CLINICAL TRIAL PROTOCOL

Trial Title:	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
Short Title:	ADX-629 versus Placebo in Chronic Cough
Protocol Number:	ADX-629-CC-001
Clinical Phase:	2
IND Number	[redacted]
Sponsor:	Aldeyra Therapeutics, Inc. 131 Hartwell Avenue, Suite 320 Lexington, MA, 02421, United States of America
Protocol Version & Date	2.0, 16 June 2022

This trial will be conducted in accordance with the ethical principles that originate from the Declaration of Helsinki and that are consistent with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines on Good Clinical Practice (GCP) and regulatory requirements as applicable.

CONFIDENTIAL

CLINICAL TRIAL PROTOCOL APPROVAL

PROTOCOL TITLE: 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 NUMBER: ADX-629-CC-001

The undersigned have reviewed the format and content of and have approved the Clinical Trial Protocol. The undersigned agrees that the trial will be carried out in compliance with the Clinical Trial Protocol, Good Clinical Practice, Declaration of Helsinki (with amendments), and local legal and regulatory requirements.

Any modifications of the Clinical Trial Protocol must be agreed upon by the Sponsor and the Investigator and must be documented in writing.

Sponsor Approval:

INVESTIGATOR STATEMENT

PROTOCOL TITLE: 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

I understand that all information concerning ADX-629 in connection with this clinical trial and not previously published is confidential. This confidential information includes the Investigator's Brochure, Clinical Trial Protocol, case report form, clinical methodology, and basic scientific data.

I will not initiate this clinical trial without approval from the Institutional Review Board (IRB)/ Research Ethics Board (REB), and I understand that any changes in the protocol must be approved in writing by Aldeyra Therapeutics, Inc., and the IRB/REB before they can be implemented, except when necessary to eliminate immediate hazards to the subjects.

I will use only the informed consent form approved by Aldeyra Therapeutics and by my IRB/REB and will fulfill all responsibilities for submitting pertinent information to the IRB/REB responsible for this clinical trial.

By my signature below, I attest that I have read, understand, and agree to abide by all the conditions, instructions, and restrictions contained in Protocol Number ADX-629-CC-001, and will conduct the clinical trial in accordance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines on Good Clinical Practice (GCP) and applicable regulatory requirements.

Site Name

Site Address

Investigator's Printed Name

Investigator's Signature Date

PROTOCOL AMENDMENT SUMMARY

[redacted]

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
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PROTOCOL SYNOPSIS

Name of Sponsor: Aldeyra Therapeutics, Inc.
Protocol Number: ADX-629-CC-001
Title of the Trial: 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
Short Title: ADX-629 versus placebo in chronic cough
Investigational Product: ADX-629
Phase of Development: 2
Participating Countries and Number of Sites: Approximately 10 sites in the United States of America (USA)
Trial Objectives: *Primary Objective:* • 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 *Secondary Objectives:* • 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
Trial 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. Within each treatment period, subjects will receive their allocated treatment for 2 weeks. Each subject will have a washout period of 14 days ±2 days between the two trial periods and will undergo an end-of-trial visit approximately 14 days 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 be visited by research staff, on consecutive days. At screening, on Day 0, and Day 13 of each treatment period, the subject will be fitted with a cough recorder to collect cough count data over a period of 24 hours. On the consecutive day, the cough recorder will be removed once the 24-hour recording has been completed. The trial will include five cough recorder sessions in total.

The trial duration for each subject will be approximately 11 weeks as follows: up to 3 weeks for screening, 2 weeks for each treatment period, 14 days ±2 days washout between treatment periods, and an end-of-trial visit approximately 14 days after the last dose of trial treatment.

Number of Subjects:

Approximately 50 subjects are planned for enrollment.

Subject Population:

Inclusion Criteria:

Subjects who fulfill all of the following criteria (as applicable) are eligible for enrollment in the trial:

1. Male or female adults (≥18 to ≤80 years of age at screening).
2. Written informed consent must be provided before any protocol-specific screening procedures are performed.
3. History of refractory or unexplained chronic cough for >1 year prior to screening that is unresponsive to at least 8 weeks of targeted treatment for identified underlying triggers including reflux disease, asthma, and post-nasal drip; or for which no objective evidence of an underlying trigger can be determined after investigation.
4. [redacted]
5. [redacted]
6. Chest radiograph or computed tomography (CT) scan performed within 5 years before screening and after the onset of chronic cough that does not demonstrate any abnormality considered to be significantly contributing the chronic cough, in the opinion of the Investigator
7. Females of childbearing potential (i.e., ovulating, pre-menopausal, and not surgically sterile) who:
   a. have a negative serum pregnancy test at screening,
   b. are not breastfeeding or lactating, and
   c. agree to use a highly effective method of acceptable contraceptive for the trial duration and at least 30 days after the last dose in the trial.

8. Females of non-childbearing potential must be either surgically sterile (i.e., hysterectomy, bilateral tubal ligation, salpingectomy, or bilateral oophorectomy at least 26 weeks prior to screening) or post-menopausal, defined as spontaneous amenorrhea for at least 1 year, with follicle-stimulating hormone (FSH) blood levels of equal or greater than 40 mIU/mL at the Screening Visit.
9. Males who are surgically sterile, or:
    a. males with female partners of childbearing potential who agree to use a highly effective method of acceptable contraceptive for at least 30 days after the last dose in the trial, and
    b. agree to abstain from sperm donation through 30 days after administration of the last dose of the trial treatment.
10. [redacted]

Exclusion Criteria:

Subjects who fulfill any of the following criteria are not eligible for enrollment in the trial:

1. Current smoker (e.g., cigarettes, e-cigarettes, nicotine patches) including cannabis products; or previous smoker having given up smoking ≤12 months before screening or has a history of smoking >20 pack-years or the equivalent nicotine strength at any time or has positive cotinine test results at screening.
2. [redacted]
3. Active upper respiratory tract infection or recent significant change in pulmonary status that, in the opinion of the Investigator, could affect the conduct or outcome of the trial and that is documented by a physician within 4 weeks before the first dose of trial treatment.
4. Uncontrolled hypertension with systolic blood pressure ≥160 mmHg or diastolic blood pressure ≥90 mmHg at screening.
5. Prolonged QT interval corrected for heart rate using Fridericia's formula (QTcF) >440 ms or shortened QTcF <340 ms at screening, or history of significant tachycardia, bradycardia, acute or chronic cardiovascular disease or any clinically significant abnormalities in rhythm, conduction, or morphology of the resting electrocardiogram (ECG).

6. Elevated alanine aminotransferase (ALT), aspartate aminotransferase (AST), or bilirubin levels >2.0 × upper normal limits.
7. History or presence of gastrointestinal, hepatic disease, or any other condition known to interfere with absorption, distribution, metabolism, or excretion of drugs.
8. Acute or chronic renal disease or medical history of renal disease with estimated glomerular filtration rate (eGFR) ≤30 mL/min/1.73 m^2 calculated by Chronic Kidney Disease Epidemiology (CKD-EPI) equation or spot urine protein to creatinine ratio (sUPCR) >2000 mg/g (226 mg/mmol, as an estimate of approximate proteinuria >2 g/day) at screening.
9. History of any malignancy within 5 years of screening except for basal cell or squamous cell in situ skin carcinomas or carcinoma in situ of the cervix that has been treated with no evidence of recurrence.
10. Taking disallowed concomitant medications (strong CYP1A2, CYP2B6, and CYP3A4 inhibitors) during the trial period.
11. History of severe hypersensitivity or ongoing clinically significant hypersensitivity to ADX-629.
12. User of recreational or illicit drugs or history of drug or alcohol abuse within the last 6 months, or a positive urine drug test or alcohol breath test at screening.
13. Positive serology test for Hepatitis B virus (HBV), Hepatitis C virus (HCV), or human immunodeficiency virus (HIV-1 and HIV-2) at screening.
14. Positive screening test for, or current infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), or documented history of prior infection in the past 3 months prior to screening.
15. Current or recent participation in another interventional trial within 90 days prior to screening.
16. Any clinically significant abnormalities or findings from examination, tests, or medical history that may compromise subject safety. Potential issues of concern should be raised with the Medical Monitor.
17. Any unstable or uncontrolled acute or chronic diseases/conditions that in the Investigator's opinion could affect the conduct or outcome of the trial.
18. Currently taking an angiotensin converting enzyme inhibitor (ACEI) or has used an ACEI within 3 months of screening.

Investigational Product, Dose, and Mode of Administration:

The investigational product is ADX-629 300 mg tablets. Subjects will take 300 mg (one tablet) BID for 14 days.

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. Within each treatment period, subjects will receive their allocated treatment for 2 weeks.

Reference Product, Dose, and Mode of Administration:

Placebo tablets to match ADX-629 300 mg tablets. Subjects will take one tablet BID for 14 days.

Duration of Treatment:

The duration of intake of trial medication will be 28 days (14 days ADX-629, 14 days placebo); the trial duration for each subject, including screening, washout, and end-of-trial visit, will be approximately 11 weeks.

Endpoints:

Primary Endpoints:

- 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

Key Secondary Endpoint for Assessment of Efficacy:

- Change from baseline in awake cough frequency per hour after 2-week treatment

Secondary Endpoints:

- Change from baseline in 24-hour cough frequency per hour after 2-week treatment
- 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
- Clinician Global Impression of Change (CGIC) score

Safety:

During the trial, safety will be assessed by evaluation of the following:

- Physical examination, including review of the major body systems, height, and weight
- Vital signs including blood pressure, heart rate, respiratory rate, temperature, and oxygen saturation
- Standard 12-lead ECG
- Laboratory parameters (including hematology, serum biochemistry, urinalysis, and urine/serum pregnancy testing)
- All AEs occurring after the subject signs the informed consent form and up to the last trial visit will be recorded

Efficacy:

The key secondary efficacy endpoint is change from baseline in awake cough frequency (cough count/duration of measurement [hours]). For each treatment period, baseline is the cough frequency during the recorder assessment just prior to initiation of investigational product. Though summaries will be presented for cough frequencies, due to the skewed nature of the data, a log transformation will be used prior to statistical analyses.

Statistical Methods:

[redacted] Allowing for a reduction in power due to subject withdrawals, approximately 50 subjects will be randomized.

The key secondary efficacy endpoint, change from baseline in awake cough frequency, will be analyzed using a mixed-effect model suitable for the crossover design. 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. The model will include fixed effects for treatment sequence, period, treatment, and subject nested within treatment sequence as a random effect. Period specific baselines will be included as covariates. The secondary efficacy endpoint change from baseline in 24-hour cough frequency will be analyzed using the same methods described for the key secondary efficacy endpoint.

