Clinical Study Protocol	
Study Intervention	Budesonide/Albuterol Sulfate
Study Code	AZ-RU-00004
Version	1.0
Date	29 August 2023

A Phase III, Multicentre, Randomized, Double-blind, Single-Dose, 2-Arm, 2-Period, Crossover Study to Investigate the Efficacy of PT027 Compared with Placebo on Exercise-Induced Bronchoconstriction in Adult Patients with Asthma (BREATH)

Sponsor Name: AstraZeneca Pharmaceuticals LLC

Legal Registered Address: Building 1, 21, First Krasnogvardeyskiy lane, floor 30, rooms 13 and 14, Moscow, Russian Federation

Protocol Number: AZ-RU-00004

This protocol has been subject to a peer review according to AstraZeneca Standard procedures. The protocol is publicly registered and the results are disclosed and/or published according to the AstraZeneca Global Standard - Bioethics and in compliance with prevailing laws and regulations.

Brief Title: A Study to Investigate the Effects of PT027 (Budesonide/Albuterol Sulfate) Metered-dose Inhaler Compared with Placebo on Exercise-Induced Bronchoconstriction in Adult Patients with Asthma (BREATH)

Study Phase: Phase III

Acronym: **BREATH**

Study Physician and Contact Information: AstraZeneca Study Physician name and contact information will be provided separately

Coordinating Investigator: Name and contact information will be provided separately

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF APPENDICES

1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase III, Multicentre, Randomized, Double-blind, Single-Dose, 2-Arm, 2-Period, Crossover Study to Investigate the Efficacy of PT027 Compared with Placebo on Exercise-Induced Bronchoconstriction in Adult Patients with Asthma (BREATH).

Brief Title: A Study to Investigate the Effects of PT027 (Budesonide/Albuterol Sulfate) Metered-dose Inhaler Compared with Placebo on Exercise-Induced Bronchoconstriction in Adult Patients with Asthma (BREATH)

Protocol Number: AZ-RU-00004

Rationale:

In the Russian Federation, the current clinical guidelines suggest classifying patients with asthma by the level of treatment required to maintain good disease control (MoH RF Clinical guidelines, 2021), which is also the approach adopted by the Global Initiative for Asthma guidelines (GINA guidelines, 2023). Patients with mild asthma can be controlled with Step 1 or 2 treatment and the preferred symptoms reliever option is as-needed low-dose inhaled corticosteroid (ICS) with short/rapid-acting β2-adrenoreceptor agonist (SABA).

AstraZeneca has developed a new fixed-dose combination of low-dose ICS budesonide and SABA albuterol, coded as «PT027», which has successfully proven its efficacy and safety in several international phase III clinical studies in adults, adolescents and children with asthma. Albuterol sulfate (further referred to as albuterol) is approved in Russia under the generic name of salbutamol.

The purpose of this Phase III, multicentre, randomized, double-blind, single-dose, 2-arm, 2-period, crossover study is to assess the efficacy and safety of PT027 («budesonide/albuterol (salbutamol)», metered-dose inhaler 160/180 µg) compared to placebo on exercise-induced bronchoconstriction in adult patients with asthma.

Efficacy and safety of PT027 were previously demonstrated during extensive clinical development program. But clinical centres from the Russian Federation were not involved in these clinical trials and data on Russian population was not obtained. For these reasons there is single planned PT027 study in the Russian Federation that will provide clinical data on efficacy and safety in the population of Russian patients with asthma and exercise-induced bronchoconstriction. The results of this study will provide clinical data on efficacy and safety of an innovation drug in the new region (Russian Federation), which will be an important additional data source for the PT027 approval process in Russia.

Objectives, Endpoints and Estimands:

Objectives	Endpoints
Primary	
To estimate the efficacy of PT027 (budesonide/albuterol) metered-dose inhaler as compared with placebo metered-dose inhaler after a single dose on exercise-induced bronchoconstriction in adult participants with asthma	• The maximum percentage fall from post-dose, pre-exercise baseline in forced expiratory volume in 1 second (FEV_1) observed up to 60 minutes post-exercise challenge *Population for analysis:* Full Analysis Set. The maximum percentage fall available in the 60-minute assessment period, prior to the use of rescue medication, will be calculated at Visit 3 and Visit 4. Missing results for maximum percentage fall in FEV1 (i.e., rescue medication prior to the collection of the 5 minutes measure) will not be imputed. The measure of interest is the difference between treatments in the maximum percentage fall from post-dose, pre-exercise baseline in FEV_1 observed up to 60 minutes post-exercise challenge.
Secondary	
To further estimate the efficacy of PT027 (budesonide/albuterol) metered-dose inhaler as compared with placebo metered-dose inhaler after a single dose on exercise-induced bronchoconstriction in adult participants with asthma	• The percentages of subjects with a maximum percentage fall in FEV_1 post-exercise challenge of <10% and <20%, respectively *Population for analysis:* Full Analysis Set. The percentage fall will be calculated relative to the pre-exercise FEV_1 assessment at the respective visit. The measure of interest is the odds ratio between PT027 and Placebo for each threshold separately (<10% and <20%).
	• The percentage fall from post-dose, pre-exercise baseline in FEV_1 at each timepoint within 60 minutes post-exercise challenge *Population for analysis:* Full Analysis Set. The measure of interest is the percentage fall from baseline in FEV_1 at each timepoint within 60 minutes post-exercise challenge. Only FEV_1 results prior to administration of rescue medication (within the study visit) will be included in the analyses.
	• Post-exercise FEV_1 area under the curve from 0 to 30 minutes ($AUC_{0\text{-}30min}$) *Population for analysis:* Full Analysis Set. The measure of interest is the difference between treatments in the post-exercise FEV_1 $AUC_{0\text{-}30min}$.

Objectives	Endpoints
	Only the FEV_1 $AUC_{0\text{-}30min}$ measurements prior to administration of rescue medication will be included in the analyses.
	• Time to recovery, defined as the time from completion of the exercise challenge to the first measured post-exercise challenge FEV_1 value within 10% of the post- dose, pre-exercise challenge baseline FEV_1 *Population for analysis:* Full Analysis Set. The measure of interest is the median of the time to recovery.
Safety	
To assess the safety and tolerability of PT027 (budesonide/albuterol) metered-dose inhaler as compared with placebo metered-dose inhaler after a single dose in adult participants with asthma.	Safety and tolerability will be evaluated in terms of • adverse events (AEs), • serious adverse events (SAEs), • AEs lead to discontinuation, Vital signs, physical examination, electrocardiograms (ECGs) will be analysed in terms of adverse event data. *Population for analysis:* Safety Analysis Set. The measure of interest is frequencies and percentages of participants with reported AEs.

Overall Design Synopsis:

Brief summary: The purpose of this Phase III, multicentre, randomized, double-blind, single-dose, 2-period, crossover study is to assess the efficacy and safety of PT027 (budesonide/albuterol sulfate) metered-dose inhaler compared with placebo on exercise-induced bronchoconstriction in adult patients with asthma.

Subjects will receive each study treatment on separate visits and undergo a treadmill exercise challenge test so that the effect of study treatment on exercise-induced bronchoconstriction can be evaluated.

Disclosure Statement: This is a Phase III, multicentre, randomized, double-blind, single-dose, 2-arm, 2-period, crossover study assessing the efficacy and safety of PT027 (budesonide/albuterol) compared with placebo.

Participant Population:

The target population of interest in this study is male and female participants aged 18-70 years

with asthma and exercise-induced bronchoconstriction. The study will include patients with two types of current therapy: 1) subjects currently treated only with short/rapid-acting β2-adrenoreceptor agonist (SABA) on an as-needed regimen, and 2) subjects on low-to-medium-dose inhaled corticosteroid (ICS) maintenance therapy (according to the Clinical guidelines "Bronchial asthma" of the Ministry of Health of the Russian Federation, 2021) and SABA as needed.

Number of Participants:

Approximately 107 participants will be screened to achieve 64 randomized/assigned to study intervention and 56 evaluable participants (refer to FAS population, Section 9.3) at 6 to 12 investigational centers in the Russian Federation.

Enrolled/screened*	Estimated 107 participants
Randomized/assigned	Estimated 64 participants
Evaluable participants	Estimated 56 participants

Note: * - "Enrolled/Screened" means a participant's, or their legally acceptable representative's, agreement to participate in a clinical study following completion of the informed consent process. Potential participants who are screened for the purpose of determining eligibility for the study, but are not randomized/assigned in the study, are considered "screen failures", unless otherwise specified by the protocol.

Study Arms and Duration:

Investigational Medical Product will be PT027 (budesonide/albuterol) metered-dose inhaler and a matching placebo metered-dose inhaler, which will be used as the comparator. The IMP will be administered as a single dose as follows:

- A: PT027 (budesonide/albuterol) metered-dose inhaler 160/180 µg (given as 2 inhalations of metered-dose inhaler 80/90 µg per puff)
- B: Placebo metered-dose inhaler (given as 2 inhalations)

This is a single-dose, 2-arm, 2-period, crossover study. Approximately 64 subjects will be randomized 1:1 to one of two treatment sequences – A/B or B/A, as specified in Table 1.

Table 1 Treatment Sequences

Treatment sequence	***Period 1 (Visit 3)***	***Period 2 (Visit 4)***
A/B	PT027 (BUDESONIDE/ALBUTEROL) metered-dose inhaler 160/180 µg (given as 2 actuations of 80/90 µg)	PLACEBO metered-dose inhaler (given as 2 actuations)
B/A	PLACEBO metered-dose inhaler (given as 2 actuations)	PT027 (BUDESONIDE/ALBUTEROL) metered-dose inhaler 160/180 µg (given as 2 actuations of 80/90 µg)

At Visit 3/Period 1 and Visit 4/Period 2, IMP will be administered 30 (±5) minutes prior to the PFT before exercise challenge. During the study, subjects will not be allowed to use any asthma medication other than the SABA in an as-needed regimen or ICS maintenance therapy plus SABA in an as-needed regimen that they were using before study entry. Subjects will be restricted from SABA within 6 hours before any lung function testing and/or exercise testing. Non-asthma medications which are necessary for the subject's safety and wellbeing, and which do not affect the participation in or results of the study, are allowed at the discretion of the investigator.

The randomized treatment phase will start after a 1 to 2-week screening period (Visits 1 and 2). The double-blind treatment will occur with single dosing of IMP at Visits 3 and 4, which will be approximately 1 week apart. A final follow-up visit will be conducted via a telephone call (TC) 3 to 5 days after the final in-clinic visit. The overall study duration will take approximately 3 to 4 weeks.

Data Monitoring / Other Committee:

Not applicable for this study.

Statistical Methods

The main objective of this study is to estimate the efficacy of PT027 (budesonide/albuterol) as compared with placebo based on the evaluation of the primary endpoint «maximum percentage fall from post-dose, pre-exercise baseline in FEV_1 observed up to 60 minutes post-exercise challenge». The corresponding hypotheses for the primary analysis are as follows:

- H_0: Difference between treatments «$_{\Delta}A - {}_{\Delta}B$» = 0,
- H_1: Difference between treatments «$_{\Delta}A - {}_{\Delta}B$» ≠ 0.

there: Δ - maximum percentage fall of FEV_1, A - PT027 (budesonide/albuterol), B - placebo.

The primary efficacy endpoint will be analyzed with a mixed effect model including categorical fixed effects for treatment, treatment period and treatment sequence. Continuous covariates

include period-specific pre-dose baseline FEV_1 and average pre-dose baseline FEV_1. Also, a random subject within treatment sequence effect will be specified. Post-dose, pre-exercise baseline FEV_1 will be defined as the 30 minutes post-dose value, i.e., 5 minutes before exercise challenge, at each visit for the respective treatment. The period-specific pre-dose baseline FEV_1 will be calculated separately at Visit 3 and Visit 4 as the pre-dose result, approximately 5 minutes prior to dosing. The average pre-dose baseline FEV_1 will be calculated as the mean of the period-specific pre-dose FEV_1 baselines. Estimated treatment differences and 2-sided 95% confidence intervals (CIs) will be provided.

Applied significance level (alpha): 0.05 (using a 2-sided test).

No interim efficacy analysis is planned in this study.

The secondary efficacy endpoints will be analysed using the methodology specified in Section 9.4.2.2.

Safety data will be summarized descriptively and will not be formally analyzed unless otherwise specified. Data will be presented using the safety analysis set.

Analysis sets:

Population/Analysis set	**Description**
Enrolled/Screened	All participants who sign the ICF.
Full analysis set (FAS)	All participants who are randomized to treatment and have at least one post-dose, pre-exercise baseline and at least one corresponding post-dose post-exercise FEV_1 measure at Visit 3 and/or Visit 4.
Safety analysis set	All participants who have received any amount of the study intervention.

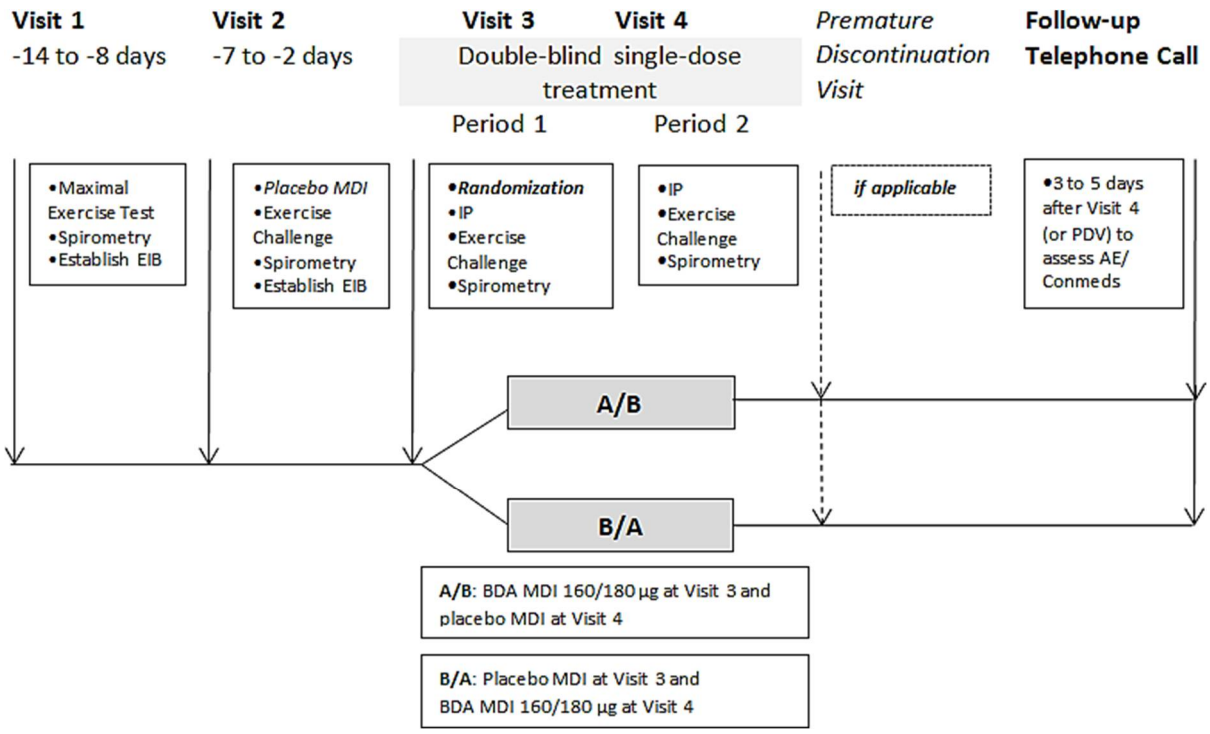
Sample size justification:

Sample size determination based on a previous clinical study NCT04234464, Phase III «TYREE» (LaForce C et al 2022) with a similar design and patient population. Using the obtained difference for maximum percentage fall from post-dose, pre-exercise baseline in FEV_1 observed up to 60 minutes post-exercise challenge equals to CCI [redacted] and corresponding SD=CCI % (the calculated SD of treatment difference based on previous study results), a sample size of 28 subjects in each treatment sequence will provide a 95% probability to detect a difference between PT027 (budesonide/albuterol) and placebo based on 2 sided 95% CI.

