[redacted]

A Double Masked, Placebo Controlled, Single Center, Randomized Clinical Trial to Assess the Safety and Efficacy of ADX-629 in Subjects with Mild Asthma Induced by the Bronchial Allergen Challenge (BAC)

Name of Sponsor	Aldeyra Therapeutics, Inc. 131 Hartwell Avenue, Suite 320 Lexington, MA 02421 USA
Protocol Identification (code or numbers)	Sponsor Study Number: ADX-629-AA-001
	[redacted] Study Number: C2D00212
Study Product(s)	Treatment A: ADX-629, 600 mg (2 x 300 mg tablets) Treatment B: Placebo, 600 mg (2 x 300 mg tablets)
Clinical Research Organization	[redacted]
Indication	Mild asthma
Clinical Trial Phase	Phase 2
Regulatory Agency	Health Canada
Protocol Version	Final 5.0
Protocol Date	19 May 2021

PROTOCOL VERSION CONTROL

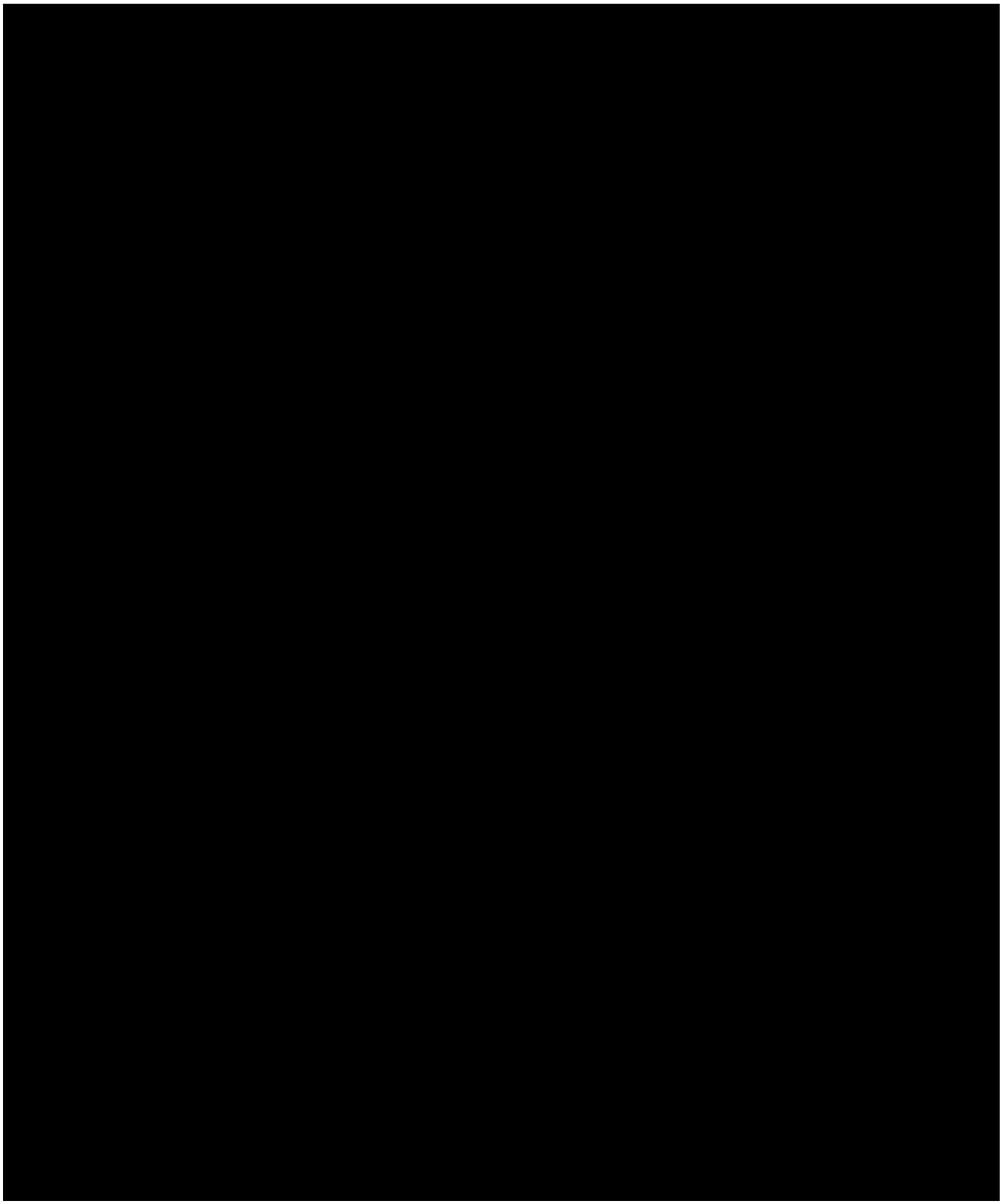
Version Number	[redacted]	Date
Final 1.0	[redacted]	20 Aug 2020
Final 2.0	[redacted]	16 Nov 2020
Final 3.0	[redacted]	24 Feb 2021
Final 4.0	[redacted]	14 Apr 2021
Final 5.0	[redacted]	19 May 2021

PROTOCOL REVISION HISTORY

The following table summarizes the updates made from Protocol Version 4.0 (14 Apr 2021) to Protocol Version 5.0 (19 May 2021).

[redacted]

[redacted]



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The following table summarizes the updates made from Protocol Version 3.0 (24 Feb 2021) to Protocol Version 4.0 (14 Apr 2021).

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The following table summarizes the updates made from Protocol Version 2.0 (16 Nov 2020) to Protocol Version 3.0 (24 Feb 2021).

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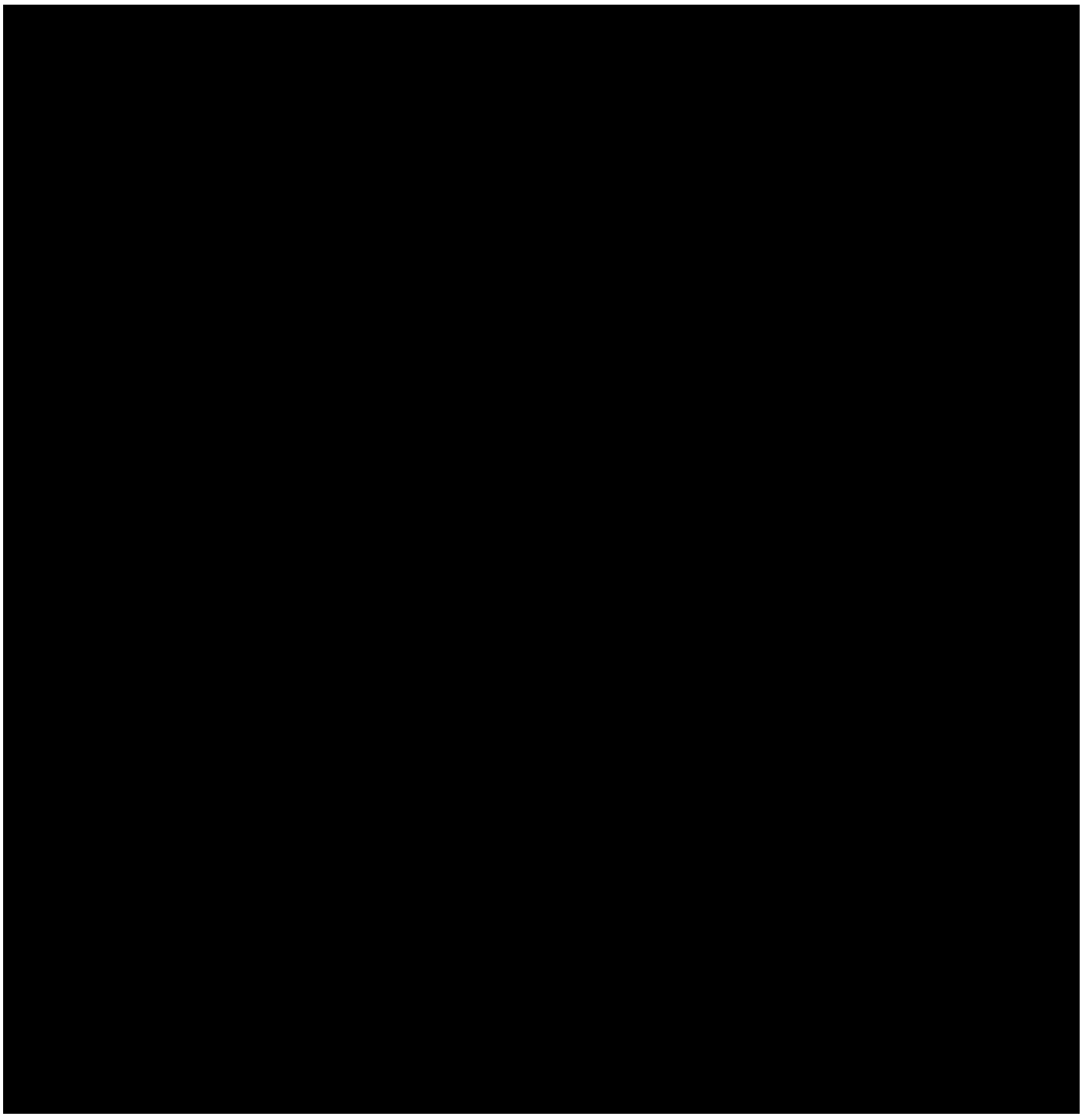

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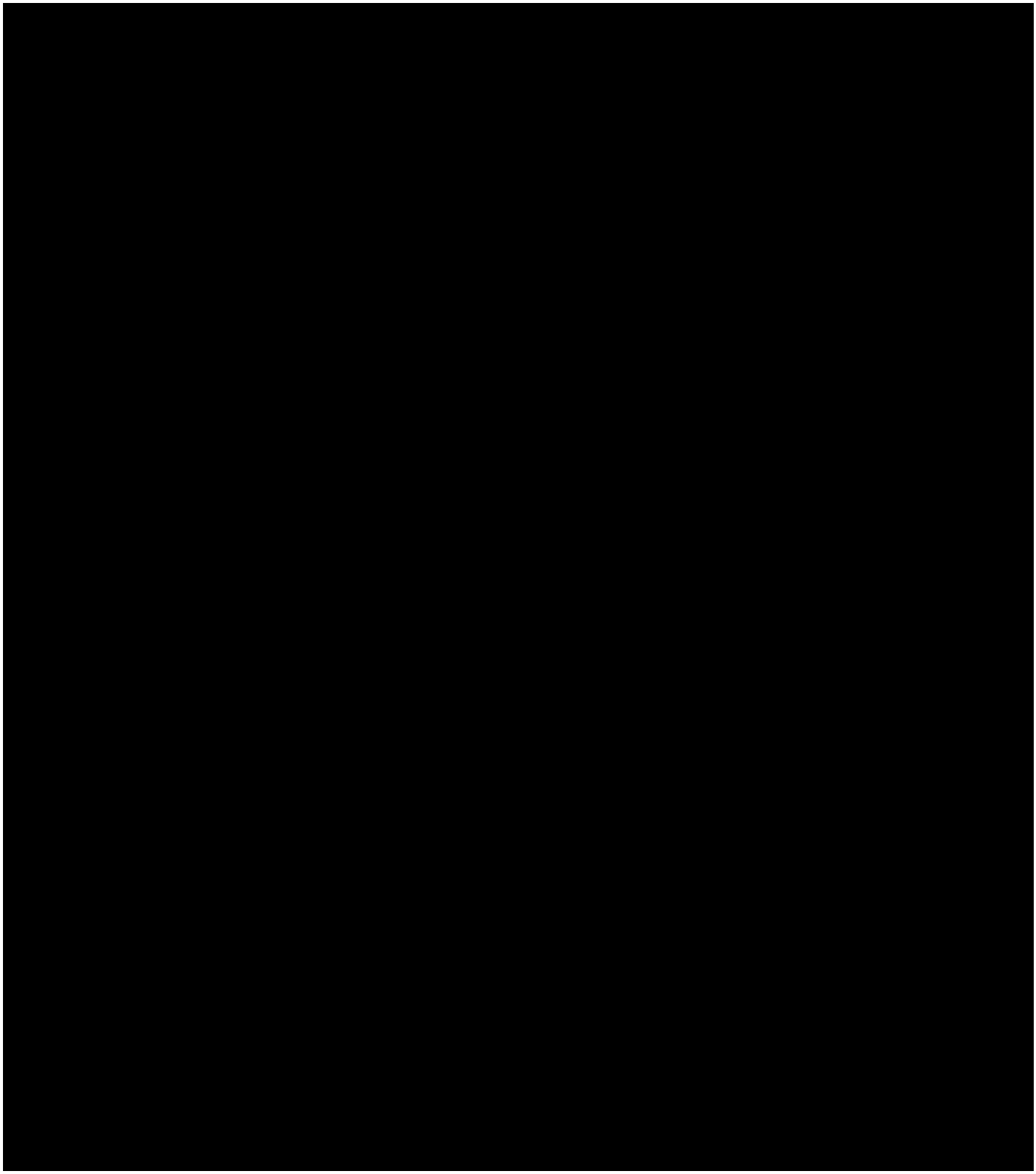
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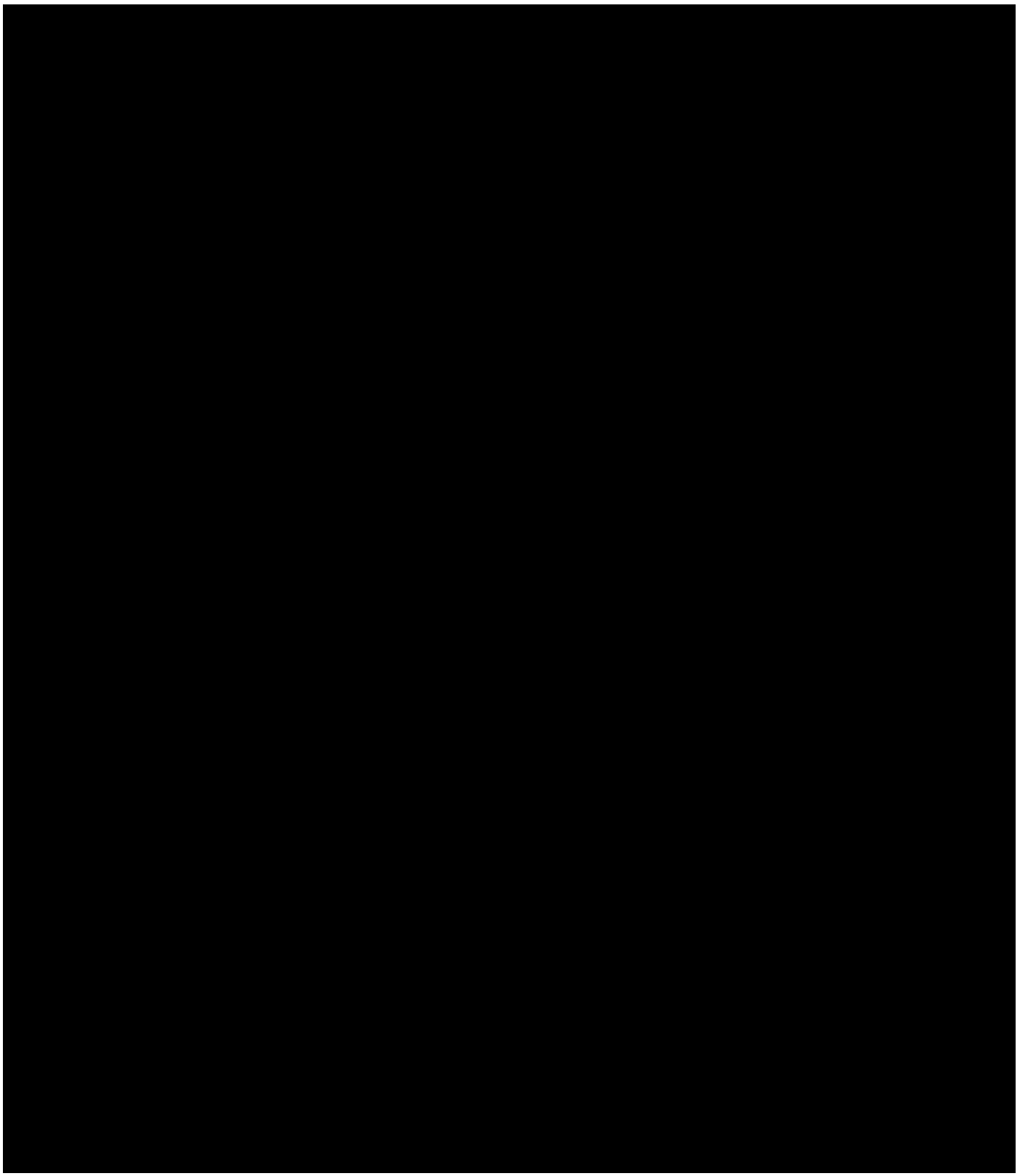