Other efficacy endpoints will be summarized and analyzed to estimate the treatment effect and corresponding 95% confidence interval using a similar model to that described for awake cough frequency. Cough frequency endpoints will be analyzed on the natural log scale.

Treatment-emergent adverse events will be summarized by treatment group and by system organ class and preferred term, in accordance with the Medical Dictionary for Regulatory Activities coding dictionary. Safety variables will be summarized descriptively by treatment.

All statistical testing will be at the 5% level of significance (2-sided) and all point estimates for the comparison between treatment groups will be accompanied by 2-sided 95% confidence intervals.

The intent-to-treat (ITT) population will be the primary analysis population for efficacy. All safety analyses will be based upon the safety set, i.e., all subjects who receive at least 1 dose of trial treatment.

Statistical methods will be detailed in the Statistical Analysis Plan, which will govern any statistical language within the protocol.

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1. ADMINISTRATIVE STRUCTURE AND CONTACT INFORMATION

Sponsor:
Aldeyra Therapeutics, Inc.
131 Hartwell Avenue, Suite 320
Lexington, MA, 02421
United States of America (USA)
Tel: +1 781-761-4904

Clinical Supplies:
Aldeyra Therapeutics, Inc.
131 Hartwell Avenue, Suite 320
Lexington, MA, 02421
USA
Tel: +1 781-257-3045

2. ABBREVIATIONS

%CV	Percent coefficient of variation
ACEI	Angiotensin converting enzyme inhibitor
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve
BD	Bronchodilator
BID	Twice daily (*bis in die*)
BMI	Body mass index
CGIC	Clinician Global Impression of Change
CKD-EPI	Chronic Kidney Disease Epidemiology
C_{max}	Maximum plasma concentration
CQLQ	Cough-Specific Quality of Life Questionnaire
CRO	Contract Research Organization
CT	Computed tomography
CYP	Cytochrome P450
DMP	Data management plan
ECG	Electrocardiogram
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
FDA	Food and Drug Administration
FEV_1	Forced expiratory volume in 1 second
FSH	Follicle-stimulating hormone
FVC	Forced vital capacity
GCP	Good Clinical Practice
GERD	Gastroesophageal reflux disease
HbsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HDL	High-density lipoprotein

HIV	Human immunodeficiency virus
ICF	Informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IP	Investigational product
IRB	Institutional Review Board
ITT	Intent-to-Treat
IUD	Intrauterine device
LCQ	Leicester Cough Questionnaire
LTRA	Leukotriene receptor antagonist
MAD	Multiple ascending dose
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MDA	Malondialdehyde
MedDRA	Medical Dictionary for Regulatory Activities
NAEB	Non-asthmatic eosinophilic bronchitis
NASH	Nonalcoholic steatohepatitis
PGIC	Patient Global Impression of Change
PK	Pharmacokinetic(s)
PP	Per protocol
PPI	Proton Pump Inhibitor
QTcF	QT interval corrected for heart rate using Fridericia's formula
RASP	Reactive aldehyde species
RBC	Red blood cell
REB	Research Ethics Board
RTSM	Randomization and Trial Supply Management
SAD	Single ascending dose
SAE	Serious adverse event
SAP	Statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
sUPCR	Spot urine protein to creatinine ratio

SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event
UACS	Upper airway cough syndrome
VAS	Visual analog scale
WHODrug	World Health Organization Drug Dictionary

3. BACKGROUND AND TRIAL RATIONALE

3.1 Refractory Chronic Cough

Cough represents one of the most frequent complaints leading patients to seek medical attention (Schappert and Burt, 2006), and is a common symptom associated with many other conditions such as respiratory infection, asthma, or chronic obstructive pulmonary disease. In cough guidelines, such as those published by the American College of Chest Physicians and the British Thoracic Society (Irwin et al., 2006; Morice et al., 2006), cough is characterized by the length of time a patient is coughing; acute – up to 3 weeks, sub-acute – from 3 to 8 weeks, and chronic – greater than 8 weeks.

Patients who present to a physician for a persistent cough are evaluated and treated for common causes of cough. Patients who continue to cough are evaluated for conditions that are commonly associated with chronic cough, such as asthma, gastroesophageal reflux disease (GERD), and upper airway cough syndrome (UACS) (Dicpinigaitis, 2011; Morice et al., 2006). A patient may be evaluated for less common diseases based on their history, other symptoms, or physical findings. Patients in whom no treatable cause of their cough can be found are characterized as having "refractory chronic cough" (Gibson et al., 2016).

The prevalence of chronic cough is estimated to affect 11% to 13% of the population (Ford et al., 2006; Song et al., 2014). Patients are most commonly women aged between 45 to 75 years. Chronic cough can seriously impair quality of life as it has physical, social, and psychosocial consequences with a marked effect on quality of life as measured by instruments such as the Leicester Cough Questionnaire (LCQ) (Birring et al., 2003b). The disabling effects of chronic cough are understandable, given that patients with the condition cough hundreds or even thousands of times per day for months to years (Smith et al., 2016).

There is a significant proportion of patients with refractory or unexplained chronic cough who do not respond to treatment of the underlying disease or do not have an underlying condition identified. Treatment options for these patients are very limited (Morice et al., 2006). Patients and clinicians will frequently try over-the-counter agents such as dextromethorphan, guaifenesin, and antihistamines with little benefit. Prescription options in the United States of America (USA) include benzonatate, codeine and related opiate products. Over-the-counter antitussive products that contain antihistamine or dextromethorphan are also widely used for cough, but these compounds have limited efficacy.

3.2 ADX-629 Background

Reactive aldehyde species (RASP) such as 4-hydroxynonenal and malondialdehyde (MDA) are toxic mediators of the mammalian immune system and are implicated in numerous disease states. The Sponsor has developed ADX-629, a proprietary new chemical entity for the treatment of chronic diseases with inflammatory and immune-mediated components, including psoriasis, ulcerative colitis, nonalcoholic steatohepatitis (NASH), acute respiratory distress

syndrome, and other diseases thought to be caused or exacerbated by elevated concentrations of RASP.

ADX-629 is a small molecule formulated for oral administration that binds rapidly and irreversibly to RASP, thus preventing RASP-mediated inflammation and other toxicities.

[redacted]

In addition to nonclinical safety studies, Phase 1 safety testing has been conducted in 85 healthy human volunteers in a single ascending dose (SAD) trial and a multiple ascending dose (MAD) trial. In the SAD trial, 41 subjects received ADX-629 and 13 subjects received placebo across all cohorts. In the MAD trial, 23 subjects received ADX-629 and 8 subjects received placebo across all cohorts. Overall, ADX-629 was found to be safe and well tolerated at the doses explored, including the maximum dose of 600 mg twice daily (BID). The adverse event (AE) profile of ADX-629 was favorable compared to placebo. A total of 6 subjects (9.4%) who received ADX-629 (up to 600 mg BID) had treatment-emergent adverse events (TEAEs) compared to 4 subjects (19.1%) who received placebo. None of the subjects had treatment interrupted or discontinued trial drug in the MAD trial.

Although PK variability was observed, a linear correlation was evident in maximum plasma concentration (C_{max}) and exposure (area under the plasma concentration-time curve [AUC]) with increasing dose. The half-life was consistent across doses and days, with mean values in multiple day exposures ranging between 3.49 and 6.83 hours, supportive of BID administration. Little to no accumulation of the drug was seen across all doses. A C_{max} of 790 ng/mL (approximately 4 µM) and an AUC_{0-12} of 3400 h*ng/mL is anticipated given the Day 10 exposure at 300 mg BID (extrapolated from 600 mg BID at steady state). This exposure is expected to yield an adequate molar ratio to achieve stoichiometric efficacy against elevated RASP. A decrease in free MDA levels was observed in the plasma of healthy volunteers over 10 days of dosing with ADX-629 600 mg BID that was statistically significantly greater than that of subjects treated with placebo. Following ingestion of a high-fat meal on Day 10 of dosing with 600 mg BID or placebo, levels of free fatty acids were statistically lower and levels of high-density lipoprotein (HDL) cholesterol were statistically significantly higher in drug-treated subjects than in placebo-treated subjects, potentially representing additional anti-inflammatory activity of ADX-629.

3.3 Trial Rationale

Chronic cough has been associated with autoimmune disease (Birring et al., 2003a). By covalently binding proteins and forming non-self-epitopes, RASP is associated with autoantibody formation (Thiele et al., 2015). In addition, chronic cough may be potentiated by the TRPV1 receptor (Long et al., 2019), which is modulated by RASP binding (Trevisani et al., 2007). Preliminary evidence also suggests that RASP is elevated in the sputum of patients with chronic cough (personal communication, Brian Day, Ph.D., National Jewish Medical Center) relative to control subjects. Thus, RASP inhibition could represent a novel approach for the treatment of chronic cough.

3.4 Benefit/Risk Assessment

The ADX-629-CC-001 clinical trial will evaluate the safety, tolerability, and efficacy of ADX-629 in subjects with refractory or unexplained chronic cough. The background and rationale detailed above suggests that subjects may benefit from treatment with ADX-629.

Safety of the clinical dosing regimen in this trial is supported by a Phase 1 clinical trial in healthy volunteers and a number of nonclinical toxicology and PK studies in which no serious safety concerns were noted at the projected therapeutic doses in man.

ADX-629 was well tolerated in healthy human volunteers at doses of up to 600 mg BID (the maximum dose tested) for 10 days. The AE profile of ADX-629 in the SAD/MAD studies was favorable compared to placebo: a total of 6 subjects (9.4%) who received ADX-629 had TEAEs, compared to 4 subjects (19.1%) who received placebo. There were no interruptions or discontinuations of trial drug administration with subjects receiving multiple doses. More information is provided in the current version of the Investigator's Brochure.

Flexibility in the format of visits is built into this protocol to facilitate the health and safety practices necessary to protect everyone involved in the trial from transmission of COVID-19 or other infections. Throughout the protocol, the term 'visit' is used to indicate interaction between the trial subject and research staff. However, trial subjects are not required to attend the clinic but may be visited at home, or at another suitable location, by, e.g., a research nurse or other appropriate member of the research team, whenever the protocol assessments allow. Other arrangements are also permitted where these will not challenge the integrity of the data, e.g., couriers may be used for distribution and collection of cough monitoring equipment to the investigative site to minimize face-to-face contact. All research staff will employ routine personal protection, hand sanitization measures, and any other applicable local guideline requirements when in close contact with trial subjects.

