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Statistical Analysis Plan

Aldeyra Therapeutics, Inc.

ADX-629-CC-001

A Randomized, Double-Blind, Placebo-Controlled, Two-Period Crossover, Phase 2 Clinical Trial to Evaluate the Safety, Tolerability, and Efficacy of ADX-629 Administered Orally to Subjects with Chronic Cough

Protocol Version: Version 2.0, 16 June 2022

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Version 1.0	14 Apr 2023

Approval

Upon reviewing this document, including the table, listing, and figure shells, the undersigned approves the statistical analysis plan. The analysis methods and data presentation are acceptable.

Signature	Date
[redacted]	
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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AdaM	analysis data model
AE	adverse event
ATC	Anatomical Therapeutic Chemical
BID	twice daily
BMI	body mass index
CGIC	Clinician Global Impression of Change
CI	confidence interval
CMH	Cochran–Mantel–Haenszel
CQLQ	Cough Quality of Life Questionnaire
CS	clinically significant
CSR	clinical study report
ECG	electrocardiogram
eCRF	electronic case report form
EOS	end of study
ET	early termination
FSH	follicle-stimulating hormone
ICF	Informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ITT	Intent-to-treat
LCQ	Leicester Cough Questionnaire
LSM	least-squares mean
MedDRA	Medical Dictionary for Regulatory Activities
NCS	not clinically significant
PGIC	Patient Global Impression of Change
PP	per-protocol
PT	preferred term
QC	quality control
QTc	corrected QT interval
QTcF	corrected QT interval according to Fridericia's formula
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SOC	system organ class
TEAE	treatment-emergent adverse event

Abbreviation	Definition
TLFs	tables, listings, and figures
VAS	Visual Analogue Scale
WHO	World Health Organization

1. INTRODUCTION

This document outlines the statistical methods to be implemented during the analyses of data collected within the scope of Study ADX-629-CC-001 [A Randomized, Double-Blind, Placebo-Controlled, Two-Period Crossover, Phase 2 Clinical Trial to Evaluate the Safety, Tolerability, and Efficacy of ADX-629 Administered Orally to Subjects with Chronic Cough]. The purpose of this statistical analysis plan (SAP) is to provide specific guidelines for the statistical analyses. Any deviations from this plan will be documented in the clinical study report (CSR).

2. STUDY DOCUMENTS

The following study documents are used for the preparation of the SAP:

- Protocol, Version 2.0, 16 June 2022
- Annotated electronic case report form (eCRF), Version 4, December 2022

3. STUDY OBJECTIVES

3.1 Primary Objective

The primary objective of this trial is:

- To evaluate the safety and tolerability of ADX-629 300 mg administered orally twice daily (BID) for 2 weeks in adult subjects with refractory or unexplained chronic cough

3.2 Secondary Objective

The secondary objectives of this trial are:

- To evaluate the efficacy of ADX-629 (300 mg) administered orally BID for 2 weeks in adult subjects with refractory or unexplained chronic cough
- To investigate the effect of ADX-629 (300 mg) administered orally BID for 2 weeks on the cough-related quality of life of adult subjects with refractory or unexplained chronic cough

3.3 Primary Endpoints

The primary endpoints of this trial are:

- Incidence and severity of treatment-emergent adverse events (TEAEs) and serious AEs (SAEs)
- Observed values and changes from baseline of:
    - Laboratory safety parameters
    - Vital signs

- 12-lead ECG parameters

3.4 Secondary Endpoints

The key secondary efficacy endpoint is change from baseline in awake cough frequency (awake cough count/duration of measurement [awake hours]).

The secondary endpoints of this trial are:

- Change from baseline in awake cough frequency at End of Treatment Period (Day 14)
- Change from baseline in 24-hour cough frequency at End of Treatment Period (Day 14)
- Change from baseline in cough severity using a VAS
- Change from baseline in Leicester Cough Questionnaire (LCQ) scores
- Change from baseline in Cough-Specific Quality of Life Questionnaire (CQLQ) scores
- Global rating of change scores for cough severity and frequency
- Patient Global Impression of Change (PGIC) score after 2-week treatment period
- Clinician Global Impression of Change (CGIC) score after 2-week treatment period

Additional Secondary Endpoints:

- Percentage of subjects with ≥30%, ≥50%, and ≥70% reduction from baseline in Awake Cough Frequency to Day 14 of Treatment Period
- Percentage of Subjects with ≥30%, ≥50%, and ≥70% reduction from baseline in 24-hour Cough Frequency to Day 14 of Treatment Period
- The number and percentage of subjects with a ≥ 30mm reduction from baseline to Day 14 of Treatment Period
- The number and percentage of subjects with a ≥ 1.3 point increase from baseline to Day 14 of Treatment Period

4. STUDY DESIGN

ADX-629-CC-001 is a Phase 2, multicenter, randomized, double-blind, placebo-controlled, two-period crossover trial to evaluate the safety, tolerability, and efficacy of ADX-629 300 mg administered orally BID for 14 days to approximately 50 adult subjects with refractory or unexplained chronic cough.

Subjects will be screened over a period of up to 3 weeks. Eligible subjects will be randomized to one of two treatment sequences. Subjects in one sequence will receive ADX-629 in Treatment Period 1 and matching-placebo in Treatment Period 2, while subjects in the other sequence will receive the matching placebo in Treatment Period 1 and ADX-629 in Treatment Period 2.

Subjects will receive their allocated treatment for 2 weeks within each treatment period. Each subject will have a washout period of 2 weeks ±2 days between the two trial periods and will undergo a follow-up assessment approximately 1 to 2 weeks after the last dose of trial treatment. Subjects will be required to attend visits for screening and at the start and end of each treatment period. Each visit will require the subject to attend the clinic or to be visited by research staff on consecutive days. At Screening (Visit 1) and on Days 0 (Visit 2 and Visit 6) and 13 (Visit 4 and Visit 8) of each treatment period, the subject will be fitted with a cough recorder to collect cough count data over a period of 24 hours. The cough recorder will be removed the next day once the 24-hour recording has been completed. The trial will include 5 cough recorder sessions in total.

The trial duration for each subject will be up to 11 weeks as follows: up to 3 weeks for screening, 2 weeks for each treatment period, a 2-week washout between treatment periods, and a 2-week follow-up period.

Should a subject discontinue trial treatment, they will be requested to participate in an early (ET) termination visit as soon as possible after the subject stops taking trial treatment. The subjects should have their follow-up visit 1 to 2 weeks after their last dose of trial treatment; however, if their ET visit is more than 1 week after their last dose, they will not be required to have a follow-up safety assessment.

The follow-up safety assessment will be conducted as an in-clinic visit for follow-up laboratory parameters, vital signs, or electrocardiogram (ECG) parameters.

The trial design is illustrated in Figure 1.

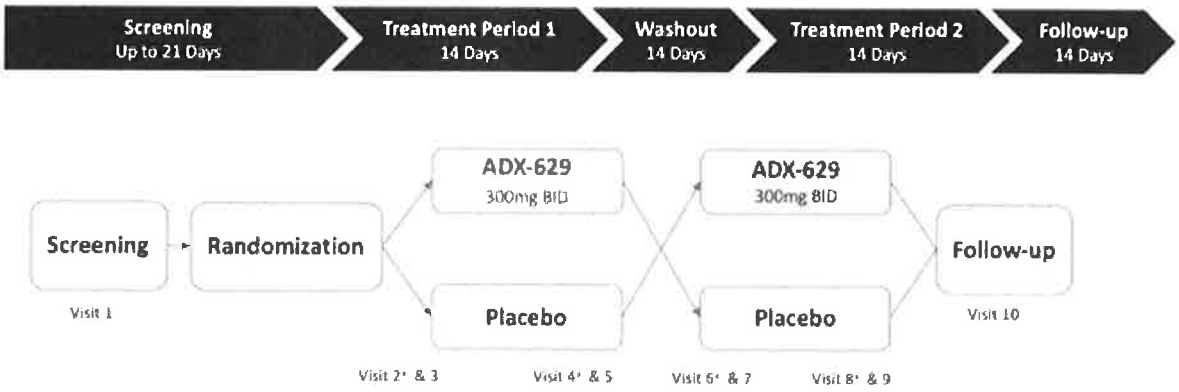


Figure 1: Schematic of Trial Design

Abbreviation: BID=twice daily.
[a] Subjects will attend the clinic or be visited by research staff on consecutive days. The cough recorder will be fitted at Screening, on Day 0, and on Day 13 of each treatment period to enable cough count data recording over a period of 24 hours.

