spent awake after sleep onset as reported in the sleep diary. Where: [a] 'Baseline' is the mean of the 2 PSG nights during the run-in period (V2). [b] 'Days 1&2' is the mean of the corresponding 2 PSG treatment nights (V3). [c] 'Baseline' is the mean value in the screening sleep diary entries at home between V2 and V3 across 7 consecutive days. [d] 'Week 4' is the mean value based on the sleep diary entries at home across the last week of double-blind study treatment.

Other efficacy endpoints
Other endpoints are described in Section 6.1.3.

Safety endpoints

- Treatment-emergent adverse events (TEAEs)‡ and 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.
- TEAEs of special interest after adjudication by an Independent Safety Board (ISB):
  - Narcolepsy- like events (e.g., excessive daytime sleepiness, cataplexy)
  - Complex sleep behaviors events.
  - Suicidal thoughts and/or behaviors.
- Change from baseline (mean of the two PSG nights at V2, run-in period) to the last value on double-blind study treatment in vital signs (systolic and diastolic blood pressures, pulse rate and body temperature)
- Change from baseline (V1) to the last value on double-blind study treatment in body weight.
- Treatment-emergent‡ ECG abnormalities.
- Change from baseline (V2, second morning) to the last value on double-blind study treatment in ECG parameters.
- Marked laboratory abnormalities on double-blind study treatment.
- Change from baseline (V2, second morning) to the last value on double-blind study treatment in laboratory variables.
- Rebound insomnia:
  - Change from baseline (V2) to the morning of V6 in WASO, TST and LPS.
- Withdrawal symptoms:
  - Change from Day 30 to Day 31 in Benzodiazepine Withdrawal Symptom Questionnaire scores.
  - AEs and ECG abnormalities emerging from Day 30 to Day 31.
- Change from baseline (mean of the two PSG nights at V2, run-in period) to Days 1&2, 15&16 and 28&29 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. • Change from baseline (V2, second morning) to the last value on double-blind study treatment in C-SSRS©. ‡ A treatment-emergent AE is any AE temporally associated with the use of study treatment (from double-blind study treatment start until 30 days after study treatment discontinuation) whether or not considered by the investigator as related to study treatment. **Pharmacokinetic endpoints** ACT-541468 plasma concentrations (and possibly several of its metabolites) 9–10 h post-dose (morning after the second PSG night) at V3, V4, and V5.
ASSESSMENTS	Refer to the schedule of assessments in Table 2.
STATISTICAL METHODOLOGY	**Analysis sets:** *Screened Analysis Set* This set includes all subjects who are screened and have a subject identification number. *Randomized Analysis Set* The Randomized Set includes all subjects who have been assigned to a study treatment. *Full Analysis Set* The Full Analysis Set (FAS) includes all subjects assigned to a study treatment and who received at least one dose of study treatment. *Modified FAS* The modified FAS (mFAS) includes all patients from the FAS who have at least one WASO assessment at Baseline and one at Days 1&2. *Per-protocol Analysis Set* The Per-protocol Analysis Set comprises all subjects from the

	mFAS who have two consecutive WASO values at Baseline and at Days 1&2, and who complied with the protocol sufficiently to allow assessment of treatment effects. *Safety Set* The Safety Set (SS) includes all subjects who received at least one dose of study treatment. Subjects will be evaluated according to the actual treatment they received, which may differ from the randomly assigned treatment. *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. All analyses will be performed at a 0.05 type I error level (two-sided) using 95% confidence intervals (CIs). Secondary efficacy variables will also be analyzed at $\alpha = 0.05$ (two-sided). **Primary efficacy analysis** This study includes 6 arms: a placebo, 4 doses of ACT-541468 and an active reference. The active reference will be excluded from all statistical tests related to dose response, but will be compared separately versus placebo. 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 and a set of pre-specified dose-response models to describe the dose-response curve. Four candidate dose-response models will be considered: one linear, and three E_{max} models. The analysis will be performed using the R-package *DoseFinding* [Bornkamp 2016]. 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 of at least 15 min with a 95% CI excluding 0.

	The primary endpoint will be summarized at each time point by treatment group using the mean, median, standard deviation, standard error, quartiles, minimum, maximum and 95% confidence limits of mean. **Secondary efficacy analyses** Similarly, an MCP-Mod-based analysis will be conducted on the secondary endpoints. Treatment effect on secondary efficacy endpoints, except for the change of WASO from baseline over time, will also be assessed using a mixed model, with treatment, country, gender and age as fixed effects and patient as random covariate. Treatment effect on the change of WASO from baseline over time will be estimated using a repeated-measures mixed model. Further exploratory analysis will be conducted to assess the relationship of the changes between the perceived efficacy (subjective measures) and the objectives measures from PSG. **Safety analysis** Safety analyses will be performed on the SS [details defined in Section 10.1.6]. *Adverse events:* AEs in subjects who were screened but not randomized will be listed. The number and percentage of subjects experiencing TEAEs and SAEs will be tabulated by treatment group 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 randomization and first day of 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 visit and treatment group 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 treatment group providing their incidence and frequency. Absolute values and changes from baseline of laboratory values during the course of the study will be summarized using the location and scale summary statistics by treatment group. The number and percentage of subjects with treatment-emergent laboratory abnormalities will be tabulated by treatment group MCP-Mod approach will also be considered for assessing the dose-response relationship for insomnia rebound effect and for withdrawal symptoms. **Other endpoints' analysis** Treatment effects on other endpoints will be evaluated and described in detail in the SAP. **Subgroup analysis** Subgroup analyses will be performed by gender.

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 enrolment 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-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. Population-based epidemiological studies suggest that 30% or more of the general population complain of sleep disruption and approximately 10% of the general population have complaints of sleep disruption with associated symptoms of distress or daytime functional impairment consistent with the diagnosis of insomnia disorder [NIH 2005, Roth 2007]. Higher prevalence rates are found in clinical practices, where about one-half of respondents to a survey reported symptoms of sleep disruption [NIH 2005, Roth 2007].

Insomnia disorder may result in difficulty falling asleep or difficulty maintaining sleep, characterized by multiple or long awakenings during the sleep period, or early morning awakenings. Difficulty maintaining sleep is the most common problem among patients with insomnia, occurring in approximately two-thirds of them [Neubauer 2014], and some studies have shown that the most common constellation of symptoms is represented by patients who concurrently suffer from difficulty both falling and staying asleep [Hohagen 1994]. Evidence now suggests that people with sleep maintenance difficulties are among the most likely to experience daytime cognitive impairment and report comorbidities [Ohayon 2010]. Therefore, problems related to sleep maintenance insomnia impact the largest percentage of insomnia sufferers, and affect them most acutely.

While the direct consequences of insomnia remain only partially understood, the comorbidities associated with insomnia have been examined in a number of studies. Individuals with insomnia report impairment in cognitive functioning, daytime fatigue,

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

1.1.3 Treatment

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

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

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

Non-benzodiazepine benzodiazepine receptor agonists have a more targeted action on one or more GABA type A receptor subtypes. Zolpidem, zolpidem controlled-release (CR) and zaleplon show affinity for the alpha-1 receptor subtype, while eszopiclone shows affinity for the alpha-2 and -3 receptor subtypes [Nutt 2006]. All of these drugs reduce latency to sleep onset, but zolpidem CR and eszopiclone have also been shown to

reduce Wake After Sleep Onset (WASO), reflecting an improvement in sleep maintenance [Ambien® USPI, Lunesta® USPI]. Although they have less impact on sleep architecture, possibly by virtue of their receptor selectivity, the drugs in this group have similar adverse effects to the benzodiazepines. In 2007 the US 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, which may include sleep-driving [FDA 2007].

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

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

Suvorexant is an oral dual orexin receptor antagonist (DORA) that was approved by the FDA in 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].

1.1.4 Unmet medical need

There are effective and safe treatments for insomnia [Schutte-Rodin 2008]. Pharmacological treatments that address sleep onset problems alone do not provide relief to people with sleep maintenance difficulties, and treatments indicated for those with sleep maintenance problems may be associated with risks of cognitive impairment, postural instability, or next-day residual sedation that may impair driving [Neubauer 2014]. This represents an important unmet medical need. There is 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. Results of nonclinical and early-phase clinical studies [ACT-541468 IB] 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 treatments