Considering, a drop-out rate of ~10% (8 subjects), the sample size in this study will be 64 randomized subjects (32 randomized subjects per study sequence arm). Due to the possible withdrawal during the screening up to 40%, it is planned to screen up to 107 subjects.

1.2 Schema

Figure 1 Study Design



Abbreviations: AE=adverse event; BDA=budesonide/albuterol; Conmeds=concomitant medication; EIB=exercise-induced bronchoconstriction; MDI=metered-dose inhaler; IP=investigational product; PDV=premature discontinuation visit.

1.3 Schedule of Activities

Table 2 Schedule of Activities

Procedure / Visit number / Day of study	Screening [a] (up to 14 days before Day 1)		Double-blind Treatment Phase [a]		Unscheduled Visit or PDV [b] (if applicable)	Follow-up TC (3 to 5 days after V4 or PDV)	Details in protocol section or appendix
			Period 1	Period 2			
Visit number	1	2	3	4			
Day of study	-14 to -8	-7 to -2	1	8±6			
Informed consent[l]	X						
Inclusion and exclusion criteria [c]	X	X					Sections 5.1 and 5.2
Randomization criteria verification [d]			X				Section 4.1.3
Demography	X						
Medical history (includes medical/surgical history, alcohol consumption and smoking) and current medical conditions	X						
Physical examination	X			X	X		Section 8.2.1
Weight measurement	X			X	X		
Height measurement and BMI calculation	X						
Pregnancy test (WOCBP only) [e]	X		X	X	X		Section 5.1
Clinical laboratory tests [f]	X						Section 8.2.5
Alcohol detection in exhaled air	X	X	X	X			Section 8.2.5
Drugs of abuse and cotinine urine testing	X	X	X	X			Section 8.2.5
Seated vital signs (blood pressure and heart rate) [g]	X	X	X	X	X		Section 8.2.2
12-lead ECG [g, h]	X	X	X	X			Sections 8.2.3 and 8.2.4
Spirometry (FEV_1) [g]	X	X	X	X			Section 8.1.1
Maximal exercise test [h]	X [i]						Section 8.1.2
ECT with Treadmill [h]		X [i, j]	X [i, j]	X [i, j]			Section 8.1.2
Confirm FEV_1 stability [k]		X	X	X			Section 4.1.3
Randomization [d]			X				
Administration of IMP (PT027/placebo)		**placebo**	X	X			
AE assessment	X	X	X	X	X	X	Section 8.3

Procedure	Visit number / Day of study	Screening [a] (up to 14 days before Day 1)		Double-blind Treatment Phase [a]		Unscheduled Visit or PDV [b] (if applicable)	Follow-up TC (3 to 5 days after V4 or PDV)	Details in protocol section or appendix
				Period 1	Period 2			
	Visit number	1	2	3	4			
	Day of study	-14 to -8	-7 to -2	1	8±6			
Concomitant medication review		X	X	X	X	X	X	Section 6.8

Notes for Table 2:

[a] The «run-in period» length at screening can be shortened at the discretion of the investigator, but the screening and double-blind (randomized) treatment phase must include at least 1 non-exercise test day between visit days.

[b] Subjects who prematurely withdraw from the study will undergo a PDV.

[c] Those subjects not meeting criteria will be considered screen failed. See Sections 4.1.1, 4.1.2, 5.1 and 5.2 for specific details.

[d] Subjects will be randomized at V3 to treatment if they demonstrate (at V3) a pre-exercise challenge FEV_1 ≥70% of predicted and a best pre-dose, pre-exercise challenge FEV_1 that does not exceed ±20% of the best pre-exercise challenge FEV_1 at V1. See Section 4.1.3 for details.

[e] A serum pregnancy test (β-hCG) will be performed at V1, V4 and PDV; and a urine β-hCG test will be performed at V3 (for women of childbearing potential only).

[f] Laboratory assessments (clinical chemistry, hematology and urinalysis) to be performed according to Section 8.2.5.

[g] The spirometry and related safety assessments to be performed in association with the exercise challenge at V1 to V4 are described in detail in Table 3 and Table 4.

[h] Heart rate to be monitored continuously during the exercise challenge and until 60 minutes after completion.

[i] After V1, every attempt should be made to have subsequent ECTs started ±2 hours of the timing of the maximal exercise test done at V1.

[j] At V2, V3, and V4, an ECT will be conducted 35 minutes after IMP administration.

[k] The pre-dose, pre-exercise challenge best FEV_1 value measured at each denoted visit (performed before exercise challenge) should not exceed ±20% of the pre-dose, pre-exercise challenge best FEV_1 value measured at V1.

[l] Upon signing the informed consent form, the subject will also be given a study participant card with emergency contact details of the Investigator and study sponsor.

Abbreviations: β-hCG=beta-human chorionic gonadotropin; BMI=body mass index; ECG=Electrocardiogram; ECT=Exercise Challenge Test; EIB=exercise-induced bronchoconstriction; FEV_1=Forced expiratory volume in 1 second; IMP=Investigational Medical Product; PDV=Premature discontinuation visit; TC=Telephone call; V=Visit; WOCBP= women of childbearing potential.

Table 3 Spirometry Assessments Relative to the Maximal Exercise Test at Visit 1

Assessments / Time, minutes	Pre-exercise challenge			Maximal exercise test	Post-exercise challenge							
	-50 (±10)	-35 (±5)	-5 (±3)	0	5 (±3[a])	10 (±3[a])	15 (±3[a])	20 (±5[a])	30 (±5[a])	40 (±5[a])	45 (±5[a])	60 (±5)
Seated vital signs (blood pressure and heart rate)	X[b]							X[b]		X[b]		X[c]
12-lead ECG	X[d]										X	
Spirometry[e]		X	X		X	X	X		X			X
Exercise challenge[f]				X								
Heart rate monitoring[g]				<----------	----------	----------	----------	----------	----------	----------	----------	---------->
AE assessment	<----------	----------	----------	----------	----------	----------	----------	----------	----------	----------	----------	---------->
Concomitant medication review	<----------	----------	----------	----------	----------	----------	----------	----------	----------	----------	----------	---------->

Notes for Table 3:

[a] Procedures of previous time point should be finished before the start of procedures of the next time point.

[b] Vital signs should be recorded with the subject in the seated position and after 5 minutes of rest.

[c] Seated vital signs at the 60-minutes post-exercise challenge time point should be recorded 5-10 minutes **AFTER** the last PFT (i.e., 65 minutes [±5 minutes]).

[d] 12-lead ECG recording at the pre-exercise challenge time point should be conducted after 10 minutes of rest.

[e] Every attempt should be made to perform the first pre-exercise (and pre-dose at Visits 2 to 4) spirometry measurement prior to 11:00 AM consistently across Visit 1 through Visit 4 (i.e., ±1 hour of the timing of the initial assessment at Visit 1).

[f] After Visit 1, every attempt should be made to have the subsequent ECTs done ±2 hours of the timing of the maximal exercise test done at Visit 1.

[g] Heart rate will be monitored continuously during the maximal exercise test and intermittently after maximal exercise test until 60 minutes after completion of the exercise challenge (i.e., intermittently during PFTs).

Abbreviations: AE=adverse event; ECG=electrocardiogram; ECT=exercise challenge test; PFT=pulmonary function test.

Table 4 Spirometry Assessments Relative to the Exercise Challenge Test and Dosing at Visits 2, 3, and 4

Assessments / Time, minutes	Pre-dose		Dose	Post-dose		Post-exercise challenge							
	-50 (±15)	-5 (±3)	0	30 (±5)	ECT 35	5 (±3[a])	10 (±3[a])	15 (±3[a])	20 (±5[a])	30 (±5[a])	40 (±5[a])	45 (±5[a])	60 (±5)
Seated vital signs (blood pressure and heart rate)	X [b]								X [b]		X [b]		X [c]
12-lead ECG	X [d]											X	
Spirometry [e, f]		X [e, f]		X		X	X	X		X			X
Administration of IMP (PT027/placebo) [g]			X										
Exercise challenge [h]					X								
Heart rate monitoring [i]					<----------								---------->
AE assessment	<----------												---------->
Concomitant medication review	<----------												---------->

Notes for Table 4:

[a] Procedures of previous time point should be finished before the start of procedures of the next time point
[b] Vital signs should be recorded with the subject in the seated position and after 5 minutes of rest.
[c] Seated vital signs at the 60-minutes post-exercise challenge time point should be recorded 5-10 minutes **AFTER** the last PFT (i.e., 65 minutes [±5 minutes]).
[d] 12-lead ECG recording at pre-dose time point should be conducted after 10 minutes of rest.
[e] At Visits 2 through 4, if the FEV_1 criteria are not met in the first spirometry measurement (i.e., 5 minutes pre-dose), 1 optional pre-dose spirometry measurement can be repeated after 30 minutes of the initial attempt. If first pre-dose FEV_1 fulfil all criteria, then the subject can proceed to dosing.
[f] Every attempt should be made to perform the first pre-exercise spirometry measurement prior to 11:00 AM consistently across Visit 1 through Visit 4 (i.e., ±1 hour of the timing of the initial spirometry performed at Visit 1).
[g] At Visit 2, subjects will receive placebo; while at Visit 3 and Visit 4 they will receive IMP (PT027 MDI or placebo MDI) depending on their randomization assignment.
[h] After Visit 1, every attempt should be made to have the subsequent ECTs done ±2 hours of the timing of the maximal exercise test done at Visit 1.
[i] Heart rate will be monitored continuously during the ECT and intermittently after ECT until 60 minutes after completion of the exercise challenge (i.e., intermittently during PFTs).

Abbreviations: AE=adverse event; ECG=electrocardiogram; ECT=exercise challenge test; FEV_1=forced expiratory volume in 1 second; IMP=Investigational Medical Product; MDI=metered dose inhaler; PFT=pulmonary function test.

2 INTRODUCTION

2.1 Study Rationale

Asthma is a common respiratory disease with a substantial burden for patients and healthcare systems. Patients with mild asthma represent the largest proportion of the asthma population, with estimates ranging from 50 to 75%. Several studies have found that up to half of exacerbations requiring emergency care occur in patients who report asthma symptoms less than once a week; thus, exacerbations are an important contributor to disease burden in mild asthma. One of the common triggers of an asthma symptoms is exercise-induced bronchoconstriction, which often leads to exercise avoidance as a means to control symptoms in this category of patients. Indeed, patients with reported mild asthma use considerable healthcare resources and commonly have an impaired quality of life (Golam SM et al 2022, Akhmerova YN et al 2023, Côté A et al 2018).

In the Russian Federation, the current clinical guidelines suggest classifying patients by the level of treatment required to maintain good asthma control (MoH RF Clinical guidelines, 2021), which is also the approach adopted by the Global Initiative for Asthma guidelines (GINA guidelines, 2023). Patients with mild asthma can be controlled with Step 1 or 2 treatment and the preferred symptoms reliever option is as-needed low-dose inhaled corticosteroid (ICS) with short/rapid-acting β2-adrenoreceptor agonist (SABA). The fixed-dosed combinations for symptom relief available on the Russian market are limited – «beclomethasone (ICS) + salbutamol (SABA)», «beclomethasone (ICS) + formoterol (rapid-acting LABA)» and «budesonide (ICS) + formoterol (rapid-acting LABA)», and expanding the available therapeutic arsenal is a very important task.

AstraZeneca has developed a new fixed-dose combination «budesonide + albuterol sulfate (further referred to as albuterol, also known in Russia under the generic name of salbutamol)» (PT027), which has successfully proven its efficacy and safety in several international phase III clinical studies in adults, adolescents and children with asthma (see Section 2.2.1). And was approved for commercial use by the US FDA on 10 January 2023 under the trade name «AIRSUPRA™».

Currently, there is no gold standard for the treatment and prevention of exercise-induced bronchoconstriction in patients with asthma in the Russian Federation. More up-to-date data are available on the features of the incidence and course of asthma in Russia, including those associated with a genetic factor (Akhmerova YN et al 2023). The effective drug combinations available on the market are limited, and newly developed combinations may have a different degree of effect in the local population.

The purpose of this Phase III, multicentre, randomized, double-blind, single-dose, 2-arm, 2-period, crossover study is to assess the efficacy and safety of PT027 («budesonide/albuterol (salbutamol)», metered-dose inhaler 160/180 μg) compared to placebo on exercise-induced bronchoconstriction in adult patients with asthma.

Efficacy and safety of PT027 were previously demonstrated during extensive clinical development program. But clinical centres from the Russian Federation were not involved in these clinical trials and data on Russian population was not obtained. For these reasons there is single planned PT027 study in the Russian Federation that will provide clinical data on efficacy and safety in the target population of Russian participants. The results of this study will provide clinical data on efficacy and safety of an innovation drug in the new region (Russian Federation), which will be an important additional data source for the PT027 approval process in Russia.

2.2 Background

2.2.1 Investigational Intervention

AstraZeneca (Sponsor) is developing budesonide/albuterol (PT027, a fixed-dose combination product; also referred to as budesonide and albuterol metered-dose inhaler [BDA MDI]) pressurized inhalation suspension product in adults, adolescents and children (≥4 years of age) with asthma. Please refer to the current Investigator Brochure for additional information.

Albuterol is a short/rapid-acting β2-adrenoreceptor agonist (SABA), inducing airway smooth muscle relaxation and reducing or preventing bronchoconstriction. Albuterol is approved in many countries in multiple formulations for treatment or prevention of bronchoconstriction, and in Russia is also known under the generic name of salbutamol. In clinical practice, albuterol is used as reliever therapy on an as-needed basis (GINA guidelines, 2023).

Budesonide is a well-established anti-inflammatory corticosteroid that exhibits potent glucocorticoid and weak mineralocorticoid activity and is approved worldwide in inhaled formulations for the treatment of asthma and chronic obstructive pulmonary disease both as a mono-product and in combination with a long-acting β2-agonist (LABA), (i.e., formoterol).

In vitro studies have demonstrated that inhaled corticosteroid (ICS) agents potentiate the effects of SABAs in reducing airway smooth muscle tone (Mendes ES et al 2008) and can reverse adrenergic receptor tolerance and desensitization (Cooper PR et al 2008). Clinically, similar functional potentiation with combined ICSs and albuterol has been observed in patients with asthma for functional measures of airway smooth muscle and airway blood flow (Mendes ES et al 2015).

Combining albuterol with budesonide in the proposed BDA MDI combination product should not only provide rapid bronchodilation, but also treat worsening airway inflammation by the addition of the budesonide component. Per current treatment guidelines (GINA guidelines, 2023), ICS/formoterol maintenance and reliever can be used in patients with asthma. Studies of budesonide and a rapid-acting LABA (formoterol) as reliever therapy have demonstrated enhanced protection from severe exacerbations in patients already receiving combination therapy for maintenance without an increase in adverse effects (O'Byrne PM et al 2005, Rabe KF et al 2006). In addition, budesonide/formoterol as

maintenance and reliever therapy or “Symbicort Maintenance And Reliever Therapy (SMART)” (available commercially as the Symbicort Turbuhaler [Symbicort] in the European Union and other markets) significantly reduced severe exacerbation risk in paediatric patients (O'Byrne PM 2007).