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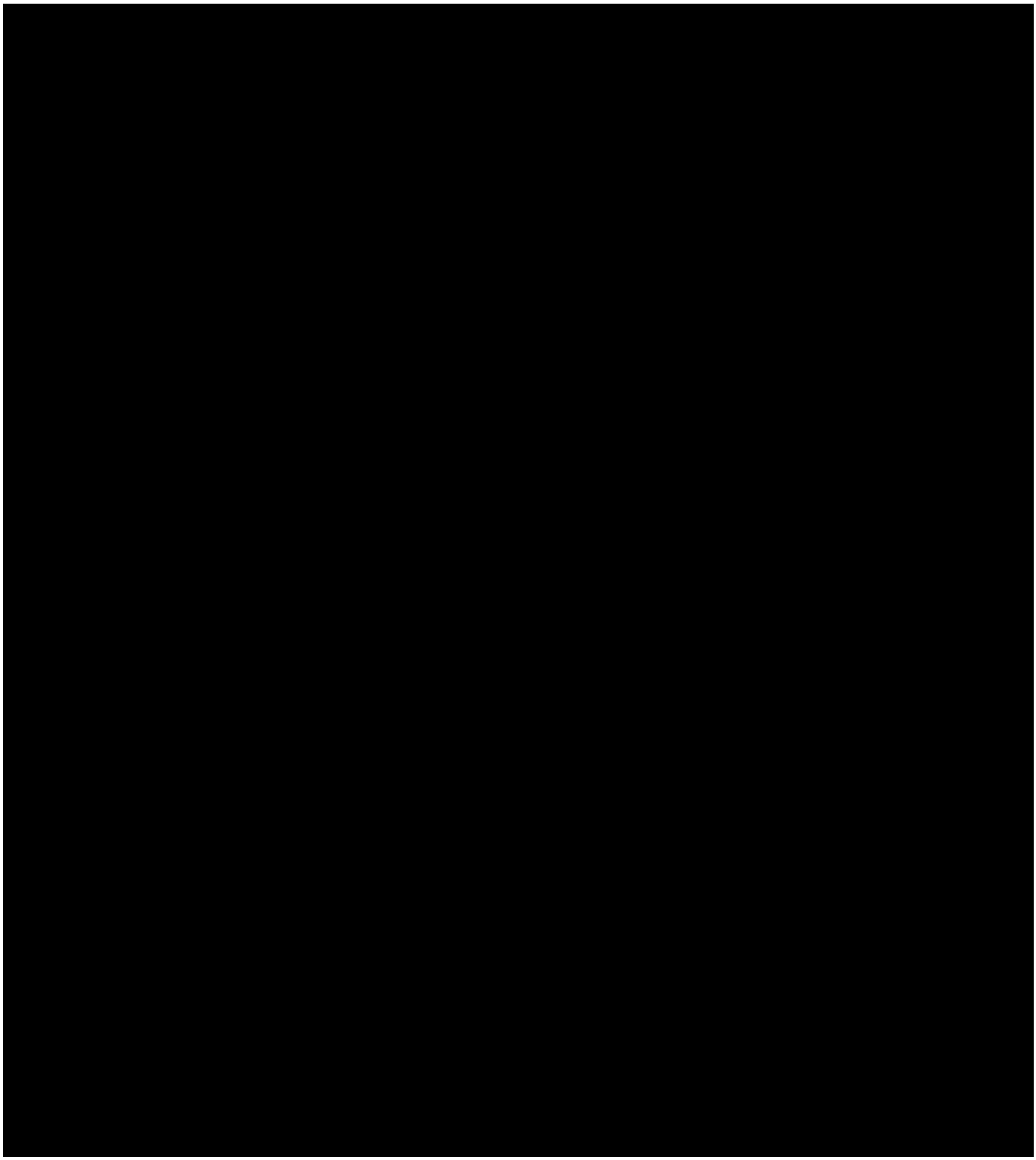

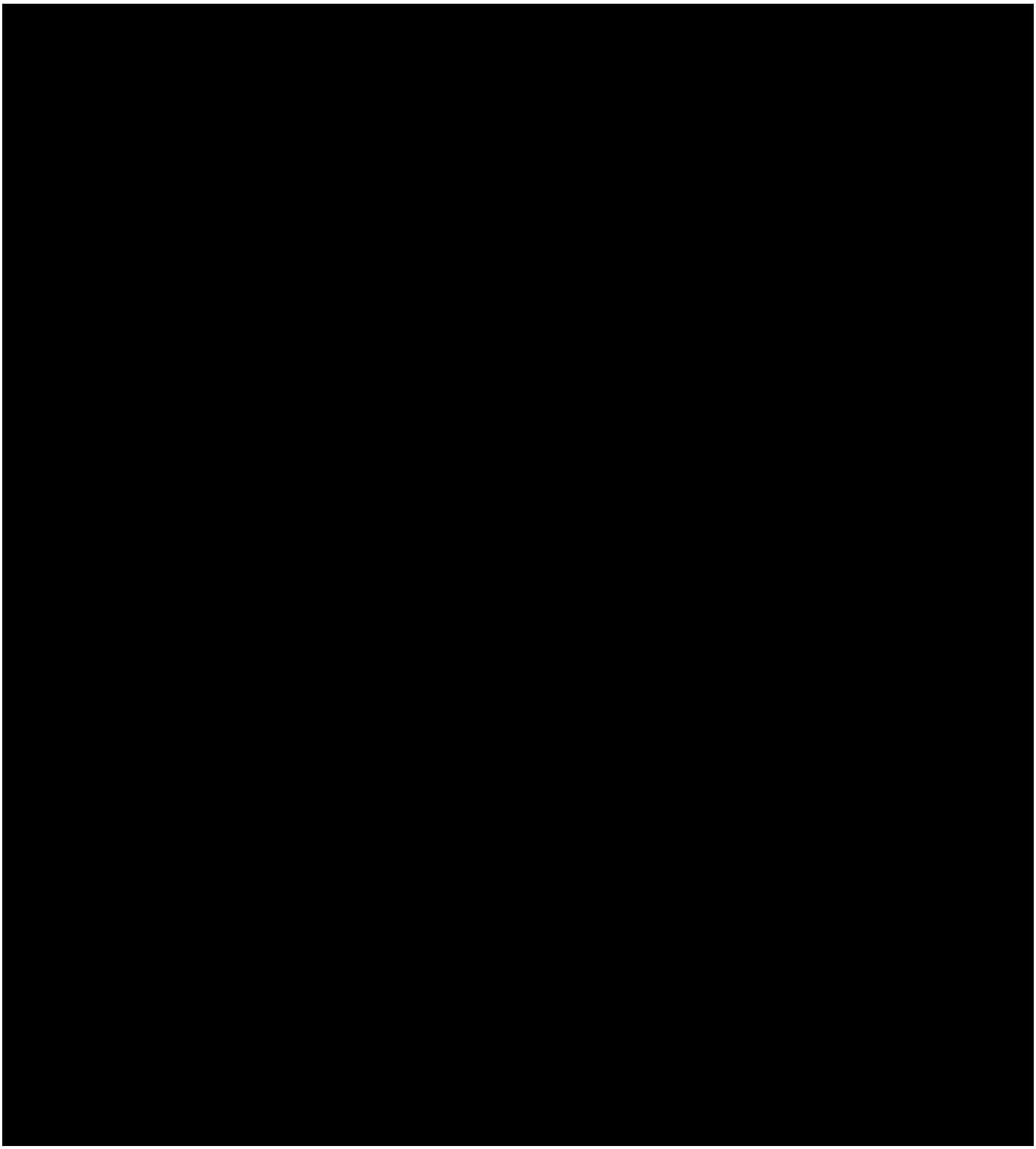

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SPONSOR APPROVAL/SIGNATURE PAGE

Title: A Double Masked, Placebo Controlled, Single Center, Randomized Clinical Trial to Assess the Safety and Efficacy of ADX-629 in Subjects with Mild Asthma Induced by the Bronchial Allergen Challenge (BAC).

I, on behalf of Aldeyra Therapeutics, Inc., approve the protocol and agree to conduct this clinical trial as outlined in the approved protocol and in accordance with the appropriate guidelines and all applicable federal government codes, acts and regulations, the ethical pricinples that have their origins in the Declaration of Helsinki and all amendments, Good Clinical Practice (GCP) requirements, The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidance E6 (R2) on Good Clinical Practice, and Tri-Council Policy Statement (Canada).

Sponsor Representative

[redacted]

[redacted]

PRINCIPAL INVESTIGATOR APPROVAL/SIGNATURE PAGE

Title: A Double Masked, Placebo Controlled, Single Center, Randomized Clinical Trial to Assess the Safety and Efficacy of ADX-629 in Subjects with Mild Asthma Induced by the Bronchial Allergen Challenge (BAC).

I agree to conduct this clinical trial as outlined in the approved protocol and in accordance with the Sponsor's guidelines and all applicable federal government codes, acts and regulations, the ethical pricinples that have their origins in the Declaration of Helsinki and all amendments, Good Clinical Practice (GCP) requirements, The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidance E6 (R2) on Good Clinical Practice, and Tri-Council Policy Statement (Canada) and to allow the Sponsor and applicable regulatory agencies the opportunity to inspect study facilities and pertinent records at reasonable times and in a reasonable manner that ensures subject confidentiality.

Principal Investigator

[redacted]

[redacted]

TABLE OF CONTENTS

1. LIST OF ABBREVIATIONS

TERM	DEFINITION
ºC	Degrees Centigrade
ºF	Degrees Fahrenheit
µg	Microgram
µmol	Micromole
µM	micromolar
ACQ	Asthma Control Questionnaire
ADaM	Analysis Dataset Model
ADRs	Adverse Drug Reactions
AE	Adverse Event
AHR	Allergen-induced shift in airway Hyper Responsiveness
ALP	Alkaline Phosphatase
ALT	Alanine Transaminase
AST	Aspartate Transaminase
ATS	American Thoracic Society
AUC	Area Under the Curve
AUC_{0-t}	Area under the plasma concentration versus time curve, from time 0 to the 't' hour
BAC	Bronchial Allergen Challenge
BAU	Bioequivalent Allergy Unit
bid	Bis in die (twice a day)
BMI	Body Mass Index
bpm	Beats per minute
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CDISC	Clinical Data Standards Interchange Consortium
CFR	Code of Federal Regulations
C_{max}	Maximum Observed Concentration
COVID-19	Corona Virus Disease 2019
CRF	Case Report Form
CRO	Clinical Research Organization
CYP	Cytochrome P450
DMP	Data Management Plan
EAR	Early Phase Asthmatic Response
ECG	Electrocardiogram
eCRF	electronic Case Report Form
eGFR	Estimated Glomerular Filtration Rate
EDC	Electronic Data Capture
FeNO	Fractional Exhaled Nitric Oxide

TERM	DEFINITION
ERS	European Thoracic Society
ETV	Early Termination Visit
FDA	Food and Drug Administration
FEV_1	Forced expiratory volume in one second
GCP	Good Clinical Practice
GGT	Gamma-Glutamyl Transpeptidase
GLP	Good Laboratory Practice
GSEM	Geometric Standard Error of the Mean
h	Hour
HDM	House Dust Mite
HNE	4-Hydroxynonenal
HR	Heart Rate
ICH	International Council for Harmonisation
ID	Identification
IEC	Independent Ethics Committee
IgE	Immunoglobulin E
IRB	Institutional Review Board
IUD	Intrauterine device
kg	Kilogram
L	Liter
LAR	Late Phase Asthmatic Response
m	Metre
MAD	Multiple Ascending Dose
Mch	Methacholine
Mch PC_{20}	Provocative Methacholine Concentration that causes a ≥ 20% fall in FEV_1 from the post- saline value
MCT	Methacholine Challenge Test
MDI	Metered Dose Inhaler
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
min	Minute(s)
mL	Millilitre
mm	Millimeter
mmHg	Millimetre of mercury
MMRM	Mixed effect Model for Repeated Measures
ms	Milliseconds
ng	Nanogram
NOAEL	No Observed Adverse Effect Level
PK	Pharmacokinetic
PO	Oral
PP	Per-Protocol

TERM	DEFINITION
QA	Quality Assurance
QTcF	Corrected value by Fredericia's formula of the interval between the Q and T waves on the electrocardiogram tracing
RASP	Reactive Aldehyde Species
REB	Research Ethics Board
SABA	Short-Acting $Beta_2$-Agonist
SAD	Single Ascending Dose
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SAS	Statistical Analysis Software
SD	Standard Deviation
SDTM	Study Data Tabulation Model
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SOP	Standard Operating Procedure
SPT	Skin Prick Test
SUSAR	Suspected Unsuspected Serious Adverse Reaction
TdP	Torsades de Pointes
TSH	Thyroid Stimulating Hormone
WOCBP	Women of Childbearing Potential

2. SPONSOR REPRESENTATIVE

[redacted]
Aldeyra Therapeutics, Inc.
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Lexington, MA 02421
USA
[redacted]

3. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

3.1 Clinical Research Organization

[redacted]

3.2 Clinical Facilities

[redacted]

[redacted]

3.3 Principal Investigator

Dr. Peter Couroux MD, FRCPC, CPI

[redacted]

3.4 Central Institutional Review Board (IRB)

Advarra
372 Hollandview Trail, Suite 300
Aurora, ON L4G 0A5
Canada

Phone: (905) 727-7989

3.5 Statistical Analyses

[redacted]

3.6 Medical Monitor

[redacted]

3.7 Clinical Laboratory Facility

[redacted]

4. STUDY SUMMARY

Title	A Double Masked, Placebo Controlled, Single Center, Randomized Clinical Trial to Assess the Safety and Efficacy of ADX-629 in Subjects with Mild Asthma Induced by the Bronchial Allergen Challenge (BAC)
Protocol Identification (code or numbers)	Sponsor Study Number: ADX-629-AA-001 [redacted] Study Number: C2D00212
Study Phase	Phase 2
Study Objectives	Primary objective: To assess the safety of ADX-629 in subjects with allergen-induced mild asthma. Secondary objective: To assess the clinical efficacy of ADX-629 in subjects with allergen-induced mild asthma.
Study Endpoints	Safety Endpoint: • Safety, as assessed by adverse events (AEs) and serious adverse events (SAEs) Efficacy Endpoints: • Change from baseline (within visit) in forced expiratory volume in one second (FEV_1) to post-BAC (during 0-3 h post-BAC [Key Efficacy Endpoint] and 3-7 h post BAC). • Absolute count and percentage differential count of sputum eosinophils and neutrophils at approximately 7 h and 24 h post-BAC. • Allergen-induced shift in airway hyper responsiveness (AHR) as assessed by Methacholine PC_{20} (Mch PC_{20}) post-BAC. • Change from baseline in fractional exhaled Nitric Oxide (FeNO) at approximately 7 h and 24 h post-BAC. Exploratory Endpoints: • Biomarkers (Reactive Aldehyde Species [RASP] and endotoxin-induced cytokine release) pre-BAC (at approximately 1 hour post-dose) and 7 h post-BAC. • Area under curve (AUC) of FEV1 during 0-3 h post-BAC and/or 3-7 h post BAC.
Study Population	Adult subjects with mild asthma and positive skin prick test to cat or house dust mite (HDM).
Study Design	ADX-629-AA-001 is a double-masked, cross-over, placebo-controlled, single center, randomized clinical trial to assess the clinical safety and efficacy of ADX-629 compared to placebo in mild cat or HDM-induced asthmatics using the BAC model. The clinical trial will consist of 9 visits to the clinic (Visits 1, 2a, 2b, 2c, 3, 4a, 4b, 5a, and 5b) over a

	period of approximately 75 days. During this period there will be 4 additional visits, 1 visit for safety lab and 3 visits for COVID-19 testing, as described below.
Study Products and Treatment arms	Treatment A: ADX-629, 600 mg (2 x 300 mg tablets), orally twice daily (PO bid) for minimum of 1 week (+3) Treatment B: Placebo, 600 mg (2 x 300 mg tablets), orally twice daily (PO bid) for minimum 1 week (+3) During Post-Treatment Period 1 and 2 (Visits 4a, 4b, 5a, and 5b), in lieu of the morning dose, 600 mg of the treatments will be administered approximately one hour prior to MCT or BAC testing.
Route of Administration	Oral
Study population	Enough subjects will be enrolled to ensure approximately 12 subjects complete the study. Subjects will be randomized (1:1) to one of the following sequences: 1. AB (N= 6) 2. BA (N= 6)
Study Conduct	**I. Medical Screening- Visit 1** All subjects will undergo a screening visit (Visit 1), which will include a written informed consent, demographics, medical/surgical/social/medication histories, vital signs, samples for standard clinical labs, Electrocardiogram (ECG), and a physical examination with height, weight and BMI. An asthma control questionnaire will be completed. A urine pregnancy test will be administered to women of childbearing potential (WOCBP). A skin prick test (SPT) will be performed to show positivity to cat or HDM allergen (≥ 3 mm wheal compared to negative control). Subjects will undergo spirometry to demonstrate baseline (pre-bronchodilator) FEV_1 of ≥ 80% of the predicted value. All lung function tests will be conducted in accordance with the site standard procedures (which is based on the American Thoracic Society/European Thoracic Society [ATS/ERS] recommendations). Post-bronchodilator FEV_1 will be measured within 15±5 minutes following 400 µg (4 puffs) of salbutamol inhalation and post-bronchodilator reversibility will be recorded. **II. Pre-Treatment Period (For 3 consecutive days) –Visits 2a, 2b and 2c** Subjects will return to the clinic for the pre-treatment period within approximately 4 weeks of the Screening visit. In all visits, staff will update the subjects' concomitant medication and collect adverse events and vital signs. Eligibility criteria will be reviewed. At Visit 2a, asthma control questionnaire will be completed. Spirometry will be performed to ensure FEV_1 ≥ 80% of the predicted value. Subjects will have a pre-BAC Methacholine challenge test (MCT) performed as per the site standard procedures. Subjects will inhale normal saline and have a baseline FEV_1 established. Subjects will then be given subsequent doubling concentrations of Methacholine (Mch) as per the site standard procedures. FEV_1 will be measured at approximately 30 and 90 seconds following nebulization. If the FEV_1 drops < 20%, the subject will be given the next highest concentration and spirometry repeated. Mch doses will continue to be administered sequentially (max concentration 4 mg/mL) until FEV_1 falls ≥ 20% of the baseline. At such time, the test will be terminated and subjects will be given 4 puffs of salbutamol, followed by a 15±5 minute waiting period prior to FEV_1 measurement. Subjects whose FEV_1

