Cover page

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

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ACT-541468

STATISTICAL ANALYSIS PLAN

FOR CLINICAL STUDY REPORT

ID-078A303

Version 3

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

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Revision history

Version date	Version	Implemented change(s)
9 May 2019	1.0	Initial version
31 March 2020	2.0	• Section 2: Added interim analysis in the design. • Section 4.1.3: Clarified definition of treatment received. • Section 5.3.1: Included a summary based on the FAS. • Section 5.3.4: Clarified which ATC classification level will be presented. • Section 5.4.1: Updated summarized categories for the combined duration of double-blind study treatment. Added clarifications for the calculation of study treatment duration at the time of an interim analysis. • Section 5.4.2: Added a condition for the calculation of the total duration of treatment interruptions. • Updated calculation of treatment compliance if wallet not returned. eCRF collected compliance will not be listed. Added clarifications for the calculation of study treatment duration and total duration of treatment interruptions at the time of an interim analysis. Included categories for number of treatment interruptions. • Section 6.1: Added measurement for ISI© Total score. Added empirical cumulative distribution function plots and subgroup analyses for some efficacy endpoints. • Section 7: Clarified handling of EOT safety assessments in the event of premature study treatment discontinuation. • Section 7.2: Updated the definition of the reporting period for TEAE and added the summary of cases sent for ISB adjudication. • Section 7.4: Updated definition of subjects at risk of having a marked ECG abnormality for criteria based on change from baseline and clarified how

		subjects will be counted. Added a sorting rules for ECG summaries. • Section 7.7: Updated the endpoints used to assess the potential of rebound insomnia. • Section 7.9: Added clarification for C-SSRS© analyses. Added a condition for the assignment of the assessments to a study period scheduled visit. • Section 7.10: Added clarification for analysis ESS© total score > 16. • Section 7.11: Added subgroups analyses for safety. • Section 10: Added interim analysis description. • Section11.2: Added a clarification and a condition for the double-blind study period definition. • Section 11.4: Clarified definition of baseline. • Section 11.7: New time window definition for PGA-S and PGI-C endpoints. • Section 12: Updated as previously mentioned changes are now included in the protocol amendment. • Section 14: Updated SAS® code
20 July 2020	• 3.0	• Section 5.1.2: Added report of ongoing subjects at the time of interim analysis and added a summary to present disposition by visit of subjects in the double-blind study period at the cut-off. • Section 5.1.3: Added a Kaplan-Meir plot to summarize time from first dose of double-blind treatment to treatment discontinuation. • Section 5.2: Added summary for all PDs and important PDs related to COVID-19. • Section 5.4.1: Added a Kaplan-Meir plot to summarize time from treatment to study discontinuation. • Section 5.4.2: Added a condition for the calculation of the total duration of treatment interruptions. • Section 11.2: Added a condition to the double-blind study period definition and to the treatment withdrawal period definition.

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LIST OF ABBREVIATIONS AND ACRONYMS

ADaM	Analysis Data Model
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BMI	Body mass index
bpm	Beats per minute
BWSQ	Benzodiazepine Withdrawal Symptom Questionnaire
CI	Confidence interval
COVID-19	Coronavirus disease 2019
CSR	Clinical study report
C-SSRS©	Columbia Suicide Severity Rating Scale©
ECG	Electrocardiogram/graphy
eCRF	Electronic case report form
ENR	Enrolled
EODBT	End-of-double-blind treatment
EOS	End-of-Study
EOT	End-of-Treatment
ESS©	Epworth Sleepiness Scale©
FAS	Full Analysis Set
FDA	Food and Drug Administration
HR	Heart rate
IDMC	Independent Data Monitoring Committee
IDSIQ	Insomnia Daytime Symptoms and Impacts Questionnaire
ISAC	Independent Statistical Analysis Center
ISB	Independent Safety Board
ISI©	Insomnia Severity Index©
LS	Least squares
MedDRA	Medical Dictionary for Regulatory Activities
NDA	New Drug Application
PD	Protocol deviation

PGA-S	Patient Global Assessment of Disease Severity
PGI-C	Patient Global Impression of Change
PSG	Polysomnography
PT	Preferred term
SAE	Serious adverse event
SAP	Statistical analysis plan
SDS©	Sheehan Disability Scale©
SDTM	Study Data Tabulation Model
SI unit	International System of Units
sLSO	Subjective latency to sleep onset
SOC	System organ class
SS	Safety Set
sTST	Subjective total sleep time
sWASO	Subjective wake after sleep onset
TBIL	Total bilirubin
TEAE	Treatment-emergent adverse event
TWS	Treatment Withdrawal Set
ULN	Upper limit of normal
VAS	Visual analog scale(s)
WHO	World Health Organization

1 INTRODUCTION

This SAP describes in detail the analyses and data presentation for the CSR for protocol ID-078A303. This study is a double-blind, joint extension study of each confirmatory study, i.e., ID-078A301 and ID-078A302. In the following text, the term "confirmatory study" (singular) will represent each of these studies (ID-078A301 and ID-078A302).

Obvious corrections to address minor formatting errors or spelling mistakes may be performed at the time of analysis without amending this document or other related documents (e.g., mock shells).

Data will be analyzed by Idorsia and/or designated Contract Research Organizations supervised by Idorsia using the SAS® version 9.4 or higher and R version 3.4.3 or higher.

The analyses for the IDMC closed session meetings will be performed by an ISAC and are detailed in a separate SAP.

Protocol ID-078A303, Final Version 3, dated 17 February 2020 was used as the basis at the time of writing this SAP.

Unless noted otherwise, summaries will be produced by treatment group as described in Section 9.1.

Only data collected on this extension study (ID-078A303) will be reported, however, some baseline data and subject characteristics data from the confirmatory study will be used.

2 STUDY DESIGN AND FLOW

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

The ID-078A303 study will be offered at every site participating in ID-078A301 and ID-078A302 (approximately 150 centers in 17 countries), and to every eligible subject.

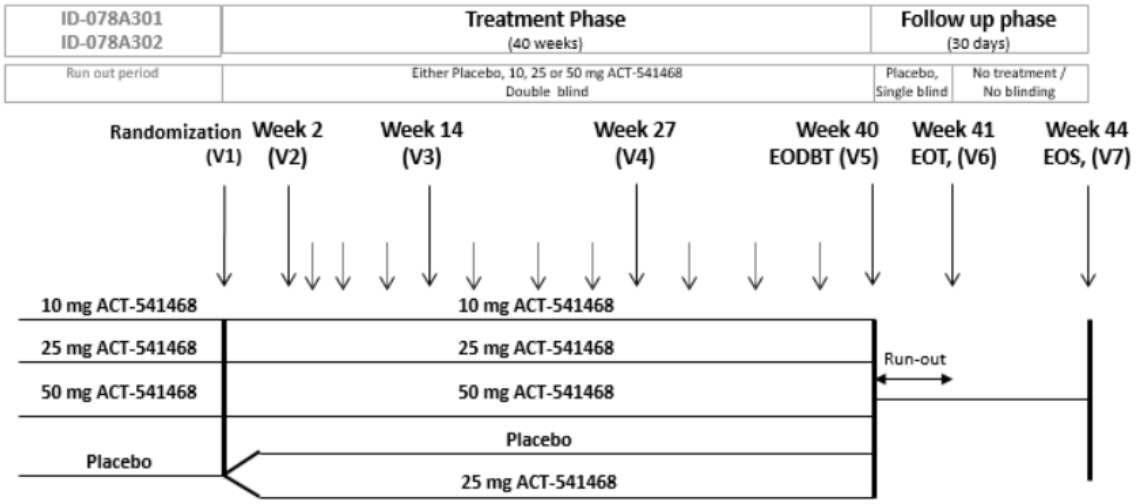
Subjects assigned to the placebo arm in the confirmatory study will be randomized to receive either placebo or 25 mg ACT-541468 in a 1:1 ratio in the extension study. Treatment allocation will be stratified by age into 2 categories: < 65 and ≥ 65 years (the age entered at the screening visit of the confirmatory study will be taken into consideration for the randomization in the extension study).

Subjects assigned to one of the ACT-541468 arms in the confirmatory study will continue on the same dose (but assigned a new randomization number).

It was expected that approximately 1260 subjects (i.e., ~70% of the total subjects in the combined confirmatory studies) would enter the extension study after completing the

confirmatory study. The overall study design, including the transition from the confirmatory study, is depicted in Figure 1.