4.1 Summary of the Schedule of Assessments

A summary of the trial assessment schedule is provided in Table 1.

Table 1: Schedule of Assessments

[redacted]

[redacted]

5. DETERMINATION OF SAMPLE SIZE

The power is increased to over 90% for treatment improvements greater than 35%. By allowing for a reduction in power due to subject withdrawals, approximately 50 subjects will be randomized.

The null (H_0) and alternative (H_1) hypotheses for the key secondary efficacy endpoint (awake cough frequency) can be expressed as:

H_0: $\mu_{ADX} = \mu_{PLA}$

H_1: $\mu_{ADX} \neq \mu_{PLA}$

where μ_{ADX} and μ_{PLA} are the mean changes from baseline in cough frequency for ADX-629 and placebo respectively.

6. MULTICENTER CLINICAL TRIAL

This trial is a multicenter study, with approximately 15 centers participating. Approximately 50 subjects will be randomly assigned, leading to approximately 3 to 5 subjects for each center.The expected low number of subjects at some centers does not allow the center to be included as a covariate in the statistical model. Since there will be centers with few subjects, the inclusion of those centers as covariates in the statistical model is not meaningful. Furthermore, pooling these centers to form one center of a size comparable to other centers has little or no scientific justification. Also, randomization was not stratified by center.

7. INTERIM ANALYSIS AND DATA MONITORING

No interim analysis is planned for this study.

8. GENERAL ANALYSIS CONSIDERATIONS

The statistical analyses will be reported using summary tables, listings, and figures (TLFs). The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) numbering convention will be used for all TLFs.

Unless otherwise noted, all statistical testing will be 2-sided and performed at the 0.05 significance level. Tests will be declared statistically significant if the calculated *P*-value is ≤ 0.05.

Continuous variables will be summarized by presenting the number of observations, means, standard deviations (SDs), medians, minimums, and maximums.

Categorical variables will be summarized by presenting counts and percentages of subjects in corresponding categories. All possible categories defined in the CRF will be populated, even with zero counts. Percentages for missing values are omitted and do not account for the percent calculation of other categories. Percentages are based on the total category count, excluding the missing category if not otherwise mentioned. The total number of subjects is used as the denominator in certain tables (e.g., adverse events [AEs]). Footnotes will specify the percent basis in those cases.

Baseline summaries will be presented by treatment sequence and include a total summary column.

Individual subject data obtained from the eCRFs, external vendors, central clinical laboratory, central ECG laboratory, and any derived data will be presented by subject in data listings.

The version of the WHODrug and Medical Dictionary for Regulatory Activities (MedDRA) coding dictionaries used for coding of concomitant medications and medical histories, respectively, will be specified in the final Medical Coding Plan.

After all the data have been verified, coded if necessary, and entered into the database, a review will be performed.

The analyses described in this plan are considered a priori in that they have been defined before breaking the blind.

Any analyses performed after breaking the blind will be considered post hoc and exploratory. Post hoc analyses will be labeled as such on the output and identified in the CSR.

All analyses and tabulations will be performed using SAS® statistical software, version 9.4 or higher (SAS Institute Inc). Tables, listings, and figures will be presented in RTF format.

The process for SAS program validation and quality control (QC) for programs and outputs is documented in the Synteract working instruction "SAS Programming Quality Control." Study-specific QC requirements can be found in APPENDIX B: SAS PROGRAMMING QUALITY CONTROL REQUIREMENTS.

8.1 Baseline Values

For this crossover study, 2 types of baseline will be defined as follows:

- The study baseline is defined as the most recent non-missing measurement(s), either scheduled or unscheduled, collected prior to the first dose of study drug in the study. Study baseline may include measurements from Visit 1 (Screening) to Visit 2, prior to the first dose in Treatment Period 1.

- The treatment period baseline is defined as the most recent non-missing measurement(s), either scheduled or unscheduled, collected before the first dose of study drug in each Treatment Period. For Treatment Period 1, baseline may include measurements from Visit 1 (Screening) to Visit 2, prior to the first dose in Treatment Period 1. For Treatment Period 2, the period baseline may include any measurement that occurs after the end of the wash-out period and prior to the first dose at Visit 7 in Treatment Period 2.

Unscheduled visits, repeat measurements, and averages may be used in the determination of baseline values, when applicable.

8.2 Handling of Missing Data

No imputations will be made for missing values. Summaries will be based on observed data only.

8.3 Early Withdrawal Assessments

Early withdrawal assessments of efficacy parameters; cough severity, Leicester Cough Questionnaire (LCQ), Cough Quality of Life Questionnaire (CQLQ), Global Rating of Change, Patient Global Impression of Change (PGIC), and Clinician Global Impression of Change (CGIC), as well as safety laboratory and ECG assessments, will be analyzed with the Day 14 assessments of the relevant withdrawal period if treatment is administered for that period. Early withdrawal assessments will be listed as Early Withdrawal.

8.4 Unscheduled Visits

Only scheduled post-baseline values will be tabulated. Post-baseline repeat/unscheduled assessments will not be included in the summary statistics. However, these repeat/unscheduled post-baseline assessments will be listed in the relevant appendices to the CSR.

9. NOTATION OF TREATMENT GROUPS AND VISITS

Notation of Treatment Groups

The following notation of treatment groups will be used throughout the report:

Full notation (as used in the study protocol)	Notation used throughout all TLFs
ADX-629 (300 mg tablets)	ADX-629
Placebo	Placebo

Notation of Treatment sequence

The following notation of treatment groups will be used throughout the report:

Full notation	Notation used throughout all TLFs
Period 1 - ADX-629; Period 2 – Placebo	S1
Period 1 - Placebo; Period 2 – ADX-629	S2

Visit Terminology

Visit	Notation used throughout all TLFs
Screening, Days -21 to Day -5, Visit 1	V1 (Screening)
Randomization/Baseline, Day 0, Visit 2	V2 (Day 0)
Treatment Period 1, Day 1, Visit 3	V3 (Day 1) / *Day 1
Treatment Period 1, Day 13, Visit 4	V4 (Day 13) / *Day 13
Treatment Period 1, Day 14, Visit 5	V5 (Day 14) / *Day 14
Treatment Period 2, Baseline, Day 0, Visit 6	V6 (Day 0)
Treatment Period 2, Day 1, Visit 7	V7 (Day 1) *Day 1
Treatment Period 2, Day 13 (±1 day), Visit 8	V8 (Day 13) / *Day 13
Treatment Period 2, Day 14, Visit 9	V9 (Day 14) / *Day 14
End of Trial, Day 29, Visit 10	V10 EOT
Early Withdrawal	Early Withdrawal[#]

*Notation for by-treatment group summaries.
[#]Listing only. Early Termination assessments to be re-assigned as per Section 6.1 Early Withdrawal Assessments for efficacy tables.
Abbreviations: FU: follow-up

10. ANALYSIS POPULATIONS

The following populations are defined for analysis:

- Screened Population: All subjects who sign the informed consent form (ICF).
- Intent-to-treat (ITT) Population: All randomized subjects.
    - The ITT population will be the primary analysis population for efficacy analyses. The subjects in the ITT population will be analyzed by the planned treatment..

- Safety Population: All subjects who receive at least one dose of trial treatment.
    - The safety population will be used for all safety analyses, and subjects will be analyzed by the actual treatment received for the safety population.
- Per protocol (PP) Population: All subjects in the ITT population who do not violate inclusion or exclusion criteria or deviate from the protocol in a way that could influence their efficacy assessment. As this trial has a crossover design, subject inclusion in this set will be considered for all periods.
    - The PP population will be used for sensitivity analyses of the efficacy data.

