

CLINICAL STUDY PROTOCOL

Protocol Number/ID: AR-DEX-22-01

Protocol Title: A randomized, double-blind, placebo-controlled, parallel-group study to assess the efficacy, safety, and tolerability of dexpramipexole administered orally for 52 weeks in participants with severe eosinophilic asthma (EXHALE-2)

Investigational Product: Dexpramipexole tablets for oral use

U.S. IND No.: 122746

EU CT-R No.: 2023-507665-25-00

Development Phase: III

Study Sponsor Areteia Therapeutics, Inc.
[REDACTED]

Medical Monitor [REDACTED]

Protocol Version Amendment 3 (24 Feb 2025)

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By signing below, the Sponsor declares that this study will be conducted in accordance with the current United States Food and Drug Administration Code of Federal Regulations, International Council for Harmonization Good Clinical Practice (ICH-GCP) standards, the Declaration of Helsinki (Brazil 2019), and local and legal requirements.

Name:

Title:

{See appended electronic signature page}

INVESTIGATOR SIGNATURE PAGE

By signing below, the investigator agrees to adhere to the clinical study protocol as written and agrees that any changes to the protocol must be approved by Sponsor before seeking approval from the Institutional Review Board (IRB) / Ethics Committee (EC).

The study will be conducted in accordance with the current International Council for Harmonization (ICH) and the guidelines Good Clinical Practice (ICH-GCP) standards, the Declaration of Helsinki (Brazil 2019), and local, ethical and regulatory requirements.

The information contained in this clinical study protocol is proprietary and provided to me in confidence and may not be disclosed to any other party, in any form, without prior authorization from the Sponsor, except to the extent necessary for the conduct of the study at this study site.

Principal Investigator:

Signature

Date

Print name

Institution Name / Site number

PROCEDURES IN CASE OF AN EMERGENCY

Emergency Contact Information

Role in Study	Name	Telephone Number
24-Hour Emergency Contact*	US/Latin America All other world regions	

PROTOCOL SYNOPSIS

Protocol number:	AR-DEX-22-01
Protocol Title:	A randomized, double-blind, placebo-controlled, parallel-group study to assess the efficacy, safety, and tolerability of dexpramipexole administered orally for 52 weeks in participants with severe eosinophilic asthma (EXHALE-2)
Investigational Product:	Dexpramipexole tablets for oral use
Name of Active Ingredient:	Dexpramipexole dihydrochloride
Indication:	Severe eosinophilic asthma
Phase of Development:	III
Study Rationale:	The results from the Phase II dose finding study with dexpramipexole in moderate to severe asthma (EXHALE-1) include significant, dose-dependent, and durable reductions of eosinophils in blood and airways. In addition, clinically meaningful, placebo-corrected, change from baseline in pre-bronchodilator (pre-BD) forced expiratory volume in 1 second (FEV₁) were observed across the dose groups at various timepoints. The safety and tolerability profile of dexpramipexole in this Phase II study was similar to placebo and supports advancing the program into Phase III. The selected doses of 75 mg and 150 mg twice daily (BID) are supported by the safety and efficacy data from the completed Phase II asthma study (EXHALE-1) along with the safety data from the Phase II and III amyotrophic lateral sclerosis studies. These doses have the potential to maintain a clinically meaningful reduction in eosinophils, which should lead to a significant reduction in severe asthma exacerbations. The objective of this clinical study is to investigate the safety, tolerability, and efficacy of dexpramipexole in participants with inadequately controlled severe eosinophilic asthma.
Study Design:	This is a Phase III, randomized, double-blind, placebo-controlled, parallel-group, multicenter study.
Study Assessments:	Efficacy: Severe asthma exacerbations, asthma control, pulmonary function, and quality of life.

	Pharmacokinetics: Plasma samples from each participant to measure drug concentrations, drawn prior to and 2 hours post investigational drug dosing. Biomarkers: Blood eosinophil count. Safety: Physical examination; vital signs (systolic and diastolic blood pressure, respiratory rate, pulse, and temperature); body weight; 12-lead electrocardiogram (ECG); clinical laboratory evaluations (hematology, blood chemistry, and urinalysis); pregnancy testing; adverse event (AE) monitoring; and concomitant medication monitoring throughout the study.
Study Objectives:	Primary Objective - To demonstrate the efficacy of dexpramipexole in reducing severe asthma exacerbations. Secondary Objectives - To demonstrate the efficacy of dexpramipexole on pulmonary function. - To demonstrate the efficacy of dexpramipexole on asthma control and quality of life - To evaluate the effect of dexpramipexole on blood eosinophils. Exploratory Objectives - To evaluate the kinetics of blood eosinophil lowering. - To examine the relationship between dexpramipexole exposure and severe asthma exacerbations and other efficacy parameters. Safety Objective - To evaluate the safety and tolerability of dexpramipexole administered for 52 weeks in participants with eosinophilic asthma.
Study Endpoints / Estimands:	Primary Endpoint - Annualized rate of severe asthma exacerbations (AAER) over 52 weeks. Primary Estimand Population: Patients with inadequately controlled asthma, on GINA 2021 Step 4 or 5 therapy with baseline AEC $\geq 0.30 \times 10^9/L$ [high strata] with a history of at least two asthma exacerbations requiring treatment with systemic corticosteroids within the past 12-months. Treatment of interest: Dexpramipexole 150 mg and Dexpramipexole 75 mg administered BID. Each dose level will be compared to placebo. Outcome variable: Annualized rate of severe asthma exacerbation events over 52 weeks. Intercurrent events:

	○ <u>Treatment discontinuation for any reason:</u> treatment policy strategy, i.e., participants who discontinue treatment will be encouraged to continue with study visits and all exacerbation events occurring up to end of Week 52 will be included in the analysis. ○ <u>Systemic corticosteroids use:</u> composite strategy, i.e., intake of systemic corticosteroids is part of the definition of asthma exacerbation. ○ <u>Start of biological therapy (precluding observation of any further exacerbation event over the 52-week period from start of treatment):</u> while-on-treatment. The exacerbations happening after the start of biological therapy are discarded. Instead, the number of exacerbations until the start of biological therapy will be included in the analysis, and the observation duration will be defined as the time from randomization to the date of the start of biological therapy. ○ <u>Death (precluding observation of any further exacerbation event over the 52-week period from the start of treatment):</u> while-on-treatment. The number of exacerbations until death will be included in the analysis, and the observation duration will be defined as the time from randomization to the date of death. • <u>Population-level summary measure:</u> Ratio (dexpramipexole 150 mg [respectively 75 mg] BID over placebo) of mean annualized exacerbation rates. <i>Key Secondary Endpoints</i> • Pre-BD FEV₁, absolute change from baseline, averaged across visits at Weeks 36, 44, and 52. • Asthma Control Questionnaire-6 (ACQ-6), change from baseline, averaged across visits at Weeks 36, 44, and 52. • Standardized version of the Asthma Quality of Life Questionnaire for 12 years and older (AQLQ+12) change from baseline to Week 52. <i>Other Secondary Endpoints:</i> • Annualized rate over 52 weeks of severe exacerbations requiring an emergency department (ED) visit or hospitalization. • Annualized rate of severe asthma exacerbations from Week 4 to Week 52. • Absolute eosinophil counts (AEC), change from baseline, averaged across visits at Weeks 36, 44, and 52 • Forced vital capacity (FVC), change from baseline, averaged over Weeks 36, 44, and 52 • FVC, change from baseline at Weeks 4, 12, 20, 28, 36, 44, and 52. • Post-bronchodilator FEV₁, change from baseline to Week 52 • Peak expiratory flow (PEF), change from baseline to Week 52 • Time to first severe asthma exacerbation • Total asthma symptom score, change from baseline to Week 52 • The EuroQol five-dimensional questionnaire (EQ-5D-5L) change from baseline to Week 52
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	Exploratory Endpoints - Correlation between dexpramipexole exposure and severe asthma exacerbations and other efficacy parameters - Pre-BD percent predicted FEV₁ in participants ages 12-17 years of age, absolute change from baseline, averaged across visits at Weeks 36, 44, and 52. Safety Endpoints The safety endpoints of this study are measured by the following assessments: physical examination; vital signs (systolic and diastolic blood pressure, respiratory rate, pulse, and temperature); body weight; 12-lead ECG; clinical laboratory evaluations (hematology, blood chemistry, and urinalysis); pregnancy testing; AE monitoring; and concomitant medication monitoring throughout the study.														
Number of planned participants:	Approximately 1395 participants (465 per treatment arm). Participants will be stratified (AEC $\geq 0.30 \times 10^9/L$ [high] and $< 0.30 \times 10^9/L$ [low]) according to their highest screening AEC value (in the event of multiple values). The proportion of participants in the high versus low eosinophil strata will be 2:1. Accordingly, within each arm, the target number of participants will be 310 in the high eosinophil stratum and 155 participants in the low eosinophil stratum.														
	<table><tr><th rowspan="2">Study arm</th><th colspan="2">Target number of participants</th></tr><tr><th>High eosinophil stratum</th><th>Low eosinophil stratum</th></tr><tr><td>Placebo</td><td>310</td><td>155</td></tr><tr><td>Dexpramipexole 75 mg BID</td><td>310</td><td>155</td></tr><tr><td>Dexpramipexole 150 mg BID</td><td>310</td><td>155</td></tr></table>	Study arm	Target number of participants		High eosinophil stratum	Low eosinophil stratum	Placebo	310	155	Dexpramipexole 75 mg BID	310	155	Dexpramipexole 150 mg BID	310	155
Study arm	Target number of participants														
	High eosinophil stratum	Low eosinophil stratum													
Placebo	310	155													
Dexpramipexole 75 mg BID	310	155													
Dexpramipexole 150 mg BID	310	155													
Study Locations:	Approximately 300 sites in multiple regions														
Study Population:	The study will include participants with inadequately controlled severe asthma, aged ≥ 12 years, on Global Initiative for Asthma (GINA) 2021 Step 4 or 5 therapy. Note: enrollment of participants of 12-17 years of age is closed.														
Inclusion criteria:	To be eligible to participate in this study, candidates must meet the following eligibility criteria at Screening Visit 1 or at the timepoint specified in the individual eligibility criterion listed below: - Signed informed consent form and assent form, as appropriate. - Male or female ≥ 18 years of age at Screening Visit 1. Asthma-related criteria - Documented physician diagnosis of asthma for ≥ 12 months prior to Screening Visit 1. - Treatment of asthma, participants must satisfy <u>all</u> the below (items a to c): - Participants who have received asthma controller medication with medium or high dose inhaled corticosteroids (ICS; ≥ 500 $\mu g/day$ fluticasone propionate dry powder formulation daily or clinically														

	comparable, per GINA 2021) on a regular basis for at least 12 months prior to Screening Visit 1. Equivalent medium and high dose ICS doses are detailed in Appendix C b. Documented treatment with a stable dose of either medium or high dose ICS for at least 3 months prior to Screening Visit 1. The ICS may be contained within an ICS/long-acting β_2 agonist (LABA) combination product. As noted in Section 5.2.2, daily oral corticosteroids are an allowed concomitant medication; participants on daily oral corticosteroids must be on a stable dose for 3 months before Screening Visit 1. c. Use of one of more additional daily maintenance asthma controller medications according to standard practice of care is required; eg, LABA, leukotriene antagonist, theophylline, long-acting muscarinic antagonists, cromolyn/nedocromil. Use of a stable dose of any additional asthma controller medications must be documented for at least 3 months prior to Screening Visit 1. 5. Pre-BD FEV₁ $\geq 40\%$ and $< 80\%$ of predicted at Screening Visit 2. 6. Variable airflow obstruction documented with at least one of the following criteria: - Bronchodilator reversibility at Screening Visit 2, as evidenced by $\geq 12\%$ and ≥ 200 mL improvement in FEV₁, 15 to 30 minutes following inhalation of 400 μg (four puffs) of albuterol/salbutamol. Participants who do not meet the bronchodilator reversibility inclusion criterion but have $\geq 10\%$ and ≥ 160 mL reversibility, may repeat the reversibility spirometry assessment once during the Screening period, at an unscheduled visit at least 7 days prior to baseline. - Bronchodilator reversibility, using the criteria above, documented in the past 24 months prior to Screening Visit 1 or during screening. - Peak flow variation of $\geq 20\%$ over a 2-week period, documented in the past 24 months prior to Screening Visit 1 or during screening. - Airflow variability in clinic FEV₁ $\geq 20\%$ between two consecutive clinic visits, documented in the past 24 months prior to Screening Visit 1 or during screening. - Airway hyperresponsiveness (provocative concentration causing a 20% fall in FEV₁ of methacholine < 8 mg/mL, or other clinically relevant bronchoprovocation testing) documented in the past 24 months prior to Screening Visit 1. 7. ACQ-6 ≥ 1.5 at Screening Visit 2. 8. Documented history of at least two asthma exacerbations requiring treatment with systemic corticosteroids (intramuscular, intravenous, or oral) within the past 12-month period prior to Screening Visit 1.
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	General medical history 9. Negative urine pregnancy test for women of childbearing potential (WOCBP; after menarche) at the Screening Visit 2 and Baseline Visit. 10. WOCBP must use either of the following methods of birth control, from Screening Visit 1 through the End of Study Visit: a. A highly effective form of birth control (confirmed by the investigator). Highly effective forms of birth control include: true sexual abstinence, a vasectomized sexual partner, Implanon, female sterilization by tubal occlusion, any effective Intrauterine device (IUD), IUD/intrauterine system (IUS), Levonorgestrel Intrauterine system, or oral contraceptive. - Or b. Two protocol acceptable methods of contraception in tandem. Women <u>not</u> of childbearing potential are defined as women who are either permanently sterilized (hysterectomy, bilateral oophorectomy, or bilateral salpingectomy), or who are postmenopausal. Women will be considered postmenopausal if they have been amenorrheic for ≥ 12 months prior to the planned date of the Baseline Visit without an alternative medical cause. The following age specific requirements apply: a. Women < 50 years old would be considered postmenopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatment and follicle stimulating hormone levels in the postmenopausal range. b. Women ≥ 50 years old would be considered postmenopausal if they have been amenorrheic for 12 months or more following cessation of all exogenous hormonal treatment.
Exclusion criteria:	Study participant candidates will be excluded from study entry if any of the following exclusion criteria exist at Screening Visit 1 or at the timepoint specified in the individual criterion listed below: Asthma-related criteria 1. A participant who experiences a severe asthma exacerbation (defined as a deterioration of asthma that results in emergency treatment, hospitalization due to asthma, or treatment with systemic corticosteroids) at any time from 4 weeks prior to Screening Visit 1. Participants who experience an asthma exacerbation during the Screening/Run-in Period may remain in screening and proceed with study visits 14 days after they have completed their course of oral steroids or returned to their pre-Screening Visit maintenance dose of oral steroids and the investigator considers participant has returned to baseline status. 2. Current diagnosis of diseases which may confound interpretation of this study's findings such as allergic bronchopulmonary aspergillosis, eosinophilic granulomatosis with polyangiitis, eosinophilic gastrointestinal diseases, hypereosinophilic syndrome, chronic obstructive pulmonary disease, idiopathic pulmonary fibrosis.

	3. Respiratory infection: Upper or lower respiratory tract, sinus, or middle ear infection within the 4 weeks before Screening Visit 1. 4. For participants aged 12 to 17 years old, AEC of $<0.15 \times 10^9/L$ at Screening Visit 1. • Note: Enrollment of participants of 12-17 years of age is closed. Prohibited medications/procedures 5. Treatment with a biologic investigational drug in the last 5 months prior to Screening Visit 1. Treatment with non-biologic investigational drugs in the previous 30 days or five-half-lives prior to Screening Visit 1, whichever is longer. Treatment with GSK3511294 (long-acting anti-IL-5) in the past 12 months. 6. Treatment with any of the following monoclonal antibody therapies within 120 days prior to Baseline Visit: benralizumab, dupilumab, mepolizumab, reslizumab, omalizumab, tezepelumab, or tralokinumab. 7. Treatment with pramipexole (Mirapex®) within 30 days of Baseline Visit. 8. Treatment with selected drugs known to have a substantial risk of neutropenia in the past 30 days prior to Screening Visit 1 (see Appendix A). 9. Bronchial thermoplasty procedure in the past 12 months prior to Screening Visit 1 or planned during the coming year. General medical history 10. Weight <40 kg at Screening Visit 2. 11. Current smoking within 12 months prior to Screening Visit 1 or a smoking history of >10 pack-years. Smoking includes tobacco, vaping, and/or marijuana use. 12. Known or suspected alcohol or drug abuse 13. Uncontrolled severe hypertension: systolic blood pressure >180 mmHg or diastolic blood pressure >110 mmHg prior to the Baseline Visit despite anti-hypertensive therapy. 14. History of malignancy that required surgery (excluding local and wide-local excision), radiation therapy and/or systemic therapy during the 5 years prior to the Baseline Visit. 15. History of human immunodeficiency virus (HIV) infection or chronic infection with hepatitis B or C. 16. A helminth parasitic infection diagnosed within 24 weeks prior to Screening Visit 1 that has not been treated with or has failed to respond to standard of care (SoC) therapy. 17. Medical or other condition likely to interfere with participant's ability to undergo study procedures, adhere to visit schedule, or comply with study requirements. 18. Known or suspected noncompliance with medication. 19. Unwillingness or inability to follow the procedures outlined in the protocol.
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	Clinical safety labs 20. Absolute neutrophil count $<2.000 \times 10^9/L$ at Screening Visit 1 or Screening Visit 2. 21. Renal dysfunction, defined as an estimated glomerular filtration rate (eGFR) $<60 \text{ mL/min/1.73m}^2$ at Screening Visit 2 (using the Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] formula [Levey et al, 2009] for age ≥ 18 years at screening. 22. Active liver disease defined as any known current infectious, neoplastic, or metabolic pathology of the liver or unexplained elevations in alanine aminotransferase (ALT), aspartate aminotransferase (AST), $>3 \times$ the upper limit of normal (ULN), or total bilirubin $>2 \times$ ULN at Screening Visit 2 confirmed by a repeat abnormal measurement of the relevant value(s), at least 1 week apart. Cardiac safety 23. History of New York Heart Association class IV heart failure or last known left ventricular ejection fraction $<25\%$. 24. History of major adverse cardiovascular event (MACE) within 3 months prior to the Baseline Visit. 25. History of cardiac arrhythmia within 3 months prior to the Baseline Visit that is not controlled by medication or via ablation. 26. History of long QT syndrome. 27. Corrected QT interval by Fridericia (QTcF) interval $>450 \text{ ms}$ for males and $>470 \text{ ms}$ for females at Screening Visit 2 or QTcF $\geq 480 \text{ ms}$ for participants with bundle branch block. 28. Clinically important abnormalities in resting ECG that may interfere with the interpretation of QTcF interval changes at Screening Visit 2, including heart rate <45 beats per minute (bpm) or $>100 \text{ bpm}$. Pregnancy/Lactation 29. Pregnant women or women breastfeeding. 30. Males who are unwilling to use an acceptable method of birth control during the entire study period (ie, condom with spermicide). Allergy/Hypersensitivity 31. Allergy or hypersensitivity to dexpramipexole or any of its components For this study, rescreening may only be permitted under specific circumstances and only after contact with a Sponsor Clinical representative. Rescreening may be permitted, for example, for a participant who qualified for this study but did not enroll within the protocol prescribed screening period of 28 days due to logistical constraints or for administrative reasons. In addition, rescreening may be appropriate, at investigator and Sponsor discretion, following mild intercurrent illness after the condition has resolved. Otherwise, individuals who do not meet the eligibility criteria for participation in this study (screen failure) may not be rescreened. In case of rescreening, reconsent is required and all screening procedures must be repeated. The participant will be assigned a new screening number. It must be
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	confirmed that participants meet all eligibility criteria under the new screening number and process before progressing to randomization/Day 1. The screening period may be extended after consultation with a medical monitor or a sponsor clinical representative (eg, to accommodate logistical or technical issues).
Study Period:	The estimated study period for this study will be approximately 2.75 years from first participant enrolled to last participant completed.
Duration of Treatment and Follow-up:	The expected duration of each participant's involvement in the study will be a maximum of 14 months (Screening through Follow-up Phase). <u>Study Phases</u> Screening Phase: Screening Visit 1 to Baseline Visit. <u>Screening Visit 1:</u> Participants will undergo screening to assess whether they satisfy the eligibility criteria. <u>Screening Visit 2:</u> Participants will take part in the Run-in Phase (of up to 21 days duration, with a minimum of 14 days) as part of the Screening period, to confirm if their current asthma medication regimen is stable. Treatment Phase: Baseline Visit through completion of Week 52. After the collection of all Baseline assessments, participants will begin investigational treatment (dexpramipexole 75 mg, 150 mg, or placebo), BID for 52 weeks. Participant eligibility will be assessed during the Screening visits and confirmed at the Baseline Visit. The last dose of investigational product will be taken the evening before the Week 52 Visit. The Week 52 Visit is the Primary Outcome Visit for the study. Follow-up Phase: Conclusion of Week 52 assessments through Week 56 Visit. During this phase, participants will have one final phone visit to collect final safety assessments following cessation of investigational product. Participants may choose to continue to the long-term extension study. These participants will transition at the Week 52 Visit and will not complete the Week 56 Visit.
Investigational Product Administrations:	Film coated tablets of dexpramipexole dihydrochloride (75 mg or 150 mg) or matching placebo, administered by mouth BID for 52 weeks Dexpramipexole dihydrochloride 75 mg (dexpramipexole, 56 mg base equivalent) Dexpramipexole dihydrochloride 150 mg (dexpramipexole, 112 mg base equivalent)
Statistical Methods:	<u>Populations</u> The following populations will be used for the analyses: The intention-to-treat population (ITT) will consist of any participant who has been allocated to a randomized treatment regardless of whether the treatment was taken or not.