4. TRIAL OBJECTIVES AND ENDPOINTS

4.1 Objectives

4.1.1 Primary Objective

The primary objective of this trial is:

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

4.1.2 Secondary Objectives

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

4.2 Endpoints

4.2.1 Primary Endpoints

The primary endpoints of this trial are:

- Incidence and severity of TEAEs and serious adverse events (SAEs)
- Observed values and changes from baseline of:
  - Laboratory safety parameters
  - Vital signs
  - 12-lead electrocardiogram (ECG) parameters

4.2.2 Key Secondary Endpoint for Assessment of Efficacy

The key secondary efficacy endpoint for assessment of efficacy of this trial is:

- Change from baseline in awake cough frequency per hour after 2-week treatment

4.2.3 Secondary Endpoints

The secondary endpoints of this trial are:

- Change from baseline in 24-hour cough frequency per hour after 2-week treatment
- Change from baseline in cough severity using a visual analog scale (VAS)
- Change from baseline in 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
- Clinician Global Impression of Change (CGIC) score

5. TRIAL DESIGN AND DESCRIPTION OF THE TRIAL

5.1 Overall Trial Design and Plan

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.

The trial measures the potential risks associated with the trial and will be explained to all potential trial subjects. Written informed consent must be obtained before any procedures or evaluations required by the protocol are performed.

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.

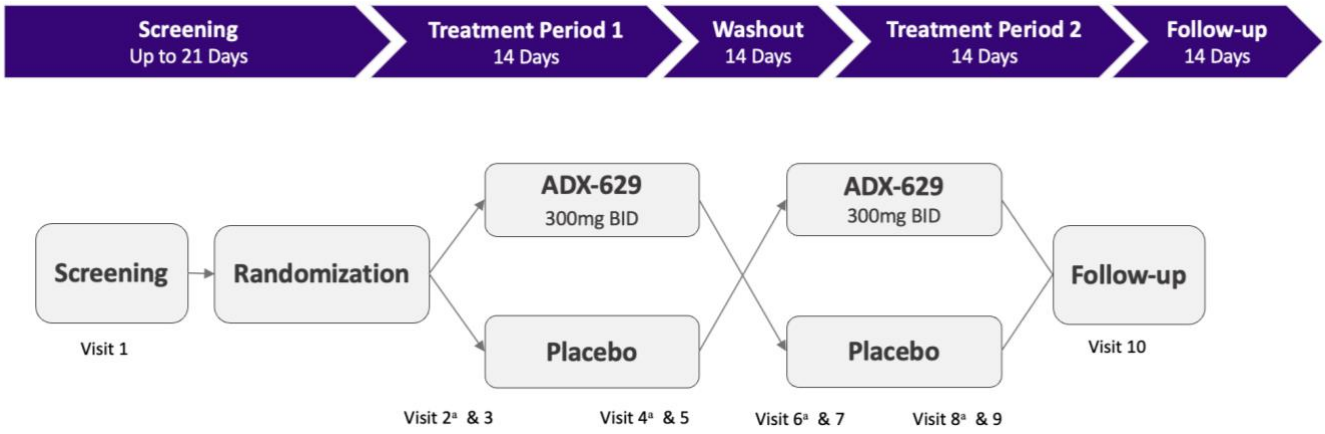
Within each treatment period, subjects will receive their allocated treatment for 2 weeks. Each subject will have a washout period of 14 days ±2 days between the two trial periods and will undergo end-of-trial visit approximately 14 days after the last dose of trial treatment. Subjects will be required 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 be visited by research staff, on consecutive days. At screening, on Day 0, and Day 13 of each treatment period, the subject will be fitted with a cough recorder to collect cough count data over a period of 24 hours. On the consecutive day the cough recorder will be removed 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 approximately 11 weeks as follows: up to 3 weeks for screening, 2 weeks for each treatment period, 14 days±2 days washout between treatment periods, and end-of-trial visit approximately 14 days after the last dose of trial treatment.

Should a subject discontinue trial treatment, they will be requested to participate in an early termination visit as soon as possible after the subject stops taking trial treatment. They should then have their end-of-trial visit approximately 14 days after their last dose of trial treatment; however, if their early termination visit is more than 1 week after their last dose, they will not be required to have a follow-up safety assessment.

The end-of-trial safety assessment will be conducted as a clinic visit for end-of-trial laboratory parameters, vital signs, or ECG parameters. The trial design is illustrated in Figure 1.

Figure 1: Schematic of Trial Design



Abbreviation: BID=twice daily.

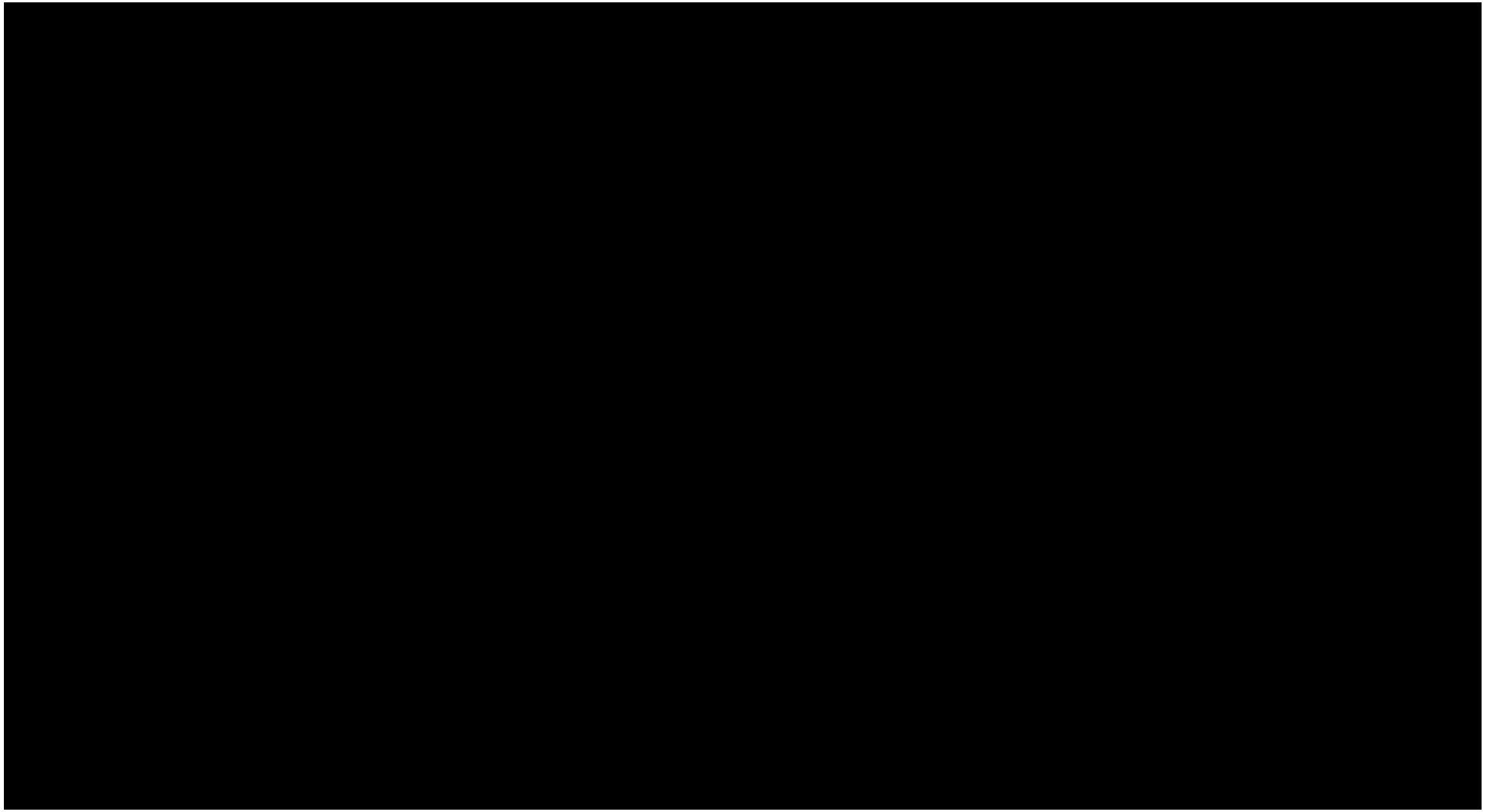
[a] Subjects will attend the clinic or be visited by research staff, on consecutive days. The cough recorder will be fitted at screening, on Day 0, and Day 13 of each treatment period, to enable cough count data recording over a period of 24 hours.