11. STUDY POPULATION

11.1 Subject Disposition

Subject disposition information will be summarized for the Screened population by treatment sequence and overall and presented by frequency counts and percentages. Percentages will be based on the number of subjects randomized. The following will be considered for summary:

- The number of subjects screened, enrolled, randomized and completed trial
- The number and percentage of subjects in each analysis population
- The number and percentage of subjects:
    - Completing Treatment Period 1
    - Withdrawing during Treatment Period 1 (with reasons)
    - Entering Treatment Period 2
    - Withdrawing during Treatment Period 2 (with reasons)
    - Completing the study trial

The percentages for the reasons for withdrawal will be calculated relative to the number of subjects who withdrew during each period.

All disposition data, including reasons for exclusion from analysis populations, will be listed for the ITT population.

11.2 Protocol Deviations

Major protocol deviations that could potentially affect the efficacy or safety conclusions of the study will be identified before database lock and unblinding of individual subject treatment information.

The data review meeting will make the decision whether a subject is excluded from the PP population. Reasons for exclusion of a subject from the analysis and protocol violations (major or minor) will be listed.

All protocol deviations, including the deviation designation (major or minor), category, and an indication of whether the deviation led to the exclusion of a subject from the PP population, will be presented in a data listing.

11.3 Eligibility

The trial population will be adult subjects with refractory or unexplained chronic cough. Refer to Inclusion and Exclusion criteria in protocol for additional details. A listing of subjects not fulfilling any eligibility criteria will be created.

11.4 Demographics, Baseline Characteristics, and History of the Disease

11.4.1 Demographic Data and Baseline Characteristics

Demographic and baseline characteristics will be summarized for the ITT population by treatment sequence and overall.

Demographic variables include:

- Age on Consent Date: Years
- Gender: Male, Female (and child-bearing status)
- Ethnicity: Hispanic or Latino, Not Hispanic or Latino, Not Reported, Unknown
- Race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Not Reported.

Age will be recalculated in years relative to the informed consent date should it be missing from the eCRF.

Baseline characteristics variables include:

- Height (cm)
- Weight (kg)
- Body Mass Index (BMI) (kg/m^2)
- Smoking History (Never, Current, Former)
- Smoking Pack Years (Years)
- Spirometry (FEV_1, FVC, FEV1/FVC Ratio)
- Number of years with chronic cough
    - Calculated as: Age at consent – Age cough began

Descriptive statistics will be presented for age, height, weight, BMI, and smoking pack years. Frequency counts and percentages will be presented for gender, childbearing potential, ethnicity, race, and smoking history (never, current, or former).

11.4.2 Medical History

The verbatim term of the medical history condition/event will be captured in the eCRF and coded using the Medical Dictionary for Regulatory Activities (MedDRA). The version of MedDRA used will be specified in the final Medical Coding Plan.

A summary table will be prepared by treatment sequence and overall for the Safety population. The summary will show the number and percentage of each system organ class (SOC) and preferred term (PT) ordered by descending subject count in the total column by SOC and PT.

Subjects may have more than 1 condition/event per SOC and PT. At each level of summarization, a subject is counted once if he/she reported 1 or more conditions/events at that level.

All medical history data will be listed.

11.4.3 History of Chronic Cough

Chronic cough history includes age cough began, underlying conditions and procedures related to chronic cough.

Procedures Related to Chronic Cough include:

- None / Not Applicable
- 24 hour esophageal pH monitoring
- Endoscopic or Videoflouroscopic Swallow Evaluation
- Barium esophagram
- Sinus imaging
- HRCT
- Bronchoscopy
- Echocardiogram
- Environmental Assessment
- Other Procedure, Specified

A summary table will be prepared by treatment sequence and overall for the Safety population. The summary will show the number and percentage of subjects reporting each underlying condition and procedure. A subject will be counted for every underlying condition and procedure listed if multiple are selected.

11.5 Prior and Concomitant Medications

All prior medications taken for cough or underlying triggers at any time prior to screening will be captured as well as any medication taken 28 days prior to screening and during the study (includes over-the counter and prescription drugs).

Prior and concomitant medication verbatim terms in the eCRF will be mapped to the World Health Organization (WHO) Anatomical Therapeutic Chemical (ATC) classification and preferred names using the WHO Drug Global dictionary, version 01 September 2022.

Partial dates will be imputed. For details on imputation rules, refer to Appendix A: Presentation of Data and Programming Specifications. Imputed dates are only used for the classification of a medication as a prior or concomitant medication; no other calculation, such as durations, will be done.

Prior medications are defined as any medication with an imputed start date before or during screening and an imputed stop date before the date of the first administration of study treatment. Concomitant medications are defined as any medication that was started before screening and with an imputed stop date on or after the start date of study treatment, that are ongoing from screening/baseline, or that are taken on or after the start date of study treatment (imputed start date on or after the first dose of study treatment). If the medication cannot be classified as a prior or concomitant medication, the medication will be considered as concomitant. Prior medications will be summarized by treatment sequence and overall by ATC class and preferred name. Concomitant medications will be summarized for each treatment group by ATC class and preferred name. These summaries will present the number and percentage of subjects using each medication.

Subjects may have more than 1 medication per ATC class and preferred name. At each level of subject summarization, a subject is counted once if he/she reported 1 or more medications at that level. Each summary will be ordered by descending subject count in the total column by ATC level and preferred name. The total column will only be used for ordering.

The following rules will be used to assign a concomitant medication to study treatment:

- A concomitant medication will be assigned to the study treatment received immediately before the medication start date.
- Any concomitant medication reported within the washout period between doses will be attributed to the previous treatment received.
- Medications where the imputed start and stop date information indicate that the mediciton was taken during both treatment periods, the medication will be assigned to both treatments for analysis.

12. EFFICACY ANALYSES AND METHODS

The key secondary and secondary efficacy analyses will be based on the ITT population and repeated for the PP population, where indicated, and summarized by treatment group.

The efficacy variables for this trial are:

- Awake cough frequency (average coughs per hour during awake period) measured via the [redacted] cough monitor.
- 24-hour cough frequency (average coughs per hour during a 24-hour period) measured via the [redacted] cough monitor.
- Cough severity scores (0 – 100) using a visual analogue scale.
- LCQ scores
- CQLQ scores
- Global Rating of Change scores for cough severity
- Global Rating of Change scores for cough frequency
- PGIC scores measured via a rating scale completed by subjects to assess the subject's response to the trial treatment. It consists of a 7point scale ranging from 'very much improved' to "very much worse."
- CGIC scores measured via a rating scale completed by Investigators to assess the subject's response to the trial treatment. It consists of a 7point scale ranging from 'very much improved' to 'very much worse.'

12.1 Cough Frequency

12.1.1 Awake Cough Frequency

The key secondary efficacy endpoint is change from baseline in awake cough frequency (total cough count during awake period /duration of awake period [hour]).

Cough frequency will be assessed using the [redacted] cough monitor, a 510k approved device that has been successfully implemented in previous clinical trials. The [redacted] cough monitor is a digital recording device that uses 2 input channels, biometric sensor and air microphone, to obtain objective cough counts. The first records sounds from the lungs and trachea through a chest contact biometric sensor and the second channel captures ambient sounds through a lapel air microphone.

Subjects will wear the cough monitor for a 24-hour period at Visit 1 (Screening), Visit 2 (Baseline - Period 1), Visit 4 (End of Period 1), Visit 6 (Baseline - Period 2), and Visit 8 (End of Period 2). The average awake cough count (per hour) will be calculated using the total number of coughs during the awake period divided by the duration of awake period (coughs / hour).

Change in Awake Cough Frequency from Baseline = Awake Cough Frequency at the End of Period - Awake Cough Frequency at Baseline, hence a negative result indicates an improvement or decrease in cough frequency, while a positive result indicates an increase. Due to the skewed nature of cough frequency data, awake cough frequency will be log transformed prior to analysis.

The null (H_0) and alternative (H_1) hypotheses for the key secondary efficacy endpoint (awake cough frequency) can be expressed as:

H_0: The geometric mean cough frequency is equal between ADX-629 and placebo.

H_1: The geometric mean cough frequency is different between ADX-629 and placebo.

A mixed-effect model suitable for the crossover design will be used to make comparisons between the two treatment groups in the changes from baseline of the natural log data. Alternative sensitivity analyses may be performed assessing the impact of any missing data on the interpretation of the results.