In some markets, Symbicort is approved for maintenance and reliever therapy. With SMART application, patients with asthma use Symbicort as maintenance inhalation medication and also on an as-needed basis in response to symptoms. The simultaneous administration of budesonide with formoterol when symptoms occur ensures that patients with asthma receive both a rapid-acting bronchodilator for symptom relief and anti-inflammatory medication to treat their persistent airway inflammation.

The BDA MDI is proposed to be available on an as-needed basis to use in response to symptoms to all patients with asthma, regardless of maintenance therapy. BDA MDI would have added effect on improvement of lung function and achieving asthma improvement beyond what is seen with albuterol and budesonide alone. Current treatment guidelines (MoH RF Clinical guidelines, 2021; GINA guidelines, 2023) recommend addition of low-dose ICS to SABA used as reliever medication as early as in GINA step 1 asthma (previously treated with SABA on an as-needed basis alone), broadening the range of asthma severity grades that would be treated by both ICS and β2-adrenoreceptor agonist. Anti-inflammatory and bronchodilation components used on an as-needed basis in a fixed-dose combination are expected to result in overall better asthma control and decreased risk of experiencing asthma symptoms than bronchodilation alone.

In MANDALA (NCT03769090) Phase III randomized, double-blind, active-comparator, multicenter study the efficacy and safety of PT027 was evaluated in patients with moderate to severe asthma (Papi A et al 2022). CCI

In DENALI (NCT03847896) Phase III randomized, double-blind, active-comparator and placebo-controlled multicenter study the efficacy of PT027 on lung function was evaluated in patients with mild to moderate asthma previously treated with as-needed SABA alone or with low-dose ICS maintenance therapy plus as-needed SABA (Chipps BE et al 2023). CCI

In TYREE (NCT04234464) Phase III randomized, double-blind, single-dose, placebo-controlled, 2-period, crossover multicenter study the efficacy and safety of PT027 was evaluated in adult and adolescent patients with asthma and exercise-induced bronchoconstriction (LaForce C et al 2022). CCI

2.2.2 Exercise-induced Bronchoconstriction

Exercise-induced bronchoconstriction (EIB) describes acute airway narrowing that occurs as a result of exercise. EIB occurs in a substantial proportion of patients with asthma, but may also occur in individuals without an asthma diagnosis. The quality of evidence supporting the recommendations for the treatment of EIB is variable. Recommendations include using an inhaled SABA at least 15 minutes before exercise in all patients with EIB. While for patients who continue to have symptoms of EIB despite the administration of an inhaled SABA before exercise, strong recommendations were made

for a daily ICS, a daily leukotriene receptor antagonist, or a mast cell stabilizing agent before exercise (Parsons JP et al 2013). Inhaled disodium cromoglycate and β2-agonists administered immediately before an exercise challenge test (ECT) also provide good protection (Molema J et al 1989, Richter K et al 2002).

2.3 Benefit/Risk Assessment

Potential risks of budesonide and albuterol combination are based on the safety data from the previous studies and also on identified and potential risks of the mono-components budesonide and albuterol.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of PT027 (budesonide/albuterol) may be found in the Investigator Brochure.

In the conditions of a single dosage of the investigational product, the risks for the study participants are minimal. In a previous study (NCT04234464, Phase III «TYREE») with the similar design and patient population 60 subjects received single-dose of PT027 (budesonide/albuterol) and placebo in two sequential study periods (LaForce C et al 2022). There were no deaths, SAEs, or discontinuations due to an AE. And there were only 2 treatment related AEs reported in the study, both of which occurred following administration of placebo.

2.3.1 Risk Assessment

Table 5 Risk Assessment

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
Study intervention – PT027 (Budesonide/Albuterol)		
Hypersensitivity Reactions, Including Anaphylaxis	Hypersensitivity reactions can occur after administration of albuterol and budesonide, components of PT027, as demonstrated by cases of anaphylaxis, angioedema, bronchospasm, oropharyngeal edema, rash, and urticaria.	After administration of the drug, the patient will be under the supervision of the investigator. The study will include patients who have previously already received ICS and/or SABA (see Section 5).
Paradoxical bronchospasm or deterioration of asthma	PT027 can produce paradoxical bronchospasm, which may be life threatening. If paradoxical bronchospasm occurs following dosing with PT027, it should be discontinued immediately, and alternative therapy should be instituted. It should be recognized that paradoxical bronchospasm, when associated with inhaled formulations, frequently occurs with the first use of a new canister. Asthma may deteriorate acutely over a period of hours or chronically over several days or longer. If the patient continues to experience symptoms after using of PT027, this	After administration of the drug, the patient will be under the supervision of the investigator. Subjects will only be discharged from the clinic after satisfactory lung function based on the investigator's clinical judgment.

Table 5 Risk Assessment

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
	may be a marker of destabilization of asthma and requires evaluation of the patient and their treatment regimen.	
Cardiovascular Effects	PT027, like other drugs containing β2-adrenergic agonists, can produce clinically significant cardiovascular effects in some patients as measured by increases in pulse rate, blood pressure, and/or other symptoms. In addition, beta-agonists have been reported to produce ECG changes, such as flattening of the T wave, prolongation of the QTc interval, and ST-segment depression. The clinical significance of these findings is unknown.	Patients with clinically significant cardiovascular disorders (especially coronary insufficiency, cardiac arrhythmias, and hypertension heart disease) and ECG abnormalities will not participate in the study (see Section 5).
Study intervention – Placebo		
Lack of efficacy/ exercise-induced bronchoconstriction	Exercise challenge testing is a mandatory procedure in this study and will be performed repeatedly.	During and after exercise challenge testing the patient will be under the supervision of the investigator. To mitigate any potential risks, all subjects will be closely monitored to ensure subject safety. Rescue medication will be provided if needed (see Section 6.8.2). At study visits, subjects will only be discharged from the clinic after satisfactory lung function based on the investigator's clinical judgment.
Study procedures		
There are no identified risks of clinical significance	All procedures correspond to the routine methodology of their implementation in patients with asthma.	For a detailed description of the individual procedures (see Section 8).

2.3.2 Benefit Assessment

The study will be conducted in accordance with International Conference on Harmonisation (ICH) guidelines. Permission from the research ethics committee (EC) will be sought and the study will start only after authorization. In the study, single-dose treatment and a comparison with placebo is necessary, to show that the presumed protection against EIB is an effect of active treatment. This study will be conducted in a similar design as previously published studies.

2.3.3 Overall Benefit/Risk Conclusion

Taking into account the measures taken to minimise risk to participants participating in this study, the potential risks identified in association with PT027 (budesonide/albuterol) are justified by the anticipated benefits that may be afforded to participants with asthma.

3 OBJECTIVES, ENDPOINTS, AND ESTIMANDS

Table 6 Objectives, Endpoints and Estimands

Objectives	Endpoints and Estimands Description
Primary	
To estimate the efficacy of PT027 (budesonide/albuterol) metered-dose inhaler as compared with placebo metered-dose inhaler after a single dose on exercise-induced bronchoconstriction in adult participants with asthma	• The maximum percentage fall from post-dose, pre-exercise baseline in forced expiratory volume in 1 second (FEV_1) observed up to 60 minutes post-exercise challenge *Population for analysis:* Full Analysis Set. The maximum percentage fall available in the 60-minute assessment period, prior to the use of rescue medication, will be calculated at Visit 3 and Visit 4. Missing results for maximum percentage fall in FEV1 (i.e., rescue medication prior to the collection of the 5 minutes measure) will not be imputed. The measure of interest is the difference between treatments in the maximum percentage fall from post-dose, pre-exercise baseline in FEV_1 observed up to 60 minutes post-exercise challenge.
Secondary	
To further estimate the efficacy of PT027 (budesonide/albuterol) metered-dose inhaler as compared with placebo metered-dose inhaler after a single dose on exercise-induced bronchoconstriction in adult participants with asthma	• The percentages of subjects with a maximum percentage fall in FEV_1 post-exercise challenge of <10% and <20%, respectively *Population for analysis:* Full Analysis Set. The percentage fall will be calculated relative to the pre-exercise FEV_1 assessment at the respective visit. The measure of interest is the odds ratio between PT027 and Placebo for each threshold separately (<10% and <20%).
	• The percentage fall from post-dose, pre-exercise baseline in FEV_1 at each timepoint within 60 minutes post-exercise challenge *Population for analysis:* Full Analysis Set. The measure of interest is the percentage fall from baseline in FEV_1 at each timepoint within 60 minutes post-exercise challenge. Only FEV_1 results prior to administration of rescue medication (within the study visit) will be included in the analyses.

Objectives	Endpoints and Estimands Description
	• Post-exercise FEV_1 area under the curve from 0 to 30 minutes ($AUC_{0-30min}$) *Population for analysis:* Full Analysis Set. The measure of interest is the difference between treatments in the post-exercise FEV_1 $AUC_{0-30min}$. Only the FEV_1 $AUC_{0-30min}$ measurements prior to administration of rescue medication will be included in the analyses.
	• Time to recovery, defined as the time from completionof the exercise challenge to the first measured post-exercise challenge FEV_1 value within 10% of the post- dose, pre-exercise challenge baseline FEV_1 *Population for analysis:* Full Analysis Set. The measure of interest is the median of the time to recovery.
Safety	
To assess the safety and tolerability of PT027 (budesonide/albuterol) metered-dose inhaler as compared with placebo metered-dose inhaler after a single dose in adult participants with asthma.	Safety and tolerability will be evaluated in terms of • adverse events (AEs), • serious adverse events (SAEs), • AEs lead to discontinuation. Vital signs, physical examination, electrocardiograms (ECGs) will be analysed in terms of adverse event data. *Population for analysis:* Safety Analysis Set. The measure of interest is frequencies and percentages of participants with reported AEs.

4 STUDY DESIGN

4.1 Overall Design

This will be a multicenter, double-blind, randomized, placebo-controlled, 2-arm, 2-period, single-dose, crossover study.

Approximately 64 subjects will be randomized 1:1 to one of two treatment sequences – A/B or B/A, as specified in Table 1. The IMP will be administered as a single dose as follows:

- A: PT027 (budesonide/albuterol) metered-dose inhaler 160/180 μg (given as 2 inhalations of metered-dose inhaler 80/90 μg per puff)
- B: Placebo metered-dose inhaler (given as 2 inhalations)

The study will consist of a 1 to 2-week screening (Visit 1 and Visit 2) and randomized treatment phase – 2 treatment visits (Visit 3 and Visit 4) with an interval of about 1 week. The double-blind treatment will occur with single dosing of IMP at Visits 3 and 4. A final follow-up visit will be conducted via a telephone call (TC) 3 to 5 days after the final in-clinic visit. The overall study duration will take approximately 3 to 4 weeks.

Screening

Visit 1 will include general screening procedures, spirometry, and demonstration of exercise-induced bronchoconstriction through standardized ECT. Those subjects continuing to meet eligibility criteria will enter a 1 to 2-week screening period to Visit 2, at which they will be administered placebo, undergo spirometry testing and confirmation of exercise-induced bronchoconstriction («run-in period»). The «run-in period» length at screening can be shortened at the discretion of the investigator, but the screening and randomized treatment phase must include at least 1 non-exercise test day between visit days.

Randomized treatment phase

At Visit 3, eligible subjects will be randomized to 1 of 2 treatment sequences (i.e., A/B or B/A), in which single doses of PT027 and placebo will be administered in separate treatment periods (i.e., Period 1 and Period 2). At Visit 4, subjects who received PT027 at Visit 3 will receive placebo, while those who received placebo at Visit 3 will receive PT027. At Visit 3/Period 1 and Visit 4/Period 2, IMP will be administered 30 (±5) minutes prior to the PFT before exercise challenge.

Safety will be monitored by spontaneously reported adverse events (AEs)/serious AEs (SAEs) and physical examination findings. Further, heart rate will be monitored continuously during the ECTs and intermittently after ECT until 60 minutes after completion of the exercise challenge.

During the study, standardized ECTs will be conducted according to American Thoracic Society (ATS)/European Respiratory Society (ERS) guidelines (see Section 8.1.2). At each visit, standard FEV_1 spirometry assessments will be performed relative to ECT and dosing, (before and after) as applicable. All spirometry and testing procedures will be in accordance with current guidelines (see Section 8.1.1).

To be eligible for the treatment phase of the study, subjects with asthma will be required to meet spirometry criteria and demonstrate exercise-induced bronchoconstriction through standardized ECT. If any of the spirometry criteria are not met at Visit 1 (or Visit 2), subjects can be retested. See Sections 4.1.1 and 4.1.2 for specific details on retesting.

During the study, subjects will not be allowed to use any asthma medication other than the SABA in an as-needed regimen or ICS maintenance therapy plus SABA in an as-needed regimen that they were using before study entry. Subjects will be restricted from SABA within 6 hours before any lung function testing and/or exercise testing (see Section 6.8.1). Non-asthma medications which are necessary for the subject's safety and wellbeing, and which do not affect the participation in or results of the study, are allowed at the discretion of the investigator.

Table 2 presents study assessments and procedures; Table 3 and Table 4 presents timed spirometry assessments relative to the ECT (and dosing, as applicable) at Visit 1 through Visit 4. Repeat assessments, if needed, will be captured in unscheduled visits. Details on study assessments are presented in Section 8.

Additional general considerations

To ensure standardization, it is recommended that sites review and remind/discuss the following with the subject on at least the day before a scheduled visit, as applicable:

- Site personnel will remind/instruct subjects not to take any prohibited asthma medications during the study. Non-asthma medications which are necessary for the subject's wellbeing and which do not affect the participation in or results of the study, are allowed. All such medication should be recorded in the subject's eCRF.
  - At every visit during which lung function testing will be performed, subjects must withhold SABA for at least 6 hours prior to start of test day procedures. If subjects have taken SABA within 6 hours before the planned lung function test, the test should not be carried out and the visit should be rescheduled.
- Subjects must comply with the life style restrictions described in the Section 5.3.
- Subjects will be required to return to the clinic at approximately the same time beginning at Visit 2 for all visits (±2 hours of timing of Visit 1). Therefore, all subjects' appointments must be scheduled with careful attention to the following criteria:

- The first spirometry assessment each at Visits 2, 3, and 4 should be completed prior to 11:00 AM and within ±1 hour of the timing of the first spirometry measurement done at Visit 1.
- After Visit 1, every attempt should be made to have subsequent ECTs done ±2 hours of the timing of the exercise challenge done at Visit 1.
- Subjects will be required to remain at clinic until completion of all protocol-defined assessments. To minimize diurnal variance, sites should make every effort to assess subjects at the same time throughout the study.

4.1.1 Screening Period – Visit 1

At Visit 1, consenting subjects are assessed to ensure that they meet eligibility criteria. Subjects who do not meet the criteria must not continue screening period and be randomized. Subjects meeting all eligibility criteria will enter a screening period.

Standard demographic data and other characteristics will be recorded and will include age and year of birth; gender, race, and/or ethnicity according to local regulations; A standard medical, disease, and surgical history, alcohol consumption, and smoking history will be obtained with review of the inclusion and exclusion criteria with the subject. Other study procedures carried out during this period will include physical examination (with weight, height, and BMI), concomitant medications review, seated vital signs (blood pressure and heart rate), 12-lead ECG, AEs assessment/review, serum pregnancy test for women of childbearing potential, blood samples for hematology and clinical chemistry, and urine samples for urinalysis. See Section 8.2 for details.

