ACT-539313

STATISTICAL ANALYSIS PLAN

FOR CLINICAL STUDY REPORT

ID-082A201

Version 3

Multicenter, double-blind, randomized, placebo-controlled, parallel-group, proof-of-concept study to evaluate the efficacy and safety of oral ACT-539313 in the treatment of adults with moderate to severe binge eating disorder

Document Number: D-22.100

1 April 2022

Revision history

Version date	Version	Implemented change(s)
23 September 2021	1	Initial version
9 February 2022	2	• Section 4.1: Added reason for exclusion from FAS. • Section 4.1.4: Updated compliance threshold for exclusion from PPS. • Section 5.3.1: Updated demographic summary for screen failures. • Section 5.3.4: Removed summary for study participants currently receiving psychological or behavioral weight-loss interventions for BED. • Section 5.4.2: Updated the calculation of treatment compliance and the treatment interruption definition. • Section 6.1.3: Added use of sandwich estimator, model diagnostic for normality assumption, and non-parametric method in case normality assumption is not met. • Section 6.1.6: Added one sensitivity analysis so called delta-adjusted tipping point. • Section 6.1.8: Updated model to perform subgroup analyses. • Section 7.3: Removed summary table for change from baseline to last value in the treatment period for hematology and blood chemistry parameters. Updated list of laboratory parameters considered for the shift table. Added boxplots for main laboratory parameters. • Section 7.6: Updated summary and graphic presentation of SSS score. • Section 11.2; Updated imputation for missing study treatment end date. • Section 11.7: Updated Table 6 and added a sentence for the time window to be considered for the SSS calculation. • Section 14.1: Updated the SAS code to account for model diagnostic and sandwich estimator.

		• Section 14.5: Added SAS code for multiple imputation under MNAR assumption for delta-adjusted tipping point analysis. • Section 14.6: Updated the SAS code for logistic regression of absence of BE episodes during the last 4 weeks of treatment. • Section 14.7: Updated the SAS code for logistic regression of improvement according to CGI-C score at Week 12. • Section 14.10: Added SAS code for subgroup analysis. • Section 14.11: Added SAS code for non-parametric analysis. • Section 14.13: Updated the MedDRA version.
1 April 2022	3	• Section 5.3.1: Added listing for screen failures. • Section 5.3.2: Removed summary of baseline disease characteristics for screen failures. • Section 5.4.2: Added clarification for treatment interruption. • Section 6.1.3.1: Updated model diagnostic plots. • Section 6.1.5: Updated plot of the mean change of the primary endpoint over time adding SE. • Section 6.1.6: Added possible error message in the SAS log for delta-adjusted tipping point analysis. • Section 14.5: Updated the SAS code for multiple imputation under MNAR assumption for delta-adjusted tipping point analysis. • Section 14.10: Updated the SAS code for subgroup analysis of race. • Section 14.14: Added triglycerides, chloride and cholesterol as marked laboratory abnormality parameters.

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AE	Adverse event
AESI	Adverse event of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BE	Binge eating
BED	Binge eating disorder
b.i.d.	Twice daily
BILI	Total bilirubin
BMI	Body mass index
BWSQ	Benzodiazepine Withdrawal Symptom Questionnaire
CGI-C	Clinical Global Impression of Change scale
CGI-S	Clinical Global Impression of Severity scale
CI	Confidence interval
COVID-19	Coronavirus disease 2019
CRO	Contract research organization
CSR	Clinical study report
C-SSRS©	Columbia-Suicide Severity Rating Scale©
CV%	Coefficient of variation
DB	Double-blind
DSM-5	Diagnostic and Statistical Manual of Mental Disorders (5th edition)
ECG	Electrocardiogram
eCRF	Electronic case report form
EDE-Q	Eating Disorder Examination Questionnaire
EDE-Q7	Eating Disorder Examination Questionnaire (7-item)
EOS	End-of-Study
EOT	End-of-Treatment
FAS	Full analysis set
GGT	Gamma-glutamyltransferase

HAMD-17	Hamilton Rating Scale for Depression (17-item)
HbA1c	Glycated hemoglobin
HR	Heart rate
ICF	Informed consent form
J2R	Jump to reference
LSMean	Least-squares mean
MAR	Missing at random
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple imputation
MMRM	Mixed model for repeated measures
MNAR	Missing not at random
MPS	Maier-Philipp subscale
[redacted]	[redacted]
PD	Protocol deviation
PGI-C	Patient Global Impression of Change scale
PGI-S	Patient Global Impression of Severity scale
PK	Pharmacokinetic
POC	Proof-of-concept
PPS	Per-protocol set
PT	Preferred term
QTc	Corrected QT interval
QTcB	QT interval corrected according to Bazett's formula
QTcF	QT interval corrected according to Fridericia's formula
RND	All-randomized analysis set
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SCR	Screened analysis set
SD	Standard deviation
SE	Standard error
SI	International system of units

SOC	System organ class
SSS	Stanford Sleepiness Scale
T3	Tri-iodothyronine
T4	Thyroxine
TEAE	Treatment-emergent adverse event
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal
USA	United States of America
WHO	World Health Organization
YBOCS-BE	Yale-Brown Obsessive-Compulsive Scale modified for Binge Eating

1 INTRODUCTION

This SAP describes in detail the analyses and data presentation for the CSR prepared for ID-082A201.

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

Data will be analyzed by Idorsia and/or designated CROs supervised by Idorsia using SAS® version 9.4 or higher and R version 3.4.3 or higher. [redacted]

This SAP is based on Version 3 of Protocol ID-082A201, dated 4 May 2021 [Table 1].

Table 1 Study documents

Document	Date, Version
Clinical Study Protocol (CSP)	04MAY2021, Version 3
eCRF specifications	01FEB2021, Version 2
Protocol deviation list	21JAN2022, Version 4

During the drafting of the current SAP, three sites withdrew from the study due to financial reasons related to COVID-19: sites 1012, 1015, and 1061. Consequently, all study participants randomized in these sites discontinued treatment and finished the study. Section 6 describes how these study participants will be considered for the efficacy analyses.

2 STUDY DESIGN AND FLOW

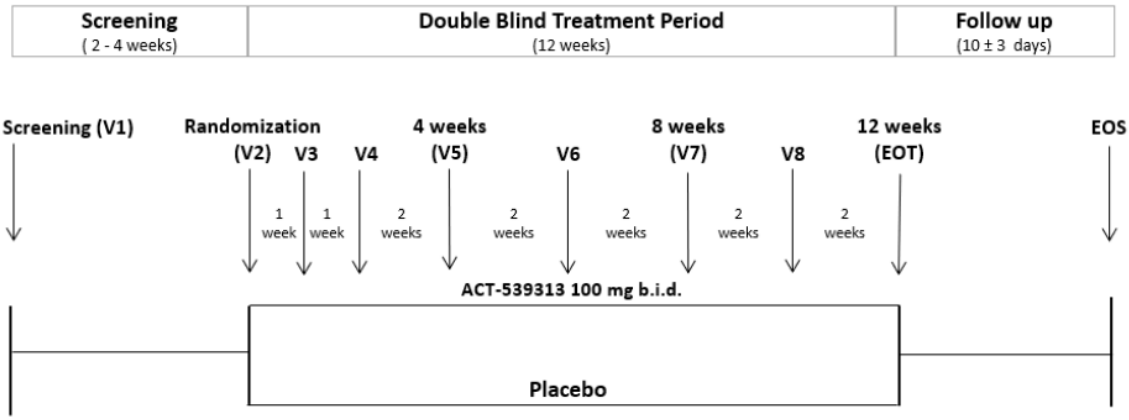
This is a Phase 2, multicenter, double-blind, randomized, placebo-controlled, parallel-group, proof-of-concept study assessing ACT-539313 at a dosing regimen of 100 mg b.i.d. vs placebo over a 12-week treatment period in adult participants (18 to 55 years of age) with moderate to severe binge eating disorder (BED).

Approximately 120 participants will be randomized to either ACT-539313 at a dose of 100 mg b.i.d., or placebo in a 1:1 ratio.

The study will be conducted at approximately 30 sites in the USA.

The study design is shown in Figure 1.

Figure 1 Study design for ID-082A201



b.i.d. = twice daily; EOS = End-of-Study; EOT = End-of-Treatment; V = Visit.

The study comprises the following 3 periods: the screening period, the treatment period and the safety follow-up period.

The **screening period** starts with the signing of the ICF at Visit 1 and ends with Randomization at Visit 2 or with a screening failure. It lasts a minimum of 14 days and up to 28 days.

The **treatment period** starts with the administration of the first dose of study treatment and ends on the day of the last dose of study treatment. The study participants will be treated for 12 weeks.

The **safety follow-up period** starts on the day after the last dose of study treatment and ends at the EOS visit (10 ± 3 days after EOT).

See Section 11.2 for detailed definitions of the study periods.

3 OBJECTIVES

The overall objective of this POC study is to evaluate the clinical efficacy, safety and tolerability of ACT-539313 100 mg administered b.i.d. compared to placebo in adult participants with moderate to severe BED over a period of 12 weeks.

3.1 Primary objectives

To assess the efficacy of 100 mg ACT-539313 in the treatment of BED.

3.2 Secondary objectives

Not applicable.

3.3 Safety objectives

To assess the safety of ACT-539313 in participants with BED.

4 ANALYSIS SETS

4.1 Definitions of analysis sets

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

The number of study participants in each analysis set defined below will be tabulated. Any study participant excluded along with reason(s) for exclusion from the FAS, PPS, or PK analysis sets will be summarized and listed.

4.1.1 Screened set

The Screened set (SCR) includes all study participants who entered screening and have a subject number.

Summaries based on the SCR set will be presented as one group (i.e., all study participants) unless otherwise specified.

4.1.2 All randomized set

The All-randomized analysis set (RND) includes all study participants from the SCR who were randomized.

4.1.3 Full analysis set

The Full analysis set (FAS) includes all study participants who were randomized, received at least one dose of study treatment, and have a baseline assessment of the primary endpoint.

In order to adhere to the intention-to-treat principle as much as possible, study participants will be evaluated according to the treatment they have been assigned to, which may differ from the treatment they received.

4.1.4 Per-protocol set

The Per-protocol set (PPS) includes all study participants from the FAS who complied with the protocol sufficiently to be likely to exhibit the treatment effects.

Criteria for sufficient compliance:

- Absence of important PDs, which may affect the primary endpoint, leading to exclusion from the PPS, as defined in a separate PD document that will be finalized before unblinding.
- Study treatment compliance is ≥ 80% [as calculated in Section 5.4.2].
- Absence of premature treatment discontinuation.

Study participants not meeting the criteria for sufficient compliance will be excluded from the PPS. Study participants will be evaluated according to the treatment they have been assigned to.

4.1.5 Safety set

The Safety set (SAF) includes all randomized study participants who received at least one dose of study treatment.

Study participants will be evaluated according to the actual treatment they received, which may differ from the randomly assigned treatment.

Actual treatment received is defined as the assigned study treatment when received at least once, or the other study treatment if the assigned study treatment was never received.

4.1.6 Pharmacokinetic analysis set

The Pharmacokinetic (PK) analysis set includes all study participants in the SAF who have at least one PK sample collected after initiation of study treatment.

Study participants will be evaluated according to the actual treatment they received. Study participants receiving placebo will be excluded from the PK set.