1.2.1 ACT-541468

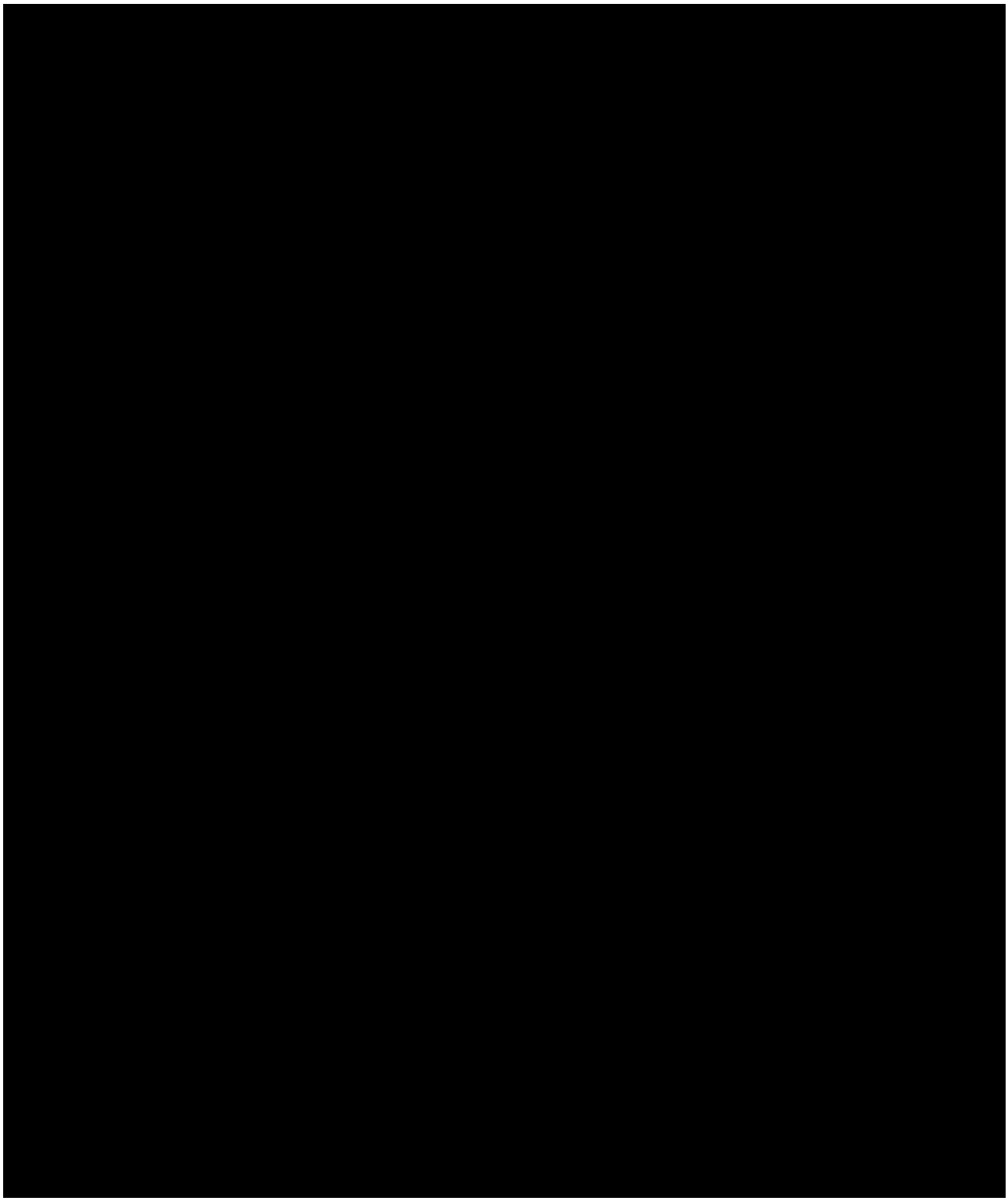
1.2.1.1 The orexin system

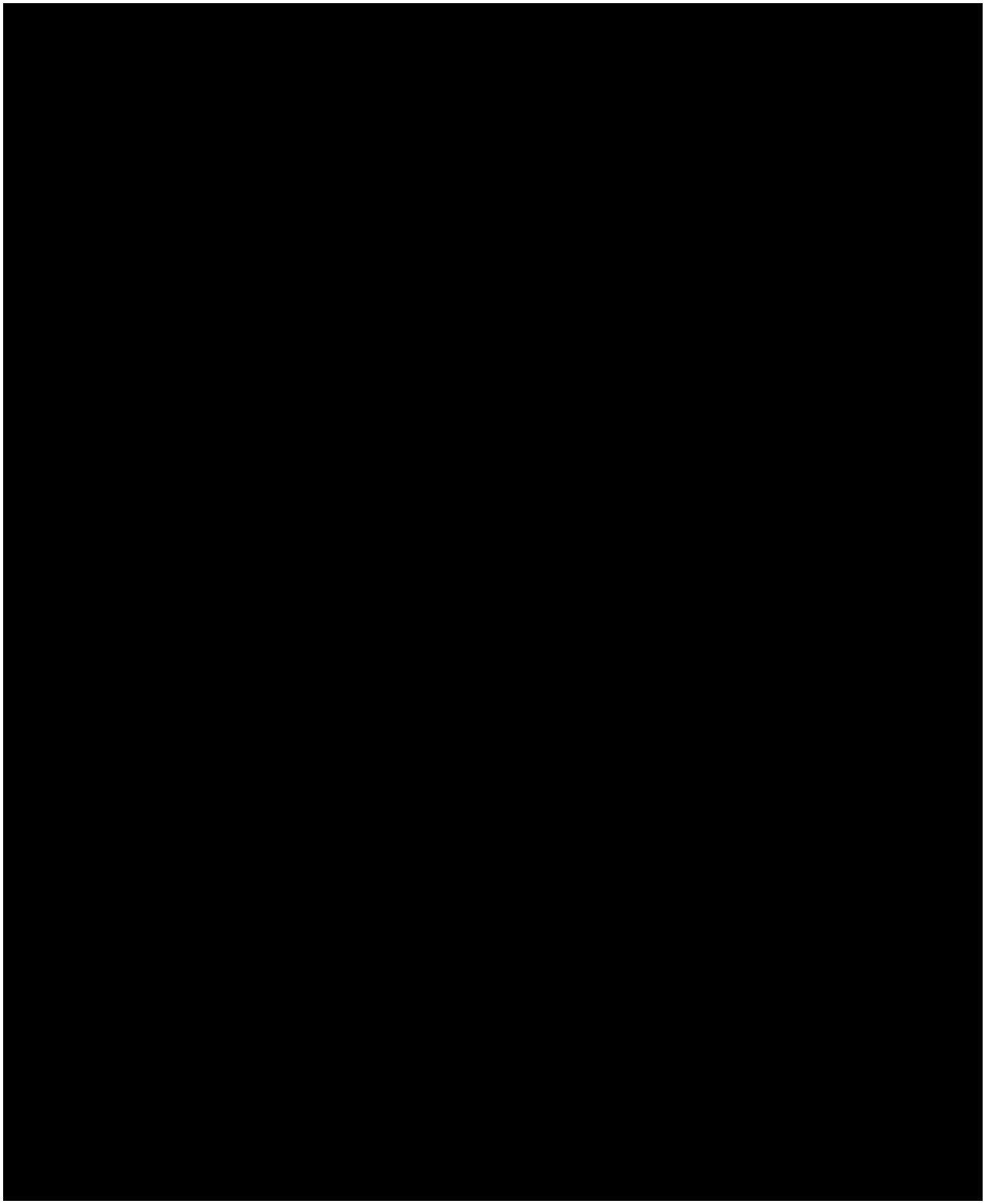
The orexin system is involved in the regulation of sleep and arousal by the central nervous system (CNS) and is currently being targeted in the development of new therapies for sleep disorders.

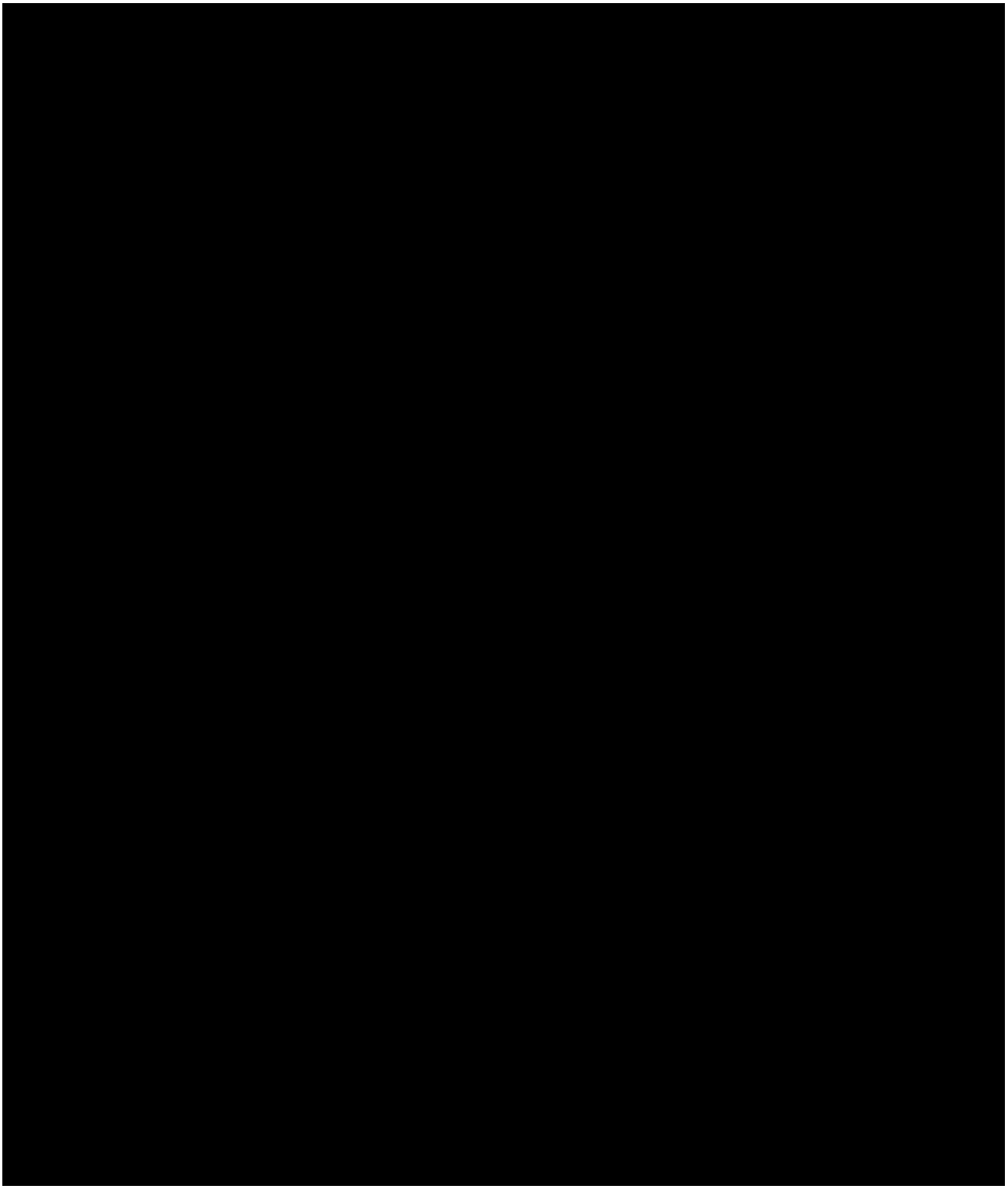
The neuropeptides orexin-A and orexin-B are synthesized in the lateral hypothalamic areas [de Lecea 1998] and activate the orexin-1 and orexin-2 receptors (OX_1 and OX_2 receptors) [Kilduff 2000]. Nerve fibers from orexin neurons make projections particularly to those regions related to waking and regulation 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, and they are 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 in the USA. For a description of the effects of suvorexant, refer to Section 1.1.3.







1.2.2 Zolpidem

Zolpidem is a non-benzodiazepine sleep medication, with a chemical structure unrelated to benzodiazepines. However, zolpidem shares some of the pharmacological properties of the benzodiazepines since it binds to the benzodiazepine receptor 1 [Stilnox® SmPC].

The zolpidem oral tablet formulation is indicated for short-term treatment of insomnia. In the United States it is indicated when insomnia is characterized by difficulties with sleep initiation; sleep latency has been shown to decrease for up to 35 days in controlled clinical studies. In Europe, zolpidem is indicated for the short-term treatment of insomnia in adults [Stilnox® SmPC].

Common undesirable effects of sleep medications have been described in Section 1.1.3. The most common reasons to discontinue zolpidem in clinical studies were daytime

drowsiness, dizziness, headaches, nausea and vomiting. The most commonly observed adverse reactions were drowsiness, dizziness and diarrhea. In addition to drowsiness, prolonged reaction time and impaired driving may occur the morning after therapy [EMA 2014]. As with benzodiazepines and non-benzodiazepine sleep medications, zolpidem may lose efficacy over time as well as induce dependence and complex sleep behaviors (such as sleep-driving) with amnesia for the events and hallucinations [Ambien® USPI, Stilnox® SmPC]. Zolpidem is contraindicated in patients with myasthenia gravis [Stilnox® SmPC].

In the United States, a lower dose than in the AC-078A201 study, 5 mg instead of 10 mg, is recommended as the initial dose in women and the dose to be considered in men [Ambien® USPI]. The recommendation of the lower starting dose of 5 mg was based on higher risk of next-morning impairment in patients taking initial doses of 10 mg, in particular with the extended release formulation of Ambien® [FDA 2013]. The 10 mg zolpidem dose group has been included in the proposed study AC-078A201 for assay validation as the efficacy and the safety of this dose have been well established in confirmatory clinical studies in adult patients with chronic insomnia [Stilnox® SmPC]. In order to ensure subject safety, sleepiness/alertness will be closely monitored and neurological examinations will be performed in the morning after each polysomnography (PSG) night at the sleep centers in this study. Based on the results of the neurological examination, the investigator will discuss with the subject and decide whether it is safe for the subject to leave the study center.

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) which will show a favorable efficacy and safety profile and to assess the safety and tolerability of the compound in adult subjects with insomnia disorder.

The efficacious dose will be established based on the change in objectively assessed WASO and safety data, such as next-day residual effect versus placebo.

1.3.2 Rationale for the 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 [Citrome 2014]. Another oral DORA, almorexant, showed objective and subjective

improvements in sleep maintenance and TST compared with placebo in two studies in subjects with primary insomnia.

The dose levels of 5, 10, 25 and 50 mg of ACT-541468 planned for this study were all investigated in Phase 1, with clear sleep-promoting effects starting at 25 mg in healthy subjects. The dose level of 50 mg is expected to cap the high-end of the dose-response relationship. The lowest dose level of 5 mg is not expected to exert a clinically relevant effect on sleep parameters.

The ACT-541468 mechanism of action, the results of nonclinical studies and Phase 1 studies in healthy young adults, and the limitations of the existing sleep medications justify the need for evaluating ACT-451468 in insomnia disorder and identifying efficacious and safe doses.

1.4 Summary of known and potential benefits and risks

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.

This study will be the first study with ACT-541468 in subjects with insomnia disorder. 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. In humans, clear CNS-depressant effects were observed starting at the dose of 25 mg. A battery of objective and subjective PD tests showed a decrease in vigilance and attention, as well as in visuomotor coordination and postural stability. There were no relevant differences between PD effects measured on Day 1 compared to Day 5. No next-day residual effects were observed after multiple evening dose administration.

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. Overall, the effects of 25 mg returned to baseline within 4–6 h in healthy young adults.

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

The developmental and reproductive toxicology program of ACT-541468 is not yet complete at this stage and therefore ACT-541468 must only be given to women of childbearing potential when the absence of pregnancy has been verified and an acceptable method of contraception is practiced. Women are not allowed to become pregnant for one month after discontinuation of ACT-541468.

Considering both the mode of action of DORAs 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, and which may include impaired capacity to drive.
- Narcolepsy-like and cataplexy symptoms.
- 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 behaviors.

[redacted]

1.4.2 Zolpidem

Zolpidem is indicated for the short-term treatment of insomnia characterized by difficulties with sleep initiation. The drug is approved in all countries participating in the study and will be used for assay validity.

The most common side effects are drowsiness (which may lead to falls and severe injuries), dizziness and diarrhea. Adverse drug reactions associated with discontinuation from clinical studies also included nausea, vomiting and falls.

In addition and in patients without concomitant illnesses, the following serious adverse reactions have been reported:

- CNS-depressant effects and next-day impairment: impaired alertness and motor coordination.
- Rare severe anaphylactic/anaphylactoid reactions.
- Abnormal thinking and behavior changes.
- Complex sleep-related behaviors.

- Compromised respiratory function.

A dose of 10 mg without dose up-titration will be used in this study.

The 10 mg zolpidem dose, which demonstrated efficacy in the pivotal trials supporting registration, is in the recommended dose range in all countries potentially participating in this trial.

1.4.3 Safety and risk minimization measures taken in the present study

A next-day sleepiness effect can be observed with zolpidem and potentially may occur with ACT-541468. On each of the mornings following drug administration in sleep centers, the subjects will undergo neurological examination 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 subject and decide whether it is safe for the subject to leave the study center. Next-day residual effect will also be evaluated with the Karolinska Sleepiness Scale and visual analog scales assessing sleepiness, to be completed by the subjects each morning.

As required by current guidelines, the Columbia Suicide Severity Rating Scale (C-SSRS©) will be completed by the subjects on the second morning of the PSG nights at V2 to V5 and on the morning after the PSG night at V6 to assess suicidality prior to randomization and during the study treatment phase.

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

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.

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 unblinded safety 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 subject's well-being.

In conclusion, based on available data on the study drugs (ACT-541468 and zolpidem) and the risk minimization measures mandated by the protocol, the expected risk-benefit assessment supports the conduct of this 4-week treatment study in adult subjects with insomnia disorder.

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 after treatment on Days 1 and 2.

2.2 Secondary objectives

The secondary objectives of the study are to evaluate the dose response of ACT-541468 on Latency to Persistent Sleep (LPS) on Days 1&2, and subjective Latency to Sleep Onset (sLSO) and subjective WASO (sWASO) at Week 4.

2.3 Other objectives

To explore the effect of ACT-541468 on sleep parameters during the study, sleep parameters will include various objective and subjective measures.

To assess the safety and tolerability of oral administration of ACT-541468 in 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, and V5) and safety.

3 OVERALL STUDY DESIGN AND PLAN

3.1 Study design

This is a multi-center, double-blind, randomized, placebo-controlled, active-reference, parallel-group, polysomnography dose-response Phase 2 study in adult subjects with insomnia disorder.