Figure 1 Study design



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

The study comprises 2 phases:

- The **double-blind treatment phase** starts when the treatment is allocated (Visit 1) and lasts 40 weeks, until the EODBT at Visit 5.
- The **safety follow-up phase** starts from the EODBT and ends 30 days after the last dose of double-blind study treatment with the EOS at Visit 7. It consists of the following two periods:
  - A single-blind placebo run-out period of 7 days (from the evening of Visit 5 until after all visit assessments have been performed at Visit 6 i.e., EOT).
  - A safety follow-up period (from EOT until EOS).

See Section 11.2 for a detailed definition of study periods.

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

Subjects treated with placebo during the confirmatory studies and randomized to ACT-541468 25 mg are excluded from the conditions mentioned above as they will not all display 6-month data, those in the extension study will only display 3-months.

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

3 OBJECTIVES

3.1 Primary objective

The primary objective of this extension study is to assess the long-term safety (including withdrawal symptoms and rebound insomnia) and tolerability of 10, 25 and 50 mg ACT-541468.

3.2 Exploratory objective

The exploratory objective is to evaluate the efficacy of 10 mg, 25 mg and 50 mg ACT-541468 on subjective sleep parameters (using an ad hoc sleep diary) and next-day functioning (using the dedicated IDSIQ) in subjects with insomnia disorder during long-term treatment.

4 ANALYSIS SETS

4.1 Definitions of analysis sets

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

The number of subjects in each analysis set defined below will be tabulated.

4.1.1 Enrolled Set

The ENR Set includes all subjects who have a subject identification number. Subject identification numbers assigned in the confirmatory studies will be identical in the extension study.

Summaries based on the ENR Set will be presented as one group (i.e., all subjects), unless specified otherwise.

For summaries by treatment group, subjects will be evaluated according to the treatment they have been assigned.

4.1.2 Full Analysis Set

The FAS includes all subjects assigned (i.e., randomized) to a study treatment.

In order to adhere to the intention-to-treat principle as much as possible:

- Subjects will be evaluated according to the study treatment and strata they have been assigned to in the extension study.
- All available data will be included.

4.1.3 Safety Set

The SS includes all subjects who received at least one dose of study treatment.

Subjects will be evaluated according to the actual treatment they received in the extension study, which may differ from the randomly assigned treatment.

Actual treatment received is defined as:

- the assigned double-blind study treatment of this study when received at least once,
- the first double-blind study treatment received in this study if the assigned double-blind study treatment of this study was never received.

The data of any subjects who received a kit/treatment that was not assigned to them will be reviewed in detail and the impact to any statistical analyses will be discussed in the clinical study report.

4.1.4 Treatment Withdrawal Set

The TWS comprises all subjects included in the SS who received at least one dose of single-blind placebo treatment in the run-out period.

Subjects will be evaluated according to the actual treatment they received as defined in Section 4.1.3.

Any subject excluded because he/she did not receive at least one dose of single-blind placebo during the run-out period will be summarized and listed.

4.2 Usage of the analysis sets

The ENR Set will be used for subject disposition and demographic summaries.

The analyses of efficacy endpoints, as well as baseline disease characteristics, will be performed using the FAS.

The SS will be used for the analysis of safety endpoints, concomitant medications and study treatment exposure.

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

5 STUDY SUBJECTS VARIABLES AND ANALYSES

5.1 Subject disposition

5.1.1 Subject not randomized

Subjects who discontinued before randomization will be summarized based on the ENR Set and will include:

- Number and percentage of subjects not randomized (based on 'Was the subject randomized?' recorded as 'No' in the 'Randomization' page).
- Primary reason for not being randomized (based on reason for not randomized entered on the 'Randomization' page).

All reasons for a subject not being randomized will be listed using the ENR Set.

5.1.2 Study disposition

Study disposition will be summarized based on the ENR Set, presented by randomized treatment group and all enrolled subjects combined, and will include:

- Number of subjects enrolled.
- Number and percentage of subjects randomized (based on non-missing randomization number).
- Number and percentage of subjects treated in the double-blind study period (based on non-missing 'Treatment start date' in the 'Study Double-Blind Treatment Log' page).
- Number and percentage of subjects who completed the double-blind study period (based on 'Reason for treatment stop' entered as 'Completion as per protocol' in the 'Study Double-Blind Treatment Log' page).
- At the time of interim analysis: number and percentage of subjects ongoing in double-blind treatment at cut-off.
- Number and percentage of subjects treated in the single-blind placebo treatment run-out period (based on a non-missing 'Treatment start date' in the 'Study Single-Blind [Run-Out] Treatment Log' page).
- Number and percentage of subjects who completed the single-blind placebo treatment run-out period (based on 'Reason for treatment stop' entered as 'Completion as per protocol' in the 'Study Single-Blind [Run-Out] Treatment Log' page).
- At the time of interim analysis: number and percentage of subjects ongoing in single-blind run-out treatment at cut-off.
- Number and percentage of subjects who completed the study (based on 'Did the subject complete the study?' recorded as 'Yes' in the 'End of Study Status' page).

- At the time of interim analysis: number and percentage of subjects ongoing in the study treatment at cut-off.

At the time of interim analysis, study disposition by visit of subjects in the double-blind study period at cut-off will be summarized based on FAS presented by randomized treatment group and all treatment groups combined, and will include:

- Number and percentage of subjects randomized.
- Number and percentage of subjects ongoing between randomization and Week 14 (Visit 3) and discontinued study between randomization and Week 14 (Visit 3).
- Number and percentage of subjects who completed Week 14 (Visit 3).
- Number and percentage of subjects ongoing between Week 14 (Visit 3) and Week 27 (Visit 4) and discontinued study between Week 14 (Visit 3) and Week 27 (Visit 4).
- Number and percentage of subjects who completed Week 27 (Visit 4).
- Number and percentage of subjects ongoing between Week 27 (Visit 4) and Week 40 (Visit 5) and discontinued study between Week 27 (Visit 4) and Week 40 (Visit 5).
- Number and percentage of subjects who completed Week 40 (Visit 5).

5.1.3 Study and study treatment completion/discontinuation

The following summary will be based on the FAS and presented by treatment group and all treatment groups combined:

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

All reasons for premature double-blind study treatment discontinuation will be listed based on the FAS.

The following summary will be based on the FAS and presented by treatment group and all treatment groups combined:

- Number and percentage of subjects who prematurely discontinued from the study (based on non-missing reason for stopping study entered in the 'End-of-Study Status' page).
- Primary reason for premature discontinuation from the study (based on reason for stopping study entered in the 'End-of-Study Status' page).

All reasons for premature study discontinuation will be listed based on the FAS.

The following summary will be based on the FAS and presented by treatment group and all treatment groups combined:

- Number and percentage of subjects who prematurely discontinued single-blind placebo treatment in the run-out period (based on reason for treatment stop entered as 'Discontinuation' in the 'Study Single-Blind [Run-Out] Treatment Log' page).
- Primary reason for premature single-blind placebo treatment discontinuation in the run-out period (based on reason for treatment discontinuation entered on the 'Study Single-Blind [Run-Out] Treatment Log' page).

All reasons for premature single-blind placebo treatment discontinuation in the run-out period will be listed based on the FAS.

Time from randomization to study discontinuation will be summarized by treatment group using Kaplan-Meier plots in the FAS. For subjects who do not complete the study at the time of the interim analysis, time to study discontinuation will be censored at the cut-off date.

5.1.4 Study enrollment

The number and percentage of subjects enrolled as well as subjects enrolled but not randomized will be displayed by country and site based on the ENR Set.

The number and percentage of subjects randomized will be displayed by country and site based on the FAS by treatment group and all treatment groups combined.

The randomization scheme and codes will be listed for randomized subjects only using the FAS.

5.2 Protocol deviations

The FAS will be used for the summary of PDs.

All PDs and important PDs will be summarized in separate tables as per pre-specified category (i.e., selection criteria, IMP, study conduct/procedure, forbidden medication, withdrawal criteria and other) by treatment group and all treatment groups combined. In addition, the same summary of all PDs and important PDs will only be provided separately for PDs related to COVID-19.

A subject may have more than one protocol deviation in a given category, but the subject will be counted only once per protocol deviation category.

A listing of PDs will be provided using the FAS. PDs related to COVID-19 will be flagged in the listing.

5.3 Subject characteristics

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

Summary tables will be produced by treatment group and all treatment groups combined. Data will be presented individually by subject in the listings.