4.2 Usage of the analysis sets

The analyses of efficacy endpoints will be performed using the FAS, and the PPS for supportive analysis.

The RND will be used for the analysis of demographic and baseline disease characteristics, and the SCR set to provide the same summaries for the screen failures.

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

The PK set will be used for the analysis of ACT-539313 plasma concentrations.

Study participants' listings will be based on the SAF, unless otherwise specified. Subject disposition will be described for the SCR.

Table 2 Usage of analysis datasets

Analysis	SCR	RND	FAS	PPS	SAF	PK set
Subject disposition	X					
Demographics and baseline disease characteristics	x	X				
Previous and concomitant medication					X	
Study drug exposure					X	
Efficacy analysis			X	(x)		
Safety and tolerability analyses					X	
PK data analysis						X

Note: X: main analysis, (x): only if > 10% difference in size with FAS.
FAS = Full analysis set; PK = pharmacokinetic; PPS = Per-protocol analysis set; RND = Randomized analysis set; SAF = Safety analysis set; SCR = Screened analysis set.

5 SUBJECT VARIABLES AND ANALYSES

5.1 Subject disposition

5.1.1 Screening failures

Screening failures will be summarized based on the SCR set and will include:

- Number (%) of study participants who did not successfully complete the screening period (based on 'Was the subject randomized?' recorded as 'No' in the 'Randomization' page).
- Primary reason for screen failure (based on reason for not randomized entered on the 'Randomization' page).

The eligibility criteria not met will be summarized. All reasons for screening failure will be listed.

Of note: No re-screening is allowed in the study.

5.1.2 Study disposition

Study participant disposition will be summarized based on the SCR, presented by randomized treatment group and all screened study participants combined, and will include:

- Number of study participants screened.
- Number (%) of study participants randomized (based on non-missing randomization number).
- Number (%) of study participants who received study treatment during the treatment period (based on non-missing 'Treatment start date' in the 'Study Treatment Log' page). Percentage will be based on randomized subjects.

- Number (%) of study participants who completed the treatment period (based on 'Reason for treatment stop' entered as 'Completion as per protocol' in the 'Study Treatment Log' page). Percentage will be based on study participants who received study treatment.
- Number (%) of study participants completing the study (based on 'Did the subject complete the study?' recorded as 'Yes' in the 'End of Study Status' page). Percentage will be based on randomized subjects.

5.1.3 Study and study treatment completion/discontinuation

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

- Number (%) of study participants who prematurely discontinued study treatment (based on 'Reason for treatment stop' entered as 'Discontinuation' in the 'Study Treatment Log' page).
- Primary reason for premature study treatment discontinuation (based on 'Discontinuation, Reason' entered on the 'Study Treatment Log' page).

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

- Number (%) of study participants 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 'Study stopped due to' entered in the 'End of Study Status' page).

All reasons for premature study treatment discontinuation and study discontinuation will be listed based on the RND.

5.1.4 Study enrollment

The number (%) of screened study participants as well as randomized will be displayed by site based on the SCR by treatment group and all treatment groups combined.

The randomization scheme and codes will be listed for randomized study participants only.

5.2 Protocol deviations

The RND 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, Investigational Medicinal Product, 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 be provided separately for PDs related to COVID-19.

A study participant with multiple occurrences of a protocol deviation is counted only once per protocol deviation category.

A listing of protocol deviations will be provided using the SCR. PDs related to COVID-19 will be flagged in the listings.

5.3 Subject characteristics

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

Summaries will be provided for all treatment groups combined as well as by treatment group separately. Data will be listed individually by study participant.

5.3.1 Demographics

Demographic data at screening, including age, sex, race, ethnicity, height, weight and BMI will be summarized and listed.

The number (%) of study participants randomized in each age category (< 30, ≥ 30 years at screening), and in each BMI category (< 30, ≥ 30 kg/m^2 at screening), will be further summarized.

The same summary and listing will be provided also for screen failures. Height, weight and BMI will not be shown since these variables are not collected for screen failures.

5.3.2 Baseline disease characteristics

Baseline disease characteristics include BE severity based on number of BE days per week and on number of BE episodes per week (both assessed during the two weeks prior to randomization [see Section 11.4 for baseline definition]). In addition, CGI-S, PGI-S, YBOCS-BE total score, HAMD-17 total score and EDE-Q total score assessed at randomization will be described.

These baseline disease characteristics will be listed and summarized.

5.3.3 Medical history and concomitant diseases at screening

Relevant medical history and current medical conditions will be coded using MedDRA.

Any disease or diagnosis is defined as previous if ‘Ongoing at informed consent’ is answered as ‘No’; all other diseases/diagnoses are considered as study concomitant (where answer is ‘Yes’).

Medical history and current (ongoing) medical conditions, excluding BED and BED-related 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 Previous and concomitant therapy

Previous and concomitant therapies 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.

Previous therapies are any treatments for which the end date is prior to signing of the ICF. Any 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 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 'Previous/Concomitant Medication' page.

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

The number (%) of study participants having taken at least one previous or 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 SAF. Previous and 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 previous, study-concomitant and study treatment-concomitant therapies separately. All concomitant therapies will be listed using the SAF and those related to an AE will be flagged.

5.4 Study treatment exposure and compliance

Summaries and listings described in this section will be based on the SAF.

5.4.1 Exposure

The duration of study treatment (including categories: ≤ 1, $> 1 – 2$, $> 2 – 4$, $> 4 – 6$, $> 6 – 8$, $> 8 – 10$, $> 10 – 12$, $> 12 – 13$, > 13 weeks) will be summarized.

The duration of treatment (in days) is defined as the difference between the treatment end date and the treatment start date plus one day. This calculation ignores periods of treatment interruption.

In addition, time from first dose of study treatment to treatment discontinuation will be summarized by treatment group using Kaplan-Meier plots.

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

5.4.2 Compliance with study treatment

Study treatment compliance will be assessed through study treatment dispensing and accountability.

The following formula will be used to calculate compliance for the treatment period:

Study treatment compliance (%) = [(number of capsules dispensed – number of capsules returned[*]) / (treatment duration – total duration of treatment interruptions)] × 0.5[**] × 100

[*] If a study participant did not return his/her bottle (e.g., it is lost), compliance will not be calculated, and the compliance will be set to missing.

[**] To account for 2 capsules taken per day (i.e., b.i.d.).

Treatment duration and total duration of treatment interruptions are calculated using the dedicated eCRF page 'Study Treatment Log' as follows:

- Treatment duration (days) = date of last drug intake of study treatment – date of first drug intake of study treatment + 1 day.
- Total duration of treatment interruptions (days) is the sum of all the treatment interruptions' durations. A treatment interruption duration = date restarted study treatment – end date of study treatment due to an interruption. For example, if a study participant stopped his/her treatment on 19MAR2021 and started again on 23MAR2021, as the treatment is taken on the start and end dates, the calculation will be 23MAR2021 – 19MAR2021 = 4 days of interruption. Should the study participant interrupt the treatment again for 7 days, the total duration of interruptions will be 11 days. Moreover, if a study participant misses one dose, either the evening or the morning dose, a treatment interruption of 1 day will be counted.

Study treatment compliance (including categories 0%, > 0% – < 50%, 50% – < 70%, 70% – < 80%, 80% – < 90%, 90% – < 100%, 100%, > 100%), treatment interruptions (Yes/No), and duration of treatment interruptions will be summarized.

The number (%) of study participants 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

The analyses of efficacy endpoints will be performed using the FAS. Efficacy data described below will be listed using the FAS.

6.1 Primary endpoint analysis

The time windows used for the primary endpoint analysis will follow the definition provided in Section 11.7.

6.1.1 Primary efficacy endpoint

The primary efficacy endpoint of this study is defined as the change from baseline to Week 12 in the number of BE days per week based on diary data.

A 'BE day' is a day in which at least one confirmed BE episode occurred.

The number of BE days per week will be calculated based on 2-week (rather than 1-week) intervals in order to improve the precision of the variable, as shown by simulations. A minimum of 7 diary entries per 14-day time interval is required, otherwise the number of BE days will be considered missing.

The number of BE days per week is defined as the number of diary days with at least one BE episode during the applicable 14-day time interval divided by the total number of diary days, times 7. A diary day is a day for which the number of BE episodes is entered in the study participant's diary (this includes a zero value, i.e., no BE episode).

6.1.2 Overall testing strategy

The H_0 to be tested is that there is no difference between ACT-539313 and placebo with respect to the primary efficacy endpoint:

$$H_0: \mu_A = \mu_P \text{ vs } H_a: \mu_A \neq \mu_P$$

Here, μ_A and μ_P is the mean change from baseline to Week 12 in the number of BE days per week in the ACT-539313 and placebo group, respectively. The null hypothesis will be tested at a two-sided 0.05 significance level.

A preview of the main analyses is given in Table 3 using the estimand terminology [ICH 2020]. Estimands are defined by five attributes: treatment condition of interest, target population, endpoint, strategy for addressing intercurrent events (i.e., premature discontinuation of treatment or use of other, forbidden, medication for BE), and population-level summary. The primary estimand is based on the primary endpoint. A supplementary estimand is obtained by changing one or more attributes. For both estimands the treatment condition is ACT-539313 b.i.d. for up to 12 weeks, whereas the alternative condition is placebo b.i.d. for the same period. The other four attributes are given in Table 3. Differences vs the primary estimand are indicated in ***bold italics***.

Table 3 Estimands for the primary objective

Estimand	Target Population	Endpoint	Strategy for addressing intercurrent events	Population-level summary
Primary Estimand	Adult study participants with BED according to DSM-5, having at least 3 BE days per week at baseline.	Change from baseline to Week 12 in the number of BE days per week	Hypothetical, i.e., endpoint data after intercurrent event are not used.	Mean change from baseline to Week 12 for each treatment group. Treatment effect expressed as difference of LSMean changes from baseline to Week 12 (ACT-539313 minus placebo; from mixed model)
Supplementary Estimand #1	Adult study participants with BED according to DSM-5, having at least 3 BE days per week at baseline.	Change from baseline to Week 12 in the number of BE ***episodes*** per week	Hypothetical, i.e., endpoint data after intercurrent event are not used.	Mean change from baseline to Week 12 for each treatment group. Treatment effect expressed as difference of LSMean changes from baseline to Week 12 (ACT-539313 minus placebo; from mixed model)

Estimand	Target Population	Endpoint	Strategy for addressing intercurrent events	Population-level summary
Supplementary Estimand #2	Adult study participants with BED according to DSM-5, having at least 3 BE days per week at baseline, ***completing 12 weeks of treatment without use of other medication***	Change from baseline to Week 12 in the number of BE days per week	Hypothetical, i.e., endpoint data after intercurrent event are not used.	Mean change from baseline to Week 12 for each treatment group. Treatment effect expressed as difference of LSMean changes from baseline to Week 12 (ACT-539313 minus placebo; from mixed model)

Intercurrent events are premature discontinuation of treatment and use of other, forbidden, medication for BE.
BE = binge eating; BED = binge eating disorder; DSM-5 = Diagnostic and Statistical Manual of Mental Disorders (5th edition); LSMeans = Least Squares Means.