	levels are not within 10% of their baseline will be given another dose of salbutamol and spirometry measurement repeated after 15±5 minutes. Mch PC_{20} will then be calculated. All MCT will be performed at the same time of the day within a timeframe of ±1.5 hours throughout the entire study. Those who qualify will undergo a multi-skin prick sensitivity test with doubling concentrations of cat/ HDM allergen extracts. A positive control and a negative control will also be administered. The wheal diameters will be measured as per the site standard procedures. Salbutamol inhaler with spacer (rescue medication) will be provided to the subject to take home at Visit 2a and rechecked at every Clinic Visit to ensure that the subjects have enough medication. The subjects will be issued a diary (including Asthma Action Plan) to keep a daily log of any changes in their health or medication use (including rescue medication) in their diary while at home. The subjects will be given the option to be confined at the study site in order to facilitate early morning visit on the next day. The next day (Visit 2b), subjects will undergo a BAC. At Visit 2b, the subjects' old diary (including Asthma Action Plan) will be collected and the subjects will be issued a new diary to keep a daily log of any changes in their health or medication use (including rescue medication) while at home. Before the test can be performed, qualified personnel will explain the procedure and expected symptoms to the subjects. The allergen concentration to be administered will be determined based on the results from the MCT and allergy SPT titrations performed at Visit 2a. The concentration of the allergen provocative concentration (PC_{20}) will then be predicted from the previous Mch PC_{20} and the skin sensitivity using the following logarithmic formula: Log10 (Allergen PC_{20}) = 0.68 log10 (Mch PC_{20} x skin sensitivity). Where skin sensitivity is the skin prick test end point dilution titration which is the lowest concentration producing a ≥3 mm wheal. (This formula may be subject to modification and is dependent on the allergen PC_{20} estimated in subjects). Following the calculation of the predicated allergen PC_{20}, subjects will undergo BAC as per the Principal Investigator and Sponsor approved Manual of Procedures. Early phase asthmatic response (EAR) is defined as a ≥ 20% fall in FEV_1 from the highest pre-inhalation FEV_1 value on at least one occasion within 3 h after the inhalation of the final concentration of allergen. In order to assess the EAR, FEV_1 will be measured at approximately 30, 60, 90, 120, and 180 minutes post allergen exposure. Late phase asthmatic response (LAR) is defined as a ≥ 15% fall in FEV_1 from the highest pre-inhalation FEV_1 value on at least one occasion between 3 and 7 h after the inhalation of the final concentration of allergen. To assess the LAR, FEV_1 will be measured every hour between 3 to 7 hours post allergen challenge. At the end of the monitoring period, 4 puffs of bronchodilator (salbutamol) will be administered to the subjects to restore FEV_1 to 90% of pretest FEV_1, if necessary. If FEV_1 does not return to normal levels, the Investigator/medical designee will assess the subject. Following the test, sputum will be induced, collected, and processed (approximately 7 h post-BAC). The subjects will be given the option to be confined at the study site in order to facilitate early morning visit on the next day. The next day (Visit 2c) sputum induction and collection (approximately 24 h post-BAC) will be performed. Additionally, a blood sample will be taken and sent to analytical lab for

	exploratory biomarkers (RASP and endotoxin-induced cytokine release). This will be considered as baseline value. At Visit 2c, the subjects' old diary will be collected and the subjects will be issued a new diary to keep a daily log of any changes in their health or medication use (including rescue medication) while at home. Subjects will also receive an asthma action plan to monitor asthma symptoms. Subjects will be asked to return to the clinic after approximately 2 weeks. Note: Safety clinical laboratory tests will be repeated within 3 days prior to the first dose of study drug to ensure continued eligibility. **III. Randomization Visit- Visit 3** Following at least 2 weeks wash-out period, eligible subjects will return to the clinic for Visit 3 to participate in the treatment periods. Clinic staff will update the subjects' concomitant medication and collect AEs and vital signs. Eligibility criteria will be reviewed. Diary cards including asthma action plan will be collected and reviewed and subjects will be issued a new diary. Asthma control questionnaire will be collected. A urine pregnancy test will be administered to WOCBP. Subjects will be randomized to either Sequence treatment AB or Sequence Treatment BA. Subjects will be dispensed ADX-629 or Placebo for at-home treatment with instructions for dosing. Subjects will receive their first dose on site. Blood sample will be collected for PK assessment at 1 hour (+5 minutes) post dose. An Electrocardiogram (ECG) will be performed at 1 hour (±15 minutes) post dose. **IV. Treatment Period 1** At home, subjects will take the treatment (Treatment A or Treatment B) orally twice per day, i.e. PO bid dosing for minimum 1 week (+3 days) and return to the Clinic for the Post-Treatment Period 1. Subjects will take the morning and evening dose at approximately the same time each day. Additionally, there will be a phone call during the treatment period to follow up on subject's health and treatment compliance. Subjects will continue to keep a daily log of any changes in their health or medication use (including rescue medication) and time of dosing in their diary while at home. They will also continue to refer to the asthma action plan, if there is any worsening of asthma control. Additionally, subjects will receive a phone call on the last day of the treatment period to remind them that their morning dose (600 mg) of the treatment will be administered onsite next day. **V. Post-Treatment Period 1 (For 2 consecutive days) - Visits 4a & 4b** Subjects will not stop treatment in order to maintain steady state concentration of the drug during the Visits 4a and 4b. Hence subjects will continue to receive their respective treatments with same schedule. However, on the days of visits 4a and 4b, subjects will receive their morning dose (600 mg) of the treatment on site approximately one hour prior to MCT or BAC. Staff will update the subjects' concomitant medication and collect AEs and vital signs. Asthma control questionnaire will be collected. Eligibility criteria will be reviewed. Diary cards including asthma action plan will be collected and reviewed and subjects will be issued a new diary. Blood and urine samples will be collected for safety clinical

	laboratory tests (CBC with differential, electrolytes [Calcium, Sodium, Potassium, Chloride], eGFR, creatinine, BUN, ALT, AST, ALP, total bilirubin, albumin, total protein, glucose, total cholesterol, triglycerides, lipase and amylase and urinalysis including assessment of microalbuminuria). At Visit 4a, pre-BAC FeNO (baseline) and baseline FEV_1 will be performed. Pre-BAC FeNO to be performed prior to baseline FEV_1. At approximately 1 hour post-dose blood samples will be taken and sent to analytical lab for exploratory biomarkers (RASP and endotoxin-induced cytokine release) prior to BAC. An additional blood sample will be collected for PK assessment at 1 hour (+5 minutes) post dose. An ECG will be performed at 1 hour (±15 minutes) post dose. Subjects will then undergo BAC with the target allergen titer dilution identified in the pre-treatment allergen challenge visit (Visit 2b). Approximately 7 h post-BAC, FeNO will be measured and then sputum will be induced, collected, and processed. FeNO to be performed prior to 7 h FEV_1 measurements. Additionally, blood samples will be taken and sent to analytical lab for exploratory biomarkers (RASP and endotoxin-induced cytokine release), at approximately 7 h post-BAC. The subjects will be given the option to be confined at the study site in order to facilitate early morning visit on the next day. At home treatment will be dispensed and/or collected based on subject's decision regarding confinement. Once all procedures are completed, subjects will be reminded to take their next day morning dose on site approximately one hour prior to MCT. The following day (Visit 4b), subjects will undergo post-BAC MCT, FeNO and sputum testing (approximately 24 h post-BAC). FeNO will be performed before any other procedure on Visit 4b. Procedures for MCT (including baseline FEV_1) will be repeated as described in Visit 2a, except that the maximum concentration of Mch used in this visit will be up to16 mg/mL. Following MCT, sputum will be induced, collected, and processed (approximately 24 h post-BAC). Any remaining at home treatment will be collected. After completion of Visit 4b study procedures, subjects will be dispensed the second treatment according to their assigned sequence and new at-home diary cards and will be asked to follow the same instructions as previously directed. Following Visit 4b, subjects will complete 2 weeks of washout period. Subjects will continue to keep a daily log any of any changes in their health or medication use (including rescue medication) and time of dosing in their diary while at home. They will also continue to refer to the asthma action plan, if there is any worsening of asthma control. Subjects will receive a phone call approximately 1 day prior to their scheduled initiation of at-home dosing as a reminder to start treatment. Staff will update the subjects' concomitant medication and rescue medication use and collect AEs. **VII. Treatment Period 2** At home, subjects will take the treatment (Treatment B or Treatment A) orally twice per day, i.e. PO bid dosing for minimum 1 week (+3 days) and return to the Clinic for the Post-Treatment Period 2. Subjects will take the morning and evening dose at the same time each day. Additionally, there will be a phone call during the treatment period to follow up on subject's health and treatment compliance. Subjects will continue to keep a daily log of any changes in their health or medication use (including rescue medication) and time of dosing in their new diary while at home. They

	will also continue to refer to the asthma action plan, if there is any worsening of asthma control. Additionally, subjects will receive a phone call on the last day of the treatment period to remind them that their morning dose (600mg) of the treatment will be administered onsite next day **VIII. Post-Treatment Period 2 (For 2 consecutive days) –Visits 5a & 5b** Subjects will return to the Clinic for the Post-Treatment Period 2 following approximately 3 weeks (+3 days) later after having completed 2 weeks of washout and 1 week (+3 days) of at-home dosing. At Visits 5a and 5b, subjects will follow same procedures as performed previously at Visits 4a and 4b, respectively. As with Visits 4a and 4b, on the days of visits 5a and 5b, subjects will receive their morning dose (600 mg) of the treatment on site approximately one hour prior to MCT or BAC. Additionally, at Visit 5b, paper diary cards including asthma action plan and any remaining at home treatment will be collected from the subjects and a urine pregnancy test will be administered to WOCBP. Subjects will complete a health check prior to clinical trial exit. **IX. Early Termination Visit (ETV)** Staff will update the subjects' concomitant medication and collect any unused at home treatments, adverse events, asthma control questionnaire, and vital signs. Paper diaries will be collected and reviewed. Urine pregnancy test for WOCBP only will be done, if not performed before on the same day.
Inclusion Criteria	1. Male or non-pregnant female, between 18 to 65 years of age (inclusive) at Screening Visit. 2. Subjects must give their signed and dated written informed consent (in English) to participate prior to commencing any study-related activities and must be willing to comply with study procedures, study restrictions, study protocol, and return for the required assessments. 3. Female subjects of either non-childbearing potential or of child-bearing potential who commit to consistent and correct use of at least one highly effective or two effective forms of contraception starting at least 4 weeks prior to the Screening Visit and for at least 30 days post last dose of study drug. 4. Generally healthy subjects with mild controlled asthma for 2 years at Screening Visit according to the Global Initiative for Asthma (GINA 2020) criteria. 5. No concomitant asthma treatment, except inhaled SABA. 6. [redacted] 7. [redacted] 8. [redacted] 9. Currently a non-smoker; having not used tobacco products (i.e. cigarettes, cigars, pipe tobacco) within the past year, and having ≤ 10 pack-years of historical use. Use

	of electronic cigarettes or other inhaled nicotine delivery products, smoking and/or inhalation of cannabis using a device (e.g. vaping) will not be allowed during the study. 10. Agree to limit caffeine and consumption of cruciferous vegetables and grilled meats. Agree to prohibit concomitant medications (strong CYP1A2, 2B6 and 3A4 inhibitors). 11. Body mass index (BMI) within the range 18.5-35.0 kg/m^2. 12. Male subjects who commit to not father a child or donate sperm from first dose until 3 months post-last dose. 13. Male subjects (with female partners of childbearing potential) who commit to consistent and correct use of at least two effective methods of birth control for the duration of the study and 30 days after the last dose of study drug. 14. AST, ALT, ALP, TSH, White Blood Count, hemoglobin, glucose, albumin, electrolytes, total proteins and total bilirubin within the normal range. 15. Acceptable lipase, amylase, GGT, CPK, total cholesterol, triglycerides, and eosinophils levels as determined by the Investigator in consultation with the medical monitor. 16. [redacted] 17. [redacted]
Exclusion Criteria	1. History and presence of clinically significant cardiovascular, renal, neurologic, hepatologic, endocrinologic, gastrointestinal, genitourinary, autoimmune, hematological, or metabolic disease other than asthma, which in the opinion of Investigator may either put the subject at risk or influence the results during the study. 2. Subjects with perennial allergy symptoms and/or possible exposure to perennial allergens (e.g. mold, dog) that occur or are anticipated to occur during the study at the discretion of the investigator. Subjects with seasonal allergy symptoms that occur or are anticipated to occur during the study should result in subject exclusion or rescheduling until the subject is out of the allergy season. 3. Any relevant pulmonary disease within 1 year prior to dosing at the discretion of the investigator. 4. Recent hospitalization with asthma in the last 6 months or any other medical condition that the Investigator deems incompatible with participation in the trial. 5. Inability to tolerate temporary withdrawal of current asthma medication. 6. Other co-morbid respiratory and sinus diseases. 7. History of frequent asthma exacerbations in the previous year. 8. The use of the following medications: beta blockers, tricyclic/polycyclic antidepressants, monoamine oxidase inhibitors within 14 days of the study. 9. History or current evidence of clinically relevant allergies or idiosyncrasy to drugs.

	10. Known intolerance or hypersensitivity to any component of the salbutamol MDI and intolerance to aerosolized β_2-adrenergic agonists. 11. Female subjects of child-bearing potential who are pregnant, lactating or using inadequate contraceptive measures. 12. Subjects that have a history of alcohol, drug or medication abuse within the past year before the study. 13. Subjects that lack cooperation or compliance, as judged by the Investigator. 14. Subjects suffering from severe psychiatric, psychological, or neurological disorders. 15. Subjects who are employees of the sponsor or CRO and/or 1st grade relatives or partners of the (principal) Investigator. 16. Inability to demonstrate the proper use of the nebulizer as determined by the staff. 17. Any clinically significant abnormal finding on the physical examination, vital signs or laboratory results at screening as deemed so by the Investigator. 18. The use of any investigational drug within 30 days of the study. 19. Allergen immunotherapy treatment with cat or HDM within the previous 5 years. 20. Any clinically significant physical findings of nasal anatomical deformities (including the presence of nasal mucosal ulceration, nasal polyps, purulent secretions, septal perforation or any other major abnormalities in the nose), which at the discretion of the Investigator, would interfere with the study procedures. 21. Any surgery requiring general anaesthesia three months before the Screening Visit or planned during the study period. 22. Known hypersensitivity to ADX-629 or any of its components. 23. History of anaphylaxis or angioedema. 24. Previous history of life-threatening asthma and/or exacerbation of asthma within 6 weeks prior to the Screening Visit. 25. Previous history of respiratory tract infection within 2 weeks prior to the Screening Visit. 26. History of risk factors for TdP (e.g., heart failure, hypokalemia, family history of long QT syndrome). 27. Persistent systolic BP >140mmHg or diastolic BP > 90mmHg. 28. [redacted] 29. Public health emergency (e.g., COVID-19): subject not complying with Public health guidelines (e.g., self-isolation), at the discretion of the Investigator and/or designee, or subjects with a positive COVID-19 test result up to 5 days prior to Visit 2a, Visit 4a or Visit 5a.
Statistical Analysis	The safety endpoint will be summarized descriptively. The key efficacy endpoint change from baseline in FEV_1 during 0-3 h post-BAC may be analyzed using a mixed effect model for repeated measures (MMRM) with the following independent factors, within-visit baseline FEV_1 as covariate, and sequence, visit, treatment, post-BAC assessment time, and interaction of treatment by post-BAC assessment time. Subject may be treated as a random effect. If deemed appropriate, baseline sputum eosinophil count may be included as an additional covariate in MMRM. AUCs may be analyzed using a mixed effect model with following terms:

	• sequence, visit (i.e., period), treatment group • subject as random effect The other efficacy endpoints may be compared between treatments using appropriate statistical models. The Statistical Analysis Plan will detail all statistical procedures and will take precedence over any statistical descriptions herein.
Safety Analysis	All study subjects who receive at least one dose of any of the study products will be included in the comparative safety analysis. Adverse events will be classified using standard Medical Dictionary for Regulatory Activities (MedDRA) terminology Version 22 or higher and presented by treatment group. Summary tables listing the type, date of onset, date and time of resolution, incidence, severity, outcome, action taken, and Investigator's opinion of relationship to the study product will be presented by treatment group for AEs reported after randomization. Concomitant medication used during the study will be tabulated by treatment by subject.
Sample Size Determination	Based on repeatability analyses in allergen-induced airway inflammation responses, a sample size of 12 subjects yields more than 80% power to detect a difference of 0.1 with standard deviation of 0.1 in change from baseline FEV_1 across treatment groups.