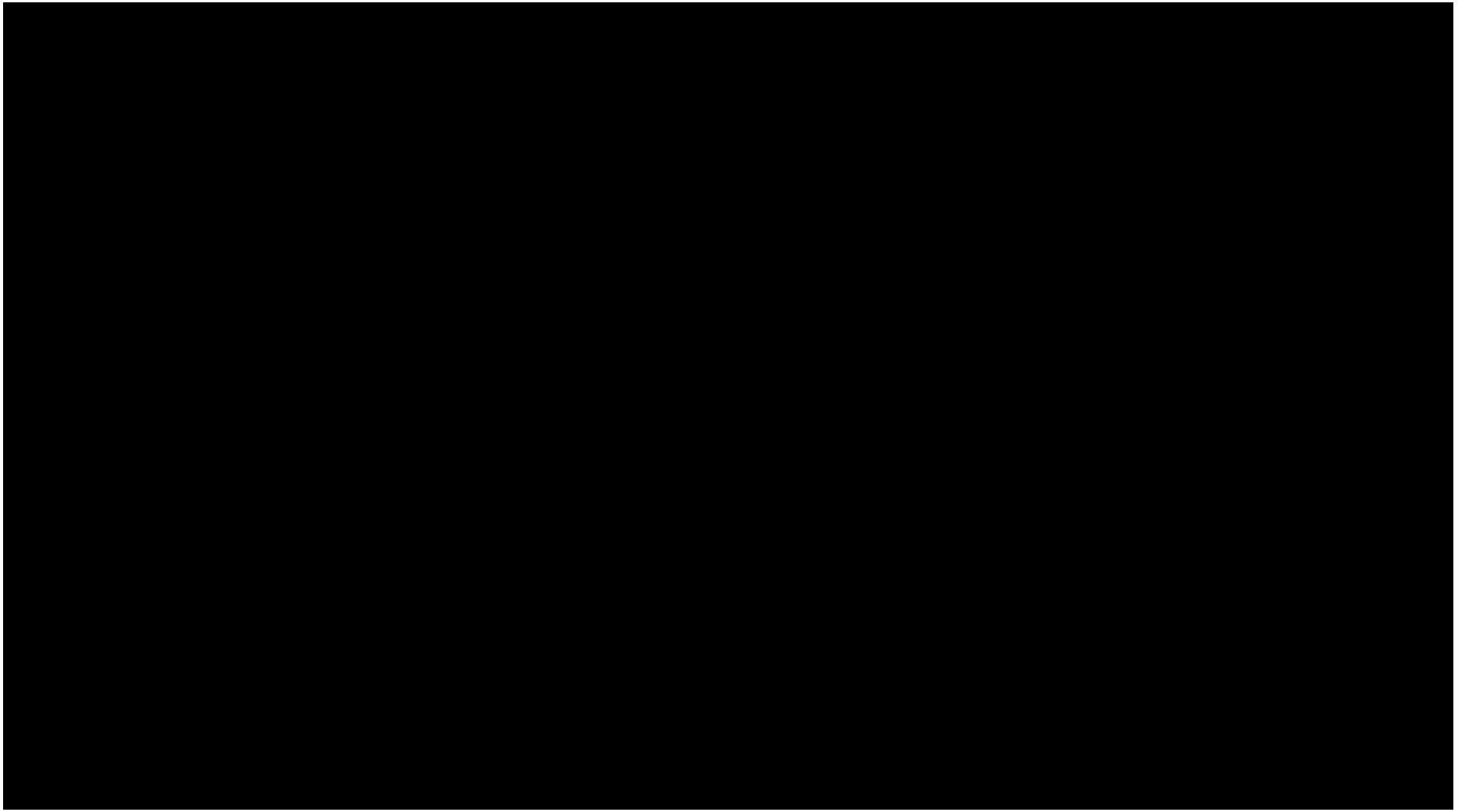
5.2 Trial Visit Schedule

5.2.1 Summary of the Schedule of Assessments

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

Table 1: Schedule of Assessments





5.2.2 Trial Visits

Visits may be conducted either at the clinic or at another location such as the subject's home, provided the equipment is available to perform the required assessments.

5.2.2.1 Screening Period Procedures - Visit 1

Visit 1 may have a duration of more than 1 day to accommodate all screening assessments; the informed consent form (ICF) signature is the start of the screening period and will be used as the date of Visit 1. Subjects who are willing to participate will sign the ICF. Subjects will then be given a trial number before the screening evaluation procedures are performed. Each subject will be given detailed information about the trial, including timelines, description of each planned visit, possible side-effects, and potential benefits. The information given to each subject will be both oral and written.

- Obtain written informed consent after review of inclusion and exclusion criteria.
- Collect demographic information (date of birth, sex, ethnicity, and race).
- Medical history, including history of chronic cough, smoking history, and medication history.
- Collect vital signs (blood pressure, heart rate, respiratory rate, temperature, and oxygen saturation).
- Record concomitant medications.
- Conduct physical examination, including review of the major body systems, and record height and weight. Body mass index (BMI) will be calculated.
- Record standard 12-lead ECG.
- Record spirometry (forced expiratory volume in 1 second [FEV_1] and forced vital capacity [FVC]).
- Review of chest radiograph or computed tomography (CT) scan of the thorax, done within 5 years before screening and after the onset of chronic cough. If a chest radiograph or CT have not done within the last 5 years, the subject is ineligible.
- Collect blood sample for routine laboratory testing (biochemistry and hematology). Testing to include follicle-stimulating hormone (FSH) in females thought to be menopausal and human chorionic gonadotropin (b-hCG) in women of childbearing potential, and Hepatitis B, C, and HIV serology in all subjects.
- Collect urine sample for urinalysis and urine/creatinine ratio.
- Perform urine drug screen.
- Perform alcohol breath test.
- Perform SARS-CoV-2 test (not required if the subject has had a negative SARS-CoV-2 test within 48 hours prior to date of informed consent signature). Results obtained by antigen testing or polymerase chain reaction testing are acceptable.
- Record cough severity VAS.
- Complete LCQ.
- Complete CQLQ.
- Record any pre-treatment AEs with onset after the subject has signed the ICF.

- Subjects will be fitted with a cough recorder by 10:00 am, which must be worn for 24 hours of recording time. The cough recorder may be returned to the investigative site by courier after the 24-hour recording.

Subjects who fulfill the trial eligibility criteria will be given appointments for their participation in the trial.

If a subject visit falls outside the screening period window or repeat assessments are required, screening may be extended with approval from the Medical Monitor. If extended beyond 21 days, some of the screening procedures and assessments may need to be repeated.

Subjects who have screen failed may be re-screened once if their eligibility characteristics have changed. Subjects who are re-screened must be assigned a new subject number. The re-screening process for such subjects must be discussed with the Medical Monitor.

5.2.2.2 Randomization (Day 0)

The inclusion and exclusion criteria will be reviewed to confirm the subject's eligibility for the trial. Eligible subjects will be randomized to one of the two treatment sequences according to the randomization schedule.

5.2.2.3 Treatment Period Procedures - Visits 2 and 6

This visit may be conducted at the clinic or another location such as the subject's home, according to the preference of the subject.

The following assessments and procedures will be performed:

- Collect vital signs (blood pressure, heart rate, respiratory rate, temperature, and oxygen saturation).
- Record changes in concomitant medications.
- Record any AEs since the last visit.

Subjects should be fitted with a cough recorder by 10:00 am. The cough recorder must be worn for 24 hours between fitting and disconnection.

5.2.2.4 Treatment Period Procedures - Visits 3 and 7

The following assessments and procedures will be performed:

Before Dosing:

- Review inclusion and exclusion criteria (Visit 3 only).
- Collect vital signs (blood pressure, heart rate, respiratory rate, temperature, and oxygen saturation).
- Record changes in concomitant medications.
- Symptomatic physical examination may be performed, if deemed necessary (e.g., to record any changes since screening or due to an AE). This may require an additional visit to the investigative site.

- Record standard 12-lead ECG.
- Collect blood sample for routine laboratory testing (biochemistry and hematology).
- Collect urine sample for urinalysis and urine/creatinine ratio.
- Perform urine pregnancy test (women of childbearing potential).
- Perform urine drug screen.
- Perform SARS-CoV-2 test (Day 1 of Treatment Period 2 only).
- Record cough severity VAS.
- Complete LCQ.
- Complete CQLQ.
- Record any AEs since the last visit.
- The cough recorder will be disconnected 24 hours after fitting and retained by the investigative site.
- The first dose of trial treatment will be dispensed, and subjects will take the first dose (this must be after the completion of the cough monitoring).
- Visit 7 only: Unused trial medication and empty containers from Treatment Period 1 will be returned.

After Dosing:

- Collect vital signs (blood pressure, heart rate, respiratory rate, temperature, oxygen saturation) and record 2 hours (±30 minutes) after dosing.
- Dispense trial treatment to take home.

The subject will take the second dose of trial treatment at home before bedtime and will continue to take the randomized treatment twice daily for 14 days.

5.2.2.5 Treatment Period Procedures - Visits 4 and 8

This visit may be conducted at the clinic or at another location such as the subject's home, according to the preference of the subject.

The following assessments and procedures will be performed:

- Collect vital signs (blood pressure, heart rate, respiratory rate, temperature, and oxygen saturation).
- Record changes in concomitant medications.
- Symptomatic physical examination may be performed, if deemed necessary (e.g., to record any changes since screening or due to an AE). This may require an additional visit to the investigative site.
- Record any AEs since the last visit.

Subjects should be fitted with a cough recorder by 10:00 am. The cough recorder must be worn for 24 hours between fitting and disconnection. The subject will take the trial treatment at home before bedtime and will continue to take the randomized treatment twice daily.

5.2.2.6 Treatment Period Procedures - Visits 5 and 9

The following assessments and procedures will be performed:

Before Dosing:

- Collect vital signs (blood pressure, heart rate, respiratory rate, temperature, and oxygen saturation).
- Record changes in concomitant medications.
- Symptomatic physical examination may be performed, if deemed necessary (e.g., to record any changes since screening or due to an AE). This may require an additional visit to the investigative site.
- Record standard 12-lead ECG.
- Collect blood sample for routine laboratory testing (biochemistry and hematology).
- Collect urine sample for urinalysis and urine/creatinine ratio.
- Perform urine pregnancy test (women of childbearing potential).
- Record cough severity VAS.
- Complete LCQ.
- Complete CQLQ.
- Record global rating of change for cough severity and frequency, PGIC, CGIC.
- Record any AEs since the last visit.
- The cough recorder will be disconnected 24 hours after fitting and retained by the investigative site.

After Dosing:

- Collect vital signs (blood pressure, heart rate, respiratory rate, temperature, oxygen saturation) and record at 2 hours (±30 minutes) after dosing.

Subjects will be instructed to take the last dose of trial treatment in the evening at the usual time.

5.2.2.7 End-of-Trial visit - Visit 10

The following assessments and procedures will be performed at the clinic:

- Collect vital signs (blood pressure, heart rate, respiratory rate, temperature, and oxygen saturation).
- Record changes in concomitant medications.
- Conduct physical examination, including review of the major body systems.
- Record standard 12-lead ECG.
- Collect blood sample for routine laboratory testing (biochemistry and hematology).

- Collect urine sample for urinalysis and urine/creatinine ratio.
- Record any AEs since the last visit.
- Unused trial medication and empty containers from Treatment Period 2 will be collected or returned.

5.2.2.8 Early Withdrawal Visit Procedures

If a subject withdraws/is withdrawn from the trial, the following assessments should be performed:

- Collect vital signs (blood pressure, heart rate, respiratory rate, temperature, and oxygen saturation).
- Record changes in concomitant medications.
- Conduct physical examination, including review of the major body systems. This may require an additional visit to the investigative site.
- Record standard 12-lead ECG.
- Collect blood sample for routine laboratory testing (biochemistry and hematology).
- Collect urine sample for urinalysis and urine/creatinine ratio.
- Record cough severity VAS.
- Complete LCQ.
- Complete CQLQ.
- Record global rating of change for cough severity and frequency, PGIC, CGIC.
- Record any AEs since the last visit.
- Unused trial treatment and empty containers will be collected or returned.

5.3 End of Trial Definition

A subject is considered to have completed the trial if they have completed all phases of the trial, including the end-of-trial visit.