	• The modified ITT (mITT) population will consist of all randomized participants who received at least one dose of investigational product, irrespective of their protocol adherence and continued participation in the study. Efficacy analyses will be performed in the mITT population and will consider participants in the treatment arm they were randomized to and in the screening AEC stratum as used at randomization. • The safety population will consist of all randomized participants who received at least one dose of investigational product. Participants will be analyzed according to the treatment they received. The primary analysis of the primary endpoint will be performed in the mITT population restricted to the AEC $\geq 0.30 \times 10^9/L$ stratum. <u>Participant allocation method</u> The study will randomize approximately 1395 participants in a 1:1:1 ratio to either dexpramipexole 75 mg BID, dexpramipexole 150 mg BID, or placebo. The randomization will use permuted blocks and will be stratified by region (United States [US] versus ex-US), age (12 to <18 years versus ≥ 18 years), AEC ($< 0.30 \times 10^9/L$ versus $\geq 0.30 \times 10^9/L$). The enrollment into AEC strata will be capped for each treatment arm so that the AEC $\geq 0.30 \times 10^9/L$ stratum represents approximately two-thirds of the study population. The primary and key secondary endpoints for the two doses will be primarily evaluated in the baseline AEC $\geq 0.30 \times 10^9/L$ stratum. In order to maintain strong control of the familywise overall type I error at the two-sided 0.05 level, when testing two doses, primary and key secondary endpoints, the following hierarchical testing procedure will be employed. 1. The primary endpoint (AAER ratio) will first be tested for the 150 mg BID dose versus placebo. If the test of the 150 mg BID dose versus placebo is significant at the $p < 0.05$ level the procedure continues, otherwise it stops. 2. The primary endpoint (AAER ratio) is then tested for the 75 mg BID dose versus placebo. If the tests for both doses are significant ($p < 0.05$) for the primary endpoint versus placebo, then the key secondary endpoints will be tested using a hierarchical procedure using $p < 0.05$ to determine statistical significance. Each hypothesis will be formally tested only if the preceding one is significant at the $p < 0.05$ level. The order for hierarchical testing will be: 3. Absolute change from baseline in pre-BD FEV₁ averaged across visits at Weeks 36, 44, and 52 for dexpramipexole 150 mg BID versus placebo. 4. Absolute change from baseline in pre-BD FEV₁ averaged across visits at Weeks 36, 44, and 52 for dexpramipexole 75 mg BID versus placebo.
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	5. Absolute change from baseline in mean ACQ-6 score averaged across visits at Weeks 36, 44, and 52 for dexpramipexole 150 mg BID versus placebo. 6. Absolute change from baseline in mean ACQ-6 score averaged across visits at Weeks 36, 44, and 52 for dexpramipexole 75 mg BID versus placebo. 7. AQLQ+12 change from baseline to Week 52 for dexpramipexole 150 mg BID versus placebo. 8. AQLQ+12 change from baseline to Week 52 for dexpramipexole 75 mg BID versus placebo. <u><i>Analysis of the Primary Endpoint</i></u> The primary comparison will be performed in randomized participants with baseline AEC $\geq 0.30 \times 10^9/L$ included in the mITT population and will include all severe exacerbations which occurred at any time from randomization to end of Week 52. The AAER will be analyzed using a generalized linear model, assuming the number of exacerbations has a negative binomial probability distribution and that its mean is related to covariate factors with a ‘log link’ function. The logarithm of time on study will be used as an offset variable. The model used for primary comparison will include covariates for: • Fixed class effects: treatment (dexpramipexole 150 mg BID versus dexpramipexole 75 mg BID versus placebo), geographic region (US versus ex-US), age (12 to <18 years versus ≥ 18 years), oral corticosteroids intake as part of SoC asthma therapy (use versus non-use) and baseline AEC ($\geq 0.40 \times 10^9/L$ versus ≥ 0.30 to $< 0.40 \times 10^9/L$); • Continuous linear covariates: natural logarithm of the number of exacerbations in the previous year, baseline percentage of the predicted pre-BD FEV₁. This method assumes that missing data are missing at random (MAR). MAR is assumed for the primary analysis as for participants who discontinue treatment, every effort will be made to obtain continued follow-up. Therefore, all exacerbations will be included in the analysis, including those which occurred after investigational product discontinuation. If a participant stays in study until the end of the 52-week treatment period, all severe exacerbation events observed up to the Week 52 Visit will be included in the primary analysis, regardless of whether the participant maintained the investigational product. If a participant withdraws from study prior to the end of the 52-week treatment period, all observed severe exacerbation events up to the last contact date will be included in the analysis, and the observation duration is defined as the time from randomization to the last contact date.
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	Mean exacerbation rates for each treatment arm and the estimate of the rate ratio will be derived with their 95% confidence interval, based on the primary efficacy model described above. To assess the robustness of primary analysis results towards departures from the underlying assumption, sensitivity analyses, including controlled multiple imputation (including but not limited to Jump-to-Control and Dropout Reason-based imputations) will be performed, allowing for different assumptions to be used. Full details of all sensitivity and supplemental analyses will be specified in the Statistical Analysis Plan (SAP). <u><i>Analysis of Key Secondary Endpoints</i></u> All key secondary endpoints will be evaluated in the baseline $AEC \geq 0.30 \times 10^9/L$ stratum and only the data from that stratum will be used in the models. The absolute change from baseline in pre-BD FEV_1 across visits from Week 36 to Week 52 will be analyzed using a mixed-effect model for repeated measures (MMRM) approach. The model will include change from baseline in FEV_1 values at all post-baseline timepoints up to Week 52 as response variables, and treatment, all factors used at randomization, visit, treatment-by-visit interaction, baseline FEV_1 value, and baseline-by-visit interaction as covariates. All measurements will be included in the model, regardless of any treatment discontinuation, as participants will be encouraged to return to the clinic and to undergo assessment until Week 52. The primary result obtained from the model will be the average of the treatment effects at Week 36, Week 44, and Week 52. The absolute change from baseline in mean ACQ-6 scores across Weeks 36, 44, and 52 will be analyzed using an MMRM approach. The model will include change from baseline in mean ACQ-6 scores at all post-baseline timepoints up to Week 52 as response variables, and treatment, baseline mean ACQ-6 score, all stratification factors used at randomization, visit, treatment-by-visit interaction as covariates. All measurements will be included in the model, regardless of any treatment discontinuation, as participants will be encouraged to return to the clinic and to undergo assessment until Week 52. The absolute change from baseline in mean AQLQ+12 scores to Week 52 will be analyzed using an MMRM approach. The model will include change from baseline in mean AQLQ+12 scores at Week 28 and Week 52 as response variables, and treatment, baseline mean AQLQ+12 score, all stratification factors used at randomization, visit, treatment-by-visit interaction as covariates. All measurements will be included in the model, regardless of any treatment discontinuation, as participants will be encouraged to return to the clinic and to undergo assessment until Week 52. The analyses of the primary and key secondary endpoints will be performed in the $AEC < 0.30 \times 10^9/L$ stratum using the same methods as described for the AEC
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	$\geq 0.30 \times 10^9/L$ stratum, with the exception that the adjustment for baseline AEC values will be $< 0.15 \times 10^9/L$ versus ≥ 0.15 to $< 0.30 \times 10^9/L$. These analyses will be used for descriptive purposes only. The analyses of the primary and key secondary endpoints will be repeated for the overall mITT ie, combining the baseline AEC $\geq 0.30 \times 10^9/L$ and $< 0.30 \times 10^9/L$ strata. The model will also include adjustment for baseline AEC strata. These analyses will be used for descriptive purposes only. <u>Analysis of Safety</u> The safety analysis will be descriptive and conducted in the safety population. The safety summary will include treatment emergent adverse events (TEAEs), serious adverse events (SAEs), AEs leading to discontinuation, clinical laboratory safety data, vital signs, physical examination, and ECG data.
Sample size determination:	<u>Sample Size</u> The sample size will be approximately 465 participants per arm, which corresponds to 310 and 155 participants per arm in the high and low eosinophil strata (screening AEC $\geq 0.30 \times 10^9/L$ and $< 0.30 \times 10^9/L$), respectively. The study will randomize approximately 1395 participants in a 1:1:1 ratio to either dexpramipexole 150 mg BID (high dose), dexpramipexole 75 mg BID (low dose), or placebo. The enrollment into AEC strata will be capped so that the AEC $\geq 0.30 \times 10^9/L$ stratum represents approximately two-thirds of the study population. The primary objective of this Phase III asthma exacerbation study is to demonstrate that dexpramipexole reduces the AAER compared to placebo in the population of participants with baseline AEC $\geq 0.30 \times 10^9/L$. The annualized exacerbation rate is assumed to follow a negative binomial distribution, with shape parameter $k=0.8$ (overdispersion). This value is the average of the shape parameters estimated in four recent trials [Bleecker et al, 2016; Brightling et al, 2021; Castro et al, 2018; FitzGerald et al, 2016]. The mean annualized exacerbation rate with placebo is assumed to be 1.1. The sample size of 310 participants per arm in the high baseline eosinophil strata provides at least 95% power to demonstrate superiority of dexpramipexole 150 mg BID over placebo at a two-sided significance level of 0.05. Sample size was determined assuming a 40% reduction from placebo in the annualized exacerbation rate (1.1 vs. 0.66) [Zhu and Lakkis, 2014]. Based on historical data demonstrating comparable clinical outcomes despite differences in eosinophil lowering effects [Ortega et al, 2014, Bleecker et al, 2016; FitzGerald et al, 2016] and lack of clear dose response on FEV₁ in the dexpramipexole Phase II asthma study, a similar treatment effect size with the 75 mg BID dose is assumed. Assuming a similar treatment effect size with the 75 mg BID dose, the same marginal power is achieved in that dose group as well.

	The number of participants included in the low eosinophil stratum is based on a 2:1 stratification for AEC above and below $0.30 \times 10^9/L$ and does not assume specific power calculations for the low AEC stratum, which is expected to achieve attenuated clinical responses, consistent with prior development programs in severe eosinophilic asthma [Bleecker et al, 2016; FitzGerald et al, 2016]. When adding the AEC $<0.30 \times 10^9/L$ stratum the total sample size for the entire study will be approximately 1395 participants. The IDMC will review safety data at regular intervals to be defined further in the IDMC charter. An independent adjudication committee will provide an external, systematic, and unbiased assessment of blinded events of deaths, cardiac arrhythmia (bradyarrhythmia, supraventricular, and ventricular), non-fatal myocardial infarction, and non-fatal stroke (hemorrhagic and ischemic).
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LIST OF ABBREVIATIONS

AAER	annualized asthma exacerbation rate
ACQ	Asthma Control Questionnaire
AE	adverse event
AEC	absolute eosinophil count
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALS	amyotrophic lateral sclerosis
ALT	alanine aminotransferase
AM3 device	integrated home spirometry/eDiary
ANC	absolute neutrophil count
AQLQ+12	Standardized version of the Asthma Quality of Life Questionnaire for 12 years and older
AST	aspartate aminotransferase
AUC	area under the curve
β-hCG	beta human chorionic gonadotropin
BID	twice daily
bpm	beats per minute
CBC	complete blood count
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CRO	contract research organization
CRSwNP	chronic rhinosinusitis with nasal polyps
DILI	drug induced liver injury
DPI	dry powder inhaler
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	electronic case report form
EAD	eosinophilic associated disorders
ED	emergency department
EDC	electronic data capture
eDiary	electronic Diary
eGFR	estimated glomerular filtration rate
EOS	end of study
EQ-5D-5L	EuroQol five dimensions 5 levels
FDA	Food and Drug Administration
FEV ₁	forced expiratory volume in 1 second
FSH	follicle stimulating hormone
FVC	forced vital capacity
GCP	Good Clinical Practice
GINA	Global Initiative for Asthma
GLP	Good Laboratory Practice
HFA	hydrofluoroalkane propellant
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals
ICS	inhaled corticosteroids
IDMC	Independent Data Monitoring Committee
IL	Interleukin
IM	Intramuscular
IRB	Institutional Review Board
IRT	interactive response technology
ITT	intention-to-treat population
IUD	intrauterine device
IUS	intrauterine system
IV	Intravenous

LABA	long-acting β 2 agonist
MACE	major adverse cardiovascular event
MAR	missing at random
mITT	modified intention-to-treat population
mmol	Millimole
MMRM	mixed-effect model for repeated measures
NOAEL	No observed adverse effect level
PEF	peak expiratory flow
PK	Pharmacokinetic
pMDI	pressurized metered dose inhaler
PRO	patient reported outcome
pre-BD	pre-bronchodilator
q3day	once every 3 days
QTcF	corrected QT interval by Fridericia
RBC	red blood cells
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SOA	Schedule of Assessments
SoC	standard of care
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment emergent adverse event
ULN	upper limit of normal
US	United States
WBC	white blood cells
WOCBP	women of childbearing potential

1. INTRODUCTION

Areteia Therapeutics is developing dexpropionolone, an oral small molecule eosinophil lowering agent, for the treatment of patients with severe eosinophilic asthma. This protocol describes a study to evaluate the effect of dexpropionolone treatment in participants with this condition who are on Global Initiative for Asthma (GINA) 2021 Step 4 or 5 treatment on a regular basis for at least 12 months and on a stable dose for at least 3 months before Screening Visit 1. This treatment regimen must include a minimum of two controller drugs taken on a daily basis, one of them being medium- or high dose inhaled corticosteroids (ICS) as defined by GINA 2021 Box 3-6 ([Appendix C](#)). This study will be conducted in compliance with Good Clinical Practices (GCP) including the Declaration of Helsinki and all applicable regulatory requirements.

1.1. Disease Overview

Asthma is a highly prevalent, chronic airway disease characterized by airway inflammation, reversible airflow obstruction, and bronchial hyperresponsiveness [[GINA, 2021](#)]. Asthma affects an estimated 24.6 million (8.2%) Americans and 315 million people worldwide [[GINA, 2021](#); [Akinbami et al, 2012](#)]. Asthma remains a serious public health problem despite both significant advances in understanding asthma pathophysiology and the development of new drug therapies directed to specific mechanistic targets of airway inflammation.

The pathophysiology of asthma consists of two related but distinct phenomena: bronchial inflammation and airway smooth muscle constriction. Although asthma was historically considered a uniform clinical entity, current research has identified multiple asthma endotypes (pathophysiologically distinct subtypes), including eosinophilic and neutrophilic subtypes of asthma [[Svenningsen and Nair, 2017](#)]. Eosinophilic asthma is the most common endotype, comprising more than half of all asthmatics [[GINA, 2021](#)]. Eosinophilic asthma is characterized by bronchial inflammation consisting of eosinophils, activated T helper cell type 2 lymphocytes, and mast cells. Inflammation associated with asthma leads to histologically identifiable tissue remodeling consisting of smooth muscle hyperplasia and collagen deposition beneath the basement epithelium [[Israel and Reddel, 2017](#)]. Some inflammatory mediators result in airway smooth muscle constriction and bronchial hyperresponsiveness, while other mediators, such as interleukin-13, cause mucous secretion and goblet cell hyperplasia and play a major role in asthma pathogenesis [[Israel and Reddel, 2017](#)].

Asthma is clinically characterized by symptoms of cough, reversible airflow obstruction, wheezing, shortness of breath, and chest tightness. Drugs used to treat asthma are divided into those providing acute short-term relief (“reliever” or “rescue” medications) and those providing long-term control (“controller” medications). Reliever medications typically provide rapid onset bronchodilation whereas controller medications provide durable increases in forced expiratory volume in 1 second (FEV₁), decreased bronchial inflammation, or fewer exacerbations [[GINA, 2021](#)].

The standard of care (SoC) for treating asthma includes ICS, long-acting β -agonists (LABA), and leukotriene antagonists. Additional treatment options for patients with inadequately controlled severe eosinophilic asthma are 1) systemic corticosteroids used acutely for asthma exacerbations or chronically in patients with severe asthma, 2) advanced treatment options such as monoclonal antibodies to immunoglobulin E (omalizumab), IL-5 (mepolizumab, reslizumab),

the IL-5 receptor alpha (benralizumab), the IL-4 receptor alpha (dupilumab), and thymic stromal lymphopoietin (tezepelumab).

1.1.1. Asthma Exacerbations – a High Burden to the Healthcare System

While the introduction of ICS, LABA, and leukotriene antagonists have contributed to improving asthma management and reducing asthma-related hospitalization and mortality, the disease remains poorly controlled in up to 45% of GINA 3, 4, and five patients [Busse, 2021]. When SoC therapies with medium-high dose ICS/LABA are insufficient in controlling symptoms and severe asthma exacerbations, other therapies such as systemic corticosteroids or advanced therapies with injectable biologics can be added to the treatment armamentarium.

However, due to multiple factors (injection hesitancy, reimbursement challenges, asthma specialist oversight), less than 10% [data on file] of eligible patients are currently being treated with these advanced therapies (eg, injectable biologics). As a result, many patients with inadequately controlled severe asthma may have recurrent severe asthma exacerbations, which may require emergency room visits, hospitalization, and added cost burden to the healthcare system.

Dexpramipexole, an oral drug with a potential for efficacy similar to the advanced therapies (eg, injectable biologics), may be able to address an important gap in currently available asthma treatments.

1.2. Dexpramipexole

Dexpramipexole was initially identified by its neuroprotective activity in vitro and consequently its initial clinical development was focused on the treatment of amyotrophic lateral sclerosis (ALS) [Gribkoff and Bozik, 2008]. The safety and efficacy of dexpramipexole was evaluated in a Phase III pivotal study (233AS302; EMPOWER) in participants with ALS, which failed to demonstrate efficacy [Cudkiewicz et al, 2013]. However, a substantial, durable, and targeted reduction in absolute eosinophil counts (AEC) was observed [Dworetzky et al, 2017]. Subsequently, the clinical development of dexpramipexole pivoted to the treatment of eosinophilic asthma and other eosinophilic associated disorders (EADs).

1.2.1. Mode of Action

Dexpramipexole is an eosinophil maturation inhibitor. The molecular target for dexpramipexole is currently unknown, and the mechanism by which dexpramipexole produces these effects on eosinophils is under further investigation. Current findings indicate that dexpramipexole has a targeted effect on eosinophil hematopoiesis in the bone marrow by inhibiting the maturation of eosinophil precursor cells. In aggregate, these data demonstrate that dexpramipexole effectively reduces blood and tissue eosinophils and therefore may be effective in the treatment of eosinophilic asthma and other EADs

1.2.2. Nonclinical Studies

Dexpramipexole has been assessed in studies of safety pharmacology, single- and repeat-dose toxicity, and genotoxicity, as well as in reproductive and developmental toxicity studies conducted in accordance with Good Laboratory Practice (GLP) [Investigator's Brochure]. No dedicated primary pharmacology studies have been conducted with dexpramipexole. Current findings suggest that dexpramipexole has a targeted effect on eosinophil hematopoiesis in the

bone marrow by inhibiting the maturation of precursor cells, but no molecular target has been identified. Dexpramipexole has not been found to interact at high affinity with any receptors, ion channels, transporters, kinases, or enzymes across multiple broad pharmacologic screens.

Pharmacokinetic (PK) studies show that dexpramipexole has an absolute bioavailability of approximately 100% following administration by oral gavage to rats. The time to maximum concentration is approximately 1 to 2 hours in rats and 1 to 3 hours in minipigs. Dexpramipexole demonstrated low protein binding in Sprague-Dawley rat, Göttingen minipig, and human plasma. The overall mean percent unbound values ranged from 93.4% to 94.7% across the three species. Dexpramipexole was shown to cross the blood-brain barrier in rats, mice, and minipigs, and it distributes in the brain at significantly higher levels than in plasma. Studies with [^{14}C]-dexpramipexole in rats indicated that radioactivity was widely distributed into tissues within 2 hours post-dose and elimination was nearly complete by 240 hours post-dose. The tissues of the excretory, secretory, endocrine, and vascular/lymphatic systems demonstrated the highest concentrations of radiolabel. Mass balance studies established urinary excretion as the major route of elimination.

In safety pharmacology studies, dexpramipexole significantly increased respiratory rate, decreased tidal volume, and increased minute volume in Sprague-Dawley rats at ≥ 150 mg/kg. In a human ether-a-go-go-related gene assay, dexpramipexole was found to have a very low potential for cardiac delayed rectifier current inhibition, with a measured half maximal inhibitory concentration of 101.6 μM . A cardiovascular safety study was conducted in minipigs where dexpramipexole was associated with decreases in body temperature and PR intervals that were considered slight in magnitude and not adverse.

In repeat-dose toxicology studies in Sprague-Dawley rats, the main findings were mortality at doses ≥ 500 mg/kg/day and decreased body weight gain and food consumption, predominantly in males at 300 mg/kg/day. In minipigs, emesis and inappetence were noted after 2 weeks of dosing at 75 mg/kg/day and four animals were found dead at 75 mg/kg/day between Days 27 and 45 for which a test article related effect could not be ruled out. Transient convulsions that did not affect the overall health of the animals were observed in several rats and one minipig in the highest dose groups (500 mg/kg/day and 75 mg/kg/day, respectively). There was no indication of any organ specific toxicity. It should be noted that in the pivotal 6-month toxicity study conducted in rats the no observable adverse effect level (NOAEL) was 100 mg/kg for males and 300 mg/kg for females. Furthermore, in the pivotal 9-month toxicity study conducted in minipigs, the study report indicates 50 mg/kg as the NOAEL for both genders. However, in a response letter from the Food and Drug Administration (FDA; Neurology Division), dated 24 Aug 2011, the agency stated that the NOAEL should be 25 mg/kg. Therefore, exposure safety margins based on area under the concentration-time curve (AUC_{inf}) values at these NOAEL doses are 14.5-fold and 62-fold for male and female rats, respectively, and 18.7-fold for minipigs compared to the proposed clinical dose of 150 mg twice daily (BID). In a full battery of genotoxicity studies, dexpramipexole was not genotoxic or teratogenic.

In fertility and embryonic development studies conducted in rats, mean estrous cycle length, mean number of estrous cycles, mating, fertility, fecundity indices and uterine parameters were unaffected by dexpramipexole. A significant increase in the percent abnormal sperm and a significant decrease in sperm concentration per cauda epididymis were observed at 500 mg/kg and considered test article related. Sperm motility and sperm concentration per gram cauda

epididymis at 500 mg/kg/day were unaffected by treatment. Embryo-fetal development studies were conducted in rats and rabbits. In rats, uterine parameters (mean number of corpora lutea, number of implantation sites, number of viable fetuses, number of resorptions, pre-implantation loss, and post-implantation loss) in all treated groups were unaffected by dexpramipexole. The 500 mg/kg dose was associated with decreases in fetal body weights that correlated with decreases in maternal body weights. No test article related fetal external, visceral, or skeletal malformations were observed in any dose group. An increased incidence of incompletely ossified bones (variation) of the skull (jugal, parietal, and supra occipital bone) and sternebrae was noted at 500 mg/kg. The incidence of the incompletely ossified supra occipital bone was statistically significant ($p < 0.05$) compared to control animals. These effects at 500 mg/kg were considered to be associated with the lower maternal and fetal body weights observed in this group; however, a possible developmental effect of dexpramipexole could not be ruled out. In rabbits, uterine parameters were unaffected in any treated group. Mean gravid uterine weight, final body weight, adjusted final body weight, and adjusted weight change were unaffected in any treated group. Mean fetal body weights in the treated groups were unaffected and there were no test article related fetal external, visceral, or skeletal malformations and variations in any treated group. In a pre- and post-natal development study conducted in rats, reductions in maternal body weights were observed at the high dose (150 mg/kg) that correlated with reduced pup weights and paired epididymides weights. Maternal doses as high as 150 mg/kg did not affect survival post-weaning, clinical observations, body weight gains, body weights, absolute or relative food consumption, sexual maturation, learning and memory, motor activity, mating and fertility, Cesarean-sectioning or litter parameters, or necropsy observations of the F1 generation. Test article exposure was confirmed in pups on Day 21 postpartum in all dose groups.

In addition to the studies summarized here and in the Investigator's Brochure, additional studies planned include mouse and rat carcinogenicity studies.

Refer to the [Investigator's Brochure](#) for more details.

1.2.3. Clinical Studies

1.2.3.1. Clinical Pharmacology

In Phase I clinical studies, a total of 294 healthy adult and 24 renally impaired participants received dexpramipexole. The initial clinical pharmacology studies investigated the safety, tolerability, and PK of dexpramipexole at single doses up to 600 mg and multiple doses up to 300 mg BID (Studies KNS-760704-CL001, KNS-760704-CL002, 223HV103). These studies demonstrated that dexpramipexole exposure, measured by either both maximum plasma concentration or AUC, generally increased in a dose-proportional manner following single doses of 50 mg to 600 mg and following multiple doses from 50 mg to 300 mg BID. Dexpramipexole is primarily excreted unchanged in urine (74-90% of dose) and has a half-life of 6 to 8 hours at the dose range to be studied in the asthma program.

Dexpramipexole was generally well tolerated in these Phase I studies. No serious adverse events (SAEs), or deaths were reported. A summary of completed clinical pharmacology studies and more detailed information can be found in the Investigator's Brochure.

1.2.3.2. Clinical

To date, 1312 participants have been exposed to dexpramipexole: 318 participants across 10 completed Phase I clinical pharmacology studies, 888 participants in Phase II and III ALS studies (including open-label extensions), and 106 participants in Phase II asthma and other EAD studies.

1.2.3.2.1. Safety summary

In the Phase III ALS (233AS302, EMPOWER) study, a total of 942 participants were randomized and received investigational product, of which 474 participants received dexpramipexole 150 mg BID and 468 participants received placebo. Dexpramipexole was well tolerated relative to placebo, as evidenced by the similar rates of participants completing the study in both groups. In addition, with the exception of neutropenia, the incidence of AEs was similar between dexpramipexole and placebo. Furthermore, a modest dose-dependent increase in heart rate was observed with dexpramipexole.

During the Phase II asthma study (KNS-760704-AS201, EXHALE) in eosinophilic asthma, 27 participants received placebo, and 22, 26, and 28 participants received dexpramipexole 37.5, 75, and 150 mg BID, respectively, for 12 weeks. Dexpramipexole was well tolerated, with 74 of the 76 (97%) participants in the three dexpramipexole arms completing the 12-week primary assessment phase on drug. The proportion of participants reporting treatment emergent adverse event (TEAEs) during the primary assessment phase was similar between treatment groups: nine participants (33.3%) in the placebo group and seven participants (31.8%) in the 37.5 mg BID, 12 participants (46.2%) in the 75 mg BID, and 12 participants (42.9%) in the 150 mg BID dexpramipexole dose groups.

No SAEs were reported. Most TEAEs were mild or moderate in severity and were not considered by the investigator to be related to investigational product; among those that were considered related, there were no treatment- or dose-related trends. All treatment related TEAEs were mild or moderate in severity. No participant who received dexpramipexole was discontinued from the study due to an AE. Refer to the [Investigator's Brochure](#) for more details.

1.2.3.2.2. Efficacy summary

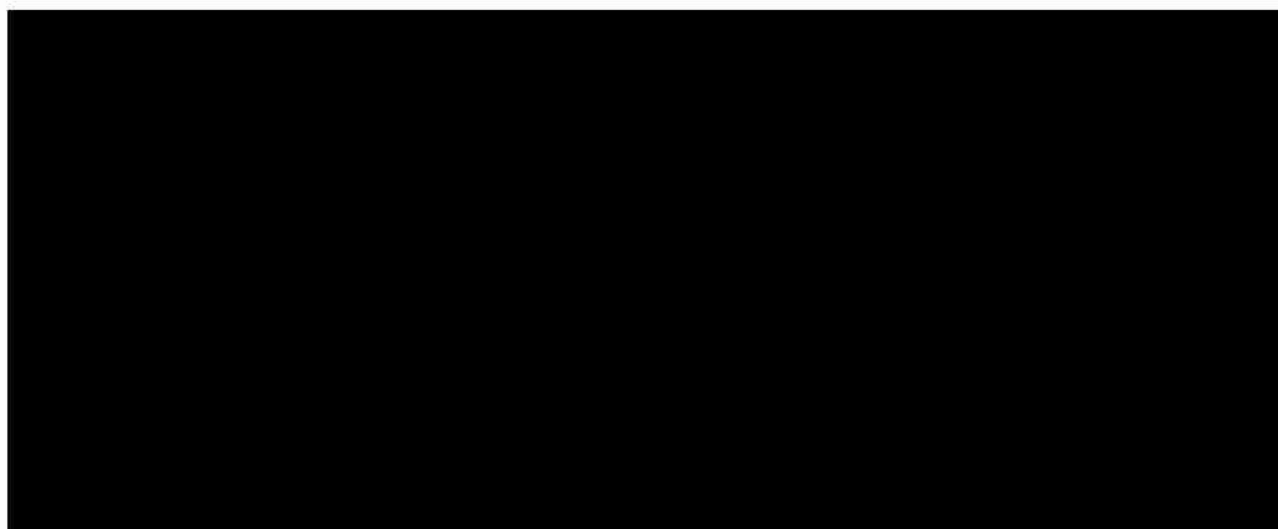




Figure 1: Phase II Asthma Study – Absolute Eosinophil Count Over Time



Abbreviations: AEC=absolute eosinophil count; BID=twice daily; BL=Baseline

Refer to the [Investigator's Brochure](#) for more details.

1.3. Known and Potential Risks and Benefits

Dexpramipexole 150 mg BID has been demonstrated to lower blood eosinophils from 80 to 94%, and tissue eosinophils from 90 to 97%, in asthma and CRSwNP, respectively. This magnitude of eosinophil lowering is comparable to that of approved anti-IL-5/5R biologics. Current evidence points to the clinical efficacy of anti-IL-5/5R biologics largely resulting from their eosinophil lowering activity. Given this, dexpramipexole treatment could significantly reduce asthma exacerbations in both the 75 mg and 150 mg BID dose groups.

Dexpramipexole has been well tolerated and generally safe in over 1300 participants enrolled in completed clinical trials. Modest increases in heart rate and infrequent transient laboratory defined neutropenia have been noted, however neither have been associated with clinical sequelae, see [Investigator's Brochure](#) Sections 6.3.8.2 and 6.3.8.1, respectively. This protocol includes a comprehensive monitoring plan for all participants.

An expanded risk-benefit summary is provided in the [Investigator's Brochure](#).

1.4. Study Rationale

When SoC therapy with medium to high dose ICS/LABA is insufficient in controlling symptoms and severe asthma exacerbations, other therapies such as systemic corticosteroids or advanced therapies with injectable biologics can be added to the treatment armamentarium.