5.3.1 Demographics and baseline characteristics

Demographic data at screening of the respective confirmatory study (ID-078A301 or ID-078A302) including age, sex, race, ethnicity, height, weight, BMI and region (US, other) will be summarized and listed using the ENR Set and using the FAS.

The number and percentage of subjects randomized in each age category (< 18, 18 – < 65, 65 – < 75, 75 – < 85, 65 – < 85, ≥ 85 years at screening of confirmatory study), in each BMI category (< 25, 25–30, > 30 kg/m^2 at screening of confirmatory study), and in each region (US, other) will be further summarized using the ENR Set and using the FAS.

The number of subjects treated in each age category (< 18, 18 – < 65, 65 – < 85 and ≥ 85 years at screening of confirmatory study) by sex will be summarized based on the SS.

5.3.2 Baseline disease characteristics

Baseline disease characteristics will come from baseline disease characteristics of the confirmatory study and include: dissatisfaction with sleep quantity or quality (Y/N), difficulty initiating sleep (Y/N), difficulty maintaining sleep characterized by frequent awakenings or problems returning to sleep after awakenings (Y/N), early morning awakening with inability to return to sleep (Y/N) and sleep disturbance causing significant distress or impairment in social, occupational, educational, academic, behavioral, or other important areas of functioning (Y/N).

These baseline disease characteristics, including the time since insomnia diagnosis (in years) at randomization of ID-078A301 or ID-078A302, will be listed and summarized.

An incomplete (day or month missing) or missing insomnia diagnosis date will be imputed using the 15th day of the month (in case only the day is missing) or 1 July (in case day and month are missing).

In the event that the insomnia diagnosis imputed date is after the randomization date of the confirmatory study, then the randomization date of the confirmatory study –1 day will be used as insomnia diagnosis date.

5.3.3 Previous and concomitant diseases

Relevant medical history and current medical conditions will come from the respective confirmatory study (ID-078A301 or ID-078A302) and are coded using MedDRA terminology.

Any disease or diagnosis is defined as previous if 'Ongoing at informed consent signed' is answered as 'No' in the eCRF of confirmatory studies or extension study.

Medical history at screening of the confirmatory study (i.e., those procedures or diagnoses reported at screening of the respective confirmatory study or those recorded as 'not ongoing' in the eCRF at the signing of the informed consent of the extension study) and current medical conditions (i.e., those conditions recorded as 'ongoing' in the eCRF at the signing of the informed consent of the extension study), excluding insomnia-related conditions and symptoms, will be summarized separately and listed.

Summaries will be presented for each treatment group by primary SOC and PT.

Medical history will be sorted by SOC and PT within each SOC by descending frequency based on all treatment groups combined.

The MedDRA version used for reporting will be specified in the footnote of the applicable output.

5.3.4 Concomitant therapy

Therapies collected will be coded using the WHO Drug Global reference dictionary that employs the WHO ATC classification system. The WHO Drug Global version used for reporting will be specified in the footnote of the applicable output.

Study concomitant therapies are any treatments that are either ongoing at the date the informed consent of the extension study was signed or initiated during the time from the date the informed consent of the extension study was signed up to EOS. 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 'Concomitant Medication' page.

Double-blind study treatment concomitant therapies (a subset of study-concomitant therapies) are any treatments that are either ongoing at the start of double-blind study treatment or initiated during the double-blind study period until 1 day after the last dose of double-blind study treatment.

The number and percentage of subjects having taken at least one concomitant therapy will be summarized by ATC classification level 4 (or next highest available level) and individual preferred name within each ATC classification based on the SS.

Concomitant therapy will be sorted by ATC class and preferred name within each ATC class by descending frequency based on all treatment groups combined.

Summary tables will be provided for study concomitant and double-blind study treatment-concomitant therapies separately. An additional summary table will be provided for double-blind study treatment concomitant therapies at baseline (i.e., therapy started on, or is ongoing at the double-blind study treatment start date). All concomitant therapies will be listed using the SS. The period (double-blind, run-out, Section 11.2) for which the concomitant therapy started will be displayed in the listing and those related to an adverse event (AE) will be flagged.

An incomplete (day or month missing) or missing concomitant therapy date will be imputed as described in Table 1. The 'lower limit' and 'upper limit' refer to the earliest and latest possible dates, respectively. As an example: if concomitant therapy start date is MAR2017 (day missing), the lower limit is 01MAR2017 and the upper limit is 31MAR2017; if concomitant therapy start date is 2017 (day and month missing), the lower limit is 01JAN2017 and the upper limit is 31DEC2017.

Table 1 Imputation rules for an incomplete or missing concomitant therapy date

Field	Incomplete date	Missing date
Concomitant therapy end date	The upper limit.	No imputation; the therapy is considered as ongoing.
Concomitant therapy start date	The rules below apply in the order presented: 1. For concomitant therapy reported as ongoing from the confirmatory study, the lower limit is used. 2. If the (imputed) concomitant therapy end date is on or after the start of double-blind study treatment, and if the double-blind study treatment start falls within the upper and lower limits (inclusive), the double-blind study treatment start date is used. 3. If the concomitant therapy resolution date is missing, and if the double-blind study treatment start falls within the upper and lower limits (inclusive), the double-blind study treatment start date is used. 4. In all the other cases, the lower limit is used.	Whichever is the earlier of the concomitant therapy end date or double-blind study treatment start date*.

* If a concomitant therapy is reported as ongoing (from confirmatory study) and if the onset date is missing then the double-blind study start date of the confirmatory study is used.

The purpose of imputing concomitant therapy dates is only to assign a concomitant therapy to a specific treatment phase for the summary tables and listings. However, only the actual dates as reported in the eCRF will be listed. No imputed date is considered in the medical evaluation of a concomitant therapy or an individual AE.

5.4 Study treatment exposure and compliance

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

5.4.1 Study treatment exposure

The duration of double-blind study treatment, and single-blind placebo run-out treatment (including categories: ≤ 4, > 4–8, > 8–12, > 12–16, > 16–20, > 20–24, > 24–28, > 28–32, > 32–36, > 36–40, > 40 weeks for double-blind study treatment; and 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, ≥ 10 days for single-blind placebo run-out treatment) and duration of double-blind study treatment in subject-years will be summarized for the extension study. The definition of a year is 365.25 days.

The duration of treatment (in days) is defined as the difference between the respective (double-blind/run-out) treatment end date and the respective (double-blind/run-out) treatment start date plus one day. This calculation ignores periods of treatment interruption. Summary for run-out will be based on the TWS.

Additionally, the duration of double-blind study treatment in the confirmatory and extension study is calculated as double-blind study treatment end date of the extension study – double-blind study treatment start date of the confirmatory study + 1 day (including categories: ≤ 12, > 12–16, > 16–20, > 20–24, > 24–28, > 28–32, > 32–36, > 36–40, > 40–44, > 44–48, > 48–52, > 52 weeks for double-blind study treatment in the confirmatory and extension study) and duration in subject-years will be summarized. Interruptions between studies including the run-out period will be ignored. This analysis excludes the subjects who switched from placebo to 25 mg.

The calculation of study treatment duration at the time of an interim analysis will be slightly modified: for subjects who are still on study treatment at the interim cut-off date, this date will be used instead of the double-blind study treatment end date of the extension study. This also means that subjects who complete study treatment after the interim cut-off date will be considered as ‘study treatment ongoing ‘ for the interim report.

Time from first dose of double-blind treatment to treatment discontinuation will be summarized using Kaplan-Meier plots in the SS. For subjects who did not complete the treatment at the time of the interim analysis, time to treatment discontinuation will be censored at the cut-off date.

The duration of treatment along with reason for treatment stop will be listed.

5.4.2 Study treatment compliance

Study treatment compliance will be assessed through study treatment accountability.

The following formula will be used to calculate compliance for both the double-blind study period and the run-out period:

Study treatment compliance (%) = ([number of tablets dispensed – number of tablets returned*] / [treatment duration – total duration of treatment interruptions]) × 100

* If a subject did not return his/her wallet (e.g., the wallet is lost), the study treatment compliance will not be calculated and the compliance for the period will be set to missing.