Although summaries will be presented for cough frequencies, a log transformation will be used prior to statistical analyses because of the skewed nature of the data. The cough frequency counts will be log transformed prior to calculation of the change from baseline value for each subject. The resulting changes from baseline on the natural log scale will be used as dependant value in statistical testing. All statistical testing will be at the 5% level of significance (2-sided), and 2-sided 95% confidence intervals will accompany all point estimates for the comparison between treatment groups.

A mixed-effect model suitable for the crossover design will be used to compare the two treatment groups' change from baseline in cough frequency on the log scale. The model will include fixed effects for treatment sequence [S1, S2], period [Period 1, Period 2], treatment [ADX-629, placebo] and correlated errors due to treatment. The period-specific baseline values will be included as a covariate.

If there are zero cough frequencies within the data, all values will have 0.1 added to their cough frequency (equating to 1 cough every 10 hours) prior to transforming the data.

The least-squares mean (LSM) change from baseline on the log scale will be presented for each treatment group and the difference between treatment groups.

Estimates from the mixed-effect model will be back-transformed to estimate the ratio comparison to baseline for each treatment group, and the difference between treatment groups will be back-transformed to estimate the ratio comparison to baseline for the ADX-629 group adjusted for placebo. All ratios will be accompanied by the corresponding 95% confidence interval (CI) and p-value.

[redacted]

All model assumptions will be checked by evaluating model residuals. Should the evaluation of residuals indicate a problem with the model assumptions, an alternative analysis will be performed by analyzing the count data on the original scale (observed counts) where the point estimate and confidence interval of the Hodges-Lehmann's median difference for paired groups will be used[1].

The analysis wll also be performed for subgroups based on baseline awake cough frequency median, tercile and quartile classifications as follows:

- Median (< Median/ >= Median)
- Tercile (< Tercile 1/ >= Tercile 1, < Tercile 2/ >= Tercile 2)
- Quartile (< Quartile 1/ >= Quartile 1, < Quartile 2/ >= Quartile 2, < Quartile 3/ >= Quartile 3)

Baseline for the above classifications will be the average of the pre-dose values in period 1 and period 2 for each subject.

The key secondary efficacy analysis of awake cough frequency will be repeated for the PP population.

Additionally, the number and percentage of subjects with ≥ 30%, ≥ 50% and ≥ 70% reduction from baseline, at Day 14, will also be presented by treatment group.

Subjects will be classified as a responder/non-responder for each category (≥ 30%, ≥ 50% and ≥ 70% reduction) and treatment groups will be compared using a generalized estimating equation (GEE) for logistic regression with an exchangeable working correlation structure. The model will include fixed effects for treatment sequence [S1, S2], period [Period 1, Period 2] and treatment [ADX-629, placebo]. The period-specific baseline values will be included as a covariate. The odds ratio between ADX-629 and placebo, 95% confidence intervals for the odds ratio, and P-value for the covariate-adjusted treatment comparison will be presented.

[redacted]

Should the GEE model not converge, the model may be adjusted by removing factors or changing the correlation structure. If the GEE is found to be not appropriate for the data a Fisher's exact test will be used to calculate the odss ratio. The final model will be specified in the footnotes of the appropriate tables.

12.1.2 24-hour Cough Frequency

The secondary efficacy endpoint of 24-hour cough frequency will be calculated as:

- 24-hour cough frequency = (total cough count/duration of measurement [hour])

The 24-hour average cough count (per hour) will be calculated using the total number of coughs divided by the total duration.

The 24-hour cough frequency after the 2-week treatment will be analyzed using the same methods described for the key secondary efficacy endpoint, including the subgroup analysis by median, tercile and quartile classifications of the baseline awake cough frequency.

The analysis of change from baseline in 24-hour cough frequency will be repeated for the PP population.

12.1.3 Subgrop Analyses

Subgroup analyses may be performed to generate additional data in a population with baseline awake cough frequency of <25 and ≥25 coughs/hour.

Analysis for the cough frequency endpoints may be provided for the following subgroups of baseline factors:

- Awake baseline cough frequency (<25, ≥25 coughs/hour)
- Duration of cough (<10, ≥10 years)
- Potential comorbidities and medical conditions associated with cough (i.e. GERD, asthma, bronchitis)

- Cough modulating and cough-inducing medications, including proton pump inhibitiors (omeprazole, pantaprazole), antihistamines (ranitidine, loratadine, cetirizine, fexofenadine, diphenhydramine), inhaled corticosteroids (fluticasone, mometasone), benzonatate, non-steriod anti-inflammatory drugs (ibuprofen), leukotriene receptor antagonists (singulair), statins, and trazadone. (Ding, et al., 2020)

12.2 Patient Reported Outcomes

[redacted]

12.2.1 Cough Severity using VAS

Participants will be asked to rate the severity of their cough over the past 24 hours using a 100 mm Cough Severity VAS single-item questionnaire with the response ranging from 0 ('No Cough') to 100 ('Extremely Severe Cough').The cough severity will be measured using a 100 mm VAS. Subjects will be asked to rate their cough severity at Screening, Baseline (Day 1) and Day 14 of each treatment period. A score of ≥40 mm on the Cough Severity VAS at Screening is required for randomization into the study.

The changes from baseline in cough severity VAS scores (mm) will be analyzed using a similar approach described for the key secondary efficacy endpoint, including the subgroup analysis by median, tercile and quartile classifications of the baseline awake cough frequency, except that the scores will not be log-transformed prior to analysis.

The number and percentage of subjects with a ≥ 30mm reduction from baseline, to Day 14, will be presented by treatment group.

The LSM changes from baseline will be presented for each treatment, and the treatment effect will be the difference between the LSM changes from baseline. The difference in LSM estimates and the corresponding 95% CIs and p-values will be presented.

[redacted]

12.2.2 LCQ and CQLQ Scores

A secondary efficacy endpoint includes the change from baseline in the LCQ and CQLQ total scores at end of each treatment period.

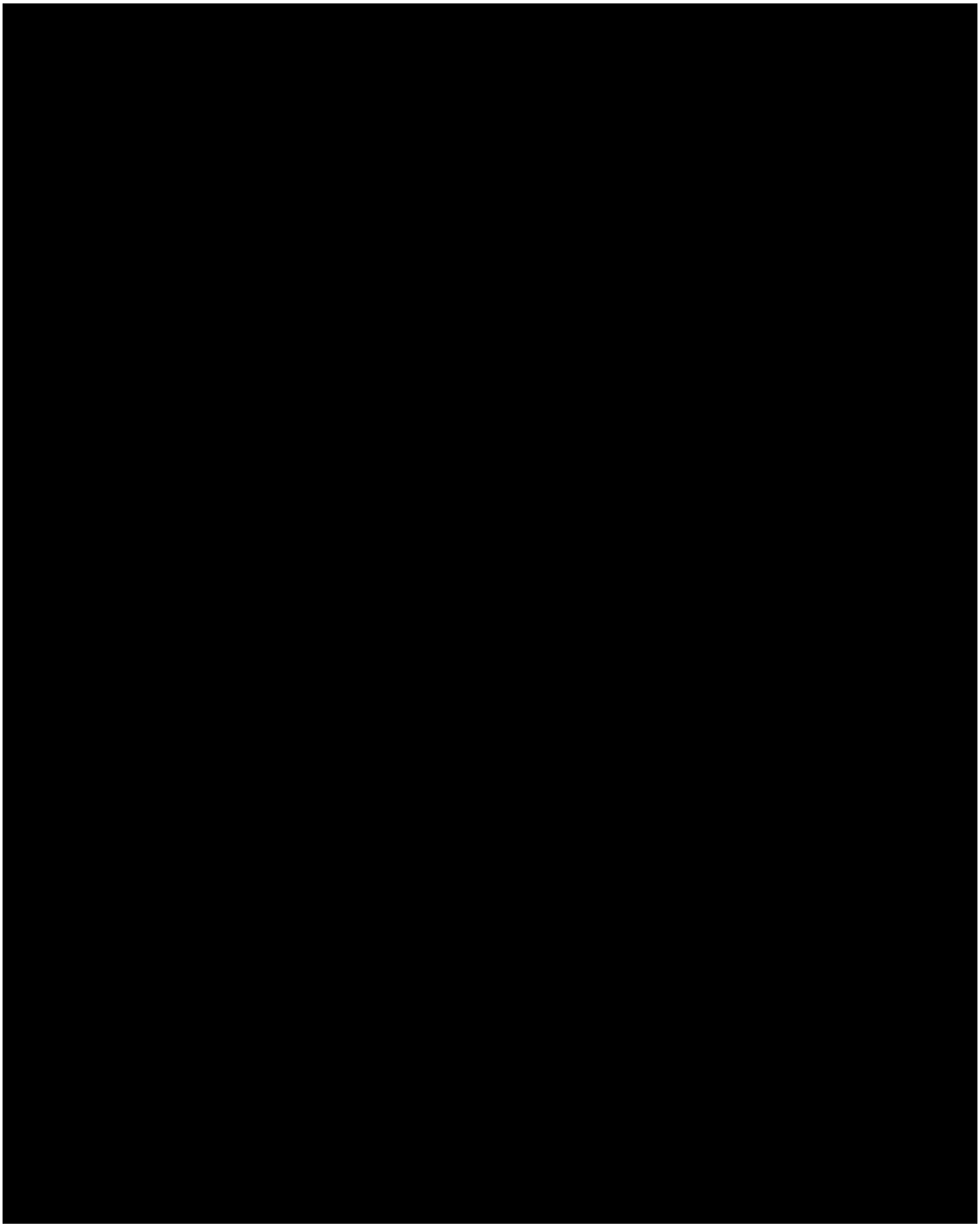
Subjects will complete the LCQ and CQLQ at Screening, Days 1 and 14 of each treatment period. A higher score indicates a better quality of life.