However, due to multiple factors (injection hesitancy, reimbursement challenges, asthma specialist oversight) less than 10% [data on file] of eligible patients are currently being treated with these advanced therapies (eg, injectable biologics). As a result, many patients with inadequately controlled severe asthma may have severe asthma exacerbations, which may require emergency room visits, hospitalization, and increases the cost burden to the healthcare system.

Several monoclonal antibodies are approved for the treatment of eosinophilic asthma (eg, mepolizumab, reslizumab, and benralizumab). These drugs lower eosinophils in both blood and airways. Current understanding is that they improve asthma by lowering eosinophils, rather than by altering cell activation or signaling [Jacobsen et al, 2021; Kelly et al, 2017; Pavord et al, 2021; Van Hulst et al, 2021]. An oral alternative to these advanced injectable therapies, such as dexpramipexole, would allow more eligible patients with inadequately controlled severe asthma to obtain effective therapy.

Results from the Phase II dose finding study in moderate to severe asthma (KNS-760704-AS201; EXHALE) include significant, dose-dependent, and durable reductions of eosinophils in blood and airways. In addition, clinically meaningful, placebo-corrected, pre-bronchodilator (pre-BD) FEV₁ changes from baseline were noted across the dose groups at various timepoints. The safety and tolerability profile of dexpramipexole in this study was similar to placebo and supports advancing into Phase III studies.

The objective of this clinical study is to investigate the safety, tolerability, and efficacy of dexpramipexole in participants with inadequately controlled severe eosinophilic asthma.

1.4.1. Design Rationale

This is a Phase III registrational study that is designed as a randomized, double-blind, placebo-controlled, parallel-group, multicenter study to establish the benefit risk profile in a severe eosinophilic asthma population. The primary endpoint is the annualized asthma exacerbation rate (AAER) which is consistent with recent precedent of global regulatory approvals and guidelines. The key secondary endpoints include pre-BD FEV₁ change from baseline and is considered a core outcome for asthma clinical trials [Tepper et al, 2012], reflecting potential improvement in lung function. The study is 52-weeks in duration and provides sufficient exposure to assess safety and efficacy.

1.4.2. Dose Rationale

The 75 mg and 150 mg BID doses will be tested in this study. These doses were chosen based on the blood and tissue eosinophil lowering observed in the Phase II asthma study (KNS-760704-AS201; EXHALE) and the Phase II CRSwNP study (KNS-760704-CS201), demonstrating comparable or near-comparable eosinophil lowering with currently approved anti-IL-5/5R biologics. Safety data from the Phase II asthma study (EXHALE) and the Phase II and III ALS studies indicate dexpramipexole at these doses are well tolerated. In sum, these doses provide an

optimal dose range to examine dose response relationships and allow the assessment of benefit to risk of dexpramipexole.

1.5. Study Population

The study will include participants with inadequately controlled severe asthma, aged ≥ 12 years, on GINA 2021 Step 4 or 5 therapy. Note: enrollment of participants of 12-17 years of age is closed.

2. STUDY OBJECTIVES AND PURPOSE

2.1. Primary Objective

The primary objective of the study is to demonstrate the efficacy of dexpramipexole in reducing severe asthma exacerbations.

2.2. Secondary Objectives

The secondary objectives of this study are:

- To demonstrate the efficacy of dexpramipexole on pulmonary function.
- To demonstrate the efficacy of dexpramipexole on asthma control and quality of life.
- To evaluate the effect of dexpramipexole on blood eosinophils.

2.3. Exploratory Objectives

The exploratory objectives of this study are:

- To evaluate the kinetics of blood eosinophil lowering.
- To examine the relationship between dexpramipexole exposure and severe asthma exacerbations and other efficacy parameters.

2.4. Safety Objective

The safety objective of this study is to evaluate the safety and tolerability of dexpramipexole administered for 52 weeks in participants with eosinophilic asthma.

2.5. Primary Efficacy Endpoint / Estimand

The primary endpoint of this study is the annualized rate of severe asthma exacerbations (AAER) over 52 weeks.

The primary estimand is characterized by the following attributes:

- **Population:** Patients with inadequately controlled asthma, on GINA 2021 Step 4 or 5 therapy with baseline $AEC \geq 0.30 \times 10^9/L$ [high strata] with a history of at least two asthma exacerbations requiring treatment with systemic corticosteroids within the past 12-months.
- **Treatment of interest:** Dexpramipexole 150 mg and Dexpramipexole 75 mg administered BID. Each dose level will be compared to placebo.
- **Outcome variable:** Annualized rate of severe asthma exacerbation events over 52 weeks.
- **Intercurrent events:**
 - Treatment discontinuation for any reason: treatment policy strategy, i.e., participants who discontinue treatment will be encouraged to continue with study visits and all exacerbation events occurring up to end of Week 52 will be included in the analysis.
 - Systemic corticosteroids use: Strategy: composite strategy, i.e., intake of systemic corticosteroids is part of the definition of asthma exacerbation.
 - Start of biological therapy (precluding observation of any further exacerbation event over the 52-week period from start of treatment): while-on-treatment strategy. The exacerbations happening after the start of biological therapy are discarded. Instead,

- the number of exacerbations until the start of biological therapy will be included in the analysis, and the observation duration will be defined as the time from randomization to the date of the start of biological therapy.
- Death (precluding observation of any further exacerbation event over the 52-week period from the start of treatment): while-on-treatment strategy. The number of exacerbations until death will be included in the analysis, and the observation duration will be defined as the time from randomization to the date of death.
 - **Population-level summary measure:** Ratio (dexpramipexole 150 mg [respectively 75 mg] BID over placebo) of mean annualized exacerbation rates.

2.6. Secondary Efficacy Endpoints

2.6.1. Key Secondary Efficacy Endpoints

- Pre-BD FEV₁, absolute change from baseline, averaged across visits at Weeks 36, 44, and 52.
- Asthma Control Questionnaire-6 (ACQ-6), change from baseline, averaged across visits at Weeks 36, 44, and 52.
- Standardized version of the Asthma Quality of Life Questionnaire for 12 years and older (AQLQ+12) change from baseline to Week 52.

2.6.2. Other Secondary Efficacy Endpoints

- Annualized rate over 52 weeks of severe exacerbations requiring an emergency department (ED) visit or hospitalization.
- Annualized rate of severe asthma exacerbations from Week 4 to Week 52.
- Absolute eosinophil counts (AEC), change from baseline, averaged across visits at Weeks 36, 44, and 52
- Forced vital capacity (FVC), change from baseline, averaged over Weeks 36, 44, and 52
- FVC, change from baseline at Weeks 4, 12, 20, 28, 36, 44, and 52.
- Post-bronchodilator FEV₁, change from baseline to Week 52
- Peak expiratory flow (PEF), change from baseline to Week 52
- Time to first severe asthma exacerbation
- Total asthma symptom score, change from baseline to Week 52
- The EuroQol five-dimensional questionnaire (EQ-5D-5L) change from baseline to Week 52

2.7. Exploratory Endpoints

- Correlation between dexpramipexole exposure and severe asthma exacerbations and other efficacy parameters.
- Pre-BD percent predicted FEV₁ in participants ages 12-17 years of age, absolute change from baseline, averaged across visits at Weeks 36, 44, and 52.

2.8. Safety Endpoints

The safety endpoints of this study are measured by the following assessments: physical examination; vital signs (systolic and diastolic blood pressure, respiratory rate, pulse, and temperature); body weight; 12 lead electrocardiogram (ECG); clinical laboratory evaluations (hematology, blood chemistry, and urinalysis); pregnancy testing; and AE monitoring throughout the study.

2.9. Measures to Minimize/Avoid Bias

This is a randomized, double-blind, placebo-controlled study. Participants, investigators, and the Sponsor's study team will remain blinded from the randomization allocation until final database lock of the study. Randomization data are kept strictly confidential until the time of unblinding and will not be accessible to anyone involved in the conduct of the study. Confidentiality of randomization data is required to limit the occurrence of potential bias arising from the influence that the knowledge of treatment may have on the recruitment and allocation of participants. Blinding will minimize bias based on participant selection, baseline characteristics, clinical endpoints, and AE reporting. Specifics on how the blind for the investigational product and certain laboratory results are maintained are provided in [Section 5.4](#).

3. STUDY DESIGN

3.1. Study Overview

This study will be a randomized, double-blind, placebo-controlled, parallel-group study in approximately 1395 participants, aged ≥ 12 years, with severe eosinophilic asthma. This study will evaluate the efficacy, safety, and tolerability of two doses of dexpramipexole (75 mg and 150 mg) administered BID. Informed consent (and assent where applicable) will be obtained from participants before the initiation of any study-specific procedures. This will be a global, multicenter study in approximately 300 centers. Note: enrollment of participants of 12-17 years of age is closed.

The duration that each participant is expected to be in this study is a maximum of 14 months (Screening through Follow-up Phase) or the occurrence of one of the following events, whichever occurs first:

A recommendation of discontinuation by the investigator or Sponsor,

A decision by the participant to discontinue for any reason,

A decision by the investigator to discontinue the participant if medically necessary, or

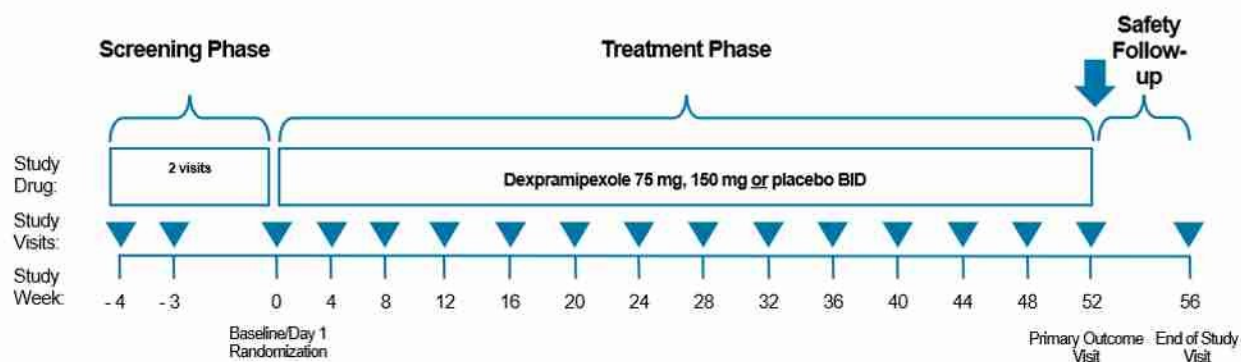
An administrative decision is made to end the study.

The Screening Phase consists of two study visits over 28 days. Following the Screening Phase, eligible participants will enter the Treatment Phase starting from the Baseline Visit through the End of Treatment Visit. During the Treatment Phase, participants will receive BID dosing of investigational product for 52 weeks. The last dose of investigational product will be taken the evening before the Week 52 Visit. During the Treatment Phase, participants will have study assessments performed at the site every 4 weeks. Following Week 52, participants will discontinue investigational product and enter the Final Follow-up Phase with a phone visit on Week 56.

At Week 52, participants may choose to continue to the long-term extension study. These participants will transition at the Week 52 Visit and will not complete the Week 56 Visit.

3.2. Schematic Diagram of Study Design

Figure 2: Study Schema



Abbreviations: BID=twice daily

3.3. Independent Data Monitoring Committee

The Independent Data Monitoring Committee (IDMC) will be commissioned for the dexpramipexole asthma clinical development program. This committee is comprised of externally-based individuals with expertise in eosinophilic asthma, biostatistics, and/or clinical research. The primary responsibilities of the IDMC are to review and evaluate the safety data at periodic intervals during the course of the study, and make recommendations to the Sponsor regarding the conduct of the clinical study.

The IDMC will receive blinded by treatment group or unblinded (if necessary) confidential reports from an independent statistician for review, which have to be handled strictly confidentially. None of these reports can be delivered to unauthorized persons.

The IDMC responsibilities, procedures, and safety data to be reviewed by the IDMC are described in the IDMC charter. In the above capacities, the IDMC is advisory to the Sponsor and will function independently from all other individuals associated with the conduct of the study.

3.4. Adjudication of Cardiac Events

An independent adjudication committee will provide an external, systematic, and unbiased assessment of blinded events of deaths, cardiac arrhythmia (bradyarrhythmia, supraventricular, and ventricular), non-fatal myocardial infarction, and non-fatal stroke (hemorrhagic and ischemic) during the Phase III studies. The committee will operate in accordance with an Adjudication Committee Charter/Manual of Operations, which will also provide detail on specific information the committee requires to enable a thorough adjudication.

3.5. End of Study

The end of study is defined as when the last participant has completed their last scheduled contact. A participant is considered to have completed the study when they have completed their last scheduled contact.

4. SUBJECT ENROLLMENT AND WITHDRAWAL

4.1. Number of Participants

Approximately 1395 participants will be studied at centers globally (approximately 300 sites).

4.2. Inclusion Criteria

To be eligible to participate in this study, candidates must meet the following eligibility criteria at Screening Visit 1 or timepoint specified in the individual eligibility criterion listed below:

1. Signed informed consent form and assent form, as appropriate.
2. Male or female ≥ 18 years of age at Screening Visit 1.

Asthma-related criteria

3. Documented physician diagnosis of asthma for ≥ 12 months prior to Screening Visit 1.
4. Treatment of asthma, participants must satisfy all the below (items a to c):
 - a. Participants who have received asthma controller medication with medium or high dose ICS (≥ 500 $\mu\text{g/day}$ fluticasone propionate dry powder formulation daily or clinically comparable, per GINA 2021) on a regular basis for at least 12 months prior to Screening Visit 1. Equivalent medium and high dose ICS doses are detailed in [Appendix C](#).
 - b. Documented treatment with a stable dose of either medium or high dose ICS for at least 3 months prior to Screening Visit 1. The ICS may be contained within an ICS/LABA combination product. As noted in [Section 5.2.2](#), daily oral corticosteroids are an allowed concomitant medication; participants on daily oral corticosteroids must be on a stable dose for 3 months before Screening Visit 1.
 - c. Use of one or more additional daily maintenance asthma controller medications according to standard practice of care is required; eg, LABA, leukotriene antagonist, theophylline, long-acting muscarinic antagonists, cromolyn/nedocromil. Use of a stable dose of any additional asthma controller medications must be documented for at least 3 months prior to Screening Visit 1.
5. Pre-BD $\text{FEV}_1 \geq 40\%$ and $< 80\%$ of predicted at Screening Visit 2.
6. Variable airflow obstruction documented with at least one of the following criteria:
 - a. Bronchodilator reversibility at Screening Visit 2, as evidenced by $\geq 12\%$ and ≥ 200 mL improvement in FEV_1 , 15 to 30 minutes following inhalation of 400 μg (four puffs) of albuterol/salbutamol. Participants who do not meet the bronchodilator reversibility inclusion criterion but have $\geq 10\%$ and ≥ 160 mL reversibility, may repeat the reversibility spirometry assessment once during the Screening period, at an unscheduled visit at least 7 days prior to baseline.
 - b. Bronchodilator reversibility, using the criteria above, documented in the past 24 months prior to Screening Visit 1 or during screening.

- c. Peak flow variation of $\geq 20\%$ over a 2-week period, documented in the past 24 months prior to Screening Visit 1 or during screening.
 - d. Airflow variability in clinic $FEV_1 \geq 20\%$ between two consecutive clinic visits, documented in the past 24 months prior to Screening Visit 1 or during screening.
 - e. Airway hyperresponsiveness (provocative concentration causing a 20% fall in FEV_1 of methacholine < 8 mg/mL, or other clinically relevant bronchoprovocation testing) documented in the past 24 months prior to Screening Visit 1.
7. ACQ-6 ≥ 1.5 at Screening Visit 2.
8. Documented history of at least two asthma exacerbations requiring treatment with systemic corticosteroids (intramuscular, intravenous, or oral) within the past 12-month period prior to Screening Visit 1.

General medical history

9. Negative urine pregnancy test for WOCBP at Screening Visit 2 and Baseline Visit.
10. Women of childbearing potential (WOCBP; after menarche) must use either of the following methods of birth control, from Screening Visit 1 through the End of Study Visit (refer to [Section 8.3.3.1](#) for details):
- a. A highly effective form of birth control (confirmed by the investigator). Highly effective forms of birth control include: true sexual abstinence, a vasectomized sexual partner, Implanon, female sterilization by tubal occlusion, any effective Intrauterine device (IUD), IUD/intrauterine system (IUS), Levonorgestrel Intrauterine system, or oral contraceptive.
- OR**
- b. Two protocol acceptable methods of contraception in tandem.

Women not of childbearing potential are defined as women who are either permanently sterilized (hysterectomy, bilateral oophorectomy, or bilateral salpingectomy), or who are postmenopausal. Women will be considered postmenopausal if they have been amenorrheic for 12 months prior to the planned date of the Baseline Visit without an alternative medical cause. The following age specific requirements apply:

- c. Women < 50 years old will be considered postmenopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatment and follicle stimulating hormone (FSH) levels in the postmenopausal range.
- d. Women ≥ 50 years old will be considered postmenopausal if they have been amenorrheic for 12 months or more following cessation of all exogenous hormonal treatment.

4.3. Exclusion Criteria

Study participant candidates will be excluded from study entry if any of the following exclusion criteria exist at Screening Visit 1 or at the timepoint specified in the individual criterion listed below:

Asthma-related criteria

1. A participant who experiences a severe asthma exacerbation (defined as a deterioration of asthma that results in emergency treatment, hospitalization due to asthma, or treatment with systemic corticosteroids) at any time from 4 weeks prior to Screening Visit 1.

Participants who experience an asthma exacerbation during the Screening/Run-in Period may remain in screening and proceed with study visits 14 days after they have completed their course of oral steroids or returned to their pre-Screening Visit maintenance dose of oral steroids and the investigator considers participant has returned to baseline status.

2. Current diagnosis of diseases which may confound interpretation of this study's findings such as allergic bronchopulmonary aspergillosis, eosinophilic granulomatosis with polyangiitis, eosinophilic gastrointestinal diseases, hypereosinophilic syndrome, chronic obstructive pulmonary disease, idiopathic pulmonary fibrosis.
3. Respiratory infection: Upper or lower respiratory tract, sinus, or middle ear infection within the 4 weeks before Screening Visit 1.
4. For participants aged 12 to 17 years old, AEC of $<0.15 \times 10^9/L$ at Screening Visit 1.
 - Note: enrollment of participants of 12-17 years of age is closed.

Prohibited medications/procedures

5. Treatment with a biologic investigational drug in the last 5 months prior to Screening Visit 1. Treatment with non-biologic investigational drugs in the previous 30 days or five-half-lives prior to Screening Visit 1, whichever is longer. Treatment with GSK3511294 (long-acting anti-IL-5) in the past 12 months.
6. Treatment with any of the following monoclonal antibody therapies within 120 days prior to Baseline Visit: benralizumab, dupilumab, mepolizumab, reslizumab, omalizumab, tezepelumab, or tralokinumab.
7. Treatment with pramipexole (Mirapex[®]) within 30 days of Baseline Visit.
8. Treatment with selected drugs known to have a substantial risk of neutropenia in the past 30 days prior to Screening Visit 1 (see [Appendix A](#)).
9. Bronchial thermoplasty procedure in the past 12 months prior to Screening Visit 1 or planned during the coming year.

General medical history

10. Weight <40 kg at Screening Visit 2.
11. Current smoking within 12 months prior to Screening Visit 1 or a smoking history of >10 pack-years. Smoking includes tobacco, vaping, and/or marijuana use.
12. Known or suspected alcohol or drug abuse
13. Uncontrolled severe hypertension: systolic blood pressure >180 mmHg or diastolic blood pressure >110 mmHg prior to the Baseline Visit despite anti-hypertensive therapy.
14. History of malignancy that required surgery (excluding local and wide-local excision), radiation therapy and/or systemic therapy during the 5 years prior to the Baseline Visit.

15. History of human immunodeficiency virus (HIV) infection or chronic infection with hepatitis B or C.
16. A helminth parasitic infection diagnosed within 24 weeks prior to Screening Visit 1 that has not been treated with or has failed to respond to SoC therapy.
17. Medical or other condition likely to interfere with participant's ability to undergo study procedures, adhere to visit schedule, or comply with study requirements.
18. Known or suspected noncompliance with medication.
19. Unwillingness or inability to follow the procedures outlined in the protocol.

Clinical safety labs

20. Absolute neutrophil count (ANC) $<2.000 \times 10^9/L$ at Screening Visit 1 or Screening Visit 2.
21. Renal dysfunction, defined as an estimated glomerular filtration rate (eGFR) $<60 \text{ mL/min/1.73m}^2$ at Screening Visit 2 (using the Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] formula [Levey et al, 2009]).
22. Active liver disease defined as any known current infectious, neoplastic, or metabolic pathology of the liver or unexplained elevations in alanine aminotransferase (ALT), aspartate aminotransferase (AST), $>3x$ the upper limit of normal (ULN), or total bilirubin $>2x$ ULN at Screening Visit 2 confirmed by a repeat abnormal measurement of the relevant value(s), at least 1 week apart.

Cardiac safety

23. History of New York Heart Association class IV heart failure or last known left ventricular ejection fraction $<25\%$.
24. History of major adverse cardiovascular event (MACE) within 3 months prior to the Baseline Visit.
25. History of cardiac arrhythmia within 3 months prior to the Baseline Visit that is not controlled by medication or via ablation.
26. History of long QT syndrome.
27. Corrected QT interval by Fridericia (QTcF) interval $>450 \text{ ms}$ for males and $>470 \text{ ms}$ for females at Screening Visit 2 QTcF $\geq 480 \text{ ms}$ for participants with bundle branch block.
28. Clinically important abnormalities in resting ECG that may interfere with the interpretation of QTcF interval changes at Screening Visit 2, including heart rate <45 beats per minute (bpm) or >100 bpm.

Pregnancy/Lactation

29. Pregnant women or women breastfeeding
30. Males who are unwilling to use an acceptable method of birth control during the entire study period (ie, condom with spermicide).

Allergy/Hypersensitivity

31. Allergy or hypersensitivity to dexpramipexole or any of its components.

4.4. Enrollment and Method of Subject Assignment

A signed and dated Institutional Review Board (IRB)/Ethics Committee (EC)-approved informed consent/assent form (ICF) must be obtained from participants before any study assessments occur.

Participating study sites are required to document all candidates initially considered for inclusion in this study. If a participant is excluded from the study, the reasons for exclusion should be documented in the participant's source documents and on the participant screening log.

Participants signing the ICF/assent document(s) are considered *enrolled*. Any participant identification number allocated to an enrolled participant will not be reused.

Participants may be *randomized* after all Baseline assessments have been completed and after the site investigator has confirmed eligibility following the Screening/Run-in Period. No participant may be randomized prior to the collection and assessment of all Baseline assessments and confirmation of eligibility.

The study will utilize an interactive response technology (IRT) system. Participants will be randomized with equal probability (1:1:1 ratio) to either dexpramipexole 75 mg BID, dexpramipexole 150 mg BID, or placebo. The randomization will use permuted blocks and will be stratified by region (US versus ex-US), age (12 to <18 years versus ≥ 18 years), and AEC ($<0.30 \times 10^9/\text{L}$ versus $\geq 0.30 \times 10^9$ cells/L). In addition, the IRT will manage the limitation of enrollment into the AEC $\geq 0.30 \times 10^9/\text{L}$ stratum to two-thirds of the total number of participants.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from participants and investigator staff. A participant randomization list will be produced by the IRT provider using a validated system that automates the random assignment of participant numbers to randomization codes. These randomization codes are linked to the different treatment arms, which in turn are linked to medication numbers. A separate medication list will be produced by or under the responsible Drug Supply Management using a validated system that automates the random assignment of medication numbers to medication packs containing each of the study treatments.

Prior to dosing, all participants who fulfill all inclusion and none of exclusion criteria will be randomized via IRT to one of the treatment arms at Day 1. The investigator or his/her delegate will call or log on to the IRT and confirm that the participant fulfills all the inclusion and none of exclusion criteria. The IRT will assign a randomization number to the participant, which will be used to link the participant to a cohort and a treatment arm and will specify a unique medication number for the first package of dexpramipexole/placebo to be dispensed and administered to the participant. The randomization number will not be communicated to the caller.

4.5. Participant Withdrawal and Study Termination

4.5.1. Withdrawal from Study or Study Treatment

All participants have the right to withdraw from the study or study treatment at any point without prejudice. In addition, the investigator can discontinue any participant at any time if medically necessary. It will be documented whether or not each participant completed the clinical study. If study treatment or observations are discontinued, the reason will be recorded, and the Sponsor should be notified promptly.

The reasons that a participant may permanently discontinue, or the investigator may permanently discontinue a participant from a clinical study could be from one or more of the following:

- AE(s)
- Death
- Participant withdrew consent
- Lost to follow-up
- Pregnancy
- Participant unable or unwilling to comply with study visit schedule
- Other, specify

The applicable reason(s) above will be recorded in the electronic case report form (eCRF) and participants should be encouraged to complete the Early Termination visit and the subsequent Safety Follow-up visit. All data collected up until the time of participant withdrawal is to be entered into the eCRF. Participants who discontinue investigational product prematurely should remain in the study and continue with the originally scheduled study visits.

4.5.2. Lost to Follow-up

A participant will be considered lost to follow-up if he or she fails to return for two consecutive scheduled visits and is unable to be contacted by the study site staff.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit within the visit window time frame and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (three telephone calls and a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts will be documented in the participant's medical record or study file.

Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

4.6. Participant Stopping Criteria

4.6.1. Individual Participant Dosing Stopping Criteria

During the study, participants will have clinic visits at regular intervals. Dosing with investigational product should be temporarily discontinued or stopped in the following scenarios:

4.6.1.1. Temporary discontinuation

- ANC $<1.000 \times 10^9/L$ per [Table 3](#).

- At the discretion of the site investigator for medical reasons.