The end of the trial is defined as the date of the last visit or scheduled procedure shown in the schedule of assessments (Table 1) for the last subject in the trial.

5.4 Duration of Treatment

The duration of intake of trial medication will be 28 days (14 days ADX-629, 14 days placebo); the trial duration for each subject, including screening, washout, and end-of-trial, will be approximately 11 weeks.

6. SELECTION OF TRIAL POPULATION

6.1 Description of Trial Population

The trial population will be adult subjects with refractory or unexplained chronic cough.

6.2 Number and Source of Subjects

Approximately 50 subjects are planned for enrollment. Potential subjects will be identified from clinic records.

6.3 Inclusion Criteria

Subjects who fulfill all of the following criteria (as applicable) are eligible for enrollment in the trial:

1. Male or female adults (≥18 to ≤80 years of age at screening).
2. Written informed consent must be provided before any protocol-specific screening procedures are performed.
3. History of refractory or unexplained chronic cough for >1 year prior to screening that is unresponsive to at least 8 weeks of targeted treatment for identified underlying triggers including reflux disease, asthma and post-nasal drip; or for which no objective evidence of an underlying trigger can be determined after investigation (see **Error! Reference source not found.**).
4. [redacted]
5. [redacted]
6. Chest radiograph or CT scan performed within 5 years before screening and after the onset of chronic cough that does not demonstrate any abnormality considered to be significantly contributing the chronic cough, in the opinion of the Investigator.
7. Females of childbearing potential (i.e., ovulating, pre-menopausal, and not surgically sterile) who:
   a. have a negative serum pregnancy test at screening,
   b. are not breastfeeding or lactating, and
   c. agree to use a highly effective method of acceptable contraceptive (see Section 7.9.2) for the trial duration and at least 30 days after the last dose in the trial.
8. Females of non-childbearing potential must be either surgically sterile (i.e., hysterectomy, bilateral tubal ligation, salpingectomy, or bilateral oophorectomy at least 26 weeks prior to screening) or post-menopausal, defined as spontaneous amenorrhea for at least 1 year, with FSH blood levels of equal or greater than 40 mIU/mL at the Screening Visit.

9. Males who are surgically sterile, or:
   a. males with female partners of childbearing potential who agree to use a highly effective method of acceptable contraceptive (see Section 7.9.2) for at least 30 days after the last dose in the trial, and
   b. agree to abstain from sperm donation through 30 days after administration of the last dose of the trial treatment.
10. [redacted]

6.4 Exclusion Criteria

Subjects who fulfill any of the following criteria are not eligible for enrollment in the trial:

1. Current smoker (e.g., cigarettes, e-cigarettes, nicotine patches) including cannabis products; or previous smoker having given up smoking ≤12 months before screening, or has a history of smoking of >20 pack-years or the equivalent nicotine strength (see Section 7.9.3) at any time or has positive cotinine test result at screening.
2. [redacted]
3. Active upper respiratory tract infection or recent significant change in pulmonary status that, in the opinion of the Investigator, could affect the conduct or outcome of the trial and that is documented by a physician within 4 weeks before the first dose of trial treatment.
4. Uncontrolled hypertension with systolic blood pressure ≥160 mmHg or diastolic blood pressure ≥90 mmHg at screening.
5. Prolonged QT interval corrected for heart rate using Fridericia's formula (QTcF) >440 ms or shortened QTcF <340 ms at screening, or history of significant tachycardia, bradycardia, acute or chronic cardiovascular disease or any clinically significant abnormalities in rhythm, conduction, or morphology of the resting ECG.
6. Elevated alanine aminotransferase (ALT), aspartate aminotransferase (AST), or bilirubin levels >2.0 × upper normal limits.
7. History or presence of gastrointestinal, hepatic disease, or any other condition known to interfere with absorption, distribution, metabolism, or excretion of drugs.
8. Acute or chronic renal disease or medical history of renal disease with estimated glomerular filtration rate (eGFR) ≤30 mL/min/1.73 m^2 calculated by Chronic Kidney Disease Epidemiology (CKD-EPI) equation or spot urine protein to creatinine ratio (sUPCR) >2000 mg/g (226 mg/mmol, as an estimate of approximate proteinuria >2 g/day) at screening.

9. History of any malignancy within 5 years of screening except for basal cell or squamous cell in situ skin carcinomas or carcinoma in situ of the cervix that has been treated with no evidence of recurrence.
10. Taking disallowed concomitant medications (strong CYP1A2, CYP2B6, and CYP3A4 inhibitors) during the trial period (Section 7.9).
11. History of severe hypersensitivity or ongoing clinically significant hypersensitivity to ADX-629.
12. User of recreational drugs or has a recent history of drug or alcohol abuse within the last 6 months, or a positive urine drug test or alcohol breath test at screening.
13. Positive serology test for Hepatitis B virus (HBV), Hepatitis C virus (HCV), or HIV-1 and HIV-2 at screening.
14. Positive screening test for, or current infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), or documented history of prior infection in the past 3 months prior to screening.
15. Current or recent participation in another interventional trial within 90 days prior to screening.
16. Any clinically significant abnormalities or findings from examination, tests, or medical history that may compromise subject safety. Potential issues of concern should be raised with the Medical Monitor.
17. Any unstable or uncontrolled acute or chronic diseases/conditions that in the Investigator's opinion could affect the conduct or outcome of the trial.
18. Currently taking an angiotensin converting enzyme inhibitor (ACEI) or has used an ACEI within 3 months of Screening.

6.5 Removal of Subjects from Therapy or Assessment

Participation in the trial is strictly voluntary. A subject has the right to withdraw from the trial at any time and for any reason. If they choose to withdraw from the trial, the Investigator must be informed immediately. The Investigator has the right to terminate participation of any subject at any time if it is in the subject's best interest. The reason and circumstances for premature discontinuation will be documented in the subject's electronic case report form (eCRF).

A subject may be discontinued from treatment for any of the following reasons:

- Withdrawal of consent by the subject.
- Severe lack of compliance with trial treatment in Treatment Period 1 (i.e., <80% or >120% compliance).
- Increase from baseline in serum creatinine by ≥0.3 mg/dL or ≥50%.
- Major protocol deviation, e.g., requirement for a disallowed concomitant medication or non-drug therapies (see Table 3, Section 10.1.2).

- Trial treatment must be discontinued in subjects who become pregnant in the trial. The pregnancy will be reported and followed up as per guidance in (see Section 8.3.2). However, the subject should still undergo relevant post-randomization procedures and visits if possible and safe to do so.
- Investigator's decision that it is not in the best interest of the subject to continue.
- Lost to follow-up: The subject stopped coming to the investigative site for visits, and trial personnel were unable to contact the subject.

Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the subject should continue or discontinue trial treatment.

If possible, an early termination visit should be conducted (i.e., procedures for the end of Treatment Period 1 Visit 4 or Treatment Period 2 Visit 8). The subject will be permanently discontinued from the trial treatment but will continue to be observed for AEs, if possible, until the scheduled end-of-trial visit (Visit 10).

If the subject withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a subject withdraws from the trial, they may request destruction of any samples taken and not tested, and the Investigator must document this in the investigative site trial records.

Lost to Follow-up:

A subject will be considered lost to follow-up if they repeatedly fail to return for scheduled visits and are unable to be contacted by the investigative site. The following actions must be taken if a subject fails to participate in a required trial visit:

- The investigative site must attempt to contact the subject and reschedule the missed visit as soon as possible. They should counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether the subject wishes to or should continue in the trial.
- Before a subject is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.
- Should the subject continue to be unreachable, they will be considered to have withdrawn from the trial.

6.6 Replacement Policy

Subjects who discontinue or are withdrawn from the trial before taking any trial treatment may be replaced with Sponsor approval.

Subjects who discontinue or are withdrawn from the trial after taking one or more doses of trial treatment will not be replaced.

6.7 Stopping or Suspending the Trial

The Sponsor may decide to discontinue or suspend the trial if there is insufficient accrual of subjects, or if new information arises that has an adverse impact on the benefit/risk assessment.

7. INVESTIGATIONAL PRODUCTS

7.1 Treatments Administered

The investigational product (IP) is ADX-629 that will be manufactured and supplied as 300 mg tablets. Placebo tablets to match ADX-629 300 mg tablets will be manufactured using the same excipients as the active product (Table 2).

Subjects will be randomized to receive both ADX-629 and placebo in one of two treatment sequences:

- ADX-629 300 mg (one tablet) BID for 14 (±2) days in Treatment Period 1 followed, after a 2-week washout, by placebo (one tablet) BID 14 (±2) days in Treatment Period 2.
- Placebo (one tablet) BID for 14 (±2) days in Treatment Period 1 followed, after a 2-week washout, by ADX-629 300 mg (one tablet) BID for 14 (±2) days in Treatment Period 2.

[redacted]

The last dose of trial treatment will be taken at the end of Treatment Period 2.

Information about the IPs is available in Table 2.

Table 2: Description of the Investigational Products

Name of Investigational Product	ADX-629	Placebo
Dosage form:	Tablet	Tablet
Unit dose strength:	300 mg ADX-629	0 mg
Route of administration:	Oral, twice daily	Oral, twice daily

7.2 Identity of the Investigational Products

ADX-629 is a small molecule with a quinoline core that acts as a RASP sequestering agent by irreversibly binding aldehydes. [redacted]

7.3 Limiting Bias

Bias is limited by strict adherence to the inclusion and exclusion criteria, the use of a randomization schedule, and application of the trial design. All measurement procedures are clearly defined in advance and will be consistently and precisely applied.

7.3.1 Method of Assigning Subjects to Treatment Groups

Subjects who meet all the inclusion criteria and none of the exclusion criteria 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. Within each treatment period, subjects will receive their allocated treatment for 2 weeks.

The randomization schedule will be produced by [redacted]. The treatment will be allocated via a web-based electronic data capture system.

7.3.2 Blinding and Unblinding Procedures

This is a double-blind clinical trial. Treatment assignments will be blinded to the Investigator, subjects, and all the clinical and research staff. The trial blind will not be broken until the clinical trial is completed and after the database has been locked.

[redacted], is the randomization system in use for this trial. Blinded kit allocation to eligible subjects will be managed by investigative site staff via [redacted] modules (randomization and resupply).