In the choice of intercurrent events it was considered that, in symptomatic settings, it is not the usual practice to continue to assess effectiveness in subjects after they have stopped taking the assigned treatment [O'Neill 2012]. Also, if an alternative (or additional) drug is started, this could influence the outcome for a subject [O'Neill 2012]. Therefore, two types of intercurrent events were considered: premature discontinuation of double-blind treatment (ACT-539313 or placebo) and use of other forbidden medication for BE.

Excluding measurements obtained after an intercurrent event will lead to a hypothetical strategy estimand (ICH E9[R1]). A hypothetical strategy is related to the scenario in which the intercurrent events would not occur (i.e., all subjects completing the 12 weeks of assigned treatment without using forbidden BE medication), which is a reasonable approach for this proof-of-concept study.

6.1.3 Statistical model

A linear mixed effects model will be used for the analysis of change from baseline in the number of BE days per week.

The analysis model will include the baseline number of BE days per week, treatment group (ACT-539313; placebo), sex, BMI category (< 30; ≥ 30 kg/m^2), time point (Weeks 1–2;

3–4; 5–6; 7–8; 9–10; 11–12), and the interaction of treatment by time point and baseline by time point.

An unstructured covariance matrix will be used to model the correlation among repeated measurements. A restricted maximum likelihood approach in combination with the Newton Raphson Algorithm 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 the analysis fails to converge, the following structures will be tested in a subsequent order until model-convergence is achieved: heterogeneous Toeplitz; Toeplitz; autoregressive; compound symmetry. A sandwich estimator will be used to address the potential mis-specification of the aforementioned structured covariance matrixes.

To test the null hypothesis (H_0), appropriate contrasts will be used to test the treatment difference of interest (i.e., the difference in least squares [LS] mean change from baseline between ACT-539313 vs placebo at Week 12) [see Section 14.1].

The LSMean for each treatment group per time point will be displayed along with associated standard errors and 95% CIs. For the ACT-539313 comparison with placebo, the placebo-adjusted LSMean will be displayed along with associated standard error, 95% CI and unadjusted two-sided p-value. The null hypothesis will be rejected if the 95% CI around this difference excludes zero.

6.1.3.1 Model diagnostic and checks for normality

In order to assess the normality assumption of the MMRM, QQ-Plots and histograms (including an overlay of a normal density curve) of the studentized residuals, and figures comparing the studentized residuals versus the predicted residuals will be produced.

If the normality assumption does not hold, the primary endpoint will be analyzed using a non-parametric rank analysis of covariance [Quade 1967, Koch 1982, Koch 2016, Stokes 2012] adjusted for the baseline value as follows:

1. Produce standardized ranks for the baseline value (covariate) and the change from baseline to Week 12 variable (response).
2. Fit a linear regression model with the standardized ranks of the baseline variable and the change from baseline to Week 12 variable as independent and dependent variable, respectively. Retain the regression residuals.
3. Apply the Cochran-Mantel-Haenszel mean score test using the residuals as scores to compare treatment groups. The p-value from this test will be used to test the null hypothesis.

The rank analysis of covariance does not provide an interpretable treatment effect estimate. Therefore, the magnitude of the treatment effect will be estimated using the unadjusted

non-parametric win ratio [Wang 2016] between ACT-539313 and placebo with corresponding 95% CI, derived via bootstrap (10,000 samples) using the bias-corrected method [Carpenter 2000] on the log-transformed win ratio. The rejection of the null hypothesis will be solely based on the p-value from the rank analysis of covariance and not the 95% CI of the unadjusted win ratio estimator.

All study participants with a valid value for the change from baseline to Week 12 will be ranked based on these values (such that larger decreases are associated with better ranks). Study participants with a missing value for the change from baseline to Week 12 will be assigned worse ranks than study participants with available change from baseline to Week 12 values based on their last available change from baseline value prior to Week 12. Study participants with a non-missing baseline value but no post-baseline data will be excluded from the analysis. Mid-ranks are used in the event of ties.

6.1.4 Handling of partially missing data

Partially missing data refers to some missing entries in the BE diary that should be filled in daily.

Partially missing data for the BE diary will be handled as follows: a minimum of 7 days of entries per 14-day time interval is required; otherwise, the mean value will be considered missing for that time point.

This approach uses implicit imputation: missing data points are given the same value as the mean of the non-missing data points of that same time point or week.

The (partially) missing data patterns of the primary efficacy endpoint will be shown with a shift table for each treatment group. The table will show the shifts in the number of available BE values (categorized as < 7, 7–10, 11–14 days) from baseline to Week 3–4, Week 7–8, and Week 11–12 (Week 1–2, Week 5–6 and Week 9–10 will be available in the listing).

6.1.5 Descriptive statistics

The primary efficacy endpoint along with its observed values (i.e., bi-weekly averages of BE episodes; see Table 6) will be summarized using descriptive statistics.

A plot of the mean (± SE) change from baseline over time (per weeks, as defined in Table 6) for the number of BE days by treatment group will be provided together with a summary table.

The incidence and pattern of missing values will be explored to assess the appropriateness of the statistical analysis and possible impact on results. The incidence of missing data and the observed missing data patterns for the primary endpoint at Baseline and time point (Weeks 1–2; 3–4; 5–6; 7–8; 9–10; 11–12) will be presented for each treatment group. The

missing data patterns will be sorted from completely missing to completely observed by the order of the first occurrence of missing data.

The mean change from baseline of the primary efficacy endpoint, for both study completers and for premature study withdrawals, will be plotted over time (Weeks 1–2; 3–4; 5–6; 7–8; 9–10; 11–12) and displayed in a summary table by treatment group. In case the percentage of study withdrawals will be above 15%, the reasons for study withdrawals will also be plotted.

The same plot and table will also be provided for study treatment completers and study treatment discontinuers.

Based on the exploration of the observed missing data patterns, further sensitivity analyses to those described below may be performed.

6.1.6 Sensitivity analyses

The linear mixed effects model (or MMRM) relies on the MAR assumption. That is, conditional on the statistical model and observed values of the outcome, the probability of missing data does not depend on the unobserved values of that outcome. Consequently, the study participant's missing values are estimated based on similar study participants who remain in the study. MAR is a common assumption for analyses associated with a hypothetical strategy estimand.

Sensitivity analyses will be performed to assess the robustness of the conclusions of the main analysis to departures from the MAR assumption. For this, a model that assumes MNAR will be used [Mallinckrodt 2013]. This model will be based on MI methodology [Rubin 1987] and will be specifically used to assess the bias that can result when the outcomes for participants who discontinue differ from those who complete. Sensitivity analyses will be performed for the analysis of the primary endpoint.

As a general approach, imputations will be performed on observed values (i.e., bi-weekly averages at Baseline, Weeks 1–2, 3–4, 5–6, 7–8, 9–10, 11–12) specifying a minimum and a maximum threshold. The change from baseline will not be imputed to avoid imputation of nonsensical values (e.g., an imputed change from baseline to Week 12 equal to −5 with a baseline of 4 would lead to an implicit imputed value of −1 for Week 12, which is not possible). The boundaries will range from 0 to 7.

When an intended imputed value is outside the defined boundaries, this value will be discarded, and the procedure will draw another value for imputation. The maximum number of discarded values will be set to 100 for each imputed dataset, i.e., an imputed dataset will not be generated if more than 100 values have been discarded (SAS will print an error message in the log: "*An imputed variable value is not in the specified range after 100 tries*"). If more than 20% of the planned imputed datasets are not produced, the results for that analysis will not be shown as this would likely lead to unreliable conclusions. Once

all the multiply-imputed datasets are generated, the change from baseline to Week 12 will be calculated from the bi-weekly averages for each data set.

In all the MI analyses described below, a single preliminary step will be performed to obtain a monotone missing data pattern [see Section 11.6]. That is, any non-monotone (or intermediate) missing data of the bi-weekly averages will be imputed using the MCMC methodology [Schafer 1997] under MAR assumptions within each treatment group. This assumption is considered reasonable given that study participants could miss intermediate visits due to reasons unrelated to their BE disorder (e.g., scheduling conflicts or COVID-19). The MCMC imputation will be performed by treatment group, and the variables included in the model are: sex, BMI (continuous), baseline, and time point (Weeks 1–2, 3–4, 5–6, 7–8, 9–10, 11–12). The MCMC methodology assumes a multivariate normal distribution of these variables [see SAS® code in Section 14.2].

As a reference for the sensitivity analyses under MNAR (described below), the main analyses will be repeated using MI methodology under MAR. Imputation for monotone missing data will be performed sequentially, one time point at a time using the linear regression method [Ratitch 2013]. A linear regression model will be fitted sequentially for each time point (i.e., Weeks 1–2 and then Weeks 3–4, Weeks 5–6, Weeks 7–8, Weeks 9–10, Weeks 11–12) with treatment (ACT-539313; placebo), sex, BMI category, baseline, and any prior time point (e.g., Weeks 1–2 when fitting the linear regression model to Weeks 3–4 values and so on) as predictors. Missing values are then replaced for each visit sequentially (i.e., Weeks 1–2 and then Weeks 3–4, Weeks 5–6, Weeks 7–8, Weeks 9–10, Weeks 11–12) by predictions from the respective linear regression model [Rubin 1987]. Note that values imputed at Weeks 1–2 are included when fitting the linear regression model to Weeks 3–4 values (the same approach will be implemented for the imputation of the other time points). The resulting multiple data sets are analyzed using the same statistical model as for the primary analysis (i.e., linear mixed effects model with the same factors). Results from these analyses are combined using Rubin's methodology [Rubin 1987]. The results obtained from this MI analysis are expected to be similar to the main MMRM analysis since both methods rely on the same MAR assumption.

Two sensitivity analyses assuming MNAR will be performed: a control-based imputation method called J2R [Carpenter 2013] and a delta-adjusted imputation method [Yan 2009]. In each method, study participants from the placebo group that prematurely discontinue or withdraw from the study are assumed to evolve in the same way as placebo study participants who remain in the study (i.e., MAR is assumed for the placebo group). Study participants who withdraw from the study due to site closure will not be penalized. Therefore, they are assumed to evolve in the same way as the study participants who remain in the study from the same treatment group (i.e., MAR is assumed for these study participants).

The J2R imputation method can be considered conservative as it assumes that study participants from the ACT-539313 group who prematurely discontinue, or withdraw, from the study exhibit the same future evolution as placebo study participants. The same sequential procedure using linear regression models for imputing monotone missing data as described above will be used. However, predictions to replace the missing values in the ACT-539313 group will be based on data from the placebo study participants only. Consequently, the factor for treatment is omitted from the sequential regression models. After imputation, the multiply-imputed datasets are then analyzed and combined as described above. Note that the same linear mixed effects model as in the main analysis will be used.

A delta-adjusted imputation method will be used to progressively stress test the MAR assumption of the main analysis. That is, a tipping-point analysis will be performed to see how severe departures from the MAR assumption must be to overturn the conclusions of the main analysis (i.e., the point where significant results become non-significant). The assumption here is that study participants from the ACT-539313 group who discontinue from the study would have, on average, their observed efficacy score worsened by some amount (delta) compared with the efficacy observed from study participants of the same ACT-539313 group that remain in the study. A series of analyses with progressively increasing deltas ($\delta_{\text{BE days per week}}$ = 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2; from less conservative to more conservative) will be performed. The delta adjustment will only be made to the multiply-imputed values (based on the MAR assumption) for the subjects in the ACT-539313 group. Note that a delta of zero corresponds to the standard MAR-based MI analysis that is described above to obtain a reference for the sensitivity analyses. Again, the same linear mixed effects model as in the main analysis will be used.