In order to have approximately 300 subjects randomized, approximately 750 subjects will be screened. Subjects will be randomized in a 1:1:1:1:1:1 ratio to oral fixed doses of either ACT-541468 5 mg, 10 mg, 25 mg, 50 mg, placebo or zolpidem 10 mg (estimated screen failure rate is up to 60%). Treatment allocation will be stratified by gender. The study will be conducted in approximately 38 sites in approximately 6 countries.

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 the investigator's opinion.

3.1.1 Study phases

The study comprises the following consecutive phases:

3.1.1.1 Screening Phase

Screening phase: Lasts a minimum of 14 days and maximum of 28 days. It starts with the signing 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 Visit 1 (V1), 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 until Visit 2 (V2).

The **run-in period** occurs between Day –14 and Day –1 and starts with V2. V2 consists of 2 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. A sleep diary must be completed for at least 7 consecutive days from V2 to randomization.

3.1.1.2 Treatment Phase

Treatment phase: Consists of a double-blind treatment period followed by a run-out period.

The **double-blind treatment period** starts with the first dose of double-blind study treatment in the first evening of Randomization Visit (V3, Day 1). The **End of Double-Blind treatment** (EODB) is reached in the second morning of V5 (Day 30) after the last dose of double-blind study treatment and after all second morning assessments have been performed.

The **run-out period** starts in the evening of Day 30 (V6) with the last dose of single-blind study treatment. The end of the run-out period corresponds to the **End of Treatment** (EOT). EOT is reached after all morning assessments have been performed in the morning of Day 31 (V6).

Safety follow-up phase: Starts after EOT (Day 31) and lasts at least 30 days (i.e., until Day 61).

End of Study (EOS) for a single subject is defined as the date of the 30-day follow-up telephone call (Day 61). 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

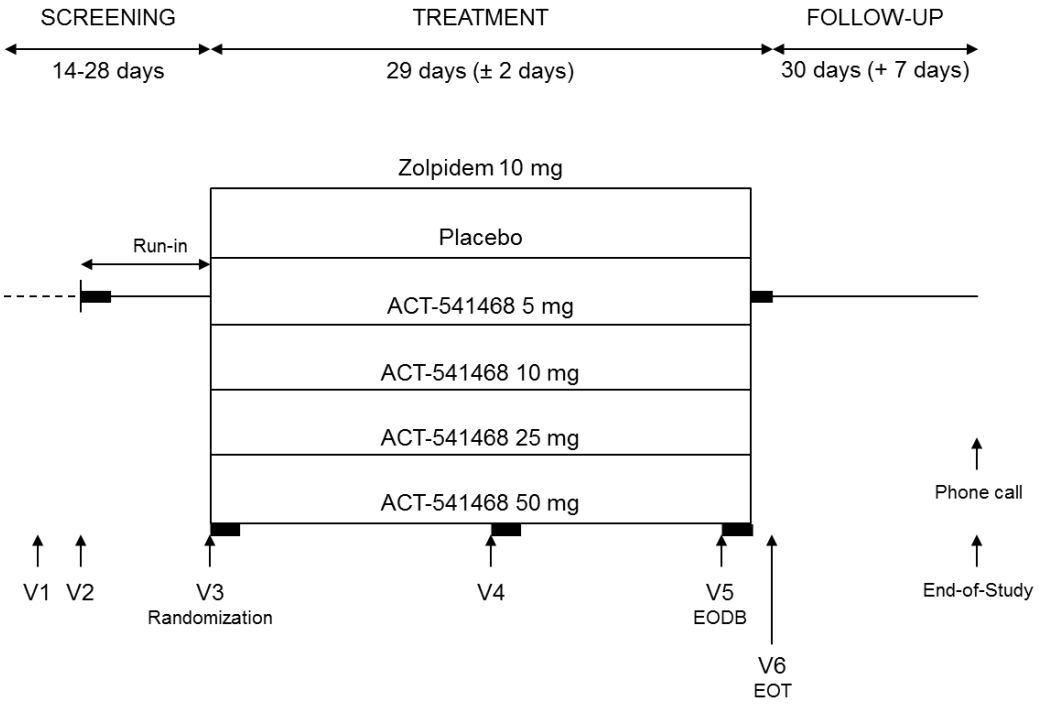
subject is declared lost to follow-up [see also Section 8.2], EOS is the date of last successful contact for this subject.

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 2] and are described in Section 7.

The overall study design is depicted in Figure 1.

Figure 1 Study design



V = Visit; ▬ = PSG nights; EODB = End of Double-Blind treatment; EOT = End of Treatment.

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 subjects will be treated for approximately 4 weeks. For an individual subject, the study is completed with EOS, Day 61 (30-day safety follow-up telephone call). The duration of participation in the study of a subject is expected to be approximately 12 weeks.

3.2 Study design rationale

This is a multi-center, double-blind, randomized, placebo-controlled, active-reference, parallel-group, polysomnography dose-response study.

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

The placebo arm will support the evaluation of the absolute efficacy of each ACT-541468 dose. One active reference treatment arm (zolpidem 10 mg) is included for assay validity.

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

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

The subjects will be treated for four weeks with double-blind study treatment, an appropriate treatment duration to investigate the maintenance of the effect on sleep parameters and to assess ACT-541468 safety and tolerability prior to the onset of Phase 3 clinical studies.

Upon active treatment discontinuation, a one-day run-out period (V6) on single-blind placebo treatment is planned to investigate possible withdrawal effects and rebound insomnia, as recommended by health authorities [EMA 2011]. Rebound insomnia is the re-emergence of sleep symptoms, with a worse severity than at baseline level. Withdrawal symptoms are a set of physical symptoms and emotions that subjects experience after abrupt discontinuation or drastic reduction of a substance.

3.3 Site personnel 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 CRO (i.e., Clinilabs).

Documentation of technologists' prior experience and training, and study-specific training, will be maintained at each clinical trial 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 adult male and female subjects (aged 18 to 64 years inclusive) with insomnia disorder. For more details on inclusion and exclusion criteria, see Sections 4.3 and 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 which would be different from that in the general population.

Insufficient sleep quantity is defined in this study by self-reported history of ≥ 30 minutes to fall asleep, of wake time during sleep ≥ 30 minutes and of TST ≤ 6.5 hours during the night. Those 3 self-reported parameters must be present on at least 3 nights per week for at least 3 months prior to the screening visit and on the sleep diary sleep data collected during the period between V1 and the first PSG assessment (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 Insomnia Severity Index (ISI©) score ≥ 15 at screening.

4.2 Rationale for the selection of the study population

The study will recruit adult subjects, from 18 to 64 years, inclusive. A separate dose-finding study will be performed in 50 elderly subjects. Studies in children of less than 12 years and adolescents will not be performed before efficacy and safety of ACT-541468 have been established in adults.

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 result in different drug exposure level in female and male subjects [FDA 2013]. Thus, stratification according to gender will be done and subgroup analysis will be performed. Since this study is the first trial of ACT-541468 conducted in subjects with insomnia disorder, concomitant treatments for insomnia (pharmacological or not) or concomitant medication 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, V2 and V3 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 18–64 years (inclusive) (V1).
3. A woman of childbearing potential must provide:
   - Negative serum pregnancy test (V1).
   - Negative urine pregnancy test (V3).
   - Agreement to undertake pregnancy tests up to 30 days after EOT.
   - Agreement to use the contraception scheme as described in Section 4.5.2 of the protocol from Screening up to at least 30 days after EOT.
4. Body mass index (BMI): $18.5 \leq$ BMI (kg/m^2) < 32.0 (V1).
5. Insomnia disorder according to DSM-5 criteria (V1).
6. Self-reported history of all of the following on at least 3 nights per week and for at least 3 months prior to V1:
   - $\geq$ 30 minutes to fall asleep
   - Wake time during sleep $\geq$ 30 minutes
   - TST $\leq$ 6.5 h
7. ISI© score $\geq$ 15 (V1).
8. Willing to comply with all aspects of the study protocol (V1, V2, V3).
9. 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).
10. 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):
    - $\geq$ 30 minutes to fall asleep
    - Wake time during sleep $\geq$ 30 minutes
    - TST of $\leq$ 6.5 h

11. Usual bedtime between 21:30 and 00:30 as reported on sleep diary completed between V1 and V2 (to be checked at V2).
12. Regular time in bed between 6 and 9 hours as reported on sleep diary completed between V1 and V2 (to be checked at V2).
13. Meeting the following sleep parameters on the 2 PSG nights (V2):
    - Mean LPS ≥ 20 min (with none of the two nights < 15 min), and
    - Mean WASO ≥ 30 min (with none of the two nights < 20 min), and
    - 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, V2 and V3 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 ≥ 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 ≥ 3 time zones within 1 week prior to the screening visit, or planned travel ≥ 3 time zones during study (V1).
6. Pregnant, planning to become pregnant or lactating (V1, V3).
7. Hematology or biochemistry test results deviating from the normal range to a clinically relevant extent as per judgment of the investigator (V1, V2).
8. AST and/or ALT > 2 × ULN and/or direct bilirubin > 1.5 × ULN (V1, V2).
9. 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).
10. Unstable medical condition, significant medical disorder or acute illness, within 1 month prior to the screening visit, which in the opinion of the investigator could affect the subject's safety or interfere with the study assessments (V1).
11. Systolic blood pressure (BP) > 150 mmHg and diastolic BP > 90 mmHg (V1, V2).
12. Resting pulse rate < 50 or ≥ 100 beats per minute (V1, V2).
13. Any of the following conditions related to corrected QT (QTc) intervals (V1, V2):
    - A prolonged QTc interval (QTc greater than 450 ms). If QTc is greater than 450 ms 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.

- A history of additional risk factors for torsade de pointes (e.g., heart failure, hypokalemia, family history of long QT syndrome).

14. 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 C-SSRS© (V1, V2).
    - Lifetime history of suicide attempt (V1).
15. 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).
16. Treatment with another investigational drug within 1 month prior to V1.
17. Known hypersensitivity or contraindication to drugs of the same class as the study treatment or to any excipients of the study drug formulation, or to zolpidem, including myasthenia gravis (V1).
18. 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 h after EOT (V6), including over-the-counter (OTC) medication and herbal medicines.
19. CBT within one month prior to V1.
20. Treatment with moderate to strong CYP3A4 inhibitors, CYP3A4inducers, sensitive CYP3A4 substrates, P-gP substrates, BCRP substrates, and CYP2B6 substrates [as defined in Appendix 4] within 1 week prior to V1 until 24 h after EOT.
21. Consumption of grapefruit or grapefruit juice within 1 week prior to V1 until 24 h after EOT.
22. 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).
23. 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).
24. Heavy tobacco use (≥ 10 cigarettes per day), and/or inability to refrain from smoking for at least 14 hours during the night (V1).
25. Apnea/hypopnea index (AHI) ≥ 10/h on the first PSG screening night according to American Academy of Sleep Medicine (AASM) criteria [Meoli 2001, CMS 2008] (V2).
26. 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).

27. Periodic limb movement with arousal index (PLMAI) ≥ 10/h on the first PSG screening night (V2).

4.5 Criteria for women of childbearing potential

4.5.1 Definition of childbearing potential

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

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

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

4.5.2 Acceptable methods of contraception

Women of childbearing potential [see definition in Section 4.5.1] must follow the below contraception scheme from Screening up to at least 30 days after EOT:

- Two methods of contraception, one from Group 1 and one from Group 2, defined as follows:
  - Group 1: Oral, implantable, transdermal, or injectable hormonal contraceptives or intrauterine devices. If a hormonal contraceptive is chosen from this group, it must be taken for at least 1 month prior to randomization.
  - Group 2: Diaphragm, female condom or cervical cap, partner's use of a condom.

OR

- Sterilization of the male partner with documented post-vasectomy confirmation of the absence of sperm in the ejaculate.

OR

- Tubal sterilization (tubal occlusion / ligation at least 6 weeks prior to screening).

OR

- True abstinence from intercourse with a male partner only when this is in line with the preferred lifestyle of the subject.

Rhythm methods or the partner's use of a condom alone are not considered acceptable methods of contraception for this study.

The methods of birth control used (including non-pharmacological methods) must be recorded in the eCRF.

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

5 TREATMENTS

5.1 Study treatment

The study drugs are ACT-541468, over-encapsulated zolpidem, ACT-541468-matching placebo, and over-encapsulated zolpidem-matching placebo. Single-blind study drug will be administered at V2 and V6 and used for the swallow test at V1, if applicable. Double-blind study treatment will be administered from V3 to EODB (V5).

5.1.1 Investigational treatment and matching placebo: Description and rationale

ACT-541468 will be administered orally once daily in the evening during the double-blind treatment period. ACT-541468 doses will include: 5 mg, 10 mg, 25 mg and 50 mg. The rationale for the selection of these ACT-541468 doses is described in Section 1.3.2.

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

5.1.2 Active reference: Description and rationale

Zolpidem 10 mg will be administered orally once daily during the double-blind treatment period (V3 to EODB).

Zolpidem is provided by Actelion as zolpidem tartrate, in over-encapsulated tablets of the commercially available Stilnox®. Each tablet contains 10 mg of zolpidem and excipients.

In this study zolpidem will be administered at a dose of 10 mg. This dose has been well established in confirmatory clinical studies in adult subjects with chronic insomnia [see Section 1.2.2].

5.1.3 Study treatment administration

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 evening meal (including at V2 and V6). Each capsule will be swallowed whole. The date and time of treatment intake will be recorded in the sleep diary by the subject when taken at home and by the site personnel in the eCRF during the PSG nights.

5.1.3.1 Study treatment administration during the different study phases

5.1.3.1.1 Screening phase

At V1, after signing the ICF and preferably prior 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 his/her 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, 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), in the evening of each of the two PSG nights.

5.1.3.1.2 Treatment phase

During the double-blind treatment period, subjects will receive orally once daily two capsules as shown in Table 1.