During the trial, the randomization code must not be broken except in emergency situations where the identification of a subjectjs trial treatment is required by the qualified Investigator for further management of the subject's condition. The qualified Investigator (Principal Investigator or delegated sub-Investigator) will unblind the subject's treatment using the [redacted] unblinding module. In case of emergency in which neither the Principal Investigator nor the sub-Investigator are available, the Medical Monitor may, as a last resort, perform the unblinding using the [redacted] unblinding module. In any case of unblinding, the date, time, and reason for breaking the blind will be recorded, and the Sponsor and Medical Monitor will be notified. This information will be stored in the subject's source files with as few of the investigative site staff unblinded as is clinically reasonable.

7.4 Selection of Doses and Timing of Dose for Each Subject

[redacted]

7.5 Packaging and Labeling

The Sponsor will be responsible for ensuring that ADX-629 and placebo tablets are manufactured in accordance with applicable current Good Manufacturing Practice regulations and requirements.

ADX-629 tablets or placebo will be provided in treatment kits for each period between trial visits. Each of the product bottles is capped with a child-resistant closure liner with an induction seal.

The IP will be administered as 300 mg tablets, i.e., one tablet BID for 14 days. BID dosing means every 12 (±1) hours. Each container will hold sufficient tablets to cover the time until the next scheduled visit, plus overage in case the scheduled visit is delayed.

The IP will be labeled according to the requirements of local law and legislation.

Further details regarding packaging, labeling and accountability are provided in the pharmacy manual.

7.6 Storage, Handling, and Dispensing of Investigational Products

Investigational product will be shipped from the Sponsor's storage direct to investigative sites as soon as subject screening commences at the site. Each investigative site will maintain an inventory record of the kits received and dispensed.

[redacted]

Treatment kits will be dispensed to trial subjects as follows:

- Visit 3, Day 1 of Treatment Period 1: ADX-629 300 mg or placebo (one tablet) BID dosing for 14 days.
- Visit 7, Day 1 of Treatment Period 2: placebo or ADX-629 300 mg (one tablet) BID dosing for 14 days.

The IP will be provided to trial subjects only, i.e., eligible subjects who have provided written, informed consent and have been randomized.

7.7 Drug Inventory and Accountability

The Investigator must keep an accurate accounting of the number of IP units delivered to the investigative site, dispensed to subjects, returned to the Investigator by the subject, and returned to the Sponsor or other disposition during and at completion of the trial. The IP must be dispensed to subjects only by an appropriately qualified person. The IP is to be used in accordance with the protocol by subjects who are under direct supervision of the Investigator. The Investigator should maintain records that adequately document that the subjects were provided the doses specified by the protocol and reconcile all IP received at the investigative site before final disposition. At the end of the trial or as directed, all IP, including unused, partially used, and empty containers, will be returned to the Sponsor, and destroyed.

7.8 Treatment Compliance

The prescribed dosage, timing, and mode of administration of trial treatment should not be changed from the protocol schedule. Departures from the intended regimen will be reported as protocol noncompliance. Subjects must return empty containers and unused trial treatment as compliance will be assessed by tablet counts.

The Investigator or designee will assess the subject's compliance by performing a tablet count on return of unused trial treatment. Subjects who exhibit poor compliance, i.e., not 100% compliant without adequate explanation, should be counseled on the importance of good compliance with the dosing regimen. Severe lack of compliance is defined as <80% or >120% of the correct dosing and is a reason for discontinuation of the subject from the trial (Section 6.5).

7.9 Prior and Concomitant Therapy

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

Subjects will be instructed to notify the investigative site about any new medications taken after the start of screening. Subjects will be asked at each visit if any medications have been taken since the previous visit. All concomitant medications and significant non-drug therapies (including physical therapy and blood transfusions) administered after the subject has started the trial treatment must be listed in the subject's eCRF and source documents. The drug name and dose taken will be recorded in the eCRF and source documents.

7.9.1 Prohibited Medications and Non-drug Therapies

Disallowed and restricted medications and other products are summarized in Table 3.

Table 3: Prohibited Medications and Non-drug Therapies

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]

Investigators are encouraged to contact the trial Medical Monitor if they need to discuss any concomitant medications.

7.9.2 Contraceptive Guidance

Females of childbearing potential must agree to use a highly effective method of contraceptive for the trial duration and at least 30 days after the last dose of trial treatment.

Highly effective contraception is defined as:

- Surgically sterile (hysterectomy, bilateral tubal ligation, salpingectomy, bilateral oophorectomy at least 26 weeks prior to screening),

- Post-menopausal, defined as spontaneous amenorrhea for at least 1 year, with FSH blood levels of equal or greater than 40 mIU/mL at screening,
- An approved hormonal contraceptive such as oral contraceptives, patches, implants, injections, rings, or hormonally impregnated intrauterine device (IUD), or
- An IUD.

All male subjects who are not surgically sterile must use a highly effective method of contraceptive (a barrier method and any other acceptable method of contraception) with their female partners during their participation in the trial and for 30 days after the last dose of trial treatment. Male subjects must abstain from sperm donation during their participation in the trial and for 30 days after the last dose of trial treatment.

7.9.3 Smoking Pack-Years

Cigarette smoking pack-years are calculated by multiplying the number of packs of 20 cigarettes smoked per day by the number of years the person has smoked. For example, one pack year is equal to smoking one pack per day for 1 year, or two packs per day for half a year, and so on.

[redacted]

Table 4: Estimation of Smoking Pack-Years of Non-tobacco Products

[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

8. TRIAL ASSESSMENTS

8.1 Assessment of Efficacy

8.1.1 Key Secondary Efficacy Assessment

Objective cough counts measured as 24-hour sound recordings using a custom-built digital recording device. The key secondary efficacy endpoint is the change from baseline in awake cough frequency, calculated as the (total cough count while awake)/(duration awake) and expressed in hours. For each treatment period, baseline is the cough frequency during the recorder assessment just prior to initiation of investigational product.

8.1.2 Secondary Efficacy Assessments

Secondary efficacy assessments are:

- The change from baseline in 24-hour cough frequency will be assessed from the same 24-hour cough monitoring used to measure awake cough frequency.
- Cough severity measured using a 100 mm VAS. Subjects will be asked to rate their cough severity over the previous 2 weeks at screening, and over the previous 24 hours at other timepoints.
- Global rating of change scores for cough frequency and severity.
- Patient Global Impression of Change: 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."
- Quality of life will be assessed using the LCQ, which is a cough-specific assessment (Birring et al., 2003b). The LCQ comprises three, 7-point domain scores: physical, psychological, and social. A higher score indicates a better quality of life.
- Quality of life will be further be assessed using the CQLQ.

8.2 Pharmacokinetic, Pharmacodynamic, and Other Measurements

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

8.3 Assessment of Safety

Safety will be assessed by physical examination and monitoring of AEs, laboratory safety parameters, vital signs, and standard 12-lead ECGs. Unscheduled assessments will be performed if clinically warranted by the Investigator or designee.

8.3.1 Adverse Events

All AEs occurring during the trial, from the time the subject signs informed consent until the subject completes the trial, will be reported. Any SAEs that occur within 30 days of the end of treatment will also be reported. SAEs will be reported to the regulatory authorities and Institutional Review Boards (IRBs)/Research Ethics Boards (REBs) according to local regulations and will be followed up until the event is resolved or stabilized.

8.3.1.1 Definitions

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.

8.3.1.2 Adverse Event Reporting

Adverse events will be collected with a non-leading question at each visit: "Have you experienced any change in your health or in your general condition since your last visit?" as well as by reporting those events directly observed and spontaneously reported by the subject. Clearly related signs, symptoms, and abnormal diagnostic procedures should preferably be grouped together and recorded as a single diagnosis or syndrome whenever possible. Intensity (mild, moderate, or severe) and relationship to trial treatment (related or unrelated) as well as action taken, seriousness and outcome should be recorded in the AE page of eCRF. Start and end date and time of the event will also be recorded as precisely as possible.

Abnormal laboratory values or vital signs abnormalities are to be recorded as AEs only if they are medically relevant, i.e., symptomatic, requiring corrective treatment, leading to discontinuation or fulfill a criterion for an SAE.

In the case of chronic disease, if the disease is known and documented when the subject enters the trial, only worsening (increased frequency or intensity of the episodes) will be documented as an AE.

Severity

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]

Relationship to Trial Treatment

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.

Action Taken with Investigational Product

The Investigator will be asked to record action taken in relation to the trial or trial treatment and to other treatments. The categories in relation to the trial or trial treatment are:

- No action taken
- Investigational product dose reduced
- Investigational product discontinued temporarily
- Investigational product discontinued permanently
- Not applicable

Outcome

The Investigator will be asked to record the outcome by choosing one of the following alternatives:

- Recovered
- Recovering
- Not recovered
- Recovered with sequelae
- Unknown

8.3.1.3 Reporting of Serious and Significant Adverse Events

Any new and unexpected AEs must be reported to the IRB/REB as required by local regulations.

Suspected unexpected serious adverse reactions (SUSARs) are AEs that are considered by the Investigator and Sponsor to be related to trial treatment and are both unexpected (i.e., the nature or severity is not expected from the information provided in the Investigator Brochure) and serious. ADX-629 is at an early stage of development, therefore, any SAE deemed related to the trial treatment will be considered unexpected and will be reported as a SUSAR.

The Investigator must complete and submit an SAE report for all SAEs, regardless of the causal relationship to trial treatment as soon as possible, in any case within 24 hours of having received information on the event. The initial report can be followed by a follow-up report as soon as the Investigator obtains more specific information on the event. Every effort should be made to document further any SAE that is fatal or life-threatening within 1 week (7 days) after the initial notification.

The Investigator must also send (preferably by email or fax) copies of all examinations carried out and the dates on which these examinations were performed, to [redacted], the Sponsor's representative:

[redacted]

Laboratory reference ranges should be included for all laboratory results.

Care should be taken to ensure that the subject's identity is protected and the subject's identifiers in the clinical trial are not included on any copy of source documents provided to the Sponsor.

Suspected unexpected serious adverse reactions are subject to expedited reporting to the Regulatory Authorities and IRB/REB as appropriate. Investigators will be notified by the [redacted] Safety Management of all SAEs that require prompt submission to their IRB/REB. Investigators should provide written documentation of IRB/REB notification for each report to the Sponsor or [redacted]. The Sponsor or [redacted] will ensure that the appropriate regulatory authorities are notified of all reportable SAEs.

The Sponsor or Sponsor's representative may make expedited reports of all SAEs that are expected and causally related to the IP to the Competent Authorities, according to local regulations.