Visit 1 will also include spirometry (lung function testing and baseline FEV_1 determination) and subjects suitable for the study will perform a maximal exercise test on a treadmill in which maximal aerobic capacity is defined. Heart rate will be monitored continuously during the maximal exercise test and heart rate will be noted when the test is stopped and at specific time points as per Table 3.

Spirometry FEV_1 determinations will be made as per Table 3. To be eligible for the treatment phase of the study, subjects will be required to meet the following criteria at Visit 1:

- Pre-exercise challenge best FEV_1 ≥70% of predicted value
- EIB as demonstrated by a ≥20% decrease from the 5-minute pre-exercise challenge absolute FEV_1

If any of the spirometry criteria are not met at Visit 1, subjects can be retested within 2 to 10 days of the initial visit. Only 1 retest will be permitted for reasons related to technical issues (i.e., acceptability) and/or pre-exercise FEV_1 ≥70% predicted, prior to randomization. The 1 retest will also be permitted for a lack of FEV_1 drop (i.e., negative EIB outcome) at Visit 1 only if the FEV_1 drop is between 15% and <20%. Those subjects not meeting criteria will be considered screen failed.

4.1.2 Screening Period – Visit 2

At Visit 2, a standardized ECT with spirometry FEV_1 determinations will be performed according to Table 4 for continuing eligibility determination. The first spirometry assessment will be performed beginning at approximately the same time as the subject's initial assessmentat Visit 1 (±1 hour) and before 11:00 AM. Subjects will be administered placebo, with an ECT conducted 35 minutes after placebo administration.

Subjects will be required to meet the following criteria:

- The pre-dose, pre-exercise challenge best FEV_1 ≥70% of predicted value
- The pre-dose, pre-exercise challenge best FEV_1 value measured not exceeding ±20% of the pre-exercise challenge best FEV_1 value measured at Visit 1
- The post-dose, pre-exercise challenge best FEV_1 ≥70% of predicted value
- EIB as demonstrated by a ≥20% decrease from the post-dose, pre-exercise challenge FEV_1
- No development of a respiratory tract infection or asthma exacerbation between Visit 1 and 2. The visit can be rescheduled once within 7 to 10 days for an upper respiratory tract infection (e.g., common cold) that resolves and does not interfere with the subject's ability to perform the study procedures.

If any of the spirometry criteria are not met at Visit 2, subjects can be retested within 2 to 10 days of the initial visit. Only 1 retest will be permitted for reasons related to technical issues (i.e., acceptability) and/or pre-exercise FEV_1 ≥70% predicted and/or exceeding ±20%, prior to randomization. No retest will be allowed for a lack of FEV_1 drop (i.e., negative EIB outcome). Those subjects not meeting criteria will be considered screen failed.

4.1.3 Randomized treatment phase – Visits 3 and 4

The treatment phase consists of 2 visits (Visit 3 and Visit 4). At Visit 3, eligible subjects will be randomized (1:1) to receive 1 of 2 treatment sequences (A/B or B/A).

At Visits 3 and 4, subjects will also be required to continue to meet the following criteria:

- The pre-dose, pre-exercise challenge best FEV_1 ≥70% of predicted value
- The pre-dose, pre-exercise challenge best FEV_1 value measured did not exceed ±20% of the pre-exercise challenge best FEV_1 value measured at Visit 1
- The post-dose, pre-exercise challenge best FEV_1 ≥70% of predicted value (this is for safety reasons; however, if this criterion is not met, it is at the investigator's discretion to proceed if it is considered that there is no safety risk for the subject to proceed to the ECT).

If any of the spirometry criteria are not met at Visit 3 or 4, subjects can be retested. Those subjects not meeting criteria will be withdrawn. See Sections 4.1.1 and 4.1.2 for specific details on retesting.

Investigational product will be administered to eligible subjects at Visit 3 and Visit 4. To allow for proper preparation of IMP, it is recommended that the seal around the study day treatment box is opened with sufficient time prior to dosing and the instructions for administration of IMP followed:

- After IMP is primed (see the separate manual for instructions on MDI handling and cleaning) and ready for use, provide assigned IMP to the subject
- IMP will be administered in the clinic
- Complete post-dose assessments presented in Table 2 and Table 4 (in particular, standardized ECT with spirometry FEV_1 determinations will be made according to Table 4)

4.1.4 Unscheduled visit

Repeat assessments/visits, if needed, will be captured in unscheduled visits and the procedures carried out during an unscheduled visit will be determined by the investigator.

4.1.5 Follow-up period

Procedures will be performed according to study visits and procedures presented in Table 2. The safety follow-up TC contact will occur 3 to 5 days after Visit 4 or PDV. The study procedures carried out during the follow-up period will include recording of concomitant medications and AEs.

4.2 Scientific Rationale for Study Design

This is a multicenter, double-blind, randomized, placebo-controlled, 2-arm, 2-period, single-dose, crossover study of the effects on exercise-induced bronchoconstriction in adult patients with asthma .

Currently, there is no gold standard for the treatment and prevention of exercise-induced bronchoconstriction in patients with asthma in the Russian Federation. More up-to-date data are available on the features of the incidence and course of asthma in Russia, including those associated with a genetic factor (Akhmerova YN et al 2023). The effective drug combinations available on the market are limited, and newly developed combinations may have a different degree of effect in the local population.

The purpose of this study is to assess the efficacy and safety of PT027 («budesonide/albuterol (salbutamol)», metered-dose inhaler 160/180 µg) compared to placebo on exercise-induced bronchoconstriction in adult patients with asthma in Russian population.

This local Phase III study is conducted in addition to the three main international Phase III studies: MANDALA (NCT03769090) – exacerbation risk study, DENALI (NCT03847896) – lung function study and TYREE (NCT04234464) – exercise-induced bronchoconstriction study (see Section 2.2.1).

Asthma patients with exercise-induced bronchoconstriction, who use their SABA reliever therapy prophylactically before exercise to prevent exercise-induced bronchoconstriction, may benefit from a

fixed-dosed combination (budesonide/albuterol MDI), taken prior to exercise, to prevent asthma symptoms. This study will assess the efficacy and safety of single-dose PT027 (budesonide/albuterol) MDI as compared with placebo MDI in subjects with asthma and exercise-induced bronchoconstriction. It is important to evaluate whether PT027 MDI would prevent or reduce bronchoconstriction when used prophylactically.

Spirometry is one of the fundamental outcome measures used in asthma studies. It provides an objective and highly reproducible measure of airflow limitation caused by smooth muscle contraction or structural changes. Forced expiratory volume in 1 s (FEV_1) is recommended as the primary endpoint for studies of bronchodilator therapy by the American Thoracic Society (ATS) and the European Respiratory Society (ERS) in their official statement on asthma control and exacerbations (Halpin DMG et al 2019). FEV_1 recorded after withholding bronchodilators for their duration of action, is a strong, independent predictor of future exacerbation risk, and has been used in the majority of asthma clinical trials as the primary lung function endpoint in recent decades (Reddel HK et al 2009). This is in line with regulatory recommendations for clinical trials in asthma that also consider FEV_1 as the most suitable variable with the clarification that in a case of exercise-induced bronchoconstriction /asthma the relevant endpoint should be the prevention of a fall in FEV_1 following exercise using a standardised (treadmill) exercise test (EMA Guideline on the clinical investigation of medicinal products for the treatment of asthma 2015).

Accordingly, the primary endpoint in this study will be based on an assessment of the FEV_1 change: «The maximum percentage fall from post-dose, pre-exercise baseline in forced expiratory volume in 1 second (FEV_1) observed up to 60 minutes post-exercise challenge». A similar primary endpoint was used in a previous TYREE (NCT04234464) study (LaForce C et al 2022).

4.2.1 Justification for Placebo Control

Evaluation of efficacy and safety compared to placebo is a highly sensitive and generally accepted approach in phase II and III studies of combined drugs (Recommendation of the Board of the Eurasian Economic Commission of September 2, 2019 №25 «Guidelines for preclinical and clinical development of combined drugs»). This approach provides optimal comparative data for subsequent interpretation, is ethically justified and does not carry any additional risks in the conditions of lung function study with single dose administration. Placebo-controlled clinical trials in patients with mild asthma are in line with international guidelines (EMA Guideline, 2015).

In a previous placebo-controlled study (NCT04234464, Phase III «TYREE») with the similar design and patient population there were no deaths, SAEs, or discontinuations due to an AE (LaForce C et al 2022). There were only 2 TEAEs which occurred following administration of Placebo MDI and only one patient was demanded an additional use of bronchodilators after ECT.

Also, there are several other placebo-controlled clinical trials of exercise-induced asthma published

(Ostrom NK et al 2015, Hawksworth RJ et al 2002, Dockhorn RJ et al 1997). There is no evidence of significant adverse events and additional risks associated with the use of placebo in these clinical trials.

During and after exercise challenge testing the patient will be under the supervision of the investigator. Rescue medication will be provided (see Section 6.8.2).

4.3 Justification for Dose

The studied PT027 (budesonide/albuterol) MDI dosing regimen – «160/180 µg, given as 2 inhalations/actuations of MDI 80/90 µg per puff», corresponds to that in previous studies and in line with approved by the US FDA recommended dosage for commercial product «AIRSUPRA™».

To maintain a double-blind design, a placebo will be applied in a similar way (2 inhalations/actuations).

4.4 End-of-study Definition

For the purpose of Clinical Trial Transparency (CTT) the definition of the end of the study differs under FDA and EU regulatory requirements:

European Union requirements define study completion as the last visit of the last subject for any protocol related activity.

Food and Drug Administration requirements defines two completion dates:

Primary Completion Date – the date that the final participant is examined or receives an intervention for the purposes of final collection of data for the primary outcome measure, whether the clinical study concluded according to the pre-specified protocol or was terminated. In the case of clinical studies with more than one primary outcome measure with different completion dates, this term refers to the date on which data collection is completed for all of the primary outcomes.

Study Completion Date – the date the final participant is examined or receives an intervention for purposes of final collection of data for the primary and secondary outcome measures and AEs (for example, last participant's last visit), whether the clinical study concludes according to the pre-specified protocol or is terminated.

A participant is considered to have completed the study if they have completed all phases of the study including the last scheduled procedure shown in the SoA.

5 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age and gender

1 Female or male participant must be 18 to 70 years of age inclusive, at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2 Documented history of asthma (as defined by GINA criteria) for at least 6 months prior to Visit 1.

3 Receiving one of the following asthma therapies with stable dosing for at least 4 weeks before Visit 1 (no other asthma therapies are permitted during the study):

SABA in an as-needed regimen, or

Low-to-medium dose maintenance therapy with ICS and SABA in an as-needed regimen.

4 Each pre-exercise challenge (and pre-dose at Visits 2 and 3) best FEV_1 determination from the beginning of screening and before randomization ≥70% of predicted normal value. At Visit 2 pre-dose FEV_1 best value not exceeding ±20% of the best value measured at Visit 1 pre-exercise. See Sections 4.1.1, 4.1.2, 4.1.3 for procedural details.

5 EIB as defined by a ≥20% decrease from pre-exercise challenge best FEV_1 observed within 60 minutes after an exercise challenge at Visit 1 and at Visit 2 (one retest will be allowed for a lack of FEV_1 drop (i.e., negative EIB outcome) at Visit 1 only if the FEV_1 drop is between 15% and <20%.). See Sections 4.1.1, 4.1.2 for procedural details.

6 Demonstrate acceptable spirometry performance (i.e., meet ATS/ERSacceptability/repeatability criteria).

7 Demonstrate acceptable MDI administration technique.

Note: Use of a spacer device during the randomized treatment phase is not permitted.

Weight

8 Body mass index (BMI) within the range <40 kg/m^2 (inclusive).

Sex and Contraceptive/Barrier Requirements

9 Contraceptive use by males or females should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

Male participants:

Male subjects who are sexually active must be surgically sterile or agree to use a double-barrier method of contraception (condom with spermicide) from the first dose of randomized study drug until 2 weeks after their last dose, and must not donate sperm during their study participation period.

Female participants:

Women of childbearing potential* must agree to 1 of the following to prevent pregnancy:

- Practice abstinence
- If a female of childbearing potential and sexually active, agrees to prevent pregnancy by using 1 of the following methods of birth control from the date the ICF is signed until 2 weeks after the final dose of study drug is taken:
  - Hormonal contraception (e.g., oral contraceptive, contraceptive implant, or injectable hormonal contraceptive)
  - Double-barrier birth control (e.g., condom plus intrauterine device, diaphragm plus spermicide, or condom plus spermicide)
  - Maintenance of a monogamous sexual relationship with a male partner who has been surgically sterilized by vasectomy

* *Note:* Women are considered to be of non-childbearing potential if they are physiologically incapable of becoming pregnant, including any female who is 2 years post-menopausal, or surgically sterile, defined as having a bilateral oophorectomy, hysterectomy, or tubal ligation). For purposes of this protocol, menopausal women are defined as women ≥50 years old who are amenorrhoeic for 12 consecutive months or more following cessation of all exogenous hormonal treatment.

Informed Consent

10 Capable of giving signed informed consent as described in Appendix A which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

5.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

1 As judged by the investigator, any historical or current evidence of a clinically significant disease including, but not limited to: cardiovascular (e.g., congestive heart failure, known aortic aneurysm, clinically significant cardiac arrhythmia, coronary heart disease), hepatic, renal, hematological, infectious, neuropsychological, endocrine (e.g., uncontrolled diabetes mellitus, uncontrolled thyroid disorder, Addison's disease, Cushing's syndrome), or gastrointestinal (e.g., poorly controlled peptic ulcer, gastroesophageal reflux disease) disorders. Significant is defined as any disease which in the investigator's opinion makes it undesirable for the participant to participate

in the study, or which could affect the efficacy or safety analysis if the disease/condition exacerbated during the study.

2 Chronic obstructive pulmonary disease or other significant lung disease (e.g., chronic bronchitis, emphysema, bronchiectasis with the need of treatment, cystic fibrosis, bronchopulmonary dysplasia), including regular or occasional use of oxygen.

3 Subject has a history of life-threatening asthma, defined by past intubations for asthma, or intensive care unit admission for asthma within the prior 24 months.

4 Subjects unable to tolerate the lung function testing performed after ECT at Visit 1 or 2 without use of rescue medication.

5 Current smokers, former smokers with >10 pack-years history, or former smokers whostopped smoking <6 months (including all forms of tobacco, e-cigarettes [vaping], andmarijuana).

6 Subjects with contraindications to ECT according to ATS/ERS guidelines.

7 Completed treatment for lower respiratory infection within 6 weeks prior to Visit 1, regardless if resulting in accompanying asthma symptoms aggravation or not.

8 Upper respiratory infection involving antibiotic treatment not resolved within 7 days prior to Visit 1.

9 Cancer not in complete remission for at least 5 years before Visit 1.

Note: Subjects with squamous cell carcinoma of the skin, basal cell carcinoma of the skin, in situ carcinoma of the cervix, or localized prostate cancer are eligible, if in the opinion of the investigator, the condition has been clinically controlled and the subject's participation in the study would not represent a safety concern.

10 Hospitalization for psychiatric disorder or attempted suicide within 1 year of Visit 1.

11 History of psychiatric disease, intellectual deficiency, poor motivation, or other conditions if their magnitude is limiting informed consent validity.

Prior/Concomitant Therapy

12 Systemic corticosteroids use (any dose and any indication) within 3 months before Visit1.

13 Subjects receiving regular maintenance treatment with prohibited anti-inflammatory or long-acting bronchodilator asthma medication (inhaled, nebulized, oral, or systemic) within 1 month prior to Visit 1.