LCQ Scores:

The following three 7-point domain scores, total categories, and total score will be considered for summaries of the LCQ:

LCQ (as collected on the eCRF)

- Physical Score *(Range, 1 to 7)*
- Psychological Score *(Range, 1 to 7)*
- Social Score *(Range, 1 to 7)*
- Total Score *(Range, 3 to 21)*



CQLQ Scores:

The CQLQ consists of 28 questions on a 4-point scale, and the following domain scores will be considered for summaries:

CQLQ (scores calculated manually by adding the scores of the items listed)

- Physical Complaints (Items: 4, 8, 10, 13, 14, 15, 17, 22, 23)
- Psychosocial Issues (Items: 1, 18, 24, 25, 27)
- Functional Abilities (Items: 2, 3, 19, 20, 21)
- Emotional Well-being (Items: 7, 9, 12, 16)
- Extreme Physical Complaints (Items: 5, 6, 11, 12)
- Personal Safety Fears (Items: 9, 26, 28)
- Total Score (Items: All)

Only two items, 9 and 12, are overlapped categories. Item 9 appears in the emotional well-being and personal safety fears category, and item 12 appears in the emotional well-being and extreme physical complaints categories.

If any individual item within a domain of the CQLQ is missing for a subject, the domain score will be considered missing for that subject.

Summary statistics of each domain at baseline and Day 14 and the change from baseline in each domain will be presented by visit and treatment group.

The changes from baseline (period baseline) in quality of life Total Score (measured by LCQ and CQLQ) will be analyzed using a similar approach described for the key secondary efficacy endpoint, including the subgroup analysis by median, tercile and quartile classifications of the baseline awake cough frequency, except that the scores will not be log-transformed prior to analysis.

The number and percentage of subjects with a $\geq$ 1.3 point increase from baseline, to Day 14, will be presented by treatment group.

The LSM changes from baseline will be presented for each treatment, and the treatment effect will be the difference between the LSM changes from baseline. The difference in LSM estimates and the corresponding 95% CIs and p-values will be presented.

[redacted]

12.2.3 Global Rating of Change Scores for Cough Severity and Frequency

Subjects will complete the Global Rating of Change on Day 14 of each treatment period.

Subjects will rate the Change in Cough Frequency and Change in Cough Severity on the following scale:

- Worse
- About the Same
- Better

Frequency counts will summarize the Global Rating of Change scores and percentages for cough frequency and cough severity change scores separately for each treatment group. The difference between treatment groups, for the change, will be tested using the Cochran–Mantel–Haenszel (CMH) row mean score difference test. The p-value for the difference will be presented.

In addition to the change, the degree of change (for both cough severity and cough) frequency will also be provided on the following scale:

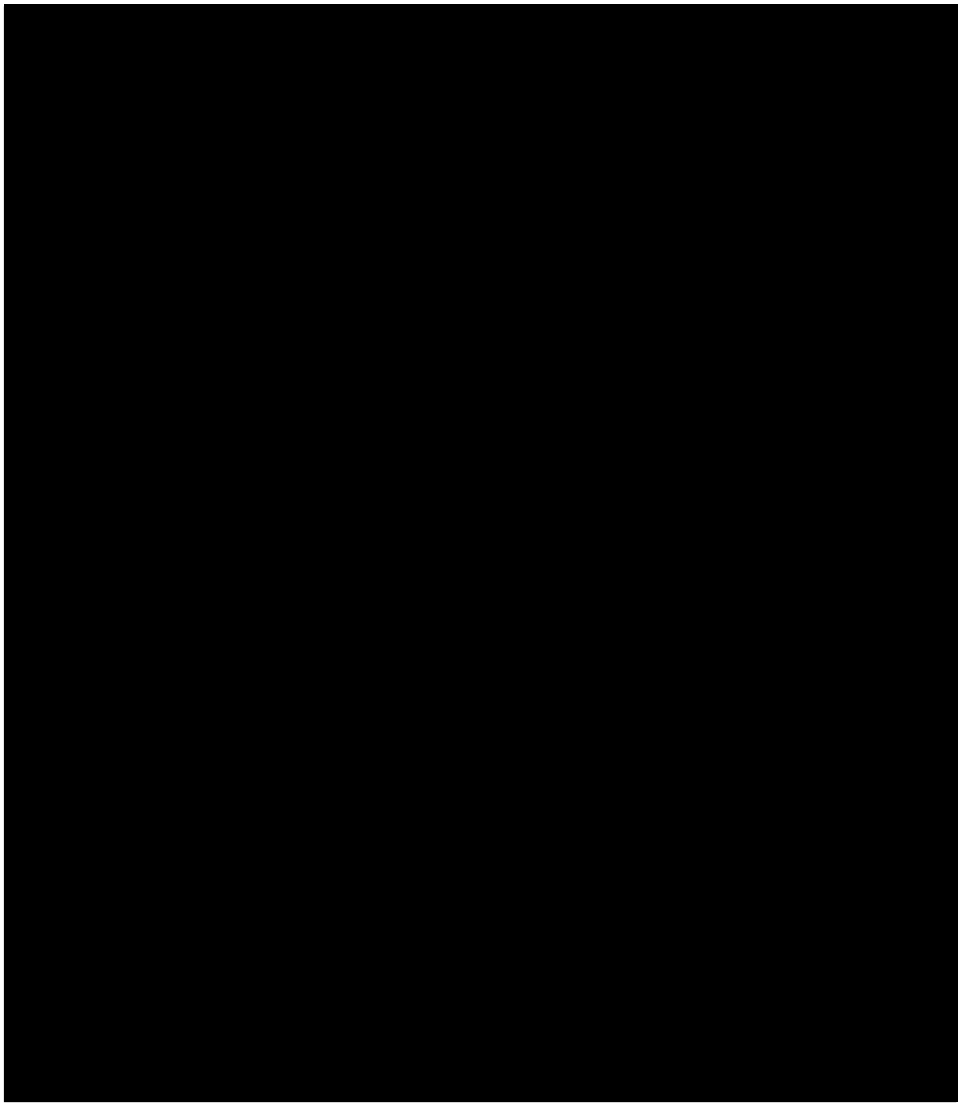
1. A Very Great Deal Better
2. A Great Deal Better
3. A Good Deal Better
4. Moderately Better
5. Somewhat Better
6. A Little Better
7. Almost the Same; Hardly Any Better at All
8. Almost the Same; Hardly Any Worse at All
9. A Little Worse
10. Somewhat Worse
11. Moderately Worse
12. A Good Deal Worse
13. A Great Deal Worse
14. A Very Great Deal Worse

The degree of change will be summarized by frequency counts and percentages for each treatment group.