Treatment duration and total duration of treatment interruptions in the double-blind or run-out period are calculated using the dedicated eCRF page 'Study Treatment Log' as follows:

- Treatment duration (days) = date of last drug intake of double-blind study treatment (run-out single-blind placebo treatment) – date of first drug intake of double-blind study treatment (run-out single-blind placebo treatment) + 1 day.
- Total duration of treatment interruptions (days) is the sum of all treatment interruption durations. A treatment interruption duration = date restarted double-blind study treatment (run-out single-blind placebo treatment) – end date of double-blind study treatment (run-out single-blind placebo treatment) due to an interruption −1 day. For example, a subject stopped his treatment on 19MAR2019 and started again on 23MAR2019, as the treatment is taken on the start and end date the calculation will be 23MAR2019–19MAR2019 – 1 day = 3 days of interruption. Should the subject interrupt the treatment again for 7 days, the total duration of interruptions will be 10 days. In case of a treatment interruption duration of 0 days, the interruption will be counted but the duration of 0 days will not be included in the summary for the duration of treatment interruption. For subjects who complete the study treatment for a given study period but end on an interruption before continuing study treatment in the next study period, the start date of the next study period is used as the date of restarted study treatment of the given study period. E.g., if a subject completed double-blind study treatment with an interruption on 23JUN2019 and then started the treatment withdrawal period on 26JUN2019, the duration of that treatment interruption will be (26JUN2019 – 23JUN2019) – 1 day = 2 days.

The calculation of study treatment duration and total duration of treatment interruptions at the time of an interim analysis will be slightly modified: for subjects who are still on study treatment at the interim cut-off date, this date will be used instead of the last drug intake of double-blind study treatment (run-out single-blind placebo treatment). For subjects who have an ongoing treatment interruption at the interim cut-off date, the interim cut-off date will be used instead of the date restarted double-blind study treatment (run-out single-blind placebo treatment). Subjects who complete study treatment after the interim cut-off date will be considered as 'study treatment ongoing' for the interim report.

The percentage of days treated is defined as follows:

- Percentage of days treated: 100 × (treatment duration – total duration of treatment interruptions)/treatment duration.

Study treatment compliance (including categories 0%, > 0% – < 50%, 50% – < 70%, 70% – < 80%, 80% – < 90%, 90% – < 100%, 100%, > 100%), number of treatment interruptions per subject by category (0, 1, 2, 3, 4, > 4 interruptions), duration of treatment interruptions and percentage of days treated (including categories 0%, > 0% – < 50%, 50% – < 70%,

70% – < 80%, 80% – < 90%, 90% – < 100%, 100%) will be summarized for the double-blind and run-out period, separately. The summaries of the run-out period will be based on the TWS.

The number and percentage of subjects who have treatment interruptions, and the corresponding reasons will be tabulated.

Study treatment compliance, dispensing and accountability data will be listed.

6 EFFICACY VARIABLES AND ANALYSES

Unless noted otherwise, the analyses of efficacy endpoints will be performed using the FAS. Efficacy data described below will be listed using the FAS.

6.1 Analysis of exploratory efficacy variables

The exploratory efficacy endpoints are measured on subject questionnaires and defined as:

- Change from baseline[a] over time[b] in sTST.
- Change from baseline[a] over time[b] in sLSO.
- Change from baseline[a] over time[b] in sWASO.
- Change from baseline[a] over time[b] in IDSIQ scores (i.e., total score; alert/cognition, mood and sleepiness domain scores).
- Change from baseline[a] over time[b] in the following visual analog scale (VAS) scores collected in the sleep diary: quality of the sleep, depth of the sleep, daytime alertness and daytime ability to function.
- Change from baseline (baseline as defined in Section 11.4) to Visit 3 (Week 14), Visit 4 (Week 27) and Visit 5 (Week 40) in ISI© scores.
  - The number and percentage of subjects with ≥ 6 points decrease in ISI© total score from baseline to Visit 3 (Week 14), Visit 4 (Week 27) and Visit 5 (Week 40) will be tabulated.
- Change from baseline[a] over time[b] in number of self-reported awakenings.
- Change from baseline (baseline as defined in Section 11.4) over time in PGA-S scores (daytime symptoms).
- Change from baseline (baseline as defined in Section 11.4) over time in PGI-C scores (daytime symptoms).

[a] For subjects randomized to placebo in ID-078A301 or ID-078A302 and who are randomized to 25 mg ACT-541468 in this extension study, baseline is the mean value based on the last sleep diary / IDSIQ entries performed at home during a 7-day window (excluding any polysomnography [PSG] nights) in the confirmatory study. For all other subjects, baseline is the mean value based on the screening sleep diary / IDSIQ entries performed at home in the 7 days immediately preceding the first PSG at Visit 3 of the confirmatory studies.

[b] Over time is the mean value of each time point defined in Table 6 (except for run-out week) based on the sleep diary / IDSIQ entries. According to the protocol it is planned to be completed at home daily during the last week of each consecutive 4-week double-blind study treatment period.

sTST (in minutes) is based on the time reported by the subject in item 9 of the sleep diary i.e., the answer to the question "In total, how long did you sleep last night?".

sLSO (in minutes) is the self-reported time to fall asleep as reported in item 5 of the sleep diary, i.e., the answer to the question "How long did it take you to fall asleep?".

sWASO is the self-reported time spent awake after sleep onset as reported in item 7 of the sleep diary, i.e., the answer to the question "In total, how long did these awakenings last?".

The morning VAS consists of three questions: quality of subjects' sleep, depth of sleep and sleepiness in the morning. The evening VAS consists of two questions: daytime alertness and ability to function. The VAS scores are collected in the sleep diary and answered on a continuous bipolar (or unipolar for sleepiness in the morning) scale ranging from 0–100 points; for all questions, a higher score reflects a better outcome.

The IDSIQ has 3 domains assessing Alert/Cognition, Mood, and Sleepiness [Table 2]. A total score can also be obtained. For each domain, the item responses in the respective domains are summed (each item is based on a categorical scale ranging from 0–10). Prior to summation, items 1, 2, 8, 10 and 14 must be reversed [see Table 2 for details regarding scoring]. For the Total score, all item responses are summed.

Table 2 Insomnia Daytime Symptoms and Impacts Questionnaire description

Domain	Scoring	Minimum/Maximum score
Alert/cognition	Daily: sum of Item 1*, Item 2*, Item 3, Item 9, Item 10*, Item 14*	Minimum score: 0 Maximum score: 60 Higher score: greater burden of illness
	Weekly average: mean of the daily domain score over 7 days	
Mood	Daily: sum of Item 4, Item 5, Item 6, Item 7	Minimum score: 0 Maximum score: 40 Higher score: greater burden of illness
	Weekly average: mean of the daily domain score over 7 days	
Sleepiness	Daily: sum of Item 8*, Item 11, Item 12, Item 13	Minimum score: 0 Maximum score: 40 Higher score: greater burden of illness
	Weekly average: mean of the daily domain score over 7 days	
Total score	Daily: sum of all domains above	Minimum score: 0 Maximum score: 140 Higher score: greater burden of illness
	Weekly average: mean of the daily domain score over 7 days	

* Item 1, Item 2, Item 8, Item 10, and Item 14 scores are reverse scored prior to summation.

A plot of the mean change from baseline over time (per month as defined in Table 6) for sTST, sWASO, sLSO and IDSIQ scores (i.e., Total score; Alert/Cognition, Mood and Sleepiness domain scores) will be provided together with a summary table.

Observed values and change from baseline over time in sTST, sWASO, sLSO and IDSIQ scores (i.e., total score; alert/cognition, mood and sleepiness domain scores) will be summarized by age group at screening in the confirmatory study (< 65; ≥ 65 years) and overall using descriptive statistics.

A longitudinal data analysis method (i.e., linear mixed-effects model) will be used for the analysis of change from baseline in sTST, sWASO, sLSO and IDSIQ scores (i.e., total score; alert/cognition, mood and sleepiness domain scores), separately. All available data, regardless of occurrence of intercurrent events (e.g., study treatment discontinuation, the use of prohibited medication), will be included in the model. Subjects who are randomized (switched) from placebo to 25 mg in this study will be excluded from this longitudinal analysis as their exposure to treatment and timing of assessments are not aligned with the other treatment groups.

The analysis model will adjust for the baseline value of the relevant response variable (either sWASO, sLSO, sTST or IDSIQ scores), age group as per assigned strata (< 65; ≥ 65 years), treatment (10 mg; 25 mg; 50 mg; placebo), visit (Month 6 [Week 12]; Month 9 [Week 24]; Month 12 [Week 36]; as defined in Table 6), and the interaction of treatment by visit, and baseline by visit (SAS® code available in Appendix 1).

An unstructured covariance matrix, shared across treatment groups, will be used to model the correlation among repeated measurements. A restricted maximum likelihood approach will be used to derive (unbiased) estimates of variance components. The Kenward-Roger approximation will be used to compute the denominator degrees of freedom and adjust standard errors [Kenward 1997]. If this analysis fails to converge, the use of the heterogeneous Toeplitz covariance structure, shared across treatment groups, will be explored.