4.6.1.2. Permanent discontinuation

- The participant becomes pregnant. Investigational product must be discontinued immediately, and the participant followed until resolution of the pregnancy. Report the pregnancy, according to the instructions in [Section 8.3.3](#).
- The participant withdraws consent.
- The participant experiences a medical emergency that necessitates permanent discontinuation of investigational product.
- At the discretion of the site investigator for medical reasons.
- At the discretion of the site investigator or Sponsor for participant non-adherence to the study requirements.
- Unexplained increases in transaminases (ALT or AST) or total bilirubin as follows:
 - ALT or AST > 8x ULN
 - ALT or AST > 5x ULN for more than 2 weeks
 - ALT or AST > 3x ULN and total bilirubin > 2x ULN or INR > 1.5
 - ALT or AST > 3x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
- Bradyarrhythmia: extreme sinus bradycardia (HR < 40 bpm), sinus pause (≥ 6 second pause between beats), total A/V nodal block
- Sustained supraventricular and ventricular arrhythmias ([Section 8.1.3.1](#))
- Prolonged QT interval: QTcF > 500 ms, or increase from baseline: QTc > 60 ms
- Recurrence of severe neutropenia (ANC < 0.500 × 10⁹/L) upon rechallenge after recovery from initial severe neutropenia
- SAE of infection concurrent with ANC < 1.500 × 10⁹/L

In the event the investigational product is discontinued, the participant should complete the Investigational Product Discontinuation Visit and be encouraged to continue attending all study visits as per the Schedule of Assessment (SOA) ([Table 2](#)). In the event the participant does not agree to attend onsite visits, future visits may be conducted remotely.

4.7. Study Stopping Criteria

4.7.1. Independent Data Monitoring Committee Stopping Rules

The IDMC will use all available evidence and their collective judgment in making a recommendation to stop or modify the study for safety. Any statistical considerations are not a substitute for the committee's medical, scientific, or statistical expertise.

4.7.2. Sponsor Discontinuation Stopping Criteria

The Sponsor will review data on an ongoing basis and may, on discussion with the IDMC, terminate the study for any clinically significant drug related safety signal (eg, serious hypersensitivity reactions or drug induced liver injury, etc).

Premature termination of a study may also occur because of a regulatory authority decision, change in opinion of the IRB/EC, drug safety problems, or at the discretion of the Sponsor. In addition, the Sponsor retains the right to discontinue development at any time.

If the Sponsor decides to prematurely terminate or discontinue the study, the Sponsor will promptly notify all participating investigators. Upon Sponsor notification of the study being terminated or discontinued, it is the responsibility of the investigator to contact all participating participants and the pharmacy (if applicable) within 30 days of the Sponsor notification. Final study visits should occur within 30 days of the last participant contacted. As directed by the Sponsor, all remaining study products and materials must be collected and all eCRFs completed to the greatest extent possible.

The Sponsor, or designee, will inform the applicable health authorities and the IRBs/EC of study termination or discontinuation including the reasons for doing so, within the locally applicable timelines.

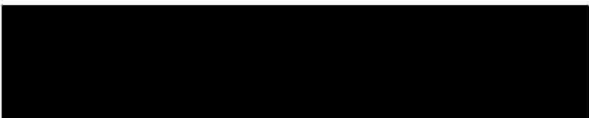
Similarly, Sponsor or designee will inform all relevant vendors, 3rd parties, any study committees (IDMC) of the date, reason for study termination or discontinuation. All ongoing activities will be brought to a finalization stage as much as possible and study documentation/materials are transferred to the Sponsor or designee as part of study closure within an agreed timeframe.

5. TREATMENT OF PARTICIPANTS

5.1. Study Medication

Investigational product, dexpramipexole, information is described in [Table 1](#).

Table 1: Investigational Product

Product Name:	Dexpramipexole
Active ingredient	Dexpramipexole dihydrochloride
Dosage Form:	Film coated tablet
Unit Dose	Dexpramipexole dihydrochloride 75 mg (dexpramipexole, 56 mg base equivalent) or 150 mg (dexpramipexole, 112 mg base equivalent) administered BID
Route of Administration	Oral
Physical Description	White, filmcoated, capsule shaped tablets containing the following excipients: microcrystalline cellulose, mannitol, crospovidone, and magnesium stearate. The coating contains polyvinyl alcohol, titanium dioxide, polyethylene glycol 3350 and talc.
Manufacturer	

Abbreviation: BID=twice daily

5.1.1. Placebo

Placebo will be supplied by the Sponsor to the clinical study site. Placebo film coated tablets will look identical to the investigational product and will contain microcrystalline cellulose, mannitol, crospovidone, sucrose octaacetate, and magnesium stearate (vegetable source). The coating contains polyvinyl alcohol, titanium dioxide, polyethylene glycol 3350 and talc. Placebo will be administered in the same manner as active, in an amount matched to the dose within the active arm(s).

5.1.2. Packaging and Labeling

Investigational product will be provided by the Sponsor. Medication labels will comply with regulatory requirements. The storage conditions for each medication provided will be described on the medication label.

Investigational product will be packaged in white, high-density polyethylene bottles with foil-induction seals and polypropylene child-resistant closures. A 9-gram polyester coil is inserted into the bottle to displace the head space.

5.1.3. Investigational Product Dispensing

The investigational product will arrive at the site ready for dispensation to participants upon randomization and allocation of investigational product bottle(s) within the IRT.

Investigational product may be dispensed only by a pharmacist or designee following allocation of investigational product bottle by the IRT. Investigational product is to be dispensed only to participants enrolled in this study. Returned investigational product may not be dispensed to or administered to another participant.

The first dose of investigational product will be administered at the site by authorized site staff at the conclusion of the Baseline assessments from the assigned investigational product bottle(s). Following the initial administration onsite, the remainder of investigational product bottle(s) will be provided to the participant to continue dosing at home.

Participants should be instructed to take a dose of investigational product BID, morning and evening, approximately 12 hours apart, approximately the same time each day, for the duration of their participation in the study. If a dose of investigational product is missed, the participant should be instructed to take the missed dose immediately, if within four hours of the missed scheduled dose. However, no more than one missed dose (one tablet) should be taken at any one time and no more than two tablets of investigational product should be taken in any 12-hour period.

5.1.4. Storage

The investigational product should be stored at room temperature (15°C to 25°C) as specified in the Pharmacy Manual. Access should be strictly limited to the principal investigator, pharmacist, or qualified designee at the site.

Upon dispensation to the study participant, the pharmacist or qualified designee should reiterate the storage condition requirements to be followed, as specified in the Pharmacy Manual.

5.1.5. Investigational Product Compliance and Accountability

The investigator or designee must maintain an inventory record of the investigational product received and dispensed to all participants to assure the regulatory authorities and the Sponsor that the new investigational product will not be dispensed to any person who is not a participant under the terms and conditions set forth in this protocol. Investigational product accountability forms and/or specific instructions can be found in the Pharmacy Manual.

The investigational product supplied for use in this study is to be prescribed only by the principal investigator or designated sub-investigators and may not be used for any purpose other than that outlined in this protocol

At the end of the study, reconciliation must be made between the amount of investigational product supplied, dispensed, and subsequently returned to the Sponsor or designee. A written explanation must be provided for any discrepancies.

5.1.6. Investigational Product Disposal or Return

All unused investigational product will be destroyed onsite (or returned to the depot for destruction) once the investigational product has been inventoried and the monitor has reviewed

the accountability records. In the event that investigational product needs to be returned for any other reason, the site will receive a written request listing the investigational product lot number(s) to be returned and the reason for the return request.

5.1.7. Product Complaints

Sites are required to report any product complaints to the Sponsor immediately but no later than 24 hours from the time of awareness, by phone or email as follows:

United States of America and Latin America:

[REDACTED]

All other geographic areas:

[REDACTED]

All regions:

[REDACTED]

Product Complaint: Is defined as any written, electronic, or oral communication that alleges deficiencies related to the identity, durability, reliability, quality, safety, effectiveness or performance of a product, after it is released for distribution.

5.2. Concomitant Medications and Procedures

A concomitant medication is any drug or substance administered between the Screening Visit and the participant's last study visit. Concomitant medication must be recorded in the participant's source documentation records and on the eCRF, when applicable.

A concomitant procedure is any therapeutic intervention (eg, surgery, physical therapy) or diagnostic assessment (eg, blood gas measurement, bacterial cultures) performed between the Screening Visit and the participant's last study visit. Concomitant procedures are not recorded on the participant's eCRF. The event that caused the need for the concomitant procedure should be recorded if that event is determined to be an AE. In addition, any AEs related to administration of these concomitant procedures must be documented on the appropriate eCRF.

5.2.1. Prohibited Concomitant Medications/Procedures

The following medications/treatments are prohibited during the study:

- Investigational drugs
Use of investigational drugs is prohibited for the duration of the study.
- Monoclonal antibody therapy
The use of the following monoclonal antibody therapies are prohibited throughout the duration of the study: benralizumab, dupilumab, mepolizumab, reslizumab, omalizumab, tezepelumab, or tralokinumab.
- Pramipexole
The use of pramipexole is prohibited throughout the duration of the study.

- Selected drugs known to have substantial risk of neutropenia
Drugs known to have a substantial risk of neutropenia, as listed in [Appendix A](#), are prohibited for the duration of the study.
- Selected drugs known to have substantial risk of QT prolongation. Drugs known to have a substantial risk of QT prolongation ([Appendix B](#)) are prohibited for the duration of the study.
- Bronchial thermoplasty procedure

5.2.2. Permitted Concomitant Medications

Per inclusion criterion 4, participants enrolled on the study must be on a stable dose of asthma controller medications, including but not limited to ICS/LABA, long-acting muscarinic antagonists, leukotriene receptor antagonists, and oral corticosteroids. Participants should remain on the same background asthma medications throughout the duration of the study except during the treatment of an asthma exacerbation. Additional systemic corticosteroids may be used if medically indicated to treat an asthma exacerbation that occurs during the study. If necessary, participants may have their background therapy changed from one clinically equivalent treatment to another (eg, change from one type of medium dose ICS to another type of medium dose ICS) after discussion with the medical monitor.

5.2.3. Reliever (Rescue) Medications

Participants will use reliever/rescue medications prescribed by their medical provider and these medications will not be provided through the study itself. The following reliever medications are permitted during the study (other relievers should be reviewed with the Clinical Research Associate):

- Short-acting beta agonists
- ICS/formoterol dual inhaler

The use of maintenance and reliever therapy is allowed in the study. In specific, ICS/formoterol combination inhalers may be used as reliever/rescue medications.

5.3. Restrictions

Participants will have to comply with the following restrictions during the study:

- Participants must not donate blood or plasma from informed consent through End of Study Visit (Final Safety Follow-up Visit [Week 56]).
- Participants should avoid strenuous exercise within 60 minutes prior to any onsite visit.

5.4. Study Blinding

5.4.1. Treatment Blinding

This is a double-blind, placebo-controlled study. Participants, investigators and other site study staff, the Sponsor and contract research organization (CRO) study team will remain blinded from

randomization until final database lock of the study. Participants will be randomly assigned to their treatment group according to a computer-generated pseudorandom code using the methods described in [Section 4.4](#).

Randomization data are kept strictly confidential until the time of unblinding and will not be accessible to anyone involved in the conduct of the study. The identity of the treatments will be concealed by the use of investigational drugs that are identical in packaging, labeling, schedule of administration and in appearance.

5.4.2. Blinding of Complete Blood Count Results

Dexpramipexole lowers eosinophil and basophil counts such that these values could indicate active treatment assignment. All study related lab results will be processed through a central laboratory facility contracted for the study or as otherwise noted in [Appendix D](#).

Screening and Baseline complete blood count (CBC) results will not be blinded to any study personnel or participants. However, the site staff, participants, CRO, and Sponsor personnel will be blinded to all post-Baseline AEC, absolute basophil count, total white blood cell (WBC) count, and WBC% differential results from the central laboratory collected during the study.

Other CBC results, including ANC, absolute lymphocyte counts, absolute monocyte count, absolute counts of immature or atypical cells, platelet count, and all red blood cell (RBC) indices will not be blinded during the study.

Site staff must also avoid having participants (or themselves) inadvertently unblinded by non-study CBC results from tests performed at a lab unaffiliated with the study (ie, an undesignated local lab) during the time a given participant is active in this study.

5.4.3. Emergency Unblinding

Unblinding of treatment assignment for a participant may be necessary due to a medical emergency.

In the case of an emergency where, in the opinion of the investigator, discontinuation of study treatment is not sufficient, and the study treatment must be unblinded to evaluate further course of action, the investigator can unblind study treatment for a specific participant.

If a participant is unblinded, the investigator should contact the Sponsor immediately to inform of the unblinding. The investigator must be able to confirm that unblinding of the participant is necessary and directly impacts the immediate medical management or welfare of the participant. The participant will be considered discontinued from the study.

The date and reason for unblinding must be documented in the source documents.

6. STUDY PROCEDURES AND ASSESSMENTS

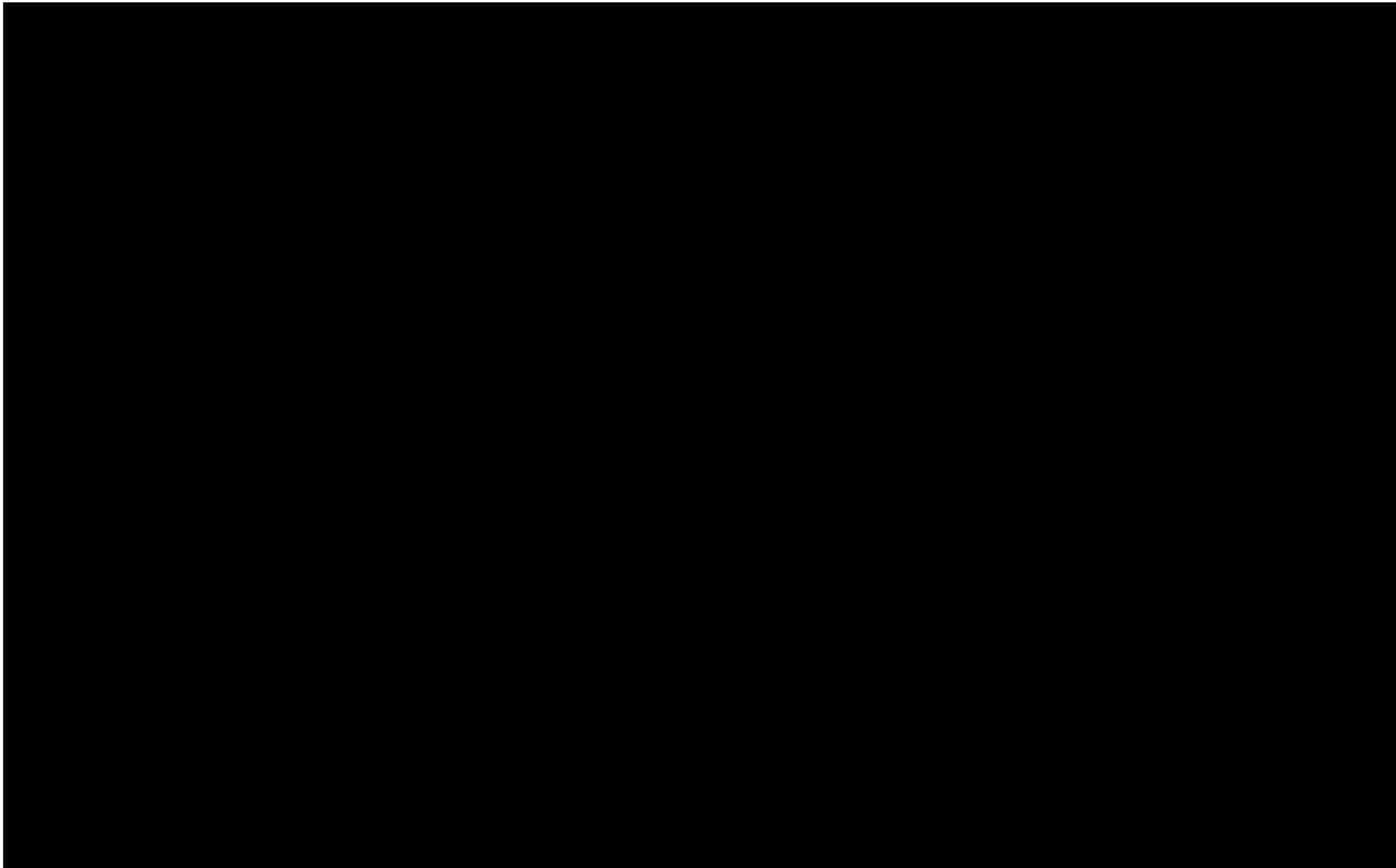
This study consists of three study periods containing 17 visits over the course of 56 weeks.

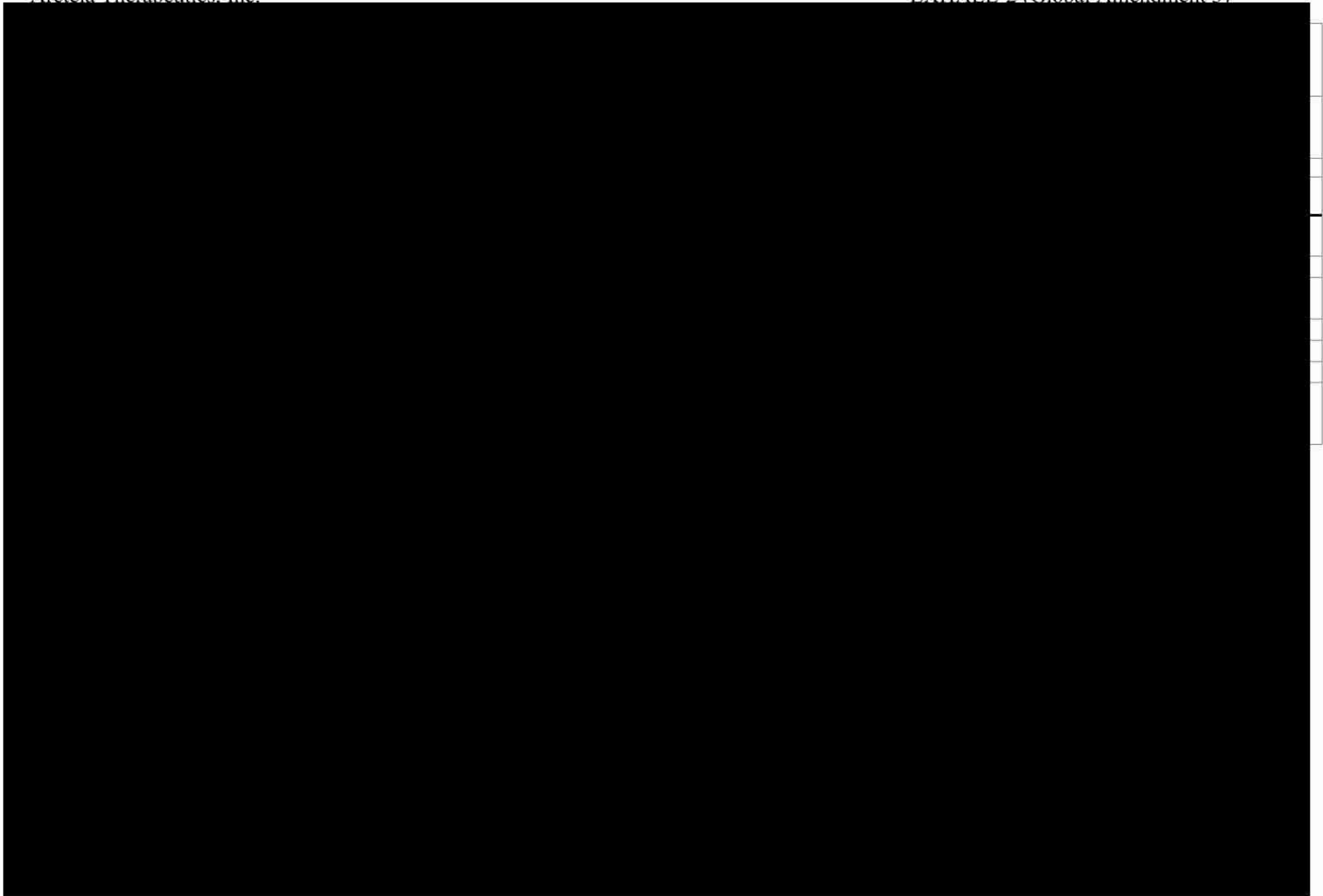
- **Screening Phase:** Screening Visit 1 to Baseline Visit.
Screening Visit 1: Participants will undergo screening to assess whether they satisfy the eligibility criteria.
Screening Visit 2: Participants will take part in the Run-in Phase (Screening Visit 2 to Baseline Visit; up to 21 days duration, with a minimum of 14 days) as part of the Screening period, to confirm if their current asthma medication regimen is stable. The screening period may be extended after consultation with a medical monitor or a sponsor clinical representative (eg, to accommodate logistical or technical issues).
- **Treatment Phase:** Baseline Visit through completion of Week 52 Visit.
Participant eligibility will be assessed during the Screening visits and confirmed at the Baseline Visit. After the collection of all Baseline assessments, participants will begin investigational treatment (dexpramipexole 75 mg, 150 mg, or placebo), BID for 52 weeks. The last dose of investigational product will be taken the evening before the Week 52 Visit. The Week 52 visit is the Primary Outcome Visit for the study.
- **Follow-up Phase:** Conclusion of Week 52 assessments through Week 56 Visit.
During this phase, participants will have one final phone visit to collect final safety assessments following cessation of investigational product. Participants may choose to continue to the long-term extension study. These participants will transition at the Week 52 Visit and will not complete the Week 56 Visit.

6.1. Schedule of Events/Assessments

The Schedule of Assessments is provided in [Table 2](#).

Table 2: Schedule of Assessments







6.2. Informed Consent

Discussion about participation and consent for the study should occur at or before Screening Visit 1 once an initial discussion about the overall study and possible participant qualification has been completed. Written informed consent, and assent for participants, where applicable, will be obtained for this study by the principal investigator or designee from all participants before performing any protocol-specific procedure. A copy of the ICF will be provided to the participant.

Please see the Schedule of Assessments (Table 2) for a detailed schedule and Section 7 for details of all tests required in each panel.

6.3. Screening

Participant eligibility will be assessed during the Screening visits and confirmed at the Baseline Visit. Screening assessments are to be completed within the 28 days prior to the Baseline Visit (first dose of investigational product).

For this study, rescreening may only be permitted under specific circumstances and only after contact with a medical monitor or sponsor clinical representative. The screening period may be extended after consultation with a medical monitor or a sponsor clinical representative (eg, to accommodate logistical or technical issues). In addition, rescreening may be appropriate, at investigator and Medical Monitor/Sponsor discretion, following mild intercurrent illness after the condition has resolved. Otherwise, individuals who do not meet the eligibility criteria for participation in this study (screen failure) may not be rescreened.

In case of rescreening, reconsent is required and all screening procedures must be repeated. The participant will be assigned a new screening number. It must be confirmed that participants meet all eligibility criteria under the new screening numbers and process before progressing to randomization/Day 1.

Acceptable documentation for historical asthma exacerbation events

The Screening Phase consists of two visits to ensure participants qualify based on eosinophil counts, prior to performing further screening testing.

Documentation evidencing two prior severe asthma exacerbations in the past 12 months will be required to confirm eligibility. Verbal history of these events obtained from the participant will not be accepted for the purpose of confirming eligibility. In the absence of adequate documentation, such participants will be considered ineligible.

Examples of adequate documentation may include:

- Copies of discharge summaries from a healthcare facility indicating that a participant was hospitalized/treated with systemic steroids for an asthma exacerbation.
- Signed and dated notes from a referring physician, including information regarding diagnosis and treatment of an exacerbation with systemic steroids.
- Evidence of prescription for systemic steroids used during an exacerbation.

- A documented conversation between the treating/referring physician or nurse/nurse practitioner certifying that a participant was treated for an exacerbation with steroids at their clinic or under their supervision. The dates (month/year) of the exacerbations and verbal confirmation that appropriate prescriptions were provided is necessary. This option should be used only if reasonable attempts to procure participant records have been unsuccessful.

Definition of “treatment with systemic corticosteroids” may be:

- Treatment with systemic corticosteroids in a participant not on maintenance oral corticosteroids
- Doubling or more of the oral corticosteroid dose in a participant on maintenance oral corticosteroids
- Administration of any intravenous (IV) or intramuscular (IM) systemic corticosteroids.