For all the analyses described above which use MI methodology, 100 multiply-imputed datasets are created. The decision to impute 100 datasets was based on O'Kelly [O'Kelly 2014], where it is stated that the number of imputations should typically be between 20 and 100 [Graham 2007]. Similar recommendations have also been provided by other authors [Bodner 2008, Von Hippel 2009, White 2011].

For each planned sensitivity analysis, the LSMean estimate of the difference in change from baseline between ACT-539313 vs placebo at Week 12 will be provided, together with its estimated standard error and associated p-value. The LSMean estimate of the change from baseline for each treatment group at Week 12 will also be provided, together with its estimated standard error and associated p-value.

A plot over time for the primary efficacy endpoint showing the LSMean of each treatment group per imputation method (i.e., MAR; J2R; delta-adjusted including $\delta = 0$) will be provided.

Any missing diary data due to the COVID-19 pandemic is considered missing completely at random and satisfies the assumption underlying the main analysis (linear mixed-effects model, assuming missing at random). Nevertheless, efforts will be made to retain study participants in the trial and adhere to the schedule of assessments. Visits are performed at regular and short intervals for the investigator to closely follow-up with the diary completion. The COVID-19 pandemic may lead to missed or postponed visits, but the study participant's BE diary can still be evaluated at the next visit to collect the information for the primary endpoint. In addition, the study protocol accounts for remote visits in case study participants cannot, are not allowed to, or are not willing to travel to the investigator's site because of the COVID-19 pandemic. The paper-based BE diary, used to assess the primary endpoint, will be filled in by the study participants at home and subsequently reviewed by the investigator during the clinic visits. If in-person visits will be not possible because of the COVID-19 pandemic, the data will be reviewed remotely via a telephone call or a video call; delivery of BE diary booklets and/or study treatment to the trial participants' home is also foreseen under such circumstances.

6.1.7 Supportive analyses

The main analysis performed for the primary efficacy endpoint [Section 6.1.3] will be repeated using the PPS to assess the effect protocol deviations may have on the results.

In addition, the main analysis performed for the primary efficacy endpoint [Section 6.1.3] will be repeated considering all data collected to evaluate the effect intercurrent events may have on the results (see Section 14.12 for the list of BE forbidden medications).

6.1.8 Subgroup analyses

Subgroup analyses for the primary efficacy endpoint will be performed to investigate the consistency of the treatment effect (i.e., ACT-539313 vs placebo) across subgroups defined by:

Age:	18–29, 30–55 years
Sex:	Male, female
Race:	Black, White, other
BMI:	$< 30, \geq 30$ kg/m^2

Treatment effect estimates (LS Means) and their 95% CIs (obtained by conducting the primary analysis by subgroup) will be presented as forest plots with vertical reference lines at 'no effect' as well as at the 'overall treatment effect'. P-values for treatment by subgroup interaction will be provided for exploratory purposes, based on the primary analysis model extended with treatment by time and by subgroup interaction.

6.2 Secondary endpoint analysis

Not applicable.

6.3 Analysis of exploratory efficacy variables

The following efficacy endpoints will be summarized using descriptive statistics:

- Change from baseline up to Week 12 (EOT) in the number of BE episodes per week[a].
- Absence of BE episodes ('Yes'[b]/'No') during the last 4 weeks of the treatment period[c].
- Change from baseline to Week 12 (EOT) in the total score of the YBOCS-BE.
- Change from baseline to Week 12 (EOT) in the subscales scores (i.e., compulsive/obsessive, restraint, control) of the YBOCS-BE.
- Change from baseline to Week 6 (Visit 6) and to Week 12 (EOT) in the HAMD-17 total score.
- Change from baseline to Week 6 (Visit 6) and to Week 12 (EOT) in the HAMD-17 subitems 10 and 11.
- Change from baseline to Week 6 (Visit 6) and to Week 12 (EOT) in the HAMD-17 Maier-Philipp Subscale (MPS) score.
- Change from baseline to Week 12 (EOT) in EDE-Q7 global score and 3 subscales scores (i.e., dietary restraint, shape/weight overvaluation, body dissatisfaction).
- CGI-C score at Week 12 (EOT).
- PGI-C score at Week 12 (EOT).
- Change from baseline to Week 12 (EOT) in the CGI-S score.
- Change from baseline to Week 12 (EOT) in the PGI-S score.
- Change from baseline to Week 12 (EOT) in body weight.
- Change from baseline to Week 12 (EOT) in HbA1c[d].
- Improvement[e] according to CGI-C score at Week 12 (EOT).

[a] 'Number of BE episodes per week' is defined as the number of BE episodes in the applicable 14-day time interval divided by the total number of diary days, times 7.

[b] 'Yes' is defined as BE episodes equal to 0.

[c] 'Last 4 weeks of the treatment period' are defined as study days 57–84 [see Section 11.7].

[d] Glycated hemoglobin.

[e] Improvement according to CGI-C score is defined as CGI-C at Week 12 equal to "Much Improved" or "Very much improved". If CGI-C at Week 12 is missing, the study participant will be assumed to not have improved.

The above variables related to change from baseline will be summarized along with their observed values.

The YBOCS-BE is an interviewer-administered assessment developed to measure the severity of obsessive-compulsive symptoms in subjects with a diagnosis of obsessive-compulsive disorder modified to measure the BE thoughts and behaviors. The YBOCS-BE

presents three subscales: compulsive/obsessive (Items #1, 2, 3, 6, 7 and 8), restraint (Items #4 and 9), and control (Items #5 and 10).

The HAMD-17 is an indicator of depression and anxiety. The HAMD-17 consists of 17 items, with most items providing a score that ranges between 'Absent' and 'Almost all the time'. The MPS sub-score combines items 1 (depressed mood), 2 (guilt), 7 (work and activities), 8 (psychomotor retardation), 9 (psychomotor agitation), and 10 (anxiety, psychic).

EDE-Q7 is a self-reported questionnaire containing 7 of the 28 questions from the EDE-Q about eating behaviors (Items #1, 3, 4, 22, 23, 25 and 26). The EDE-Q7 presents three subscales: dietary restraint (Items #1, 3 and 4), shape/weight overvaluation (Items #22 and 23), and body dissatisfaction (Items #25 and 26).

The CGI-C is a 1-item, 7-point scale that ranges from "Very much improved" to "Very much worse".

The PGI-C is a 1-item, 7-point scale that ranges from "Very much improved" to "Very much worse".

The CGI-S is a 1-item, 7-point scale that ranges from "Normal, not at all ill" to "Among the most extremely ill patients".

The PGI-S is a question concerning the overall severity of symptoms and impact that the study participant may have experienced due to his/her BE episodes over the 7 days preceding the PGI-S completion. It ranges from "No binge eating" to "Severe".

The exploratory efficacy endpoints will be tested at two-sided 5% significance level. No further Type I error control is applied; hence, these analyses are to be considered descriptive.

The MMRM [Section 6.1.3], will be fitted for:

- The change from baseline to Week 12 (EOT) in the number of BE episodes per week, with a covariate for the baseline number of BE episodes (rather than the number of BE days) per week.
- The change from baseline to Week 12 (EOT) in EDE-Q7 global score and 3 subscales, with a covariate for the time points limited to Week 4 (Visit 5), Week 8 (Visit 7), and Week 12 (EOT).
- The change from baseline to Week 12 (EOT) in the total score of the YBOCS-BE and in the subscales scores (i.e., compulsive/obsessive, restraint, control), with a covariate for the time points limited to Week 4 (Visit 5), Week 8 (Visit 7) and Week 12 (EOT).

- The change from baseline to Week 6 (Visit 6) and to Week 12 (EOT) in the HAMD-17 total score, subitems 10 and 11, and MPS score, with a covariate for the time points limited to Week 6 (Visit 6) and Week 12 (EOT).

Absence of BE episodes will be analyzed using a logistic regression model with a factor for treatment group, sex and BMI category, and a covariate for the baseline number of BE episodes per week. For study participants who discontinued treatment prematurely, the outcome will be set to 'No absence'.

The CGI-C and PGI-C scores at Week 12 (EOT) will be compared between treatment groups using the Kruskal-Wallis test. Missing assessments at Week 12 will be imputed using last on-treatment observation carried forward.

The change from baseline to Week 12 (EOT) in the CGI-S score, PGI-S score, body weight and HbA1c will be analyzed using an ANCOVA model with a factor for treatment group and a covariate for baseline score. Missing assessments for CGI-S and PGI-S score at Week 12 will be imputed using last on-treatment observation carried forward.

The improvement according to CGI-C score at Week 12 (EOT) will be analyzed using a logistic regression model with a factor for treatment group.

[redacted]

7 SAFETY VARIABLES AND ANALYSES

7.1 Overview of safety analyses including subgroup analyses

The SAF will be used for tables and listings of safety data, unless otherwise stated.

Unless noted otherwise, only the treatment-emergent safety data will be considered in tables and figures.

All safety data described below will be listed.

7.2 Adverse events

TEAEs are defined as AEs that started or worsened on or after study treatment start date up to the EOS.

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

The number (%) of study participants experiencing a TEAE (including SAEs, AESIs, AEs leading to premature discontinuation and/or temporary interruption of study treatment) will be summarized by SOC and/or PT, and/or maximum intensity.

AESIs, defined as AE PTs denoting *somnolence* and *fatigue* will be summarized separately [Section 14.13]. Additionally, this summary will be provided by 2-week interval (Week 1–2 until Week 11–12).

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-539313 group, then in the placebo group. After this sorting, SOCs are presented in alphabetical order and PTs are sorted alphabetically within each SOC.

The following AE summary tables will be provided:

- Treatment-emergent AEs.
- Treatment-emergent AEs during the treatment period[a].
- TEAEs during the treatment period[a] related to study treatment.
- AEs leading to premature discontinuation of study treatment.
- AEs leading to temporary interruption of study treatment.
- Treatment-emergent SAEs (including occurrences).
- Treatment-emergent SAEs related to study treatment (including occurrences).
- Treatment-emergent AESIs.
- Treatment-emergent AEs during the safety follow-up period.
- TEAEs with fatal outcome.
- TEAEs related to study treatment with fatal outcome.
- Total number of deaths.

[a] Includes only those TEAEs occurring (i.e., that started or worsened) during the treatment period [see Section 11.2].

All AEs will be listed, and AESI and SAE will be flagged in the AE listing.

Separate listings will be provided for AEs leading to premature discontinuation of study treatment, AEs leading to temporary interruption of study treatment, SAEs and AESI.

All deaths will be listed, with cause of death, using the SCR set.

An AE listing, using the SCR set, will also be provided for study participants who were not randomized (i.e., screen failures) and study participants who were randomized but did not take study treatment. This listing will therefore include any study participants who discontinued the study due to AE but did not receive any study treatment.

Any other summary required for disclosure to public database will be generated as appropriate.

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 in both hematology and blood chemistry laboratory parameters.

The main laboratory parameters will be displayed graphically using boxplots considering only scheduled visit (re-test and unscheduled assessments excluded) and will be grouped (i.e., shown in the same panel) as follows:

- Hemoglobin, hematocrit, platelets, leukocytes (white blood cell count)
- Glucose, uric acid, cholesterol, triglycerides
- Total bilirubin, ALT, AST
- ALP, GGT

Marked laboratory abnormalities are defined in the appendix [Section 14.14]. The number (%) of participants with treatment-emergent 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 participants 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, GGT and BILI.
- Lipids: total cholesterol and triglycerides.
- Hematology: hemoglobin, hematocrit, platelets, leukocytes (absolute count), neutrophils (absolute count), lymphocytes (absolute count).