Appropriate contrasts will be used to test the treatment differences of interest (i.e., the difference in least squares [LS] mean change from baseline between ACT-541468 10 mg vs placebo, ACT-541468 25 mg vs placebo and ACT-541468 50 mg vs placebo at Month 6, Month 9 and Month 12, see Appendix 1). Month 6 is the mean value based on the sleep diary / IDSIQ entries performed at home over the 7 days in Week 12 of the extension study; Month 9 (Week 24) and Month 12 (Week 36) are defined similarly.

The LS mean for each treatment group per time point will be displayed along with associated standard errors and 95% CIs. For each ACT-541468 dose level comparison with placebo, the placebo-adjusted LS mean will be displayed along with associated standard errors, 95% CI and unadjusted two-sided p-value.

Observed values and change from baseline over time in VAS scores, ISI©, number of self-reported awakening, PGA-S and PGI-C will also be summarized using descriptive statistics.

Empirical cumulative distribution function plots of the observed cases of sWASO, sLSO, sTST and IDSIQ endpoints, separately, at Months 6, 9 and 12 for each treatment group will be provided. A summary will be provided showing the cumulative number and percentage of subjects meeting certain thresholds for sWASO, sLSO, sTST and IDSIQ endpoints, separately, for the observed range of values.

For sTST, sWASO, sLSO, each IDSIQ domain and total scores, VAS scores and number of self-reported awakenings, subjects must have at least 2 days of data during each week to calculate a weekly mean. Otherwise, the mean value will be considered missing for that week. The approaches above imply implicit imputation: the missing data points are given the same value as the mean of the non-missing data points of that same time point or week.

Subgroup analyses for sTST, sWASO, sLSO, each IDSIQ domain and total scores endpoints will be performed to investigate the consistency of the treatment effect (i.e., ACT-541468 vs placebo) across subgroups defined as:

- Age at screening of confirmatory study: < 65, ≥ 65 years and < 75, ≥ 75 years.

Specific subgroup analyses for sTST and each IDSIQ domain and total scores endpoints are defined below:

- Sex: Male, female.
- Region: US, other (non-US).
- BMI at screening of confirmatory study: < 30, ≥ 30 kg/m^2.
- Race: White, Black or African American, Other*;

* The 'Other' category will not be considered for subgroup analyses due to the mix of races and small number of subjects limiting the ability (i.e., low power) to detect differences between treatment groups. 'Other' includes: American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, Asian and Other (Entry for multiple races was to be reported under category 'Other'. Similarly, 'Not permitted as per legislation/regulation' was to be also grouped within this category 'Other').

The same model as for the longitudinal analysis (i.e., linear mixed-effects model) will be fitted with the additional factor for subgroup, and the interaction of subgroup by treatment, subgroup by visit, and subgroup by treatment by visit. Subjects who are randomized (switched) from placebo to 25 mg in this study will be excluded from these longitudinal analyses.

Of note, age group will not be included as a covariate in the model of the subgroup analyses by age.

Treatment effect estimates (LS mean and associated 95% CI for the ACT-541468 comparison with placebo) at Month 6, 9 and 12 will be presented via forest plots.

At the time of interim analysis, treatment will still be ongoing for some subjects so the efficacy beyond 6 months should be interpreted with caution.

7 SAFETY VARIABLES AND ANALYSES

7.1 Overview of safety analyses including subgroup analyses

Unless noted otherwise, the SS will be used for tables and listings of safety data. Safety data described below will be listed.

In the event of permanent study treatment discontinuation, it is recommended per protocol to perform the safety assessments of Visit 5 within 7 days of the last double-blind study treatment intake. Although some subjects may be considered as being off study treatment, the time from the last double-blind study treatment intake to the Visit 5 assessments is expected to be short. Therefore, for subjects who prematurely discontinue treatment, the safety data (laboratory tests, ECG, vital signs) measured within 7 days of the last double-blind study treatment intake will be included as being taken during double-blind study treatment. A subject who prematurely discontinues treatment may continue the planned study visits until EOS, without the run-out period. Therefore, for subjects who prematurely discontinue treatment, the safety data (laboratory tests, ECG, vital signs) measured more than 7 days from the last double-blind study treatment intake will be excluded from analyses.

Any unscheduled or re-test measurements will be excluded for determining last values during the double-blind treatment period. All scheduled, re-test and unscheduled measurements will be included for determining baseline values.

7.2 Adverse events

Unless noted otherwise, the AE summary tables will include TEAEs occurring during the extension study i.e., AEs that started or worsened on or after double-blind study treatment start date of the extension study up to 30 days after double-blind study treatment end date. An AE that started or worsened during any unplanned double-blind study treatment interruption (e.g., due to AE) will be considered as treatment-emergent. In addition, an AE that started or worsened during a planned double-blind study treatment interruption (i.e., the run-out period or safety follow-up period) that falls in the treatment-emergent time window defined above, will be considered as treatment-emergent.

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

The number and percentage of subjects experiencing a TEAE occurring during the extension study (including SAEs, AESIs after adjudication by the ISB, and AEs leading to premature discontinuation or temporary interruption of double-blind study treatment) will be summarized by SOC and/or PT, and/or maximum intensity.

Each AESI category (i.e., excessive daytime sleepiness, cataplexy, complex sleep behavior including hallucinations/sleep paralysis, suicide/self-injury, narcolepsy-like symptoms) will be summarized by PT separately.

A subject with multiple intensities reported for an AE will be summarized under the maximum intensity recorded for the event.

Apart from the summaries of occurrences, where each event is counted, a subject with multiple occurrences of an AE is counted only once in the AE category (e.g., SOC, PT). If a single AE worsens on the same treatment group, then this event will be considered as one occurrence.

AEs will be sorted by descending frequency, first in the ACT-541468 50 mg dose level, then in the ACT-541468 25 mg dose level, then in the ACT-541468 10 mg, then in the placebo treatment group, and finally in the ex-placebo/ACT-541468 25 mg. After this ordering, SOCs are presented in alphabetical order with PT sorted within SOC in alphabetical order.

The following AE summary tables will be provided:

- TEAEs,
- TEAEs during the double-blind study period[a],
- TEAEs occurring (i.e., that started or worsened) during the treatment withdrawal period (based on the TWS),
- TEAEs during the double-blind study period[a] related to study treatment as assessed by the investigator and/or sponsor,
- AEs leading to premature discontinuation of double-blind study treatment,
- AEs leading to temporary interruption of double-blind study treatment,
- Treatment emergent SAEs (including occurrences),
- Treatment emergent SAEs related to study treatment (including occurrences),
- Most frequent (threshold to be defined at time of reporting) non-serious TEAEs (including occurrences),
- Treatment emergent AESIs after ISB adjudication,
- TEAEs during the double-blind study period[a] related to abuse (as defined in the document *Search specifications for safety monitoring)*,

- TEAEs during the double-blind study period[a] based on selected Standardized MedDRA Queries or pre-defined search criteria (as defined in the document *Search specifications for safety monitoring)*,
- TEAEs with fatal outcome,
- Total number of deaths (those occurring on or after double-blind study treatment start date of the extension study up to 30 days after double-blind study treatment end date).

[a] Includes only those TEAEs occurring (i.e., that started or worsened) during the double-blind study period [see Section 12.2].

All AEs will be listed including AEs recorded as ongoing at the start of double-blind study treatment.

An AE listing will be provided also for subjects who were not randomized and subjects who were randomized but did not take double-blind study treatment. Subjects who were not randomized due to an AE or discontinued the study due to an AE will be reported in that listing. In addition, a separate listing will be provided for deaths with cause of death using the ENR Set.

AEs submitted for adjudication will be listed flagging separately: AEs that were adjudicated as an AESI and AEs that were considered an AESI as per the investigator's judgment.

The number of subjects (including occurrences) with at least one case submitted for ISB adjudication will be summarized and listed.

An incomplete (day or month missing) or missing AE date will be imputed as described in Table 3. The 'lower limit' and 'upper limit' refer to the earliest and latest possible dates, respectively. As an example: if AE onset date is MAR2017 (day missing), the lower limit is 01MAR2017 and the upper limit is 31MAR2017; if AE onset date is 2017 (day and month missing), the lower limit is 01JAN2017 and the upper limit is 31DEC2017.