5. STUDY SCHEMATIC

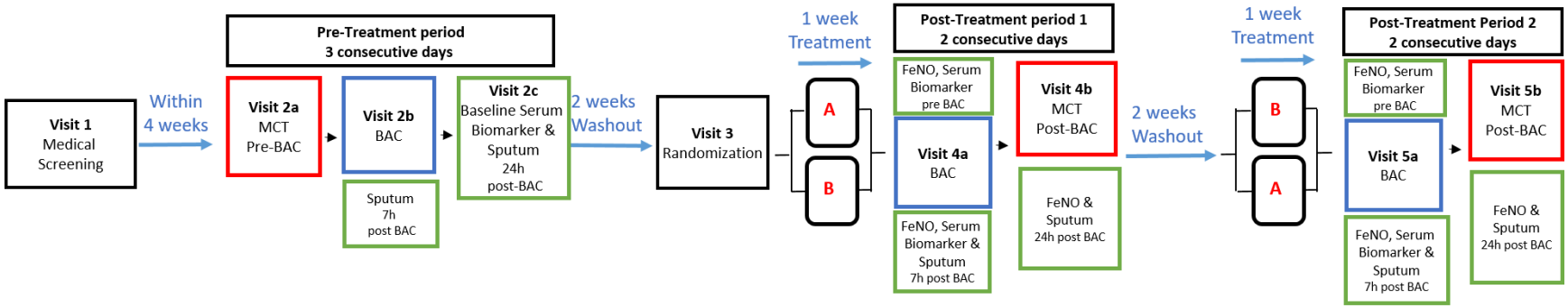
5.1 Schedule of Assessments

[redacted]

[redacted]

[redacted]

5.2 Study Design



MCT: Methacholine Challenge Test; BAC: Bronchial Allergen Challenge; FeNO: Fractional Exhaled Nitric Oxide
A: ADX-629 600 mg PO bid for 7 (+3) Days
B: Placebo 600 mg PO bid for 7 (+3) Days

6. INTRODUCTION

6.1 Background and Study Rationale

Type I allergy is an immune-disorder which results from the inappropriate formation of Immunoglobulin E (IgE) antibodies against proteins and glycoproteins from plants, insects, animals, and fungi, most of which are normally considered harmless. The cross-linking of IgE antibodies on effector B cells by allergens activates an immunological cascade leading to some or all of the symptoms of Type I allergy which may include rhinitis, conjunctivitis, asthma, and anaphylactic shock.

Asthma is a serious global health problem and one of the most common diseases in the Western world. Allergic asthma is the most common form of asthma, with over 50% of the asthma population being affected by allergic asthma.[1] Asthma is a chronic inflammatory disorder of the airways in which a variety of cell types and cellular elements play a role. Airway inflammation produces four forms of airflow limitations: acute bronchoconstriction, swelling of the airway wall, mucus hypersecretion, and airway wall remodeling. The chronic inflammation causes an associated increase in airway hyper-responsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness, and coughing. These episodes are usually associated with widespread, but variable airflow obstruction that is often reversible, either spontaneously or with treatment.[2]

[redacted]

[redacted]

6.2 ADX-629

ADX-629 is a small molecule with a quinoline core that acts as a reactive aldehyde species (RASP) inhibitor by irreversibly binding to RASP. ADX-629 is being developed for the treatment of systemic immune-mediated and inflammatory diseases, including psoriasis, inflammatory bowel disease, asthma, ulcerative colitis, non-alcoholic steatohepatitis, and other diseases believed to be caused, or exacerbated, by elevated concentrations of RASP. In an animal model of cytokine release syndrome, ADX-629 treatment resulted in broad-based reduction in inflammatory cytokines, including TH2 cytokines that mediate allergy. In addition, ADX-629 has demonstrated activity in animal models of ulcerative colitis, multiple sclerosis, and non-alcoholic steatohepatitis. ADX-629 is a close structural analog of reproxalap, which is now in Phase 3 clinical trials for the treatment of dry eye disease and allergic conjunctivitis, two ocular inflammatory diseases. [22]

6.3 Nonclinical Safety and Toxicology

Nonclinical safety pharmacology and toxicology studies were conducted with ADX-629 in rats and dogs. After 28 days of oral administration in good laboratory practice (GLP) toxicology studies, the no adverse effect levels (NOAELs) for rats and dogs were 500 mg/kg/day and 100 mg/kg/day, the highest doses tested.[22] *In vivo* safety pharmacology studies have shown that ADX-629 is unlikely to affect central nervous system function, cardiovascular function, or respiratory function in humans at clinically relevant doses.[22]

6.4 Benefit/Risk Assessment

Free RASP (e.g., malondialdehyde [MDA] and 4-hydroxynonenal [HNE]) are toxic, leading to inflammation and molecular dysfunction by reacting with cellular biomolecules, and have been implicated in many immune-mediated and inflammatory diseases. ADX-629 binds to free RASP via a rapid, two-step reaction involving Schiff base formation followed by a ring closure, resulting in stable and non-reactive ADX-629-RASP adducts that are subsequently degraded.[22]
The potential benefit of RASP inhibition in immune-mediated and inflammatory diseases has been demonstrated by the first-in-class RASP inhibitor reproxalap (ADX-102), which has been shown beneficial in treating ocular inflammation, including dry eye disease and allergic conjunctivitis across numerous Phase 2 and Phase 3 clinical trials, and is now in Phase 3 clinical testing. ADX-629 is being investigated for the treatment of systemic, immune-mediated, and inflammatory conditions thought to be caused or exacerbated by elevated RASP levels.[22]

Secondary pharmacology studies, which include a large panel of ligand binding assays, ion channel assays, transporter assays, and enzyme inhibition studies, suggest that there is a low risk of off-target effects due to treatment with ADX-629. In addition, in vitro studies have shown that ADX-629 has a very low potential to inhibit the delayed rectifier potassium current. Results of preclinical studies demonstrate that ADX-629 has a low risk of genotoxicity.[22] ADX-629 plasma concentrations are projected to have reached at least 10 µM, exceeding reported levels of RASP in humans with inflammatory diseases. The data support the potential of ADX-629, and RASP inhibition in general, in treating inflammation and fibrosis.[22]

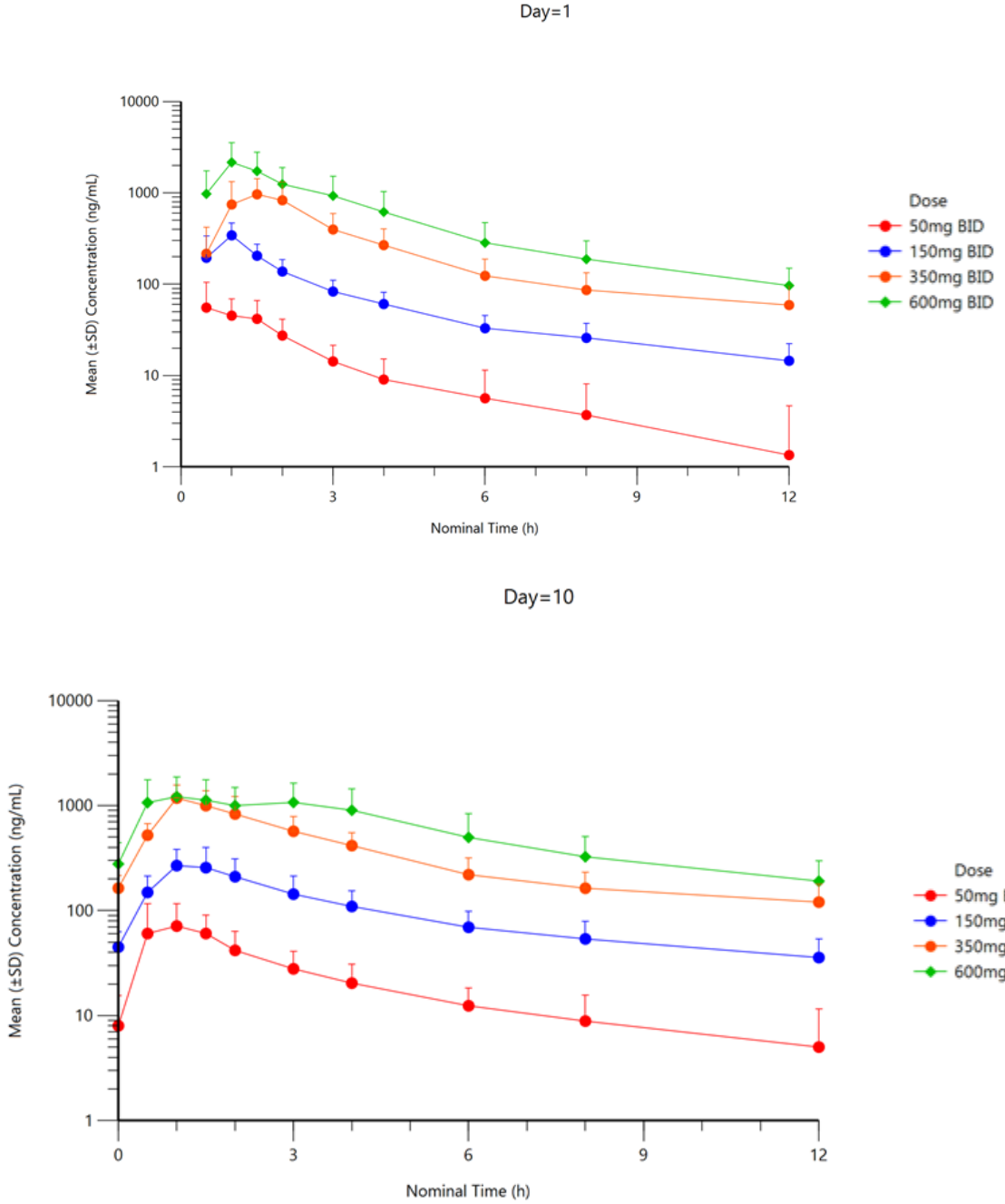
Genotoxicity studies have shown no potential for mutagenicity or clastogenicity of ADX-629.[22]

6.5 Effects in Humans

The ADX-629 Phase 1 clinical trial was a first-in-human, randomized, double-blind, placebo-controlled trial with a 3:1 randomization of ADX-629 and placebo. The clinical trial was comprised of single ascending dose (SAD) and multiple ascending dose (MAD) protocols. The MAD drug exposure was 10 days of twice -per-day (BID) administration. The clinical trial was performed with subjects housed in a clinical research unit; the drug compliance was 100%. Overall, ADX-629 was found to be safe and tolerable. The adverse event profile of ADX-629 was favorable compared to placebo: A total of 6 (9.4%) subjects receiving ADX-629 had treatment emergent adverse events, compared to 4 (19.1%) subjects who received placebo. There were no interruptions or discontinuations of study drug administration.[22]
No clinically meaningful changes were observed in hepatic or renal analytes, including transaminases (ALT and AST), alkaline phosphatase (ALP), amylase, gamma-glutamyl transpeptidase (GGT), bilirubin, creatinine kinase and creatinine. No changes in serum glucose were observed. No clinically meaningful changes were observed in heart rate (HR), blood pressure (systolic, diastolic and orthostatic changes), respiratory rate, pulse oximetry, or temperature. No clinically significant hematological changes were observed. ADX-629 did not lead to QTcF prolongation. There were no subjects who had QTcF > 500 msec or a change of > 60 msec from baseline. Five subjects had a change of >30 msec from baseline but did not require intervention or study drug interruption or discontinuation, and all subjects remained asymptomatic. Three of these five subjects were in the SAD portion of the study (one each in the 100 mg, 200 mg, and 700 mg dose cohorts) and the remaining two subjects were in the MAD portion of the study (one each in the
150 mg BID and 300 mg BID dose cohorts). [22]

Healthy volunteers were dosed with 600 mg of ADX-629 BID for 10 days in the top (highest) dose cohort. The observed Cmax on Day 1 was 1920 ng/mL (67.4%CV) and 1458 ng/mL (46.6%CV) on Day 10. The 0 to 12 hour area under the curve (AUCtau) was 5710 h*ng/mL (61.5 %CV) on Day 1 and 6,800 h*ng/mL (37.9 %CV) on Day 10. The observed half-life of the drug was 3.98 h (22.9 %CV) on Day 1 and 4.56 h (12.1 %CV) on Day 10. Plots of the Data are shown in below figures:[22]

Mean Concentration vs Time Plot by Dose in Healthy Volunteers on Day 1 and Day 10 of Dosing (Semi-Log)



These results indicate that no cyp autoinduction was observed over the course of 10 days as no significant increase in clearance was observed between Day 1 and Day 10. Although pharmacokinetic (PK) variability was evident, a linear correlation was observed in C_{max} and AUC as dose increased. The half-life ($t_{1/2}$) was consistent across cohorts and days, and mean values

in multiple day exposures ranged between 3.07 to 6.20 hours. Little to no accumulation of the drug was seen across all cohorts.[22]

A decrease in free MDA levels was observed in the plasma of healthy volunteers over 10 days of dosing with ADX-629 600mg BID that was statistically 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 HDL were statistically higher in drug-treated subjects than in placebo-treated subjects, potentially representing additional anti-inflammatory activity of ADX-629.[22]

6.6 Rationale for Dose Selection

Clinical development of ADX-629 in inflammatory disease is supported by safety testing in human healthy volunteers in single and multiple ascending dose (10 day), placebo-controlled Phase I trials. Overall, ADX-629 was found to be safe and tolerable at the doses explored, including the maximum dose of 600 mg BID. [22]

The dose for Phase 2 clinical trials of ADX-629 of 300 mg BID PO is based on conservative margins from 28-day nonclinical assessments and drug exposure in humans in the Phase 1 clinical trial, which generally exceeds levels of RASP reported in human inflammatory disease.[22]

7. OBJECTIVES AND ENDPOINTS

7.1 Study Objectives

Primary objective:

To assess the safety of ADX-629 in subjects with allergen-induced mild asthma.

Secondary objective:

To assess the clinical efficacy of ADX-629 in subjects with allergen-induced mild asthma.

7.2 Study Endpoints

Safety Endpoint:

- Safety, as assessed by adverse events (AEs) and serious adverse events (SAEs)

Efficacy Endpoints:

- Change from baseline (within visit) in forced expiratory volume in one second (FEV1) to post-BAC (during 0-3 h post-BAC [Key Efficacy Endpoint] and 3-7 h post BAC).
- Absolute count and percentage differential count of sputum eosinophils and neutrophils at approximately 7 h and 24 h post-BAC.
- Allergen-induced shift in airway hyper responsiveness (AHR) as assessed by Methacholine PC20 (Mch PC20) post-BAC.
- Change from baseline in fractional exhaled Nitric Oxide (FeNO) at approximately 7 h and 24 h post-BAC.

Exploratory Endpoints

- Biomarkers (RASP and endotoxin-induced cytokine release) pre-BAC (at approximately 1 hour post-dose) and 7 h post-BAC.
- Area under curve (AUC) of FEV1 during 0-3 h post-BAC and/or 3-7 h post BAC.

8. CLINICAL TRIAL DESIGN

ADX-629-AA-001 is double-masked, cross-over, placebo-controlled, single center, randomized clinical trial to assess the clinical safety and efficacy of ADX-629 compared to placebo in mild cat or HDM-induced asthmatics using the BAC model. The study will consist of 9 visits to the clinic (Visits 1, 2a, 2b, 2c, 3, 4a, 4b, 5a, and 5b) over a period of approximately 75 days (Please refer study design section 5.2). During this period there will be 4 additional visits, 1 visit for safety lab and 3 visits for COVID-19 testing, as described below. The clinical trial will be conducted as follows:

1. Medical Screening: Visit 1
2. COVID-19 test within 5 days prior to Pre-Treatment Period
3. Pre-Treatment Period (For 3 consecutive days)
    i. Visit 2a
    ii. Visit 2b
    iii. Visit 2c
4. Washout (2 weeks)
5. Additional visit for safety sample blood collection within 3 days of Visit 3
6. Randomization Visit: Visit 3
7. Treatment Period 1 (at home treatment taken for 1 week [+ 3 days])
8. COVID-19 test prior to Post-Treatment Period 1
9. Post-Treatment Period 1 (For 2 consecutive days):
    i. Visit 4a
    ii. Visit 4b
10. Washout (2 weeks)
11. Treatment Period 2 (at home treatment taken for 1 week [+ 3 days])
12. COVID-19 test prior to Post-Treatment Period 2
13. Post-Treatment Period 2 (For 2 consecutive days):
    i. Visit 5a
    ii. Visit 5b

A re-screening visit will be included to the subjects who failed under previous versions of the Protocol.

The end of study is defined as the time at which the last subject has completed all study procedures in the clinical trial. Upon completion of the clinical trial, the study product will no longer be available to the subject but the Investigator can, at their discretion, discuss alternative treatments with the subject.

9. SUBJECT SELECTION

9.1 Number of Subjects

Enough subjects will be enrolled to ensure approximately 12 subjects complete the study.