Note: During the treatment phase, subjects are not allowed to use any asthma treatments/medications (of any class) other than the IP and the permitted SABA or ICS treatment that was started before screening. No subject can be on other asthma maintenance therapies. See Section 6.8.1 for details.

14 Subjects with a known or suspected hypersensitivity to budesonide, albuterol (salbutamol) or any

of the excipients of the product.

15 Having received any marketed (e.g., omalizumab, mepolizumab, reslizumab, benralizumab, dupilumab) or investigational biologic within 3 months or 5 half-livesbefore Visit 1, whichever is longer, or any other medication specifically prohibited by the protocol within the indicated exclusionary time periods.

16 Treatment with any IMP within the last 30 days (or 5 half-lives, whichever is longer) of Visit 1.

17 Inability (and/or unwillingness) to abstain from protocol-defined prohibited medications during the study.

18 Use of any herbal products by inhalation or nebulizer within 2 weeks of Visit 1 and/or the unwillingness to stop during the study duration.

19 Received a live attenuated vaccination within 7 days of Visit 1.

20 Significant abuse of alcohol or drugs, in the opinion of the investigator.

Prior/Concurrent Clinical Study Experience

21 Current participation in any interventional study.

22 Previous enrolment or randomization in the present study.

Diagnostic Assessments

23 Clinically significant laboratory abnormalities in the opinion of the Investigator, or having any of the following results at screening:

(a) a serum creatinine value >1.5 times the upper limit of the reference range

(b) a serum total bilirubin value >1.5 times the upper limit of the reference range

(c) a serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) value >2.5 times the upper limit of the reference range

Note: if laboratory tests have to be repeated, the results should be available for review before randomization.

24 Any of the following results at Visit 1:

(a) an abnormal electrocardiogram (ECG) that is, in the investigator's opinion, clinically significant

(b) a QT interval corrected by Fridericia (QTcF) interval >480 ms

Other Exclusions

25 Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site).

26 Judgment by the investigator that the participant should not participate in the study if the participant is unlikely to comply with study procedures, restrictions, and requirements.

27 For females only - currently pregnant (confirmed with positive pregnancy test) or breast-feeding.

28 Having a scheduled/planned hospitalization during the study.

5.3 Lifestyle Considerations

5.3.1 Caffeine, Alcohol, and Tobacco

Subjects must not ingest xanthine and/or xanthine analogue (caffeine)-containing foods or beverages or caffeine-containing medications for at least 6 hours before each study visit and throughout the duration of each study visit. Examples of such products include coffee, tea, chocolate, and cola. Decaffeinated beverages are acceptable.

Subjects should avoid having a large meal at least 2 hours prior to a study visit.

Use of tobacco products will not be allowed from screening until after the final follow-up visit. Alcohol-containing beverages are not recommended throughout the study. It is forbidden to drink alcohol the day before any visit to the center.

5.3.2 Illicit drugs

Illicit drugs or drugs of abuse will not be allowed. If any illicit drugs or drugs of abuse are used by the subject during the study, the dates of use and the amount will be documented and the subject will be discontinued from study drug and withdrawn from the study at the discretion of the Investigator.

5.3.3 Activity

Subjects should avoid intensive physical exercise during the 24 hours prior to the visits.

5.4 Screen Failures

A screen failure occurs when a participant who has consented to participate in the clinical study is not subsequently assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may not be rescreened.

5.5 Criteria for Temporarily Delaying

Not applicable for this study.

6 STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

Study interventions are all pre-specified, IMPs and NIMPs, medical devices and other interventions (e.g., surgical and behavioral) intended to be administered to the study participants during the study conduct.

6.1 Study Intervention(s) Administered

AstraZeneca will centrally supply IMPs (PT027 (budesonide/albuterol) and placebo) for further packaging and labelling in Russian Federation.

IMPs will be supplied "IN-BULK" form or as Finished Product (released for circulation in foreign Markets). Packaging/Repackaging and Labelling/Relabelling, QC and QP release will be performed by Russian Manufacturing site in fully compliance with local and AZ GMP requirements. Additional labelling (is required) can be performed by the site.

Placebo will be supplied "IN-BULK" with further Packaging, Labelling, QC and QP release will be performed by Russian Manufacturing site in fully compliance with local and AZ GMP requirements. CCI

Both IMPs will be provided as metered-dose inhalers. CCI

Details of all study interventions are presented in Table 7. Subjects will be randomized to receive both IMPs in one of two treatment sequences – A/B or B/A, as specified in Table 1.

A description of the use of rescue medication (NIMP) is provided in Section 6.8.2.

Table 7 Study Intervention

Arm name	PT027 (A)	Placebo (B)	Rescue medication
Intervention name	Budesonide/Albuterol (salbutamol)	Placebo	CCI
Type	drug	Placebo	drug
Dose formulation	inhalation suspension in metered-dose inhaler	inhalation suspension in metered-dose inhaler	inhalation suspension in metered-dose inhaler
Unit dose strength(s)	80 µg budesonide and 90 µg albuterol* per puff.	0 µg of active product** ** - each puff contains 183 µg of porous particles and 63 µg of	100 µg salbutamol per puff

Arm name	PT027 (A)	Placebo (B)	Rescue medication
	* - each puff contains 108 µg albuterol sulfate corresponding to 90 µg albuterol base per actuation	hydrofluoroalkane-134a propellant made to be identical inappearance to PT027	
Dosage level(s)	2 actuations	2 actuations	1-2 actuations
Route of administration	inhalation	Inhalation	inhalation
Regimen	single use	single use	as-needed
Use	experimental	Placebo	rescue medication
IMP or NIMP	IMP	IMP	NIMP
Sourcing	provided centrally by the Sponsor	provided centrally by the Sponsor	provided centrally by the Sponsor
Packaging and labelling	IMP ("IN-BULK" or Finished Product for Foreign Country) will be provided in metered-dose inhalers. Packaging/Repackaging, Labelling/Relabelling, QC, Batch release of Finished Product will be performed in accordance with global AZ and local GMP regulatory guidelines. The labels will fulfil GMP Annex 13 requirements for labelling.	IMP ("IN-BULK") will be provided in metered-dose inhalers. Packaging, Labelling, QC, Batch release of Finished Product will be performed in accordance with global AZ and local GMP regulatory guidelines. The labels will fulfil GMP Annex 13 requirements for labelling.	Commercial Product. Each canister will be labelled as required per country requirement.

6.2 Preparation, Handling, Storage, and Accountability

- IMP metered-dose inhalers should be stored below 25°C (77°F) in a dry place. Excursions permitted up to 30°C (86°F).
- The investigator or designee (e.g., unblinded pharmacist) must confirm appropriate conditions (e.g., temperature) have been maintained during transit for all study intervention received at the site and throughout the entire study until authorisation is provided for on-site destruction or removal of the IMP, reflecting completion of the study. In the event of a temperature excursion detected at any time during the study, sites will follow the reporting procedures for notifying AstraZeneca (or designated party); release of IMP for clinical use can only occur once the event has been reviewed and approval is provided by AstraZeneca (or designated party).
- Inhalers for both IMPs (PT027 and placebo) look identical except for the labels. CCI

CCI

- Only participants enrolled in the study may receive study intervention, and only authorised site staff may supply, prepare, or administer study intervention. All study intervention must be stored in a secure, environmentally-controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorised site staff.
- The investigator, institution, or the head of the medical institution (where applicable), is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

Further guidance and information for the final disposition of unused study interventions are provided in the Investigational Product Handling Manual.

6.2.1 Dose Preparation

The IMPs will be delivered in a ready-to-use form.

6.2.2 Dose Administration

The IMP will be administered as a single dose as follows:

- A: PT027 (budesonide/albuterol) metered-dose inhaler 160/180 µg (given as 2 inhalations of metered-dose inhaler 80/90 µg per puff)
- B: Placebo metered-dose inhaler (given as 2 inhalations)

At Visit 2, subjects will be administered placebo.

At Visits 3 and 4 subjects will receive both IMPs in one of two treatment sequences – A/B or B/A, as specified in Table 1.

IMP will be administered 30 (±5) minutes prior to the PFT before exercise challenge.

Handling instructions for the MDI device will be available for each site in the form of a “Site Manual” document throughout the study.

The importance of the device priming requirements should be emphasized. Priming of the IMP MDI must occur. Device priming should *not* be conducted in the same room as spirometry assessments are being conducted.

6.3 Assignment to Study Intervention

Participants will be randomized 1:1 to one of two treatment sequences – A/B or B/A, as specified in Table 1. Randomization will be stratified by background ICS therapy (ICS or no ICS).

All participants will be centrally assigned to randomized study intervention using an IWRS. Before the study is initiated, IWRS access and instruction will be provided to each site.

Returned study intervention should not be re-dispensed to the participants.

6.4 Blinding

This is a double-blind study: neither the participant nor any of the Investigators or Sponsor staff who are involved in the treatment or clinical evaluation and monitoring of the participants will be aware of the study intervention received.

The IWRS will provide to the Investigator(s) or pharmacists the kit identification number to be allocated to the participant at the dispensing visit. Study intervention will be dispensed at the study visits summarised in SoA. Routines for this will be described in the IWRS user manual that will be provided to each center.

In this study the following personnel will have access to the randomization list during the study, prior to database lock:

- Those carrying out the packaging and labelling of IMP
- Those generating the randomization list and IRT/RTSM system
- The AstraZeneca supply chain department
- Unblinded AstraZeneca designees (if applicable)

CCI [redacted]

The randomisation code should not be broken except in medical emergencies when the appropriate management of the participant requires knowledge of the treatment randomisation. The investigator documents and reports the action to AstraZeneca, without revealing the treatment given to participant to the AstraZeneca staff.

AstraZeneca retains the right to break the code for SAEs that are unexpected and are suspected to be causally related to a study intervention and that potentially require expedited reporting to regulatory authorities. Randomisation codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual participant have been made and documented.The

IWRS will be programmed with blind-breaking function. Unblinding should only occur within the IWRS system. In case of an emergency, in which the knowledge of the specific blinded study intervention will affect the immediate management of the participant's condition (e.g., antidote available), the therapy can be unblinded by authorized representatives of the study site. Participant safety must always be the first consideration in making such a determination. If a participant's intervention assignment is unblinded, the Sponsor must be notified within 24 hours after breaking the blind. The Investigator documents and reports the event to AstraZeneca, without revealing the treatment given to participant to the AstraZeneca staff.

6.5 Study Intervention Compliance

When participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date, and time if applicable, of dose administered in the clinic will be recorded in the source documents and recorded in the eCRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

6.6 Dose Modification

Not applicable for this study.

6.7 Continued Access to Study Intervention After the End of the Study

Not applicable for this study, there will be no intervention following the end of the study.

6.8 Prior and Concomitant Therapy

6.8.1 Prior and Concomitant Medications

All prescription drugs, herbal products, vitamins, minerals, and over-the-counter medications taken within 3 months before screening will be recorded as previous medications. All medications taken after screening and through the follow-up TC will be recorded as concomitant therapy in eCRF along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose, frequency and route

In addition to the Sponsor-provided IP, the only other asthma treatments/medications (of any class) allowed during the study are the asthma medications (ie, SABA as needed alone or ICS with SABA as needed, as applicable) that were started before screening and continued as part of maintenance treatment. See the inclusion criteria for details.

During the study, subjects should maintain stable dosing of their maintenance and/or as needed therapy

as presented at screening. Dose changes to maintenance therapy are discouraged unless clinically indicated in accordance with current guidelines. Investigators should notify the Study Physician of any change to maintenance therapy for study subjects; considerations should be made to subject drug compliance and other factors in advance of making changes to maintenance therapy.

If, following the ECT, the investigator considers that the subject is experiencing asthma symptoms which are not tolerable, then rescue SABA can be administered.

Table 8 lists the restricted and prohibited medications during the study. The Study Physician should be contacted if there are any questions regarding concomitant or prior therapy.

Table 8 Restricted and Prohibited Concomitant Medications

Use Category	Type of medication/ treatment	Timeline/instructions
Restricted	*Medications that may affect reversibility and FEV_1 testing*	At the start of each treatment visit, subjects must withhold SABA for at least 6 hours prior to start of test day procedures. If a subject has taken SABA within 6 hours before the planned FEV1 test, the test should not be carried out and the subject's visit should be rescheduled.
Prohibited	*Systemic corticosteroids (prohibited at least 3 months before Visit 1 and during the study)*	Systemic corticosteroids (e.g., oral, parenteral, intraocular, intraarticular, rectal) is prohibited for the duration of the study, including both the Screening and randomized Treatment Periods, and within 3 months before Visit 1
	Other Medications (prohibited at least 1 month before Visit 1 and during the study (unless otherwise specified))	• Any asthma medication (except Sponsor-provided IP during Visits 3 and 4 and the permitted SABA as needed alone or ICS with SABA as needed treatment that was started before screening and continued as part of maintenance treatment (see inclusion criteria), regular SABA use (eg, four times a day [QID]) is not permitted) is not permitted)) • Inhaled disodium cromoglycate or inhaled nedocromil sodium • 5-lipoxygenase inhibitors (ie, zileuton) • Inhaled short-acting anticholinergics (or short-acting muscarinic antagonists [SAMA], ie, ipratropium) • Inhaled long-acting muscarinic antagonists (LAMA) • Phosphodiesterase-4 inhibitors (ie, roflumilast) • Leukotriene receptor antagonists (ie, montelukast, zafirlukast), also for the treatment of other allergic conditions • Xanthine and theophylline • Omalizumab, benralizumab, mepolizumab, reslizumab, dupilumab, or any other monoclonal or polyclonal therapy for any reason during the study or within 3 months or 5 half-lives before Visit 1, whichever is longer; (locally administered biologics, eg, intra-ocular, are allowed) • Beta-2-adrenergic blockers, including eye-drops; (For the purpose of this study, metoprolol is considered to have beta-2-adrenergic receptor blocking ability.)

6.8.2 Rescue Medicine

AstraZeneca will supply rescue medication – [redacted] (salbutamol, SABA), 100 µg metered dose inhaler, to the study site.

If, following the ECT, the investigator considers that the subject is experiencing asthma symptoms which are not tolerable, then rescue medication ([redacted]) can be administered according to local routine practice. The date and time of rescue medication administration as well as the name and dosage regimen of the rescue medication must be recorded.

Use of rescue medication following the exercise challenge test may impact the interpretation of the IMP treatment effect. Subjects who have any rescue medication administered during the post-dose assessments will be censored at the time of receiving rescue medication.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix A.

7.1 Discontinuation of Study Intervention

Note that discontinuation from study intervention is *not* the same thing as a discontinuation or withdrawal from the study (see Section 7.2).

If study intervention is permanently discontinued, the participant should, if at all possible, remain in the study. See the SoA for data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed.

7.1.1 QTc Stopping Criteria

If a clinically significant finding is identified (including, but not limited to, changes from baseline in QT interval corrected using Bazett's formula [QTcB] or Fridericia's formula [QTcF]) after enrolment, the investigator or qualified designee will determine if the participant can continue on the study intervention and if any change in participant management is needed. This review of the ECG printed at the time of collection must be documented. Any new clinically relevant finding should be reported as an AE.

