Statistical Analysis Plan AC-078A202

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

ClinicalTrials.gov Identifier NCT02841709

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

STATISTICAL ANALYSIS PLAN FOR CLINICAL STUDY REPORT

Protocol AC-078A202

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

Investigational Drug	ACT-541468
Idorsia Document Number	D-17.014
Document Status/Version Number	Final Version 2.0
Date	12 July 2017

Author
Reviewers

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS AND ACRONYMS

AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
CI	Confidence interval
C-SSRS©	Columbia Suicide Severity Rating Scale
CV%	Coefficient of Variation
DSST©	Digit Symbol Substitution Test
ECG	Electrocardiogram
FAS	Full analysis set
IDMC	Independent Data Monitoring Committee
ISB	Independent Safety Board
ISI©	Insomnia Severity Index
KSS	Karolinska Sleepiness Scale
LPS	Latency to Persistent Sleep
LS	Least squares
MCP-Mod	Multiple Comparison Procedure – Modeling
MedDRA	Medical Dictionary for Regulatory Activities
mFAS	modified Full analysis set
NAW	Number of Awakenings
PK	Pharmacokinetic
PPS	Per-protocol analysis set
PSG	Polysomnography
PT	Preferred term
QTcB	QT interval corrected according to Bazett's formula
QTcF	QT interval corrected according to Fridericia's formula
REM	Rapid eye movement

RND set	Randomized analysis set
SAE	Serious adverse event
SAP	Statistical analysis plan
SCR set	Screened analysis set
SDS©	Sheehan Disability Scale
sLSO	Subjective Latency to Sleep Onset
sNAW	Subjective Number of Awakenings
SOC	System organ class
SQ	Sleep Quality
SS	Safety set
sTST	Subjective Total Sleep Time
sWASO	Subjective Wake After Sleep Onset
SWS	Slow wave sleep
TBIL	Total bilirubin
TD	Target dose
TIB	Time in bed
TST	Total sleep time
ULN	Upper limit of normal
VAS	Visual analog scale
WASO	Wake After Sleep Onset
WHO	World Health Organization
WHO DRL	WHO Drug Reference Listing

1 INTRODUCTION

This statistical analysis plan (SAP) describes in detail the analyses and data presentation for the final clinical study report.

Obvious corrections to address minor formatting errors or spelling mistakes may be performed at the time of analysis without amending this document.

Data will be analyzed by Idorsia and/or designated contract research organizations using Statistical Analysis System version 9.3, and for the Multiple Comparison Procedure – Modeling (MCP-Mod) analysis, R version 3.1.2 will be used. The analyses for the closed session in the Independent Data Monitoring Committee (IDMC) meetings will be performed by an independent statistical analysis center.

Protocol AC-078A202, Final Version 2, dated 10 August 2016 was used when writing this SAP.

2 STUDY DESIGN

This is a multi-center, double-blind, randomized, placebo-controlled, 5-period, 5-treatment crossover, polysomnography (PSG) dose-response Phase 2 study to assess the efficacy and safety of ACT-541468 in elderly subjects with insomnia disorder.

Approximately 50 subjects will be randomized in a 1:1:1:1:1 ratio to five different sequences of five study treatments according to a Latin square design as shown in Table 1. The five study treatments are ACT-541468 5 mg (Dose 1), 10 mg (Dose 2), 25 mg (Dose 3), 50 mg (Dose 4), and placebo. In each treatment period, subjects are to receive one of five study treatments in the order of the sequence they are randomized to.

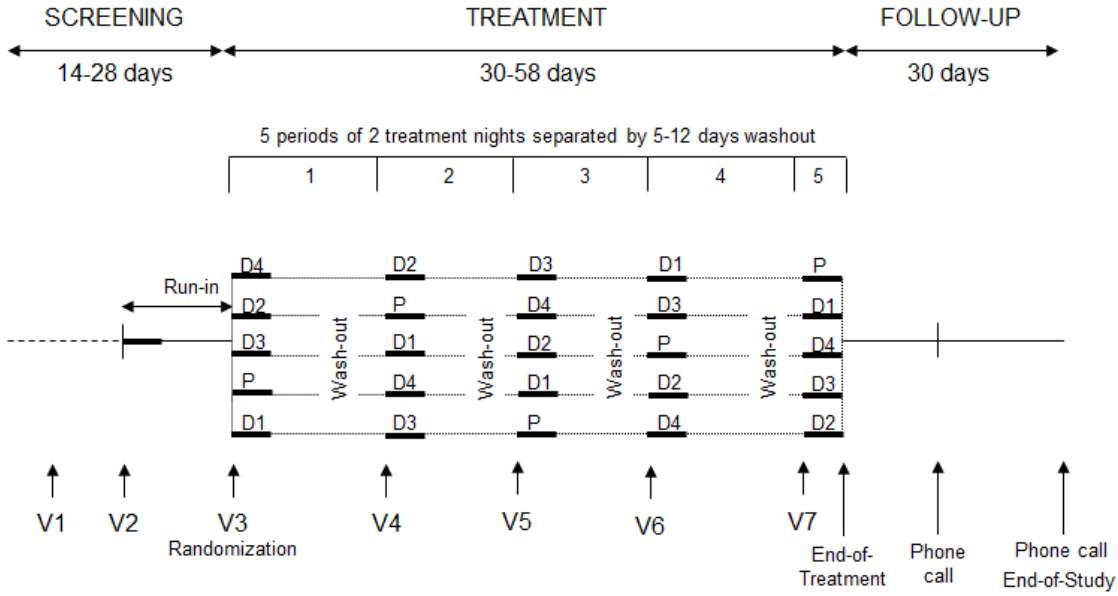
Table 1 Latin square design sequences

		Treatment period (double-blind)				
		1	**2**	**3**	**4**	**5**
Sequence	**1**	Dose 4	Dose 2	Dose 3	Dose 1	Placebo
	2	Dose 2	Placebo	Dose 4	Dose 3	Dose 1
	3	Dose 3	Dose 1	Dose 2	Placebo	Dose 4
	4	Placebo	Dose 4	Dose 1	Dose 2	Dose 3
	5	Dose 1	Dose 3	Placebo	Dose 4	Dose 2

The study design is shown in Figure 1. Single-blind placebo (two capsules of ACT-541468-matching placebo) is administered at V2 (run-in) and double-blind study treatment is administered at V3, V4, V5, V6 and V7. To keep the blind, a placebo capsule matching ACT-541468 will be administered concomitantly with one capsule of ACT-541468 for the 5, 10, and 25 mg doses, while for the 50 mg dose, two capsules of ACT-541468 25 mg will be administered. The double-blind treatment phase consists of five treatment periods starting with the first dose of study treatment in the first evening of

the randomization visit (V3) and ending in the second morning of V7. Each treatment period consists of two consecutive PSG nights on the assigned study treatment which is directly followed by a 5- to 12-day washout period. The End-of-Treatment is reached in the second morning of V7 after the last dose of double-blind treatment and after all morning assessments have been performed.

Figure 1 Study design



Note: V = Visit; ▬ = PSG nights; D = dose; P = placebo.

3 OBJECTIVES

3.1 Primary objective

The primary objective of the study is to evaluate the dose response of ACT-541468 on the change of Wake After Sleep Onset (WASO) assessed by PSG on the first 2 days of each treatment period.

3.2 Secondary objectives

The secondary objective of the study is to evaluate the dose response of ACT-541468 on Latency to Persistent Sleep (LPS) on the first 2 days of each treatment period.

3.3 Other objectives

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

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

To explore the relationship between exposure (concentration of ACT-541468 approximately 9–10 h post-dose) and safety.