In the evening of a PSG night (V3, V4 and V5), the capsules will be taken at the site, approximately 30 minutes before lights off (= habitual bedtime ± 5 minutes). At home (from Day 3 to Day 14, and from Day 17 to Day 27) the capsules will be taken at bedtime.

Table 1 Capsules to be taken according to the treatment

Treatment group		**Number (and dose strength) of ACT-541468 capsules**	**Number of ACT-541468-matching placebo capsules**	**Number of over-encapsulated zolpidem 10 mg capsules**	Number of over-encapsulated zolpidem-matching placebo capsules
ACT-541468	5 mg	1 (5 mg)	1	0	0
	10 mg	1 (10 mg)	1	0	0
	25 mg	1 (25 mg)	1	0	0
	50 mg	2 (25 mg)	0	0	0
Placebo		0	2	0	0
Zolpidem		0	0	1	1

During the run-out period, at V6, 2 capsules of ACT-541468-matching placebo will be taken approximately 30 minutes before lights off (= habitual bedtime ± 5 minutes), in the evening of the PSG night, at the site.

5.1.3.2 Missed doses

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

5.1.4 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 (IRT) system to get a subject number allocated to the subject.

At V2 (Days –14 to –6) and run out V6 (Day 30), subjects will receive single-blind placebo treatment.

At randomization (V3, Day 1), 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 kit number which matches the treatment arm 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.

5.1.5 Blinding

5.1.5.1 V2 (run-in) and V6 (run-out)

At V2 and V6, placebo treatment 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 personnel, the monitors, Actelion personnel, and CROs involved in the conduct of the study will be unblinded to treatment.

5.1.5.2 Double-blind treatment period

From V3 until EODB, the study will be performed in a double-blind fashion. The subjects, the investigator and study personnel, the monitors, Actelion personnel, and CROs involved in the conduct of the study will remain blinded to the study treatment. The Clinical Trial Supplies Manager will monitor the depot stock levels in collaboration with the study team based on recruitment data and site activation. Site stocks will be maintained according to the settings in the IRT system.

Until the time of unblinding for final data analysis, the randomization list is kept strictly confidential, and accessible only to authorized persons who are not involved in the conduct of the study.

5.1.6 Unblinding

5.1.6.1 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.

5.1.6.2 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 QS documents.

5.1.6.3 Unblinding for suspected unexpected serious adverse reaction (SUSARs)

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 treatment assignment will not be communicated to site personnel or to the Actelion Clinical Trial Team. Unblinded SUSAR information will be provided to respective health authorities and independent ethics committees (IECs) or institutional review board (IRBs) only. SUSARs will be reported to investigators in a blinded fashion.

5.1.6.4 Emergency procedure for unblinding

The investigator, study personnel and Actelion personnel must remain blinded to the subject's treatment assignment. The identity of the study treatment may be revealed only if the subject experiences a medical event, the management of which would require knowledge of the blinded treatment assignment. In this case, the investigator can receive the unblinded treatment assignment through the IRT. In these situations, the decision to unblind resides solely with the investigator. Whenever 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 personnel.

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

5.1.7 Study treatment supply

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

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

5.1.7.1 Study treatment packaging and labeling

Swallow test, V2 and V6:
Study treatment is supplied as a site kit and provided in childproof bottles containing 36 capsules.

V3 to EODB:
Study treatment is supplied as a subject kit containing 5 wallets. Each wallet contains capsules for 7 days of treatment (14 capsules).

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

5.1.7.2 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.

5.1.7.3 Study treatment dispensing

The subjects will receive sufficient study treatment to cover the period from V3 up to EODB. If a wallet is lost or damaged, a replacement kit can be requested through the Treatment Replacement module of the IRT system. Subjects are asked to return all used, partially used and unused study treatment wallets at EODB. 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.

5.1.7.4 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 CRA will collect used and unused treatment kits, which will be sent to the warehouse, where Actelion personnel or a deputy will check treatment reconciliation. In certain circumstances, used and unused study treatment containers may be destroyed at the site once study treatment accountability is finalized and has been checked by Actelion

personnel or the deputy, and written permission for destruction has been obtained from Actelion.

5.1.8 Study treatment accountability and compliance with study treatment

5.1.8.1 Study treatment accountability

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

At V2 (run-in) and V6 (run out):
- Bottle number.
- Number of capsules dispensed.

Double-blind treatment period:
- Dispensed subject kit number at randomization (V3, Day 1).
- Date and number of capsules dispensed at randomization (V3, Day 1).
- Date and number of capsules returned at EODB (V5, Day 30).

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

If the subject forgets to bring the study treatment at V4, he/she will be assigned a new kit from the IRT and the subject must be instructed to not take any capsules from the remaining study treatment kit and to return it at EODB.

5.1.8.2 Study treatment compliance

Study treatment compliance is based on study treatment accountability. Study treatment compliance for the double-blind treatment period (Day 1 to EODB) will be calculated by site personnel using the below formula and entered in the eCRF.

Compliance = [(number of capsules dispensed - number of capsules returned) / total number of capsules that must have been taken during the period*] × 100

* The period is defined as from V3 (Day1) to EODB. The number of capsules that should have been taken is 58.

During the double-blind treatment period (Day 1 to EODB), compliance is expected to be at least 70% per week. Compliance values below this 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.

5.1.9 Study treatment dose adjustments and interruptions

Study treatment dose adjustments are not permitted.

Study treatment may be temporarily interrupted in response to an AE, a diagnostic or therapeutic procedure, a laboratory abnormality, or for administrative reasons. Study-specific criteria for interruption of study treatment are described in Section 5.1.11.

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

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

Study treatment dose interruptions must be recorded in the eCRF.

5.1.10 Premature discontinuation of double-blind study treatment

The decision to prematurely discontinue study treatment may be made by the subject, the investigator, or Actelion personnel. The main reason for discontinuation must be documented in the eCRF and in the subject's medical charts (e.g., tolerability- or efficacy-related if decision of the subject; due to pre-specified study treatment discontinuation criteria, an adverse event or lack of efficacy if decision of the investigator; study terminated if decision from Actelion).

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

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

Study-specific criteria for discontinuation of study treatment are described in Section 5.1.11.

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's consent for this limited participation in the study has not been withdrawn.

The subject is recommended to return for an EODB visit within one week of last intake of study treatment and to agree to be called for a safety follow-up 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.

5.1.11 Study-specific criteria for premature discontinuation of double-blind study treatment

On the second mornings of V3 and V4, the investigator will review with the subject the results of the safety evaluation after the two PSG nights [details described in Section 7.2.3] and evaluate the presence of any signs or symptoms of possible next-day residual effect or any other adverse event that the subject may have experienced. If there are signs of next-day residual effect or any other AEs, the investigator must evaluate whether continuing treatment at home is compatible with the subject's lifestyle and does not affect the subject's safety. The investigator has the responsibility to decide whether it is safe for the subject to leave the center and to continue in the study.

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

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

5.2 Previous and concomitant therapy

5.2.1 Definitions

A previous therapy is any treatment for which the end date is prior to signing 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 period until 1 day after the last dose of double-blind study treatment.

5.2.2 Reporting of previous/concomitant therapy in the eCRF

The use of all study-concomitant therapies (including contraceptives and traditional and alternative medicines, e.g., plant-, animal-, or mineral-based medicines) will be recorded in the eCRF. Previous therapy must be recorded in the eCRF if discontinued less than 30 days prior to signing of the 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 medication is to be discouraged and concomitant medication preferably not be changed during the course of the study.

5.2.4 Forbidden concomitant therapy

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

The following concomitant therapies are forbidden during the study [see also Appendix 4]:

- Treatment with another investigational drug until EOS.
- Prohibited CNS-active medications, including OTC and herbal medicines, until 24 hours after EOT.
- 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. CBT and other psychological therapies, excluding common advices 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 caffeine/day
  – after 4 pm on non-PSG nights
  – after 2 pm on the days of PSG nights.
- Alcohol consumption [for definition of drinks, see Appendix 2]:
  – > 2 drinks a day
  – less than 3 hours before going to bed on non-PSG nights
  – within 24 hours prior to PSG night and during all PSG visits.
- Heavy tobacco use (≥ 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[a] to Days 1&2[b] as determined by PSG.

WASO is the time (min) 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 an adequate endpoint for dose-finding studies [EMA 2011].

Total time in bed is fixed at 480 min (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.

Where:
[a] 'Baseline' is the mean of the 2 PSG nights during the run-in period (V2).
[b] 'Days 1&2' is the mean of the corresponding 2 PSG treatment nights (V3).

6.1.2 Secondary efficacy endpoints

The secondary efficacy endpoints of this study are: sleep initiation endpoints such as LPS and sLSO and a sleep maintenance endpoint such as sWASO.

Sleep-initiation endpoints:
Change from Baseline[a] to Days 1&2[b] in mean LPS.

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

Change from Baseline[c] to Week 4[d] in mean sLSO.

sLSO is the self-reported time to fall asleep, as reported in the sleep diary.

Sleep-maintenance endpoint:
Change from Baseline[c] to Week 4[d] in mean sWASO.

sWASO is the self-reported time spent awake after sleep onset as reported in the sleep diary.

Where:

[a] 'Baseline' is the mean of the 2 PSG nights during the run-in period (V2).
[b] 'Days 1&2' is the mean of the corresponding 2 PSG treatment nights (V3).
[c] 'Baseline' is the mean value in the screening sleep diary entries at home between V2 and V3 across 7 consecutive days.
[d] 'Week 4' is the mean value based on the sleep diary entries at home across the last week of double-blind study treatment.

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:

- WASO and sWASO,
- LPS and sLSO,
- TST and subjective TST (sTST),
- SQ,
- Sleep stages S1, S2, SWS and REM,
- Shifts from S2, SWS or REM to S1 or awake,
- Wake time during sleep,
- Frequency of awakenings as measured by PSG and self-reported,
- Sleep Efficiency (SE) (defined as 100 × (TST / time in bed),
- ISI© scores,
- Next-day performance.

6.2 Safety endpoints

- TEAEs[1] and SAEs up to 30 days after study treatment discontinuation.
- AEs leading to premature discontinuation of the double-blind study treatment.
- TEAEs of special interest after adjudication by ISB:
  - Narcolepsy-like events (e.g., excessive daytime sleepiness, cataplexy)
  - Complex sleep behaviors events.
  - Suicidal thoughts and/or behaviors.
- Change from Baseline (mean of the two PSG nights at V2, run-in period) to the last value on double-blind study treatment in vital signs (systolic and diastolic BP, pulse rate and body temperature),
- Change from baseline (V1) to the last value on double-blind study treatment in body weight.
- Treatment-emergent ECG abnormalities from V3 until EOT.
- Change from baseline (V2, second morning) to the last value on double-blind study treatment in ECG parameters.
- Marked laboratory abnormalities on double-blind study treatment.
- Change from baseline (V2, second morning) to the last value on double-blind study treatment in laboratory variables.
- Rebound insomnia
  - Change from baseline (V2) to the morning of V6 in WASO, TST and LPS.
- Withdrawal symptoms:
  - Change from Day 30 to Day 31 in the Benzodiazepine Withdrawal Symptom Questionnaire (BWSQ) scores.
  - AEs and ECG abnormalities emerging from Day 30 to Day 31.
- Change from baseline (mean of the two PSG nights at V2, run-in period) to mean of the two PSG nights of V3 (Days 1&2), V4 (Days 15&16) and V5 (Days 28&29) 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.

[1] A treatment-emergent AE is any AE temporally associated with the use of study treatment (from double-blind study treatment start until 30 days after study treatment discontinuation) whether or not considered by the investigator as related to study treatment.

- Change from baseline (V2, second morning) to the last value on double-blind study treatment in C-SSRS©.

6.3 Pharmacokinetic endpoints

Concentration of ACT-541468 (and possibly several of its metabolites) approximately 9–10 h post-dose at V3, V4, and V5.

7 VISIT SCHEDULE AND STUDY ASSESSMENTS

7.1 Study visits

The study visits are listed in Table 2. For all visits, the subjects must be seen on the designated day with an allowed visit window of ± 2 days. A follow-up safety telephone call must be performed 30 days (+ 7 days) after intake of the last dose of study treatment.

7.1.1 Screening/re-screening

Screening starts with the signing 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 other 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, the subject cannot participate in the run-in and has to 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 2].