Table 3 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	The rules below apply in the order presented: 1. For AEs reported as ongoing from the confirmatory study, the lower limit is used. 2. If the (imputed) AE end date is on or after the start of double-blind study treatment, and if the double-blind study treatment start falls within the upper and lower limits (inclusive), the double-blind study treatment start date is used. 3. If the AE resolution date is missing, and if the double-blind study treatment start falls within the upper and lower limits (inclusive), the double-blind study treatment start date is used. 4. In all the other cases, the lower limit is used.	Whichever is the earlier of the AE resolution date or double-blind study treatment start date*.

AE = adverse event.
*If an AE is reported as ongoing (from confirmatory study) and if the onset date is missing then the double-blind study start date of the confirmatory study should be used.

The purpose of imputing AE dates is only to assign an AE to a specific treatment phase for the summary tables and listings. However, only the actual dates as reported in the eCRF will be listed. No imputed date is considered in the medical evaluation of an AE.

7.3 Laboratory tests

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

Descriptive summary statistics for each scheduled visit (re-test excluded) will be provided for observed values and change from baseline (baseline as defined in Section 11.4) in both hematology and blood chemistry laboratory parameters.

The change from baseline to the last value (re-test and unscheduled assessments excluded) in the double-blind study period for hematology and blood chemistry parameters will be summarized.

Marked laboratory abnormalities are defined in Table 4. The number and percentage of subjects with marked laboratory abnormalities during double-blind study treatment will be tabulated. In the event of multiple occurrences, 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, i.e., those having at least one post-baseline value for a given parameter.

Shift from baseline to worst value post-baseline based on laboratory normal ranges will be provided for the following laboratory parameters:

- Liver enzymes: ALT, AST, gamma-glutamyl transpeptidase and TBIL.
- Thyroid hormones: thyroid-stimulating hormone, free triiodothyronine and free thyroxine.
- Lipids: total cholesterol and triglycerides.
- Hematology: leucocytes, neutrophils, lymphocytes, and eosinophils.

All laboratory data for subjects with at least one marked laboratory abnormality during double-blind study treatment will be listed. Any local laboratory data collected will be listed separately.

Table 4 Marked abnormalities in laboratory parameters for reporting

Laboratory parameter	**Criteria for marked laboratory abnormalities**
Hematology (SI unit)	
Hemoglobin (g/L)	< 100 < 80 > 20 above ULN or > 20 above baseline if baseline > ULN > 40 above ULN or > 40 above baseline if baseline > ULN
Hematocrit (%)	< 32% (Male); < 28% (Female) < 20% > 60% (Male); > 55% (Female)

Laboratory parameter	**Criteria for marked laboratory abnormalities**
	> 65%
Platelets (10^9/L)	< 75 < 50 > 600 > 999
Leucocytes (10^9/L)	< 3.0 < 2.0 > 20.0 > 100.0
Neutrophils (10^9/L)	< 1.5 < 1.0
Eosinophils (10^9/L)	> 5.0
Eosinophils (%)	> 5%
Lymphocytes (10^9/L)	< 0.8 < 0.5 > 4.0 > 20.0
Reticulocyte (%)	> 2.5%
Blood chemistry (SI unit)	
ALT (U/L)	> 3 × ULN > 5 × ULN > 10 × ULN
AST (U/L)	> 3 × ULN > 5 × ULN > 10 × ULN
ALP (U/L)	> 2.5 × ULN > 5 × ULN
Total bilirubin (µmol/L)	> 2 × ULN > 5 × ULN
Creatinine (µmol/L)	> 1.5 × ULN or > 1.5 × baseline if baseline > ULN > 3 × ULN or > 3 × baseline if baseline > ULN

Laboratory parameter	**Criteria for marked laboratory abnormalities**
Creatinine clearance (ml/min/1.73 m^2)	< 30 < 60
Albumin (g/L)	< 30 < 20
Calcium (mmol/L)	< 2.0 < 1.75 > 2.9 > 3.1
Potassium (mmol/L)	< 3.2 < 3.0 > 5.5 > 6.0
Sodium (mmol/L)	< 130 > 150 > 155
Chloride (mmol/L)	< 74 > 131
Creatine kinase (µg/L)	> 5 × ULN > 10 × ULN
Gamma-glutamyl transferase (U/L)	> 2.5 × ULN > 5 × ULN
Blood urea nitrogen (mmol/L)	> 2.5 × ULN > 5 × ULN
Uric acid (µmol/L)	> 590 > 720
Glucose (mmol/L)	< 3 < 2.2 > 8.9 > 13.9
TSH (mIU/L)	< 0.28 > 6.6
Free T_3 (pmol/L)	< 2.8 > 7.8
Total T_3 (nmol/L)	< 0.9

Laboratory parameter	Criteria for marked laboratory abnormalities
	> 3.6
Free T_4 (pmol/L)	< 7.2 > 24
Total T_4 (nmol/L)	< 53 > 210
Triglycerides	> 5.7 mmol/L
Total cholesterol	> 2 × ULN

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; SI unit = International System of Units; TSH = thyroid-stimulating hormone; T_3 = triiodothyronine; T_4 = thyroxine; ULN = upper limit of normal.

Elevated liver parameters during double-blind study treatment will be summarized: the number and percentage of subjects meeting the criteria defined below within a given central laboratory sample will be tabulated by treatment group. Percentages will be based on the number of subjects at risk, i.e., those having at least one post-baseline value for all parameters within the given criteria.

- AST or ALT > 3 × ULN.
- AST or ALT > 5 × ULN.
- AST or ALT > 10 × ULN.
- TBIL > 1.5 × ULN and > 2 × ULN.
- ALP > 1.5 × ULN.
- (ALT or AST > 3 × ULN) and (TBIL > 1.5 × ULN).
- (ALT or AST > 3 × ULN) and (TBIL > 2 × ULN).

7.4 Electrocardiography

Unless noted otherwise, ECG summaries and listings will include scheduled, re-test and unscheduled assessments.

Descriptive summary statistics for each scheduled visit (re-test excluded) will be provided for observed values and change from baseline (baseline as defined in Section 11.4) to Visit 3 (Week 14), Visit 4 (Week 27), Visit 5 (Week 40) and Visit 6 (Week 41) in ECG parameters (QT corrected according to Fridericia's formula, QT corrected according to Bazett's formula, heart rate, PR, and QRS).

Marked ECG abnormalities are defined in Table 5. The following summaries will be provided for each ECG parameter:

- Number and percentage of subjects having a marked ECG abnormality during the double-blind study period,
- Number and percentage of subjects having a marked ECG abnormality during the treatment withdrawal period (based on the TWS).

For the summaries above, percentages will be based on the number of subjects at risk: those having at least one post-baseline value in the study period under consideration per ECG parameter for criteria based on post-baseline values only, or those having a baseline value and at least one post-baseline value in the study period under consideration per ECG parameter for criteria based on change from baseline. For non-mutually exclusive criteria (i.e., HR < 45 bpm and < 50 bpm), a subject will be counted only once in the event of multiple occurrences but may be reported in more than one marked ECG abnormality criterion of a given parameter. For mutually exclusive criteria (e.g., HR and QTc), only the subject's worst post-baseline value (or worst change from baseline value) will be counted.

ECG findings during the double-blind study period and during the treatment withdrawal period (based on the TWS) will be summarized separately and listed.

ECG abnormality categories and findings will be sorted by descending frequency, first in the ACT-541468 50 mg dose level, then in the ACT-541468 25 mg dose level, then in the ACT-541468 10 mg, then in the placebo treatment group, and finally in the ex-placebo/ACT-541468 25 mg. After this sorting, ECG abnormality categories will be presented in alphabetical order with ECG finding sorted within ECG abnormality category in alphabetical order.

All ECG values for subjects with at least one marked ECG abnormality during double-blind study period or during the treatment withdrawal period will be listed.

Table 5 Marked abnormalities in ECG parameters

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

bpm = beats per minute; ECG = electrocardiogram; HR = heart rate; QTcB = QT corrected according to Bazett's formula; QTcF = QT according to Fridericia's formula.

7.5 Vital signs and body weight

Each summary will include only scheduled assessments (re-test excluded) and listings will include both scheduled and unscheduled assessments.

The change from baseline (baseline as defined in Section 11.4) to Visit 3 (Week 14), Visit 4 (Week 27), Visit 5 (Week 40) and the run-out period Visit 6 (Week 41) in vital signs (systolic and diastolic blood pressure, and pulse rate) will be summarized. The observed values at baseline and each scheduled post-baseline visit will also be summarized.