4 GENERAL ANALYSIS CONSIDERATIONS

Unless noted otherwise, all statistical summaries will be presented by dose group and in the following order: Placebo, ACT-541468 5 mg, ACT-541468 10 mg, ACT-541468 25 mg, ACT-541468 50 mg.

Categorical data will be summarized by frequency counts and percentages. Unless specified otherwise, percentages will be based on the total number of subjects in the corresponding dose group.

Continuous data will be summarized using descriptive statistics (N, mean, standard deviation, median, minimum and maximum).

5 ANALYSIS SETS

A subject must have given informed consent to be included in any analysis set.

The number of subjects in each analysis set defined below will be tabulated by dose group (including single-blind placebo). Any subject excluded along with reason(s) for exclusion from each analysis set will be summarized and listed.

5.1 Screened analysis set

The Screened analysis set (SCR set) includes all subjects who entered screening and have a subject identification number. Unless noted otherwise, summaries based on the SCR set will be presented as one group (i.e., All subjects).

5.2 Randomized analysis set

The Randomized analysis set (RND set) includes all subjects who have been assigned to a double-blind study treatment (i.e., a treatment sequence).

5.3 Full analysis set

The Full analysis set (FAS) includes all subjects from the RND set who received at least one dose of double-blind study treatment.

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

- Subjects will be evaluated according to the study treatment (i.e., treatment sequence) they have been assigned to (which may be different from the study treatment [or treatment sequence] they actually receive).
- All available data are included.

5.4 Modified full analysis set

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

5.5 Per-protocol analysis set

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

Criteria for sufficient compliance:

- Subject has taken required treatment on both PSG nights during run-in period and Days 1 and 2 of each treatment period,
- Absence of major protocol deviations (i.e., those leading to exclusion from the PPS), as defined in a separate protocol deviation document.

Subjects not meeting the criteria above will be excluded from the PPS.

5.6 Safety set

The Safety set (SS) includes all randomized subjects who received at least one dose of study treatment (including single-blind placebo). Subjects will be evaluated according to the actual dose (i.e., treatment sequence) they received (based on the kit number, visit and period recorded on the 'Study Double Blind Treatment Dispensing & Accountability' page), which may differ from the randomly assigned dose (or treatment sequence). One SS will be defined per dose group (including single-blind placebo).

5.7 Pharmacokinetic analysis set

The Pharmacokinetic analysis set (PK set) includes all subjects in the SS who have at least one PK sample collected after initiation of study drug.

6 STUDY SUBJECTS VARIABLES AND ANALYSES

6.1 Screening failures

The following summaries will be based on the SCR set:

- Number (%) of subjects who discontinued during screening phase (based on 'Was the subject randomized?' recorded as 'No' in the 'Randomization' page),
- Number (%) of subjects who discontinued during screening period and not treated in the run-in period (based on 'Was the subject randomized?' recorded as 'No' in the 'Randomization' page, missing 'Date of capsules dispensed' in the 'Study Single Blind Treatment Dispensing & Accountability' page at V2 and no assessments at V2),

- Number (%) of subjects who failed screening during the run-in period (based on 'Was the subject randomized?' recorded as 'No' in the 'Randomization' page, and either a non-missing 'Date of capsules dispensed' in the 'Study Single Blind Treatment Dispensing & Accountability' page at V2, or a non-missing assessment recorded at V2),
- Primary reasons for screening phase discontinuation (i.e., inclusion/exclusion criteria not met, subject withdrew consent, or other).

Subjects may be re-screened once. For these subjects, only the timing and reason of the last screen failure will be reported in the summary table. Re-screened subjects that are randomized will be excluded from this summary. However, all reasons for screening failure will be included in the listing.

Demographic data for subjects who fail screening and corresponding reason(s) for screen failure will be listed.

6.2 Subject disposition

The following will be based on the SCR set and presented by randomized treatment sequence and as one group (i.e., All subjects):

- Number of subjects screened,
- Number of subjects treated in single-blind placebo treatment run-in period (based on non-missing date of capsules dispensed at Visit 2),
- Number of subjects randomized (based on non-missing randomization number),
- Number of subjects treated in first double-blind treatment period (based on non-missing double-blind treatment start date at Visit 3),
- Number of subjects treated in second double-blind treatment period (based on non-missing double-blind treatment start date at Visit 4),
- Number of subjects treated in third double-blind treatment period (based on non-missing double-blind treatment start date at Visit 5),
- Number of subjects treated in fourth double-blind treatment period (based on non-missing double-blind treatment start date at Visit 6),
- Number of subjects treated in fifth double-blind treatment period (based on non-missing double-blind treatment start date at Visit 7),
- Number of subjects completing the first safety follow-up phone call (based on non-missing date of phone call on the 'Safety Follow-up Phone Call Summary' page),
- Number of subjects completing the end of study safety follow-up (based on non-missing date of phone call on the 'Safety Follow-up Phone Call Summary - EOS' page).

The following summaries will be based on the FAS:

- Number (%) of subjects who prematurely discontinued double-blind study treatment (based on discontinuation reason entered as 'Premature Discontinuation' in the 'Study Double Blind Treatment Log' page),
- Primary reasons for premature double-blind study treatment discontinuation (based on discontinuation reason entered in the 'Premature Discontinuation of Study Treatment' page).

Reasons for premature double-blind study treatment discontinuation will be assigned to the dose group of the last drug intake before date of premature treatment discontinuation.

The following summaries will be based on the RND set:

- Number (%) of subjects who prematurely discontinued from study (based on discontinuation reason entered in the 'Study Discontinuation' page),
- Primary reasons for premature discontinuation from the study (based on discontinuation reason entered in the 'Study Discontinuation' page).

Reasons for premature study discontinuations will be assigned to the dose group of the last drug intake before date of premature study discontinuation.

Premature treatment and study discontinuations will be listed based on the RND set.

6.3 Protocol deviations

The RND set will be used for the protocol deviation summary tables and the SCR set for listings. Important and other protocol deviations will be summarized per pre-specified category (i.e., During screening period; During run-in period; During follow-up phase; Non-study phase specific) as one group (i.e., All subjects). Important and other protocol deviations during double-blind treatment phase will be summarized by dose group. A subject with multiple occurrences of a protocol deviation is counted only once per protocol deviation category and dose group. A listing of all protocol deviations will be provided.

6.4 Subject characteristics

Unless noted otherwise, summaries and listings described in this section will be based on the FAS. Summaries will be presented as one group (i.e., All subjects). Data will be listed individually by subject.

6.4.1 Demographics

Demographic data including age, gender, race, ethnicity, height, and baseline weight and body mass index will be listed and summarized. In addition, age categories (< 65, 65–74, ≥ 75 years), and BMI categories (< 25, 25 to 30, > 30 kg/m^2) will be summarized.

6.4.2 Medical history and current medical conditions

Relevant medical history and current medical conditions will be coded using MedDRA terminology. Medical history and current (ongoing) medical conditions, excluding insomnia-related conditions and symptoms, will be summarized and listed. Summaries will be presented by primary system organ class (SOC) and preferred term (PT). The MedDRA version used for reporting will be specified in the footnote of the applicable output.

6.4.3 Previous and concomitant therapies

Therapies collected will be coded using the WHO Drug Reference Listing (WHO DRL) dictionary that employs the WHO Anatomical Therapeutic Chemical (ATC) classification system. The WHO DRL version used for reporting will be specified in the footnote of the applicable output.

Number (%) of subjects having taken at least one previous or concomitant treatment will be summarized by ATC class and individual PT within each ATC class based on the SS. Summaries will be provided for previous, study-concomitant and study treatment-concomitant therapies defined below.