Per inclusion criterion #6, documentation evidencing prior variable airway obstruction may also be utilized to satisfy study entry requirements. If such documentation is not available, participants must demonstrate bronchodilator reversibility during the screening assessment, per [Section 7.2.2](#)

Examples of adequate documentation in the past 24 months (or during screening for bronchodilator reversibility, peak flow variation, or FEV₁ variation) may include:

- Copies of the results of prior bronchodilator reversibility testing, as evidenced by $\geq 12\%$ and ≥ 200 mL improvement in FEV₁, 15 to 30 minutes following inhalation of albuterol/salbutamol.
- Records showing peak flow variation of $\geq 20\%$ over a 2-week period
- Clinic records showing airflow variability in clinic FEV₁ $\geq 20\%$ between two consecutive clinic visits
- Spirometer printout or clinic records showing airway hyperresponsiveness (provocative concentration causing a 20% fall in FEV₁ of methacholine < 8 mg/mL)

6.3.1. Screening Visit 1

At Screening Visit 1, the following assessments are to be completed (the general sequence for performing assessments should follow the order below):

- Signed informed consent (if not completed prior to the initial Screening Visit)
- Assessment of eligibility
- Demographics CBC with differential; including the qualifying eosinophil count

6.3.2. Screening Visit 2 (Day -21 to -14)

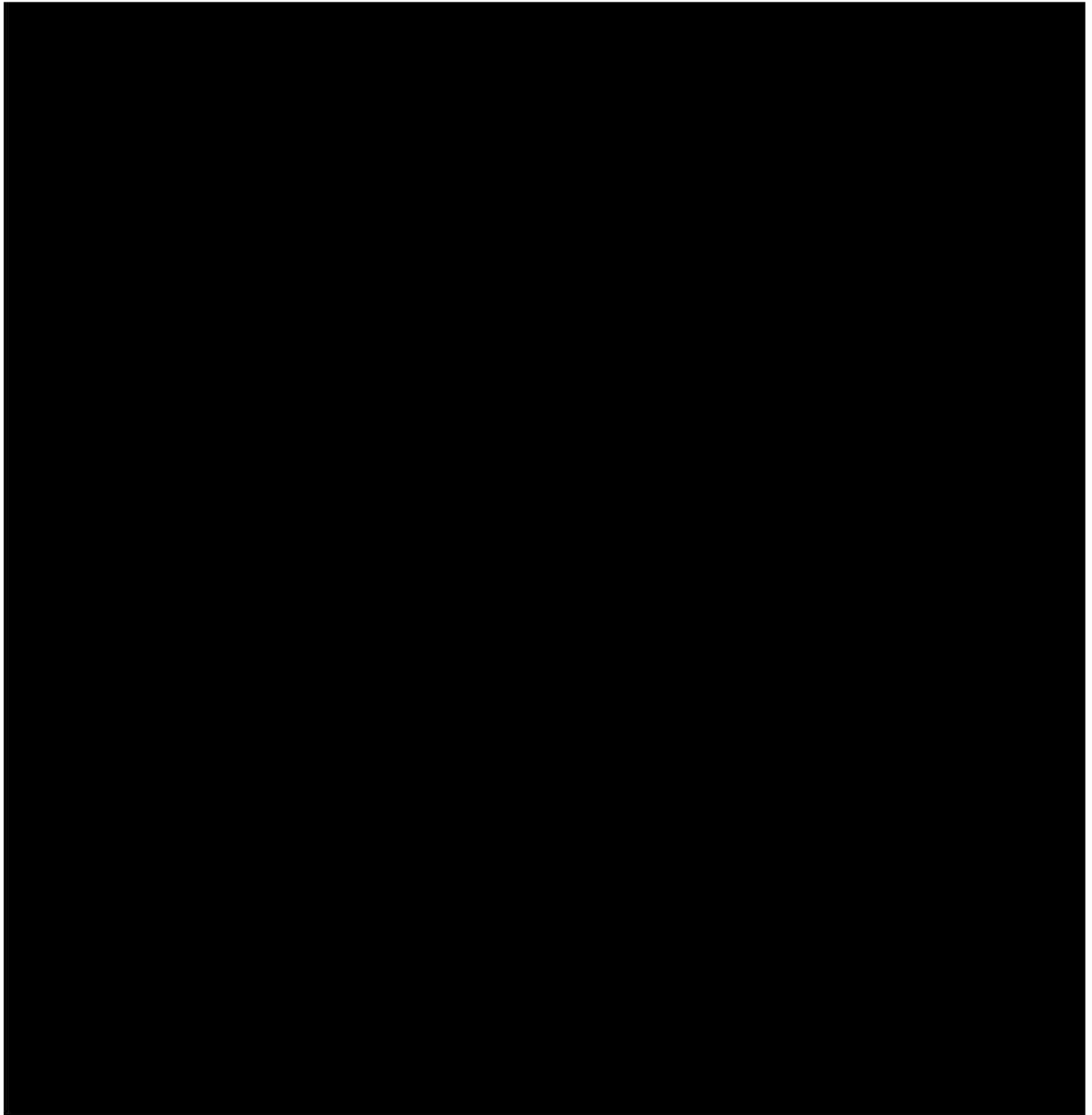
At Screening Visit 2, the following assessments are to be completed (the general sequence for performing assessments should follow the order below):

Participants should hold their asthma medication the morning of Screening Visit 2. If the participant has not withheld their asthma medications according to [Table 4](#), the entire Screening Visit 2 must be rescheduled as soon as possible.

6.4. Baseline Visit / Randomization (Day 1) – Visit 1

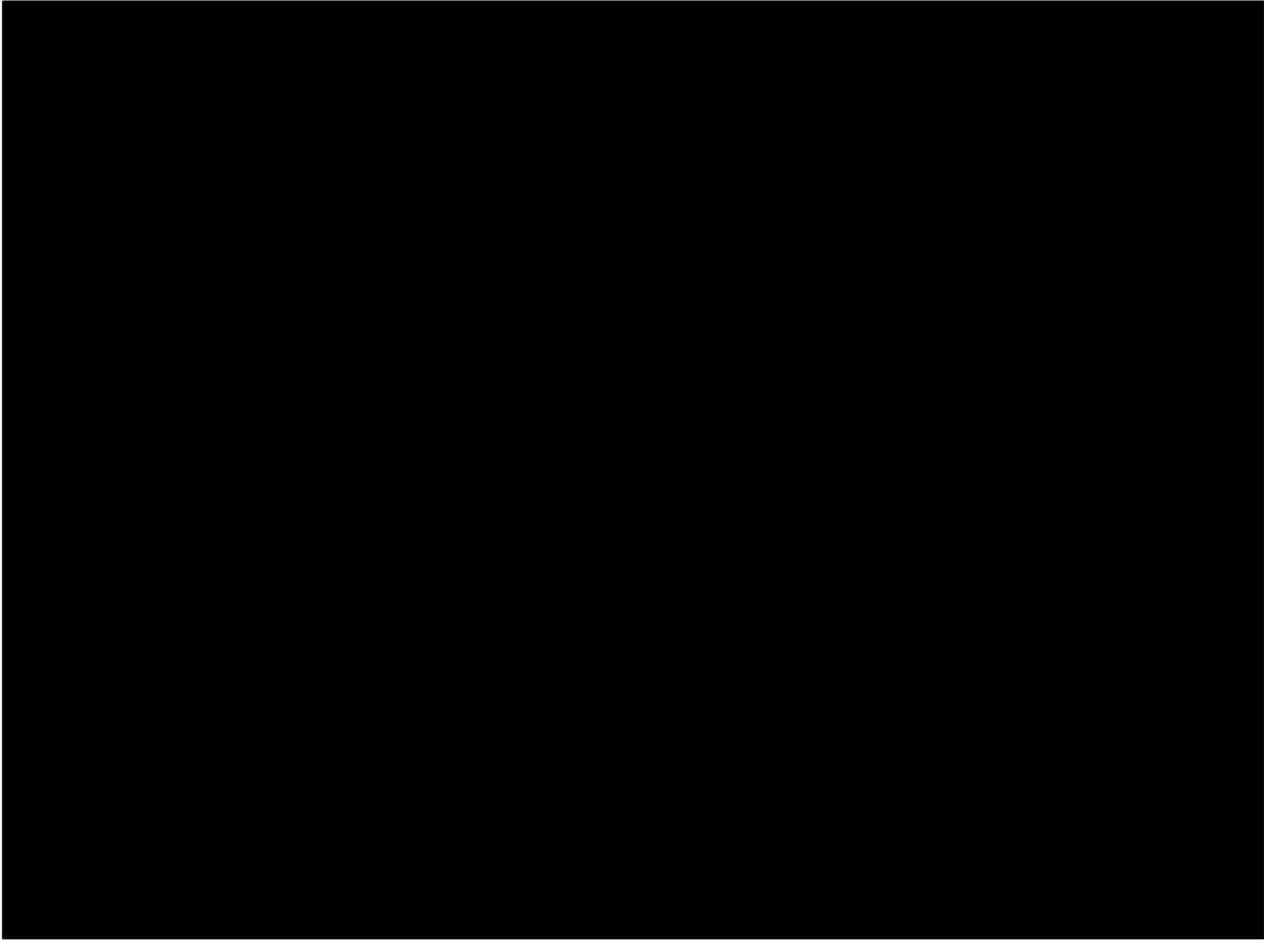
Following the completion of the Screening Phase (including a minimum of 2 weeks of Run-in) and confirmation of eligibility, baseline assessments will be performed prior to dosing of investigational product on Day 1.

Participants should hold their morning asthma medication the morning of the Baseline Visit. If the participant has not withheld their asthma medications according to [Table 4](#), the **entire Baseline Visit must be rescheduled as soon as possible.**



6.5. Week 4

Participants should hold their investigational product **AND** asthma medication the morning of this visit. If the participant has not withheld their investigational product or asthma medications, the visit must be rescheduled as soon as possible.

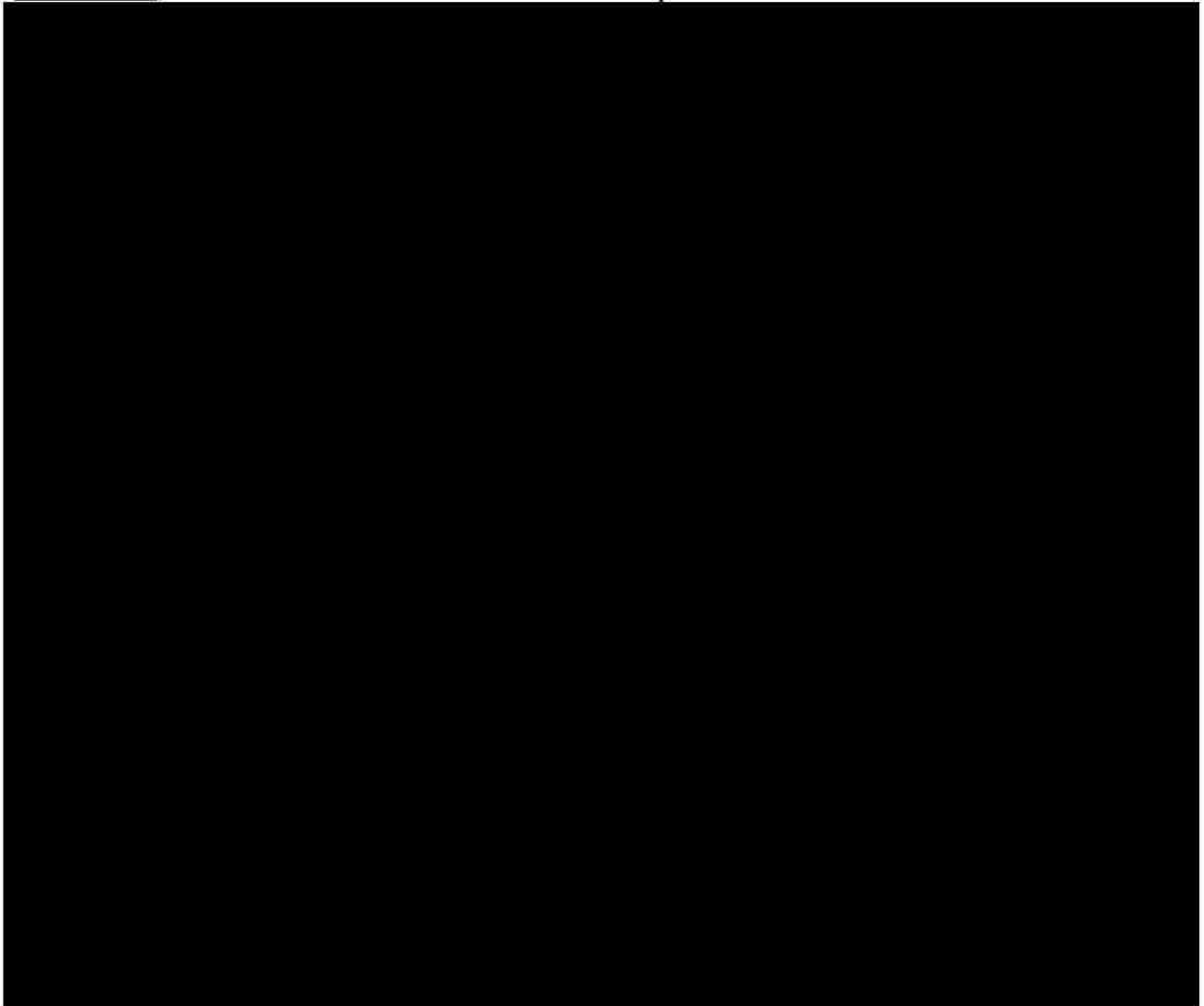


6.6. Week 8



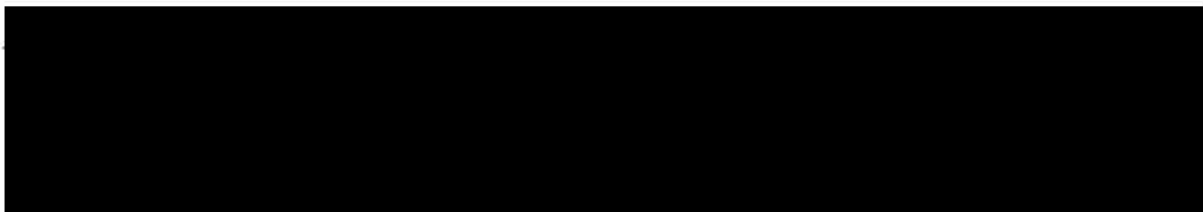
6.7. Week 12

Participants should hold their investigational product AND asthma medication the morning of this visit. If the participant has not withheld their investigational product or asthma medications, this visit must be rescheduled as soon as possible.



6.8. Week 16

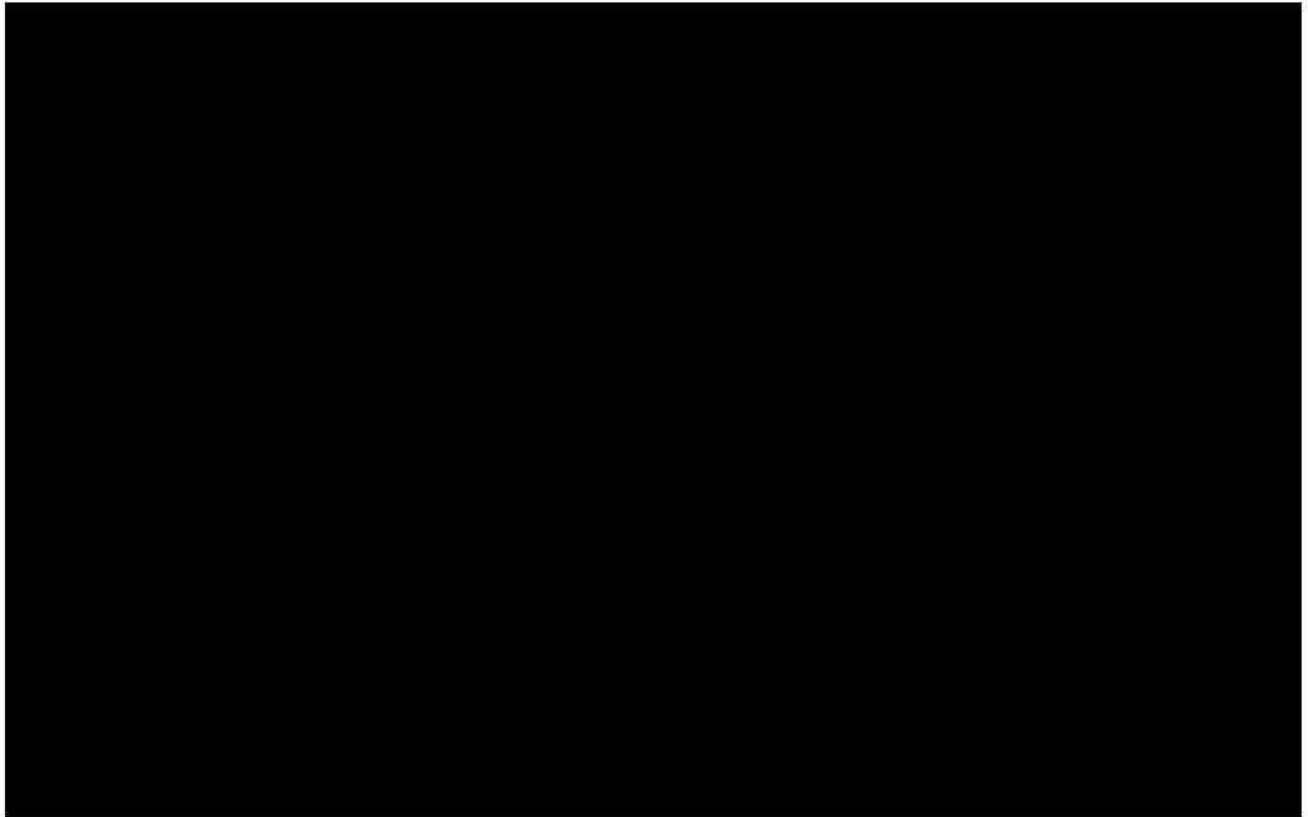
Participants will be instructed to hold their investigational product and asthma medication the morning of this visit. If asthma medication and/or investigational product was not withheld, the visit does not need to be rescheduled as this visit is limited to the assessments below.





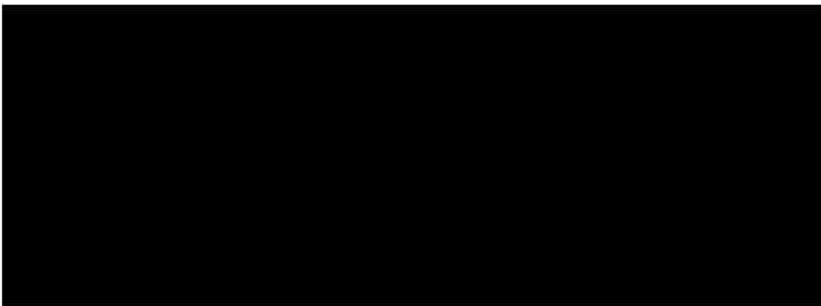
6.9. Week 20

Participants should hold their investigational product AND asthma medication the morning of this visit. If the participant has not withheld their investigational product or asthma medications, this visit must be rescheduled as soon as possible.



6.10. Week 24

Participants will be instructed to hold their investigational product and asthma medication the morning of this visit. If asthma medication and/or investigational product was not withheld, the visit does not need to be rescheduled as this visit is limited to the assessments below.



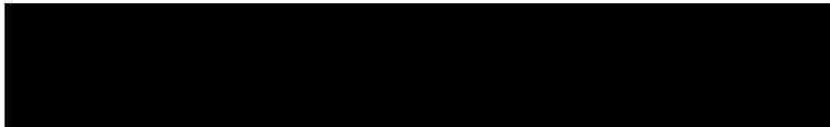
6.11. Week 28

Participants should hold their investigational product AND asthma medication the morning of this visit. If the participant has not withheld their investigational product or asthma medications, this visit must be rescheduled as soon as possible.



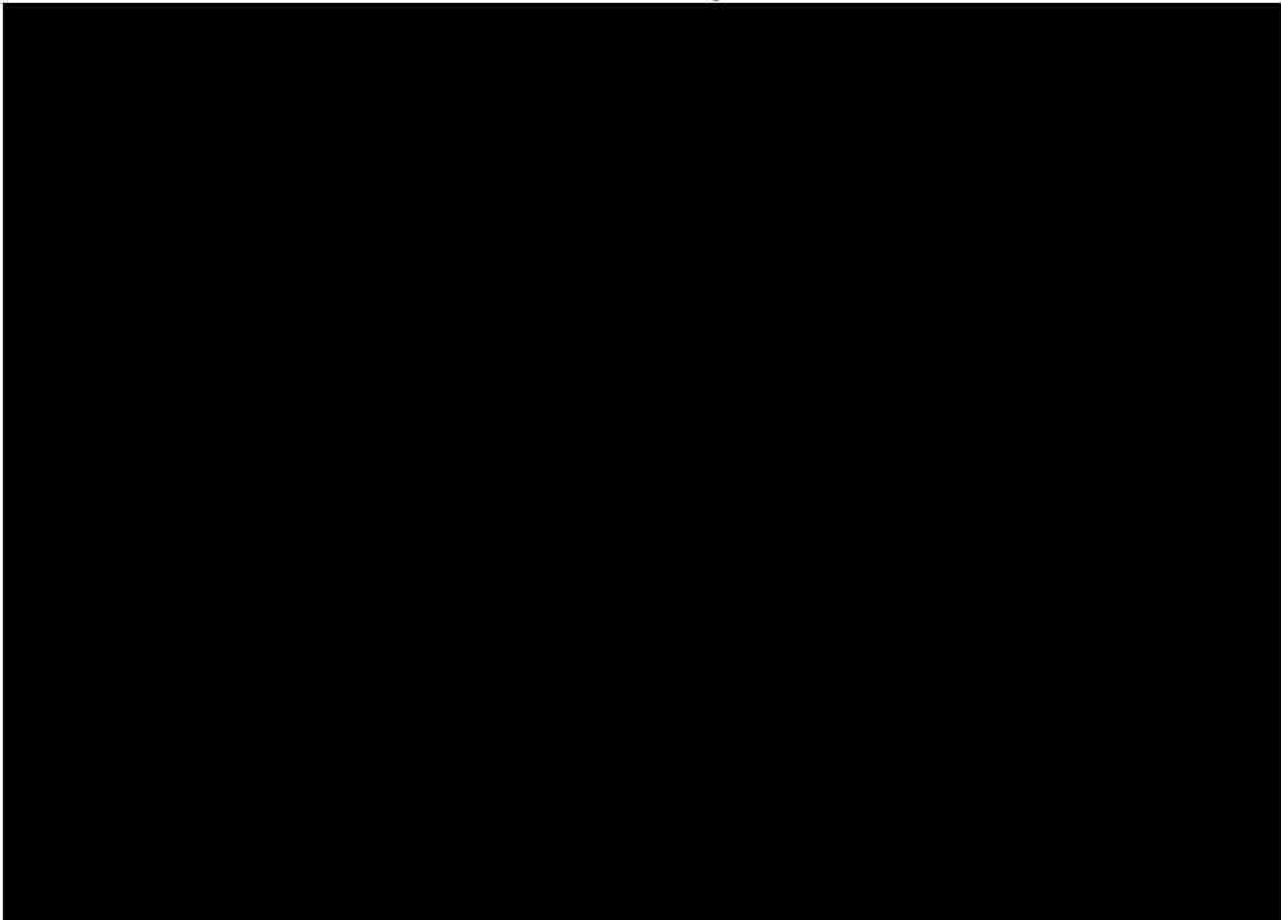
6.12. Week 32

Participants will be instructed to hold their investigational product and asthma medication the morning of this visit. If asthma medication and/or investigational product was not withheld, the visit does not need to be rescheduled as this visit is limited to the assessments below.



6.13. Week 36

Participants should hold their investigational product **AND** asthma medication the morning of this visit. If the participant has not withheld their investigational product or asthma medications, this visit must be rescheduled as soon as possible.



6.14. Week 40

Participants will be instructed to hold their investigational product and asthma medication the morning of this visit. If asthma medication and/or investigational product was not withheld, the visit does not need to be rescheduled as this visit is limited to the assessments below.



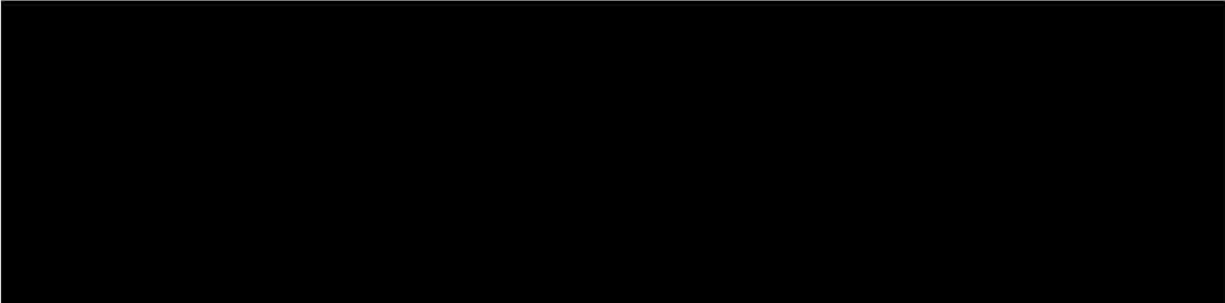
6.15. Week 44

Participants should hold their investigational product **AND** asthma medication the morning of this visit. If the participant has not withheld their investigational product or asthma medications, this visit must be rescheduled as soon as possible.



6.16. Week 48

Participants will be instructed to hold their investigational product and asthma medication the morning of this visit. If asthma medication and/or investigational product was not withheld, the visit does not need to be rescheduled as this visit is limited to the assessments below.



6.17. Week 52 (Primary Endpoint)

Participants should hold their investigational product AND asthma medication the morning of this visit. If the participant has not withheld their asthma medications, this visit must be rescheduled as soon as possible. The last dose of investigational product is to be taken the evening before the Week 52 Visit.

6.18. Week 56 (4 Weeks Post Final Dose) – Final Safety Follow-up

Participants who do not roll over into the long-term extension study will have a Final Safety Visit by phone at Week 56. The following assessments will be completed during this visit:



6.19. Investigational Product Discontinuation Visit

Participants who discontinue investigational product prematurely should remain in the study, attend the Investigational Product Discontinuation Visit (within 7 days of last dose if investigational product), and continue with the originally scheduled study visits after the Investigational Product Discontinuation Visit as described in the SOA ([Table 2](#)). If a participant is unwilling or unable to attend all subsequent visit(s), they will be contacted via telephone, email, or text as preferred by the participant by the investigator/designated representative and allow sites to contact their doctors for protocol-specific data, if willing. Additionally, the investigator should at least aim to have the participant attend the Week 52 Visit (Primary Outcome Visit) and complete Week 56 Visit for safety assessments. While every effort should be made to obtain all efficacy and safety information at these timepoints, at a minimum, vital status should be assessed wherever possible through the end of the study.

6.20. Early Termination Visit

Participants who discontinue investigational product prematurely and withdraw consent to attend further study visits, will be asked to return within 7 days of the last dose of investigational product to have the Early Termination visit performed (same assessments as Week 52 [Primary Outcome Visit] Visit).

In addition, if the participant agrees, he/she will be contacted by the site to ascertain if he/she has experienced an AE/SAE within 30 days after the last dose of investigational product.

6.21. Unscheduled Visit

Participants with signs or symptoms consistent with a possible infection should contact the study site. Investigators will determine if a participant is experiencing an infection and if they should return for an unscheduled visit. Unscheduled visits in response to possible infection will include a clinical evaluation and a CBC with differential through the central laboratory. If a participant has laboratory findings of neutropenia, then the site will follow the guidance in [Section 7.1.6.1.1](#). Additional laboratory testing may be performed as clinically indicated.