9.2 Inclusion Criteria for Study Volunteers

1. Male or non-pregnant female, between 18 to 65 years of age (inclusive) at Screening Visit.
2. Subjects must give their signed and dated written informed consent (in English) to participate prior to commencing any study-related activities and must be willing to comply with study procedures, study restrictions, study protocol, and return for the required assessments.
3. Female subjects of either non-childbearing potential or of child-bearing potential who commit to consistent and correct use of at least one highly effective or two effective forms of contraception starting at least 4 weeks prior to the Screening Visit and for at least 30 days post last dose of study drug.
4. Generally healthy subjects with mild controlled asthma for 2 years at Screening Visit according to the Global Initiative for Asthma (GINA 2020) criteria[23].
5. No concomitant asthma treatment, except inhaled SABA.
6. [redacted]
7. [redacted]
8. [redacted]
9. Currently a non-smoker; having not used tobacco products (i.e. cigarettes, cigars, pipe tobacco) within the past year, and having ≤ 10 pack-years of historical use. Use of electronic cigarettes or other inhaled nicotine delivery products, smoking and/or inhalation of cannabis using a device (e.g. vaping) will not be allowed during the study.
10. Agree to limit caffeine and consumption of cruciferous vegetables and grilled meats. Agree to prohibit concomitant medications (strong CYP1A2, 2B6 and 3A4 inhibitors).
11. Body mass index (BMI) within the range 18.5-35.0 kg/m^2.
12. Male subjects who commit to not father a child or donate sperm from first dose until 3 months post-last dose.
13. Male subjects (with female partners of childbearing potential) who commit to consistent and correct use of at least two effective methods of birth control for the duration of the study and 30 days after the last dose of study drug.
14. AST, ALT, ALP, TSH, White Blood Count, hemoglobin, glucose, albumin, electrolytes, total proteins and total bilirubin within the normal range.
15. Acceptable lipase, amylase, GGT, CPK, total cholesterol, triglycerides, and eosinophils levels as determined by the Investigator in consultation with the medical monitor.

16. [redacted]
17. [redacted]

9.3 Exclusion and Restriction Criteria for Study Volunteers

9.3.1 Exclusion Criteria

1. History and presence of clinically significant cardiovascular, renal, neurologic, hepatologic, endocrinologic, gastrointestinal, genitourinary, autoimmune, hematological, or metabolic disease other than asthma, which in the opinion of Investigator may either put the subject at risk or influence the results during the study.
2. Subjects with perennial allergy symptoms and/or possible exposure to perennial allergens (e.g. mold, dog) that occur or are anticipated to occur during the study at the discretion of the investigator. Subjects with seasonal allergy symptoms that occur or are anticipated to occur during the study should result in subject exclusion or rescheduling until the subject is out of the allergy season.
3. Any relevant pulmonary disease within 1 year prior to dosing at the discretion of the investigator.
4. Recent hospitalization with asthma in the last 6 months or any other medical condition that the Investigator deems incompatible with participation in the trial.
5. Inability to tolerate temporary withdrawal of current asthma medication.
6. Other co-morbid respiratory and sinus diseases.
7. History of frequent asthma exacerbations in the previous year.
8. The use of the following medications: beta blockers, tricyclic/polycyclic antidepressants, monoamine oxidase inhibitors within 14 days of the study.
9. History or current evidence of clinically relevant allergies or idiosyncrasy to drugs.
10. Known intolerance or hypersensitivity to any component of the salbutamol MDI and intolerance to aerosolized β_2-adrenergic agonists.
11. Female subjects of child-bearing potential who are pregnant, lactating or using inadequate contraceptive measures.
12. Subjects that have a history of alcohol, drug or medication abuse within the past year before the study.
13. Subjects that lack cooperation or compliance, as judged by the Investigator.
14. Subjects suffering from severe psychiatric, psychological, or neurological disorders.
15. Subjects who are employees of the sponsor or CRO and/or 1st grade relatives or partners of the (principal) Investigator.
16. Inability to demonstrate the proper use of the nebulizer as determined by the staff.

17. Any clinically significant abnormal finding on the physical examination, vital signs or laboratory results at screening as deemed so by the Investigator.
18. The use of any investigational drug within 30 days of the study.
19. Allergen immunotherapy treatment with cat or HDM within the previous 5 years.
20. Any clinically significant physical findings of nasal anatomical deformities (including the presence of nasal mucosal ulceration, nasal polyps, purulent secretions, septal perforation or any other major abnormalities in the nose), which at the discretion of the Investigator, would interfere with the study procedures.
21. Any surgery requiring general anaesthesia three months before the Screening Visit or planned during the study period.
22. Known hypersensitivity to ADX-629 or any of its components.
23. History of anaphylaxis or angioedema.
24. Previous history of life-threatening asthma and/or exacerbation of asthma within 6 weeks prior to the Screening Visit.
25. Previous history of respiratory tract infection within 2 weeks prior to the Screening Visit.
26. History of risk factors for TdP (e.g., heart failure, hypokalemia, family history of long QT syndrome).
27. Persistent systolic BP >140mmHg or diastolic BP > 90mmHg.
28. [redacted]
29. Public health emergency (e.g., COVID-19): subject not complying with Public health guidelines (e.g., self-isolation), at the discretion of the Investigator and/or designee, or subjects with a positive COVID-19 test result up to 5 days prior to Visit 2a, Visit 4a or Visit 5a.

9.3.2 Restrictions and Concomitant Medications

Once the clinical trial has begun, the subjects will be instructed to take only the study medication(s) described in the protocol. If the subject takes any other medication during the clinical trial, the Investigator will record the necessary information and may notify the Sponsor, if judged to be significant.

Items restricted prior to and during the course of this clinical trial are described in the table below:

Restricted Item	Start of Restriction	End of Restriction
SABAs	8 hours Prior to MCT, BAC	-
Long acting bronchodilators i.e. formeterol, salmeterol	48 hours prior to MCT, BAC	End of last study visit
Ipratropium bromide	24 hours prior to MCT, BAC	End of last study visit
Tiotropium	72 hours prior to MCT, BAC	End of last study visit
Theophylline	48 hours prior to MCT, BAC	End of last study visit

Restricted Item	Start of Restriction	End of Restriction
Leukotriene modifiers i.e., Singular (montelukast)	7 days prior to MCT, BAC	End of last study visit
Cholinesterase inhibitor	2 weeks prior to Screening	End of last study visit
Beta blockers, tricyclic/polycyclic antidepressants, monoamine oxidase inhibitors	14 days before Medical Screening -Visit 1	End of last study visit
Antihistamines i.e., cetirizine, fexofenadine or loratadine	7 days prior to the Medical Screening-Visit 1 and Visit 2a and 12 to 24 hours prior to MCT, BAC	End of last study visit
Cromolyn sodium	8 hours prior to MCT, BAC	End of last study visit
Nedocromil	48 hours prior to MCT, BAC	End of last study visit
Concomitant CYP1A2, 2B6 and 3A4 Substrates	24 hours prior to MCT, BAC	End of last study visit
Strong CYP1A2, 2B6 and 3A4 inhibitors	24 hours prior to MCT, BAC	End of last study visit
Acetaminophen	72 hours before Medical Screening -Visit 1	End of last study visit
Coffee, tea, cola, caffeinated beverages, chocolate (No more than one serving per day)	First dose of the study products for each treatment period	Last dose of the study products for each treatment period
Allergen immunotherapy treatment with cat or HDM	5 years before Medical Screening Visit 1	End of last study visit
Investigational drug/product	30 days before Medical Screening Visit 1	End of last study visit
Smoking (used tobacco products i.e., cigarettes, cigars, pipe tobacco, electronic cigarettes or other inhaled nicotine delivery product)	12 months before Medical Screening Visit 1	End of last study visit
Smoking and/or inhalation of cannabis using a device (e.g., vaping)	Screening Visit 1	End of last study visit
Alcohol	12 hours before Medical Screening Visit 1	End of last study visit
Cruciferous vegetables (1-2 servings per week)	First dose of the study products for each treatment period	Last dose of the study products for each treatment period

Restricted Item	Start of Restriction	End of Restriction
Grilled meats (1-2 servings per week)	First dose of the study products for each treatment period	Last dose of the study products for each treatment period
Green leafy vegetables	2 hours prior to FeNO	-
Eating and drinking anything	1 hour prior to FeNO	-
Any surgery requiring general anaesthesia	3 months before Medical Screening Visit 1	End of the last study visit
Oral corticosteroids	30 days prior to Medical Screening-Visit 1	End of the last study visit
Intranasal corticosteroids	2 weeks prior to Medical Screening-Visit 1	End of the last study visit
Inhaled corticosteroids	2 weeks prior to Medical Screening-Visit 1	End of the last study visit
Exposure to perennial allergens (e.g. mold, dog)	End of Medical Screening -Visit 1	End of last study visit

A complete listing of medications that are CYP Inhibitors and Inducers are available online at http://medicine.iupui.edu/clinpharm/ddis/main-table.

No other concurrent medications, other than mentioned in the above restriction table, are allowed during the trial conduct unless deemed necessary per the investigator's medical judgement.

Subjects who violate any of the above restrictions may be excluded or dropped from the clinical trial at the discretion of the Investigator. Individual exceptions to the above restrictions may be approved by the Sponsor and/or Investigator.

9.3.3 Female Subjects of Childbearing Potential

A woman is considered of childbearing potential (WOCBP) if she is not postmenopausal, not congenitally sterile; not diagnosed as infertile (and not undergoing treatment to reverse infertility); or has not undergone successful surgical sterilization (such as tubal ligation, bilateral oophorectomy, or hysterectomy). A woman is considered of non-childbearing potential if she is postmenopausal (naturally postmenopausal [no menses] for at least 1 year), surgically sterile (tubal ligation, bilateral oophorectomy, or hysterectomy), congenital sterility, or diagnosed as infertile and not undergoing treatment to reverse infertility.

WOCBP must commit to consistent and correct use of at least one highly effective or two effective forms of contraception starting at least 4 weeks prior to the Medical Screening Visit and until 30 days after the last administration of investigational product, such as total abstinence, intrauterine device, a double-barrier method, oral, transdermal, injected or implanted non- or hormonal contraceptive.

Subjects on hormonal contraceptives must have been on the same hormonal contraceptive for at least one month before the Medical Screening Visit and continue throughout the duration of the study.

WOCBP will be instructed to contact the Investigator immediately if they suspect they might be pregnant.

9.3.4 Male Subjects

Male subjects must commit to not father a child or donate sperm from first dose until 3 months post-last dose.

Male subjects (with female partners of childbearing potential) must commit to consistent and correct use of at least two effective methods of birth control from the Medical Screening Visit until 30 days after the last administration of investigational product.

- Condom and diaphragm with spermicide (foam, cream, gel, sponge)
- Condom and cervical cap with spermicide (foam, cream, gel, sponge)
- Non-hormonal intrauterine device (IUD)

Female partner(s) of male volunteers also have the option to use the following highly effective hormonal method of contraception: implants, injectables, combined oral contraceptives, and IUDs.

10. STUDY PRODUCT AND RANDOMIZATION

10.1 Study Product and Treatment

The following products will be used in the study:

Test Product (Treatment A)

2 x 300 mg ADX-629 tablet taken PO bid for minimum 1 week (+3 days)

Placebo (Treatment B)

2 x 300 mg Placebo tablet taken PO bid for minimum 1 week (+3 days)

Dosing Instructions:

- [redacted]
- The subjects should take each dose at least 60 mins before food.
- There should be a gap of at least 4 hours between the two doses per day.
- The subjects should not take broken tablets; however minor tablet defects like chipping or scratching are acceptable.
- In case of an overdose, the subjects should hold the next dose and inform clinic immediately.
- In case of a missed dose, the subjects should take the dose when they remember only if their next scheduled dose is not within time frame of 4 hours. If the next scheduled dose is within time frame of 4 hours then subject should not take their missed dose and take the next dose at scheduled time.
- A minimum of two days of BID dosing during each treatment period are required before BAC/MCT.
- During Post-Treatment Periods 1 and 2 (Visits 4a, 4b, 5a, and 5b), in lieu of the morning dose, 600 mg of the treatments will be administered approximately one hour prior to MCT or BAC testing.

10.2 Randomization Sequence

At Visit 3, eligible subjects will be randomized to one of the two sequences shown below. The randomization will be generated in blocks of two with each sequence occurring once in each block.

The randomization schedule will be generated by using SAS® statistical software (Version: 9.4 or higher; SAS Institute Inc., USA). The randomization schedule will be generated by a biostatistician of [redacted] Limited.

The randomization schedule will be maintained under controlled access. The personnel involved in the dispensing of investigational products will be accountable for ensuring compliance to the

randomization schedule. The analytical staff concerned will not have access to the randomization schedule during the course of analysis.

Treatments will be administered according to a two-treatment, two-period, and two-sequence design.

	Period 1	Period 2
Sequence 1	A	B
Sequence 2	B	A

Number of subjects per sequence = 6

10.3 Masking and Unmasking

10.3.1 Masking

This is a double-masked clinical trial. Investigators, qualified site personnel (except pharmacy staff), and subjects will be masked to the investigational product administered. The Sponsor will also be masked to the IP administered until database lock. Only the pharmacy staff and Scientific Affairs staff involved with preparing the randomization will have access to the treatment under evaluation.

10.3.2 Emergency Unmasking

Emergency unmasking should only be performed when necessary to treat the subject. Most often, knowledge of the possible treatment assignments is sufficient to treat a clinical trial subject who presents with an emergency condition.

The investigator should make every effort to contact the Medical Monitor to discuss the subject's emergency and the need to unmask, prior to unmasking any subject.

In situations in which the investigator has tried but is unable to reach the Medical Monitor, best judgement on the part of the investigator should be used, based on the nature and urgency of the clinical situation, and may proceed with unmasking without having successfully reached and discussed the situation with the Medical Monitor. Once a subject's treatment assignment has been unmasked, the Medical Monitor should be notified within 24 hours of unmasking of the treatment, without revealing the treatment.

The emergency unmasking should be performed by the designated site personnel. The investigator must also indicate in source documents and in the CRF that the mask was broken and provide the date, time, and reason for breaking the mask.

Any AE or SAE associated with breaking the mask must be recorded and reported as specified in the protocol. The investigator has the responsibility to contact the Sponsor or designee within 24 hours of unmasking. In the event of a drug-related, serious, unexpected AE, the Sponsor's Pharmacovigilance Department or designee will be provided with the treatment assignment for the subject for regulatory reporting.

If treatment assignment is unmasked, the treatment will be discontinued immediately, and the subject will be discontinued from the clinical trial.

The mask may be broken in the case of a pregnancy should the subject desire this information.

11. STUDY CONDUCT

11.1 COVID-19 Screening

The following procedures will be performed as part of COVID-19 screening:

- Subjects will be pre-screened based upon a COVID-19 questionnaire at each clinic visit;
- Body temperature will be measured at each visit. This measurement may be in addition to other vitals taken at the visit;
- A nasal/nasopharyngeal/oropharyngeal swab will be collected for COVID-19 testing within 5 days prior to Visits 2a, 4a and 5a.
- Most recent COVID-19 test result (performed at Cliantha) will be reviewed prior to Visit 2a, 4a and 5a. Subject will be allowed to continue only if COVID-19 test result is negative.

Subject's further participation in the study will be based on the results of the COVID-19 test results and procedures.

11.2 Medical Screening: Visit 1 (Day - 28 to Day - 2)

The following activities will be completed at Visit 1:

- Verification of subject Identification (ID).
- Subjects will be asked to sign the Informed Consent Form.
- Demographic data including date of birth, age, race and ethnicity will be recorded.
- Medical, surgical, and social history and prior/concomitant medication use will be completed for each subject (see Section 12.2.2).
- An asthma control questionnaire will be completed.
- Vital signs (blood pressure, heart rate, respiratory rate, and oral temperature) will be measured (see Vital Signs Section 12.2.4).
- Height and weight will be measured and BMI will be calculated.
- A physical examination will be performed (see Physical Examination Section 12.2.3).
- Electrocardiogram (ECG) will be performed.
- A urine sample will be collected for urinalysis (see Clinical Laboratory Tests Section 12.2.1).
- Blood samples will be collected for clinical chemistry and complete blood count (CBC) with differential analysis (see Clinical Laboratory Tests Section 12.2.1).

- A urine pregnancy test will be performed (for all WOCBP). Subjects with a positive result will be excluded (see Clinical Laboratory Tests Section 12.2.1).
- The subjects will be evaluated for study inclusion, exclusion, and restriction criteria.
- A skin prick test (SPT) will be performed to show positivity to cat or HDM allergen (≥ 3 mm wheal compared to negative control) (see Skin Prick Test Section 12.1.1).
- Subjects will undergo spirometry to demonstrate baseline (pre-bronchodilator) FEV_1 of ≥ 80% of the predicted value Post-bronchodilator FEV_1 will be measured within 15±5 minutes following 400 µg (4 puffs) of salbutamol inhalation and post-bronchodilator reversibility will be recorded (see Spirometry Section 12.1.2).
- Adverse events and concomitants medications will be recorded before subject leaves the site (see Adverse Event Query/Concomitant Medication Query Section 12.2.5).