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

Study concomitant therapies are any treatments that are either ongoing at the signing of informed consent, or initiated during the time from the signing of informed consent up to 30 days after study treatment discontinuation. The use of all study-concomitant therapies (including contraceptives and traditional and alternative medicines, e.g., plant-, animal-, or mineral-based medicines) is to be recorded in the 'Previous/Concomitant Medication' page.

Study treatment concomitant therapies (a subset of study-concomitant therapies) are any treatments taken at least once during at least one treatment period. Study treatment concomitant therapies will be assigned to a dose group (including single-blind placebo) according to the time windows defined in Section 13.2 and the concomitant therapy start and end dates. One therapy might be concomitant to one or several treatment periods.

Previous and study concomitant therapies will be presented as one group (i.e., All subjects). Study treatment concomitant therapies will be presented by dose group (including single-blind placebo) and as one group (i.e., All subjects).

All concomitant therapies will be listed using the SS.

An incomplete (day or month missing) or missing concomitant therapy date will be imputed as described in the algorithm below. The 'lower limit' and 'upper limit' refers to the earliest and latest possible dates, respectively.

As an example: If concomitant therapy end date is MAR2017 (day missing), the lower limit is 01MAR2017 and the upper limit is 31MAR2017. If concomitant therapy end date is 2017 (day and month missing), the lower limit is 01JAN2017 and the upper limit is 31DEC2017.

The following algorithm will be applied for therapies having an incomplete start date and/or end date:

Previous therapy:
If therapy end date (upper limit) is before the signing of the informed consent form.

Study concomitant therapies:
1. If therapy end date (lower limit) is after the signing of the informed consent form and ≤ 30 days after study treatment discontinuation, or

2. If therapy is ongoing (no end date).

Study treatment concomitant therapies:
If therapy start and end dates are incomplete:

If therapy start date (upper limit) is ≤ run-in single-blind placebo treatment start date and either:

1. the therapy is ongoing (no end date), or

2. the therapy end date (lower limit) is ≥ last study treatment intake.

Here, therapy is assigned to all dose groups.

If only therapy end date is incomplete:

When therapy is taken during at least one treatment period (including single-blind placebo) and end date (lower limit) is ≥ last study treatment intake.

If only therapy start date is incomplete:

When therapy is taken during at least one treatment period (including single-blind placebo) and start date (upper limit) is ≤ run-in single-blind placebo treatment start date.

6.5 Study treatment exposure and compliance

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

For each dose group, the number (%) of subjects receiving zero, one or two days of double-blind treatment will be tabulated by dose group (including single-blind placebo).

Double-blind treatment exposure and compliance data will be listed along with reasons for treatment end.

7 ANALYSIS OF THE PRIMARY VARIABLE

7.1 Endpoint: Objective sleep maintenance

The primary efficacy endpoint relates to objective sleep maintenance and is assessed through the absolute change in WASO from Baseline to Days 1 and 2.

Baseline is the mean of the two PSG nights during the run-in period (V2). Days 1 and 2 is the mean of the corresponding two PSG treatment nights for a given treatment period.

WASO is the time (min) spent awake after onset of persistent sleep [see definition of LPS in Section 8.1] until lights on as determined by PSG. The PSG recording is centrally scored by independent scorers.

7.2 Handling of missing data

For the main analysis, no imputation will be performed for missing WASO values. However, if one of the two values is missing either for Baseline or for Days 1 and 2, the single value available will be used as the mean for this time point. This implies implicit imputation: the missing data point is given the same value as the non-missing data point.

7.3 Statistical hypothesis, model and method of analysis

The primary statistical analysis will be performed on the mFAS.

To evaluate the dose response relationship of ACT-541468 on the change from baseline in WASO, this study uses the generalized MCP-Mod methodology [Bretz 2005, Pinheiro 2006, Pinheiro 2014]. This approach combines a Multiple Comparison Procedure (MCP) to assess the efficacy of ACT-541468 versus placebo followed by a modeling (Mod) step to characterize the dose response relationship and to identify a dose (or dose range) that has shown signs of a clinically relevant effect.

The MCP-Mod analysis will be performed using the R *DoseFinding* package version 0.9.14 [Bornkamp 2016].

Details on how the primary endpoint will be analyzed within the MCP-Mod framework are provided below.

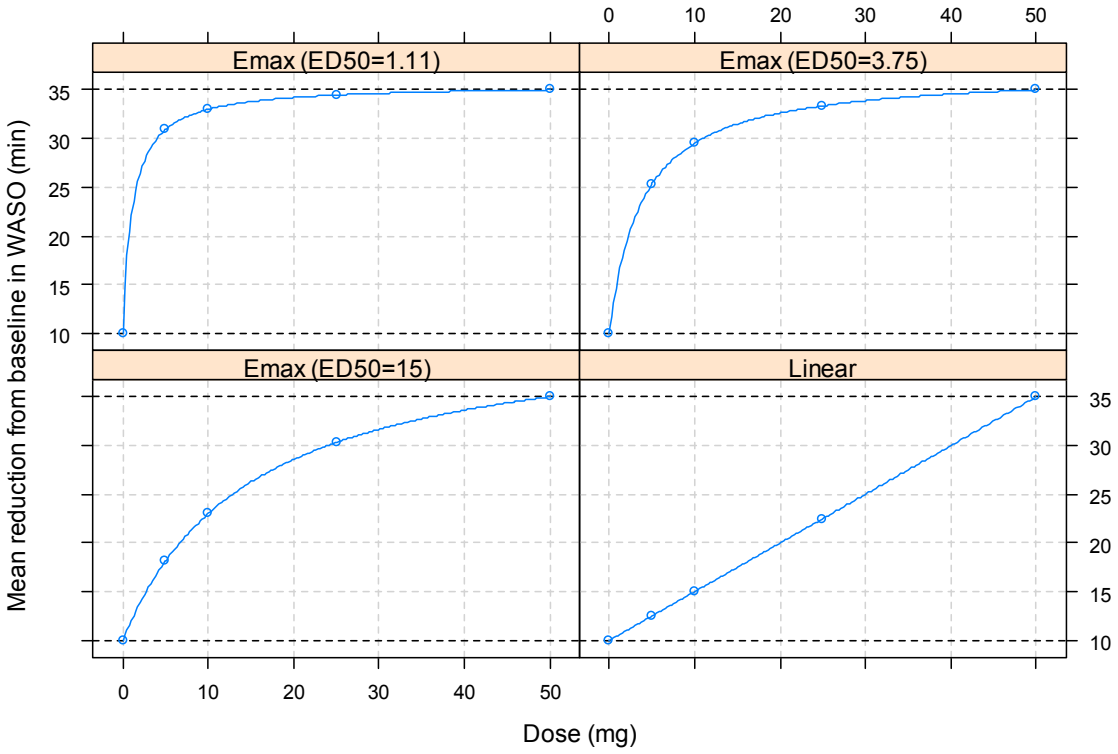
7.3.1 Design

7.3.1.1 Candidate dose response models

To begin, the set of pre-specified candidate parametric dose response models that could possibly represent the underlying dose response shape are determined. For this study,

four pre-specified dose response models are considered: three E_{max} models and one linear model. A graphical display of these models is shown in Figure 2. Here, the maximum mean reduction in WASO from baseline to Days 1 and 2 with ACT-541468 50 mg dose is assumed to be 25 minutes longer than with placebo.

Figure 2 Candidate dose response models



The following describes how the parameters (i.e., ED_{50}) of these models are calculated.

For the purpose of determining optimal contrasts, only the standardized form $f^0(d,\theta^0)$ of the dose response model $f(d,\theta)=\theta_0+\theta_1 f^0(d,\theta^0)$ needs to be considered [Bretz 2005], i.e., the scale parameters (θ_0 and θ_1) are removed from the functional form.