The change from baseline (baseline as defined in Section 11.4) to Visit 5 (Week 40; or last value on study) in body weight will be summarized.

7.6 Withdrawal symptoms

The TWS will be used to assess the potential for withdrawal symptoms.

The BWSQ assesses the main symptoms which might be experienced by subjects during withdrawal from benzodiazepines. The questionnaire consists of 20 items with each item rated by the subject as either 0 (No), 1 (Yes–moderate) to 2 (Yes–severe). The BWSQ total score (possible range: 0–40) for the observed values and change from the last available assessment on double-blind study treatment to the end of the treatment withdrawal period will be summarized. Observed values will also be summarized.

The number and percentage of subjects with a BWSQ total score above 20 will be tabulated by visit. The number and percentage of subjects with one or more BWSQ symptom scored as ‘severe’ will be tabulated by visit.

In addition, withdrawal symptoms after double-blind study treatment discontinuation will be assessed through the incidence of AEs, and marked ECG abnormalities, occurring during the treatment withdrawal period [see Section 11.2]. As described in their respective sections, the incidence of AEs [Section 7.2] and marked ECG abnormalities [Section 7.4] occurring during the treatment withdrawal period (between Visit 5 and Visit 6) will be summarized.

7.7 Rebound insomnia

The TWS will be used to assess the potential for rebound insomnia.

The change from baseline (baseline as defined in Section 6.1) to the treatment withdrawal period (Visit 6, Week 41, see Section 11.7) in the subjective sleep parameter sTST will be summarized using descriptive statistics.

Empirical cumulative distribution function plots of this subjective sleep parameter for each treatment group will be provided together with a summary showing the cumulative number and percentage of subjects meeting certain thresholds for the observed range of values.

7.8 Next-day residual effect

Sheehan Disability Scale©

The 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). Number of days lost (school, work or normal daily responsibilities) and number of days underproductive (school, work or normal daily responsibilities) are also collected and will be summarized.

The change from baseline[a] to Visit 3 (Week 14), Visit 4 (Week 27), Visit 5 (Week 40) and run-out period Visit 6 (Week 41) in each SDS© item (impairment of work, social life, family life / home responsibilities, number of days lost and number of days underproductive) and Total score will be summarized. The Total score will be calculated only for subjects with all the three items available: impairment of work, social life and family life / home responsibilities. Observed values will also be summarized.

[a] For subjects entering ID-078A303 and assigned to the same treatment arm as that of the confirmatory studies (ACT-541468 10 mg, 25 mg, or 50 mg, or placebo), baseline is the mean of the two PSG morning assessments at Visit 3 of the run-in period in the confirmatory study. For subjects entering ID-078A303 who received placebo in the confirmatory studies and who are randomized (switched) to 25 mg of ACT-541468 in the extension study, baseline is as defined in Section 11.4.

Visual Analog Scales

The change from baseline over time (baseline and over time as defined in Section 6.1) in morning sleepiness VAS score will be summarized. Observed values will also be summarized.

7.9 Columbia Suicide Severity Rating Scale©

The 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 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.

Based on the C-SSRS©, the number and percentage of subjects with suicidal ideation by category, suicidal behavior by category, suicidal ideation or behavior and/or self-injurious behavior without suicidal intent, 1) during the double-blind study period and 2) during the treatment withdrawal period (based on TWS) will be tabulated separately. Percentages will be based on the number of subjects with at least one post-baseline C-SSRS© assessment, in the corresponding period. The assessment will be assigned to a study period based on a scheduled visit as follows: V1 (Day 1) = not assigned any study period; V3 (Week 14), V4 (Week 27) and V5 (Week 40) = double-blind study period; V6 (Week 41) = Treatment withdrawal (or Run-out) period.

Shift from baseline (baseline as defined in Section 11.4) showing any change in suicidal ideation and suicidal behavior, 1) during the double-blind study period and 2) during the treatment withdrawal period (based on TWS), will be provided separately. 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, and 3) Suicidal behavior (subjects with both suicidal ideation and suicidal behavior are included in the suicidal behavior category and not in the suicidal ideation category). 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).

7.10 Epworth Sleepiness Scale©

The ESS© is a validated questionnaire designed to provide a subjective measure of daytime sleepiness. The ESS© consists of eight situations on chances of dozing; each situation is evaluated with a score that ranges from 0 (never dozing) to 3 (high chance of dozing). The eight items will be summed into a total score of daytime sleepiness.

The change from baseline (baseline as defined in Section 11.4) to Visit 3 (Week 14), Visit 4 (Week 27), Visit 5 (Week 40) and end of the run-out period Visit 6 (Week 41) in ESS© total score will be summarized. Observed values will also be summarized.

The number and percentage of subjects meeting the criteria defined below will be tabulated:

- ESS© total score > 16 at last value before start of treatment in the extension (it corresponds to last value before start of treatment collected on Day 1 of extension study or in the confirmatory study), Visit 3 (Week 14), Visit 4 (Week 27), Visit 5 (Week 40) and end of the run-out period (Visit 6, Week 41).

- ESS© total score > 4 points increase from previous visit at Visit 3 (Week 14), Visit 4 (Week 27), Visit 5 (Week 40) and end of the run-out period (Visit 6, Week 41).

7.11 Subgroup analysis of safety variables

Summaries of TEAEs occurring (i.e., that started or worsened) during the double-blind study period [see Section 12.3] by SOC and PT will be performed on the following subgroups:

Age at screening of confirmatory study	< 65, ≥ 65 years and <75; ≥75
BMI at screening of confirmatory study	< 25, 25–30, > 30 kg/m^2
Sex	Male, female
Race	White, Black or African American, Other*

* The 'Other' category will not be considered for subgroup analyses due to the mix of races and small number of subjects limiting the ability (i.e., low power) to detect differences between treatment groups. 'Other' includes: American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, Asian and Other (Entry for multiple races was to be reported under category 'Other'. Similarly, 'Not permitted as per legislation/regulation' was to be also grouped within this category 'Other').

8 PHARMACOKINETIC VARIABLES AND ANALYSES

Pharmacokinetic data, i.e., plasma concentrations of ACT-541468 (collected at the discretion of the investigator) will only be listed.

9 GENERAL STATISTICAL METHODOLOGY

9.1 General rules for data presentations

Data are listed and summarized as described below.

The tables for ID-078A303 will use the following header structure (label and order):

ACT-541468 10 mg N = xxx	*ACT-541468 25 mg N = xxx*	*ACT-541468 50 mg N = xxx*	*Placebo N = xxx*	*Ex-placebo/ACT-541468 25 mg N = xxx*

- *ACT-541468 10 mg:* subjects continuing in the extension trial at the same dose level of 10 mg
- *ACT-541468 25 mg:* subjects continuing in the extension trial at the same dose level of 25 mg
- *ACT-541468 50 mg:* subjects continuing in the extension trial at the same dose level of 50 mg

- *Placebo:* subjects continuing in the extension trial assigned to placebo arm
- *Ex-placebo/ACT-541468 25 mg:* subjects continuing in the extension trial that switch from placebo to 25 mg

Where N indicates the total number randomized or treated appropriate to the analysis set in the corresponding treatment group, unless otherwise specified.

All listings will be sorted by randomized treatment or actual treatment received (appropriate to the analysis set), country, subject number (ascending) and, when appropriate, by visit / date of assessment (ascending).

Listings based on the ENR Set will present a treatment group label "Subject not randomized" for subjects who were not randomized and will be listed after the subjects who were randomized.

Unless noted otherwise, the following descriptive statistics will be used to summarize data: number and percentage of subjects for categorical variables or descriptive statistics (number of non-missing values, mean, standard deviation, median, Q1, Q3, minimum, maximum) for continuous variables.

10 INTERIM ANALYSES

This study includes an IDMC and ISB that will assess safety of ACT-541468 on a regular basis as per IDMC and ISB charters, respectively.

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

An interim analysis was introduced as part of amendment protocol Version 3, dated 17 February 2020, to support global regulatory filings.

The interim analysis will be conducted when all subjects who did not prematurely discontinue study treatment have reached Visit 3.

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

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

The interim analysis will be based upon a snapshot of the clinical trial database and will include all clean safety and efficacy data as of approximately end of July (a cut-off date

will be fixed to ensure all subject data up to and including Visit 3 are included). All visits and assessments that have been done before and on this cut-off date will be considered for the interim analysis. All analyses described in this SAP will be performed for the interim analysis.