Table 2 Visit and assessment schedule

		SCREENING PHASE (14–28 days)							TREATMENT PHASE (29 days ± 2 days)																FOLLOW-UP PHASE
VISITS	**Number**	**1**	**-**	**2**				**-**	**3**				**-**	**4**					**5**				**6**		**Safety follow-up[8]**
	Name	**Screening period**		**Run-in period**					**PSG treatment nights**				**At home**	**PSG treatment nights**				**At home**	**Last PSG treatment nights / Permanent discontinuation[6]**				**Run-out period**		
	Time	**Between Day –28 and –14**	**At home 7 to 21 Days**	**1st night Day –14 to Day –7**		**2nd night Day –13 to Day –6**		**At home 5 to 12 Days up to Day –1**	**1st night Day 1 to Day 2**		**2nd night Day 2 to Day 3**		**Day 3–14 (± 2 days)**	**1st night Day 15 to Day 16**		**2nd night Day 16 to Day 17**		**Day 17–27 (± 2 days)**	**1st night Day 28 to Day 29**		**2nd night Day 29 to Day 30**		**Day 30 to Day 31**		**Day 61 (+ 7 days)**
				1st Evening	1st Morning	2nd Evening	2nd Morning		1st Evening	1st Morning	2nd Evening	2nd Morning		1st Evening	1st Morning	2nd Evening	2nd Morning		1st Evening	1st Morning	2nd Evening	2nd Morning	Evening	Morning	
Informed consent		X																							
Inclusion and exclusion criteria		X		X					X																
Demographics		X																							
Medical history		X																							
Physical examination, body weight and height[11]		X																				X[6]			
Vital signs and body temperature		X			X		X			X		X			X		X			X		X[6]		X	
12-lead ECG		X					X					X										X[6]		X	
Hematology, blood chemistry		X					X					X					X					X[6]			
Pregnancy test[1]		X							X													X[6]			X
Drug and alcohol tests		X		X		X			X		X			X		X			X		X		X		
PK sampling										X[10]		X			X[10]		X			X[10]		X			
PSG				X[4]		X			X		X			X		X			X		X		X		
ISI©		X																				X[6]			
Sleep diary (incl. VAS)[2]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Neurological					X		X			X		X			X		X			X		X		X	

exam[9]																								
C-SSRS[©7]	X					X					X					X					X[6]		X	
DSST[©7]				X		X			X		X			X		X			X		X[6]			
SDS[© 7]				X		X			X		X			X		X			X		X[6]			
KSS[7]				X		X			X		X			X		X			X		X[6]			
BWSQ[7]						X										X					X[6]		X	
Randomization								X																
Study drug intake			X[3]		X[3]			X		X		X	X		X		X	X		X		X[3]		
Concomitant medications	X		X	X	X	X		X	X	X	X		X	X	X	X		X	X	X	X	X[6]	X	X	
SAEs and AEs[5]	X		X	X	X	X		X	X	X	X		X	X	X	X		X	X	X	X	X[6]	X	X	X

1. For women of childbearing potential, serum test at V1 and 5 and urine test at V3, and 1 month after last dose of study drug intake. **2.** The hand-held device is handed out to the subject, in order to be completed at home without interruption from V1 to V6. **3.** Placebo single-blind treatment. **4.** Includes assessment of AHI, PLMAI, SpO_2. **5.** SAE and AE reporting and follow-up: all SAE and AEs from signed ICF up to 30 days after double-blind study drug discontinuation. **6.** In the event of permanent discontinuation, safety assessments of V5 are recommended to be performed within 24 hours of last study drug intake. **7.** Approximately 30 to 60 minutes after PSG lights on. **8**. Telephone call. **9.** Performed approximately 1 hour after lights on. Repeat every 30 min until subject safe to leave center. **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. **11.** Height only at V1.

AE = adverse event; AHI = apnea/hypopnea index; BWSQ = Benzodiazepine Withdrawal Symptom Questionnaire; C-SSRS = Columbia Suicide Severity Rating Scale; DSST = Digital Symbol Substitution Test; ECG = electrocardiogram; ICF = Informed Consent Form; KSS = Karolinska Sleepiness Scale; PK = pharmacokinetic; PLMAI = Periodic Limb Movement with Arousal Index; PSG = polysomnography; SAE = serious adverse event; SDS = Sheehan Disability Scale; SpO_2 = oxygen saturation by pulse oximetry; VAS = visual analog scales.

7.2 Study assessments

The mandatory study assessments are listed in Table 2.

All study assessments are performed by qualified study personnel (medical, nursing, or specialist technical personnel) 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 a PSG night:
  - Drug and alcohol test
  - Evening questionnaire in sleep diary (including visual analog scales [VAS])
  - Recording of concomitant medications
  - AEs and SAEs
  - Study drug intake (30 minutes before lights off)
- In the morning after a PSG night, after completion of normal morning routine (e.g., using the bathroom, eating breakfast):
  - Vital signs and body temperature
  - DSST©
  - ISI© (V5, second morning)
  - SDS©
  - KSS
  - C-SSRS©
  - BWSQ (only second morning at V2, V4, V5 and V6)
  - Morning questionnaire in sleep diary (including VAS)
  - Recording of concomitant medications
  - AEs and SAEs
  - Neurological examination*
  - Hematology and blood chemistry; PK sampling* (second morning)
  - 12-lead ECG (only second morning at V2, V3 and V5)

* The neurological examination must be performed approximately 1 hour after lights on and repeated approximately every 30 min until the subject is safe 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.

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

- Laboratory parameters
- ECG parameters
- PSG recordings

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

If the Principal Investigator (PI) delegates any study procedure/assessment for a subject, to an external facility, he/she must inform Actelion to whom these tasks are delegated. The set-up and oversight must 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.
- Polysomnographic device.

Use of hand-held device
Patients will be required to complete the following questionnaires on a hand-held device: ISI©, SDS©, KSS, C-SSRS©, BWSQ, 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 Efficacy assessments

7.2.2.1 Polysomnography

PSG data will be used to assess objective sleep parameters (WASO and LPS) as well as data on sleep architecture (sleep stages). 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 personnel. 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 sleep diary between V1 and V2); this time is then considered as the habitual bedtime and held constant (± 5 min) throughout the study. Study medication is administered 30 minutes (± 5 min) 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 take place at V2 (between Day –14 and Day –6), V3 (Days 1&2), V4 (Days 15&16) and V5 (Days 28&29). At V6 (Day 30), a single PSG night immediately follows V5. The first PSG screening night (V2) also includes AHI, PLMAI, and SpO_2 assessments.

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 remains 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 cognitive activity (such as reading, listening to radio, etc.), and is recommended not to have a watch or access to any clock. The lights remain switched off until the 480 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 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 subject and decide whether it is safe for the subject to leave the study center.

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 file receipt by the CRO. Based on this information, the investigator assesses the subject's potential eligibility.

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

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).

7.2.2.2 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 every day at home and at the site until V6.

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

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

7.2.2.2.1 Morning and evening questionnaire

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

During the Screening period, the subject's answer to the sleep diary question "What time did you go to bed last night?" is expected to be in the time window of 21:30 to 00:30, for at least 50% of the nights, and the median of these values defined as the usual bedtime (used to set the habitual bedtime) is also expected to be in the same time window. The subject's regular time in bed (i.e. time calculated from "What time did you go to bed last night?" until "What time did you get out of bed this morning?") is expected to be in the time window of 6 to 9 hours, for at least 50% of the nights.

For further details, see Appendix 10.

7.2.2.2.2 Visual analog scales

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

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

For further details, see Appendix 10.

7.2.2.3 Insomnia Severity Index©

The ISI© assesses the severity of a patient's insomnia by scoring the severity of sleep-onset and sleep maintenance difficulties and any insomnia-related interference with daytime functioning [see Appendix 6]. The assessment is on a 5-point scale (0–4), where the composite score is obtained by summing the 7 rated dimensions measuring the subject's perception of his or her insomnia. A score of 15–21 indicates a moderate level of insomnia and a score of 22–28 indicates severe insomnia. An ISI© total score < 10 indicates that the subject's 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 a license agreement for the use of the ISI©.

7.2.3 Safety assessments

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

7.2.3.1 Weight and height

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

Body weight will be measured at Screening (V1) and EODB, and recorded in the eCRF. BMI will be calculated at V1 according to the BMI formula (weight in kg/m^2) and displayed automatically upon entry of weight and height in the eCRF.

7.2.3.2 Vital signs

Systolic and diastolic BP, pulse rate and body temperature will be measured non-invasively at each study visit from screening (V1) to V6. 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 measurements and conditions will be collected in the eCRF.

7.2.3.3 Physical examination

Physical examination is to be performed at screening (V1) and on second morning of V5 (recommended within 24 hours after last dose of double-blind study drug intake). 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, which meet the definition of an AE [Section 9.1.1] must be recorded on the AE form of the eCRF.

7.2.3.4 Digit Symbol Substitution Test©

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 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.

7.2.3.5 Sheehan Disability Scale©

The SDS© consist of 3 questions on impairment of work, social life, and family life/home responsibilities [see 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©.

7.2.3.6 Karolinska Sleepiness Scale

The Karolinska Sleepiness Scale (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.

7.2.3.7 Columbia Suicide Severity Rating Scale©

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

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

The C-SSRS© also captures information about the intensity of ideation, specifically the frequency, duration, controllability, deterrents, and reasons for the most severe types of ideation. In addition, the C-SSRS© captures information using yes/no question and answers on suicidal behaviors, specifically actual, interrupted, and aborted attempts; preparatory acts or behaviors; and if suicidal behaviors were present during the assessment period. More than one classification can be selected provided they represent separate episodes. For actual attempts only, the actual or potential lethality is classified for the initial, most lethal, and most recent attempts. The C-SSRS© will be completed at all study visits. At V1 (Screening) the C-SSRS© will be completed for the subject lifetime history of suicidal ideation and behaviors. At all other visits, the C-SSRS© will be completed for ideation and behaviors since the previous visit.

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

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

7.2.3.8 Benzodiazepine Withdrawal Symptoms Questionnaire

The BWSQ, also called the Tyrer Withdrawal Symptoms Questionnaire, assesses the main symptoms which might be experienced by subjects during withdrawal from benzodiazepines [see Appendix 9] [Tyrer 1990]. The questionnaire consists of 20 items. The symptoms will be rated from 0 (No), 1 (Yes-moderate) to 2 (Yes-severe). The questionnaire will be self-administered using the hand-held device.

7.2.3.9 Neurological examinations

In the morning following each PSG night (V2, V3, V4, V5 and V6), 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 the subject is safe to leave the center [also see Section 7.2]. The time when the subjects is considered safe to leave the center will be recorded in the eCRF.

7.2.3.10 ECG assessment

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

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. QTc (ms) will be calculated according to:

- Bazett's formula: $QTc = QT / (RR)^{1/2}$

  and

- Fridericia's formula: $QTc = QT / (RR)^{1/3}$, 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). If the central review confirms that the repeated ECG shows a QT_C interval greater than 450 ms, the subject cannot be enrolled into the study.

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

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

7.2.4 Laboratory assessments

7.2.4.1 Type of laboratory

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

Exceptional circumstances which will require recording of local laboratory results of the parameters described in Section 7.2.4.2 (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 the event of specific (pre-defined) laboratory abnormalities, the central laboratory will alert Actelion personnel and the concerned site personnel. 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 signing of informed consent must be recorded on the Medical History page of the eCRF. Any clinically relevant laboratory abnormalities detected after signing 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.

7.2.4.2 Laboratory tests

Hematology

- Hemoglobin (g/L)
- Hematocrit (L/L)
- Erythrocytes (10^9/L)
- Reticulocyte (%)
- 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 (µg/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, i.e., triiodothyronine (T3; total and free) and thyroxine (T4; total and free), and thyroid stimulating hormone.

Pregnancy test

A serum pregnancy test for women of childbearing potential will be performed at screening and on the second morning of V5. A urine pregnancy test will be performed at randomization (V3) and 30 days after last dose of double-blind study drug intake (safety follow-up). The urine pregnancy test kit will be provided by the central laboratory. If pregnancy is suspected during the study, a serum pregnancy test must be performed immediately.

Other tests

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

Study drug is administered as described in Section 5 only if the results of the pregnancy tests and other tests are negative.

7.2.5 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 randomization (V3, Day 3), V4 (Day 17), and V5 (Day 30, EODB). 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.

The date and the time of blood sample collection will be entered in the eCRF. The date and time of the last study treatment dosing before blood draw will be entered in the eCRF. The site personnel will ship the plasma samples to the central laboratory. The central laboratory will ship the samples to Actelion Preclinical Drug Metabolism and Pharmacokinetics department, who are in charge of the PK analysis.

8 STUDY COMPLETION AND POST-STUDY TREATMENT/MEDICAL CARE

8.1 Study completion as per protocol

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

8.2 Premature withdrawal from study

Subjects may voluntarily withdraw from the study without justification for any reason at any time. Subjects are considered withdrawn 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 from the study, 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, on balance, he/she believes that continued participation in the study would be contrary to the best interests of the subject. Withdrawal from the study may also result from a decision by 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 personnel to the subject's home), respecting the subject's right to privacy. If the subject is still unreachable after all contact attempts listed above, he/she will be considered to be lost to follow-up.

If premature withdrawal occurs for any reason, the reason (if known) for premature withdrawal from the study, along with who made the decision (subject, investigator, or Actelion personnel) 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 should make efforts to schedule a last appointment / telephone call to assess the safety and well-being of the subject, collect unused study treatment and discuss follow-up medical care. Data obtained during this last appointment / telephone call will be recorded in the subjects' medical records but it will not be collected in the eCRF. The investigator must provide follow-up medical care for all subjects who are prematurely withdrawn from the study, or must refer them for appropriate ongoing care, as described in Section 8.4.

8.3 Premature termination or suspension of the study

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

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

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

After the subject's study completion or premature withdrawal from the study, whichever applies, the investigator/delegate will explain to subjects what treatment(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 treatment-emergent AE is any AE temporally associated with the use of study treatment (from double-blind study treatment initiation until 30 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 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 9.2.1]. 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 signing of informed consent and up to 30 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 inpatient hospitalization, or prolongation of existing hospitalization.
- Resulting in persistent or significant disability or incapacity.
- Congenital anomaly or birth defect.
- Medically significant: refers to important medical events that may not immediately result in death, be life-threatening, or require hospitalization but may be considered to be SAEs when, based upon appropriate medical judgment, they may jeopardize the subject, and may require medical or surgical intervention to prevent one of the outcomes listed in the definitions above.

The following reasons for hospitalization are not considered as SAEs:

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

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

9.2.2 Reporting of serious adverse events

All SAEs occurring after signing of informed consent up to 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 the 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 Actelion Global Drug Safety within 24 hours of the investigator's first knowledge of the event.

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

The SAE forms must be sent to Actelion Global Drug Safety (contact details are provided on the SAE form). The investigator must complete the SAE form in English, and must assess the event's causal relationship to the study treatment.