The functional form of the E_{max} model is defined as $f(d,\theta)=E_0+E_{max}\frac{d}{ED_{50}+d}$, where d = dose; E_0 = placebo (basal) effect; E_{max} = maximum change in effect associated with dose; ED_{50} = dose that is expected to give half of the maximum change.

The standardized form of the E_{max} model is therefore $f^0(d,\theta^0)=\frac{d}{ED_{50}+d}$, which represents the percentage (p) of the maximum change from the basal effect associated with dose (d) (since the standardized E_{max} model is the same as the functional form when E_0 = 0 and E_{max} = 1). Rearranging the formula above gives $ED_{50}=\frac{d(1-p)}{p}$. The specification of ED_{50} will fully parameterize the standardized form of the model.

The ED_{50} for each E_{max} model (i.e., 1.11, 3.75, 15) was calculated assuming a p of 90%, 80%, and 40% at an ACT-541468 dose (d) of 10 mg, 15 mg, and 10 mg, respectively.

The calculation of each optimal contrast [see Section 7.3.2.1] depends on the pre-defined estimates of ED_{50} and dose levels (including placebo as 0 mg). Since three E_{max} models are pre-specified, three different sets of testing contrasts will be determined for the E_{max} model (family).

The functional form of the linear model is defined as $f(d,\theta)=E_0+\delta d$, where d = dose; E_0 = placebo (basal) effect. Hence, the standardized form of the linear model is a function of dose only $f^0(d)=d$. Since no parameter estimates θ^0 are required, the determination of the appropriate single testing contrast is derived based on dose alone.

To ensure no inflation of type I error, the pre-specified parameter values θ^0 (i.e., ED_{50}) are not to be changed after the blind is broken.

7.3.2 Analysis

Key components of MCP-Mod at the analysis stage include:

- MCP step: Testing for the presence of a dose response signal,
- Mod step: Selecting the best dose response model for the observed data out of a pre-specified set of candidate models, and
- Mod step: Estimating target dose(s) of interest via modeling.

7.3.2.1 Implementation of the MCP step

The MCP step consists of testing a set of optimal contrasts: each testing contrast representing one of the pre-specified dose response models. This step addresses the issue of possible model misspecifications (the reason why multiple candidate dose response shapes are pre-defined) and also includes the associated adjustments for multiplicity within a rigorous hypothesis testing framework.

For a single given candidate dose response model, the optimal contrast for testing the hypothesis of a flat dose-response profile with maximal power is given by:

$$\boldsymbol{c}_{\mathrm{m}}^{\mathrm{opt}} \propto \hat{\boldsymbol{S}}^{-1}\left(\boldsymbol{\mu}_{\mathrm{m}}^{0} - \frac{\boldsymbol{\mu}_{\mathrm{m}}^{0\prime}\hat{\boldsymbol{S}}^{-1}\boldsymbol{1}}{\boldsymbol{1}'\hat{\boldsymbol{S}}^{-1}\boldsymbol{1}}\right)$$

Where $\boldsymbol{\mu}_{\mathrm{m}}^{0}$ is the standardized mean response at each dose for a given candidate dose response model (m) and $\hat{\boldsymbol{S}}$ denotes the estimated variance-covariance of $\hat{\boldsymbol{\mu}}_d$ [Pinheiro 2014] (i.e., the estimated mean response per individual dose level from the observed data; further details below).

In the calculation of the optimal contrasts (one for each candidate dose response model $\boldsymbol{c}^{\mathrm{opt}}{}_{1,\ldots,}\ \boldsymbol{c}^{\mathrm{opt}}{}_{4}$), $\boldsymbol{\mu}_{\mathrm{m}}^{0}$ relies on the standardized form of the dose response model (not the complete functional form).

For convenience, the contrast coefficients are normalized such that $\|\boldsymbol{c}^{\mathrm{opt}}\| = 1$.

Once data are available, the optimal contrasts are applied to $\hat{\boldsymbol{\mu}}_d$.

For each candidate dose response model (m), the null hypothesis H_0: $(\boldsymbol{c}^{\mathrm{opt}}{}_{\mathrm{m}})'\boldsymbol{\mu} = 0$ (absence of a dose-response relationship) will be tested against the two-sided alternative H_1: $(\boldsymbol{c}^{\mathrm{opt}}{}_{\mathrm{m}})'\boldsymbol{\mu} \neq 0$ (existence of a dose response). $\boldsymbol{\mu}$ is the true, but unknown vector of means.

The t-test statistic associated with each of the candidate dose response models is given by $T_m = \dfrac{(\boldsymbol{c}_{\mathrm{m}}^{\mathrm{opt}})'\hat{\boldsymbol{\mu}}}{\left[\boldsymbol{C}'\hat{\boldsymbol{S}}\boldsymbol{C}\right]_{\mathrm{m,m}}^{1/2}}$ with $[\mathrm{A}]_{\mathrm{m,m}}$ denoting the m^{th} diagonal element of the matrix A, and $\boldsymbol{C} = [\boldsymbol{c}^{\mathrm{opt}}{}_{1,\ldots,}\ \boldsymbol{c}^{\mathrm{opt}}{}_{4}]$ representing the matrix containing the optimal contrasts.

The test statistic used for establishing an overall dose-response signal will be the maximum of the individual model contrast test statistics $T_{\max} = \max_{\mathrm{m}}(T_{\mathrm{m}})$, or alternatively, the associated multiplicity adjusted *p*-value associated with $T_{\max}$.

Analysis will only proceed to the modeling (Mod) step if a statistically significant dose-response signal is established, i.e., the null hypothesis is rejected under any candidate dose response model (adjusted two-sided *p*-value < 0.05).

7.3.2.2 Implementation of the Mod step

The Mod step involves model selection, fitting the univariate dose response profile, and estimating target dose(s) based on the fitted model.

A two-stage approach will be used to fit the dose-response model to the observed data. This approach utilizes generalized least squares [Pinheiro 2014] and relies on asymptotic

results, but has the appeal of being a general purpose application as it depends only on $\hat{\boldsymbol{\mu}}_d$ and $\hat{\boldsymbol{S}}$. For example, the obtained (adjusted) estimates for $\hat{\boldsymbol{\mu}}_d$ and $\hat{\boldsymbol{S}}$ inherit the missing data assumptions of the underlying first stage model.

First stage

A linear mixed effects model (first stage model) will be used to calculate estimates for $\hat{\boldsymbol{\mu}}_d$ (i.e., least squares [LS] mean estimates for each ACT-541468 dose level and placebo) and $\hat{\boldsymbol{S}}$ (i.e., variance-covariance matrix of $\hat{\boldsymbol{\mu}}_d$).

The change from baseline in WASO (assumed to be normally distributed) will be modeled using a fixed effect for dose group (placebo and each ACT-541468 dose level), an additional fixed effect for period (five periods), a linear slope to adjust for WASO at baseline, and a random effect for subject.

The variance of the change from baseline in WASO is assumed to be constant across each dose group, therefore a compound symmetry structure for $\hat{\boldsymbol{S}}$ will be considered.

The LS mean for each treatment group will be displayed along with associated standard errors and 95% confidence intervals (CIs). For each ACT-541468 dose level comparison to placebo, the placebo-adjusted LS mean will be displayed along with associated standard error, 95% CI and unadjusted two-sided *p*-value.

Second stage

Among the candidate dose response models with a significant contrast test (i.e., adjusted two-sided *p*-value < 0.05) identified in the MCP step, the dose response model parameters (e.g., ED_{50}) are estimated by fitting the dose response model (family) to the estimates obtained from the mixed effects model ($\hat{\boldsymbol{\mu}}_d$ and $\hat{\boldsymbol{S}}$) in the first stage. The best fitting dose response model (E_{max} or linear) will be selected based on the gAIC (smaller is better). This chosen dose response model will then be used to estimate the target dose.