7.2 Participant Discontinuation/Withdrawal From the Study

Discontinuation of the participant from the study by the investigator

A participant may be discontinued from the study at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons. Some reasons for study withdrawal include:

- An AE or other unacceptable toxicity considered to jeopardize the safety of a subject participating in the study.
- Subjects who suffer 1 severe exacerbation or worsening of asthma that in the investigator's opinion could affect short-term disease course or stability of lung function will be discontinued if the Sponsor and the investigator decide that it is in the best interest of the subject to withdraw from the study.
- General or specific change(s) in the subject's condition that render(s) him/her ineligible for further participation according to the inclusion/exclusion criteria.
- Non-compliance: in the opinion of the investigator, the subject is non-compliant with the requirements of the Clinical Study Protocol (e.g., post-enrollment eligibility violation).
- Lost to Follow-up: please see section 7.3.
- Intercurrent illness: a condition, injury, or disease unrelated to the primary diagnosis that became apparent during treatment and necessitated the subject's termination from the study,

e.g., a symptomatic lower respiratory tract infection that puts the subjects at potential risk and interferes with the subject's ability to carry out the required procedures.

- Pregnancy; if a female subject becomes pregnant, she will be immediately withdrawn from the study.

Voluntary withdrawal from the study by the participant

- A participant may withdraw from the study at any time at the participant's own request for any reason (or without providing any reason).
- A participant who wishes to withdraw from the study must be informed by the investigator about modified follow-up options (e.g., telephone contact, a contact with a relative or treating physician, or information from medical records).
- If the participant withdraws from the study, AstraZeneca may retain and continue to use any samples collected before such a withdrawal of consent for the purposes the participant originally consented unless the participant withdraws consent for use of samples already collected. If the participant specifically withdraws consent for any use of samples, it must be documented in the site study records by the investigator and the investigator must inform the Study Team. Destruction of any samples taken and not yet tested should be carried out in line with documented sample withdrawal wishes in conjunction with what was stated in the informed consent and local regulation.

The date and the reason for study withdrawal must be recorded on the eCRF. The subject will be asked to complete a premature discontinuation visit (PDV) and the follow-up TC (except ICF withdrawal). The safety follow-up TC contact will occur 3 to 5 days after the last study visitor PDV, as indicated in the Schedule of Assessments (Table 2).

Once a subject is withdrawn from the study, the subject may not re-enter the study. If a subject withdraws from participation in the study, then his/her enrollment/randomization code cannot be reused. Withdrawn subjects will not be replaced.

7.3 Lost to Follow-up

A participant will be considered lost to follow-up if the participant repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

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

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible. The participant should be counselled on the importance of maintaining the assigned visit schedule. At this time ascertain whether the participant should or wishes to or continue in the study.

- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls, texts, emails, and if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, the participant will be considered to have withdrawn from the study.

8 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarised in the Section 1.3 SoA. Protocol waivers or exemptions are not allowed.

Urgent safety concerns should be discussed with AstraZeneca immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

In the event of a significant study-continuity issue (e.g., caused by a pandemic), alternate strategies for participant visits, assessments, medication distribution and monitoring may be implemented by AstraZeneca or the investigator, as per local health authority/ethics requirements.

The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed 15 mL. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 Efficacy Assessments

Planned timepoints for all efficacy assessments are provided in the Section 1.3 SoA.

Efficacy assessments include ECTs with spirometry (FEV_1) measurements.

8.1.1 Lung function measurement by spirometry (FEV_1)

The procedure should be carried out in compliance with the ATS/ERS guidelines and the recommendations on spirometry of the Ministry of Health of the Russian Federation (Graham BL et al 2019, MoH RF Spirometry (methodological guide)).

The spirometry/exercise challenge test procedure will be carried out on the equipment of the clinical center by qualified, properly certified personnel with the skills of spirometric measurements. All measurements during the study in a particular patient should be performed on the same equipment.

Calibration of the spirometer should be carried out daily before starting operation of the device or more often if it is provided by the manufacturer's instructions. If the calibration results are unsatisfactory, the calibration should be performed again.

Spirometry should be performed as specified in Table 3 and Table 4. The measurements are to be made with the subject seated in an upright position (preferably), or if not comfortable, a standing position is also acceptable. The same position should be used for all spirometry measures during the entire study. The head must not be tilted during measurements. During the breathing maneuvers, the thorax should be able to move freely; hence tight clothing should be loosened.

The subject should rest for at least 15 minutes prior to the initial test. Multiple maneuvers are necessary. For each pre-dose and/or pre-exercise challenge spirometry, a maximum of 8 maneuvers can be performed, and the highest value obtained from 3 acceptable and 2 repeatable spirometry maneuvers will be used. For the pre-dose PFTs, FEV_1 and forced vital capacity repeatability will be required. For each post-exercise challenge spirometry, the highest value of 2 acceptable spirograms will be used.

Pre- and post-exercise FEV_1 will be performed at Visit 1 and pre-dose, post-dose, and post-exercise at Visit 2 through Visit 4. The 5-minute pre-exercise post-dose spirometry assessment at Visit 2 through Visit 4 is crucial to accurately measure baseline FEV_1 prior to exercise testing. The subject and site personnel should be adequately prepared for this assessment prior to the exercise test.

During the procedure, the patient should be closely monitored in order to avoid undesirable phenomena associated with sharp and deep exhalation (for example, syncopal state). If dizziness appears or the patient's well-being worsens, a pause may be made and the study continued when the undesirable symptoms have passed.

When performing breathing maneuvers, it is necessary to control the absence of air leakage (for this purpose, additional fixation of the lips around the mouthpiece with fingers is possible), obstruction of the mouthpiece with the tongue. If the patient has removable dentures, it is recommended not to remove them during spirometry, however, in a situation where they prevent the patient from tightly grasping the mouthpiece and cause air leakage, the study should be continued without them.

Demonstration of exercise-induced bronchoconstriction

Subjects will be required to meet the following criteria at Visit 1 (see Section 4.1.1) and Visit 2 (see Section 4.1.2):

- EIB as demonstrated by a ≥20% decrease from the 5-minute pre-exercise challenge absolute FEV_1

8.1.2 Exercise challenge testing

During the study, standardized ECTs will be conducted according to American Thoracic Society (ATS)/European Respiratory Society (ERS) guidelines (Crapo RO et al 2000).

A standardized maximal exercise test on a treadmill in which maximal aerobic capacity is defined will be completed at Visit 1. At Visits 2 through 4, an ECT, with duration of 6 to 8 minutes, at approximately 80% to 95% of maximal aerobic capacity will be performed on atreadmill as specified in Table 2, Table 3 and Table 4.

Details on exercise testing will be provided in a separate manual (measurement procedures should be performed in accordance with the manual).

Subjects will also be reminded that prior to the visits they must comply with the life style restrictions described in the Section 5.3.

The ECT should be done at approximately the same time (±2 hours of the timing of exercise challenge done at Visit 1) at each subsequent visit. Before any procedure is done the subjects should rest for at least 15 minutes. The subject needs to be stable before the test.

During the maximal exercise challenge, the subject's heart rate will be monitored continuously. Maximal heart rate should be noted when the test is stopped at Visit 1. After the establishment of exercise challenge criteria at Visit 1, subjects will undergo standardized ECTs at Visit 2 for eligibility determination and at Visit 3 and Visit 4 (30 [±5] minutes after IP administration). Heart rate will be monitored continuously during the ECTs until 60 minutes after ECT completion. See Section 4.1.2 for details on spirometry assessments and timing relative to ECTs (and dosing).

If the subject has been diagnosed with an intercurrent illness or suffers a severe asthma exacerbation before a visit, the subject will be withdrawn from the study, depending on the reason. See Section 7.2 for details. The visit can be rescheduled once within 7 to 10 days for an upper respiratory tract infection (e.g., common cold) that resolves and does not interfere with the subject's ability to perform the study procedures.

If at any visit an exercise test and/or the post-exercise lung function tests need to be stopped prematurely (i.e., the FEV_1 drops > 40% [which requires treatment with SABA]), or the subject has asthma symptoms that require treatment with SABA as judged by the investigator, the subject's visit will be stopped. After an appropriate observation period, if the subject's condition has stabilized as judged by the investigator, the subject's visit will end.

8.2 Safety Assessments

Planned time points for all safety assessments are provided in the Section 1.3 SoA.

8.2.1 Physical Examinations

A complete physical examination will be performed and include assessments of the following; general appearance, respiratory, cardiovascular, abdomen, skin, head and neck (including ears, eyes, nose, and throat), lymph nodes, thyroid, musculoskeletal (including spine and extremities), and neurological systems.

Physical examination will be performed at timepoints as specified in the Section 1.3 SoA.

8.2.2 Vital Signs

Vital signs will be performed at timelines as specified in the Section 1.3 SoA.

Blood pressure and pulse measurements will be assessed with the subject in the seated position with a completely automated device. Manual techniques will be used only if an automated device is not available. Duration of rest before these measurements are specified in Table 3, Table 4.

Vital signs will consist of 1 pulse and 3 blood pressure measurements (3 consecutive blood pressure readings will be recorded at intervals of at least 1 minute). The average of the 3 blood pressure readings will be recorded on the eCRF.

8.2.3 Resting 12-lead Electrocardiogram

12-lead ECG will be performed at timepoints as specified in the Section 1.3 SoA.

The 12-lead ECG will be after the subject has been resting supine for at least 10 minutes. The subject should be examined using the same ECG machine throughout the study, where feasible.

After ECGs have been recorded, the investigator or designated physician will review each of the ECGs and may refer to a local cardiologist, if appropriate. A paper copy should be filed inthe subject's medical records. If an abnormal ECG finding at screening/baseline is considered to be clinically significant by the investigator, it should be reported as an AE. For all ECGs, details of rhythm, PR, RR, QRS, and QT intervals, as well as an overall evaluation will be recorded.

8.2.4 Heart rate monitoring during exercise challenge testing

During the exercise challenge at Visit 1, the subject's heart rate will be monitored continuously for 60 minutes as detailed in Table 3. At Visit 1, Maximal heart rate should be noted when the maximal exercise test is stopped at Visit 1.

At Visit 2 through Visit 4 standardized ECTs will be conducted and the subject's heart rate will be monitored continuously for 60 minutes as detailed in Table 4.

8.2.5 Clinical Safety Laboratory Tests

Blood and urine samples for determination of clinical chemistry, hematology, and urinalysis will be taken only at Screening (Visit 1).

A serum pregnancy test (β-human chorionic gonadotropin [β-hCG]) will be performed at Visit1, 4 and PDV; urine β-hCG test will be performed at Visit 3 (for women of childbearing potential only).

Urine samples will be taken during Visits 1-4 for drugs of abuse and cotinine testing. The analysis will be carried out using test strips. The list of psychoactive agents for testing includes marijuana, benzodiazepines, barbiturates, opiates, methadone, phencyclidine, cocaine, amphetamines.

Also, during Visits 1-4 alcohol detection test will be performed using breathalyser.

Additional safety samples may be collected if clinically indicated at the discretion of the investigator. The date, time of collection and results (values, units, and reference ranges) will be recorded on the appropriate eCRF.

The clinical chemistry, hematology, and urinalysis will be performed at a local laboratory at site or laboratory contracted by Sponsor if site is not feasible to perform any of the required tests. Sample tubes and sample sizes may vary depending on laboratory method used and routine practice at the site.

The following laboratory variables will be measured (see Table 9).

Table 9 Laboratory Safety Variables

Hematology/Hemostasis (whole blood)	Clinical Chemistry (serum or plasma)
Basophils (%)	Albumin
Basophils Abs	Alanine transaminase
Eosinophils (%)	Alkaline phosphatase
Eosinophils Abs	Aspartate transaminase
Hemoglobin	Bilirubin, total
Hematocrit	Calcium, total
Mean Corpuscular Hemoglobin	Chloride
Mean Corpuscular Hemoglobin Concentration	Cholesterol, total
Mean Corpuscular Volume	Creatinine
Monocytes (%)	Creatine kinase
Monocytes Abs	Gamma-glutamyl transpeptidase
Neutrophils (%)	Glucose (random)
Neutrophils Abs	Magnesium
Red blood cells (erythrocytes)	Phosphate

Table 9 Laboratory Safety Variables

White blood cells (leukocytes)	Potassium
Platelet count	Protein, total
Lymphocytes Abs	Sodium
Lymphocytes (%)	Triglycerides
	Urea
Urine	Serum β-hCG pregnancy (Visit 1, 4 and PDV) [a]
Urine β-hCG pregnancy (at Visit 3) [a]	
Urine hemoglobin	
Urine erythrocytes	
Urine protein	
Urine albumin	
Urine glucose	

Abbreviations: Abs=absolute; β-hCG=β-human chorionic gonadotropin; PDV=premature discontinuation visit
[a] β-hCG pregnancy testing for women of childbearing potential only

8.3 AEs, SAEs, and Other Safety Reporting

The Principal Investigator is responsible for ensuring that all staff involved in the study are familiar with the content of this section.

The definitions of an AE or SAE can be found in Appendix B.

Participants (or, when appropriate, a caregiver, surrogate, or the participant's legally authorised representative) will notify the investigator or designees of symptoms. These must then be assessed by the investigator and if considered an AE it will be reported by the investigator.

The investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE.

AE variables

The following variables will be collected for each AE:

- AE (verbatim)
- The date and time when the AE started and stopped
- Maximum intensity (Appendix B)
- Changes in intensity (report only the maximum intensity)
- Whether the AE is serious or not (Appendix B)
- Investigator causality rating against the IMP(s) (yes or no)

- Action taken with regard to IMP(s)
- AE caused participant's withdrawal from the study (yes or no)
- Administration of treatment for the AE
- Outcome

In addition, the following variables will be collected for SAEs:

- Date AE met criteria for SAE
- Date investigator became aware of SAE
- AE description
- AE is serious due to
- Date of hospitalisation
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to study procedure(s)
- Causality assessment to other medication

8.3.1 Time Period and Frequency for Collecting AE and SAE Information

Adverse Events will be collected from the time of signing of the ICF and throughout the treatment period and including the follow-up period (Visit 4 or PDV).

Serious Adverse Events will be recorded in eCRF from the time of signing of the ICF.

If the investigator becomes aware of an SAE with a suspected causal relationship to the IMP that occurs after the end of the clinical study in a treated participant, the investigator shall, without undue delay, report the SAE to AstraZeneca.

8.3.2 Follow-up of AEs and SAEs

Any AEs that are unresolved at the participant's last AE assessment or other assessment/visit as appropriate in the study are followed up by the investigator for as long as medically indicated, but without further recording in the eCRF. AstraZeneca retains the right to request additional information for any participant with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

8.3.3 Causality Collection

The investigator should assess causal relationship between IMP and each AE, and answer 'yes' or 'no' to the question 'Do you consider that there is a reasonable possibility that the event may have been

caused by the IMP?'

For SAEs, causal relationship should also be assessed for other medication and study procedures. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as 'yes'.

A guide to the interpretation of the causality question is found in Appendix B.

8.3.4 AEs Based on Examinations and Tests

Deterioration as compared to baseline in protocol-mandated vital signs, laboratory tests and instrumental examination results should only be reported as AEs if they meet any of the following:

- fulfil any of the SAE criteria
- are the reason for discontinuation of the IMP
- are clinically relevant as judged by the investigator (which may include but is not limited to consideration as to whether intervention or non-planned visits were required or other action was taken with the IMP, e.g., dose adjustment or drug interruption).

If deterioration in a vital sign, laboratory or instrumental examination result is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated vital sign, instrumental examination result will be considered as additional information. Wherever possible the reporting investigator uses the clinical term. In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE unless unequivocally related to the disease under study (DUS).

The results from the protocol mandated examinations and vital signs will be summarised in the CSR.

8.3.5 AEs Based on Signs and Symptoms

All signs or symptoms spontaneously reported by the participant or reported in response to the open question from the study site staff: 'Have you had any health problems since the previous visit/you were last asked?', or revealed by observation will be collected and recorded in the eCRF.