Global rating of change scale will be remapped and given scores to create a continuous endpoint. A lower score will be considered a more positive outcome. The continuous endpoint will be summarized for each treatment group and appropriate hypothesis testing may be performed as a post-hoc analysis, if justified by the data.

All analyses will be repeated for the median, tercile and quartile group classifications based on the baseline awake cough frequency as described in the Key Secondary Efficacy Analyses Section.

Global Rating of Change Scores for Cough Severity and Frequency Scales:



12.2.4 Patient Global Impression of Change (PGIC) Score and Clinical Global Impression of Change (CGIC) Score

The PGIC and CGIC will be completed on Day 14 of each treatment period.

The PGIC and CGIC are rating scales that assess the change in cough frequency since commencing study treatment.

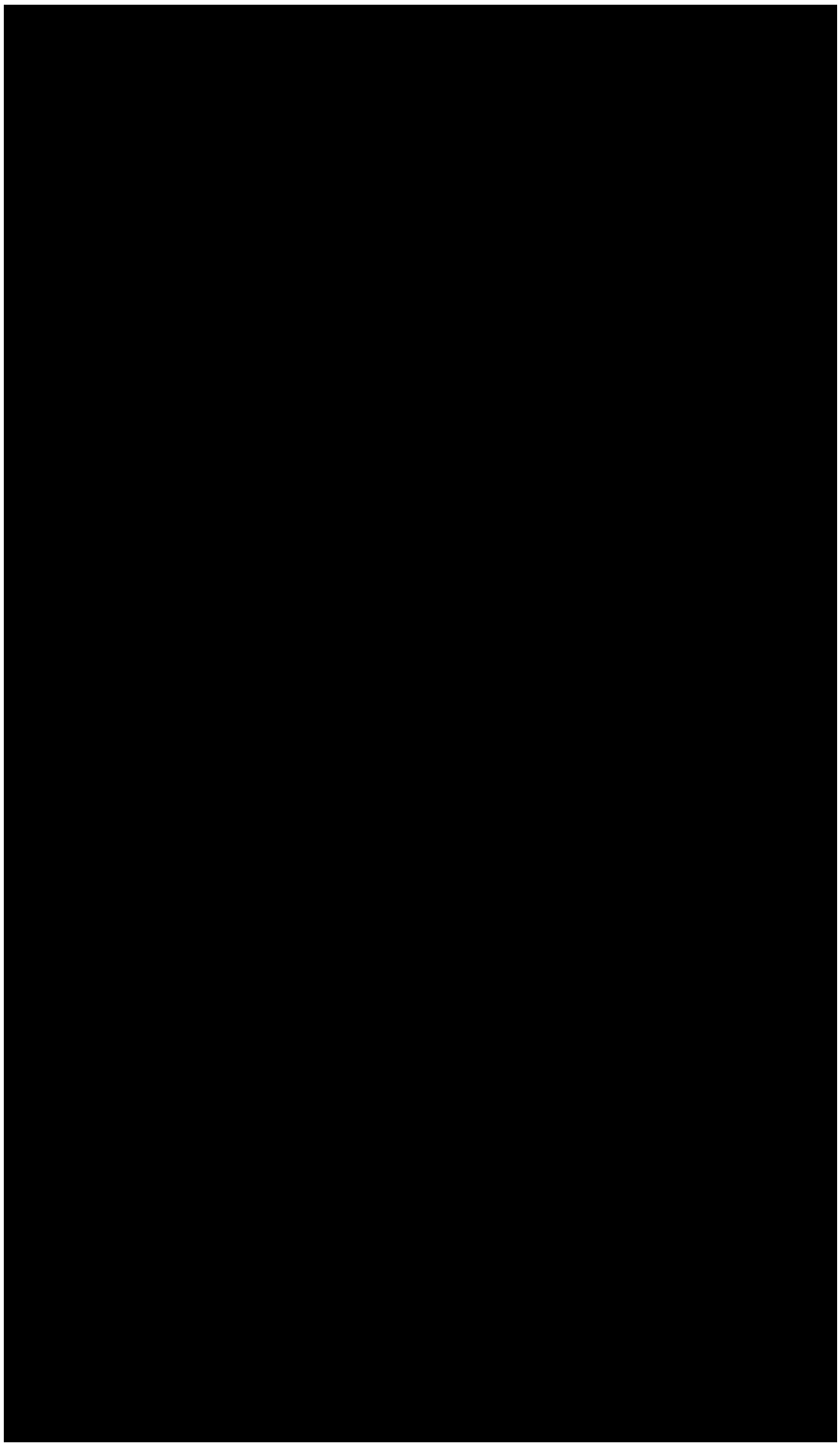
Patient Global Impression of Change is a rating scale completed by subjects to assess change in cough frequency since commencing trial medication. It consists of a 7-point scale ranging from "very much improved" to "very much worse." Clinician Global Impression of Change: A rating scale completed by Investigators to assess the subject's response to the trial treatment. It consists of a 7 point scale ranging from 'very much improved' to "very much worse."

[redacted]

The PGIC and CGIC scores will be presented by frequency counts and percentages for each treatment group. The difference between treatment groups for PGIC and CGIC will be tested using the CMH row mean score difference test. The p-value for the difference will be presented.

The analysis will be repeated for the median, tercile and quartile group classifications based on the baseline awake cough frequency as described in the Key Secondary Efficacy Analyses section.

The PGIC and CGIC scores will also be remapped and given scores to create a continuous endpoint. A lower score will be considered a more positive outcome. The continuous endpoint will be summarized for each treatment group and appropriate hypothesis testing may be performed as a post-hoc analysis, if justified by the data.



13. PHARMACOKINETIC ANALYSES

There are no PK, pharmacodynamics, or other assessments in this trial.

14. EXTENT OF EXPOSURE

Study treatment exposure will be summarized for each treatment group using the total number of doses taken and the duration of treatment.

Duration of study treatment will be calculated as follows:

- Duration of study treatment administration (days) = date/time of last administration – date/time of first administration

Study treatment compliance will be calculated as follows:

- Compliance (%): (actual number of used tablets in total) / (number of prescribed tablets to be taken) × 100
- Actual number of used tablets: number of tablets dispensed – number of tablets returned
- Prescribed number of tablets to be taken: duration of study treatment administration (days) × number of daily tablets

Study treatment compliance will be summarized by treatment group using counts and percentages as categorized below:

- >100%
- >90% to 100%
- >80% to 90%
- >70% to 80%
- <=70%

15. SAFETY ASSESSMENTS AND ANALYSES

All safety analyses will be based on the Safety population.

15.1 Adverse Events

15.1.1 Definition of Adverse Events

An AE is defined as any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship to this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the treatment administered.

An SAE is defined as any untoward medical occurrence that at any dose:

- Results in death, or
- Is life-threatening, i.e., the subject was at immediate risk of death at the time of the event, or
- Requires in-patient hospitalization or prolongation of existing hospitalization, or
- Results in persistent or significant disability or incapacity, or
- Is a congenital anomaly/birth defect; or
- Is an important medical event, i.e., may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed above. Examples of such events are: bronchospasms requiring intensive treatment in an emergency room or at home, blood dyscrasias, or convulsions that do not result in hospitalization. Development of cancer, drug dependency, or drug abuse are most often considered as SAEs.

The following are not considered to be SAEs:

- Any elective procedures that require admission to hospital as well as any planned elective procedures (e.g., angioplasty) planned prior to signing the inform consent form, unless the underlying condition has worsened or the procedure results in a worsening of the subject's condition. Such conditions should be recorded in the subject's medical history.
- A visit to an emergency room or other hospital department for <24 hours that does not result in admission to hospital unless the reason is considered to be an important medical event or a life-threatening event. These should be recorded as AEs.

  Severity of an AE is defined as a qualitative assessment of the degree of intensity of an AE as determined by the Investigator or reported by the subject. The assessment of severity is made irrespective of relationship to trial procedures or seriousness of the event and should be evaluated according to the following scale:

[redacted]

Assessment of causality is based on the following considerations: associative connections (time or place), pharmacological explanations, previous knowledge of the drug, presence of characteristic clinical or pathological phenomena, exclusion of other causes, or absence of alternative explanations.