Based on the selected dose response model, the predicted mean (95% CI) dose response profile for the change from baseline in WASO will be graphically displayed.

7.3.2.3 Dose selection based on WASO

Estimation of a target dose (TD) will be performed on the basis of the fitted dose response model (E_{max} or linear) chosen in the second stage. The estimated TD will be the lowest dose strength anywhere within the studied dose range (0 mg to 50 mg) which shows a clinically meaningful effect (i.e., 15 minutes better than predicted mean value of placebo) and a statistically significant effect (i.e., lower 95% CI of the predicted mean value at TD > observed mean value of placebo). Note: the choice of 95% CI is not driven by the purpose of controlling type I error rates.

To aid understanding of the accuracy/variation associated with the selected dose response model, the following parameters of interest will be derived using a nonparametric bootstrap technique.

- The 0.025, 0.5 (median) and 0.975 bootstrap percentiles of the predicted mean (on the change in reduction in WASO of ACT-541468 relative to placebo) for the chosen dose response model,
- The 0.025, 0.5 (median) and 0.975 bootstrap percentiles of the target dose defined as 15 minutes better than predicted mean value of placebo,
- The 0.025, 0.5 (median) and 0.975 bootstrap percentiles of the target dose defined as 20 minutes better than predicted mean value of placebo,
- If the E_{max} model is selected, the 0.025, 0.5 and 0.975 bootstrap percentiles of the E_0, ED_{50} and E_{max} will be presented.

The nonparametric bootstrap technique will proceed as follows:

1. Sample, with replacement, the data available at each period per subject until the resampled dataset contains the same number of subjects as in the original dataset,
2. From the resampled dataset, calculate and store the parameter estimates that define the dose response model,
3. Repeat steps 1 and 2 numerous times (say 1000) to derive the bootstrap distribution for each parameter,
4. Use the bootstrap distribution to calculate the parameters of interest described above.

7.3.3 Other

The primary endpoint will also be summarized by gender and overall using descriptive statistics.

7.4 Supportive/sensitivity analyses

Sensitivity analyses will be conducted on the PPS if this analysis set differs from the mFAS significantly (e.g., > 10% reduction in number of subjects).

Change from baseline to Days 1 and 2 in mean WASO will also be analyzed using a linear mixed effects model with the same factors as in the main analysis with the addition of region, race, gender, and age.

If the proportion of missing WASO values is significant (e.g., > 10% of expected data points missing based on the FAS), a sensitivity analysis will be conducted using the FAS to assess the influence of missing data on the main analysis. A data point is considered missing if both WASO assessments are missing at a given visit (i.e., Baseline or Days 1 and 2 of each treatment period). After the missing data is imputed, the change from baseline to Days 1 and 2 in mean WASO will be analyzed using the same linear mixed effects model as in the main analysis. A worst case scenario for imputing missing data will be considered: If the missing post-baseline value is for a dose group other than

placebo, then the worst post-baseline value recorded for that subject on any other dose group (including placebo) will be imputed. If the missing post-baseline value is for placebo, then the best post-baseline value recorded for that subject on any other dose group will be imputed. The dose group to which the missing value is imputed is based on the assigned treatment sequence. If the baseline value is missing, then the mean of all available baseline values will be imputed. A subject missing baseline as well as all post-baseline WASO values will be excluded from this analysis.

Using the FAS, the number (%) of subjects missing both WASO assessments at Baseline (run-in period) and Visits 3, 4, 5, 6, and 7 will be presented by randomized treatment sequence and as one group (i.e., All subjects).

8 ANALYSIS OF THE SECONDARY EFFICACY VARIABLES

The analysis of the secondary efficacy variable will be performed on the FAS.

8.1 Objective sleep onset

The secondary efficacy endpoint relates to objective sleep onset and is assessed through the absolute change in LPS from Baseline to Days 1 and 2.

Baseline is the mean of the two PSG nights during the run-in period (V2), and Days 1 and 2 is the mean of the corresponding two PSG treatment nights for a given treatment period.

LPS is the time (min) 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 rapid eye movement (REM), as determined by PSG.

The same MCP-Mod analysis as performed for the primary endpoint will be conducted to evaluate the dose response of ACT-541468 on the secondary efficacy endpoint. Three E_{max} models with an ED_{50} of 1.11, 3.75, 15, respectively, and one linear model will be considered. Summary statistics will also be provided.

9 ANALYSIS OF OTHER EFFICACY VARIABLES

The analysis of other efficacy variables will be performed on the FAS.

For endpoints based on objective assessments (e.g., WASO, LPS and Total Sleep Time [TST] as determined by PSG):

- Baseline is the mean of the two PSG nights during the run-in period (V2),
- Days 1 and 2 is the mean of the corresponding two PSG treatment nights for a given treatment period.

For endpoints based on subjective assessments (e.g., subjective WASO [sWASO], subjective Latency to Sleep Onset [sLSO], subjective TST [sTST], Sleep Quality [SQ]):

- Baseline is the mean value of the sleep diary entries during the run-in period (V2),
- Days 1 and 2 is the mean value of the corresponding sleep diary entries for a given treatment period.

9.1 Objective and subjective sleep maintenance

Summary statistics will be provided for:

- Absolute values of WASO at Baseline and Days 1 and 2 by gender and overall,
- WASO over time (by hour of the night and by quarter of the night),
- Absolute values of sWASO at Baseline and Days 1 and 2 by gender and overall,
- Absolute change in sWASO from Baseline to Days 1 and 2 by gender and overall.

9.2 Objective and subjective sleep onset

Summary statistics will be provided for:

- Absolute values of LPS at Baseline and Days 1 and 2 by gender and overall,
- Absolute values of sLSO at Baseline and Days 1 and 2 by gender and overall,
- Absolute change in sLSO from Baseline to Days 1 and 2 by gender and overall.

9.3 Objective and subjective Total Sleep Time

TST is the amount of actual sleep time (min), i.e., time spent in epochs scored as non-wake as determined by PSG.

sTST is the self-reported time (min) spent asleep as reported in the sleep diary.

Summary statistics will be provided for:

- Absolute values of TST at Baseline and Days 1 and 2 by gender and overall,
- Absolute change in TST from Baseline to Days 1 and 2 by gender and overall,
- Absolute values of sTST at Baseline and Days 1 and 2 by gender and overall,
- Absolute change in sTST from Baseline to Days 1 and 2 by gender and overall.

9.4 Sleep Quality

SQ is the sleep quality as determined by scores on the visual analog scale (VAS; mm).

Summary statistics will be provided for:

- Absolute values of SQ at Baseline and Days 1 and 2,
- Absolute change in SQ from Baseline to Days 1 and 2.

9.5 Sleep architecture

Absolute change from Baseline to Days 1 and 2 in the duration (min) and percentage of TST in each sleep stage (S1, S2, SWS and REM) will be summarized over the whole night, and for each quarter of the night. Absolute values will also be summarized.

Absolute change from Baseline to Days 1 and 2 in the latency (min) to each sleep stage (S1, S2, SWS, and REM) will be summarized. Absolute values will also be summarized.

9.6 Objective and subjective sleep continuity

Mean values are the mean of the two PSG treatment nights at each visit.

Absolute change from Baseline to Days 1 and 2 in mean number of shifts from S2, SWS or REM to S1 or wake for the whole night will be summarized. Absolute values will also be summarized.

Absolute change from Baseline to Days 1 and 2 in mean wake time during sleep (defined as the time [min] spent in epochs scored as wake between LPS and last epoch not scored wake) for the whole night will be summarized. Absolute values will also be summarized.