All laboratory data for participants with at least one marked laboratory abnormality during the treatment period will be listed. Any local laboratory data collected will be listed separately.

Elevated liver parameters during the treatment period will be summarized: the number (%) of study participants 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 study participants having at least one post-baseline value for all parameters listed below.

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

A summary table for study participants falling into the Hy's Law criteria will be provided [Andrade 2019]. This will include study participants meeting all the following criteria:

- AST or ALT > 3 × ULN
- BILI > 2 × ULN
- ALP < 2 × ULN

7.4 Electrocardiography

ECG analyses are based on data received from the central reader. 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 in ECG parameters (QT, QRS, QT corrected according to Fridericia's formula, QT corrected according to Bazett's formula, heart rate, and PR interval).

Marked ECG abnormalities are defined in Table 4. The number (%) of study participants with a marked ECG abnormality will be provided for each ECG parameter.

Percentages will be based on the number of participants having at least one post-baseline value for criteria based on post-baseline values only, or those having a baseline value and at least one post-baseline value per ECG parameter for criteria based on change from baseline. For non-mutually exclusive criteria (i.e., HR, PR and QRS), a subject will be counted only once in case of multiple occurrences but may be reported in more than one marked ECG abnormality criterion of a given parameter. For mutually exclusive criteria (i.e., QTc), only the subject's worst post-baseline value (or worst change from baseline value) will be counted.

ECG findings during the treatment period will be summarized separately and listed. ECG abnormality categories and findings will be sorted by descending frequency, first in the ACT-539313 treatment group and then in the placebo group. 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 study participants with at least one marked ECG abnormality during the treatment period will be listed.

Table 4 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 interval corrected according to Bazett's formula; QTcF = QT interval corrected 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 to each visit (Week 1, 2, 4, 6, 8, 10, 12) in vital signs (systolic and diastolic blood pressure, respiratory rate, temperature, body weight, and pulse rate) will be summarized. The observed values at baseline and each scheduled post-baseline visit will also be summarized.

7.6 Daytime sleepiness

Daytime sleepiness will be assessed using the SSS during the first two weeks of study treatment. The SSS is filled in twice daily, at breakfast before morning dose (pre-dose) and around midday, prior to lunch time (post-dose).

The SSS is a 1-item, 7-point scale that ranges between "Feeling active, vital, alert, or wide awake" and "No longer fighting sleep, sleep onset soon; having dream-like thoughts".

Daytime sleepiness is defined daily as any score > 3 on the SSS after the morning dose (post-dose).

The number of days per week with daytime sleepiness is defined as the number of diary days with at least an SSS score > 3, during the first 2 weeks of treatment only, divided by

the total number of diary days, times 7. A minimum of 7 diary entries during this 14-day time interval is required, otherwise the number of daytime sleepiness days will be considered missing. A diary day is a day for which the rate of daytime sleepiness is entered in the study participant's diary. This approach uses implicit imputation: if a subject does not have 14 entries but has at least 7, missing data points are given the same value as the mean of the non-missing data points of that same time point or week.

The mean number of days with daytime sleepiness pre- and post-dose during the 2-week period will be summarized by treatment group. In addition, the observed value and change from baseline at each study day will be summarized by treatment group. The number (%) of study participants with a post-dose SSS score ≤ 3, 4, 5, 6 and 7, having a pre-dose SSS score ≤ 3 and equal to 4 will be provided by treatment group.

The SSS score pre- and post-dose over the 2-week period will be produced by treatment group using series plot (mean ± SE) and boxplots. In addition, the series plot will be provided only for study participants with AESIs.

7.7 Withdrawal symptoms

7.7.1 Benzodiazepine Withdrawal Symptoms Questionnaire

The BWSQ consists of 20 items with each item rated by the subject as either 0 (No), 1 (Yes-moderate), or 2 (Yes-severe). The change in BWSQ Total score (possible range: 0 to 40) from the last available assessment during the treatment period to EOS will be summarized. Observed values will also be summarized.

The number (%) of study participants with a BWSQ Total score above 20 will be tabulated by visit (EOT and EOS).

The number (%) of study participants with one or more BWSQ symptom scored as 'severe' will be tabulated by visit (EOT and EOS).

In addition, withdrawal symptoms after study treatment discontinuation will be assessed through the incidence of AEs occurring during the safety follow-up period. As described in the respective section [Section 7.2], the incidence of AEs occurring during the safety follow-up period will be summarized.

7.7.2 Hamilton Depression Rating Scale

The change in HAMD-17 Total score from the last available assessment during the treatment period to EOS will be summarized. Observed values will also be summarized.

7.8 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).

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

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.

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

Based on the C-SSRS©, the number (%) of study participants with suicidal ideation by category, suicidal behavior by category, suicidal ideation or suicidal behavior, and/or self-injurious behavior without suicidal intent, during the treatment period and the safety follow-up period will be tabulated. Percentages will be based on the number of study participants with at least one post-baseline C-SSRS© assessment. The assessments done at Week 1, 2, 4, 6, 8, 10, 12 will be assigned to the treatment period while the assessment done at EOS will be assigned to the safety follow-up period.

Shift from baseline showing any change in suicidal ideation and suicidal behavior during the treatment period and the safety follow-up period will be provided. Study participants 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 (study participants with both suicidal ideation and suicidal behavior are also included in the suicidal behavior category).

8 PHARMACOKINETIC VARIABLES AND ANALYSES

PK analyses will be performed using the PK set.

Descriptive statistics for the ACT-539313 plasma concentrations collected prior to the morning dosing at Week 4, Week 8 and Week 12 will be provided by age group and overall: n, mean, SD, CV%, m (number of non-zero concentrations), geometric mean, geometric SD, geometric CV%, median, minimum and maximum. These concentration values will also be displayed graphically by visit: scatter plots vs BMI by sex; and boxplots for age categories (18–29, 30–55 years) and all ages combined.

Concentration values below the lower limit of quantification will be displayed in listings as ‘BLQ’ and handled as zero in the calculations for mean, CV%, SD, median, minimum,

and maximum, but handled as missing for the calculation of the geometric mean, geometric SD, and geometric CV%.

All individual ACT-539313 plasma concentration data will be listed.

Plasma samples might also be used by Idorsia Preclinical Pharmacokinetics and Metabolism department for exploratory assessments of circulating metabolites of ACT-539313.

9 GENERAL STATISTICAL METHODOLOGY

9.1 General rules for data presentations

Data are listed and summarized as described below.

The tables will use the following header structure (label and order):

ACT-539313 100 mg *N = xxx*	*Placebo* *N = xxx*

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), subject number (ascending) and, when appropriate, by visit / date of assessment (ascending). Listings related to the SCR set will present a treatment group label ‘screening failure’ to indicate study participants who were not randomized and will be listed after the study participants who were randomized or received study treatment, as relevant.

Unless noted otherwise, the following descriptive statistics will be used to summarize data: number (%) of study participants for categorical variables, or descriptive statistics (number of non-missing values, mean, SD, median, Q1, Q3, minimum, maximum) for continuous variables.

9.2 Handling of missing dates

An incomplete date (day or month missing), or missing concomitant therapy / AE date, will be imputed as described in Table 5. The ‘lower limit’ and ‘upper limit’ refer to the earliest and latest possible dates, respectively.

As an example: if concomitant therapy start date / AE onset date is MAR2021 (day missing), the lower limit is 01MAR2021 and the upper limit is 31MAR2021; if concomitant therapy start date / AE onset date is 2021 (day and month missing), the lower limit is 01JAN2021 and the upper limit is 31DEC2021.

Table 5 Imputation rules for an incomplete or missing concomitant therapy or AE date

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

AE = adverse event.

The purpose of imputing concomitant therapy / AE dates is only to assign a concomitant therapy / AE to a specific study period for the summary tables. No imputed date is considered in the medical evaluation or causal relationship to an individual AE.

10 INTERIM ANALYSES

No 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*).

11 GENERAL DEFINITIONS AND DERIVATIONS

11.1 Treatment start and end dates

Study treatment start or end date is the earliest or latest, respectively, date of dose intake recorded on the 'Study Treatment Log' page.

11.2 Study periods

The Screening period is defined as the time from the informed consent date until one day before the study treatment start date, or date of screening failure.

The treatment period is defined as the time from the day of study treatment start until the day of EOT (Week 12), or, for those who prematurely discontinued study treatment (i.e., those without an EOT date), until the day of study treatment end date. In case of missing

study treatment end date, EOT will be imputed using the last available visit/assessment date.

The safety follow-up period is defined as the time from one day after EOT until EOS date.

11.3 Treatment day and Study day

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

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

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

The first day of study treatment is Treatment day 1.

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

Treatment day (days) = Date of assessment/event – Start date of 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, Study day will be positive and will be 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 will be 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

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

The baseline number of BE days per week is defined as the number of diary days with at least one BE episode divided by the total number of diary days during the 14 days prior to randomization (Study day –14 to –1), times 7 [see Section 6.1.1 for definition of diary day]. A minimum of 6 entries for each of the 2 weeks preceding randomization is required per inclusion criteria to ensure study participant compliance with filling in the BE diary.

Study participants with no data for a given parameter before the first treatment administration will have a missing baseline (and missing change from baseline) for this parameter.

11.5 Change from baseline

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

11.6 Missing data patterns

A monotone missing data pattern is defined as follows: given a dataset with variables Y1, Y2, …, Yt (in that order) and Vj is missing for a particular subject, then all subsequent variables Vk, k > j, are missing for that subject. In addition, given the same dataset and Vj is observed for a particular subject, then all previous variables Vk, k < j, are also observed for that subject. Monotone missing data patterns are typically encountered when a subject prematurely withdraws from a study and is expected to be more likely seen than non-monotone missing data patterns.

In the examples below, an 'X' indicates that the variable is observed in the corresponding group and a '.' means that the variable is missing.

Example of monotone missing data patterns:

Subject	Y1	Y2	Y3
1	X	X	X
2	X	X	.
3	X	.	.

When missing data are non-monotone, data can also be missing at intermediate visits (i.e., missing at a given visit, but observed again at the next visit). Non-monotone missing data patterns are commonly turned into monotone missing data patterns using MI (based on MCMC), which are then subsequently analyzed using MI methods based on monotone missing data.

Example of non-monotone missing data patterns:

Subject	Y1	Y2	Y3
1	X	X	X
2	.	X	X
3	.	.	X
4	.	X	.
5	X	.	X

11.7 Time window definitions for calculating efficacy and safety endpoints collected through diary

BE episodes (efficacy) and daytime sleepiness (safety; measured using the SSS) are the endpoints collected daily through a diary. The BE diary will be filled in from the start of the screening period until EOT while the SSS will only be filled in during the first 2 weeks of treatment (from randomization [Visit 2] to Visit 4).

Table 6 defines the time windows used to calculate number of BE episodes/days per week.