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

Follow-up information about a previously reported SAE must also be reported within 24 hours of receiving it. Actelion Global Drug Safety personnel may contact the investigator to obtain further information.

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

The expectedness of an adverse reaction is determined by the sponsor in the RSI section provided in the most recent version of the IB for ACT-541468 [ACT-541468 IB] and the Stilnox® SmPC for zolpidem [Stilnox® SmPC]. Any SAE that is assessed as related and unexpected against the RSI of the ACT-541468 IB [ACT-541468 IB] or the Stilnox® SmPC [Stilnox® SmPC] 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 Pregnancy

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

9.3.1 Reporting of pregnancy

Irrespective of the treatment received by the subject, any pregnancy occurring after study start (i.e., signing of informed consent) up to 30 days following study treatment discontinuation must be reported within 24 hours of the investigator's knowledge of the event.

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

9.3.2 Follow-up of pregnancy

Any pregnancies must be followed up to their conclusion and the outcome must be reported to Actelion Global Drug Safety.

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

9.4 Study safety monitoring

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

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 at least one 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 included.

10.1.4 Modified Full Analysis Set

The modified FAS (mFAS) includes all patients from the FAS and who have at least one WASO assessment at baseline and one at Days 1&2.

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 Baseline and at Days 1&2, and who complied with the protocol sufficiently to allow relevant assessment of treatment effects.

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

10.1.6 Safety Set

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

10.1.7 Pharmacokinetic 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 treatment as randomized. Secondary and exploratory efficacy endpoint analyses will be performed on the FAS, while PPS will be used for sensitivity analyses.

Safety analyses will be performed on the SS based on treatment as received.

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

Table 3 describes the analysis sets used for the analysis of each data set.

Table 3 Usage of analysis sets

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

For variables that are collected only once at each visit (e.g., laboratory parameters), the unique pre-randomization value collected at V2 will be used as the baseline value.

10.2.1 Primary efficacy variable

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

WASO is defined in Section 6.1.1.

Where:

[a] 'Baseline' is the mean of the 2 PSG nights during the run-in period (V2).
[b] 'Days 1&2' is the mean of the corresponding 2 PSG treatment nights (V3).

Missing values
No imputation will be performed for missing WASO values.

If one of the two values is missing either for Baseline or for Days 1&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 variables

The secondary efficacy endpoints include LPS, sLSO and sWASO using the variables below:

Sleep-initiation endpoints:

- LPS absolute change from Baseline[a] to Days 1&2[b].
- sLSO absolute change from Baseline[c] to Week 4[d].

Sleep-maintenance endpoint:

- sWASO absolute change from Baseline[c] to Week 4[d].

LPS, sWASO and sLSO are defined in Section 6.1.2.

Where:

[a] 'Baseline' is the mean of the 2 PSG nights during the run-in period (V2).
[b] 'Days 1&2' is the mean of the corresponding 2 PSG treatment nights (V3).

[c] 'Baseline' is the mean value in the screening sleep diary entries at home between V2 and V3 across 7 consecutive days.
[d] 'Week 4' is the mean value based on the sleep diary entries at home across the last week of double-blind study treatment.

Missing values
Same as for the primary endpoint, no imputation are to be used for secondary endpoints.

10.2.3 Other efficacy variables

Other exploratory efficacy endpoints include:

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

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

Sleep-maintenance endpoint:
- WASO absolute change from Baseline[a] to Days 15&16[e], and to Days 28&29[f],
- WASO over time (by hour of the night and by quarter of the night),
- sWASO absolute change from Baseline[c] to Weeks 1&2&3[g].

Sleep-initiation endpoint:
- LPS absolute change from Baseline[a] to Days 15&16[e], and to Days 28&29[f],
- sLSO absolute change from Baseline[c] to Weeks 1&2&3[g].

Total sleep time endpoint:
- TST absolute change from Baseline[a] to Days 1&2[b], Days 15&16[e], Days 28&29[f].
- sTST absolute change from Baseline[c] to Weeks 1&2&3&4[h].

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.

Sleep quality (SQ):
- Change from Baselinec to Weeks 1&2&3&4[h] in SQ.

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

Sleep architecture:
- Mean[i] 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[i] latency to each sleep stage (S1, S2, SWS, and REM).

Sleep continuity:
- Mean[i] number and frequency of shifts from S2, SWS or REM to S1 or wake for the whole night.
- Mean[i] wake time during sleep: time spent in epochs scored as wake between LPS and last epoch not scored wake for the whole night.
- Mean[i] 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[c] to Weeks 1&2&3&4[h] in self-reported number of awakenings.

Sleep efficiency (SE):
- SE absolute change from Baseline[a] to: Day 1&2[b], Day 15&16[e] and Day 28&29[f].

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

Insomnia severity
- Change from Baseline (V1) to the second morning of V5 (Day 30) in ISI© scores.

Next-day performance
- Change from Baseline[c] to Weeks 1&2&3&4[h] in next-day performance assessed at home by scores on the VAS assessing morning sleepiness, daytime alertness and daytime ability to function.

Where:

[a] 'Baseline' is the mean of the 2 PSG nights during the run-in period (V2).

[b] 'Days 1&2' are the mean of the corresponding 2 PSG treatment nights (V3).

[c] 'Baseline' is the mean value in the screening sleep diary entries at home prior to start of study treatment between V2 and V3 across 7 consecutive days.

[d] 'Week 4' is the mean value based on the sleep diary entries at home across the last week of double-blind study treatment.

[e] 'Days 15&16' is the mean of the corresponding 2 PSG treatment nights (V4).

[f] 'Days 28&29' is the mean of the corresponding 2 PSG treatment nights (V5).
[g] 'Weeks 1&2&3' is the mean value based on the sleep diary entries at home while on double-blind study treatment at Week 1, Week 2 and Week 3.
[h] 'Weeks 1&2&3&4' is the mean value based on the sleep diary entries at home while on double-blind study treatment at Week 1, Week 2, Week 3 and Week 4.
[i] mean values calculated based on the 2 PSG treatment nights of each visits.

Endpoints and related variables are also summarized in Appendix 11.

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.

Adverse events:
An AE is defined as any event, which is recorded on the AE eCRF module regardless of the onset date.

TEAEs are those with onset date/time ≥ start date/time of double-blind study treatment and ≤ 30 days, after end of study treatment. AEs, including AEs of special interest, with onset prior to study treatment which worsened during the treatment phase will also be reported as TEAEs.

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.

Missing values:
No imputation is performed for missing values. If laboratory data are missing at the EOT Visit, the results of the latest available post-baseline laboratory tests performed prior to EOT date/time are used for the analysis.

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

No other imputation will be performed for safety parameters except for laboratory values at EOT.

ECG:
- Clinically abnormal ECG on double-blind study treatment,
- Change in ECG parameters on double-blind study treatment,
- Treatment-emergent ECG abnormalities.

Withdrawal symptoms:
Withdrawal symptoms will be assessed by change from V5 to V6.

- BWSQ results,
- Incidence of AEs and ECG abnormalities.

Insomnia rebound:
In order to assess the potential rebound insomnia, for each of the variables, the change from the worst PSG night of V2 to V6 in WASO, TST, and LPS will be analyzed specifically.

Other safety parameters of interest:
Change from V2 (mean of the two PSG nights at V2, run-in period) to Days 1&2, 15&16 and 28&29 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.

Change from V2 (second morning) to the last value on double-blind study treatment in C-SSRS©.

Vital signs:
Change from Baseline (mean of the two PSG nights at V2, run-in period) to the last value on double-blind study treatment in vital signs (temperature, BP, pulse rate, and body weight).

10.2.5 Other variables

Pharmacokinetic
Plasma concentrations of ACT-541468 (9–10 h post-dose) at V3, V4 and V5 will be collected.

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. All analyses will be performed at a 0.05 type I error level (two-sided) using 95% confidence intervals (CIs). Secondary efficacy variables will also be analyzed at $\alpha = 0.05$ (two-sided).

10.3.2 Analysis of the primary efficacy variable(s)

10.3.2.1 Hypotheses and statistical model

This study has 6 arms: a placebo, 4 doses of ACT-541468 and an active reference. The active reference will be excluded from all statistical tests related to dose-response, but will be compared descriptively separately versus placebo.

The study is using an MCP-Mod approach [Bretz 2005, Pinheiro 2006] 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 (as defined by the primary efficacy endpoint). 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) longer 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 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 and a set of pre-specified dose-response models to describe the dose-response relationship.

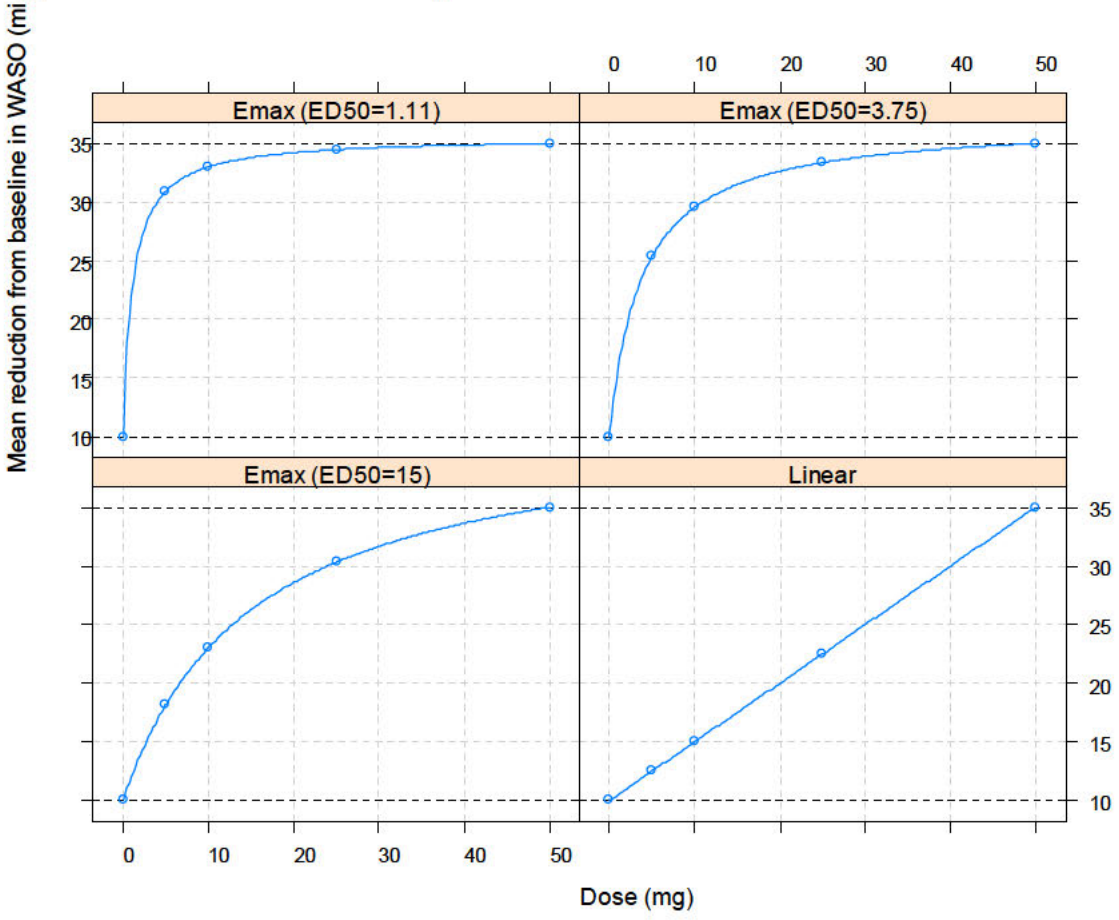
Four candidate dose response models will be considered: one linear, and three E_{max} models. Figure 2 shows the candidate dose-response curves for the mean reduction from baseline in WASO.

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 means (for change from baseline in WASO) of each dose group estimated by fitting an analysis of covariance (ANCOVA) model adjusted for baseline WASO and gender. 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 of at least 15 min with a 95% CI excluding 0.

The primary endpoint will be summarized at each time point by treatment group using the mean, median, standard deviation, standard error, quartiles, minimum, maximum and 95% confidence limits of mean.

Figure 2 Modeled 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&2 in mean WASO will also be analyzed using an ANCOVA model with the same factors as the main analysis [Section 10.3.2.3] with possible addition of region, race and age. Each of the 4 doses of ACT-541468 will be compared to placebo applying Dunnett's test.

The active comparator will be compared separately versus placebo using an ANCOVA model of Days 1&2 mean WASO value with a factor for treatment group (placebo or active comparator) and a covariate for Baseline mean WASO and gender.

10.3.3 Analysis of secondary efficacy variables

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

Treatment effect on secondary efficacy endpoints, except for the change of WASO from Baseline over time, will also be assessed using a mixed model, with treatment, region, gender and age as fixed effects and patient as random covariate.

Treatment effect on the change of WASO from baseline over time will be estimated using a repeated-measures mixed model.

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

10.3.4 Analysis of other 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 as well as 95% CIs.

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

10.3.4.1 Subgroup analyses

Subgroup analyses will be performed by gender. This will be done using the ANCOVA described above. Additional subgroup analyses will be described in the SAP.

10.3.5 Analysis of the safety variables

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

Analysis of safety and tolerability endpoints

Safety and tolerability quantitative endpoints will be summarized using descriptive statistics (mean, standard deviation, median, 1st and 3rd quartiles, minimum, and maximum) while frequency counts and proportions will be used for categorical data. Unless stated otherwise, percentages will be computed on the total sample size of the given treatment arm.