Absolute change from Baseline to Days 1 and 2 in mean number of awakenings (defined as the number of awakenings between first epoch and last epoch not scored wake) will be summarized for the whole night, for each quarter of the night, and for each hour of the night. Absolute values will also be summarized.

Absolute change from Baseline to Days 1 and 2 in the mean self-reported number of awakenings will be summarized. Absolute values will also be summarized.

9.7 Sleep efficiency

Sleep efficiency (%) is defined as 100 × (TST [min] / total time in bed [min]) where total time in bed is fixed to 480 min during the PSG nights.

Absolute change from Baseline to Days 1 and 2 in Sleep efficiency will be summarized. Absolute values will also be summarized.

9.8 Insomnia severity

The Insomnia Severity Index (ISI©) is a validated instrument to quantify perceived insomnia severity [Bastien 2001]. The ISI is composed of seven items that evaluate (1) severity of sleep-onset (initial), (2) sleep maintenance (middle), (3) early morning awaking (terminal) problems, (4) satisfaction with current sleep pattern, (5) interference with daily functioning, (6) noticeability of impairment attributed to the sleep problem, and (7) level of distress caused by the sleep problem. Each item is scored as 0 (not at all), 1, 2, 3 or 4 (extremely) and the time interval considered is the last 2 weeks. Total scores range from 0–28 with high scores indicating greater insomnia.

Absolute values at screening (V1) will be summarized.

9.9 Next-day performance

Daytime alertness and daytime ability to function are to be assessed once per treatment period (i.e., on the second PSG evening). Morning sleepiness is to be assessed twice per treatment period (i.e., on the first and second PSG evening).

Absolute change from Baseline to Days 1 and 2 in next-day performance assessed by scores on the VAS (mm) assessing morning sleepiness, daytime alertness and daytime ability to function. Absolute values will also be summarized.

10 SAFETY ANALYSIS

Unless noted otherwise, the SS will be used for summaries and listings of safety data.

All safety data will be listed.

10.1 Adverse events

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

AEs will be assigned to the dose group based on the AE start date. AEs with an incomplete or missing start date will not be assigned to a treatment period.

Treatment-emergent AEs are those that occurred from the start of the treatment period [see Section 13.1] until 5 days after last study treatment intake in each treatment period (or until the start of the next treatment period, if earlier).

Non-treatment emergent AEs are those that occurred before the first treatment period or more than 5 days after the last study treatment intake of a given treatment period until the start of the next treatment period, or until the end of the last treatment period [see Section 13.2].

Post-treatment emergent AEs are those that occurred after the end of the last treatment period [see Section 13.2].

AEs will be summarized (frequency counts and percentages) by SOC and/or PT, and maximum intensity. AEs occurring during the run-in single-blind placebo treatment period will also be included in AE summaries defined below (except for AEs leading to premature discontinuation or temporary interruption, or on-treatment deaths).

Deaths (whether on-treatment or not), and AEs (whether treatment-emergent or not) leading to premature study treatment discontinuation or temporary interruption will be assigned to the dose group (including single-blind placebo) of the last dose taken before death or onset of AE, respectively.

The following AE summaries will be provided:

- Treatment-emergent AEs,

- Treatment- and non-treatment emergent AEs,
- Post-treatment emergent AEs,
- Treatment-emergent AEs related to study treatment,
- Treatment- and non-treatment emergent AEs related to study treatment,
- AEs leading to premature discontinuation of double-blind study treatment,
- AEs leading to temporary interruption of double-blind study treatment,
- Occurrence of treatment and non-treatment emergent non-serious AEs,
- Treatment-emergent serious AEs (SAEs),
- Treatment- and non-treatment emergent SAEs,
- Occurrence of treatment- and non-treatment emergent SAEs,
- Treatment-emergent SAEs related to study treatment,
- Treatment- and non-treatment emergent SAEs related to study treatment,
- Treatment- and non-treatment emergent AEs with fatal outcome,
- Treatment- and non-treatment emergent AEs related to study treatment with fatal outcome,
- Deaths with cause of death.

All AEs will be listed as well as all deaths with cause of death. In addition, separate listings will be provided for AEs leading to discontinuation of double-blind study treatment, and SAEs.

Treatment-emergent AEs of special interest (AESI) both according to investigator (based on the question 'Do you consider this AE an Adverse Event of Special Interest (AESI)?' recorded as 'Yes' on the 'Adverse Event' page), and after adjudication by an Independent Safety Board (ISB), will be summarized. The following summaries will be provided:

- Treatment- and non-treatment emergent AESI as per investigator,
- Treatment- and non-treatment emergent AESI after ISB adjudication.

AESI will be listed separately.

A subject with multiple intensities reported for an AE will be summarized under the maximum intensity recorded for the event. A subject with multiple occurrences of an AE is counted only once in the AE category (e.g., SOC, PT).

An incomplete (day or month missing) or missing AE date will be imputed as described in the Table 2 below. The 'upper limit' refers to the latest possible date.

As an example: If AE resolution date is MAR2017 (day missing), the upper limit is 31MAR2017. If AE resolution date is 2017 (day and month missing), the upper limit is 31DEC2017.

Table 2 Imputation rules for an incomplete or missing AE date

Field	Incomplete date	Missing date
AE resolution date	The upper limit.	No imputation; the AE is considered as ongoing.
AE onset date	No imputation.	No imputation.

10.2 Laboratory data

Laboratory analyses are based on data received from the central laboratory. Unless noted otherwise, laboratory data will be converted into SI units, and summaries and listings will include unscheduled assessments.

Descriptive summary statistics of the observed values and absolute changes from baseline to the morning after the second PSG night (scheduled visit) in both hematology and blood chemistry laboratory parameters will be provided. Only scheduled assessments will be considered for this summary.

Baseline is the scheduled assessment performed on the evening of the first PSG night. This assessment is planned immediately prior to treatment intake and is the baseline value for the dose group that immediately follows the assessment. Subjects missing baseline data on a particular parameter will have a missing baseline (and change from baseline) for that parameter.

Descriptive summary statistics of the observed values and absolute changes from baseline [as per definition in Section 13.4] to the last value in the study in hematology and blood chemistry laboratory parameters will be provided, and presented as one group (i.e., All subjects).

Marked laboratory abnormalities are defined in Table 3 below. A marked laboratory abnormality will be assigned to the dose group where it is present regardless of its presence in previous treatment periods.

The number (%) of subjects with marked laboratory abnormalities will be tabulated. A subject will be counted only once, but may be reported in more than one marked laboratory abnormality criterion of a given parameter. Percentages will be based on the number of subjects at risk: those not meeting the criterion at baseline (or having a missing baseline value) and having at least one post-baseline value for a given parameter and treatment period.

All laboratory data for subjects with at least one marked laboratory abnormality will be listed.