Participants with worsening of asthma symptoms may require unscheduled evaluation between visits. Participants may perform unscheduled spirometry (an 'Optional PFT') to assess their respiratory status. Study site personnel must document the participant's progress until their asthma worsening has resolved.

7. PROTOCOL ASSESSMENTS

Refer to [Section 6](#) for timing of the following protocol assessment collection.

7.1. Assessment of Safety

7.1.1. Adverse Events

Participants will be carefully monitored for AEs by the investigator during the designated study period (see [Section 8](#) for details).

7.1.2. Demographics and Medical History

Demographic and baseline characteristics will be collected during the designated study period (see [SOA](#) for details).

7.1.3. Vital Signs

Vital signs will be measured in the seated upright position after the participant has been rested for 5 minutes (systolic and diastolic systemic blood pressure in mmHg, respiratory rate per minute, pulse per minute and temperature).

7.1.4. Physical Examination

Physical examinations may be conducted by a qualified, delegated physician, trained physician's assistant, or nurse practitioner as acceptable according to local regulation. The physical examination should include a focused examination, which may include general, respiratory, cardiovascular, neurological, abdominal, and extremities evaluations, and recording of weight.

7.1.5. 12-lead ECG

The Baseline Visit 12-lead ECGs will be performed in triplicate with tracings at least 1 minute apart.

All 12-lead ECGs will be collected in the supine position after the participant has been rested for 5 minutes. Circumstances that may induce changes in heart rate or otherwise stimulate the participant should be avoided throughout the resting and ECG recording periods.

Baseline and Week 52 12-lead ECGs must be done before post-BD spirometry.

Post-baseline ECGs at Weeks 4, 12, and 28 will be a single tracing and performed 2 hours post-dose of study treatment as noted in the SOA.

Results of 12-lead ECGs will be centrally evaluated.

7.1.6. Clinical Laboratory Assessments

Specimens for central clinical laboratory assessments will be obtained at the timepoints in the SOA ([Table 2](#)). Please review the Central Lab Manual for collection, processing, and shipment instructions.

7.1.6.1. Hematology and differential

Blood draws for hematology will include

7.1.6.1.1. Monitoring and management of laboratory defined Neutropenia

Laboratory defined neutropenia, defined as an ANC $<1.500 \times 10^9/L$, has been observed in both the dexpramipexole ALS and eosinophilic asthma clinical development programs. In completed studies with dexpramipexole, neutropenia has been observed as a transient reversible laboratory finding generally not associated with clinically meaningful AEs, including infections.

Participants in this study will be monitored every 4 weeks for the possible development of neutropenia (ANC $<1.500 \times 10^9/L$) and appropriate action and testing should be performed, as outlined in Table 3.

All cases of neutropenia will be followed by repeating the CBC with differential until the neutropenia resolves (ANC $\geq 1.500 \times 10^9/L$).

Additionally, participants should be directed to contact the study site if they experience signs or symptoms consistent with a possible infection. Investigators will determine if a participant is experiencing an infection and if they should return for an unscheduled visit. Unscheduled visits in response to possible infection will include a clinical evaluation and a CBC with differential.

Table 3: Neutropenia Dose Interruption and Laboratory Test Repeat Recommendations

Neutrophils	Investigational Product ³	Repeat CBC with Differential ¹	Neutropenia Case Report Form ¹
$\geq 1.000 \times 10^9/L$ to $<1.500 \times 10^9/L$ regardless of symptoms ^{2,5}	No action	Weekly	Weekly
$\geq 0.500 \times 10^9/L$ to $<1.000 \times 10^9/L$ without signs or symptoms of infection	Withhold	Weekly	Weekly
$\geq 0.500 \times 10^9/L$ to $<1.000 \times 10^9/L$ with signs or symptoms of infection ^{2,5}	Withhold	Minimum of q3day or more frequent if clinically indicated ⁴	Weekly
$<0.500 \times 10^9/L$ without signs or symptoms of infection ⁵	Withhold	Minimum of q3day or more frequent if clinically indicated ⁴	Weekly
$<0.500 \times 10^9/L$ with signs or symptoms of infection ^{2,5}	Withhold	Minimum of q3day or more frequent if clinically indicated ⁴	Weekly

¹Site staff to collect the neutropenia eCRF page weekly until the ANC is $\geq 1.500 \times 10^9/L$.

²Permanently discontinue IP for participants who develop an SAE of infection concurrent with ANC $< 1.500 \times 10^9/L$.

³Restarting investigational product requires 1) resolution of the neutropenia ($\geq 1.500 \times 10^9/L$) and 2) consultation with the medical monitor, or designee.

⁴Monitoring should be conducted at least every 3 days until ANC recovers to $> 1.000 \times 10^9/L$ and/or signs of infection resolve, and then repeat CBC with differential weekly until the ANC is $\geq 1.500 \times 10^9/L$.

⁵Refer to [Appendix D](#) for management of neutropenia

Abbreviations: ANC=absolute neutrophil count; CBC=complete blood count; eCRF=electronic case report form; q3day=once every 3 days

In cases of neutropenia, the Investigator should consult with local experts, follow local standard of care and simultaneously consult with the Medical Monitor. Additional information on the management and treatment of cases of neutropenia is included in [Appendix D](#). The Medical Monitor should be consulted regarding all cases of neutropenia. In cases where investigational product is withheld, the Medical Monitor must be informed.

Restarting investigational product requires 1) resolution of the neutropenia ($\geq 1.500 \times 10^9/L$) and 2) consultation with the Medical Monitor, or designee.

If a participant has severe neutropenia (ANC $< 0.500 \times 10^9/L$) and recovers ($\geq 1.500 \times 10^9/L$) and then experiences a recurrence of severe neutropenia on rechallenge, they will be permanently discontinued from treatment. Participant may remain in the study for the efficacy and safety assessments.

Laboratory defined events of neutropenia (ANC $< 1.500 \times 10^9/L$) will be reported to the Medical Monitor by the central lab. Participants with an ANC result of $< 1.500 \times 10^9/L$ will be contacted by site staff and the neutropenia eCRF assessment page will be completed. The information required for this eCRF will be obtained by the site staff through an interview with the participant contemporaneous with the event. The site staff should repeat the neutropenia eCRF assessment page weekly until the ANC is $\geq 1.500 \times 10^9/L$.

To obtain control cases, the neutropenia eCRF page will be collected from all participants at the Baseline and Week 20 visits.

7.1.6.2. Chemistry

Blood draws for chemistry will include [REDACTED]

7.1.6.2.1. Liver safety

The ongoing monitoring of standard serum liver test results will be performed for all participants ([Section 7.1.6.2](#)).

In participants with normal serum liver test results at baseline, any of the following laboratory criteria are indicative of drug induced liver injury (DILI), once other causes of liver injury have been excluded:

- ALT $\geq 5 \times$ ULN or

- ALT ≥ 3 x ULN, and total bilirubin > 2 X ULN, and no or minimal elevations in ALP or
- ALP ≥ 2 x ULN when the source of increased ALP levels is the liver

Tests for exclusion of alternative causes of liver injury should include viral serology, serum autoantibodies and liver imaging studies.

Clinically significant lab abnormalities suggestive of DILI or the alternative cause of DILI must be reported as AE/SAE.

7.1.6.3. Urinalysis

Urinalysis parameters to be assessed will include:

7.1.6.4. Urine pregnancy and serum FSH

Urine β -hCG/pregnancy, qualitative (for WOCBP) will be performed locally at the visits using the supplies provided by the central laboratory. In addition, FSH will be measured at Screening Visit 2 to confirm postmenopausal status in female participants < 50 years old who have been amenorrheic for ≥ 12 months.

7.2. Assessment of Efficacy

The following clinical tests/assessments will be performed to assess the efficacy of dexpramipexole, as found in the subsections below. Refer to [Section 6](#) for the timing of assessments.

7.2.1. Severe Asthma Exacerbations

At each visit, participant should be asked if there has been severe asthma exacerbations since previous visit.

A severe asthma exacerbation is defined as any of the following four events:

1. A worsening of asthma requiring treatment with systemic corticosteroids (oral use for at least 3 consecutive days or a single intravenous (IV) or intramuscular (IM) route), or
2. An emergency department (ED)* visit (defined as evaluation and treatment for < 24 hours in an ED) due to asthma that required systemic corticosteroids (as per the above).
3. An inpatient hospitalization due to asthma (defined as admission to an inpatient facility and/or evaluation and treatment in a healthcare facility for ≥ 24 hours) that required treatment with systemic corticosteroids (as defined above in #1) or
4. Death due to asthma.

*Note that an urgent care visit will be considered an ED visit.

In participants currently on concomitant oral corticosteroids, a doubling of the oral dose for at least 3 consecutive days or a single IV or IM dose is needed to meet criterion #1 above. If an exacerbation event is not associated with deterioration in at least one of the pre-specified objective measurements of “worsening” ([Section 7.2.4.1](#)), the investigator will have to justify

the decision for defining the event as an exacerbation and record it in the eCRF. If less than 7 days have elapsed since the end date of an asthma exacerbation and the start date of a new asthma exacerbation, the second event will be considered a relapse of the prior asthma exacerbation.

The start of an exacerbation is defined as the start date of systemic corticosteroids or of a temporary increase in a stable oral corticosteroid background dose, date of ED or urgent care visits requiring systemic corticosteroids, or date of hospital admission due to asthma, whichever occurs earlier. The end date of an exacerbation is defined as the last date of systemic corticosteroids or of a temporary increase in a stable oral corticosteroid background dose, date of ED or urgent care visit, or date of hospital discharge, whichever occurs later.

Protocol defined asthma exacerbation events are collected as efficacy endpoints via the “Severe Exacerbations” eCRF form.

7.2.2. Spirometry

7.2.2.1. Pre-BD spirometry (FEV₁)

For all in clinic site visits, participants will be instructed to withhold their asthma medication on the morning of the visit, per [Table 4](#).

- **Pre-bronchodilator spirometry should be collected between 6 AM and 12 noon local time and should be collected within ± 2 hours of the Baseline Visit to minimize diurnal variation.**
- **Every effort should be made to collect the Weeks 36, 44 and 52 Pre-BD spirometry within ± 1 hour of the time of day that the Baseline spirometry was collected.**

Participants who present for Screening Visit 2 but have not withheld their asthma medication, should have their visit rescheduled as soon as feasible.

Pre-BD FEV₁ is considered the core clinical outcome measure of airway obstruction in efficacy trials in asthma [[Reddel Pepper et al, 2009](#); [Pepper et al, 2012](#)]. FEV₁ is the volume of air that can forcibly be expired in 1 second.

Spirometry will be collected according to the American Thoracic Society / European Respiratory Society guidelines on standardization of spirometry [[Graham et al, 2019](#)] according to [Section 6](#), Schedule of Assessments. Spirometry will be obtained on all participants during the study.

Table 4: Intervals for Holding Asthma Medications Prior to Spirometry

Medication	Examples (proprietary names Capitalized)	Minimum washout prior to performing Spirometry
Short-acting bronchodilator	albuterol, salbutamol, levalbuterol, Xopenex	6 hours

Medication	Examples (proprietary names Capitalized)	Minimum washout prior to performing Spirometry
Long-acting bronchodilator	Advair, arformoterol, Dulera, formoterol, olodaterol, Symbicort, salmeterol	12 hours
Ultra-long-acting bronchodilator	Breo, vilanterol, Arcapta, indacaterol	24 hours
Xanthines	theophylline	12 hours
Short-acting muscarinic antagonist	Atrovent, ipratropium	8 hours
Long-acting muscarinic antagonist	acclidinium, glycopyrrolate, glycopyrronium, tiotropium, umeclidinium	24 hours
Leukotriene antagonist (LTRA)	Accolate, montelukast, Singulair, zafirlukast	12 hours
5-Lipoxygenase Inhibitor	zileuton, Zyflo	6 hours (immediate release) 12 hours (extended release)

7.2.2.2. Post-BD spirometry (FEV₁)

Participants will perform post-BD spirometry at specific visits as noted in the SOA.

After completing the pre-BD spirometry, participants will inhale four puffs of albuterol/salbutamol metered dose inhaler (approximately 100 µg albuterol/salbutamol base per actuation), with each actuation 1 minute apart. Post-BD spirometry must be assessed within 15 to 30 minutes after inhalation of albuterol/salbutamol. Post-BD spirometry at Week 52 will be performed after the ECG so that albuterol/salbutamol does not impact the ECG results.

The variable airflow obstruction inclusion criterion (Inclusion criterion #6) must be fulfilled during the Screening Phase (either by demonstration of bronchodilator reversibility during the Screening Phase or documentation of historical variable airflow obstruction).

For participants qualifying via the bronchodilator reversibility criterion (Inclusion criterion 6a), if the participant does not meet the reversibility eligibility criterion at the Screening Visit 2 spirometry but has an improvement of $\geq 10\%$ and ≥ 160 mL FEV₁ reversibility, a second reversibility spirometry attempt can be performed at least 7 days before the Baseline Visit (see [Section 6.3.2](#)).

Detailed methodology for performing the spirometry procedure can be found in the applicable study related manuals/documents.

7.2.3. Peripheral Blood Absolute Eosinophil Count

Blood eosinophil counts will be obtained at every onsite study visit. Ideally, samples should be collected between 6 AM and 12 noon to minimize diurnal variation.

7.2.4. Patient Reported Outcomes

Patient reported outcomes (PRO) data will be captured electronically either via the eDiary integrated into the AM3 device or via an electronic tablet (ie, ACQ-6, AQLQ+12, and EQ-5D-5L). Site personnel will be trained on the use of both devices. Detailed procedures for using both devices, and participant training on use of the AM3 eDiary, will be described in a separate instruction manual. Site staff will train participants on the importance and the use of the required devices as part of Screening Visit 2.

At home PRO assessments will be performed on an eDiary device and will start the evening of Screening Visit 2 with the requirement to continue assessments as specified in the SOA.

The investigator/authorized delegate will check participant's adherence to the eDiary assessment at each study visit. Frequent compliance checks between visits will be necessary to ensure sufficient data is available.

7.2.4.1. Electronic Diary (eDiary)

Asthma Daytime Symptom Diary, Asthma Nighttime Symptom Diary

The Asthma Daytime Symptom Diary and Asthma Nighttime Symptom Diary are asthma PRO instruments that have been accepted by the FDA Clinical Outcome Assessments Qualification Program. Each consists of six symptom questions, each on a scale of 0 ('None') to 10 ('As bad as you can imagine'). The Asthma Daytime Symptom Diary will be completed every evening before bedtime, the Asthma Nighttime Symptom Diary will be completed every morning upon waking in the eDiary. These assessments start the evening of Screening Visit 2 and continue through the morning of the Final Study Visit (Week 52 Visit or Early Termination; see [Section 6.17](#)).

Additional eDiary questions

Additionally, each morning, participants will record in the eDiary if they had any nighttime awakenings due to asthma symptoms that required the use of rescue medication. The number of rescue medication inhalations (puffs) and nebulizer treatments taken will be recorded by the participant in the eDiary. Each morning, participants will record the number of inhalations taken since bedtime. Each bedtime, participants will record the number of inhalations taken since morning.

There will be triggers in the eDiary device to alert both the participants and study center when the below worsening thresholds are crossed. After receiving an eDiary alert, the participant and study center will be given instructions to make contact with each other for further evaluation, if deemed necessary by the investigator.

Worsening of asthma and related eDiary alerts

Worsening of asthma is defined as at least one of the following criteria:

- Decrease in morning peak flow $\geq 20\%$ on at least 2 consecutive days compared with baseline, and/or
- An increase in rescue medication use of four or more puffs on at least 2 consecutive days compared with the average use during the Run-in, OR use of ≥ 12 puffs on any one day, and/or
- An additional nebulized β_2 agonist use on at least 2 consecutive days compared with the average use during the Run-in, and/or
- An increase of 2 nights with awakenings due to asthma requiring rescue medication over a 7-day period compared with the average during baseline, and/or ≥ 6 out of previous 7 nights with awakenings due to asthma requiring rescue medication (this criterion should be met on 2 consecutive days), and/or
- An increase in the mean Asthma Daytime and Nighttime Symptom Diary score of at least two units above the baseline average (see [Section 11.4.1](#)) or the highest possible score (daily score of 10), on at least 2 consecutive days. The mean Asthma Daytime and Nighttime Symptom Diary total asthma symptom score is defined as the mean of all completed items for a given calendar day.

The participant will be provided with an integrated home spirometry/eDiary device (AM3) at Screening Visit 2. Home PEF testing will be performed by the participant in the morning upon awakening (and prior to taking their morning asthma controller). Participants should perform three successive peak flow maneuvers with the highest of the three values being used for evaluation.

If any of these criteria are met while a participant is in the Run-in, or treatment periods of the study, they may be withdrawn if, in the opinion of the investigator, it is appropriate to do so.

Worsening of asthma symptoms may require unscheduled evaluation between visits. Study site personnel must document the participant's progress until the asthma worsening has resolved.

7.2.4.2. Asthma Control Questionnaire (ACQ-6)

The ACQ is a validated tool designed for use as a measurement of asthma symptom control [[Juniper et al, 1999](#)]. The ACQ measures both the adequacy of asthma control and change in asthma control, which may occur either spontaneously or as a result of treatment.

The ACQ-6 has six self-administered questions (five questions about asthma symptoms, and one question on rescue bronchodilator use). Participants are asked to recall how their asthma has been during the previous week and to respond to the symptom and bronchodilator use questions on a 7-point scale (0=no impairment, 6= maximum impairment). Questions are weighted equally and scored from zero (totally controlled) to six (severely uncontrolled). The mean ACQ-6 score is the mean of the responses. Mean scores of ≤ 0.75 indicate well-controlled asthma, scores between 0.75 and ≤ 1.5 indicate partly controlled asthma, and a score >1.5 indicates uncontrolled asthma [[Juniper et al, 2006](#)]. Individual changes of at least 0.5 are considered to be clinically meaningful and is the responder definition for ACQ [[Juniper et al, 2005a](#)]. All participants enter the study with a mean ACQ-6 score ≥ 1.5 .

The ACQ-6 will be completed at the site using an electronic tablet at the timepoints specified in the SOA.

7.2.4.3. Standardized version of the Asthma Quality of Life Questionnaire for 12 years and older (AQLQ+12)

The AQLQ, a disease-specific health-related quality of life instrument was developed to measure the functional impairments experienced by adults 17 years and older with asthma [Juniper et al, 1992]. This questionnaire has been updated over time and is considered the gold standard for measuring asthma quality of life for adults (18–80 years) [Juniper et al, 1999]. More recently the same scale was validated for use in patients 12 years and older [Juniper et al, 2005b].

This study will use the standardized version of the Asthma Quality of Life Questionnaire for 12 years and older [Juniper et al, 2005b]. Participants will be asked to recall their experiences during the previous 2 weeks and to score each of the 32 questions on a 7-point scale ranging from 7 (no impairment) to 1 (severe impairment). The overall score is calculated as the mean response to all questions. The four domain scores (symptoms, activity limitations, emotional function and environmental stimuli) are the means of the responses to the questions in each of the domains. The minimally important difference on the AQLQ+12 is 0.5 on a 7-point scale [Juniper et al, 2005b].

The AQLQ+12 will be completed at the site using an electronic tablet at the timepoints specified in the SOA.

7.2.4.4. EuroQol-5 Dimensional Questionnaire (EQ-5D-5L)

The EuroQol five-dimensional questionnaire (EQ-5D) is a generic measure of health status that provides a simple descriptive profile and a single index value that can be used in the clinical and economic evaluation of health care and in population health surveys [Rabin and de Charro, 2011]. EQ-5D was introduced in 1990 by the EuroQol Group has been widely used in different countries by clinical researchers in a variety of clinical settings [About EQ-5D-5L, 2022].

This study will use the EQ-5D-5L. Each participant will rate their health “today” on each of five dimensions: mobility, self-care, usual activities, pain/discomfort, anxiety/depression [About EQ-5D-5L, 2022]. Each dimension has five response options (no problems, slight problems, moderate problems, severe problems, and extreme problems) that reflect increasing levels of difficulty. The participant is asked to indicate his/her current health state by selecting the most appropriate level in each of the five dimensions resulting in a one-digit number that expresses the level selected for that dimension. The digits for the five dimensions can be combined into a five-digit number that describes the patient’s health state.

The questionnaire also includes a visual analogue scale, where the participant will be asked to rate current health status on a scale of 0 to 100, with 0 being “the worst health you can imagine” and 100 being “the best health you can imagine”.

The EQ-5D-5L will be completed at the site using an electronic tablet at the timepoints specified in the SOA.

7.3. Assessment of Pharmacokinetics

Plasma samples from each participant will be drawn to measure drug concentrations as per the SOA. Samples will be drawn prior to dosing with investigational drug, and 2 hours post dose. For participants that permanently discontinue investigational product but continue in the study, PK assessments following investigational product discontinuation should not be performed.

Methods for the collection, processing, storage, and shipment of PK samples will be provided in the Study Laboratory Manual.

Plasma PK samples will be taken and stored during the course of this study.

8. ADVERSE EVENTS

8.1. Definitions

8.1.1. Adverse Event

An adverse event (AE) is any untoward medical occurrence associated with the use of a drug in humans and which does not necessarily have to have a causal relationship with this treatment. An AE can be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product [ICH E2A Guideline, 1994].

Isolated laboratory, vital sign, or ECG abnormalities should be recorded as AEs only if associated with one of the following:

- a. clinical findings (abnormal finding on physical exam, symptoms, or disease),
- b. corrective treatment, or consultation, or
- c. study drug interruption or discontinuation

8.1.2. Serious Adverse Event

A SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is life threatening, ie, the participant was, in the opinion of the investigator, at immediate risk of death from the event as it occurred (it does not include an event that, had it occurred in a more severe form, might have caused death)
- Results in a significant, persistent or permanent change, impairment, damage or disruption in the participant's body function/structure, physical activities and/or quality of life
- Requires in-participant hospitalization or prolongs hospitalization
- Is a congenital anomaly/birth defect, or
- Is an important medical event

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse.

A distinction should be drawn between serious and severe AEs. Severity is an estimate or measure of the intensity of an AE, while the criteria for serious AEs are indications of adverse participant outcomes for regulatory reporting purposes. A severe AE need not necessarily be considered serious and a serious AE need not be considered severe. For example, nausea that persists for several hours may be considered severe nausea, but not an SAE. On the other hand, a myocardial infarction that may be considered minor could be an SAE if it prolonged hospitalization.

A prescheduled or elective procedure or a routinely scheduled treatment requiring hospitalization will not be considered an SAE.

- The prescheduled or elective procedure or routinely scheduled treatment are those that were scheduled (or was on a waiting list to be scheduled) prior to obtaining an individual's consent to participate in the study.
- The condition requiring the prescheduled or elective procedure or routinely scheduled treatment were the study pre-existing conditions and did not worsen or progress in the opinion of the site investigator between the participant's consent to participate in the study and the time of the procedure or treatment.
- The prescheduled or elective procedure or routinely scheduled treatment is the sole reason for hospital admission.

Protocol defined asthma exacerbation events are collected as efficacy endpoints ([Section 7.2.1](#)) and should only be reported as safety events if they meet the criteria for an SAE.

8.1.3. Adverse Events of Special Interest

An adverse event of special interest (AESI; serious or non-serious) is one of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the Sponsor can be appropriate. Such an event warrants further investigation to characterize and understand it.

In this study, supraventricular and ventricular cardiac arrhythmias, MACE, and severe or unusual infections are classified as AESIs. Clinical accuracy of the reported cardiac AESIs will be adjudicated by an independent adjudication committee (see [Section 3.4](#)).

8.1.3.1. Cardiac arrhythmias

The following events of supraventricular and ventricular arrhythmias will require ongoing monitoring and prompt communication to the Sponsor:

- Supraventricular arrhythmias: inappropriate sinus tachycardia, paroxysmal atrial tachycardia, atrial flutter, atrial fibrillation
- Ventricular arrhythmias: ventricular tachycardia, ventricular flutter, ventricular fibrillation

Detailed information for supraventricular and ventricular cardiac arrhythmia will be collected in the eCRF.

The event also must be reported to the Sponsor via the SAE Report Form within 24 hours if the event meets SAE criteria.

The study drug treatment must be interrupted and could be discontinued by the investigator after consulting with the Sponsor.

8.1.3.2. Major adverse cardiovascular events (MACE)

MACE includes cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke (ischemic and hemorrhagic).

MACE must be reported to the Sponsor via the SAE Report Form within 24 hours.

8.1.3.3. Severe or unusual infections

Severe or unusual infection is defined as any infection fulfilling any of the below criteria:

- life threatening
- requires hospitalization
- requires treatment with parenteral antibiotic/antiviral/antifungal agent
- helminth infection
- opportunistic infection
- resulted in a permanent discontinuation of study drug

Participants who develop an SAE of infection concurrent with ANC $<1.500 \times 10^9/L$ will be permanently discontinued from IP.

Specific analyses of infection AEs in study participants with the laboratory defined neutropenia will be performed, as detailed in [Section 11.5.4.3](#) and [Section 11.5.4.4](#).

8.2. Assessment of Adverse Events

8.2.1. Adverse Event Severity

The severity of AEs will be assessed by the investigator using the 3-point scale below in [Table 5](#):

Table 5: Adverse Event Severity Definitions

Severity	Definition
Mild	Symptom(s) barely noticeable to participant or does not make participant uncomfortable; does not influence performance or functioning; treatment not ordinarily needed for relief of symptom(s) but may be given.
Moderate	Symptom(s) of a sufficient severity to make participant uncomfortable; performance of daily activity is influenced; participant is able to continue in study; treatment for symptom(s) may be needed.
Severe	Symptom(s) cause severe discomfort; symptoms cause incapacitation or significant impact on participant's daily life; severity may cause discontinuation of treatment with investigational product; treatment for symptom(s) may be given and/or participant may be hospitalized.

8.2.2. Relationship to Investigational Product

The relationship between the AE and the investigational product will be assessed by using a binary assessment. The investigator should determine whether there is a 'reasonable possibility' or 'no reasonable possibility' that the investigational product caused the event based on the following definitions:

Reasonable possibility - There is a reasonable possibility that the administration of the investigational product caused the AE. There is evidence to suggest a causal relationship between the investigational product and the AE.