Table 6 Time windows (in days) to calculate weekly averages for the efficacy endpoints BE episodes/days collected daily through the diary

Weeks	Study day (14-day window)
1–2	1–14
3–4	15–28
5–6	29–42
7–8	43–56
9–10	57–70
11–12	71–84

For the calculation of absence of BE episodes ('Yes'/'No') during the last 4 weeks of the treatment period, a minimum of 4 out of 7 diary entries are required for days 57–63, 64–70, 71–77 and 78–84, otherwise the outcome will be set to 'No absence'. Absence of BE episodes ('Yes') is defined as BE episodes equal to 0.

For the calculation of SSS, study days falling in the time window 2–15 will be considered for the analyses since study day 1 corresponds to assessments done on the day of the randomization where information on the SSS should not be collected.

11.8 Time window definitions for calculating exploratory efficacy and safety endpoints collected during site visits

The exploratory efficacy endpoints YBOCS-BE, PGI-S, CGI-S, PGI-C, CGI-C, EDE-Q, and HAMD-17 are collected during specific site visits [Table 7].

The safety endpoint C-SSRS© is collected during all site visits [Table 8].

For both efficacy and safety endpoints, if more than one assessment falls within the same time window, the assessment which is performed closest to the target study day will be considered for the analysis.

Table 7 Time windows (in days) for visit-based exploratory efficacy endpoints: YBOCS-BE, PGI-S, CGI-S, PGI-C, CGI-C, EDE-Q, HAMD-17

Week	Target study day	Window	Endpoint
Baseline	1	1–1	YBOCS-BE, PGI-S, CGI-S, EDE-Q, HAMD-17
1	8	2–14	CGI-C, PGI-C
4	29	22–36	YBOCS-BE, PGI-S, CGI-S, PGI-C, CGI-C, EDE-Q
6	43	37–49	HAMD-17
8	57	50–64	YBOCS-BE, PGI-S, CGI-S, PGI-C, CGI-C, EDE-Q
12	85	78–92	YBOCS-BE, PGI-S, CGI-S, PGI-C, CGI-C, EDE-Q, HAMD-

CGI-C = Clinical Global Impression of Change scale; CGI-S = Clinical Global Impression of Severity scale; EDE-Q = Eating Disorder Examination Questionnaire; HAMD-17 = Hamilton Rating Scale for Depression (17-item); PGI-C = Patient Global Impression of Change scale; PGI-S = Patient Global Impression of Severity scale; YBOCS-BE = Yale-Brown Obsessive-Compulsive Scale modified for Binge Eating.

Table 8 Time windows (in days) for C-SSRS©

Week	Target study day	Window
Baseline	1	1–1
1	8	5–11
2	15	12–18
4	29	22–36
6	43	37–49
8	57	50–64
10	71	65–77
12	85	78–92

C-SSRS© = Columbia-Suicide Severity Rating Scale©

12 CHANGES OR CLARIFICATIONS TO ANALYSES PLANNED IN THE STUDY PROTOCOL

12.1 Changes to the analyses planned in the study protocol

Demographics and disease characteristics will be analyzed using the RND and the same summaries will be produced also for screen failures using the SCR. The FAS and PPS will not be used for these analyses.

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.

12.4 Additional analyses to those planned in the study protocol

Not applicable.

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14 APPENDICES

14.1 SAS® code for Mixed Model for Repeated Measures

This model is used, for example, for the main analyses of the primary and some exploratory efficacy endpoints. Assuming the data are in 'long' format (i.e., one row for each subject/visit) example SAS® statements for the primary endpoint analysis are:

```
proc mixed data=data;
      class SUBJID SEX BMIGR TRT VIS;
      model CHG = BASE SEX BMIGR TRT VIS TRT*VIS BASE*VIS / ddfm=kr
      residual outp=mixtable;
      lsmeans TRT*VIS / diff cl;
      repeated VIS / subject=SUBJID type=un;
      estimate 'ACT-539313 vs placebo at Week 12' TRT 1 -1 TRT*VIS 0 0 0 0 0 1 0 0
      0 0 0 -1 / cl;
      ods output lsmeans=lsmeans estimates=estimates StudentPanel=StudentPanel
      FitStatistics=aic NObs=nobs;
run;
```

The dataset *data* includes baseline number of BE days (BASE) as well as changes (CHG) from baseline to Weeks 1–2, 3–4, 5–6, 7–8, 9–10, 11–12 (VIS) and BMI as categorical variable (BMIGR). Furthermore, TRT equals 1 and 2 for ACT-539313 and placebo, respectively. The model option *residual*, *outp=mixtable* and the statement *ods outout* are used to run the model diagnostic for the main analysis only.

If a sandwich estimator has to be used, the option *'empirical'* will be added to the proc mixed statement: proc mixed data=data empirical.

14.2 SAS® code for multiple imputation with MCMC for monotone missingness mechanism

This SAS® statement is used to set the missing data with a monotone pattern for the preliminary step of the multiple imputation. Assuming the data are in 'wide' format (i.e., one row for each subject with one variable for each visit) example SAS® statements are:

```
proc mi data=data  wide nimpute=100 seed=401293 minimum=. . 0 0 0 0 0 0 0
      maximum=. . 7 7 7 7 7 7 7 out=data  mono;
      by  TRT  ;
      var SEX BMI BASE OBST1 OBST2 OBST3 OBST4 OBST5 OBST6;
      /* BMI is continuous */
      mcmc impute=monotone;
run;
```

The dataset *data_wide* includes baseline number of BE days (BASE) as well as number of BE days at Week 1–2 (OBST1), Week 3–4 (OBST2), Week 5–6 (OBST3), Week 7–8 (OBST4), Week 9–10 (OBST5) and Week 11–12 (OBST6). The dataset *data_mono* includes the same variables but with eventual non-monotone missing data for BASE or OBST1 or OBST2 or OBST3 or OBST4 or OBST5 or OBST6 being imputed. The imputation is performed 100 times, so *data_mono* includes 100 different data sets, one for each non-monotone missing data imputation.

14.3 SAS® code for multiple imputation under MAR assumption

This SAS® statement is used to perform multiple imputation under MAR assumption after the dataset has being set to a monotone missingness pattern. Assuming the data are in 'wide' format (i.e., one row for each subject with one variable for each visit) and with a monotone pattern, example SAS® statements are:

```
/* multiple imputation */
proc mi data=data  mono nimpute=1 seed=375910 minimum=. . . 0 0 0 0 0 0 0
      maximum=. . . 7 7 7 7 7 7 7 out=data  mi noprint;
      by   IMPUTATION  ;            /* flag variable for imputation from proc mi */
      class TRT SEX BMIGR;
      var TRT SEX BMIGR BASE OBST1 OBST2 OBST3 OBST4 OBST5 OBST6;
      monotone regression;
run;
```

The dataset *data_mono* includes baseline number of BE days (BASE) as well as number of BE days at Week 1–2 (OBST1), Week 3–4 (OBST2), Week 5–6 (OBST3), Week 7–8 (OBST4), Week 9–10 (OBST5) and Week 11–12 (OBST6), and BMI as categorical variable (BMIGR). The dataset *data_mi* includes the same variables but without missing data because eventual monotone missing data for BASE or OBST1 or OBST2 or OBST3 or OBST4 or OBST5 or OBST6 have been imputed.

The following SAS® statements are used to perform the analysis with the MMRM and to combine all the 100 datasets produced with the MI under MAR assumption. Assuming the data are in 'long' format (i.e., one row for each subject/visit) after *data_mi* has been transposed to *data_mi_long*, with a monotone pattern and without missing data, example SAS® statements are:

```
/* analyze the results */
ods output lsmeans=mixparms diffs=diffparms (where=(  TRT='PLACEBO' and
      VIS=  VIS));
proc mixed data=data_mi_long;
      by   IMPUTATION  ;            /* flag variable for imputation from proc mi */
      class SUBJID SEX BMIGR TRT VIS;
      model CHG = BASE SEX BMIGR TRT VIS TRT*VIS BASE*VIS / ddfm=kr;
```

```
        lsmeans TRT*VIS / diff cl;
        repeated VIS / subject=SUBJID type=un;
run;
```

The model is the same as for the main analysis [Section 14.1] but is run for each of the 100 datasets produced with the MI under MAR assumption (_IMPUTATION_).

The results are then combined with the following SAS® statements:

```
/* combine the results */
proc mianalyze parms=mixparms;
        class TRT VIS;
        modeleffects TRT*VIS;
run;
proc mianalyze parms=diffparms;
        class TRT VIS;
        modeleffects TRT*VIS;
run;
```

The dataset *mixparms* includes the LSMeans from the 100 imputed datasets and the dataset *diffparms* includes the treatment differences (ACT-539313 – Placebo) from the 100 imputed datasets.

14.4 SAS® code for multiple imputation under MNAR assumption for the jump to reference method

This SAS® statement is used to perform multiple imputation under MNAR assumption after the dataset has being set to a monotone missingness pattern. Imputations are performed sequentially for each time point: Week 1–2 (OBST1) then Week 3–4 (OBST2) then Week 5–6 (OBST3) then Week 7–8 (OBST4) then Week 9–10 (OBST5) and finally Week 11–12 (OBST6). Assuming the data are in 'wide' format (i.e., one row for each subject with one variable for each visit) and with a monotone pattern, example SAS® statements are:

```
/*** multiple imputation ***/

/*** OBST1 ***/
proc mi data=data  mono nimpute=1 seed=163882 minimum=. . . 0 0 maximum=. . . 7 7
        out=data  mi2 noprint;
        by   IMPUTATION  ;              /* flag variable for imputation from proc mi */
        class TRT SEX BMIGR;
        var SEX BMIGR BASE OBST1;
        monotone regression;
        mnar model (OBST1 / modelobs=(TRT='PLACEBO'));
```

```
run;
```

The dataset *data_mono* includes baseline number of BE days (BASE) as well as BMI as categorical variable (BMIGR) and the number of BE days at all time points (i.e., Week 1–2, Week 3–4, Week 5–6, Week 7–8, Week 9–10 and Week 11–12), but imputations are performed sequentially for each time point. In this case is Week 1–2 (OBST1). The model imputes missing data taking information from subjects receiving placebo (modelobs = (TRT = 'PLACEBO')).