8.3.1.4 Discontinuation Due to Adverse Events

The onset of an AE is not necessarily a reason for premature withdrawal from the trial or for temporary or permanent discontinuation of trial treatment. If the Investigator decides to discontinue trial treatment permanently because of an AE, this must be documented in the eCRF.

8.3.1.5 Follow-up of Adverse Events

The Investigator must ensure that follow-up of the subject is appropriate to the nature of the event, and that it continues until resolution or until agreed with the Sponsor.

The Investigator should take all appropriate measures to ensure the safety of the subjects. In particular, he or she should follow-up the outcome of any AEs until they return to normal, or the subject's condition stabilizes.

If the Investigator learns of an SAE during the 30 days after the subject's final trial visit and if the Investigator considers the SAE to be causally related to the IP, this should be reported to the Sponsor within 1 day.

8.3.2 Pregnancy

In the event of pregnancy, the IP must be discontinued, and the Sponsor informed immediately (i.e., within 1 working day).

Pregnancy in a female trial subject, or in a female partner of a male trial subject, during the trial period or within 4 weeks after the last dose of IP, must be reported to the Sponsor on the pregnancy reporting form within 24 hours of knowledge of its occurrence by the investigative site staff. The pregnancy will be followed up until the outcome has been determined. Any SAE experienced during pregnancy, or if the outcome of the pregnancy is a congenital anomaly or birth defect, the procedure for reporting SAEs (Section 8.3.1.3) will be followed.

8.3.3 Clinical Laboratory Analysis

The following clinical laboratory safety assessments will be performed at the times indicated in the schedule of assessments (Table 1).

Safety Laboratory Tests:

- Hematology: hemoglobin, hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), red blood cell (RBC) count, white blood cell count with differential (neutrophils, lymphocytes, monocytes, eosinophils, and basophils), and platelet count.
- Serum 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). Spot urine protein to creatinine ratio (sUPCR) will also be performed.

Pregnancy Tests: Women of childbearing potential will have a serum pregnancy test at screening, and urine pregnancy tests before the first dose at the start of each treatment period (Visit 3 and Visit 7). FSH will be measured at screening only in females thought to be menopausal if pregnancy status is unknown.

Serologies for HIV, Hepatitis B, and Hepatitis C: HIV Ab, HbsAg, HbsAb, and HCV Ab (screening only).

SARS-CoV-2: Specimens for SARS-CoV-2 testing will be analyzed centrally.

Urine Drug Screen: Tests for amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, and opiates.

Cotinine Test: Test for nicotine.

Alcohol breath test: This will be performed locally at screening only.

Instruction on urine and blood sample processing and shipping are available in the laboratory manual.

8.3.4 Other Safety Variables

Other safety variables include:

- Physical examination, including review of the major body systems, height, and weight
- Vital signs including blood pressure, heart rate, respiratory rate, temperature, and oxygen saturation
- Standard 12-lead ECG
- Changes in concomitant medication

8.4 Demographic Data, Baseline Characteristics, and History of the Disease

The following information will be recorded at screening:

- Age, gender, ethnicity, and race
- Medical history
- Medication history
- History of chronic cough
- Smoking history
- Spirometry (FEV_1, FVC)

9. DATA MANAGEMENT

9.1 Case Report Forms

Data will be collected on eCRFs that are specifically designed for this trial. The Investigator or person designated by him or her will record subject data as accurately as possible in the eCRFs.

The Investigator must provide an electronic signature to attest to the accuracy and completeness of all the data. If any changes are made to an eCRF after a form has been locked and electronically signed, the Investigator will be required to perform an additional electronic signature authorizing agreement with any new information or changes to the eCRF.

All corrections on the eCRF will be automatically tracked and a reason for change is always required.

9.2 Data Management Plan and Database Design

Detailed information on data management will be provided in a data management plan (DMP) that will be written specifically for this trial. All plans and deviations will be documented in the DMP, unless a trial-specific plan, guideline, or specification is created.

The trial database will be defined according to the corresponding eCRFs and the trial protocol. The setup will be checked by another person, and the database will be tested using dummy eCRFs. Standard design templates will be used and trial-specific items will be created as required.

9.3 Data Management

Data validation or data cleaning procedures are designed to assure validity and accuracy of clinical data. They consist of reviewing data entered, and computerized edit checks and queries for identifying data values that are out of range, protocol violations, incomplete or inconsistent. The DMP will specify the checks that are to be performed on subject data to raise data discrepancies or queries and will define the electronic edit checks and data validation queries to be created for the trial. All trial-specific and standard data validation programming will be tested in a separate testing environment prior to use on production data.

Queries will be raised for all errors discovered in the clinical data, when information is missing, or needs further clarification.

9.4 Handling of External Data

External data consists of data that are not recorded on eCRFs. Data may be received in electronic format or paper printout. Key variables will be defined to uniquely identify each sample record. File and data formats will be agreed with the external data provider. Any data transferred between the external data provider and data management must contain the origin, date created, date sent and number of records at minimum. The source of all external data will be specified in the DMP.

9.5 Database Lock

All data entry, verification, medical encoding, and data validation activities will be finalized before the database is locked. Quality control activities will be completed to acceptable error rates. All unnecessary user privileges to the trial will be removed, except for the Data Manager who will perform the database lock.

In exceptional circumstances, when critical reasons justify, there may be a need to perform updates to the database after it has been locked. A database that is locked and released for analysis will only be unlocked if an error is identified that will significantly affect the statistical outcome of the analysis of the efficacy parameters or change the safety profile of the trial.

10. STATISTICAL ANALYSES

A formal Statistical Analysis Plan (SAP) will be developed and finalized prior to locking and unblinding the trial database. The full details of data presentations and analyses will be provided in the SAP. Additional statistical analyses other than those described in this section may be performed if deemed appropriate and included in the SAP. Unscheduled measurements will be excluded from the descriptive statistics and statistical analysis but will be included in listings. The SAP may detail deviations in the planned analyses described within this protocol. Any deviations from the final SAP will be discussed in the final trial report.

10.1 Trial Subjects

10.1.1 Disposition of Subjects

- The number and percentage of subjects will be presented overall and by treatment sequence:
  - In each analysis population
  - Completing Treatment Period 1
  - Withdrawing during Treatment Period 1 (with reasons)
  - Entering Treatment Period 2
  - Withdrawing during Treatment Period 2 (with reasons)
  - Completing the trial

10.1.2 Protocol Deviations

Deviations from the protocol will be categorized as “minor” or “major” in cooperation with the Sponsor. Deviations will be assessed regularly and finalized prior to database lock.

10.1.3 Analysis Population Definitions

The following analysis populations will be presented:

- Screened Population: All subjects who sign the ICF.
- Randomized Population: All subjects who are randomized.
- Intent-to-treat (ITT) Population: All randomized subjects.
- Safety Population: All subjects who receive at least one dose of trial treatment.
- 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.

All safety analyses will be based upon the Safety Population. Subjects will be analyzed by the treatment received.

The ITT Population will be the primary analysis population for efficacy. Subjects will be analyzed by planned treatment. The PP set will be used for a sensitivity analysis of the efficacy data.

After all the data have been verified, coded if necessary, and entered into the database, a review will be performed. The purpose of this review will be to define the analysis sets. The review will also check the quality of the data, identify outliers, and make decisions on how to deal with any data issues (e.g., missing values, withdrawals, protocol deviations). After the pre-analysis review, resolution of all issues and documentation of all decisions, the database will be locked.

10.2 General Considerations

10.2.1 Statistical Hypotheses

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.

All statistical testing will be at the 5% level of significance (2-sided) and all point estimates for the comparison between treatment groups will be accompanied by 2-sided 95% confidence intervals.

10.2.2 Determination of Sample Size

[redacted]

Allowing for a reduction in power due to subject withdrawals approximately 50 subjects will be randomized.

10.2.3 Data Summaries

All endpoints will be summarized by treatment group and visit. Baseline data will be summarized by treatment sequence and by treatment group.

Continuous data will be summarized using descriptive statistics (e.g., mean and standard deviation) and categorical data will be summarized using frequency tables (counts and percentages).

10.3 Demographics, Baseline Characteristics and Concomitant Medications

Demographics, baseline characteristics, medical history and prior medication data will be summarized by treatment sequence (and overall) and, if some subjects withdraw from the trial prior to Treatment Period 2, by treatment group, using the safety set. Concomitant medications will be summarized by the World Health Organization Drug Dictionary (WHODrug) preferred name, ATC class, and treatment group.

The most current version of the WHODrug and Medical Dictionary for Regulatory Activities (MedDRA) coding dictionaries will be used for the concomitant medications and medical histories, respectively.

10.4 Treatment Compliance

Treatment compliance will be assessed through tablet counts and will be summarized by treatment group.

10.5 Analysis of Safety Data

No imputation will be used for handling missing data, with the exception of conservative approaches taken for missing AE information (e.g., intensity). Details of such conventions will be documented in the SAP.

TEAEs will be summarized by treatment group and by system organ class and preferred term, in accordance with the MedDRA coding dictionary. Safety variables will be summarized descriptively by treatment. The number of subjects reporting each AE preferred term will be tabulated for all TEAEs and separately for those considered as at least possibly related to trial treatment by the Investigator.

Changes from baseline in laboratory parameters, vital signs and ECG data will be summarized by treatment group and timepoint. Baseline will be taken as the last measurement prior to dosing within the specific trial period.

10.6 Analysis of Efficacy Data

Efficacy data will be summarized by treatment group.

The key secondary efficacy endpoint is change from baseline in awake cough frequency (cough count/duration of measurement [hour]). For each treatment period, baseline is the cough frequency during the recorder assessment just prior to initiation of IP. Though summaries will be presented for cough frequencies, due to the skewed nature of the data, a log transformation will be used prior to statistical analyses.

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. The model will include fixed effects for treatment sequence, period, treatment, and subject nested within treatment sequence as a random effect. Period specific baselines will be included as covariates.

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

The mean change from baseline (on the log scale) will be presented for each treatment group and the difference between treatment group means will be presented, along with associated standard errors and 95% confidence intervals. The mean changes from baseline 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 their corresponding 95% confidence intervals and p-values.

Using a mixed-effect model is suitable when assuming missing data is missing at random. Alternative sensitivity analyses may be performed assessing the impact of any missing data on the interpretation of the results. These analyses will be detailed in the SAP.

All model assumptions will be checked by evaluating model residuals. If the evaluation of residuals indicates a problem with the model assumptions, an alternative transformation of the data or non-parametric analyses may be considered.