No reasonable possibility - There is no reasonable possibility that the administration of the investigational product caused the AE. There is no temporal relationship between the investigational product and event onset, or an alternative etiology has been established.

8.3. Requirements For Additional Safety Data Collection

8.3.1. Medication Errors

A medication error is an unintended failure or mistake in the treatment process by study drug that either causes harm to the participant or has the potential to cause harm to the participant.

The situations designated as medication errors in this study include:

- Wrong investigational product administered to participant
- Study drug not administered as indicated, eg, wrong route or wrong site of administration
- Study drug not taken as indicated eg, tablet dissolved in water when it should be taken as a solid tablet
- Accidental overdose (see [Section 8.3.2](#))
- Accidental exposure, eg, wrong participant received study drug
- Study drug not stored as instructed eg, kept in the refrigerator when it should be at room temperature

Medication errors are not regarded as AEs, but AEs may occur as a consequence of a medication error. Medication errors with or without an associated AE should be recorded as medication errors in the eCRF.

Medication errors and an associated SAE should be recorded in the eCRF and reported as described in [Section 8.4.1](#). Medication errors and an associated non-serious AE should be recorded in the eCRF as described in [Section 8.4.2](#).

8.3.2. Overdose

An overdose is any dose of investigational product given to a participant or taken by a participant that exceeds the dose described in the protocol (more than two doses in a 12-hour period).

Overdose itself is not considered an AE; however, if the overdose results in clinical signs and symptoms, it requires an expedited reporting via SAE form as if it is SAE (within 24 hours).

Dosing information and clinical signs and symptoms should also be recorded on the corresponding eCRF pages.

There is no known antidote for an overdose of dexpramipexole.

8.3.3. Pregnancy

Pregnant women are excluded from the study. If a participant or participant's partner becomes pregnant during the course of the study, the investigational product administration must be discontinued, and the pregnancy should be followed through to outcome. Follow-up information on newborns from pregnant participant or participant partners will be sought.

Participants should not become pregnant during the study. Participants must be counseled to the contraception requirements of the protocol and should contact the site as soon as possible if they (or their partner) suspect a pregnancy. If a participant becomes pregnant, investigational product must be discontinued *immediately*.

The site investigator must report the pregnancy to the Sponsor using a study pregnancy form within 24 hours of the study site staff becoming aware of the pregnancy. The pregnancy should be followed to term. The site investigator or study site staff must report the outcome of the pregnancy to the Sponsor or its designated representative.

Please note that congenital abnormalities or birth defects in the offspring of male or female participants should be reported if conception occurs during the study treatment period and the study follow-up period.

8.3.3.1. Contraception requirements

For the purpose of this protocol, a woman is considered of childbearing potential (WOCBP), ie, fertile, following menarche and until becoming postmenopausal unless permanently sterile.

WOCBP must take the appropriate precautions to avoid pregnancy during studies with dexpramipexole and for at least 1 month after their last dose of study treatment (through Final Study Visit).

For the purpose of this protocol, a man is considered fertile after puberty unless permanently sterile by bilateral orchiectomy.

Male participants with partners of childbearing potential must take the appropriate precautions to avoid pregnancy during studies with dexpramipexole and for at least 1 month after their last dose of study treatment (through Final Study Visit).

Highly effective birth control methods that result in a failure rate of less than 1% per year when used consistently and correctly include those methods in [Table 6](#).

Table 6: Highly Effective Birth Control

-
- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation
 - Oral
 - Intravaginal
 - Transdermal
 - Progestogen-only hormonal contraception associated with inhibition of ovulation ¹
 - Oral
 - Injectable
 - Implantable ¹
 - Intrauterine device (IUD) ¹
 - Intrauterine hormone-releasing system (IUS) ¹
 - Bilateral tubal occlusion ¹
 - Vasectomized partner ^{1,2}
 - Sexual abstinence ³
-

¹ Contraception methods considered to have low user dependency.

² Vasectomized partner is a highly effective birth control method provided that partner is the sole sexual partner of the women of childbearing potential study participant and that the vasectomized partner has received medical assessment of the surgical success.

³ In the context of this protocol sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the participant.

Protocol acceptable birth control methods that result in a failure rate of more than 1% per year include those methods in Table 7. If a highly effective method of birth control is not used by the participant or partner, a combination of two forms of protocol acceptable birth control must be used in tandem, consistently and correctly for the participant to qualify for the study.

Table 7: Protocol Acceptable Birth Control (When Used in Tandem)

-
- Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action
 - Male or female condom with or without spermicide ¹
 - Cap, diaphragm or sponge with spermicide ¹
-

¹ A combination of male condom with either cap, diaphragm or sponge with spermicide (double barrier methods) are also considered acceptable

Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method are not acceptable methods of contraception.

8.4. Adverse Event Reporting and Follow-up

8.4.1. Serious Adverse Events

All SAEs that occur from consent through EOS must be recorded on the source documents and reported to Sponsor's Global Pharmacovigilance Department representative within 24 hours of awareness of the event using the SAE Report Form. SAEs for randomized participants must be entered into the eCRF from time of consent onwards.

The investigator should provide any follow-up information for the event to the Sponsor on an updated SAE Report Form within 24 hours of learning of the new information. The Sponsor will

contact the investigator, if necessary, to clarify any of the event information or request additional information.

Where appropriate, if required by local regulations or procedures, the investigator should report these events to the IRB/EC and/or national regulatory authority in addition to the Sponsor.

8.4.2. Non-Serious AEs

All non-serious AEs that occur from consent through EOS must be assessed and recorded on the source documents. AEs for randomized participants will be entered into the CRF from time of consent onwards, regardless of causal relationship to the investigational product.

8.4.3. Follow-up of Adverse Events

Adverse events or abnormal test findings must be followed until the event (or its sequelae) or the abnormal test finding resolves, stabilizes at a level acceptable to the Sponsor/investigator and/or returns to Baseline values. For details on follow-up of laboratory defined neutropenia please refer to [Section 7.1.6.1.1](#).

Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study and he/she considers the event to be reasonably related to the study drug or study participation, the investigator must promptly notify the Sponsor.

8.5. Expectedness

8.5.1. Expectedness Determination

The Sponsor's Safety Department representative will be responsible for determining whether an AE is expected or unexpected for the purpose of reporting suspected unexpected serious adverse reaction (SUSAR) to regulatory authorities. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the safety information previously described for the investigational product in the current/approved version of the Investigator's Brochure.

9. DATA COLLECTION

9.1. Use of Electronic Case Report Form

Participants data will be collected using an electronic data capture (EDC) system that comply with 21 Code of Federal Regulations Part 11 and data integrity requirements. External data collected outside of EDC system will be transferred and processed according to study-specific data agreements. To access EDC, the users are required to be trained by a qualified person on the technical features of the EDC including the content of the eCRFs created within the EDC system for study data collection. Upon completion of training, each user is assigned a password-protected user ID to access the EDC system. User ID is a unique account and must not be shared with anyone including the study staff.

Entry of data into the eCRFs must be completed by investigative site staff within 3 days after each visit per clinical study agreement with the site. Prior to the database being locked, the investigator or designee will review, approve and sign/date each completed eCRF. This signature serves as attestation of the investigator's responsibility for ensuring that all data entered in the eCRF are complete, accurate and authentic. At the end of the study, a copy of the data will be provided to the site containing the final data of all participants at the site, an audit trail of activity on the data, and any data queries and responses. The data will be electronically delivered using storage devices (eg, USB).

9.2. Study Site Monitoring

The Sponsor has ethical, legal and scientific obligations to carefully follow this study in accordance with established research principles and applicable regulations. The investigator, as part of his/her responsibilities, is expected to cooperate with the Sponsor in ensuring that the study adheres to the protocol and GCP requirements.

As part of a concerted effort to fulfill these obligations, the Sponsor's monitor will visit the center(s) during the study in accordance with the monitoring plan set forth for this study. The investigator will permit the Sponsor to monitor the study as frequently as is deemed necessary and provide access to medical records/source documents to ensure that data are being recorded adequately, that data are verifiable, and that protocol adherence is satisfactory.

10. SAMPLE MANAGEMENT

PK samples will be drawn and stored during the course of the study until the time at which the PK assay is run. Remaining PK samples will be destroyed after completion of the clinical study report.

11. STATISTICAL CONSIDERATIONS

This is a Phase III, randomized, double-blind, placebo-controlled, parallel-group, multicenter study in approximately 300 centers across regions.

A total of approximately 1395 participants with severe eosinophilic asthma will be randomly allocated in a 1:1:1 ratio (465 participants per group) to either dexpramipexole 75 mg BID, dexpramipexole 150 mg BID, or placebo, administered orally for 52 weeks. The randomization will use permuted blocks and will be stratified by region (Ex-US versus US), age (12 to <18 years versus ≥ 18 years), AEC ($<0.30 \times 10^9/L$ versus $\geq 0.30 \times 10^9/L$). The enrollment into AEC strata will be capped for each treatment arm so that the AEC $\geq 0.30 \times 10^9/L$ stratum represents two-thirds of the study population.

Individuals are expected to participate in the study for approximately 13 months (14 months if the subject participates in the Safety Follow-up) from screening, or until the occurrence of one of the following events, whichever occurs first:

- A recommendation of discontinuation by the investigator or Sponsor,
- A decision by the participant to discontinue for any reason,
- Sponsor's decision to stop the study prematurely.

A separate Statistical Analysis Plan (SAP) will be developed and finalized before database lock and study unblinding and will provide a more detailed description of data analysis and presentation.

All personnel involved with the analysis and conduct of the study will remain blinded until database lock. Clinical study protocol deviations will be identified prior to database lock, in a blinded fashion.

11.1. Statistical Hypotheses and Multiple Testing Strategy

The primary and key secondary hypotheses tested in this study are detailed in [Table 8](#).

Table 8: Primary and Key Secondary Hypotheses

Null hypotheses	Alternative hypotheses
Primary comparison	
H₀₁ : AAER ratio for the dexpramipexole 150 mg BID group versus placebo in the AEC $\geq 0.30 \times 10^9/L$ stratum = 1	H₁₁ : AAER ratio for the dexpramipexole 150 mg BID group versus placebo in the AEC $\geq 0.30 \times 10^9/L$ stratum $\neq 1$
H₀₂ : AAER ratio for the dexpramipexole 75 mg BID group versus placebo in the AEC $\geq 0.30 \times 10^9/L$ stratum = 1	H₁₂ : AAER ratio for the dexpramipexole 75 mg BID group versus placebo in the AEC $\geq 0.30 \times 10^9/L$ stratum $\neq 1$
Key secondary comparisons	
H₀₃ : Difference in mean absolute change from baseline in pre-BD FEV ₁ averaged across visits at Weeks 36, 44, and 52 for dexpramipexole 150 mg BID versus placebo in the AEC $\geq 0.30 \times 10^9/L$ stratum (dexpramipexole 150 mg BID minus placebo) = 0	H₁₃ : Difference in mean absolute change from baseline in pre-BD FEV ₁ averaged across visits at Weeks 36, 44, and 52 for dexpramipexole 150 mg BID versus placebo in the AEC $\geq 0.30 \times 10^9/L$ stratum (dexpramipexole 150 mg BID minus placebo) $\neq 0$
H₀₄ : Difference in mean absolute change from baseline in pre-BD FEV ₁ averaged across visits at Weeks 36, 44, and 52 for dexpramipexole 75 mg BID versus placebo in the AEC $\geq 0.30 \times 10^9/L$ stratum (dexpramipexole 75 mg BID minus placebo) = 0	H₁₄ : Difference in mean absolute change from baseline in pre-BD FEV ₁ averaged across visits at Weeks 36, 44, and 52 for dexpramipexole 75 mg BID versus placebo in the AEC $\geq 0.30 \times 10^9/L$ stratum (dexpramipexole 75 mg BID minus placebo) $\neq 0$
H₀₅ : Difference in mean absolute change from baseline in mean ACQ-6 score averaged across visits at 36, 44, and 52 weeks for dexpramipexole 150 mg BID versus placebo in the AEC $\geq 0.30 \times 10^9/L$ stratum (dexpramipexole 150 mg BID minus placebo) = 0	H₁₅ : Difference in mean absolute change from baseline in mean ACQ-6 score averaged across visits at 36, 44, and 52 weeks for dexpramipexole 150 mg BID versus placebo in the AEC $\geq 0.30 \times 10^9/L$ stratum (dexpramipexole 150 mg BID minus placebo) $\neq 0$
H₀₆ : Difference in mean absolute change from baseline in mean ACQ-6 score averaged across visits at 36, 44, and 52 weeks for dexpramipexole 75 mg BID versus placebo in the AEC $\geq 0.30 \times 10^9/L$ stratum (dexpramipexole 75 mg BID minus placebo) = 0	H₁₆ : Difference in mean absolute change from baseline in mean ACQ-6 score averaged across visits at 36, 44, and 52 weeks for or dexpramipexole 75 mg BID versus placebo in the AEC $\geq 0.30 \times 10^9/L$ stratum (dexpramipexole 75 mg BID minus placebo) $\neq 0$
H₀₇ : Difference in mean absolute change in mean AQLQ+12 score from baseline to Week 52 for dexpramipexole 150 mg BID versus placebo in the AEC $\geq 0.30 \times 10^9/L$ stratum (dexpramipexole 150 mg BID minus placebo) = 0	H₁₇ : Difference in mean absolute change in mean AQLQ+12 score from baseline to Week 52 for dexpramipexole 150 mg BID versus placebo in the AEC $\geq 0.30 \times 10^9/L$ stratum (dexpramipexole 150 mg BID minus placebo) $\neq 0$
H₀₈ : Difference in mean absolute change in mean AQLQ+12 score from baseline to Week 52 for dexpramipexole 75 mg BID versus placebo in the AEC $\geq 0.30 \times 10^9/L$ stratum (dexpramipexole 75 mg BID minus placebo) = 0	H₁₈ : Difference in mean absolute change in mean AQLQ+12 score from baseline to Week 52 for dexpramipexole 75 mg BID versus placebo in the AEC $\geq 0.30 \times 10^9/L$ stratum (dexpramipexole 75 mg BID minus placebo) $\neq 0$
The direction of superiority of dexpramipexole is indicated by a AAER ratio less than one and a difference in means greater than 0	

Abbreviations: AAER=annualized asthma exacerbation rate; ACQ=Asthma Control Questionnaire; AEC=absolute eosinophil count; AQLQ+12=standardized version of the Asthma Quality of Life Questionnaire for 12 years and older; BID=twice daily; FEV₁=forced expiratory volume in 1 second; pre-BD=pre-bronchodilator

To strongly control the overall type I error rate for all tested endpoints across dose groups, a hierarchical testing procedure will be applied at a two-sided 5% significance level, ie, each hypothesis will be formally tested only if the preceding one is significant at the 5% level. The primary hypothesis H₀₁ will be tested first, followed by the primary hypothesis H₀₂, followed by the key secondary hypotheses H₀₃ to H₀₈, according to the order specified in Table 8. If all

secondary null hypotheses are rejected, the remaining list of secondary endpoints to be tested according to the hierarchical order that will be specified in SAP.

11.2. Sample Size and Power for the Primary Endpoint

The sample size is based on the primary objective to demonstrate that dextramipexole reduces the AAER compared to placebo in the stratum of participants with screening AEC $\geq 0.30 \times 10^9/L$.

The sample size will be approximately 465 participants per arm, which corresponds to 310 and 155 participants in the high and low eosinophil strata (screening $\geq 0.30 \times 10^9/L$ and $< 0.30 \times 10^9/L$), respectively.

Since the primary comparison will be performed on all available data, including those collected after treatment discontinuation, no adjustment of the required number of randomized participants to account for any unevaluable participants is applied.

The AAER is assumed to follow a negative binomial distribution, with shape parameter $k=0.8$ (overdispersion). This value is the average of the shape parameters estimated in four recent trials. [Bleecker et al, 2016; Brightling et al, 2021; Castro et al, 2018; FitzGerald et al, 2016]. The assumed mean AAER with placebo is based on results of these previous studies.

A reduction of 40% in exacerbation rate is the targeted treatment effect size. The sample size of 310 participants per arm in the high screening eosinophil strata provides at least 95% power to demonstrate superiority of dextramipexole 150 mg BID over placebo at a two-sided significance level of 0.05, with the assumed 40% reduction from placebo in the AAER, ie a decrease from a mean annualized exacerbation rate of 1.1 to 0.66 (AAER ratio 0.60). The sample size was calculated per Zhu and Lakkis, 2014. Based on historical data demonstrating comparable clinical outcomes despite differences in eosinophil lowering effects [Ortega et al, 2014, Bleecker et al, 2016; FitzGerald et al, 2016] and lack of clear dose response on FEV₁ in the dextramipexole Phase II asthma study, a similar treatment effect size with the 75 mg BID dose is assumed. Assuming a similar treatment effect size with the 75 mg BID dose, the same marginal power is achieved in that dose group as well.

The number of participants included in the low eosinophil stratum is based on a 2:1 stratification for AEC above and below $0.30 \times 10^9/L$ and does not assume specific power calculations for the low AEC stratum, which is expected to achieve attenuated clinical responses, consistent with prior development programs in severe eosinophilic asthma [Bleecker et al, 2016; FitzGerald et al, 2016]. When adding the AEC $< 0.30 \times 10^9/L$ stratum, the total sample size for the entire study will be approximately 1395 participants with severe asthma.

11.3. Populations for Analyses

The following populations will be used for the analyses:

- The intention-to-treat population (ITT) will consist of any participant who has been allocated to a randomized treatment regardless of whether the treatment was taken or not.

- The modified ITT (mITT) population will consist of all randomized participants who received at least one dose of investigational product, irrespective of their protocol adherence and continued participation in the study. Efficacy analyses will be performed in the mITT population and will consider participants in the treatment arm they were randomized to and in the screening AEC stratum as used at randomization. The primary analysis of the primary endpoint will be performed in the mITT population restricted to the $AEC \geq 0.30 \times 10^9/L$ stratum.
- The safety population will consist of all randomized participants who received at least one dose of investigational product. Participants will be analyzed according to the treatment they received.

11.4. General Statistical Considerations and Definitions

11.4.1. Definition of Baseline

In general, the last measurement on or prior to the date of randomization will be used as the baseline measurement. If no value is available for an outcome variable on or prior to the date of randomization, the baseline value will not be imputed and will be considered missing.

For weekly means derived from participant diaries, baseline is defined as the mean of the available data in the most recent week prior to the first dose of study treatment. If more than 3 days are missing, then the baseline weekly mean will be set to missing.

Further details regarding baseline definitions and imputation rules will be provided in the SAP.

Absolute change from baseline is defined as the absolute difference between the measurement at the relevant post-randomization timepoint and the baseline value. Percent change from baseline is defined as the absolute change from baseline divided by the baseline value.

11.4.2. Study Period

The observational period for the efficacy study analysis is the 52-week Treatment Phase after randomization (see [Section 6](#)) or period from randomization to the last contact date. Any event occurring beyond the defined observational period, even if collected in the eCRF, will not be included in the planned statistical analysis.

The observational period for the safety analysis lasts from Day 1 up until the end of the study or entry into an extension study.

All data, including that reported after the defined observational period, will be included in the participant data listings.

11.4.3. General Statistical Methods

Data will be summarized as follows

- Categorical data will be summarized in contingency tables presenting frequencies (number of participants) and percentages.

- Continuous data will be summarized using number of non-missing values (n), mean, standard deviation, median, minimum and maximum values. First and third quartiles could be added in case of well-known asymmetric distribution.

11.4.4. Missing Data Handling

All available collected data will be included in data listings and tabulations. If a value is missing at baseline then the most recent available value from screening will be used as baseline. No imputation of missing data is planned for safety endpoints. Further details regarding handling of missing efficacy data will be provided in the SAP.

11.5. Statistical Methods Analyses

11.5.1. Participant's Disposition

The number of participants in the defined study populations will be presented. Participants excluded from each population will be listed with the reason for exclusion.

Frequency and percentages of participant disposition and reasons for discontinuation of investigational product will be presented. Participants who prematurely discontinue the investigational product will be listed along with the reason for discontinuation. In addition, frequency and percentages of withdrawal from the study, together with reasons, will be presented.

11.5.2. Demographic and Baseline Characteristics

Demographics and baseline participant characteristics including baseline measurements of efficacy parameters will be summarized by treatment group and by baseline AEC strata ($<0.30 \times 10^9/L$ versus $\geq 0.30 \times 10^9/L$) in the mITT population.

11.5.3. Efficacy Analysis

Unless otherwise specified, efficacy analyses are conducted in the mITT population and with respect to AEC stratum.

11.5.3.1. Primary efficacy endpoint

The primary estimand of the study is defined and analyzed as described in [Section 2.5](#).

Supplemental and key secondary estimands will be fully described in the SAP.

11.5.3.1.1. Primary Analysis Method (Primary hypothesis H₀₁ and H₀₂)

The AAER comparisons (dexpramipexole 150 BID versus placebo and dexpramipexole 75 BID versus placebo) will be performed primarily in the screening AEC $\geq 0.30 \times 10^9/L$ stratum, according to treatment group as assigned at randomization in the mITT population. It will include all severe exacerbations which occurred at any time during the 52-week double-blind treatment period, assuming missing data are MAR.

The summary measure is the ratio (dexpramipexole 150 mg BID/75 mg BID over placebo) of mean annualized AAER in the population of participants with screening AEC $\geq 0.30 \times 10^9/L$, regardless of treatment discontinuation.

MAR is assumed for the primary analysis, as for participants who discontinue treatment, every effort will be made to obtain continued follow-up. Therefore, all exacerbations will be included in the analysis, including those which occurred after investigational product discontinuation. If a participant withdraws from study prior to the end of 52-week treatment period, all observed severe exacerbation events up to the last contact date will be included in the analysis, and the observation duration is defined as the time from randomization to the date of study discontinuation.

If a participant remains on study until the end of the 52-week treatment period, all severe exacerbation events observed up to the Week 52 Visit will be counted, regardless of whether the participant maintained the study investigational product. If a participant withdraws from study prior to the end of 52-week treatment period, all observed severe exacerbation events up to the date of study discontinuation will be included in the analysis, and the observation duration is defined as the time from randomization to the date of study discontinuation.

The AAER will be analyzed using a generalized linear model, assuming the number of exacerbations per participant has a negative binomial probability distribution and that its expected value is related to covariate factors with a 'log link' function. The logarithm of time the participant's observation time will be used as an offset variable. The model will include covariates for:

- Fixed class effects: treatment (dexpramipexole 150 mg BID versus dexpramipexole 75 mg BID dose versus placebo), geographic region (US versus ex-US), age (12 to <18 years versus ≥ 18 years), oral corticosteroids intake as part of SoC asthma therapy (use versus non-use) and, for the analysis in the AEC $\geq 0.30 \times 10^9/L$ stratum, screening AEC ($\geq 0.40 \times 10^9/L$ versus ≥ 0.30 to $< 0.40 \times 10^9/L$).
- Continuous linear covariates: natural logarithm of the number of exacerbations in the previous year, baseline percentage of the predicted pre-BD FEV₁.

The mean AAER for each treatment arm and the estimate of the AAER ratio will be derived along with their 95% CI, based on the primary efficacy model described above.

11.5.3.1.2. Sensitivity and supplemental analyses

To assess the robustness of primary analysis results towards departures from the underlying MAR assumption, additional sensitivity analyses, will be performed, allowing for different

assumptions to be used. A tipping point analysis will be performed for the primary endpoint, using similar multiple imputation methodology to examine the impact of varying the rate parameter for missing data in participants who withdrew from the study early.

A supplemental analysis will be performed using the same method as described above for the primary analysis but using on-treatment measurements only (ie, excluding measurements collected after treatment discontinuation). The supplemental estimand targeted by this analysis is considering treatment discontinuation as an intercurrent event to be treated with a while-on-treatment strategy.

Full details of all sensitivity and supplemental analyses will be specified in the SAP.

11.5.3.2. Key Secondary Efficacy Endpoints

11.5.3.2.1. FEV₁ Analysis (hypotheses H₀₃ and H₀₄)

The absolute change from baseline in pre-BD FEV₁ across visits from Week 36 to Week 52 will be analyzed using a mixed-effect model for repeated measures (MMRM) approach. The key secondary endpoint will be evaluated in the AEC $\geq 0.30 \times 10^9/L$ screening stratum and only the data from that stratum will be used in the model. The model will include change from baseline in FEV₁ values at all post-baseline timepoints up to Week 52 as response variables, and treatment, all stratification factors used at randomization, visit, treatment-by-visit interaction, baseline FEV₁ value, and baseline-by-visit interaction as covariates. Treatment, factors used at randomization and visit will be treated as categorical variables. Baseline FEV₁ value will be treated as continuous variable.

All measurements will be included in the model, regardless of any treatment discontinuation, as participants will be encouraged to return to the clinic and to undergo assessment until Week 52. The analysis will be based on the restricted maximum likelihood method, and an unstructured correlation matrix will be used to model the within-participant errors. If the model fails to converge, alternative correlation structures will be used as will be described in the SAP. The primary result obtained from the model will be the average of the treatment effects at Week 36, Week 44, and Week 52. Statistical inferences on-treatment comparisons for the change from baseline in FEV₁ over the period from Week 36 to Week 52 will be derived from the mixed-effect model. Difference in least square mean change from baseline, with corresponding 95% CI and p-value (using Kenward-Roger approximation for the degrees of freedom) will be provided for the treatment comparison. Additionally, descriptive statistics including number of participants, mean, standard error and least squares mean of change from baseline in FEV₁ will be provided by treatment group and visit.

The summary measure is the difference between active treatment groups (dexpramipexole 150/75 mg BID minus placebo) in mean change from baseline in pre-BD FEV₁ averaged over the period from Weeks 36 to 52 in the population of participants with screening AEC $\geq 0.30 \times 10^9/L$, regardless of treatment discontinuation.

A supplemental analysis will be performed using the same method as described above, but using on-treatment measurements only (ie, excluding measurements collected after treatment discontinuation). Full details of all sensitivity and supplemental analyses will be provided in the SAP.

11.5.3.2.2. Mean ACQ-6 score (hypotheses H05 and H06)

The absolute change from baseline in mean ACQ-6 scores will be derived at all assessment timepoints and will be analyzed by MMRM.