For shift analyses, only subjects with values at both considered time points (i.e., baseline and last value on double-blind treatment) will be included.

Adverse events
AEs in subjects who were screened but not randomized will be listed.

The number and percentage of subjects experiencing TEAEs and SAEs will be tabulated by treatment group 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 randomization and first day of 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 visit and treatment group will be provided for observed values and absolute changes from baseline, in both hematology and blood chemistry laboratory tests. All laboratory data transferred are taken into account regardless of whether they correspond to scheduled (per protocol) or unscheduled assessments. Marked laboratory abnormalities will be summarized for each laboratory variable by treatment group providing their incidence and frequency. Absolute values and changes from baseline of laboratory values during the course of the study will be summarized using summary statistics by treatment group.

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

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

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

Withdrawal symptoms
Change of BWSQ from V5 to V6 will be described through shift tables (V5 vs V6) and summarized using descriptive statistics.

MCP-Mod approach will be used to assess the dose-response relationship for the change from V5 to V6 of BWSQ.

Incidence of AEs and ECG abnormalities occurring between V5 and V6 will be summarized. As for BWSQ, an MCP-Mod approach will be used to determine the dose response of the occurrence of any of those events.

Insomnia rebound effect
In order to assess the potential rebound insomnia, descriptive statistics are provided for the change from the worst PSG screening night to V6 in WASO, TST, and LPS.

Similarly to withdrawal symptoms, MCP-Mod will be used to assess the dose-response relationship for the occurrence of worsening of any of the 3 parameters.

Vital signs
Change from baseline to the last value on double-blind study treatment will be summarized.

Other safety parameters of interest
Change from V2 (morning of run-in PSG nights) to Days 1&2, 15&16 and 28&29 (morning) in KSS, DSST©, and in SDS© will be summarized.

Similarly, change from V2 (morning of run-in second PSG night) to V5 (morning of second PSG night) C-SSRS© will be summarized.

All scale analyses will be performed according to their respective manual and interpretation guides.

Exposure-safety analysis
The exposure-safety relationship will be explored using $C_{9\text{-}10h}$ (plasma concentrations of ACT-541468 in the morning of the second PSG night at V3, V4, and V5) 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.

Pharmacokinetic
Plasma concentrations of ACT-541468 will be analyzed by descriptive statistics, including arithmetic mean, 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 ad interim). Therefore, no adjustment for multiple testing is required. This study includes an IDMC and ISB that will assess safety of ACT-541468 on regular basis as per IDMC and ISB charter, 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 Day 1&2 with an ACT-541468 dose is 25 minutes larger than with placebo (standard deviation = 40 minutes), and values from 8% of subjects are not available for analysis, a sample size of approximately 250 (i.e., 50 subjects per arm allocated in a 1:1:1:1:1 ratio) provides between 89–92% power (power is 90% when averaged over all candidate models; see 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.

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

50 subjects will also be randomly assigned to the zolpidem arm. This sample size provides 80% power to detect a difference in mean reduction in WASO from baseline to Days 1&2 of 23 minutes versus placebo (50 subjects with no dropout) at a 5% two-sided significance level using a two-sample independent t-test assuming a common standard deviation of 40 minutes.

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

eCRF data will be captured via electronic data capture (using the Rave system provided by Medidata Solutions, Inc., a web-based tool). The investigator and site personnel will be trained to enter and edit the data via a secure network, with secure access features (username, password, and identification – an electronic password system). A complete electronic audit trail will be maintained. The investigator/delegate will approve the data (i.e., confirm the accuracy of the data recorded) using an electronic signature (ref. to US 21 CFR Part 11).

Entries recorded by the subject on the hand-held device (i.e., sleep diary, VAS, ISI©, C-SSRS©, KSS, SDS©, BWSQ) and on paper (i.e., DSST©) are considered source data. Site personnel will review and ensure completeness and readability of the subject's 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 / Pregnancy forms) submitted to Actelion and any CROs, subjects must be identified only by number, and never by their name or initials, date of birth, hospital numbers, or any other identifier. The investigator/delegate must keep a subject identification code list, at the site, showing the screening/randomization number, the subject's name, date of birth, and address or any other locally accepted identifiers. Documents identifying the subjects (e.g., signed ICFs) must not be sent to Actelion, and must be kept in strict confidence by the investigator/delegate.

11.3 Database management and quality control

Electronic CRFs 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 personnel on an ongoing basis to look for unexpected patterns in data and for study monitoring. If discrepant data are detected, a query specifying the problem and requesting clarification will be issued and visible to the investigator/delegate via the eCRF. All electronic queries visible in the system either require a data correction (when applicable) and a response from the investigator/delegate to clarify the queried data directly in the eCRF, or simply a data correction in the eCRF. 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, ECGs, PSGs and hand-held device data will be processed through a central laboratory / CRO and the results will be sent electronically 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.

Adverse events are coded according to the latest MedDRA™ version 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 personnel and the investigators will ensure that the study is conducted in full compliance with ICH-GCP Guidelines, the principles of the “Declaration of Helsinki”, and with the laws and regulations of the country in which the research is conducted.

12.2 Independent Ethics Committee / Institutional Review Board

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

Modifications made to the protocol or the ICF after receipt of the approval must also be submitted as amendments by the investigator to the IEC/IRB in accordance with local procedures and regulations [see Section 12.6].

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

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

12.3 Informed consent

It is the responsibility of the investigator/delegate to obtain informed consent according to ICH-GCP and Declaration of Helsinki guidelines and local regulations from each individual participating in this study. 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 trial and it shall be verified that the subject has understood the information (e.g., by asking the subject to explain what is going to happen).

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

Site personnel authorized 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 personnel 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 Clinical Study Report (CSR). IECs/IRBs will be provided with listings of protocol deviations as per local requirements.

12.6 Protocol amendments

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

12.7 Essential documents and retention of documents

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

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

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

These records must be kept by the investigator for as long as is necessary to comply with 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 the event 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 subject's data. The printouts will be considered as the official clinical study records and must be filed either with the subject 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 personnel involved in the study are present during the SIV and will dedicate enough time to it. Site Information Technology support should also be available during the SIV.

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

During the study, the CRA will contact and visit the site regularly and must be permitted, on request, to have access to study facilities and all source documents needed to verify adherence to the protocol and the completeness, consistency, and accuracy of the data being entered in the eCRFs and other protocol-related documents. 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 personnel must be available during monitoring visits and allow adequate time to meet with the CRA to discuss study related issues.

The investigator agrees to cooperate with the CRA(s) to ensure that any issues detected in the course of these monitoring visits are resolved. If the subject is hospitalized or dies in a hospital other than the study site, the investigator is responsible for contacting that hospital in order to document the SAE, in accordance with local regulations.

A close-out visit will be performed for any initiated site when there are no more active subjects and all follow-up issues have been resolved. If a site does not enroll any subjects, the close-out visit may be performed prior to study database closure at the discretion of 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 contents listing the essential documents. All study-related documentation must be maintained in the ISF.

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

The ISF must be stored in a secure and access-restricted area during and after the study. It must be kept by the site for as long as needed to comply with any applicable rules and regulations, ICH-GCP, as well as instructions from 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., standard operating procedures) 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 personnel must cooperate with the auditor(s) and allow access to all study documentation (e.g., subject records) and facilities.

12.11 Inspections

Health authorities and/or 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 personnel must cooperate with inspector(s) and allow access to all study documentation (e.g., subject records) and study facilities.

12.12 Reporting of study results and publication

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 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 personnel prior to submission to a peer-reviewed journal or presentation at a congress.

Authorship will be determined in accordance with the International Committee of 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

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14 APPENDICES

Appendix 1 Thresholds for 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

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
Thyroid stimulating hormone (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
Triiodothyronine, Total (T3)	M/F	ng/dL	60	181	59.9	181.1	NA	NA	NA	NA	nmol/L	0.9	2.8	0.8	2.9	NA	NA	NA	NA
Thyroxine, Free (FT4)	M/F	ng/dL	0.9	1.8	0.8	1.9	NA	NA	NA	NA	pmol/L	11.6	23.2	11.5	23.3	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

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, and to refrain from drinking alcohol at least 3 hours before going to bed.

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 drink 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 (V6).

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 Valproic acid	F	
	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, passiflora	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 2 pm, and no more than twice a week. Dosage is limited to 30 mg of active ingredient in each tablet. Extended release formulations are forbidden.

GABA = gamma-aminobutyric acid; 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 within 1 week prior to V1 and are forbidden until 24 hours after EOT (V6).

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

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

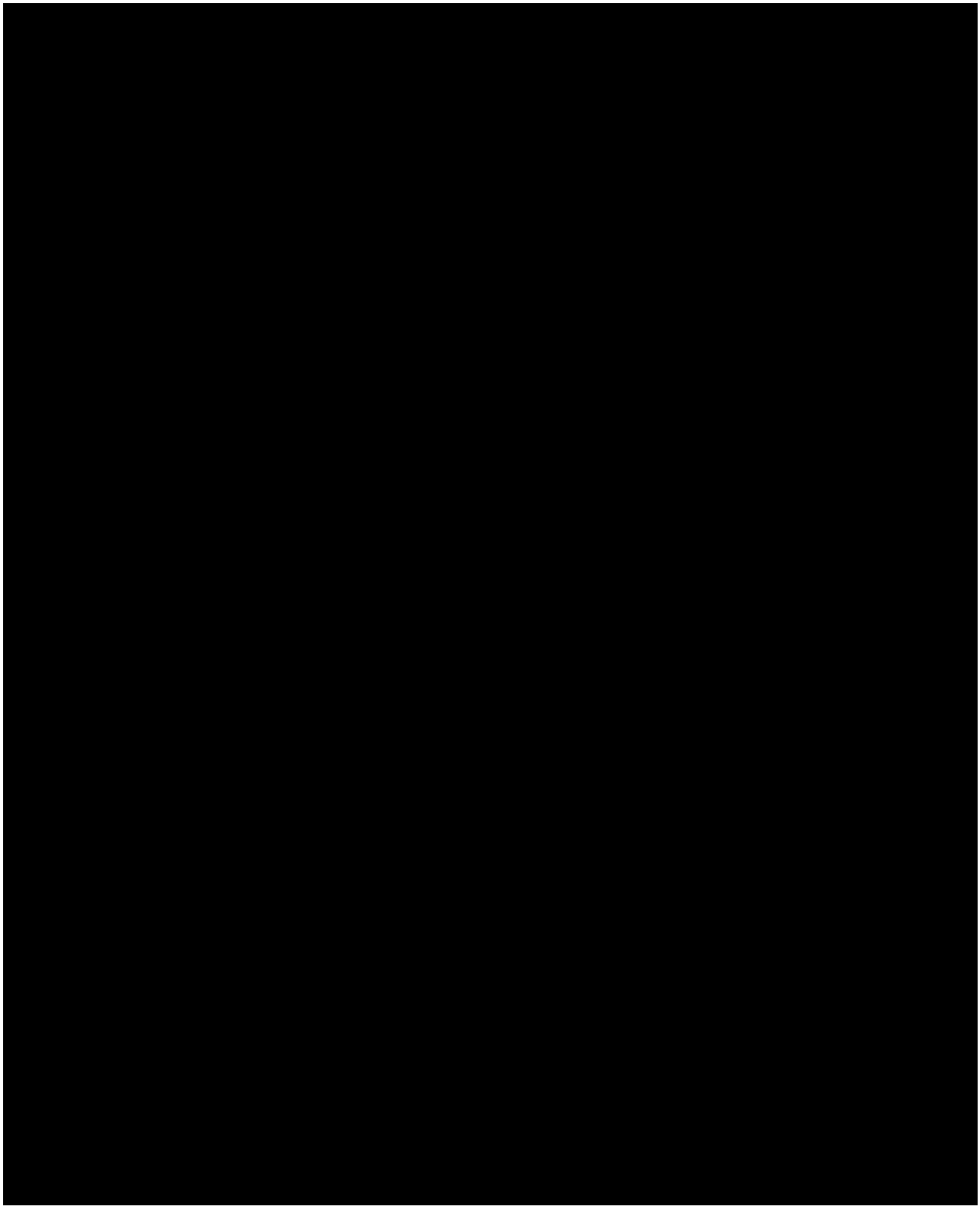
CYP3A4 substrates: alfentanil, apixaban, budesonide, buspirone, cisapride, crizotinib, cyclosporine, darifenacin, dihydroergotamine, domperidone, dronedarone, erlotinib, ergotamine, erythromycin, felodipine, fentanyl, halofantrine, ketamine, lovastatin, lurasidone, maraviroc, midazolam, nifedipine, nisoldipine, 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.