11.3 Pre-Treatment Period (3 consecutive days): Visit 2a, 2b and 2c (Day 1, 2 and 3)

- Subjects will return to the clinic for the pre-treatment period within approximately 4 weeks of Screening Visit.
- At all visits, the following procedures will be performed:
  - Verification of Subject ID.
  - The subjects will be evaluated for study inclusion, exclusion and restriction criteria.
  - Vital signs (blood pressure, heart rate, oral temperature and respiratory rate) will be measured (see Vital Signs Section 12.2.4).
  - Adverse Event Query/Concomitant Medication Query: All subjects will be evaluated regarding their health status (see Adverse Event Query/Concomitant Medication Query Section 12.2.5).

Visit 2a (Day 1):

- Asthma control questionnaire will be completed.
- Spirometry will be performed to ensure FEV_1 ≥ 80% of the predicted value.
- Subjects will have a pre-BAC MCT performed as per the site standard procedures.
- Subjects will inhale normal saline and have a baseline FEV_1 established.
- Subjects will then be given subsequent doubling concentrations of Mch as per the site standard procedures (see Section 12.1.3).
- FEV_1 will be measured at approximately 30 and 90 seconds following nebulization. If the FEV_1 drops < 20%, the subject will be given the next highest concentration and spirometry repeated.
- Mch doses will continue to be administered sequentially (max concentration 4 mg/mL) until FEV_1 falls ≥ 20% of the baseline. At such time, the test will be

terminated and subjects will be given 400 µg (4 puffs) of salbutamol, followed by a 15 ±5 minute waiting period prior to FEV_1 measurement.

- Subjects whose FEV_1 levels are not within 10% of their baseline will be given another dose of salbutamol as per Investigator's discretion and spirometry measurement repeated after 15±5 minutes. Mch PC_{20} will then be calculated.
- All MCT will be performed at the same time of the day within a timeframe of ±1.5 hours throughout the entire study.
- Those who qualify will undergo a multi-skin prick sensitivity test with doubling concentrations of cat/ HDM allergen extracts. A positive control and a negative control will also be administered. The wheal diameter will be measured as per the site standard procedures (see Multi-skin prick sensitivity test Section 12.1.4).
- At Visit 2a, the subjects will be issued a diary (including Asthma Action Plan) to keep a daily log of any changes in their health or medication use (including rescue medication) in their diary while at home.
- Salbutamol inhaler with spacer (rescue medication) will be provided to the subject to take home at Visit 2a and rechecked at every Clinic Visit to ensure that the subjects have enough medication.
- The subjects will be given the option to be confined at the study site in order to facilitate early morning visit on the next day.

Visit 2b (Day 2):

- The next day after Visit 2a, subjects will undergo a BAC.
- Before the test can be performed, qualified personnel will explain the procedure and expected symptoms to the subjects.
- The allergen PC_{20} to be administered will be determined based on the results from the MCT and allergy SPT titrations performed at Visit 2a (see Section 12.1.5).
- Following the calculation of the predicted allergen PC_{20}, post-saline FEV_1 i.e. baseline FEV_1 will be recorded (see Section 12.1.5).
- Subjects will then be given inhaled allergens as per the site's procedure until a 20% drop in FEV1 is observed, or a maximum concentration of 5000 BAU/mL is given.
- When a drop in FEV_1 of 20% from baseline has finally been achieved the challenge will be terminated.
- In order to assess an EAR, FEV_1 will be measured at approximately 30, 60, 90, 120 and 180 minutes post allergen exposure. To assess LAR, FEV_1 will be measured every hour up to 7 hours post allergen challenge.
- At the end of the monitoring period, 4 puffs of bronchodilator will be administered to the subjects to restore FEV_1 to 90% of pretest FEV_1, if necessary. If FEV_1 does not return to normal levels, the Investigator/medical designee will assess the subject.

Following the test, sputum will be induced, collected, and processed (approximately 7 h post-BAC).

- At Visit 2b, the subjects' old diary (including Asthma Action Plan) will be collected and the subjects will be issued a new diary to keep a daily log of any changes in their health or medication use (including rescue medication) in their diary while at home.
- The subjects will be given the option to be confined at the study site in order to facilitate early morning visit on the next day.

Visit 2c (Day 3):

- The next day after Visit 2b, sputum induction and collection (approximately 24 h post-BAC) will be performed. Additionally, blood sample will be taken and sent to analytical lab for exploratory biomarkers (RASP and endotoxin-induced cytokine release). This will be considered as baseline value.
- At Visit 2c, the subjects' old diary will be collected and the subjects will be issued a new diary to keep a daily log of any changes in their health or medication use (including rescue medication) in their diary while at home. Subjects will also receive an asthma action plan to monitor asthma symptoms.
- Subjects will be asked to return to the clinic after approximately 2 weeks.

Note: Safety clinical laboratory tests will be repeated within 3 days prior to the first dose of study drug to ensure continued eligibility.

11.4 Randomization Visit: Visit 3 (Day 17)

Following at least 2 weeks wash-out period, eligible subjects will return to the clinic for Visit 3 to participate in the treatment periods.

- Verification of Subject ID.
- Clinic staff will update the subjects' concomitant medication and collect AEs and vital signs (blood pressure, heart rate, oral temperature and respiratory rate).
- Eligibility criteria will be reviewed.
- Diary cards including asthma action plan will be collected and reviewed and subjects will be issued a new diary.
- Asthma control questionnaire will be completed.
- A urine pregnancy test will be performed (for all WOCBP). Subjects with a positive result will be excluded (see Clinical Laboratory Tests Section 12.2.1)
- Subjects will be randomized to either Sequence treatment AB or Sequence Treatment BA.
- Subjects will be dispensed ADX-629 or placebo for at-home treatment. Subjects will be instructed to take the treatment orally twice per day (refer Section 10.1 for detail

dosing instructions) and return to the Clinic for the Post-Treatment Period 1. Subjects will receive their first dose on-site.

- Subjects will continue to keep a daily log of any changes in their health or medication use (including rescue medication) and time of dosing in their new diary while at home. They will also continue to refer to the asthma action plan, if there is any worsening of asthma control.
- Blood sample will be collected for PK assessment at 1 hour (+5 minutes) post dose.
- ECG will be performed at 1 hour (±15 minutes) post dose.

11.5 Treatment Period 1 (Day 17 to Day 23 [+3])

- At home, subjects will take the treatment (Treatment A or Treatment B) orally twice per day i.e. PO bid dosing for minimum 1 week (+3 days) and return to the Clinic for the Post-Treatment Period 1. Subjects will take the morning and evening dose at the same time each day.
- Subjects will continue to keep a daily log of any changes in their health or medication use (including rescue medication) and time of dosing in their diary while at home. They will also continue to refer to the asthma action plan, if there is any worsening of asthma control.

11.5.1 Reminder Phone Calls - Treatment Period 1

- There will be a phone call during the treatment period 1 to follow up on subject's health and treatment compliance.
- Additionally, subjects will receive a phone call on the last day of the treatment period to remind them that their morning dose (600 mg) of the treatment will be administered onsite next day.

11.6 Post-Treatment Period 1 (2 consecutive days): Visits 4a and 4b (Day 24 and 25)

- Subjects will not stop treatment in order to maintain steady state concentration of the drug during the **Visits 4a** and **4b**. Hence subjects will continue to receive their respective treatments with same schedule. However, on the days of visits 4a and 4b, subjects will receive their morning dose (600 mg) of the treatment on site approximately one hour prior to MCT or BAC.
- Verification of Subject ID.
- Eligibility criteria will be reviewed.
- Diary cards including asthma action plan will be collected and reviewed and subjects will be issued a new diary.
- Staff will update the subjects' concomitant medication and collect AEs and vital signs (blood pressure, heart rate, oral temperature and respiratory rate).

- Staff will collect any remaining at home treatment (either at Visit 4a and/or 4b based on subject's decision regarding confinement). At Visit 4a, subject will be dispensed at home treatment, if applicable based on their decision regarding confinement.
- Asthma Control Questionnaire will be completed at Visit 4a.
- Blood and urine sample will be collected for safety clinical laboratory tests (CBC with differential, electrolytes [Calcium, Sodium, Potassium, Chloride], eGFR, creatinine, BUN, ALT, AST, ALP, total bilirubin, albumin, total protein, glucose, total cholesterol, triglycerides, lipase and amylase and urinalysis including assessment of microalbuminuria).
- At **Visit 4a**, pre-BAC FeNO (baseline) and baseline FEV1 will be performed. Pre-BAC FeNO to be performed prior to baseline FEV1. At approximately 1 hour post-dose blood samples will be taken and sent to analytical lab for exploratory biomarkers (RASP and endotoxin-induced cytokine release) prior to BAC. An additional blood sample will be collected for PK assessment at 1 hour (+5 minutes) post dose. An ECG will be performed at 1 hour (±15 minutes) post dose.
- Subjects will undergo BAC with the target allergen titer dilution identified in the pre-treatment allergen challenge visit (Visit 2b). Approximately 7 h post-BAC, FeNO will be measured (see Section 12.1.6) and then sputum will be induced, collected, and processed. FeNO to be performed prior to 7 h FEV_1 measurements. Additionally, blood samples will be taken and sent to analytical lab for exploratory biomarkers (RASP and endotoxin-induced cytokine release), at approximately 7 h post-BAC. The subjects will be given the option to be confined at the study site in order to facilitate early morning visit on the next day.
- Once all procedures are completed, subjects will be reminded to take their next day morning dose on site approximately one hour prior to MCT.
- The following day (Visit 4b), subjects will undergo post-BAC, MCT, FeNO and sputum testing (approximately 24 h post-BAC)**.** FeNO will be performed before any other procedure on Visit 4b. Procedures for MCT (including baseline FEV_1) will be repeated as described in Visit 2a, except that the maximum concentration of Mch used in this visit will be up to 16 mg/mL. Following the MCT, sputum will be induced, collected, and processed (approximately 24 h post-BAC) (see Section 12.1.7). After completion of **Visit 4b** study procedures, subjects will be dispensed the second treatment according to their assigned sequence and at-home diaries and will be asked to follow the same instructions as previously directed.
- Following Visit 4b, subjects will complete 2 weeks of washout period. Subjects will continue to keep a daily log any of any changes in their health or medication use (including rescue medication) and time of dosing in their new diary while at home. They will also continue to refer to the asthma action plan, if there is any worsening of asthma control.

11.7 Treatment Period 2 (2 weeks after Visit 4b) (Day 39 to Day 45)

- At home, subjects will take the treatment (Treatment B or Treatment A) orally twice per day i.e. PO bid dosing for minimum 1 week (+3 days) and return to the Clinic for the Post-Treatment Period 2. Subjects will take the morning and evening dose at the same time each day.
- Subjects will continue to keep a daily log of any changes in their health or medication use (including rescue medication) and time of dosing in their new diary while at home. They will also continue to refer to the asthma action plan, if there is any worsening of asthma control.

11.7.1 Reminder Phone Calls - Treatment Period 2

- Subjects will receive a phone call approximately 1 day prior to their scheduled initiation of at-home dosing as a reminder to start treatment. Staff will update the subjects' concomitant medication and rescue medication use and collect AEs.
- There will be a phone call during the Treatment Period 2 to follow up on subject's health and treatment compliance.
- Additionally, subjects will receive a phone call on the last day of the treatment period to remind them that their morning dose (600mg) of the treatment will be administered onsite next day.

11.8 Post-Treatment Period 2 (2 consecutive days): Visits 5a and 5b (Day 46 & 47)

- Subjects will return to the Clinic for the Post-Treatment Period 2 following approximately 3 weeks (+3 days) later after having completed 2 weeks of washout and 1 week (+3 days) of at-home dosing.
- At **Visits 5a and 5b**, subjects will follow same procedures as performed previously at Visits 4a and 4b, respectively. As with Visits 4a and 4b, on the days of visits 5a and 5b, subjects will receive their morning dose (600 mg) of the treatment on site approximately one hour prior to MCT or BAC.
- Additionally, at Visit 5b, paper diary cards including asthma action plan and any remaining at home treatment will be collected from the subjects and a urine pregnancy test will be administered to WOCBP.
- Subjects will complete a health check prior to clinical trial exit.

11.9 Early Termination Visit (ETV)

The following procedures will be carried out following the premature withdrawal of any patient from the study, if possible:

- Paper diaries will be collected and reviewed.

- Any unused at home treatments will be collected.
- Patients will be queried for AEs and concomitant medication use.
- Asthma control questionnaire will be completed.
- Urine pregnancy test for WOCBP only, if not performed before on the same day.
- Vital signs (blood pressure, heart rate, oral temperature and respiratory rate) will be measured.

12. STUDY PROCEDURES AND SAFETY ASSESSMENTS

12.1 Study Procedures

12.1.1 Skin Prick Test (SPT)

At Visit 1 (Medical Screening Visit), subjects will undergo SPT.

In addition to the test allergens, positive controls and negative controls will be used during SPT challenge. A positive test is considered as ≥ 3 mm wheal compared to the negative control.

Skin Prick Test will be performed with a panel of test allergens (HDM [*Dermatophagoides pteronyssinus, Dermatophagoides fariniae*] or cat [*Felis domesticus*], mold, dog).

Skin Prick Test will be performed with a single prick device.

For detailed SPT procedure, refer to the site standard procedures.

12.1.2 Spirometry

FEV_1 measurement will be performed as described in the Study Schematic (see Section 5) and as per the site standard procedures. Spirometry training including instructions and demonstration of use will be provided to subjects at all study visits.

FEV_1 measurement is reported in litres. Normal values for FEV_1 vary according to age, sex, height, weight and ethnicity. To account for such variations, FEV_1 % predicted will be calculated. FEV_1 % predicted is defined as subject's FEV_1 value expressed as a percentage of the reference average FEV_1 for a person of similar age, sex and body composition.

At Screening Visit, baseline (pre-bronchodilator) FEV_1 will be recorded. Baseline FEV_1 should be ≥ 80% of the predicted normal after withholding SABA for > 6 hours. Post-bronchodilator FEV_1 will be measured within 15±5 minutes following 400 µg (4 puffs) of salbutamol inhalation and post- bronchodilator reversibility will be recorded.

At Visit 2a, 4b and 5b spirometry procedures will be performed pre saline, post saline and after the administration of methacholine and will be repeated until PC_{20} is found.

At Visit 2b, 4a and 5a spirometry procedures will be performed pre saline, post saline and during allergen challenge as per the allergen challenge procedures and will be repeated until FEV_1 drops ≥20% of the baseline value.

At Visit 2a, 4a and 5a, the pre-saline FEV1 will be considered as Baseline (within visit).

[redacted]

12.1.4 Multi-skin Prick Sensitivity Test

At Visit 2a, those subjects who complete MCT and continue to be eligible to participate in the study will undergo a multi-skin prick sensitivity test. This test will employ similar procedures as SPT (see Section 12.1.1). However, multi-skin prick sensitivity test will be done using doubling concentrations of cat/HDM allergen extracts as shown in table below.

Preparation of serial dilutions using a single allergen solution

[redacted]

The wheal diameter will be measured as per the site standard procedures. Skin sensitivity will be defined as the lowest allergen concentration that produces a wheal of ≥ 3 mm in diameter relative to the negative control.

12.1.5 Bronchial Allergen Challenge (BAC)

Subjects will undergo BAC at Visit 2b, 4a, and 5a. Before the BAC can be performed, qualified personnel will explain the procedure and the expected symptoms to the subjects. The allergen concentration to be administered will be determined based on the results from the MCT and allergy SPT titrations performed at Visit 2a.

[redacted]

12.1.6 Fractional Exhaled Nitric Oxide (FeNO)

FeNO will be measured at Visit 4a, 4b, 5a and 5b at following timepoints:

- Pre-BAC at Visit 4a and Visit 5a
- Approximately 7 hour post-BAC at Visit 4a and Visit 5a
- Approximately 24 hour post BAC at Visit 4b and Visit 5b.

FeNO to be performed before FEV_1 measurements and sputum induction. The detailed technique for measurement of FeNO will be covered in site standard procedures.

12.1.7 Sputum Analysis

Sputum will be analysed for absolute count, percentage differential count of sputum eosinophils and neutrophils. Sputum will be induced, collected, and processed

- Approximately 7 hour post-BAC at Visit 2b, Visit 4a and Visit 5a,
- Approximately 24 hour post BAC at Visit 2c, Visit 4b and Visit 5b.

The detailed technique of sputum collection and analysis will be covered in site standard procedures.

12.1.8 Biomarkers

Blood sample will be taken and sent to analytical lab for exploratory biomarkers (RASP and endotoxin-induced cytokine release) to be performed at an independent laboratory. Additional details regarding sample processing will be provided in separate lab manual.

Blood samples for biomarkers will be collected at following timepoints:

- Baseline at Visit 2c,
- Per-BAC at Visit 4a and Visit 5a (approximately 1 hour post dose) and
- Approximately 7 hour post-BAC at Visit 4a and Visit 5a.

12.2 Safety Assessments

Safety measurements may be obtained at the discretion of the Investigator in addition to the safety assessments described in this section.

12.2.1 Clinical Laboratory Tests

List of clinical laboratory tests that will be performed at Medical Screening Visit and within 3 days prior to the first dose of study drug is provided below. Additional tests performed at Visit 4a and 5a are also mentioned in the table with asterisk.