The Investigator will assess the causal relationship to the trial treatment according to the following classifications:

- Definite: A clinical event, including laboratory test abnormality, occurring in a plausible time relationship to drug administration and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (de-challenge) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically using a satisfactory re-challenge (the drug is readministered to determine if the same reaction occurs) procedure if necessary.
- Probable: A clinical event, including laboratory test abnormality, occurring in a plausible time relationship to drug administration and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (de-challenge) should be clinically plausible.
- Possible: A clinical event, including laboratory test abnormality, with a reasonable time sequence to the drug administration, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.
- Unlikely ("Not related"): A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable and in which other drugs, chemicals or underlying disease provide plausible explanations.
- Not related: Any event that does not meet the above criteria; there is sufficient information that etiology of the event is in no relation to the trial treatment.

15.1.2 Adverse Event Analyses

All AE summaries will be restricted to treatment-emergent AEs (TEAEs), defined as those AEs that occurred after the first dose of trial drug or existing AEs that worsened during the study after the first dose administration. If it cannot be determined whether the AE is treatment-emergent because of a partial-onset date, it will be considered treatment-emergent. Verbatim terms in the eCRFs will be mapped to PTs and SOCs using the MedDRA. The version of MedDRA used will be specified in the final Medical Coding Plan.

AEs reported with relationship to study treatment of "Definite," "Probable," and "Possible" will be considered related AEs and "Unlikely" and "Not Related" as not related AEs for all relationship-to-study-treatment summaries.

In situations with missing data, the worst-case will be applied; that is, seriousness will be assigned as "Yes" if seriousness is missing, the severity will be assigned as "Severe" if the severity is missing, and relationship to study treatment will be assigned as "Related".

The following rules will be used to assign a TEAE to a treatment:

- A TEAE will be assigned to the treatment received immediately before onset.

- Any TEAE reported within the washout period between doses will be attributed to the previous treatment received.

Each AE summary will be displayed by treatment group. Summaries displayed by SOC and PT will be ordered by descending order of incidence of SOC and PT within each system organ class. Summaries will display the number and percentage of subjects with at least 1 event by treatment group.

Summaries of the following types will be presented:

- Overall summary of TEAEs that contains an overview of each item below
- Subject incidence of TEAEs and the total number of unique TEAEs by MedDRA SOC and PT.
- Subject incidence and the total number of unique events of Related TEAEs by MedDRA SOC and PT.
- Subject incidence and the total number of unique events of Serious TEAEs by MedDRA SOC and PT
- Subject incidence and the total number of unique events of Serious Related TEAEs by MedDRA SOC and PT
- Subject incidence of TEAEs by MedDRA SOC, PT, and highest severity. At each level of subject summarization, a subject is classified according to the highest severity if the subject reported 1 or more events.

AEs will be listed for all subjects in the Safety population.

Separate listings of AEs leading to death, serious AEs (SAEs), and AEs leading to permanent treatment discontinuation will be provided.

15.2 Clinical Laboratory Evaluation

Laboratory parameters (serum chemistry, hematology, and urinalysis) will be collected at the following visits:

- Screening (Visit 1),
- Day 1 (Visit 3) and Day 14 (Visit 5) of Treatment Period 1,
- Day 1 (Visit 7) and Day 14 (Visit 9) of Treatment Period 2,
- End of Trial (Visit 10).

Laboratory Tests:

- **Hematology:** hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, red blood cell count, white blood cell count with differential (neutrophils, lymphocytes, monocytes, eosinophils, and basophils), and platelet count.
- **Serum Chemistry / Biochemistry:** ALT, AST, alkaline phosphatase, gamma-glutamyl transferase, bilirubin (total, direct, and indirect), sodium, potassium, chloride, glucose, blood urea nitrogen, creatinine, albumin, amylase, uric acid, creatine kinase, calcium, magnesium, bicarbonate, lactate dehydrogenase, triglycerides, HDL cholesterol, and low-density lipoprotein cholesterol, and eGFR/1.73 m^2 CKD-EPI.
- **Urinalysis:** Albumin, creatinine, bilirubin, glucose, ketones, blood, nitrite, pH, protein, specific gravity, and microscopy (if indicated by macroscopic findings).

An evaluation will be done to compare the units for each laboratory test. Where units differ, the units will be converted to a standard unit, and the conversion factors will be provided in analysis data model (ADaM) specifications. The reference ranges can be found in the laboratory manual in Appendix 1 'Protocol Test Summary'. Laboratory values recorded as $>x$ or $<x$, will be analysed as x.

Laboratory parameters will be summarized by treatment group using descriptive statistics at 'period baseline' and Day 14. Changes from 'period baseline' will also be summarized. For categorical urinalysis results, the number and percentage of subjects in each results category will be presented by treatment group. Here baseline is defined as the pre-dose value on the first day of administration for each period.

Additionally, laboratory parameters will be summarized overall, using descriptive statistics at study baseline and End of Trial, including change from baseline. Here, baseline is defined as the last non-missing measurement (scheduled, unscheduled, or repeat) collected before the first administration of study treatment in the study.

The categorization into low-normal-high (below lower reference range/ within reference range/ above upper reference range) of each result will also be summarized for each visit, presenting the number and percentage of subjects in each category.

Pregnancy (or follicle-stimulating hormone [FSH] levels), serology, and alcohol breath test results will not be summarized but provided in data listings.

A separate listing of any abnormal laboratory measurements recorded throughout the study will be provided.

15.2.1 Low-density Lipoprotein Cholesterol

Low-density lipoprotein cholesterol (LDL-C) values will be summarized separately. The changes from baseline in LDL-C at Day 14 will also be analyzed using a similar approach as described for the key secondary efficacy endpoint, except that the values will not be log-transformed prior to analysis.

Additionally values at Day 14 will be categorized as follows, and the number and percentage of subjects in each category presented by treatment group:

- Normal: Less than 100 mg/dL
- Borderline: 100-129 mg/dL
- High: 130 mg/dL or more.

15.3 Vital Signs

Vitals signs data will be collected on each study visit, including pre-dose and 2 hours (±30 minutes) post-morning dose on Day 1 and Day 14 of each treatment period. The following vital signs will be collected:

- Systolic blood pressure (mmHg)
- Diastolic blood pressure (mmHg)
- Respiration rate (beats/min)
- Pulse oximetry (%)
- Heart Rate (bpm)
- Temperature (C)

Vital signs will be summarized by treatment group using descriptive statistics at period baseline and at each post-baseline time point in the treatment periods. Changes from baseline will also be summarized. Here baseline is defined as the pre-dose value on the first day of administration for each period.

Additionally, vital signs will be summarized overall, using descriptive statistics at study baseline and End of Trial, including change from baseline. Here, baseline is defined as the last non-missing measurement (scheduled, unscheduled, or repeat) collected before the first administration of study treatment in the study.

Vital sign data will be listed for all subjects in the Safety population.

15.4 Physical Examination

Physical examinations, including review of the major body systems, will be performed at various timepoints throughout the trial.

Major body systems include, but are not limied to the following:

- Ears/Nose/Throat
- Cardiovascular
- Respiratory
- Dermatological
- Musculoskeletal
- Gastrointestinal
- Endocrine/Metabolic
- Hepatic
- Lymphatic
- Immunological
- Neurological

Physical examination results will be included in data listings only.

15.5 Electrocardiogram

Standard 12-lead ECGs will be performed at Screening, Day 1 and Day 14 of each treatment period, and End of Trial.

The following parameters will be collected:

- RR interval (sec)
- PR interval (msec)
- QRS (msec)
- QT (msec)
- QTcF (msec)

Descriptive statistics at baseline and at each post-baseline time point and changes from baseline will be summarized for each ECG parameter by treatment group. Baseline is defined as the pre-dose value on the first day of administration for each period.

ECG parameters will be summarized overall using descriptive statistics at study baseline and End of Trial, including change from baseline. Here, baseline is defined as the last non-missing measurement (scheduled, unscheduled, or repeat) collected before the first administration of study treatment in the study.

Overall interpretation results for ECGs will be summarized using shift tables (normal, abnormal not clinically significant [NCS], and abnormal clinically significant [CS]) comparing baseline to follow-up by treatment group. The percentages for the shit table will be calculated relative to the number of subjects that have both a baseline and follow-up assessment available at each visit.