The main analysis will be performed in the $AEC \geq 0.30 \times 10^9/L$ stratum.

The model will include change from baseline in mean ACQ-6 scores at all post-baseline timepoints up to Week 52 as response variables, and treatment, baseline mean ACQ-6 score, all stratification factors used at randomization, visit, treatment-by-visit interaction as covariates. Treatment, factors used at randomization and visit will be treated as categorical variables.

All measurements will be included in the model, regardless of any treatment discontinuation, as participants will be encouraged to return to the clinic and to undergo assessment until Week 52. The analysis will be based on the restricted maximum likelihood method, and an unstructured correlation matrix will be used to model the within-participant errors. Should the model fail to converge, alternative correlation structures will be considered (compound symmetry).

The main result obtained from the model will be the average of the treatment effects at Week 36, Week 44, and Week 52. Difference in least square mean of absolute change from baseline, with corresponding 95% CI and p-value (using Kenward-Roger approximation for the degrees of freedom) will be provided for the treatment comparison. Descriptive statistics including number of participants, and least square means scores and standard error derived from the model will be provided by treatment group for each timepoint.

The summary measure is the difference in mean change in mean ACQ-6 score from baseline averaged over weeks 36, 44, and 52 between the active treatment group (dexpramipexole 150/75 mg) BID and the placebo group in the population of participants with baseline $AEC \geq 0.30 \times 10^9/L$, regardless of treatment discontinuation.

Full details of all sensitivity and supplemental analyses will be detailed in the SAP.

11.5.3.2.3. Mean AQLQ+12 score (hypotheses H07 and H08)

The absolute change from baseline in mean AQLQ+12 scores will be derived at all assessment timepoints and will be analyzed by MMRM.

The main analysis will be performed in the $AEC \geq 0.30 \times 10^9/L$ stratum.

The model will include change from baseline in mean AQLQ+12 scores at Week 28 and Week 52 as response variables, and treatment, baseline mean AQLQ+12 score, all stratification factors used at randomization, visit, treatment-by-visit interaction as covariates. Treatment and factors used at randomization and visit will be treated as categorical variables.

All measurements will be included in the model, regardless of any treatment discontinuation, as participants will be encouraged to return to the clinic and to undergo assessment until Week 52. The analysis will be based on the restricted maximum likelihood method, and an unstructured variance covariance matrix will be used to model the within-participant correlation. Should the model fail to converge, alternative variance covariance matrix structures will be considered (eg, compound symmetry).

The main result obtained from the model will be the treatment effect at Week 52. Difference in least square mean of absolute change from baseline, with corresponding 95% CI and p-value

(using Kenward-Roger approximation for the degrees of freedom) will be provided for the treatment comparison. Descriptive statistics including number of participants, and least square means scores and standard error derived from the model will be provided by treatment group for each timepoint.

The summary measure is the difference in mean change in mean AQLQ+12 score from baseline to Week 52 between the active treatment group (dexpramipexole 150/75 mg) BID and the placebo group in the population of participants with baseline $AEC \geq 0.30 \times 10^9/L$, regardless of treatment discontinuation.

Full details of all sensitivity and supplemental analyses will be detailed in the SAP.

11.5.3.2.4. Additional secondary comparisons

The annualized rate of severe asthma exacerbations from Week 4 to Week 52, and the frequency of exacerbations requiring an ED visit or hospitalization will be analyzed by the same methods as the primary endpoint.

Time to first clinically significant exacerbation will be analyzed using Kaplan-Meier estimates and a Cox proportional hazards regression model with the same covariates as used in the analysis of the primary endpoint.

An ACQ-6 responder analysis will also be conducted, with responder being defined as a participant who had a change from baseline value ≤ -0.5 , using a Generalized Estimating Equation model.

An AQLQ+12 responder analysis will be conducted using a Generalized Estimating Equations approach. A responder is defined as a participant who had an improvement from baseline ≥ 0.5 .

Continuous endpoints (ie, FVC, peak expiratory flow, AEC) will be analyzed using an MMRM method as described for FEV₁.

More details will be provided in the SAP.

11.5.3.3. Planned subgroup analyses

To assess the homogeneity of treatment effect, the primary and key secondary efficacy endpoint analyses will be repeated in the baseline $AEC < 0.30 \times 10^9/L$ stratum using the same methods as described for the $AEC \geq 0.30 \times 10^9/L$ stratum above, with the exception that the adjustment for baseline AEC will be based on the covariate factor $AEC < 0.15 \times 10^9/L$ versus $AEC \geq 0.15$ to $0.299 \times 10^9/L$. These analyses will be carried out for descriptive purposes only.

The complete list of subgroup analyses will be provided in the SAP.

11.5.4. Safety Analysis

The safety objectives of this study are to evaluate the safety and tolerability profile of dexpramipexole. The safety analysis will be descriptive and conducted in the safety population. Any deviation from treatment as assigned at randomization will be documented. Full details of the handling of such participants will be provided in the SAP.

The safety summary will include extent of exposure to investigational product, TEAEs, SAEs, TEAEs leading to discontinuation, severe TEAEs, and TEAEs considered related to investigational product, clinical laboratory safety data, vital signs, and ECG data.

11.5.4.1. Extent of exposure

Duration of exposure, number of doses administered, number of missed doses, cumulative total dose, and average dose over the treatment period will be summarized descriptively (N, mean, standard deviation, median, minimum, and maximum). Participants who prematurely discontinue the investigational product will be listed along with the reason for discontinuation. In addition, frequency and percentages of withdrawals from the study will be presented according to reasons.

Duration of investigational product exposure will be defined as:
last dose date – first dose date + 1 day, regardless of unplanned intermittent discontinuations.

11.5.4.2. Concomitant medications

A summary of each prior medication and concomitant medication will be provided. Medication will be coded with World Health Organization drug dictionary. Participants will be counted only once by medication. Prior medications are defined as those which stopped before first dose of investigational product. Concomitant medications are defined as those which either started or continued after first dose of investigational product.

11.5.4.3. Adverse events

The Medical Dictionary for Regulatory Activities dictionary will be used for coding AEs.

The tabulation of TEAE will be based on all events that started or worsened (increase in severity) within the period from the first administration of study medication (Day1) up until 30 days after treatment discontinuation or entry into an extension study.

TEAEs will be summarized by system organ class and preferred term, and by treatment and dose group. TEAEs will also be presented according to severity. Serious AEs will be presented as a separate table.

AESIs, as defined in [Section 8.1.3](#), will be summarized descriptively by treatment group. Additionally, each AESI category will be summarized by relatedness.

Separate analyses of infections and infestation AEs in neutropenic participants will be performed:

- a. AEs occurring $\pm$ 10 days of an ANC laboratory value $<1.500 \times 10^9/L$
- b. AEs occurring in a participant who had an ANC value $<1.500 \times 10^9/L$ at any time after randomization.

11.5.4.4. Laboratory data, vital signs, and ECG

Descriptive statistics will be presented for clinical safety laboratory data, vital signs, and ECG measures by scheduled evaluation time and treatment group. Absolute laboratory values will be compared to the relevant normal reference range, as provided by the central laboratory, and classified as low (below range), normal (within range or on the limits) or high (above range). All

values falling outside the normal reference ranges will be flagged. These classifications will also be used for shift tables.

Laboratory defined neutropenia will be analyzed using a tabulation of ANC $<0.500 \times 10^9/L$, ANC 0.500 to $0.999 \times 10^9/L$, ANC 1.000 to $1.499 \times 10^9/L$, ANC 1.500 to $1.999 \times 10^9/L$, and ANC $<1.500 \times 10^9/L$. To better characterize any laboratory findings of neutropenia that may occur, a neutropenia eCRF page will be used to obtain and analyze structured clinical information. This form will solicit findings potentially related to neutropenia, including any signs or symptoms of infection. Findings potentially related to neutropenia will be tabulated by treatment group for participants with any occurrence of ANC $<1.500 \times 10^9/L$, and additionally at Baseline and Week 20 for all participants. For participants with any occurrence of ANC $<1.500 \times 10^9/L$ a tabulation of AEs potentially related to neutropenia that started ± 10 days of a neutropenic laboratory result will be presented.

11.6. Interim Analysis and Safety Monitoring

No interim analyses of safety or efficacy data are planned. The IDMC will review safety data at regular intervals to be defined further in the IDMC charter.

12. REGULATORY AND REPORTING REQUIREMENTS

12.1. Compliance with Laws and Regulations

The study will be conducted according to the principles of the Declaration of Helsinki (World Medical Association 2013), International Conference on Harmonisation (ICH)-GCP E6(R2), applicable laws and regulations of the country in which the research is being conducted, and the requirements of all local regulatory authorities regarding the conduct of the study and protection of human participants. The study will be conducted by scientifically and medically qualified persons and the rights and welfare of the participants will be respected.

12.2. Informed Consent / Assent

The investigator or the appropriate designee is responsible for obtaining written informed consent(s) and assent where applicable, from each study participant prior to conducting any study-specific procedures. The investigator must use the most current IRB/EC approved consent form when obtaining consent. At all times, all signed and dated consent forms must be available for review by Sponsor or designee.

12.3. Institutional Review Board/Ethic Committee

The investigator must receive IRB/EC approval prior to enrolling participants. The study must be approved on an annual basis by the IRB/EC representing the participating institution. Such IRB/EC must meet all requirements as described in Title 21, Part 56 of the US Code of Federal Regulations.

12.4. Public Clinical Trial Registry

The study will be listed on a public clinical trial registry per applicable regulations.

12.5. Confidentiality

The investigator and designees, employees and agents involved in this study must comply with relevant local, state, federal and regional laws, as applicable, relating to the confidentiality, privacy, and security of participant's health information. Data generated during this study or disclosed by the Sponsor to the investigator must be used as appropriate for the execution, analysis, review, and reporting of this study. Such information shall not be used for any other purposes and will remain confidential. To ensure participant safety and in adherence with regulatory guidelines, participant personal and medical information may be reviewed by representative of the Sponsor, the IRB/EC or regulatory authorities in the case of inspection. Every reasonable effort will be made to maintain strict confidentiality. Participant names will never be used when presenting in reports, published scientific journal or medical meetings.

12.6. Data Protection

The information regarding the protection of confidentiality and personal data is included in [Appendix E](#).

12.7. Financial Disclosure

The investigator must maintain compliance with the current country-specific guidelines and regulations concerning disclosure of financial interest.

12.8. Data Quality Assurance

It is expected that the investigator comply to adherence to GCP guidelines regarding clinical data management practices/procedures to ensure accurate, consistent, and reliable data.

12.9. Records Retention

The US FDA regulations require all investigators participating in clinical investigational product/device studies to maintain detailed clinical data for one of the following periods:

- At least 2 years following the date on which a New Drug Application is approved
- Two years after the Sponsor notifies the investigator that no further application is to be filed with the FDA

Similarly, current European Union Directives / Regulations and International Conference on Harmonization guidelines collectively require that essential clinical study documents (including CRFs) other than participant's medical files must be retained for the following time period:

- For at least 15 years after completion or discontinuation of the study
- Or for at least 2 years after the granting of the last marketing authorization in the European Community and when there are no pending or contemplated marketing applications in the European Community
- Or for at least 2 years after formal discontinuation of clinical development of the investigational product/device

Participant's medical files should be retained in accordance with applicable legislation and in accordance with the maximum period of time permitted by the hospital, institution or private practice. The documents can be retained for a longer period, however, if required by the applicable regulatory requirements or by agreement with the Sponsor.

To comply with these requirements, the investigator will not dispose of any records relevant to this study without either (1) written permission from the Sponsor or (2) providing an opportunity for the Sponsor to collect such records. The investigator shall take responsibility for maintaining adequate and accurate hard copy source documents of all observations and data generated during this study, including the hard copy or discs of the final data received from the Sponsor. Such documentation is participant to inspection by the Sponsor or its agents, the FDA and/or other regulatory agencies.

13. QUALITY CONTROL AND QUALITY ASSURANCE

13.1. Protocol Deviations

This study will be conducted as described in this protocol, except for an emergency situation in which the protection, safety, and well-being of the participant requires immediate intervention, based on the judgment of the investigator (or a responsible, appropriately trained professional designated by the investigator). In the event of a deviation from the protocol due to an emergency, accident, or mistake, the investigator or designee must contact the Sponsor, or their agent, at the earliest possible time via the Medical Hotline. This will allow an early joint decision regarding the participant's continuation in the study. The investigator and the Sponsor will document this decision. The IRB/EC will be informed of all protocol changes by the investigator in accordance with the IRB/EC established procedure. No deviations from the protocol of any type will be made without complying with all the IRB/EC established procedures.

At all times, the investigator and staff must adhere to study procedures and requirements described in the IRB/EC approved protocol and study-specific guidance. There must not be any preemptive changes without first notifying the Sponsor or the IRB/EC. This applies to granting any exceptions to study entry eligibility or procedures.

Important protocol deviations may significantly impact the completeness, accuracy, and/or reliability of key study data or significantly affect a participant's rights, safety, or well-being. Data will be reviewed at sufficiently frequent periodic intervals to identify, remediate, and report those important protocol deviations as appropriate.

13.2. Protocol Amendments

Investigator should communicate requests for protocol amendments directly to the Sponsor or designee. The Sponsor may be required to discuss potential protocol amendments with the appropriate regulatory agencies. The Sponsor will notify the investigator of protocol amendment, and potential changes to the informed consent. Protocol amendments must receive regulatory and ethical review and approval, including those of the institution IRB/EC.

13.3. Auditing

The Sponsor may conduct audits at the study center(s). Audits will include, but not be limited to, the verification of investigational product supply, presence of required documents, the informed consent process, and comparison of eCRFs with source documents. The investigator agrees to permit audits conducted at a reasonable time in a reasonable manner.

Regulatory authorities worldwide may also conduct GCP inspections of investigative sites during or after the study. If notified by a regulatory authority that a Sponsor study is being inspected, the investigator must contact the Sponsor immediately and must permit regulatory authority inspections to be conducted according to regulations.

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APPENDIX A. SELECTED DRUGS KNOWN TO HAVE SUBSTANTIAL RISK OF NEUTROPENIA

Acetazolamide (Diamox)	Methimazole, Thiamazole (Tapazole)
Aminoglutethimide (Elipten)	Methotrexate
Amodiaquine	Meprobamate (Miltown)
Amoxapine (Asendin)	Olanzapine (Zyprexa)
Amphotericin B	Penicillamine (Cuprimine)
Antipyrine	Phenacetin
Azathioprine (Imuran)	Phenylbutazone
Captopril (Capoten)	Phenytoin (Dilantin)
Carbamazepine (Tegretol)	Phenazone
Carbimazole (Neomercazole)	Propylthiouracil
Chloramphenicol	Procainamide (Pronestyl, Procan)
Chloroquine	Quinine
Cimetidine (Tagamet)	Quinidine (Quinaglute, Quinidex)
Clomipramine (Anafranil)	Riluzole (Rilutek)
Chlorpromazine (Thorazine)	Rituximab (Rituxan)
Chlorpropamide (Diabinese)	Spirolactone (Aldactone)
Clozapine (Clozaril)	Sulfasalazine (Azulfidine)
Colchicine (Colcrys, Mitigare)	Ticlopidine (Ticlid)
Cyclophosphamide (Cytosan)	Tocainide (Tonocard)
Dapsone (Aczone)	Tolbutamide
Deferiprone (Ferriprox)	Valproate, Valproic acid (Depakote)
Desipramine (Norpramin, Pertofrane)	Vancomycin (Vancocin)
Digoxin (Lanoxin, others)	
Dipyridamole (Persantine)	
Dipyrrone, Metamizole	
Ethosuximide (Zarontin)	
Flecainide (Tambocor)	
Flucytosine, 5-fluorocytosine	
Ganciclovir (Cytovene, Cymevene)	
Gold salts (Auranofin, Aurothioglucose, Ridaura)	
Hydroxyurea (Hydrea)	
Oral isotretinoin (Accutane, Roaccutane)	

Based on:
Andersohn et al, 2007
Coates , 2022
Gibson et al, 2014

APPENDIX B. SELECTED DRUGS KNOWN TO HAVE SUBSTANTIAL RISK OF QT PROLONGATION

Analgesic, anesthetic, and sedative drugs: Opioids – Methadone

Antiarrhythmic drugs: Amiodarone, disopyramide, dofetilide, dronedarone, ibutilide, procainamide, quinidine, sotalol, vernakalant

Antihistamines: Astemizole

Antimicrobials:

Antimalarial: Delamanid, quinidine, quinine

Antituberculous: Bedaquiline

Antineoplastic drugs: Arsenic trioxide, ivosidenib, lenvatinib, mobocertinib, selpercatinib, vandetanib

Gastrointestinal drugs: Cisapride

Antipsychotics: Chlorpromazine, IV haloperidol, sertindole, ziprasidone

Vasodilator drugs: Bepridil

Other drugs: Levoketoconazole

APPENDIX C. INHALED CORTICOSTEROID DOSE CATEGORY FOR INCLUSION CRITERION 4 (PER GINA 2021, BOX 3-6)

Daily doses in this table are shown as metered doses.

Adults and adolescents (12 years and older)			
Inhaled corticosteroid	Total daily ICS dose (mcg)		
	Low	Medium	High
Beclometasone dipropionate (pMDI, standard particle, HFA)	200-500	>500-1000	>1000
Beclometasone dipropionate (DPI or pMDI, extrafine particle, HFA)	100-200	>200-400	>400
Budesonide (DPI, or pMDI, standard particle, HFA)	200-400	>400-800	>800
Ciclesonide (pMDI, extrafine particle, HFA)	80-160	>160-320	>320
Fluticasone furoate (DPI)	100		200
Fluticasone propionate (DPI)	100-250	>250-500	>500
Fluticasone propionate (pMDI, standard particle, HFA)	100-250	>250-500	>500
Mometasone furoate (DPI)	Depends on DPI device – see product information		
Mometasone furoate (pMDI, standard particle, HFA)	200-400		>400

Abbreviations: DPI=dry powder inhaler; HFA=hydrofluoroalkane propellant; ICS=inhaled corticosteroid; pMDI=pressurized metered dose inhaler.

APPENDIX D. NEUTROPENIA MANAGEMENT AND TREATMENT GUIDANCE

This section provides a management and treatment plan for participants that become neutropenic and is complimentary to the information included in [Section 7.1.6.1.1](#). See [Figure 3](#) below for details.

Management/Assessment

To assess ANC, particularly with signs and symptoms of infection, participants may be considered for more frequent monitoring. As clinically indicated, local labs may be performed in addition to the central labs, absolute and % eosinophil counts should remain blinded for study personnel and participants unless clinically necessary or unavoidable. If it is not possible to blind absolute and % eosinophil counts, then only the PI or treating sub-Investigators should have access to this data.

Treatment

If a participant has findings of an infection, then consider treatment based on standard of care. If there is severe neutropenia ($ANC < 0.500 \times 10^9/L$) and infection consider hospitalization for broad spectrum intravenous antibiotics, increased monitoring, and granulocyte colony-stimulating factor, as clinically warranted. Selection of the appropriate antibiotic treatment should be based on the likely source of infection, local bacteria susceptibilities, and the local standard of care.

Treatment availability and standard of care differ by region; therefore, the investigator should consult local treatment guidelines for neutropenia not associated with cancer. Examples include:

- Dale DC. How I diagnose and treat neutropenia. *Curr Opin Hematol*. 2016 Jan;23(1):1-4. doi: 10.1097/MOH.0000000000000208. PMID: 26554885; PMCID: PMC4668211.
- Schouten HC. Neutropenia management. *Ann Oncol*. 2006 Sep;17 Suppl 10:x85-9. doi: 10.1093/annonc/mdl243. PMID: 17018758.

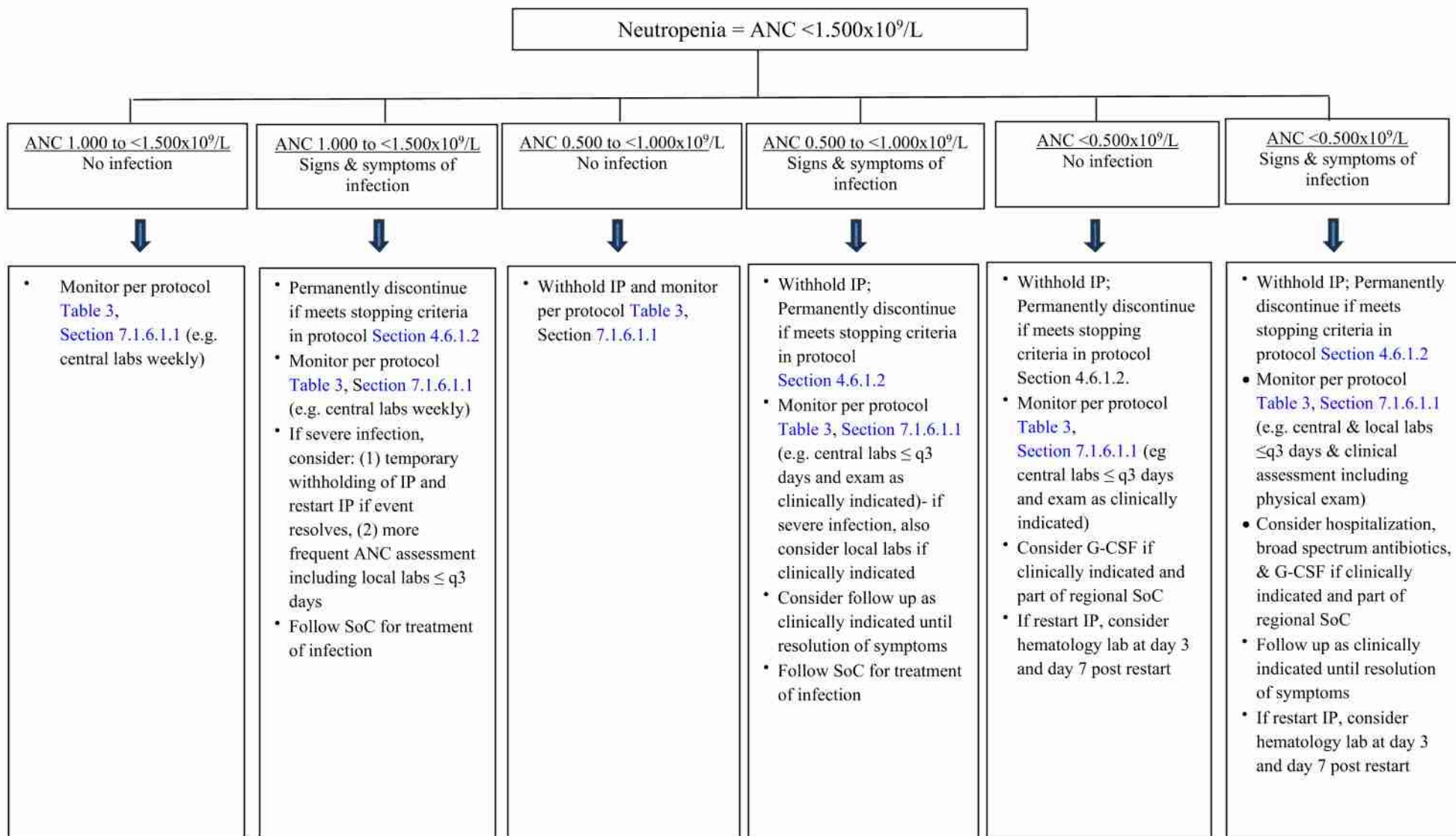
Sites should continue to closely monitor and treat participants until signs and symptoms of infection have resolved. For participants that had their investigational product temporarily withheld, investigational product can be reinitiated at the discretion of the Investigator or treating sub-Investigator and after consultation with the Medical Monitor or designee.

Events that require permanent discontinuation of investigational product

If either of the following occurs, then the participant will **permanently** discontinue investigational product. The participant may remain in the study for efficacy and safety assessments ([Section 4.6.1.2](#)):

- If a participant develops an SAE of infection concurrent with $ANC < 1.500 \times 10^9/L$
- If a participant has severe neutropenia ($ANC < 0.500 \times 10^9/L$), recovers, and experiences recurrence of severe neutropenia on rechallenge

Figure 3: Neutropenia Management and Treatment Guidance



APPENDIX E. DATA PROTECTION

Areteia Therapeutics considers the protection of the confidentiality and integrity of personal data to be a critical responsibility.

Areteia Therapeutics is committed to treating all personal data for which it is responsible and which is collected and otherwise processed in relation to any person involved in or connected to the study (including, but not limited to, participants, investigators and study staff), in compliance with all applicable data privacy laws and regulations including the General Data Protection Regulation ((EU) 679/2016).

Further, Areteia Therapeutics complies with, and is a committed participant in, the EU-U.S. Data Privacy Framework (EU-U.S. DPF) and the UK Extension to the EU-U.S. DPF, as set forth by the U.S. Department of Commerce.

Areteia Therapeutics is committed to complying with the following data protection principles when processing personal data, Areteia Therapeutics will:

- Process personal data lawfully, fairly and in a transparent manner;
- Collect personal data for specified, explicit and legitimate purposes only, and will not process it in a way that is incompatible with those legitimate purposes;
- Only process the personal data that is adequate, relevant and necessary for the relevant purposes;
- Keep the personal data accurate and up-to-date and take reasonable steps to ensure that inaccurate personal data are deleted or corrected without delay;
- Keep personal data for no longer than is necessary for the purposes for which the information is processed; and
- Take appropriate technical and organizational measures to ensure that personal data are kept secure and protected against unauthorized or unlawful processing, and against accidental loss, destruction or damage.

Personal data relating to participants in the study shall only be shared with Areteia Therapeutics in a pseudonymized format. This means that participant records and / or datasets which include personal data and which are transferred to Areteia Therapeutics shall not include information which would identify the participant or make the participant identifiable to Areteia Therapeutics. Areteia Therapeutics will have no ability to reverse engineer pseudonymized personal data transferred to it.

For the avoidance of doubt, participation in the study will involve the collection and processing of special category data which may be inclusive of personal data relating to a participant's race and ethnicity.

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Approval Task Task Verdict: Approved	
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