The dataset generated (*data_mi2*) is then used to impute the missing data at the next time point (Week 3–4) as shown in the SAS® statement below (OBST2). The process proceeds in the same way for the other time points until the last one (Week 11–12, OBST6).

```
/*** OBST2 ***/
proc mi data=data  mi2 nimpute=1 seed=163882 minimum=. . . 0 0 maximum=. . . 7 7
      out=data  mi3 noprint;
      by   IMPUTATION  ;            /* flag variable for imputation from proc mi */
      class TRT SEX BMIGR;
      var SEX BMIGR BASE OBST2;
      monotone regression;
      mnar model (OBST2 / modelobs=(TRT='PLACEBO'));
run;

/*** OBST3 ***/
proc mi data=data  mi3 nimpute=1 seed=163882 minimum=. . . 0 0 maximum=. . . 7 7
      out=data  mi4 noprint;
      by   IMPUTATION  ;            /* flag variable for imputation from proc mi */
      class TRT SEX BMIGR;
      var SEX BMIGR BASE OBST3;
      monotone regression;
      mnar model (OBST3 / modelobs=(TRT='PLACEBO'));
run;

/*** OBST4 ***/
proc mi data=data  mi4 nimpute=1 seed=163882 minimum=. . . 0 0 maximum=. . . 7 7
      out=data  mi5 noprint;
      by   IMPUTATION  ;            /* flag variable for imputation from proc mi */
      class TRT SEX BMIGR;
      var SEX BMIGR BASE OBST4;
      monotone regression;
      mnar model (OBST4 / modelobs=(TRT='PLACEBO'));
run;
```

```
/*** OBST5 ***/
proc mi data=data  mi5 nimpute=1 seed=163882 minimum=. . . 0 0 maximum=. . . 7 7
        out=data  mi6 noprint;
        by   IMPUTATION  ;              /* flag variable for imputation from proc mi */
        class TRT SEX BMIGR;
        var SEX BMIGR BASE OBST5;
        monotone regression;
        mnar model (OBST5 / modelobs=(TRT='PLACEBO'));
run;


/*** OBST6 ***/
proc mi data=data  mi6 nimpute=1 seed=163882 minimum=. . . 0 0 maximum=. . . 7 7
        out=data  mi7 noprint;
        by _IMPUTATION_;              /* flag variable for imputation from proc mi */
        class TRT SEX BMIGR;
        var SEX BMIGR BASE OBST6;
        monotone regression;
        mnar model (OBST6 / modelobs=(TRT='PLACEBO'));
run;
```

The 9 study participants forced to discontinue due to site closure will be imputed using MAR assumption setting the seed to 163882.

14.5 SAS® code for multiple imputation under MNAR assumption for the delta-adjusted tipping point method

This SAS® statement is used to perform multiple imputation under MNAR assumption after the dataset has being set to a monotone missingness pattern. Imputations are performed sequentially for each time point: Week 1–2 (OBST1) then Week 3–4 (OBST2) then Week 5–6 (OBST3) then Week 7–8 (OBST4) then Week 9–10 (OBST5) and finally Week 11–12 (OBST6). Assuming the data are in 'wide' format (i.e., one row for each subject with one variable for each visit) and with a monotone pattern, example SAS® statements for the implementation of the macro for delta-adjusted tipping point are:

```
/*** multiple imputation ***/
%macro midata(data=, smin=, smax=, sinc=, out=);
data &out;
        set   null  ;
run;
/*------------# of shift values ------------*/
%let ncase= %sysevalf( (&smax-&smin)/&sinc, ceil );
```

```
/*-------Imputed data for each shift -------*/
%do jc=0 %to &ncase;
%let sj= %sysevalf( &smin + &jc * &sinc);
proc mi data=&data seed=295104 nimpute=1 minimum=. . . 0 0 0 0 0 0 0 maximum=. . .
        7 7 7 7 7 7 7 out=outmi;
        by   IMPUTATION  ; /* flag variable for imputation from proc mi */
        class TRT ASEX BMIGR;
        monotone regression;
        mnar adjust(obst1 / shift=&sj adjustobs=(TRT = 'ACT-539313 100 mg'));
        mnar adjust(obst2 / shift=&sj adjustobs=(TRT = 'ACT-539313 100 mg'));
        mnar adjust(obst3 / shift=&sj adjustobs=(TRT = 'ACT-539313 100 mg'));
        mnar adjust(obst4 / shift=&sj adjustobs=(TRT = 'ACT-539313 100 mg'));
        mnar adjust(obst5 / shift=&sj adjustobs=(TRT = 'ACT-539313 100 mg'));
        mnar adjust(obst6 / shift=&sj adjustobs=(TRT = 'ACT-539313 100 mg'));
        var TRT ASEX BMIGR BASE obst1 obst2 obst3 obst4 obst5 obst6;
run;
data outmi;
        set outmi;
        Shift= &sj;
run;
data &out;
        set &out outmi;
run;
%end;
%mend midata;
```

%midata(data=fin_mi_mono, smin=0, smax=2, sinc=0.25, out=be5);

The 9 study participants forced to discontinue due to site closure will be imputed using MAR assumption setting the seed to 295104.

14.6 SAS® code for logistic regression of absence of BE episodes during the last 4 weeks of treatment

This model adjusts for baseline number of BE days (BASE), sex (SEX), BMI as categorical variable (BMIGR), and treatment (TRT). Reference categories are placebo for treatment and obese (BMI ≥ 30) for BMI. Example SAS® statements for the analysis are:

```
proc logistic data=data;
        class TRT (ref='PLACEBO') SEX BMIGR (ref='OBESE');
        model Y (event='1') = TRT SEX BMIGR BASE / clodds=wald orpvalue;
run;
```

This code provides confidence limit for the proportion of study participants with and without absence of BE episodes during the last 4 weeks of treatment.

```
proc freq data=data;
      table Y / binomial(level='1');
      by TRT;
run;
```

14.7 SAS® code for logistic regression of improvement according to CGI-C score at Week 12

This model adjusts only for treatment (TRT) and the reference category is placebo. Example SAS® statements for the analysis are:

```
proc logistic data=data;
      class TRT (ref='PLACEBO');
      model Y2 (event='1') = TRT / clodds=wald orpvalue;
run;
```

This code provides confidence limit for the proportion of study participants with and without improvement according to CGI-C score at Week 12.

```
proc freq data=data;
      table Y / binomial(level='1');
      by TRT;
run;
```

14.8 SAS® code for Kruskal-Wallis test of CGI-C and PGI-C scores at Week 12

Example SAS® statements for the analysis are:

```
proc npar1way data=data wilcoxon;
      class TRT;
      var CGI-C;              /* this will be updated with PGI-C for PGI-C analysis */
run;
```

14.9 SAS® code for ANCOVA of change from baseline to Week 12 in CGI-S score, PGI-S score, body weight and HbA1c

This model is used for some exploratory efficacy endpoints. Example SAS® statements for the analysis are:

```
proc mixed data=data;
      class TRT;
      model CHG = BASE TRT / noint solution;
```

```
    /* change and baseline will be updated with the corresponding endpoint */
    lsmeans TRT / diff cl;
run;
```

The dataset *data* includes baseline number of BE days (BASE) as well as change (CHG) from baseline to Week 11–12 and treatment (TRT).

14.10 SAS® code for subgroup analyses

14.10.1 Age

The dataset *data* is the same dataset used for the main analysis. The order of the variable is important: TRT equals 1 and 2 for ACT-539313 and placebo, respectively. The first AGEGR is age 18–29 and then 30–55.

```
proc mixed data=data;
    class SUBJID SEX BMIGR TRT VIS AGEGR;
    model CHG = BASE SEX BMIGR TRT VIS TRT*VIS BASE*VIS AGEGR
    AGEGR*TRT AGEGR*VIS AGEGR*TRT*VIS / ddfm=kr;
    repeated VIS / subject=SUBJID type=un;
    estimate 'Age 18-29: ACT-539313 vs placebo at Week 12'
        TRT 1 -1 TRT*VIS 0 0 0 0 0 1 0 0 0 0 0 -1 TRT*AGEGR 1 0 -1 0
        AGEGR*TRT*VIS 0 0 0 0 0 0 0 0 0 0 1 0 0 0 0 0 0 0 0 0 0 -1 0 / cl;
    estimate 'Age 30-55: ACT-539313 vs placebo at Week 12'
        TRT 1 -1 TRT*VIS 0 0 0 0 0 1 0 0 0 0 0 -1 TRT*AGEGR 0 1 0 -1
        AGEGR*TRT*VIS 0 0 0 0 0 0 0 0 0 0 0 1 0 0 0 0 0 0 0 0 0 0 -1 / cl;
    estimate 'Treatment by age interaction p-value at Week 12'
        TRT*AGEGR 1 -1 -1 1
        AGEGR*TRT*VIS 0 0 0 0 0 0 0 0 0 0 1 -1 0 0 0 0 0 0 0 0 0 0 -1 1;
run;
```

14.10.2 Sex

The dataset *data* is the same dataset used for the main analysis. The order of the variable is important: TRT equals 1 and 2 for ACT-539313 and placebo, respectively. The first SEX is female and then male.

```
proc mixed data=data;
    class SUBJID SEX BMIGR TRT VIS;
    model CHG = BASE SEX BMIGR TRT VIS TRT*VIS BASE*VIS SEX*TRT
    SEX*VIS SEX*TRT*VIS / ddfm=kr;
    repeated VIS / subject=SUBJID type=un;
    estimate 'Female: ACT-539313 vs placebo at Week 12'
        TRT 1 -1 TRT*VIS 0 0 0 0 0 1 0 0 0 0 0 -1 TRT*SEX 1 -1 0 0
        SEX*TRT*VIS 0 0 0 0 0 1 0 0 0 0 0 -1 0 0 0 0 0 0 0 0 0 0 0 0 / cl;
    estimate 'Male: ACT-539313 vs placebo at Week 12'
```

```
        TRT 1 -1 TRT*VIS 0 0 0 0 0 1 0 0 0 0 0 -1 TRT*SEX 0 0 1 -1
        SEX*TRT*VIS 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 1 0 0 0 0 0 -1 / cl;
    estimate 'Treatment by sex interaction p-value at Week 12'
        TRT*SEX 1 -1 -1 1
        SEX*TRT*VIS 0 0 0 0 0 1 0 0 0 0 0 -1 0 0 0 0 0 -1 0 0 0 0 0 1;
run;
```

14.10.3 BMI

The dataset *data* is the same dataset used for the main analysis. The order of the variable is important: TRT equals 1 and 2 for ACT-539313 and placebo, respectively. The first BMI is < 30 and then ≥ 30.

```
proc mixed data=data;
    class SUBJID SEX BMIGR TRT VIS;
    model CHG = BASE SEX BMIGR TRT VIS TRT*VIS BASE*VIS BMI*TRT
    BMI*VIS BMI*TRT*VIS / ddfm=kr;
    repeated VIS / subject=SUBJID type=un;
    estimate 'BMI < 30: ACT-539313 vs placebo at Week 12'
        TRT 1 -1 TRT*VIS 0 0 0 0 0 1 0 0 0 0 0 -1 TRT*BMI 1 -1 0 0
        BMI*TRT*VIS 0 0 0 0 0 1 0 0 0 0 0 -1 0 0 0 0 0 0 0 0 0 0 0 / cl;
    estimate 'BMI ≥ 30: ACT-539313 vs placebo at Week 12'
        TRT 1 -1 TRT*VIS 0 0 0 0 0 1 0 0 0 0 0 -1 TRT*BMI 0 0 1 -1
        BMI*TRT*VIS 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 1 0 0 0 0 0 -1 / cl;
    estimate 'Treatment by BMI interaction p-value at Week 12'
        TRT*BMI 1 -1 -1 1
        BMI*TRT*VIS 0 0 0 0 0 1 0 0 0 0 0 -1 0 0 0 0 0 -1 0 0 0 0 0 1;
run;
```