CBC with Differential*	Clinical Chemistry	Urinalysis*
• Hemoglobin • Hematocrit • White blood cell count with differential • Red blood cell count • Platelet count	• Blood Urea Nitrogen* • Creatinine * • eGFR to be reported* • Total bilirubin* • Alkaline phosphatase* • AST (also known as SGOT)* • ALT (also known as SGPT)* • Glucose* • Albumin*	• pH • Specific gravity • Protein • Glucose • Ketones • Bilirubin • Blood • Nitrites • Leukocyte esterase

CBC with Differential*	Clinical Chemistry	Urinalysis*
	• Total protein* • Electrolytes (Sodium, Potassium, Chloride, Calcium)* • Lipase* • Amylase* • GGT • CPK • Total cholesterol* • Triglyceride* • TSH	• Microalbuminuria assessment* • Microscopic urine analysis will be done if blood, nitrite and/or leukocyte esterase are present in the chemical urinalysis.

* Will be repeated at Visit 4a and Visit 5a

Urine sample for a pregnancy test will also be collected for WOCBP at Medical Screening Visit, within 3 days prior to the first dose of study drug, at Visit 3, Visit 5b, and ETV.

12.2.1.1 COVID-19 Test (SARS-CoV-2)

Within 5 days of study Visits 2a, 4a and 5a a nasal/nasopharyngeal/oropharyngeal swab will be collected at the clinical site for SARS-CoV-2 testing. Subjects with a positive test result will be excluded/withdrawn from the study.

12.2.2 Demographics and Medical, Surgical and Social History

The demographic data and a complete medical, surgical, and social history will be recorded at the Medical Screening Visit. The following demographic information will be recorded: date of birth, gender, race, ethnicity, height, and weight.

12.2.3 Physical Examination

Physical examinations will be performed as per the Study Schematic (see Section 5). Investigator will report whether findings are normal or abnormal. Additional examinations may be obtained at the discretion of the Investigator(s) and/or designee.

The physical examination at the Medical Screening Visit will consist of assessments of general appearance, skin, head and neck, lymph nodes, thyroid, musculoskeletal/extremities, cardiovascular, lungs, abdomen, and neurological system.

12.2.4 Vital Signs

All vital signs throughout the clinical trial will be measured in a rested (5 minutes) and seated position. Blood pressure, heart rate, respiratory rate and oral temperature will be measured at the Medical Screening Visit, Pre-Treatment Period (Visits 2a, 2b, and 2c), Randomization Visit (Visit 3), Post-Treatment Period 1 and 2 (Visits 4a, 4b, 5a, and 5b) and at the ETV.

12.2.5 Adverse Event Query/Concomitant Medication Query

The staff will record all adverse events observed, queried, or spontaneously volunteered by the subjects. An adverse event/concomitant medication query will be performed as scheduled as per Investigator's direction throughout the study. Subjects will be asked non-leading questions such as "How do you feel now?", "How have you felt since last asked?", or "Have you taken any medication since last asked?" If the presence of any symptom(s), adverse event(s), and/or concomitant medication is recorded, the clinical staff may advise the subjects to remain at the clinic site for safety reasons until the Investigator decides it is safe for the subjects to leave. If the subject decides to leave despite the advice of the Investigator/medical designee, he/she will be asked to sign a waiver.

12.2.6 Paper Diaries

During the study, each subject enrolled will be issued a paper diary including asthma action plan at Visits 2a, 2b, 2c, 3, 4a, 4b, and 5a, to collect the following at-home information as per Schedule of Assessments (see Section 5):

- AEs (pre-treatment and post-treatment)
- Disease symptoms
- Concomitant medication use

Paper diaries will be collected and reviewed at Visits 2b, 2c, 3, 4a, 4b, 5a, 5b, and ETV.

12.2.6.1 Asthma Action Plan

During the study, each patient enrolled will be issued an asthma action plan to monitor asthma symptoms and instruction on when to call the study site if there is any worsening of asthma control. (Refer Appendix 2 for Asthma Action plan). Patients will be instructed to refer to the asthma action plan.

12.2.7 Pharmacokinetic assessment

PK assessments to confirm ADX-629 drug levels in blood will be performed as part of the safety assessment. Blood sample will be collected for PK assessment at 1 hour (+5 min) post dose at Visit 3, Visit 4a and Visit 5a. Details about sample collection, processing, handling, shipment and details regarding laboratory will be mentioned in a separate lab manual.

12.2.8 Electrocardiogram

A 12 lead ECG will be recorded at Screening Visit and at 1 hour (±15 min) post dose on Visit 3, Visit 4a, and Visit 5a. Additional ECGs may be obtained at the discretion of the Investigator(s) or designee.

13. ANALYSES AND REPORTS

13.1 Handling of Dropouts or Missing Data

The rules for handling of dropouts or missing data will be detailed in statistical analysis plan (SAP).

13.2 Final Integrated Report

A final integrated report will be issued to the Sponsor by [redacted] which will be reviewed and released by Cliantha Quality Assurance (QA). It will contain a narrative description of the clinical and statistical procedures used during the conduct of the clinical trial. Appropriate tables and graphs will be created to summarize the data.

The regulatory agency for submission will be Health Canada. The final integrated report may also be included in submissions to other international regulatory agencies.

14. STATISTICAL CONSIDERATIONS

14.1 Statistical Plan

A SAP, detailing the intended statistical analysis of the study data, will be prepared as a separate document and finalized before database lock. Any deviation from the original statistical plan will be described and justified in the final report, as appropriate. The procedure for accounting for missing, unused and spurious data will be included in the statistical analysis plan.

All statistical analysis will be conducted using SAS®, Version 9.4 or higher. Datasets will be prepared using headings from Clinical Data Standards Interchange Consortium (CDISC) Study Data Tabulation Model (SDTM) implementation for human clinical trials and Analysis Dataset Model (ADaM).

14.2 Sample Size Calculation

Based on repeatability analyses[24] in allergen-induced airway inflammation responses, a sample size of 12 subjects yields more than 80% power to detect a difference of 0.1 with standard deviation of 0.1 in change from baseline FEV_1 across treatment groups.

14.3 Analysis Populations

Statistical analysis and data tabulation will be performed using the following analysis populations unless specified otherwise.

- Safety population include all subjects who receive at least one dose of any of the study products will be included in the safety analysis.
- Per-protocol (PP) population include subjects who are randomized and complete both treatments with at least one post-treatment efficacy assessments and who are without any major protocol deviations.

The safety population will be used for safety analyses while PP population will be used for efficacy analyses.

14.4 Statistical Analyses

14.4.1 General Descriptive Statistics

The descriptive statistics for continuous variables will be the mean, median, standard deviation (SD), minimum, maximum, and number of patients. For the log normal data, geometric mean and geometric standard error of the mean (GSEM) will be added.

Frequency distributions for all categorical variables will be presented using counts and percentages.

14.4.2 Efficacy Variables

The following efficacy variables will be summarized by treatment and timepoint using descriptive statistics;

- Change from baseline (within visit*) in forced expiratory volume in one second (FEV_1) to post-BAC (during 0-3 h post-BAC (Key Efficacy Endpoint) and 3-7 h post BAC);
- Absolute count and percentage differential count of sputum eosinophils and neutrophils at approximately 7 h and 24 h post-BAC.
- Allergen-induced shift in airway hyper responsiveness (AHR) as assessed by Methacholine PC_{20} (Mch PC_{20}) post-BAC.
- Change from baseline in fractional exhaled Nitric Oxide (FeNO) at approximately 7 h and 24 h post-BAC.

*Note: At Visit 2a, 4a and 5a, the pre-saline FEV_1 will be considered as Baseline (within-visit) and for efficacy analysis, 7 hour and 24 hour FEV_1 will be compared to the respective visit Baseline FEV_1 value. For example, FEV_1 at 7 hour (Visit 4a) will be compared to Baseline value at Visit 4a.

14.4.3 Exploratory Variables

The following exploratory variables will be summarized by treatment and timepoint using descriptive statistics:

- Biomarkers (RASP and endotoxin-induced cytokine release) pre-BAC (at approximately 1 hour post-dose) and 7 h post-BAC.
- Area under curve (AUC) of FEV1 during 0-3 h post-BAC and/or 3-7 h post BAC

14.4.4 Statistical Analysis of Efficacy Data

Generally, the key efficacy variable may be analyzed using a mixed effect model for repeated measures. The following terms may be included in the model:

- sequence, visit (i.e., period), treatment group, post-BAC assessment time as independent factors, interaction of treatment by post-BAC assessment time
- subject as random effect
- Baseline within each visit as covariate
- If deemed appropriate, additional covariates for FEV1: baseline sputum eosinophil count

AUCs may be analyzed using a mixed effect model with following terms:

- sequence, visit (i.e., period), treatment group
- subject as random effect

Baseline assessment for each period (within visit) will be defined in the SAP.

The other efficacy endpoints may be compared between treatments using appropriate statistical models.

14.5 Safety Analysis

Safety analysis will include adverse events, laboratory assessments, vital signs, and physical examinations are available. They will be tabulated by treatment using appropriate descriptive statistics specified in Section 14.4.1.

Adverse events will be classified using standard Medical Dictionary for Regulatory Activities (MedDRA) terminology Version 22 or higher and presented by treatment group. Summary tables listing the type, date of onset, date and time of resolution, incidence, severity, outcome, action taken, and Investigator's opinion of relationship to the study product will be presented by treatment group for AEs reported after the first dose of study drug.

Concomitant medication used during the study will be tabulated by treatment as well.

14.6 Interim Analyses

No interim analysis is planned at this point.

14.7 Sub-group Analyses

No sub-group analysis is planned at this point.

14.8 Exploratory Analyses

For the exploratory endpoints specified in Section 7.2 of the protocol, they will be tabulated using descriptive statistics specified in Section 14.4.1 as appropriate.

Additional exploratory endpoints may be compared between treatments using appropriate statistical models.

15. ADMINISTRATIVE STUDY RECORDS

15.1 Subject Enrollment and Identification

Patients will be enrolled into the clinical trial prior to any screening procedures being performed. All patients will be assigned a unique subject identification number. This number will be used to

identify their records until they are randomized into treatment groups. Patients who are randomized into the study will be assigned a unique randomization number which will be used to identify their records post-randomization.

15.2 Study Charts/Records and Source Documents

A study chart/record will be maintained on site for each subject to file records such as general observations, medical and medication use history, physical examination, and clinical laboratory data source documents and related documentation. The original record will be considered the data 'source document'. The source documents will be available for inspection (direct/remote) by the study monitors and/or representatives before, during, or upon completion of the clinical trial. Good documentation practices will be followed for source documentation. The Investigator will retain the originals unless otherwise specified in writing by the Sponsor.

All clinical trial data not available via electronic source will be collected by the Investigator and staff and recorded on source documents. The Investigator will assume responsibility for ensuring the completeness and accuracy of all clinical documents.

This clinical trial will be conducted; and the data will be generated, documented (recorded), and reported in compliance to the protocol, GCP standards, ICH, and other applicable local laws and regulations.

All [redacted] staff will be appropriately trained to ensure the collection of accurate, consistent, complete, and reliable data are entered onto an electronic case report form (eCRF) unique for each subject.

This clinical trial will utilize a secure and validated electronic data capture (EDC) system. [redacted] staff will enter the data for each subject into an eCRF with the exception of the data collected in an electronic or paper source (e.g., lab data, biomarker data, etc.). Data source will be described in the Data Management Plan (DMP).

The eCRF will contain edit checks and/or controls to ensure the quality, integrity, accuracy and completeness of the data entered. The Medical Monitor (medical representative) may examine eCRF for preliminary medical review (direct/remote).

The eCRF data will be maintained in a validated study database with an audit trail of all changes that are made to the database, including the reason for the data change. AEs will be coded using a standard dictionary, Medical Dictionary for Regulatory Activities (MedDRA version 22.0 or higher), while concomitant medications will be categorized using the World Health Organization Drug dictionary (the most updated version of the dictionary) at the start of the clinical trial.

Creation and validation of the EDC system and management of the data will be conducted in accordance with Title 21 of the Code of Federal Regulations (CFR) Part 11 and the FDA Guidance for Industry on Computerized Systems used in Clinical Investigations. Methods used to ensure the quality and integrity of the data will be documented in the DMP, which will be approved by Data Management provider and the Sponsor.

15.3 Retention and Availability of Investigational Records

All drug accountability records, case report forms (CRFs), source data and related regulatory documents must be retained for at least 25 years following completion of the clinical trial.

16. DRUG ACCOUNTABILITY

All study product receipt, inventory, dispensing, dosing, and reconciliation records will be maintained in compliance with federal regulations. The study product will be dispensed to qualified study subjects according to established procedures. At the end of the clinical trial (after the database has been locked) all used and unused study product, other than that which has been randomly selected for retention samples (if applicable), will be returned to Sponsor or designee.

16.1 Product Shipment

The drug supplies for this study will be shipped to:

[redacted]

16.2 Product Receipt

Upon receipt of drug supplies, the Investigator or designee will conduct an inventory and record the date received and the amount of drug received. If multiple containers of the test and/or reference products are received, the products will be randomized to dispensing inventory and retention inventory (if applicable).

Any remaining and unused investigational products (excluding reserve samples, where applicable) will be returned to the Sponsor for disposal or otherwise stored or disposed of as determined and agreed upon by the Sponsor and [redacted]

16.3 Product Storage

[redacted] The Investigator will be responsible for maintaining accurate records of drug receipt, dispensing, and return. At the end of the clinical trial, all partially used and unused study product will be returned to Sponsor.

16.4 Drug Dose Package Labeling

The study medication will be packed in individual subject's kits and labeled with study specific labels. Labels will reflect appropriate dosing and storage information, the use for the investigational purpose only, plus a unique number that will be used to assign the medication to the subject according to their randomized treatment assignment.

16.5 Reserve Samples (if applicable)

It is the responsibility of the Sponsor to ship a sufficient number of dosage units to allow the clinical research facility to maintain an appropriate sampling on-site as per applicable regulatory requirements.

Reserve samples will be handled according to the applicable regulations.

17. SUBJECT SAFETY MONITORING AND ADVERSE EVENTS

17.1 Subject Safety Monitoring

Study staff will monitor the subjects throughout the clinical trial. Between the time interval of the study periods, staff will be available for subject queries. The Investigator will be on-call throughout duration of the clinical trial. Either an Investigator or a suitably medically qualified designee must be onsite during methacholine and bronchial allergen challenges. All required medications to manage anaphylaxis, severe asthma and other potentially life threatening emergencies are available at site.

The Sponsor will designate qualified individuals to maintain a close liaison with the Investigator and study staff to ensure the clinical investigation follows the approved protocol and the research intent of GCP. Internal Standard Operating Procedures (SOPs) for compliance with applicable government regulations will also be applied. This liaison will be documented by personal and/or telephone visits prior to study initiation and during the clinical trial to enable periodic reviews as well as clarify any questions, which may arise during the clinical trial. During on-site visits, Sponsor study monitors will be provided access to all study source documents to ensure the integrity of the data. Direct/remote access to such data during the inspection or audits/monitoring of the study will be provided to IRB, Sponsor/ its representatives and regulatory authorities, but they must agree to respect the confidentiality of the data.

17.1.1 Pregnancy

Any female with a confirmed positive pregnancy result during study participation (from the time of signing the informed consent form until the end of the clinical trial) will be excluded from the clinical trial or immediately withdrawn from the clinical trial. Because of the possibility that the fetus/embryo could have been exposed to the study drug through the parent and for the subject safety, the subject will be followed until the end of the pregnancy (including spontaneous or voluntary termination).

If a subject becomes pregnant or suspects that they became pregnant during the clinical trial, or within 30 days after the study is complete, they must notify clinical site.

The pregnancy will be recorded on a Pregnancy form (provided by the clinical site or the Sponsor) and reported to the Sponsor and IRB. In the absence of a pregnancy form, an adverse event form can be used.

Attempts to contact the subject to inquire about the status and progression of the pregnancy will be made at intervals deemed appropriate (e.g., at least every three months) until an outcome of the pregnancy is known. This contact will be documented.

17.2 Adverse Events

An adverse event (AE) is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. AEs may include any changes in physical examination or laboratory parameters that are, in the Investigator's opinion, clinically significant changes.

An SAE is defined as any AE that, in the view of either the Investigator or Sponsor, results in any of the following outcomes:

- Death
- A life-threatening AE
- In-patient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Life threatening AE:	Any AE that places the subject, in the view of either the Investigator or Sponsor, at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.
Unexpected AE:	Any AE not listed in the applicable product information (e.g., drug product label or investigator's brochure) or that is not listed at the specificity or severity that has been observed.

"Unexpected," as used in this definition, also refers to AEs that are mentioned in the applicable product information as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation. If such an unexpected AE is suspected to be related to the drug then it is known as "Suspected Unexpected Serious Adverse Reactions (SUSARs)".

17.2.1 Recording Adverse Events

The staff will record all AEs observed, queried, or spontaneously volunteered by the subjects (regardless of seriousness or relationship to study treatment) in the appropriate section of the subject's case report form or source documents. Subjects experiencing AEs (including those

withdrawn from the study due to an AE) will be followed until recovery to a satisfactory state, or stabilization, or appropriate outcome is established as judged by the Investigator.