Table 3 Marked abnormalities in laboratory parameters for reporting

Laboratory parameter	Criteria for marked laboratory abnormalities
Hematology	
Hemoglobin (g/L)	< 100 (LL) < 80 (LLL) > 20 above ULN or > 20 above baseline if baseline > ULN (HH) > 40 above ULN or > 40 above baseline if baseline > ULN (HHH)
Hematocrit (%)	< 32 (Male); < 28 (Female) (LL) < 20 (LLL) > 60 (Male); > 55 (Female) (HH) > 65 (HHH)
Platelets (10^9/L)	< 75 (LL) < 50 (LLL) > 600 (HH) > 999 (HHH)
Leucocytes (10^9/L)	< 3.0 (LL) < 2.0 (LLL) > 20.0 (HH) > 100.0 (HHH)
Neutrophils (10^9/L)	< 1.5 (LL) < 1.0 (LLL)
Eosinophils (10^9/L)	> 5.0 (HH)
Eosinophils (%)	> 5% (HH)
Lymphocytes (10^9/L)	< 0.8 (LL) < 0.5 (LLL) > 4.0 (HH) > 20.0 (HHH)
Prothrombin INR	> 1.5 × ULN (HH) > 2.5 × ULN (HHH)
Reticulocyte (%)	> 2.5% (HH)
Blood chemistry	
ALT (U/L)	> 3 × ULN (HH) > 5 × ULN (HHH) > 10 × ULN (HHHH)
AST (U/L)	> 3 × ULN (HH) > 5 × ULN (HHH) > 10 × ULN (HHHH)
Alkaline phosphatase (U/L)	> 2.5 × ULN (HH) > 5 × ULN (HHH)

Laboratory parameter	**Criteria for marked laboratory abnormalities**
Total bilirubin (µmol/L)	> 2 × ULN (HH) > 5 × ULN (HHH)
Creatinine (µmol/L)	> 1.5 × ULN or > 1.5 × baseline if baseline > ULN (HH) > 3 × ULN or > 3 × baseline if baseline > ULN (HHH)
Albumin (g/L)	< 30 (LL) < 20 (LLL)
Calcium (mmol/L)	< 2.0 (LL) < 1.75 (LLL) > 2.9 (HH) > 3.1 (HHH)
Potassium (mmol/L)	< 3.2 (LL) < 3.0 (LLL) > 5.5 (HH) > 6.0 (HHH)
Sodium (mmol/L)	< 130 (LL) > 150 (HH) > 155 (HHH)
Chloride (mmol/L)	< 74 (LLL) > 131 (HH)
Creatine kinase (µg/L)	> 5 × ULN (HH) > 10 × ULN (HHH)
Gamma-glutamyl transferase (U/L)	> 2.5 × ULN (HH) > 5 × ULN (HHH)
Blood urea nitrogen (mmol/L)	> 2.5 × ULN (HH) > 5 × ULN (HHH)
Uric acid (µmol/L)	> 590 (HH) > 720 (HHH)
Glucose (mmol/L)	< 3 (LL) < 2.2 (LLL) > 8.9 (HH) > 13.9 (HHH)
TSH (mIU/L)	< 0.28 (LL) > 6.6 (HH)
Free T_3 (pmol/L)	< 2.8 (LL) > 7.8 (HH)
Total T_3 (nmol/L)	< 0.9 (LL) > 3.0 (HH)
Free T_4 (pmol/L)	< 7.2 (LL) > 30 (HH)

Laboratory parameter	Criteria for marked laboratory abnormalities
Total T_4 (nmol/L)	< 45 (LL) > 160 (HH)

ALT = alanine aminotransferase; AST = aspartate aminotransferase; INR = International Normalized Ratio; TSH = thyroid-stimulating hormone; T_3 = thyroxine; T_4 = triiodothyronine; ULN = upper limit of normal; WBC = white blood cell; LL, LLL, HH, HHH, HHHH = flags for low and high marked abnormalities.

Elevated liver parameters during double-blind treatment will be summarized: the number (%) of subjects meeting the criteria defined below within a given central laboratory sample will be tabulated by dose group. Percentages will be based on the number of subjects at risk: those not meeting the criterion at baseline (or having a missing baseline value) and having at least one post-baseline value for a given parameter and treatment period.

- Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 3 × upper limit of normal (ULN)
- AST or ALT > 5 × ULN
- AST or ALT > 10 × ULN
- TBIL > 1.5 × ULN and 2 × ULN
- Alkaline phosphatase > 1.5 × ULN
- (ALT or AST > 3 × ULN) and (TBIL > 2 × ULN)

All AST and ALT values for subjects with an AST or ALT > 3 × ULN will be listed.

10.3 Vital signs, weight and physical examination

Each summary and listing will include unscheduled assessments. Assessments from supine and sitting position will be presented together.

Absolute changes from baseline (mean of the first and second morning values after the PSG nights at V2, run-in period) to Days 1 and 2 (mean of the first and second morning values after the PSG treatment nights of each treatment period) in vital signs (systolic and diastolic blood pressure, pulse rate and body temperature) will be summarized. The absolute values at baseline and Days 1 and 2 will also be summarized.

The changes from baseline (V1 or last value before double-blind treatment) to V7 (or last value on or following double-blind study treatment) in body weight will be summarized as one group (i.e., All subjects).

Physical examination abnormalities will be listed.

10.4 Electrocardiograms

Unless noted otherwise, ECG summaries and listings will include unscheduled assessments.

The absolute change from baseline (V2, second morning) to the second morning of the PSG nights of each treatment period for ECG parameters (QTcF, QTcB, heart rate, PR, QRS) will be summarized. The absolute values will also be summarized. Only scheduled assessments will be considered for these summaries.

Marked ECG abnormalities are defined in Table 4 below. A marked ECG abnormality will be assigned to the dose group where it is present regardless of its presence in previous treatment periods.

The number (%) of subjects meeting the criteria of a marked ECG abnormality will be tabulated. Percentages will be based on the number of subjects at risk: those not meeting the criterion at baseline (or having a missing baseline value) and having at least one post-baseline value for a given parameter and treatment period.

All ECG values for subjects with at least one marked ECG abnormality will be listed.

Table 4 Marked abnormalities in ECG parameters

ECG parameter	Criteria for marked ECG abnormalities
QTcF, QTcB (ms)	> 450 and ≤ 480 (H) > 480 and ≤ 500 (HH) > 500 (HHH) > 30 and ≤ 60 increase from baseline (HH) > 60 increase from baseline (HHH)
HR (bpm)	< 45 (LLL) < 50 (LL) > 10 and ≤ 20 decrease from baseline (LL) > 20 decrease from baseline (LLL)
PR (ms)	> 200 (HH)
QRS (ms)	> 110 (HH)

HR = heart rate; QTcB = QT interval corrected according to Bazett's formula; QTcF = QT interval corrected according to Fridericia's formula. LL, LLL, H, HH, HHH = flags for low and high marked abnormalities.

10.5 Other safety parameters of interest

10.5.1 Digit Symbol Substitution Test

The Digit Symbol Substitution Test© (DSST) is a measure of attention, perceptual speed, motor speed, visual scanning and memory. The total DSST score is the number of correct symbols entered.

Absolute change from baseline (mean of the two PSG morning assessments at V2, run-in period) to Days 1 and 2 (mean of the two PSG morning assessments for a given treatment period) in total DSST score will be summarized by gender and overall. Absolute values will also be summarized.

10.5.2 Karolinska Sleepiness Scale

The Karolinska Sleepiness Scale (KSS) is 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'.

Absolute change from baseline (mean of the two PSG morning assessments at V2, run-in period) to Days 1 and 2 (mean of the two PSG morning assessments for a given treatment period) in KSS will be summarized by gender and overall. Absolute values will also be summarized.

10.5.3 Sheehan Disability Scale

Sheehan Disability Scale© (SDS) consists of three questions on impairment of work, social life, and family life/home responsibilities each on a 10-point scale. The three items will be summed into a single dimensional measure of global functional impairment that ranges from 0 (unimpaired) to 30 (highly impaired).

Absolute change from baseline (mean of the two PSG morning assessments at V2, run-in period) to Days 1 and 2 (mean of the two PSG morning assessments for a given treatment period) in SDS will be summarized by gender and overall. Absolute values will also be summarized.

10.5.4 Neurological Examination

The number (%) of subjects answering 'Yes' to the question 'Is excessive sleepiness observed one hour after lights on?' on the 'Neurological Examinations' page will be tabulated for each scheduled PSG morning by dose group (including single-blind placebo) by gender and overall.

The time from treatment until the subject is considered safe to leave the center the next day will be summarized for each scheduled PSG morning by dose group (including single-blind placebo) by gender and overall.