The secondary efficacy endpoint change from baseline in 24-hour cough frequency will be analyzed using the same methods described for the key secondary efficacy endpoint.

The changes from baseline in cough severity VAS scores and quality of life (evaluated with CQLQ) will be analyzed using a similar approach except that the scores will not be log transformed prior to analysis. Hence, mean changes from baseline will be presented, and the treatment effect will be the difference between the mean changes from baseline. The corresponding 95% confidence intervals and p-values will be presented.

Other efficacy endpoints will be summarized and analyzed to estimate the treatment effect and corresponding 95% confidence interval using a similar model to that described for awake cough frequency. Cough frequency endpoints will be analyzed on the natural log scale. Full details of analyses will be provided in the SAP, which will govern any statistical language within the protocol.

10.7 Interim Analysis

No interim analyses are planned.

11. TRIAL MANAGEMENT

11.1 Monitoring

Monitoring and project management services will be provided by the Contract Research Organization (CRO).

The trial will be monitored regularly, according to a monitoring manual that will be written specifically for this trial. The monitoring manual will define the nature of monitoring (e.g., on-site, central, or remote), monitoring frequency, and detailed procedures. In general, during monitoring visits, the monitor will ensure that the trial is being conducted according to the protocol, ICH GCP guidelines, other applicable regulations, and will compare the eCRF entries to original source data. The monitor will also make sure that the informed consent procedure has been carried out correctly and will ensure that all SAEs have been reported within the required timeframes. The monitor will check that IP accountability has been maintained and will, after completion of the trial, perform final accountability and arrange for the return or destruction of IP.

11.2 Audits and Inspections

The Sponsor has the right to perform an audit of the trial site and the CRO.

The regulatory authorities, both national and foreign, may inspect the investigative site at any time. The Investigator is responsible for notifying the Sponsor of such an inspection immediately after gaining knowledge of it.

During the audit or inspection, the Investigator will permit the auditor, IRB/REB reviewer, and regulatory inspector(s) direct access to all relevant medical records and other source data, trial-related files, and eCRFs.

11.3 Record Keeping and Archiving

The trial-specific essential documents must be retained for a period of 2 years following the date a marketing application is approved for the IP for the indication for which it is being investigated; or if no application is to be filed or if the application is not approved for such indication until 2 years after the investigation is discontinued and Food and Drug Administration (FDA) is notified. The Investigator must not destroy any trial-specific documentation before receiving written permission for this from the Sponsor.

11.4 Ethics

11.4.1 Institutional Review Board/Research Ethics Board

The trial will not commence until favorable opinion has been obtained from the appropriate IRB/REB and the Competent Authority.

If any alterations, other than changes of an administrative nature, are made to the trial protocol, a formal protocol amendment will be issued and submitted to relevant IRB/REB for approval. The amendment will not be implemented until approval has been received from the IRB/REB, except in cases where immediate

implementation is necessary to eliminate or prevent imminent hazard to the subjects. In such a case, the deviation will be reported to the IRB/REB as soon as possible.

11.4.2 Guidelines and Regulations

The trial will be conducted in accordance with the principles of the Declaration of Helsinki and in compliance with FDA Code of Federal Regulations Part 312, Section 21, ICH GCP E6 (R2), and the regulations on electronic records and electronic signature (21 CFR 11).

11.4.3 Subject Information and Consent

Before subjects enter the trial and any trial-related assessments are performed, the Investigator will explain the nature of the trial, its purpose and associated procedures, the expected duration, and potential benefits, constraints and risks associated with the trial. The subjects will also be given written information, which has been approved by the IRB/REB. Subjects will be given sufficient time (preferably at least 24 hours) to consider their participation and all their questions will be answered. The subjects will also be informed of their right to withdraw from the trial at any time without giving a reason.

If a subject agrees voluntarily to participate in the trial, he or she will sign and date the ICF. The same form will be signed and dated by the Investigator, who will file the original form in the trial site file. A copy or duplicate of the consent form will be given to the subject.

If new information becomes available that potentially affects the subject's safety or willingness to continue in the trial, or if a protocol amendment is issued that affects the subject's safety, trial procedures or any aspects of the trial that may influence the subject's decision to participate in the trial, the subject information leaflet and ICF will be revised. After the new documents have received approval from the IRB/REB and competent authorities, the subject will be asked to sign the new consent form to confirm their willingness to continue in the trial.

11.4.4 Subject Confidentiality

The Investigator(s) will respect and protect the confidentiality of the subject in all possible ways. Subject identification, other than the subject's trial number and age, will not appear in any eCRF pages or other documents given to the Sponsor. Only the Investigator and the persons authorized to verify the quality and integrity of the trial will have access to subject records where the subject can be identified.

11.5 Financing and Insurance

11.5.1 Financial Issues

Financial contracts will be signed between the Sponsor, the CRO, and the Investigator or a representative of the investigative site before commencement of the trial.

11.5.2 Insurance

The Sponsor will provide Product Liability insurance for all subjects included in the clinical trial.

11.6 Trial Report and Publications

A final clinical trial report will be prepared according to the ICH guideline on structure and contents of clinical trial reports on completion of the trial. The trial will be considered to have finished after the last subject has completed the last trial visit.

A final clinical trial report will be prepared where any subject has signed the ICF, regardless of whether the trial is completed or prematurely terminated. Where appropriate, an abbreviated report may be prepared. The clinical trial report will be in compliance with any applicable regulatory requirements, national laws in force and will be in English.

The publication of trial results will be agreed upon between the Sponsor and the Investigator(s). The Sponsor is interested in publishing the results of the trial but to prevent publication of any confidential information, the Sponsor retains the right to review all publications and presentations before they are made public and may delay any publication if necessary for reasons of intellectual property protection. However, the Sponsor will not have the right to prevent publication of the trial results indefinitely.

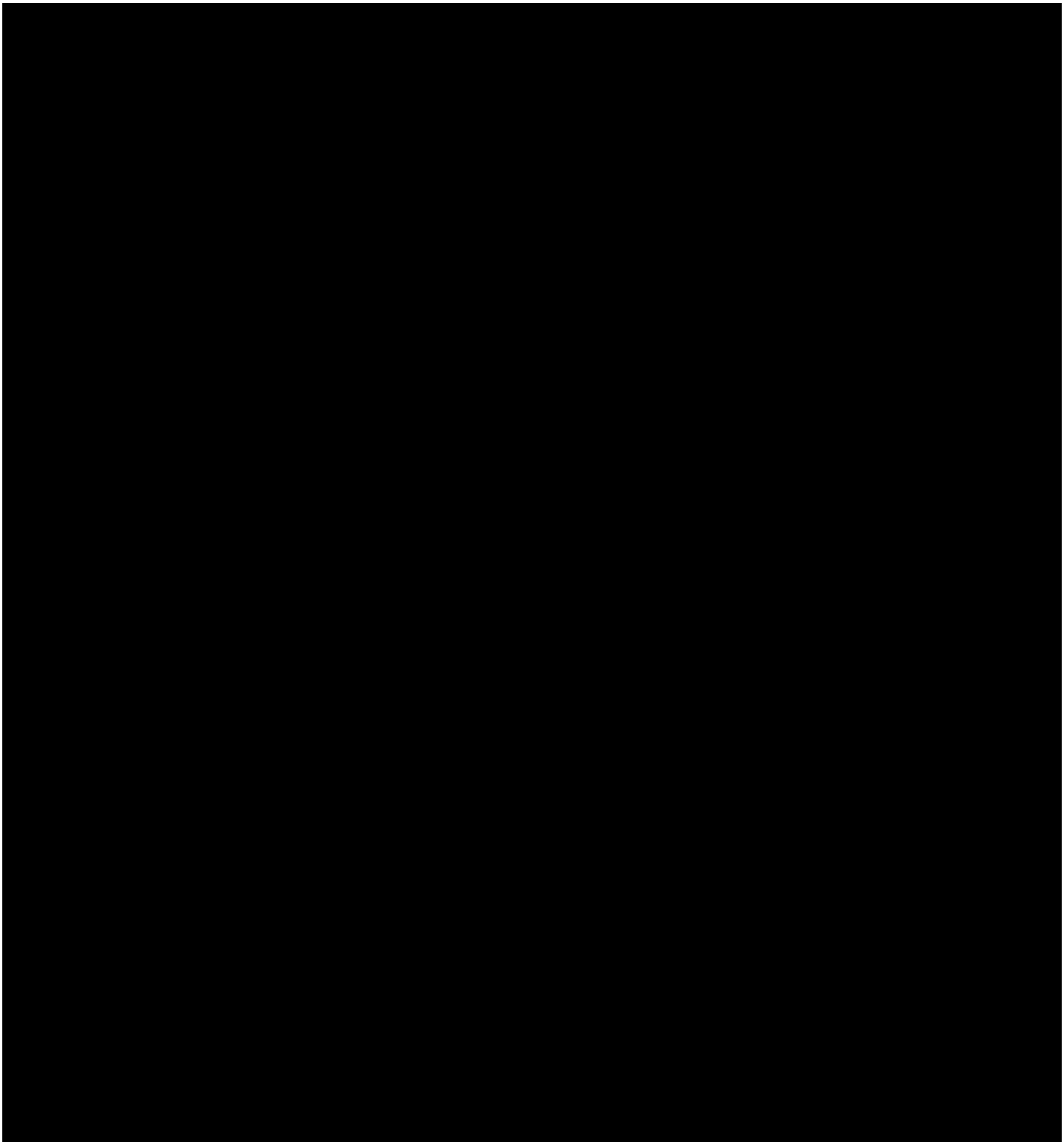
11.7 Trial Committees

No committees are associated with this trial.

12. REFERENCES

APPENDICES

APPENDIX 1: CHRONIC COUGH ALGORITHM FOR THE MANAGEMENT OF PATIENTS ≥15 YEARS OF AGE WITH COUGH LASTING >8 WEEKS



APPENDIX 2: GLOBAL RATING OF CHANGE

Site ID:	Subject ID:	Visit #:	Date:

[redacted]

Site ID:	Subject ID:	Visit #:	Date:

Global Rating of Change

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]	[redacted]		
[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	

[redacted]

APPENDIX 3: PATIENT GLOBAL IMPRESSION OF CHANGE (PGIC)

Site ID:	Subject ID:	Visit #:	Date:

[redacted]

Patient Signature: _____

Appendix 4: CLINICIAN GLOBAL IMPRESSION OF CHANGE (CGIC)

Site ID:	Subject ID:	Visit #:	Date:

[redacted]

[redacted]		[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

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