ECG data will be listed for all subjects in the Safety population.

15.6 Other Safety Test

SARS-COV-2 testing will be included in data listings only.

16. CHANGES TO PROTOCOL-SPECIFIED ANALYSES

There are no changes to the planned analyses in the protocol.

17. REFERENCES

18. APPENDICES

APPENDIX A: PRESENTATION OF DATA AND PROGRAMMING SPECIFICATIONS

General

- Specialized text styles, such as bold, italics, borders, shading, and superscripted and subscripted text, will not be used in tables, figures, and data listings (TFLs) unless they add significant value to the TFL.
- Only standard keyboard characters are to be used in tables and data listings.
- Special characters, such as nonprintable control characters and printer- or font-specific characters, will not be used in a TFL.
- Hexadecimal character representations are allowed (e.g., μ, α, and ß).
- All footnotes will be left-justified and at the bottom of a page. Footnotes must be used sparingly and add value to the TFL.

Tables

- Means and medians will be presented to 1 decimal place more than the raw data. Standard deviations will be presented to 2 decimal places more than the raw data. Minimums and maximums will be reported with the same number of decimal places as the raw data.
- Percentages will be presented to the tenth place.
- For frequency counts of categorical variables, categories whose counts are zero will be displayed for the sake of completeness. For example, if none of the subjects discontinue due to "lost to follow-up," this reason will be included in the table with a count of 0. Categories with zero counts will not have zero percentages displayed.
- Lower and upper confidence interval (CI) values must be presented to 1 decimal place more than the raw/derived data (i.e., to the same number of decimal places as the mean).
- Percentiles (e.g., 25% and 75%) must be presented to 1 decimal place more than the raw/derived data.
- For all inferential analyses, *P* values will be rounded to 4 decimal places (or at the highest level of precision) with a leading zero (0.0001). *P* values less than 0.0001 will be presented as "<0.0001."
- The last footnotes will be:
  - "Source: xxx", where xxx indicates the source table number(s), if applicable (in case aggregated results, such as the mean or median, are plotted), source listing(s) (in case individual responses are plotted), and source dataset(s) (e.g., analysis data model [ADaM]).
  - "PROGRAM SOURCE: ...\\xx.sas, DATA CUTOFF DATE: DD Mmm YYYY, RUN DATE: DD Mmm YYYY hh:mm".

Figures

- Legends will be used for all figures with more than 1 variable or item displayed. Treatment group sizes (n=xx) will be included, as appropriate.
- Figures will be in black and white but can be in color to add value to the clarity and readability of a figure. Lines must be wide enough to see the line after being copied.
- The last footnotes will be:
  - "Source: xxx", where xxx indicates the source listing number(s) and/or source dataset(s) (eg, ADaM).
  - "PROGRAM SOURCE: ...\\xx.sas, DATA CUTOFF DATE: DD Mmm YYYY, RUN DATE: DD Mmm YYYY hh:mm".
- Scatter plots will include the regression line. Add text that if a regression line is included. The figure may contain the estimates of the regression model parameters (e.g., y = a + b*x).
- Line graphs over time of change from baseline results will include a horizontal dashed reference line at zero.
- For box plots, the horizontal line will represent the median, "+" will represent the group mean, the length of the box will represent the interquartile range (25th-75th percentiles), and the whiskers will represent the minimum and maximum.

Listings

- If not otherwise specified, all data listings will be sorted by sequence/treatment, center, subject number, visit, and date/time, as appropriate.
- All date values will be presented in a SAS® statistical software, version 9.4 or higher (SAS Institute Inc) date format (e.g., 29AUG2001).
- All observed time values will be presented using a 24-hour clock format (HH:MM:SS) (e.g., 01:35:45 or 11:26). Seconds will only be reported if they were measured as part of the study.
- The last footnote will be "PROGRAM SOURCE: ...\\xx.sas, DATA CUTOFF DATE: DD Mmm YYYY, RUN DATE: DD Mmm YYYY hh:mm".

Missing or Incomplete Dates (ie, Adverse Events and Concomitant Medications)

The most conservative approach will be systematically considered. If the adverse event (AE) onset date is missing/incomplete, it is assumed to have occurred during the study treatment phase (i.e., considered a treatment-emergent AE) except if the partial-onset date or other data, such as the stop date, indicates differently. Similarly, a medication with partial start and stop dates could be considered both a prior and concomitant medication.

The following algorithms will be applied to missing and incomplete start and stop dates:

Start Dates

- If the day portion of the start date is missing, then the start date will be estimated to be equal to the date of the first dose of study treatment, provided the start month and year are the same as the date of the first dose of study treatment and stop date is either after the date of the first dose of study treatment or completely missing. Otherwise, the missing day portion will be estimated as "01."
- If both the day and month portions of the start date are missing, then the start date will be estimated to be equal to the date of the first dose of study treatment, provided the start year is the same as the date of the first dose of study treatment and stop date is either after the date of the first dose of study treatment or completely missing. Otherwise, the event will be assumed to start on the first day of the given year (e.g., ??-???-2013 is estimated as 01-JAN-2013).
- If the start date is completely missing and the stop date is either after the first dose of study treatment or completely missing, then the start date will be estimated to be equal to the date of the first dose of study treatment. Otherwise, the start date will be estimated to be the first day of the same year as the stop date. All other non-AE and non-concomitant medication day calculations where only partial dates are available will be handled as follows: the first day of the month will be used in the calculations if the day part of a start date is missing, and 01 January will be used if both the month and day parts of a start date are missing.

Stop Dates

- If only the day of resolution is unknown, the day of resolution of the event will be assumed to be the last day of the month (e.g., ??-JAN-2013 will be treated as 31-JAN-2013).
- If both the day and month of resolution are unknown, the day of resolution of the event will be assumed to be the last day of the year (e.g., ??-???-2013 will be treated as 31-DEC-2013).
- If the stop date of the event is completely missing or the event is continuing, the event resolution will be assumed to be after the first dose of study treatment, and the stop date will be imputed using the last known date on the study.

Standard Calculations

Variables requiring calculation will be derived using the following formulas:

- Body Mass Index (BMI): BMI is calculated using height and weight using and is calculated using the following formula: BMI (kg/m^2) = weight (kg) / [[height (cm) / 100]^2]
- Change from baseline: Change from baseline will be calculated using the following formula: change = postbaseline value – baseline value
- Percent change from baseline: Percent change from baseline will be calculated using the following formula: percent change from baseline = (postbaseline value – baseline value)/baseline value × 100.
- Study day: For a given date, the study day will be calculated as the number of days from the day of first dosing of study treatment, labeled day 1, therefore:

  Study day = date of event/measurement - date of first dose of study treatment + 1, for events/measurements on or after first dose

  Study day = date of event/measurement - date of first dose of study treatment, for events/measurements before first dose

- Durations (days): Durations, expressed in days, will be calculated as follows:

  Duration in days = (Stop date/time of event – Start date/time of event)/(3660x24)

  If the stop or start time is missing, only the date information will be used as follows:

  Duration in days = Stop date of event – Start date of event + 1

- Height: Height entries made in inches will be converted to centimeters using the following formula:

  Height (cm) = Height (in) × 2.54

- Weight: Weight entries made in pounds will be converted to kilograms using the following formula:

  Weight (kg) = Weight (lb)/2.2046

APPENDIX B: SAS PROGRAMMING QUALITY CONTROL REQUIREMENTS

Not applicable.

APPENDIX C: LIST OF TABLES, LISTINGS, AND FIGURES

The following proposal for Sections 14 and 16.2 is completed according to ICH E3 guidelines. The heading numbers and description are in **bold**. Minor changes from this planned index do not need to be amended in the statistical analysis plan.

Index of Section 14

[redacted]

Index of Sections 16.1.7 and 16.2

APPENDIX D: TABLE, FIGURE, LISTING LAYOUTS

Not applicable.

Appendix D1: Study-Specific Shells for Section 14

Not applicable.

Appendix D2: Study-Specific Shells for Section 16.2

Not applicable.

Appendix D3: Study-Specific Shells for Additional Tables, Figures, and Listings

Not applicable.

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