10.5.5 Columbia Suicide Severity Rating Scale

The Columbia Suicide Severity Rating Scale© (C-SSRS) is an instrument that evaluates suicidal ideation and behaviors.

The C-SSRS outcome categories are provided below. Each category has a binary response (yes/no) and are numbered and ordered below for convenience.

1 – Wish to be Dead
2 – Non-specific Active Suicidal Thoughts
3 – Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act
4 – Active Suicidal Ideation with Some Intent to Act, without Specific Plan
5 – Active Suicidal Ideation with Specific Plan and Intent
6 – Preparatory Acts or Behavior
7 – Aborted Attempt

8 – Interrupted Attempt
9 – Actual Attempt (non-fatal)
10 – Completed Suicide

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

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

Number (%) of subjects with suicidal ideation, suicidal behavior, and/or self-injurious behavior without suicidal intent based on the C-SSRS during double-blind treatment will be tabulated. Percentages will be based on the number of subjects with at least one post-baseline C-SSRS assessment.

Shifts from baseline showing any changes in suicidal ideation and suicidal behavior in each treatment period will also be provided. Subjects will be summarized under the worst of the following three categories, shown here in the order from best to worst: 1) No suicidal ideation or behavior, 2) Suicidal ideation only, and 3) Suicidal ideation and behavior. Suicidal ideation includes any one of the five suicidal ideation events (categories 1–5). Suicidal behavior includes any one of the five suicidal behavior events (categories 6–10).

10.6 Pharmacokinetic

PK analyses will be performed based on the PK set.

Descriptive statistics (n, mean, standard deviation, CV%, m [number of non-zero concentrations], geometric mean, geometric standard deviation, geometric CV%, median, minimum and maximum) of ACT-541468 plasma concentration collected approximately 9–10 h post-dose in each treatment period (excluding double-blind placebo) will be provided for each time point (morning after the first and second PSG nights), by gender and overall. Note that the protocol recommends to draw a PK sample in the morning after the first PSG night only in subjects where excessive sleepiness is observed (according to investigator opinion) one hour after lights on.

Concentration values below the lower limit of quantification (< 1.0 ng/mL) will be displayed in listings as zero with a flag and handled as zero in the calculations for mean, CV%, standard deviation, median, minimum, and maximum, but handled as missing for the calculation of the geometric mean, geometric standard deviation and geometric CV%.

All individual ACT-541468 plasma concentration data will be listed.

10.7 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 in each treatment period [excluding

double-blind placebo]) and will be based on the PK set. Safety parameters considered for this analysis will include selected AEs (e.g., somnolence and/or excessive sleepiness), changes from baseline in DSST, KSS, SDS, and morning sleepiness (VAS for 'the way you feel this morning'). $C_{9\text{-}10h}$ will be assessed against each safety parameter using graphical presentations.

11 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 a 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 independent statistical analysis center for the unblinded part.

12 CHANGES OR CLARIFICATIONS TO ANALYSES PLANNED IN THE STUDY PROTOCOL

12.1 Changes to the analyses planned in the study protocol

Analyses of secondary and exploratory efficacy endpoints will be based on the FAS (a broader analysis set) instead of the modified FAS which is linked only to the primary endpoint by requiring at least one WASO assessment at baseline and one at Days 1 and 2 of any given treatment period.

12.2 Changes in the conduct of the study / data collection

Not applicable.

12.3 Clarifications concerning endpoint definitions and related variables or statistical methods

Not applicable.

13 GENERAL DEFINITIONS AND DERIVATIONS

13.1 Treatment start and end dates

Double-blind study treatment start and end dates are the earliest and latest dates, respectively, of dose intake recorded on the 'Study Double-blind Treatment Log' page.

Run-in single-blind placebo treatment start date (i.e., the start date of the single-blind placebo treatment period), is the earliest date of dose intake (i.e., date of capsules administered) recorded on the 'Study Single Blind Treatment Dispensing & Accountability' page at V2.

Treatment period 1 start date is the earliest date of dose intake (i.e., date of capsules administered) recorded for Visit 3 on the 'Study Double Blind Treatment Dispensing & Accountability' page.

Treatment period 2 start date is the earliest date of dose intake (i.e., date of capsules administered) recorded for Visit 4 on the 'Study Double Blind Treatment Dispensing & Accountability' page.

Treatment period 3 start date is the earliest date of dose intake (i.e., date of capsules administered) recorded for Visit 5 on the 'Study Double Blind Treatment Dispensing & Accountability' page.

Treatment period 4 start date is the earliest date of dose intake (i.e., date of capsules administered) recorded for Visit 6 on the 'Study Double Blind Treatment Dispensing & Accountability' page.

Treatment period 5 start date is the earliest date of dose intake (i.e,. date of capsules administered) recorded for Visit 7 on the 'Study Double Blind Treatment Dispensing & Accountability' page.

13.2 Treatment period

A treatment period is defined as the time from the start of the treatment period [see Section 13.1] until the start of the next treatment period. The end of the last treatment period (e.g., the fifth treatment period or an earlier treatment period if subject prematurely discontinued) is the date of first safety follow-up telephone call, or 12 days after the last study treatment intake, whichever is earlier.

After the single-blind placebo treatment period, subjects are to receive one of 5 study treatments in each of the 5 double-blind treatment periods in order of the sequence they are randomized to.

These treatment periods are used to assign assessments/events to dose groups (including single-blind placebo).

13.3 Study day

The study day for an assessment or event will be calculated using the start date of double-blind study treatment as reference.

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

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

The first day of double-blind study treatment is study day 1.

For all assessment/events occurring prior to the start date of double-blind study treatment, study day will be negative and will be calculated as:

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

Study day will be displayed in the data listings.

13.4 Baseline

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

Subjects with no data on a particular parameter before the first treatment administration will have a missing baseline (and change from baseline) for this parameter.

13.5 Absolute change from baseline

The absolute change from baseline is defined as post-baseline value minus baseline value. A positive number indicates an increase as compared to baseline.

13.6 Handling of data when total sleep time is zero

If the TST is recorded as zero (i.e., subject did not fall asleep during the night), then:

- WASO and number of awakenings (NAW) is set as missing since subject is never at risk of either, and
- LPS is set as 480 minutes which is equal to the duration of time in bed (TIB).

If the sTST is recorded as zero, then similarly:

- sWASO and subjective NAW (sNAW) is set as missing,
- sLSO is set as 480 minutes.

13.7 Handling of missing/incomplete date and time fields

This section describes some general principles to be followed in the case of missing or incomplete date/time.

Missing or incomplete dates are handled as follows:

- Dates are split into 3 parts: year, month and day. Year is the top-level, month is medium level and day is low level. If a part that is expected to contain a number is numeric but the value is outside a valid range, the complete date is handled as missing. For example, if date = 44Nov2000 the whole date is considered to be missing.
- If a part that is expected to contain a number is not numeric, i.e., contains values such as ND, NA, --, ??, 2?, that part is considered to be missing.

- If a part is missing, all lower level parts are considered to be missing. This means that a ddmmyy date '21ND99' is considered as '----99'.
- If year is missing, then whole date is considered to be missing, unless reasonable assumptions support an imputation (imputation rule and rationale for assumption will be provided).

Imputation of missing or incomplete dates/times are further specified in the associated analysis section. Unless noted otherwise, the non-imputed date/time will be reported in listings.

14 REFERENCES

[Bastien 2001] Bastien C, Vallieres A, Morin C. Validation of the Insomnia Severity Index as an outcome measure for insomnia research. Sleep Med. 2001;2:297-307.

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

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

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

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

DOCUMENT HISTORY

Version	Effective Date	Reason
Final 1.0	10 May 2017	Initial release
Final 2.0	12 July 2017	Comments from dry-run review