When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

8.3.6 Disease Progression

Disease progression can be considered as a worsening of a participant's condition attributable to the

disease for which the IMP is being studied. It may be an increase in the severity of the DUS and/or increases in the symptoms of the disease. The development of wheeze, breathlessness and cough on days when the IMP was not used should be considered as disease progression and not an AE. Events, which are unequivocally due to disease progression, should not be reported as AEs during the study.

8.3.7 Disease Under Study

Symptoms of the disease under study are those which might be expected to occur as a direct result of the subject's asthmatic condition (e.g., wheeze, breathlessness, cough). Events that are unequivocally due to the disease under study should not be reported as an AE during the study unless they meet SAE criteria or lead to discontinuation of study the IMP.

8.3.8 Reporting of SAEs

All SAEs must be reported, whether or not considered causally related to the IMP. All SAEs will be recorded in the eCRF.

If any SAE occurs during the study, investigators or other site personnel will inform the appropriate AstraZeneca representatives within one day, i.e., immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative will work with the investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within one calendar day** of initial receipt for fatal and life-threatening events **and within 5 calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up will be undertaken immediately. Investigators or other site personnel will inform AstraZeneca representatives of any follow-up information on a previously reported SAE within one calendar day, i.e., immediately but **no later than 24 hours** of when he or she becomes aware of it.

Once the investigators or other site personnel indicate an AE is serious in the Electronic Data Capture (EDC) system, an automated email alert is sent to the designated AstraZeneca representative.

If the EDC system is not available, then the investigator or other study site staff reports the SAE via secure method to the appropriate AstraZeneca representative. Relevant contact information will be provided on the SAE reporting form.

When the EDC is temporarily not accessible, the AstraZeneca Study Representative should confirm that the investigator/site staff enters the SAE in the AstraZeneca EDC when access resumes.

For further guidance on the definition of an SAE, see Appendix B.

The reference document for definition of expectedness/listedness is the IB for the AstraZeneca IMP.

8.3.9 Pregnancy

All pregnancies and outcomes of pregnancy with conception dates following the first date of study intervention, including pregnancy in the partner of male participants, should be reported to AstraZeneca.

8.3.9.1 Maternal Exposure

If a participant becomes pregnant during the study intervention should be discontinued immediately.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the study intervention may have interfered with the effectiveness of a contraceptive medication. Congenital anomalies/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital anomaly/birth defect) should be followed up and documented even if the participant was discontinued from the study.

If any pregnancy occurs during the study, then the investigator or other site personnel informs the appropriate AstraZeneca representatives immediately but no later than **24 hours** after he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site **within one or 5 calendar days** for pregnancies associated with SAEs (see Section 8.3.8) and **within 30 days** for all other pregnancies.

The same timelines apply when outcome information is available.

The PREGREP module in the eCRF is used to report the pregnancy and the paper based PREGOUT module is used to report the outcome of the pregnancy.

8.3.9.2 Paternal Exposure

Male subjects who are sexually active (with females) must agree to use a double barrier method of contraception (condom with spermicide) from the first dose of randomized treatment until 2 weeks after their last dose, and must not donate sperm during their study participation period. Male subject's partner pregnancy itself is not regarded as an AE. Information about pregnancy and pregnancy outcomes (spontaneous miscarriages, planned pregnancy termination, ectopic pregnancy, congenital anomalies/birth defects and normal delivery) must be reported to the Sponsor within 24 hours of the Investigator learning of its occurrence. This information must be documented in medical records and passed to the data entry center of AstraZeneca's Patient Safety Department. Before information can

be collected and shared with AstraZeneca, consent must be obtained from the participant's partner. Once pregnancy report has been received, Investigator must obtain consent from the participant's partner before collecting any pregnancy information. The local study team should adapt the general consent form for the pregnant partner in accordance with local procedures/requirements and submit it to the relevant regulatory authorities / IRB / IEC prior to its implementation.

8.4 Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.5 Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.6 Optional Genomics Initiative

Optional Genomics Initiative research is not applicable in this study.

8.7 Biomarkers

Not applicable for this study.

8.8 Immunogenicity Assessments

Immunogenicity is not evaluated in this study.

8.9 Health Economics OR Medical Resource Utilisation and Health Economics

Health economics/Medical resource utilisation and health economics parameters are not evaluated in this study.

8.10 Study Participant Feedback Questionnaire

Not applicable for this study.

9 STATISTICAL CONSIDERATIONS

The Statistical Analysis Plan will be finalised prior to clinical data lock and it will include a more technical and detailed description of the planned statistical analyses. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.1 Statistical Hypotheses

The main objective of this study is to estimate the efficacy of PT027 (budesonide/albuterol) as compared with placebo based on the evaluation of the primary endpoint «maximum percentage fall from post-dose, pre-exercise baseline in FEV_1 observed up to 60 minutes post-exercise challenge». The corresponding hypotheses for the primary analysis are as follows:

- H_0: Difference between treatments «$_{\Delta}A$ – $_{\Delta}B$» = 0,
- H_1: Difference between treatments «$_{\Delta}A$ – $_{\Delta}B$» ≠ 0.

there: Δ - maximum percentage fall of FEV_1, A - PT027 (budesonide/albuterol), B - placebo.

9.2 Sample Size Determination

Approximately 107 participants will be screened to achieve 64 randomized/assigned to study intervention and 56 evaluable participants (refer to FAS population, Section 9.3) at 6 to 12 investigational centers in the Russian Federation.

Enrolled/screened*	Estimated 107 participants
Randomized/assigned	Estimated 64 participants
Evaluable participants	Estimated 56 participants

Note: * - "Enrolled/Screened" means a participant's, or their legally acceptable representative's, agreement to participate in a clinical study following completion of the informed consent process. Potential participants who are screened for the purpose of determining eligibility for the study, but are not randomized/assigned in the study, are considered "screen failures", unless otherwise specified by the protocol.

Sample size justification:

Sample size determination based on a previous clinical study NCT04234464, Phase III «TYREE» (LaForce C et al 2022) with a similar design and patient population. Using the obtained difference for maximum percentage fall from post-dose, pre-exercise baseline in FEV1 observed up to 60 minutes post-exercise challenge equals to CCI [redacted] and corresponding SD=CCI [redacted] (the calculated SD of treatment difference based on previous study results), a sample size of 28 subjects in each treatment sequence will provide a 95% probability to detect a difference between PT027 (budesonide + albuterol) and placebo based on 2 sided 95% CI.

Considering, a drop-out rate of ~10% (8 subjects), the sample size in this study will be 64 randomized subjects (32 randomized subjects per study sequence arm). Due to the possible withdrawal during the screening up to 40%, it is planned to screen up to 107 subjects.

Sample size calculations were performed as described in the book Chow, S., Shao, J. and Wang, H. (2008) Sample Size Calculations in Clinical Research. 2nd Edition, Chapman and Hall/CRC (Section 3.3.2). The assumptions used results are summarized in the table below:

Description	Value
Group ratio	1:1
Mean Difference	CCI %
Standard deviation	CCI %
Z for alpha=0.05	1.96
Z for beta=0.95	1.64
Superiority Margin	0
Result (number pairs, ie number of subjects in both groups)	56
Result adjusted for 10% dropout rate (number of subjects which should be randomized)	64

Calculations were performed using SAS v9.4 (proc POWER) by study statistician and validated by independent statistician.

9.3 Populations for Analyses

The following populations are defined:

Table 10 Populations for Analysis

Population/analysis set	Description
Enrolled/Screened	All participants who sign the ICF.
Full analysis set (FAS)	All participants who are randomized to treatment and have at least one post-dose, pre-exercise baseline and at least one corresponding post-dose post-exercise FEV_1 measure at Visit 3 and/or Visit 4.
Safety analysis set	All participants who have received any amount of the study intervention.

9.4 Statistical Analyses

9.4.1 General Considerations

Categorical variables will be presented as frequencies and proportions in percent. Continuous variables will be presented as means, geometric means (where applicable), standard deviations,

geometric standard deviations (where applicable), medians, minimum and maximum, and quartiles (where applicable), with number of observations. When necessary, means and geometric means will be provided with two-sided 95% confidence intervals (CI).

The data and results of the analyses will be presented in the form of tables as well as listings, sorted by treatment arms and participant numbers. Methods of analysis will be outlined in detail in the Statistical Analysis Plan.

Validated SAS software version 9.4 or R statistical package version 4.2 or higher will be used for statistical analysis and reporting of the study data. The results of the analysis presented in the clinical study report will be validated according to the company's standard operating procedures.

9.4.2 Efficacy

9.4.2.1 Primary Endpoint(s)

The fall from post-dose, pre-exercise baseline in FEV_1 will be calculated at each post-exercise FEV_1 assessment time point at Visit 3 and Visit 4. The post-dose, pre-exercise baseline FEV_1 assessment is expected to occur 30 minutes after administration of IMP and 5 minutes prior to the exercise challenge. The percentage fall in FEV_1 will be calculated proportional to the post-dose, pre-exercise FEV_1 value at each visit. The maximum percentage fall available in the 60-minute assessment period, prior to the use of rescue medication, will be calculated at Visit 3 and Visit 4.

The primary analysis will include all data obtained before subjects withdraw from the study and will use the Full analysis set (FAS).

The primary efficacy endpoint will be analyzed with a mixed effect model including categorical fixed effects for treatment, treatment period and treatment sequence. Continuous covariates include period-specific pre-dose baseline FEV_1 and average pre-dose baseline FEV_1. Also, a random subject within treatment sequence effect will be specified.

Post-dose, pre-exercise baseline FEV_1 will be defined as the 30 minutes post-dose value, i.e., 5 minutes before exercise challenge, at each visit for the respective treatment. The period-specific pre-dose baseline FEV_1 will be calculated separately at Visit 3 and Visit 4 as the pre-dose result, approximately 5 minutes prior to dosing. The average pre-dose baseline FEV_1 will be calculated as the mean of the period-specific pre-dose FEV_1 baselines. Estimated treatment differences and 95% confidence intervals (CIs) will be provided.

Applied significance level (alpha): 0.05 (using a 2-sided test).

Sensitivity analysis

Missing results for maximum percentage fall in FEV_1 are unlikely (i.e., rescue medication prior to the collection of the 5 minutes measure) and will be assumed to be missing at random. Sensitivity analyses will be conducted to explore the robustness of the primary analysis with respect to this missing data assumption. Further details will be given in the SAP.

Subgroup Analysis

Subgroup analyses will be conducted for the primary endpoint in the following subgroups of the FAS:

- by background ICS therapy (ICS or no ICS)

Additional subgroups of interest and analysis methods will be outlined in the SAP.

9.4.2.2 Secondary Endpoint(s)

Fall in post-exercise FEV_1 at individual time points

The fall in FEV_1 will be calculated at Visit 3 and Visit 4 as the difference in the baseline post-dose, pre-exercise FEV_1 assessment and each post-exercise assessment at the respective visit, as per the serial spirometry timings detailed in Table 3 and Table 4. The percentage fall will be calculated relative to the pre-exercise FEV_1 assessment at the respective visit. The post-dose, pre-exercise baseline FEV_1 is defined in Section 9.4.2.1.

The percentage fall in FEV_1 post-exercise challenge will be summarized descriptively by treatment group and planned time point within 60 minutes of the serial spirometry assessments conducted post-exercise challenge. An analysis of percentage fall in FEV_1 post-exercise challenge will be conducted using methods as per the primary analysis, with an additional adjustment for planned time point in the repeated measures model. The covariance within subject-periods will be unstructured over the time points. Only FEV_1 results prior to administration of rescue therapy (within the study visit) will be included in the analyses.

Responder analysis in post-exercise FEV_1

A binary response variable will be assigned to identify subjects with a maximum percentage fall in FEV_1 post-exercise for the two thresholds (<10% and <20%) separately at Visit 3 and Visit 4:

- Protected: Maximum percentage fall from post-dose, pre-exercise baseline in FEV_1 up to 60 minutes post-exercise challenge <10% and <20%
- Not Protected: Maximum percentage fall from post-dose, pre-exercise baseline in FEV_1 up to 60 minutes post-exercise challenge ≥10% and ≥20%

As with the primary efficacy endpoint specified in Section 9.4.2.1, the maximum percentage fall will be calculated based on post-dose FEV_1 measures prior to use of rescue medication. Subjects who have

no post-exercise FEV1 measure prior to rescue medication will have a missing responder status at the given visit.

The odds of being protected against EIB (i.e., having a maximum percentage fall in FEV1 post-exercise challenge under the corresponding threshold (<10% and <20%)) will be analyzed using a generalized linear mixed model with logit link function to compare the treatments. The model will be adjusted with fixed effects for treatment, treatment period and treatment sequence, period specific pre-dose baseline FEV1 and average pre-dose baseline FEV1 as continuous covariates, and a random subject within treatment sequence effect. The odds ratio and 95% CI will be reported for pairwise treatment comparisons. The analysis will only include maximum percentage falls in FEV1 prior to study discontinuation.

Time to recovery

Time to recovery at each of Visits 3 and 4 will be derived as the time (minutes) post-exercise challenge in which the FEV_1 result returns to within 10% of the value recorded at the post-dose, pre-exercise baseline. Only subjects who achieve a percentage fall in FEV_1 post-exercise challenge of >10% will have an event time derived; otherwise, their value will be left censored. Subjects who have any rescue medication administered during the post-dose assessments will be censored at the time of receiving rescue medication. Subjects who do not recover to within 10% of the post-dose, pre-exercise baseline will be censored at 60 minutes. The fall from post-dose, pre-exercise baseline in FEV_1 will be calculated at each of the post-exercise assessment time points at Visit 3 and Visit 4. The post-dose, pre-exercise baseline FEV_1 assessment is expected to occur 30 minutes after administration of IMP and 5 minutes prior to the exercise challenge. The percentage fall in FEV_1 will be calculated proportional to the post-dose, pre-exercise FEV_1 value at each visit.

The median time to recovery will be reported descriptively by treatment. P-values will be calculated using a period-adjusted sign test, based on categorizing subjects into period preferences (Senn S 1993). Further details will be clarified in the SAP.

Post-exercise FEV_1 $AUC_{0-30min}$

FEV_1 $AUC_{0-30min}$ will be derived for the changes from the post-dose, pre-exercise baseline using the trapezoidal rule and will be normalized by dividing by the actual time (in minutes) from dosing to the last included measurement, scheduled at 30 minutes post-exercise challenge at each of Visits 3 and 4. Only FEV_1 results prior to the use of rescue medication will be considered when calculating FEV_1 $AUC_{0-30min}$.

The post-exercise FEV_1 $AUC_{0-30min}$ will be analyzed with a similar mixed effects model as described in Section 9.4.2.1 for the change from post-dose, pre-exercise baseline in the maximum percentage fall

in FEV_1 without exercise pre-treatment. Only the FEV_1 $AUC_{0\text{-}30min}$ measurements prior to administration of rescue SABA therapy will be included in the analyses.

9.4.3 Safety

Safety data will be summarized descriptively and will not be formally analyzed unless otherwise specified. These data will be presented using the safety analysis set.

Adverse events will be coded using the most current version of MedDRA, where possible. They will be summarised by system-organ class, preferred term, severity and relationship to the study intervention as assessed by the Investigator.

Adverse events will be presented as frequencies and percentages of participants with reported AEs for each system-organ class (SOC) and preferred term (PT) in the tables by treatment groups:

- Overall table for AEs;
- AEs leading to discontinuation of study intervention;
- AEs by SOC and PT, with additional breakdown by relationship to the study intervention;
- AEs by SOC and PT, with additional breakdown by intensity;
- SAEs by SOC and PT, with additional breakdown by relationship to the study intervention;
- Additional tables can be planned and detailed in the Statistical Analysis Plan.