SDTM dataset will be based on the snapshot of the clinical database and may include data beyond the cut-off date. Then, ADaM datasets will be produced including only data up to the date of the interim cut-off.

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

11 GENERAL DEFINITIONS AND DERIVATIONS

11.1 Treatment start and end dates

Unless noted otherwise, treatment start and end dates mentioned throughout this document are in reference to the treatment received in the extension study.

Double-blind study treatment start or end date is the earliest or latest, respectively, date of dose intake recorded on the 'Study Double-Blind Treatment Log' page. Double-blind study treatment start or end date of the confirmatory study is the earliest or latest, respectively, date of dose intake recorded on the 'Study Double-Blind Treatment Log' page of either study ID-078A301 or study ID-078A302.

Run-out single-blind placebo treatment start and end date is the earliest and latest date of dose intake recorded on the 'Study Single-Blind (Run-Out) Treatment Log' page.

11.2 Study periods

The enrollment period is defined as the time from the informed consent date until one day before double-blind study treatment start date.

The double-blind study period is defined as the time from the day of double-blind study treatment start until the day of EODBT (Visit 5) or for those who prematurely discontinued double-blind study treatment (i.e., those without an EODBT date), until one day after double-blind study treatment end date (if the treatment is taken before midnight), or the day of double-blind study treatment end date (if the treatment is taken after midnight). Time of treatment intake between 00:00 and 11:59 is considered as 'after midnight', while a time between 12:00 and 23:59 is considered as 'before midnight'. For any missing or incomplete time, it is presumed that the treatment was taken before midnight. For subjects lost to follow-up, the EOS date will be used as the end of DB study treatment. For subjects who complete double-blind study treatment with an interruption before continuing the run-out single-blind placebo treatment, the end of double-blind study period is the run-out

single-blind placebo treatment start date – 1 day. For subjects who prematurely discontinue treatment, the safety data (laboratory tests, ECG and vital signs) assessment up to 7 days after last drug intake are considered in the definition of double-blind study period [see Section 7.1].

For those subjects in the TWS, the treatment withdrawal period (or the run-out period) is defined as the time from one day after the end of the double-blind study period to the latter of seven days after the end of the double-blind study period or Visit 6 date. If the latter of the two dates falls after the EOS date, then the EOS date will be used.

The safety follow-up period is defined as the time from one day after the end of the treatment withdrawal period for those starting the treatment withdrawal period (i.e., subjects in the TWS) until the EOS date; or from one day after the end of double-blind study period for those not starting the treatment withdrawal period until the EOS date.

11.3 Treatment day and study day

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

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

Treatment day (days) = Date of assessment/event – Start date of double-blind study treatment + 1 day.

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

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

Treatment day (days) = Date of assessment/event – Start date of double-blind study treatment.

The study day for an assessment or event will be calculated using the randomization date as reference.

For assessments/events occurring on or after the randomization date, the study day will be positive and calculated as:

Study day (days) = Date of assessment/event – randomization date + 1 day.

The day of randomization date is Study Day 1.

For all assessment/events occurring prior to the randomization date, study day will be negative and calculated as:

Study day (days) = Date of assessment/event – randomization date.

Treatment day and/or study day will be displayed in the data listings as appropriate.

11.4 Baseline

Unless otherwise defined in the specific analysis section, baseline is defined as follows:

1. For subjects entering ID-078A303 and assigned to the same treatment arm as that of the confirmatory studies (ACT-541468 10 mg, 25 mg, or 50 mg, or placebo), baseline is the last non-missing assessment performed or value measured before or on the day of first dose of double-blind study treatment in the confirmatory study.
2. For subjects entering ID-078A303 who received placebo in the confirmatory studies and who are randomized (switched) to 25 mg of ACT-541468 in the extension study, baseline is the last non-missing assessment performed or value measured before or on the day of first dose of double-blind study treatment in the extension study. This could be either data collected at Visit 1 of the extension study or collected in the confirmatory study. An assessment taken on the day of the double-blind study treatment start date is considered a baseline assessment and is not considered a post-baseline assessment in the double-blind study period.

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.

11.5 Change from baseline

The change from baseline is defined as post-baseline value (any assessment performed after baseline and up to EOS) minus baseline value. A positive number indicates an increase as compared to baseline.

11.6 Handling of data when subjective total sleep time is zero

If the sTST is recorded as zero:

- sWASO is set as missing since subject is never at risk.
- sLSO is set as 480 minutes.

11.7 Time window definitions for calculating subjective endpoints

Values falling in the following time window will be used to calculate weekly averages for the subjective endpoints:

Run out: the 7 consecutive days immediately following the evening of Visit 5 (i.e., 7-day window = [Treatment withdrawal period start date; Minimum (Treatment withdrawal period start date + 6 days; Visit 6 date)]).

Table 6 defines the time windows used to calculate weekly averages for certain subjective measures that will be summarized over time. These subjective measures include sTST, sWASO, sLSO, IDSIQ scores (i.e., total score; alert/cognition, mood and sleepiness domain scores), VAS scores and number of self-reported awakenings.

Weekly averages will be calculated using the data recorded in a 7-day window. The 7-day window for a given week begins on the first date the subjective measure is recorded in the given time window [see last column in Table 6]. For example, if a subject starts to record data on Study Day 17 of the time window then only values recorded from Study Day 17 to Study Day 23 (7-day window) will be considered. If a subject starts to record data on Study Day 27, only values recorded from Study Day 27 to Study Day 33 (7-day window) will be considered. The first date is specific to each type of subjective measure (e.g., for a given subject, a 7-day window from Study Day 17 to Study Day 23 could be considered for sTST at Week 4, while for IDSIQ scores at Week 4, a 7-day window from Study Day 27 to Study Day 33 may be considered). Note: values recorded by the subject beyond the considered 7-day window will not be considered in the calculation of the weekly average.

Table 6 Time windows (in days) to calculate weekly averages for certain subjective endpoints

Week	Reference 7-day window (Study day)	Time window (Study day)
4	22–28	(17; 27)
8	50–56	(45; 55)
12*	78–84	(73; 83)
16	106–112	(101; 111)
20	134–140	(129; 139)
24*	162–168	(157; 167)
28	190–196	(185; 195)
32	218–224	(213; 223)
36*	246–252	(241; 251)
40	274–280	(269; 279)

* Week 12, 24 and 36 correspond to Month 6, 9 and 12, respectively.
Values from the run-out period will not be included.

For PGA-S and PGI-C, Table 7 defines the time windows to report the values collected. All values falling in the time window defined will be considered for the analysis of these

endpoints. However, if more than one value falls into the time window, then only the first value will be used for the analysis.

Table 7 Time windows (in days) for PGA-S and PGI-C measurements

Week	Reference 7-day window (Study day)	Time window (Study day)
4	22–28	(20; 35)
8	50–56	(48; 63)
12*	78–84	(76; 91)
16	106–112	(104; 119)
20	134–140	(132; 147)
24*	162–168	(160; 175)
28	190–196	(188; 203)
32	218–224	(216; 231)
36*	246–252	(244; 259)
40	274–280	(272;287)

* Week 12, 24 and 36 correspond to Month 6, 9 and 12, respectively.
Values from the run-out period will not be included.
PGA-S = Patient Global Assessment of Disease Severity; PGI-C = Patient Global Impression of Change.

12 CHANGES OR CLARIFICATIONS TO ANALYSES PLANNED IN THE STUDY PROTOCOL

12.1 Changes to the analyses planned in the study protocol

Not applicable.

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

Summary tables for TEAEs related to study treatment, TEAEs related to abuse and TEAEs based on selected Standardized MedDRA Queries or pre-defined search criteria will include only those TEAEs occurring during the double-blind study period.

12.4 Additional analyses as compared to the study protocol

Not applicable.

13 REFERENCES

[Kenward 1997] Kenward MG, Roger JH. Small sample inference for fixed effects from restricted maximum likelihood. Biometrics 1997;53(3):983–97.

14 APPENDICES

Appendix 1 SAS® code for Mixed Model for Repeated Measures

```
ods output sliceDiffs=lsd2;
proc mixed data=data;
        class SUBJID AGE TRT VIS;
        model CHG = BASE AGE TRT VIS TRT*VIS BASE*VIS/ ddfm= kr;
        repeated VIS / subject=SUBJID type=un;
        lsmeans TRT*VIS / cl alpha=0.05;
        slice TRT*VIS / sliceby=VIS diff=control('PLACEBO' 'Month12') cl;
run;
ods output close;


/* The following code could be used as reference */
```