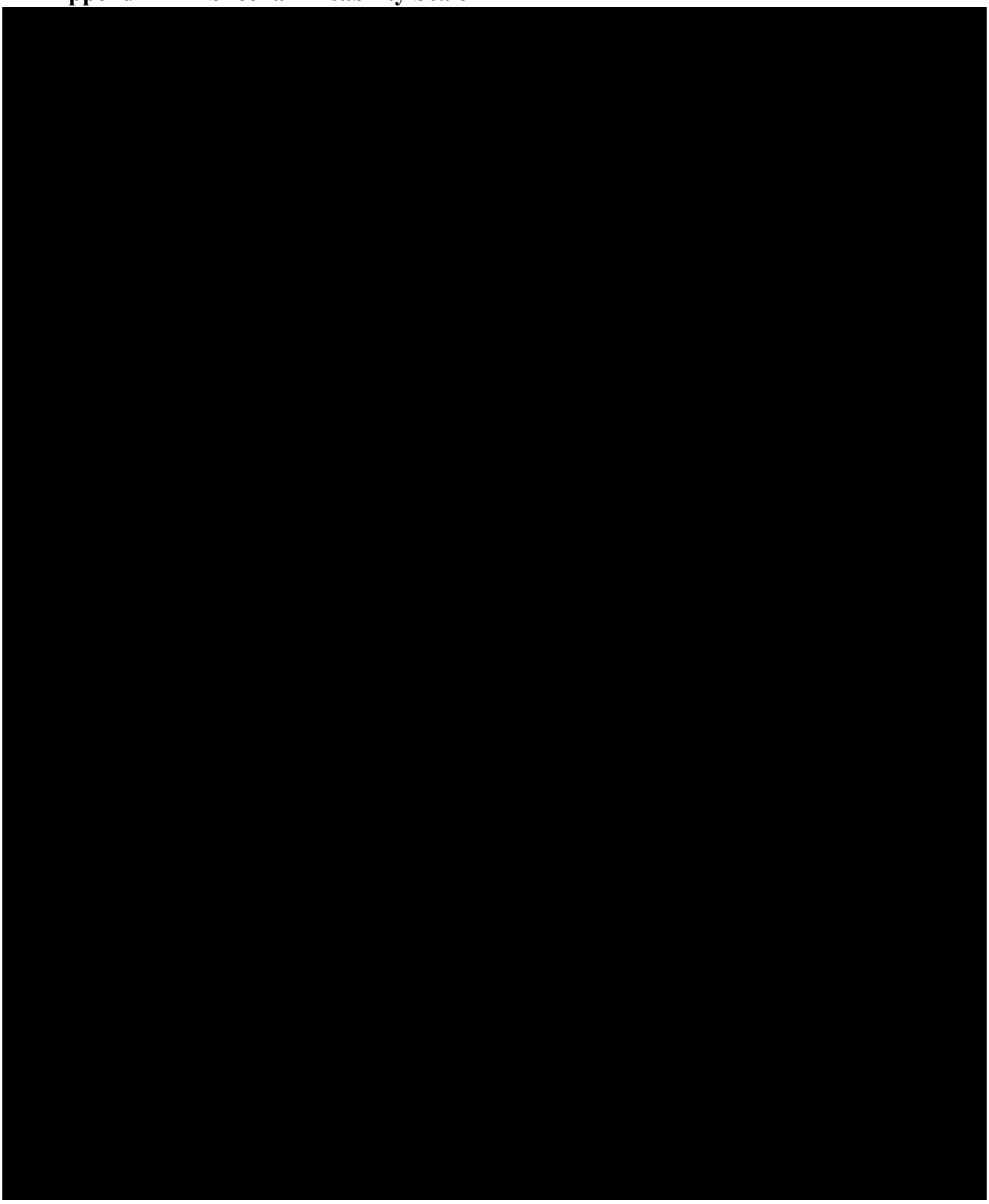
Appendix 5 Digit Symbol Substitution Test©



Appendix 6 Insomnia Severity Index©

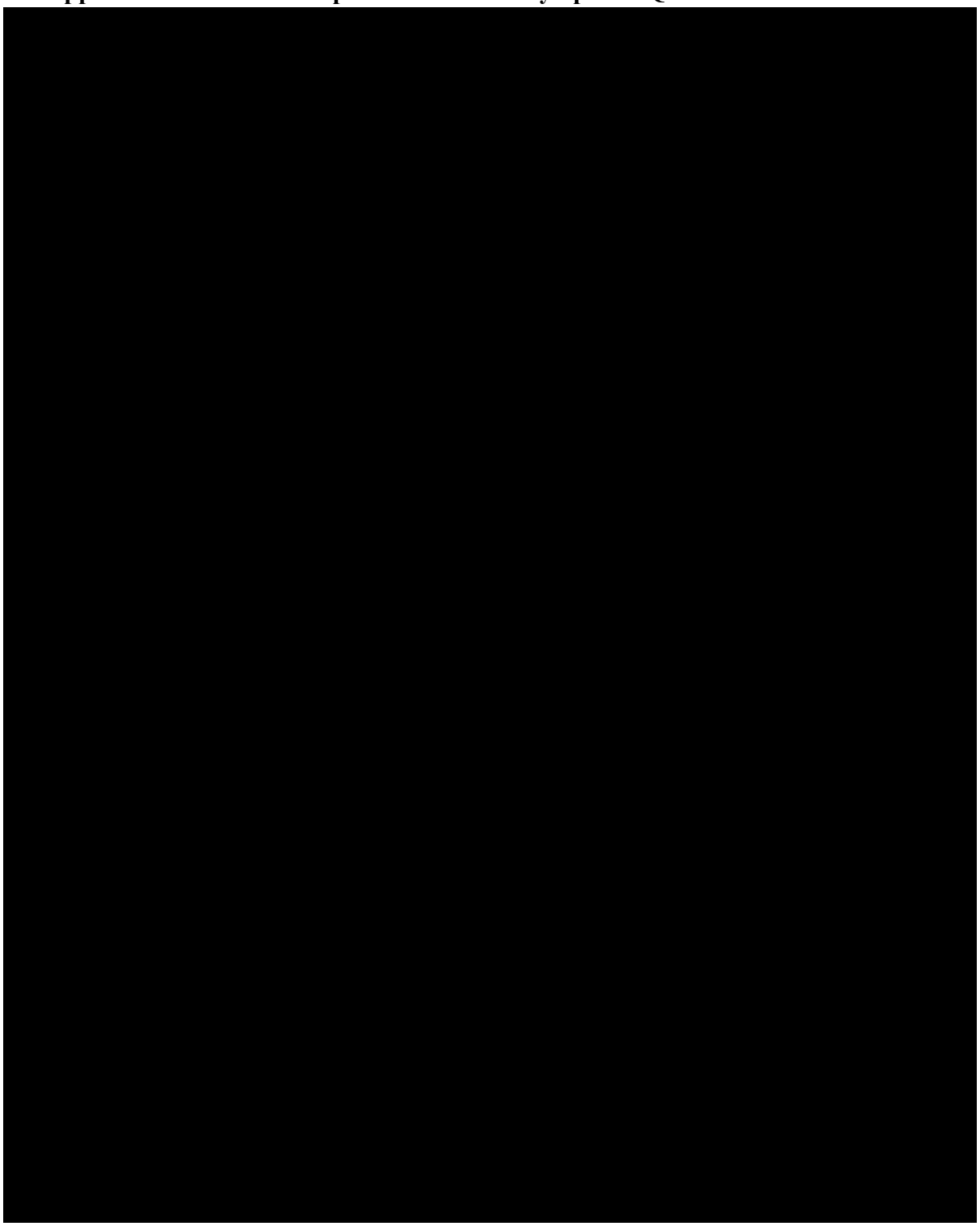
[redacted]

Appendix 7 Sheehan Disability Scale©

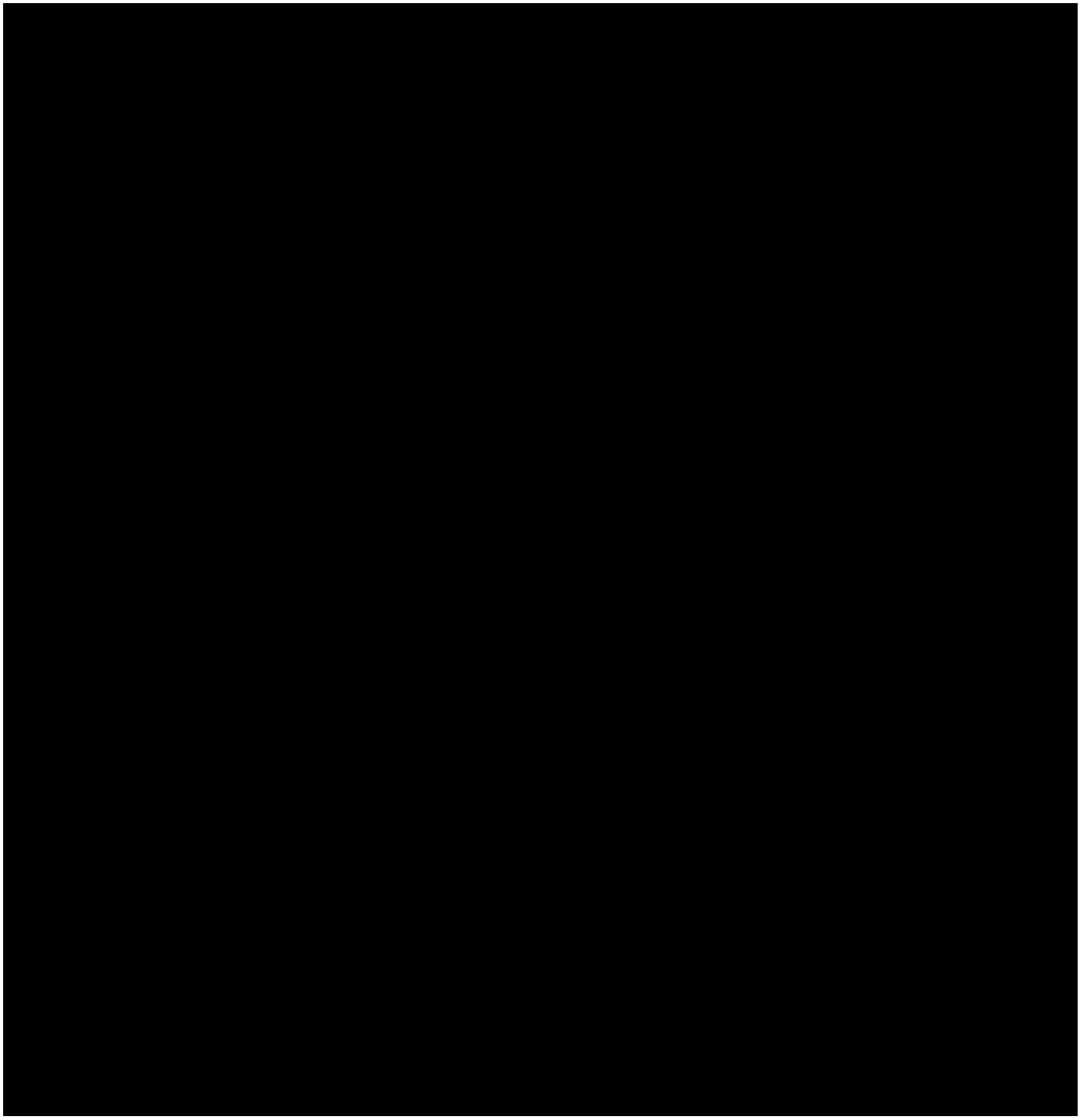


Appendix 8 Karolinska Sleepiness Scale

Appendix 9 Benzodiazepine Withdrawal Symptoms Questionnaire



Appendix 10 Sleep diary



Appendix 11 Summary table of objectives, endpoints and variables

Objectives	Variables	Endpoints	
Sleep maintenance	WASO	Change from Baseline[a] to Days 1&2[b]	Primary
	sWASO	Change from Baseline[c] to Week 4[d]	Secondary
	WASO	Change from Baseline[a] to Days 15&16[e], and to Days 28&29[f]	Exploratory
	WASO over time	Change from Baseline[a] to Days 1&2[b], Days 15&16[e], and to Days 28&29[f] by hour of the night and by quarter of the night	
	sWASO	Change from Baseline[c] to Weeks 1&2&3[g]	
Sleep initiation	LPS	Change from Baseline[a] to Days 1&2[b]	Secondary
	sLSO	Change from Baseline[c] to Week 4[d]	
	LPS	Change from Baseline[a] to Days 15&16[e], and to Days 28&29[f]	Exploratory
	sLSO	Change from Baseline[c] to Weeks 1&2&3[g]	
Total sleep time	TST	Change from Baseline[a] to Days 1&2[b], Days 15&16[e], and to Days 28&29[f]	Exploratory
	sTST	Change from Baseline[c] to Weeks 1&2&3&4[h]	
Sleep quality	VAS	Change from Baseline[c] to Weeks 1&2&3&4[h]	Exploratory
Sleep architecture	Sleep stages duration	Mean[i] 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[i] latency to each sleep stage (S1, S2, SWS, and REM).	
Sleep continuity	Shifts between sleep stages	Mean[i] number and frequency of shifts from S2, SWS or REM to S1 or wake for the whole night.	Exploratory
	Wake time during sleep	Mean[i] 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[i] 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	Change from Baseline[c] to Weeks 1&2&3&4[h]	
Sleep efficiency	SE	Change from Baseline[a] to Days 1&2[b], Days 15&16[e], and to Days 28&29[f]	Exploratory

Insomnia severity	ISI scores	Change from Baseline (V1) to V5 (Day 30, morning)	Exploratory
Next-day performance	VAS	Change from Baseline[c] to Weeks 1&2&3&4[h]	Exploratory

Where:

[a] 'Baseline' is the mean of the 2 PSG nights during the run-in period (V2).
[b] 'Days 1&2' are the mean of the corresponding 2 PSG treatment nights (V3).
[c] 'Baseline' is the mean value in the screening sleep diary entries at home prior to start of study treatment between V2 and V3 during 7 consecutive days.
[d] 'Week 4' is the mean value based on the sleep diary entries at home under last week double-blind study treatment.
[e] 'Days 15&16' is the mean of the corresponding 2 PSG treatment nights (V4).
[f] 'Days 28&29' is the mean of the corresponding 2 PSG treatment nights (V5).
[g] 'Weeks 1&2&3' is the mean value based on the sleep diary entries at home under double-blind study treatment (between V3 and V5).
[h] 'Weeks 1&2&3&4' is the mean value based on the sleep diary entries at home under double-blind study treatment (between V3 and V5).
[i] mean values calculated based on the 2 PSG treatment nights of each visits.