14.10.4 Race

The dataset *data* is the same dataset used for the main analysis. The order of the variable is important: TRT equals 1 and 2 for ACT-539313 and placebo, respectively. The variable RACE is a new variable where all categories different from 'white' and 'black' are grouped under 'other' (i.e., the new derived variable race has 3 levels: first black, then other and finally white).

```
proc mixed data=data;
    class SUBJID SEX BMIGR TRT VIS RACE;
    model CHG = BASE SEX BMIGR TRT VIS TRT*VIS BASE*VIS RACE
    RACE*TRT RACE*VIS RACE*TRT*VIS / ddfm=kr;
    repeated VIS / subject=SUBJID type=un;
    estimate 'Black: ACT-539313 vs placebo at Week 12'
        TRT 1 -1 TRT*VIS 0 0 0 0 0 1 0 0 0 0 0 -1 TRT*RACE 1 0 0 -1 0 0
```

```
        RACE*TRT*VIS 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 1 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
        -1 0 0 / cl;
    estimate 'Other: ACT-539313 vs placebo at Week 12'
        TRT 1 -1 TRT*VIS 0 0 0 0 0 1 0 0 0 0 0 -1 TRT*RACE 0 1 0 0 -1 0
        RACE*TRT*VIS 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 1 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
        0 -1 0 / cl;
    estimate 'White: ACT-539313 vs placebo at Week 12'
        TRT 1 -1 TRT*VIS 0 0 0 0 0 1 0 0 0 0 0 -1 TRT*RACE 0 0 1 0 0 -1
        RACE*TRT*VIS 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 1 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
        0 0 -1 / cl;
    contrast 'Treatment by race interaction p-value at Week 12'
        TRT*RACE 1 -1 0 -1 1 0
        RACE*TRT*VIS 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 1 -1 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
        0 -1 1 0,
        TRT*RACE 1 0 -1 -1 0 1
        RACE*TRT*VIS 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 1 0 -1 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
        0 -1 0 1;
run;
```

14.11 SAS® code for non-parametric analysis of the primary endpoint

This code produces standardized ranks for covariate baseline (BASE) and response variable change (CHG):

```
proc rank data=data nplus1 ties=mean out=ranks;
    var BASE CHG;
run;
```

Linear regression on standardized ranks:

```
proc reg data=ranks noprint;
    model CHG = BASE;
    output out=residual r=resid;
run;
```

Mean score test, using values of residuals as scores, to compare treatment groups:

```
proc freq data=residual;
    table TRT*resid / noprint cmh2;
run;
```

Bootstrapping for win/ratio estimate will be implemented using the following SAS code:

```
proc surveyselect data=data out=boot seed=380174 method=urs samprate=1 reps=10000
      outhits;
      strata TRT;
run;
```

14.12 List of BE forbidden medication

Table 9 BE forbidden medication

Medication
lisdexamfetamine (Vyvanse)
topiramate (Topamax)
bupropion (Aplenzin, Forfivo, Wellbutrin)
olanzapine (Zyprexa)
fluoxetine (Prozac)
other SSRIs such as citalopram, escitalopram, sertraline, paroxetine, fluvoxamine
SNRIS such as duloxetine, desvenlafaxine, venlafaxine
other anticonvulsants such as zonisamide and lamotrigine
bupropion-naltrexone (Contrave)
liraglutide (Saxenda)
orlistat (Alli, Xenical)
phentermine-topiramate (Qsymia)
setmelanotide (IMCIVREE)
semaglutide (Wegovy)
lorcaserin (Belviq)
phentermine (Adipex-P. Suprenza)
sibutramine (Meridia)
benzphetamine
diethylpropion
phendimetrazine

14.13 List of adverse events of special interest

Table 10 Adverse events of special interest

MedDRA code	Preferred Term
10010305	Confusional state
10013395	Disorientation
10016256	Fatigue
10016322	Feeling abnormal
10024264	Lethargy
10027175	Memory impairment
10039897	Sedation
10041052	Sluggishness
10041349	Somnolence
10079741	Sedation complication

MedDRA version 24.1.

14.14 Marked abnormalities in laboratory parameters for reporting

Table 11 Abnormal laboratory values: Hematology (SI units)

Laboratory test name (CDISC Synonym[s])	LL	LLL	HH	HHH
Hemoglobin – g/L (*baseline value within normal range*)	< 100	< 80	> ULN + 20	> ULN + 40
Hemoglobin – g/L (*baseline value >ULN*)	< 100	< 80	> baseline + 20	> baseline + 40
Hematocrit – L/L (*men*)	< 0.32	< 0.20	> 0.60	> 0.65
Hematocrit – L/L (*women*)	< 0.28	< 0.20	> 0.55	> 0.65
Platelets* – 10e9/L *(assuming no platelet cluster)*	< 75	< 50	> 600	> 999
Leucocytes* – 10e9/L	< 3.0	< 2.0	> 20.0	> 100.0
Granulocytes – % *PLUS* Neutrophils Band Form	NA	NA	> 90	> 95
Neutrophils* – 10e9/L	< 1.5	< 1.0	NA	NA
Eosinophils*– 10e9/L	NA	NA	> 5.0	NA
Lymphocytes* – 10e9/L	< 0.8	< 0.5	> 4.0	> 20

* The conventional unit for platelet count, leucocytes, neutrophils, eosinophils and lymphocytes is "/uL" but "/mm^3" may also be seen in scientific literature. Both "/uL" and "/mm^3" are interchangeable, i.e. the same conversion factor of 1 applies.

L1 = LLL, L2 = LL, H1 = HH, H2 = HHH.

NA = not applicable; ULN = upper limit of normal.

Table 12 Abnormal laboratory values: Hematology (Conventional units)

Laboratory test name (CDISC Synonym[s])	LL	LLL	HH	HHH
Hemoglobin – g/dL (*baseline value within normal range*)	< 10	< 8	> ULN + 2	> ULN + 4
Hemoglobin – g/dL (*baseline value >ULN*)	< 10	< 8	> baseline + 2	> baseline + 4
Hematocrit – % (*men*)	< 32	< 20	> 60	> 65
Hematocrit – % (*women*)	< 28	< 20	> 55	> 65
Platelets* – /uL *(assuming no platelet cluster)*	< 75000	< 50000	> 600000	> 999000
Leucocytes* – /uL	< 3000	< 2000	> 20000	> 100000
Granulocytes – % *PLUS* Neutrophils Band Form	NA	NA	> 90	> 95

Laboratory test name (CDISC Synonym[s])	LL	LLL	HH	HHH
Neutrophils* – /uL	< 1500	< 1000	NA	NA
Eosinophils* – /uL	NA	NA	> 5000	NA
Lymphocytes* – /uL	< 800	< 500	> 4000	> 20000

* The conventional unit for platelet count, leucocytes, neutrophils, eosinophils and lymphocytes is "/uL" but "/mm^3" may also be seen in scientific literature. Both "/uL" and "/mm^3" are interchangeable, i.e. the same conversion factor of 1 applies.

L1 = LLL; L2 = LL; H1 = HH; H2 = HHH.
NA = not applicable; ULN = upper limit of normal.

Table 13 Abnormal laboratory values: Blood chemistry (SI units)

Laboratory test name (CDISC Synonym[s])	LL	LLL	HH	HHH
Alanine Aminotransferase; SGPT	NA	NA	> 3 × ULN	> 5 × ULN
Aspartate Aminotransferase; SGOT	NA	NA	> 3 × ULN	> 5 × ULN
Gamma Glutamyl Transferase	NA	NA	> 2.5 × ULN	> 5 × ULN
Alkaline Phosphatase	NA	NA	> 2.5 × ULN	> 5 × ULN
Bilirubin; Total Bilirubin	NA	NA	> 2 × ULN	> 5 × ULN
Prothrombin Intl. Normalized Ratio	NA	NA	>1.5 × ULN	> 2.5 × ULN
Prothrombin Intl. Normalized Ratio (for subjects on anticoagulant treatment)	NA	NA	> 1.5 × baseline	> 2.5 × baseline
Creatinine	NA	NA	> 1.5 × ULN	> 3 × ULN
Creatinine (baseline value >ULN)	NA	NA	> 1.5 × baseline	> 3 × baseline
Glucose – mmol/L (Non-diabetic, Fasting)	< 3.0	< 2.2	> 8.9	> 13.9
Calcium – mmol/L	< 2.0	< 1.75	> 2.9	> 3.1
Ionized calcium – mmol/L	< 1.0	< 0.9	> 1.5	> 1.6
Sodium – mmol/L	NA	< 130	> 150	> 155
Potassium – mmol/L	< 3.2	< 3.0	> 5.5	> 6.0
Magnesium – mmol/L	< 0.5	< 0.4	NA	> 1.23
Phosphate – mmol/L	< 0.8	< 0.6	NA	NA
Creatine Kinase	NA	NA	> 5 × ULN	> 10 × ULN
Urate; Uric Acid – umol/L	NA	NA	> 590	> 720
Albumin – g/L	< 30	< 20	NA	NA
Glomerular Filtration Rate – ml/min/ 1.73 m2	< 60	< 30	NA	NA
Creatinine Clearance – ml/min/ 1.73 m2	< 60	< 30	NA	NA

Laboratory test name (CDISC Synonym[s])	LL	LLL	HH	HHH
Blood Urea Nitrogen	NA	NA	> 2.5 × ULN	> 5 × ULN
Chloride – mmol/L	NA	< 80	> 115	NA
Total Cholesterol – mmol/L	NA	NA	> 7	NA
Triglycerides – mmol/L	NA	NA	> 5.7	NA

L1 = LLL, L2 = LL, H1 = HH, H2 = HHH.
NA = not applicable; ULN = upper limit of normal.

Table 14 Abnormal laboratory values: Blood chemistry (Conventional units)

Laboratory test name (CDISC Synonym[s])	LL	LLL	HH	HHH
Alanine Aminotransferase; SGPT	NA	NA	> 3 × ULN	> 5 × ULN
Aspartate Aminotransferase; SGOT	NA	NA	> 3 × ULN	> 5 × ULN
Gamma Glutamyl Transferase	NA	NA	> 2.5 × ULN	> 5 × ULN
Alkaline Phosphatase	NA	NA	> 2.5 × ULN	> 5 × ULN
Bilirubin; Total Bilirubin	NA	NA	> 2 × ULN	> 5 × ULN
Prothrombin Intl. Normalized Ratio	NA	NA	> 1.5 × ULN	> 2.5 × ULN
Prothrombin Intl. Normalized Ratio (for subjects on anticoagulant treatment)	NA	NA	> 1.5 × baseline	> 2.5 × baseline
Creatinine	NA	NA	> 1.5 × ULN	> 3 × ULN
Creatinine (baseline value >ULN)	NA	NA	>1.5 × baseline	> 3 × baseline
Glucose - mg/dL (Non-diabetic, Fasting)	< 55	< 40	> 160	> 250
Calcium – mg/dL	< 8.0	< 7.0	> 11.5	> 12.5
Ionized calcium – mg/dL	< 4.0	< 3.6	> 6.0	> 6.4
Sodium – mmol/L	NA	< 130	> 150	> 155
Potassium – mmol/L	< 3.2	< 3.0	> 5.5	> 6.0
Magnesium – mg/dL	< 1.2	< 0.9	NA	> 3.0
Phosphate – mg/dL	< 2.5	< 2.0	NA	NA
Creatine Kinase	NA	NA	> 5 × ULN	> 10 × ULN
Urate; Uric Acid – mg/dL	NA	NA	> 10	> 12
Albumin – g/dL	< 3.0	< 2.0	NA	NA
Glomerular Filtration Rate – ml/min/ 1.73 m2	< 60	< 30	NA	NA
Creatinine Clearance – ml/min/ 1.73 m2	< 60	< 30	NA	NA
Blood Urea Nitrogen	NA	NA	> 2.5 × ULN	> 5 × ULN

L1 = LLL, L2 = LL, H1 = HH, H2 = HHH.

NA = not applicable; ULN = upper limit of normal.