The following details will be recorded for AEs:

- Description of event/symptom
- Onset date and time of event
- End date and time of event
- [redacted]

  [redacted]

  [redacted]

  [redacted]

- Action taken with study treatment noted as follows:
  - Dose not changed
  - Dose reduced
  - Drug interrupted
  - Drug withdrawn
  - Not applicable
  - Unknown
- Any other action taken (such as concomitant medication, non-drug therapy, hospitalization or none)
- Outcome of AE noted as follows:
  - Fatal
  - Not recovered/not resolved
  - Recovered/resolved
  - Recovered/Resolved with sequelae
  - Unknown
- Causality noted as follows:

Related:	A causal relationship between the study treatment and the AE is a reasonable possibility.
Not Related:	A causal relationship between the study treatment and the AE is not a reasonable possibility.

17.2.2 Reporting Serious Adverse Events

AEs and medical history will be coded and classified according to the MedDRA and AEs will be reported with respect to severity, duration, relationship to study drug(s) and action taken. Concomitant medications will be categorized using the World Health Organization Drug dictionary (the most updated version of the dictionary) at the start of the study.

All serious adverse experiences, whether deemed drug-related or not, will be reported to the sponsor preferable by email (or by telephone if email is not possible) immediately after the awareness by Investigator and in no case later than 24 hours, followed by a written report within 2 working days. The investigator is responsible for following all local regulations for the reporting of safety information, including the reporting of SAEs to their local IRB/REB/IEC.

The investigator must promptly report to his or her local IRB/REB/IEC all unanticipated problems involving risks to subjects. This includes death from any cause and all serious adverse events reasonably or possibly associated with the use of investigational product.

The Sponsor or their designee is responsible for appropriate reporting of relevant AEs, suspected unexpected serious adverse reactions (SUSARs) involving investigational product, to all regulatory authorities as per the below timeline:

- When neither fatal nor life-threatening, within 15 days after becoming aware of the information
- When fatal or life-threatening, immediately when possible and, in any event, within seven (7) days after becoming aware of the information
- Within eight (8) days after having informed HC of the ADR, submit a report that includes an assessment of the importance and implication of any findings

In addition, the Sponsor or designee will be responsible for the submission of safety letters (e.g., SUSARs) to the central IRB/REB/IEC and to participating investigators of all SUSARs involving IP according to applicable regulations.

After termination of the clinical trial (determined as last subject, last visit), any unexpected safety issue that changes the risk-benefit analysis and is likely to have an impact on the subjects who have participated in it, will be reported by the Sponsor as soon as possible to the competent authority(ies) concerned together with proposed actions.

The following sponsor representative is to be contacted immediately following the occurrence of a SAE:

[redacted]

17.2.3 Removal of Subjects from Clinical Trial

Subjects will be advised that they are free to withdraw from the clinical trial at any time for any reason or, if necessary, the Investigator may withdraw a subject from the clinical trial to protect the health of that subject. A subject may also be withdrawn for not complying with study procedures. The clinical report will include all reasons for early withdrawals.

All subjects who receive at least one dose of any of the study products will be included in the safety analysis. If a subject terminates from the clinical trial early, all efforts will be made to complete the ETV. In case of early termination the Investigator will fully document the reason for early termination. Reasons for early termination may include the following:

- Voluntary withdrawal by subject.
- Significant AE that led the Investigator or subject to withdraw for safety reasons.
- Non-compliance with protocol requirements (e.g., use of restricted medication, not following dosing procedures, failure to make scheduled study visits in a timely fashion).
- Pregnancy
- Significant worsening of asthma (require corticosteroids including inhaled, oral or parenteral to treat an asthma exacerbation, any subject that meets the criteria for the Red Zone as per Asthma Action Plan [Refer Appendix 2]) such that the Investigator and/or subject believes it is in the best interest of the subject to withdraw from the study and be provided alternative treatment.
- Participant enrolls in another clinical trial, or is found to have previously enrolled in this clinical trial.
- Positive COVID-19 test result.

17.2.4 Termination of Study Due to Adverse Events

If, in the opinion of the Investigator, Sponsor, Regulatory authorities or the IRB, the incidence and severity of AE(s) outweighs the benefit of continuing the clinical trial, the clinical trial may be terminated. In the event this course of action is to be pursued, the Investigator will make every attempt to communicate with the Sponsor prior to the decision to develop a complete plan of action and to assess outcomes.

18. ETHICS OF CONDUCT

This clinical trial will be conducted in compliance with the protocol and in accordance with the appropriate guidelines and all applicable federal government codes, acts and regulations, the

ethical pricinples that have their origins in the Declaration of Helsinki and all amendments, Good Clinical Practice (GCP) requirements, The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidance E6 (R2) on Good Clinical Practice, and Tri-Council Policy Statement (Canada).

19. QUALITY CONTROL AND QUALITY ASSURANCE

[redacted] will implement and maintain quality control procedures to ensure that the study is conducted, and that the data are generated, documented, and reported in compliance with the protocol, GCP and applicable regulatory documents.

- All participant data relating to the clinical trial will be recorded on electronic CRF unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must permit study-related monitoring, audits, IRB/REB/IEC review, and regulatory agency inspections and provide direct/remote access to source data documents.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol, written SOPs, study specific plans and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Separate risk management plan will be developed prior to start of the study in accordance with ICH E6 (R2).

The Sponsor may conduct audit visits at clinical study site to verify adherence to the study protocol, the protection of the rights and well-being of the subjects and the accuracy and completeness of reported study data recorded on the source documentation.

19.1 Pandemic COVID-19 Response Plan

Regulatory authorities have recognized that the Coronavirus Disease 2019 (COVID-19) pandemic may impact the conduct of clinical study. COVID-19 pandemic has created a lot of uncertainty in the current clinical research situation and has put subject's safety, protocol compliance and data validity at high risk.

Due to the COVID-19 pandemic, challenges may arise for clinical study conduct, for example, quarantines of site personnel/study participants, travel limitations, interruptions to the supply chain for the investigational product(s), or other considerations if site personnel or study participants become infected with COVID-19. These challenges may lead to difficulties in

meeting protocol specified procedures, including administration or use of investigational product, housing duration or adhering to protocol specified visits and laboratory/diagnostic testing.

To accommodate these challenges and mitigate safety risks associated with COVID-19, changes may be required from the approved protocol which include (but are not limited to) conducting the clinical trial in multiple groups, change in study procedures timing, change in subject's housing duration; ambulatory visits, additional test or parameter may be performed to standard inclusion or exclusion criteria at the discretion of Investigator/designee, etc. The changes made to the procedure will prioritize subject's safety and data validity and integrity. For any significant change, as per regulatory guidelines, a planned protocol deviation will be filed and notified to IRB and/or local regulatory (as applicable).

All participants will be pre-screened prior to enrolment into the clinical trial and evaluated for risk factors and symptoms of COVID-19 according to the most recent regional Public Health guidelines[25] available at the time of pre-screening. The screening is conducted through telephone at the time of appointment confirmation and again when the subject arrives at the clinic for any visit.

Additional health checks including body temperature or other vital sign monitoring, etc. may be performed during the clinical trial at the discretion of Investigator/designee, even if not specified in the protocol. Subject who has tested positive to COVID-19 during the study will be withdrawn from the clinical trial. This subject and other subjects in close contact will be handled as per applicable local Public Health Guidelines.

As the science and regulations are continuously being adapted to the evolving information around the pandemic, additional measures apart from the ones mentioned here may be undertaken to ensure subject safety and appropriate study conduct. The IRB and sponsor would be informed for their review and approval as applicable.

Risk Mitigation plan/Risk Evaluation and Mitigation strategy will be made to minimize the risk for COVID-19 exposure and to handle possible situations during the COVID-19 pandemic.

20. REGULATORY

20.1 Institutional Review Board/Health Canada

The Investigator agrees to provide the IRB with all appropriate material, including a copy of the protocol, consent document, and advertising text (if study-specific advertising is used). The clinical trial will not be initiated without written IRB approval of the research plan and consent document. Copies of the IRB approval will be forwarded to the Sponsor. The Investigator will provide appropriate reports on the progress of this study to the IRB and Sponsor in accordance with applicable government and/or Institute regulations and in agreement with Sponsor policy. The IRB will be informed of any modifications of the protocol or consent document. Approval in writing will be obtained from the IRB prior to implementation of any changes which may increase subject risk or which may alter the validity or objectives of the data collected. A copy of the IRB approval letter covering such alterations will be furnished by the Investigator to the Sponsor. For modifications to the protocol which are administrative in nature, or do not affect subject risk, the IRB will be notified in writing by the Investigator with a copy provided to the Sponsor.

The Investigator must promptly report to the IRB all unanticipated problems involving risks to subjects. This includes AEs and other types of problems (i.e., AEs are a subset of unanticipated problems) that the investigator is required to report to IRB.

Sponsor should submit a notification to Health Canada indicating that the clinical trial is complete.

20.2 Consent Document

A properly executed, written consent in compliance with current federal codes, GCP, acts and regulations and in accordance with ICH Guidance E6 (R2) on GCP shall be obtained from each subject prior to entering the trial or prior to performing any unusual or non-routine procedure involving risk to the subject. A copy of the consent document(s) to be used may be reviewed and approved by the Sponsor. It will be submitted by the Investigator to the IRB for review and written approval prior to the start of the study. The Investigator shall provide a copy of the consent to the subject and a signed copy shall also be maintained in the study records. Attention is directed to the basic elements required in the consent document under current federal regulations for Protection of Human Subjects:

1. A statement verifying the study involves research, an explanation of the purposes of the research, the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental.
2. A description of any reasonably foreseeable risks or discomforts to the subject.
3. A description of any benefits to the subject or to others which may reasonably be expected from the research.
4. A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject.
5. A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained and noting the possibility the applicable regulatory agencies and the study Sponsor may inspect the records.
6. For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained.
7. An explanation of whom to contact for answers to pertinent questions about the research and research subject's rights and whom to contact in the event of a research-related injury to the subject.
8. A statement that participation is voluntary and refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled; and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

Additional elements of consent, if appropriate, must be provided to the subject:

1. A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable.
2. Anticipated circumstances under which the subject's participation may be terminated by the Investigator without regard to the subject's consent.
3. Any additional costs to the subject that may result from participation in the study.
4. The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.
5. A statement that significant new findings developed during the course of the research that may relate to the subject's willingness to continue participation will be provided to the subject.
6. The approximate number of subjects involved in the study.

When seeking informed consent for applicable clinical trials, a statement may be provided to the subject that clinical trial information has been or will be submitted for inclusion in the clinical trial registry databank, if applicable.

20.3 Confidentiality

All information disclosed to the Investigator by the Sponsor, or Sponsor designees, shall be treated by the Investigators as strictly confidential. The Investigator will only use this information for the purpose of conducting the clinical trial described within this protocol. The Investigator must agree not to disclose any information contained within this protocol to any third party, except to those involved in the conduct of this clinical study and who are bound by the obligations of confidentiality.

Information concerning the study treatment, patent applications, processes, unpublished scientific data, and other pertinent information is confidential and remains the property of the Sponsor. Details should be disclosed only to those involved in the approval or conduct of the study. It is understood that the Investigator will use the information obtained during the clinical study in connection with the development of the treatment and therefore may disclose it as required to regulatory agencies. The Investigator understands that he has an obligation to provide the Sponsor with all data obtained during the study.

20.4 Investigator's Statement

The Investigator agrees to conduct the trial as outlined in the approved protocol and in accordance with the Sponsor's guidelines and all applicable federal government codes, acts and regulations, GCP requirements, and ICH guidance E6 (R2) on Good Clinical Practice. These GCP guidelines include, but are not limited to:

1. Permission to allow the Sponsor or applicable regulatory agencies to inspect study facilities and pertinent records at reasonable times and in a reasonable manner that ensures subject confidentiality. If this study is to be inspected by a regulatory agency, the Sponsor will be notified as soon as possible.

2. Submission of the proposed clinical investigation, including the protocol, consent document, and advertising text (if study-specific advertising is used) to a duly constituted IRB for approval and acquisition of written approval for each, prior to study initiation.
3. Use of a written consent document obtained prior to entry into the study or prior to the performance of any non-routine procedures that involve subject risk. The consent document(s) must contain all the elements as specified in the federal regulations and which has been previously approved by the Sponsor and the IRB.
4. Submission of any proposed change in or deviation from the protocol to the IRB, using a signed formal amendment document prepared by the Sponsor and/or Investigator. If the change or deviation increases risk to the study population, or adversely affects the validity of the clinical investigation or the subject's rights, IRB approval must be obtained prior to implementation. IRB will be notified regarding changes that do not involve risk or affect the validity of the investigation or the subject's rights.
5. Documentation and explanation of protocol deviations will be made on the appropriate case report form page, source document or by written documentation to the Sponsor.
6. The Investigator shall promptly report to the Sponsor any severe adverse event that may reasonably be regarded as caused by, or probably caused by, the study treatments.
7. The Investigator shall submit timely progress reports to the IRB and Sponsor at appropriate intervals, but not to exceed one year. The final report will be submitted to the IRB within 4 months after study completion, termination, or discontinuation.
8. The Investigator and study staff shall maintain accurate source documents from which case report form data or source documents are based and accountability records which show the receipt and disposition of all test article(s) shipped to the Investigator by the Sponsor.
9. When new information is relevant to participants' welfare, Investigator must promptly inform all participants to whom the information applies that requires to be reported to Health Canada as well.

The Investigator agrees that all information provided by the Sponsor (including pre-clinical data) protocols, case report form data or source documents, and verbal and written information, will be kept strictly confidential and confined to the personnel involved in conducting the trial. It is recognized this information may be given in confidence to the IRB.

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22. APPENDICES

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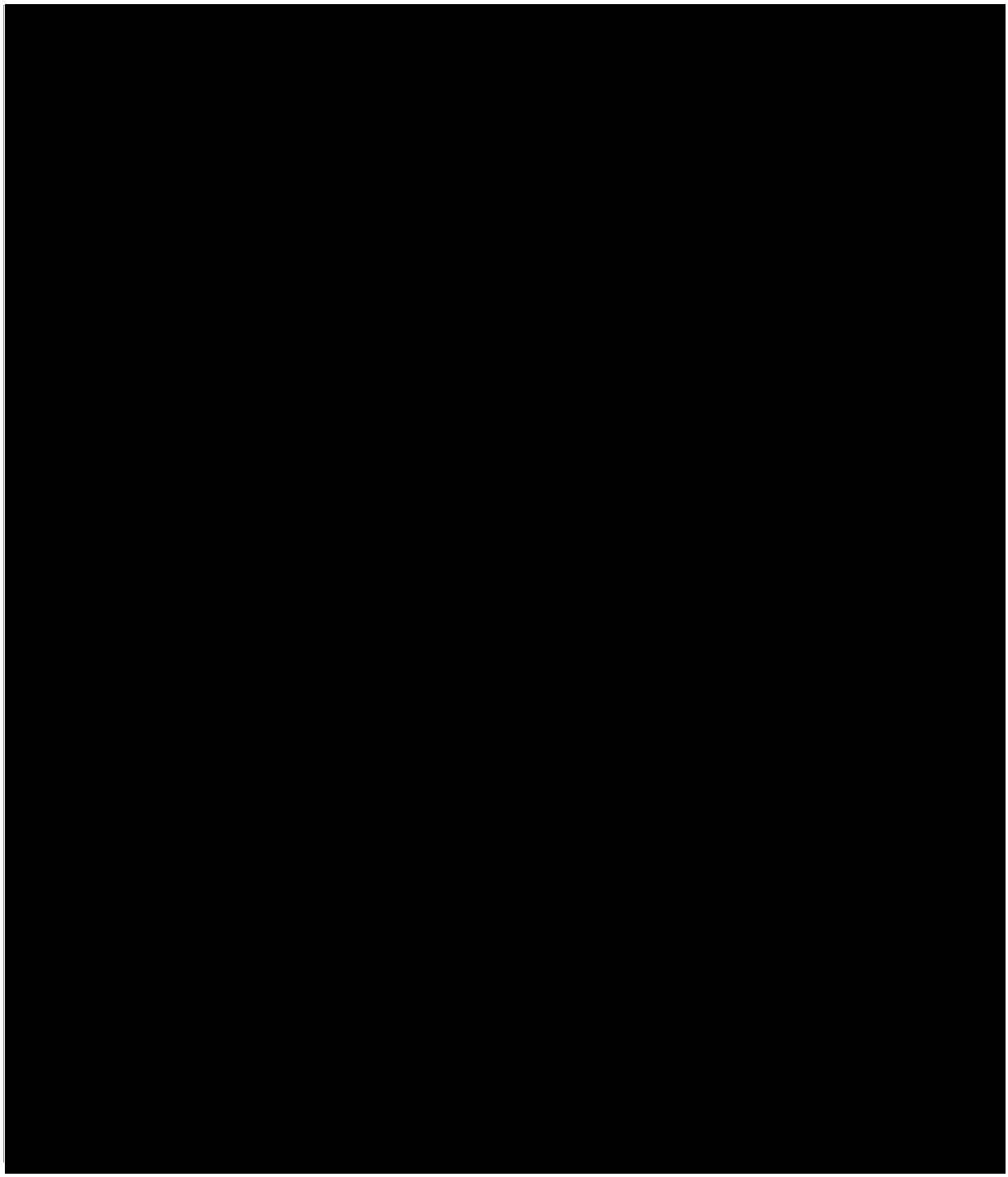
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Appendix 2: Asthma Action Plan

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