Screening laboratory values will be presented in the listings. Vital signs as well as electrocardiogram (ECG) results will be presented in tables with descriptive statistics by treatment arm for each visit for the measured values and for each visit after study intervention administration for changes relative to the initial values.

9.4.4 Other Analyses

Not applicable for this study.

9.5 Interim Analyses

No interim efficacy analysis is planned in this study.

9.6 Data Monitoring/Other Committee

Not applicable for this study.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

Appendix A Regulatory, Ethical, and Study Oversight Considerations

A 1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki as amended at 64th WMA General Assembly, Fortaleza, Brazil, October 2013 and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH GCP Guidelines
  - Applicable laws and regulations
- The protocol, revised protocol, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any revised protocol will require IRB/IEC and applicable Regulatory Authority approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- AstraZeneca will be responsible for obtaining the required authorisations to conduct the study from the concerned Regulatory Authority. This responsibility may be delegated to a CRO, but the accountability remains with AstraZeneca.
- The investigator will be responsible for providing oversight of the conduct of the study at the site and adherence to requirements of ICH guidelines, the IRB/IEC and all other applicable local regulations.

Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to AstraZeneca of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- AstraZeneca has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. AstraZeneca will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators.
- For all studies except those utilising medical devices, investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from AstraZeneca will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

Regulatory Reporting Requirements for Serious Breaches of Protocol or GCP

Prompt notification by the Investigator to AstraZeneca of any (potential) serious breach of the protocol or regulations is essential so that legal obligations and ethical obligations are met.

- A "serious breach" means a breach likely to affect to a significant degree the safety and rights of a participant or the reliability and robustness of the data generated in the clinical trial.

AstraZeneca will comply with country-specific regulatory requirements relating to serious breach reporting to the regulatory authority, IRB/IEC, and Investigators.

If any (potential) serious breach occurs in the course of the study, Investigators or other site personnel will inform the appropriate AstraZeneca representatives immediately.

In certain regions/countries, AstraZeneca has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about such breaches.

The investigator should have a process in place to ensure that:

- The site staff or service providers delegated by the investigator/institution are able to identify the occurrence of a (potential) serious breach
- A (potential) serious breach is promptly reported to AstraZeneca or delegated party, through the contacts (email address or telephone number) provided by AstraZeneca.

A 2 Financial Disclosure

Investigators and sub-investigators will provide AstraZeneca with sufficient, accurate financial information as requested to allow AstraZeneca to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the study and for one year after completion of the study.

A 3 Informed Consent Process

- The investigator or their representative will explain the nature of the study to the participant or their legally authorised representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary, and they are free to refuse to participate and may withdraw their consent at any time and for any reason during the study. Participants or their legally authorised representative will be required to sign a statement of informed consent that meets the requirements of local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB/IEC or study centre.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorised person obtaining the informed consent must also sign the ICF.

- If new information requires changes to the ICF, consider if participants must be re-consented and if so, this must be to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorised representative.

A 4 Data Protection

- Participants will be assigned a unique identifier by AstraZeneca. Any participant records or datasets that are transferred to AstraZeneca will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that their personal study-related data will be used by AstraZeneca in accordance with local data protection law. The level of disclosure and use of their data must also be explained to the participant in the informed consent.
- The participant must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorised personnel appointed by AstraZeneca, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- The participant must be informed that data will be collected only for the business needs. We will only collect and use the minimum amount of personal data to support our business activities and will not make personal data available to anyone (including internal staff) who is not authorised or does not have a business need to know the information.
- The participant must be informed that in some cases their data may be pseudonymised. The General data Protection Regulation (GDPR) defines pseudonymisation as the processing of personal data in such a way that the personal data can no longer be attributed to a specific individual without the use of additional information, provided that such additional information is kept separately and protected by technical and organisational measures to ensure that the personal data are not attributed to an identified or identifiable natural person.

Personal Data Breaches

A 'personal data breach' means a breach of security leading to the accidental or unlawful destruction, loss, alteration, unauthorized disclosure of, or access to, personal data transmitted, stored or otherwise processed.

- In compliance with applicable laws, the Data Controller[1] for the processing activity where the personal data breach occurred (AstraZeneca or respectively the site), will notify the data protection authorities without undue delay within the legal terms provided for such notification and within the prescribed form and content.
- Whilst AstraZeneca has processes in place to deal with personal data breaches it is important that investigators that work with AstraZeneca have controls in place to protect patient data privacy.

The Investigator should have a process in place to ensure that:

- allow site staff or service providers delegated by the investigator/institution to identify the occurrence of a (potential) personal data breaches.
- Any (potential) personal data breach is promptly reported to AstraZeneca or delegated party, through the contacts (e-mail address or telephone number) provided by AstraZeneca.

AstraZeneca and the site must demonstrate that they:

- have taken all necessary steps to avoid personal data breaches and
- have undertaken measures to prevent such breaches from occurring in the first place and to mitigate the impact of occurred data breaches (e.g., applying encryption, maintaining and keeping systems and IT security measures up-to-date, regular reviews and testing, regular training of employees, and developed security policies and standards).
- where possible, have developed an internal data breach reporting and investigation process and internal protocols with guidance on how to respond swiftly and diligently to the occurrence of a personal data breach.
- where it has not been possible to develop an internal data breach reporting and investigation process, the site follows AstraZeneca's instructions.

Notification of personal Data Breach to participants:

- notification to participants is done by the site for the data breaches that occurred within the processing activities for which the site is the Data Controller and for data breaches occurred within the processing activities of AstraZeneca as the Data Controller, the notification is done in

[1] The **data controller** determines the **purposes** for which and the **means** by which personal data is processed, as defined by the European Commission

collaboration with the site and is performed by the site and/or Principal Investigator, acting on behalf of AstraZeneca, so that AstraZeneca has no access to the identifying personal information of the participants. The site and/or Principal Investigator shall conduct the notification by contacting the participants using the information that they gave for communication purposes in clinical research.

- If a personal data breach occurs in a processor's systems, engaged by AstraZeneca, the processor under contractual obligations with AstraZeneca promptly and in due course after discovering the breach notifies AstraZeneca and provides full cooperation with the investigation. In these cases, to the extent AstraZeneca is the Data Controller for the processing activity where the breach occurred, it will be responsible for the notification to data protection authorities and, if applicable, to participants. If the personal data breach needs to be notified to the participants, the notification to participants is done in collaboration with the site and is performed by the site and/or Principal Investigator, acting on behalf of the Sponsor, so that AstraZeneca has no access to the identifying personal information of the participants.
- If a personal data breach involving an AstraZeneca's representative device (i.e. Study Monitor laptop), AstraZeneca representative will provide will provide AstraZeneca with all of the information needed for notification of the breach, without disclosing data that allows AstraZeneca directly or indirectly to identify the participants. The notification will be done by AstraZeneca solely with the information provided by the Study Monitor and in no event with access to information that could entail a risk of re-identification of the participants. If the data breach must be notified to the data subjects, the notification will be done directly by the Study Monitor in collaboration with the site and/or Principal Investigator, acting on behalf of the Sponsor, so that AstraZeneca has no access to the identifying personal information of the participants. The contract between AstraZeneca and the Study Monitor shall expressly specify these conditions.
- The contract between the site and AstraZeneca for performing the clinical research includes the provisions and rules regarding who is responsible for coordinating and directing the actions in relation to the breaches and performing the mandatory notifications to authorities and participants, where applicable.

A 5 Committees Structure

The safety of all AstraZeneca clinical studies is closely monitored on an on-going basis by AstraZeneca representatives in consultation with Patient Safety. Issues identified will be addressed; for instance, this could involve amendments to the CSP and letters to investigators.

A 6 Dissemination of Clinical Study Data

A description of this clinical study will be available on http://astrazenecagrouptrials.pharmacm.com and http://www.clinicaltrials.gov as will the summary of the main study results when they are available. The clinical study and/or summary of main study results

may also be available on other websites according to the regulations of the countries in which the main study is conducted.

A 7 Data Quality Assurance

- All participant data relating to the study will be recorded on eCRF. The investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy, including definition of study-critical data items and processes (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are included in the Monitoring Plan.
- AstraZeneca or designee is responsible for medical oversight throughout the conduct of the study which includes clinical reviews of study data in accordance with the currently approved protocol. Monitoring details describing clinical reviews of study data from a medical perspective are included in more detail in the Monitoring Plan.
- AstraZeneca or designee is responsible for the data management of this study including quality checking of the data.
- AstraZeneca assumes accountability for actions delegated to other individuals (eg, CROs).
- Study monitors will perform ongoing source data verification as per the Monitoring Plan to confirm that data entered into the eCRF by authorised site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for a minimum of 25 years after study archiving or as required by local regulations, according to the AstraZeneca Global retention and Disposal (GRAD) Schedule. No records may be destroyed during the retention period without the written approval of AstraZeneca. No records may be transferred to another location or party without written notification to AstraZeneca.

A 8 Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator’s site.

- Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the study are defined as source documents. Source data are contained in source documents (original records or certified copies).

A 9 Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the first site open and will be the study start date.

AstraZeneca designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of AstraZeneca. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by AstraZeneca or the investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, AstraZeneca's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development

If the study is prematurely terminated or suspended, AstraZeneca shall promptly inform the investigators, the IRBs/IECs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

Participants from terminated sites will have the opportunity to be transferred to another site to continue the study.

A 10 Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to AstraZeneca before submission. This allows AstraZeneca to protect proprietary information and to provide comments.
- AstraZeneca will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, AstraZeneca will generally support publication of multicentre studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Appendix B AEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

B 1 Definition of AEs

An AE is the development of any untoward medical occurrence in a patient or clinical study participant administered a medicinal product, and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (eg, an abnormal laboratory finding), symptom (for example nausea, chest pain), or disease temporally associated with the use of a medicinal product, whether it's considered related to the medicinal product.

The term AE is used to include both serious and non-serious AEs and a deterioration of a pre-existing medical occurrence. An AE may occur at any time, including run-in or washout periods, even if no study intervention has been administered.

B 2 Definition of SAEs

An SAE is an AE occurring during any study phase (i.e., run-in, treatment, washout, follow-up), that fulfils one or more of the following criteria:

- Results in death.
- Is immediately life-threatening.
- Requires in-patient hospitalisation or prolongation of existing hospitalisation.
- Results in persistent or significant disability or incapacity.
- Is a congenital anomaly or birth defect.
- May require medical treatment to prevent one of the outcomes listed above.

Adverse Events for **malignant tumours** reported during a study should generally be assessed as **SAEs**. If no other seriousness criteria apply, the 'Important Medical Event' criterion should be used. In certain situations, however, medical judgement on an individual event basis should be applied to clarify that the malignant tumour event should be assessed and reported as a **non-SAE**. For example, if the tumour is included as medical history and progression occurs during the study, but the progression does not change treatment and/or prognosis of the malignant tumour, the AE may not fulfil the attributes for being assessed as serious, although reporting of the progression of the malignant tumour as an AE is valid and should occur. Also, some types of malignant tumours, which do not spread remotely after a routine treatment that does not require hospitalisation, may be assessed as non-serious; examples in adults include Stage 1 basal cell carcinoma and Stage 1A1 cervical cancer removed via cone biopsy.

Life-threatening

'Life-threatening' means that the participant was at immediate risk of death from the AE as it occurred,

or it is suspected that use or continued use of the medicinal product would result in the participant's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (e.g., hepatitis that resolved without hepatic failure).

Hospitalisation

Outpatient treatment in an emergency room is not in itself a SAE, although the reasons for it may be (e.g., bronchospasm, laryngeal oedema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the participant was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important Medical Event or Medical Treatment

Medical and scientific judgement should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life threatening or result in death, hospitalisation, disability or incapacity but may jeopardise the participant or may require medical treatment to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgement must be used.

- Angioedema not severe enough to require intubation but requiring IV hydrocortisone treatment.
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine.
- Intensive treatment in an emergency room or at home for allergic bronchospasm.
- Blood dyscrasias (e.g., neutropenia or anaemia requiring blood transfusion, etc.) or convulsions that do not result in hospitalisation.
- Development of drug dependency or drug abuse.

Intensity Rating Scale:

- Mild (awareness of sign or symptom, but easily tolerated)
- Moderate (discomfort sufficient to cause interference with normal activities)
- Severe (incapacitating, with inability to perform normal activities)

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Appendix B 2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not an SAE unless it meets the criteria shown in Appendix B 2. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke

but would be an SAE when it satisfies the criteria shown in Appendix B 2.

B 3 A Guide to Interpreting the Causality Question

When assessing causality consider the following factors when deciding if there is a 'reasonable possibility' that an AE may have been caused by the medicinal product.

- Time Course. Exposure to suspect drug. Has the participant received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?
- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? Or could the AE be anticipated from its pharmacological properties?
- De-challenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?
- No alternative cause. The AE cannot be reasonably explained by another aetiology such as the underlying disease, other drugs, other host, or environmental factors.
- Re-challenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a re-challenge.
- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

In difficult cases, other factors could be considered such as:

- Is this a recognised feature of overdose of the drug?
- Is there a known mechanism?

Causality of 'related' is made if following a review of the relevant data, there is evidence for a 'reasonable possibility' of a causal relationship for the individual case. The expression 'reasonable possibility' of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship.

The causality assessment is performed based on the available data including enough information to make an informed judgment. With no available facts or arguments to suggest a causal relationship, the event(s) will be assessed as 'not related'. Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as 'no reasonable possibility'.

Appendix C Abbreviations

Abbreviation or special term	Explanation
ACQ	asthma control questionnaire
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATS	American Thoracic Society
$AUC_{0\text{-}30min}$	area under the curve from 0 to 30 minutes
BDA MDI (PT027)	budesonide/albuterol metered-dose inhaler
β-hCG	β-human chorionic gonadotropin
BMI	body mass index
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CONSORT	Consolidated Standards of Reporting Trials
CTT	Clinical Trial Transparency
DUS	disease under study
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
ECG	Electrocardiogram
eCRF	electronic case report form
ECT	exercise challenge test
EDC	Electronic Data Capture
EIB	exercise-induced bronchoconstriction
EMA	European Medicines Agency
ERS	European Respiratory Society
ERT	eResearch Technology
FAS	full analysis set
FDA	Food and Drug Administration
FEV_1	forced expiratory volume in 1 second
FVC	forced vital capacity
GCP	Good Clinical Practice
GDPR	General data Protection Regulation
GINA	Global Initiative for Asthma
GMP	Good Manufacturing Practice
GRAD	Global retention and Disposal

HFA	Hydrofluoroalkane
ICF	informed consent form
ICH	International Conference on Harmonisation
ICS	inhaled corticosteroid
Coordinating Investigator	The Coordinating Investigator is the investigator coordinating the investigators and/or activities in several study sites nationally.
IP / IMP	investigational product / investigational medicinal product
IWRS	Interactive Web Response System
LABA	long-acting β2-agonist
LAMA	long-acting muscarinic antagonists
MDI	metered-dose inhaler
MoH	Ministry of Health
NIMP	non-investigational medicinal product
PDV	premature discontinuation visit
PEF	peak expiratory flow
PT	preferred term
RF	Russian Federation
PFT	pulmonary function test
QTcF	QT interval corrected by Fridericia
SABA	short/rapid-acting β2-adrenoreceptor agonist
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SMART	Symbicort Maintenance And Reliever Therapy
SoA	schedule of activities
SoC	system-organ class
SUSAR	suspected unexpected serious adverse reactions
TEAE	treatment emergent adverse event
TC	telephone call
US	United States
WBDC	web based data capture
WOCBP	women of childbearing potential

11 REFERENCES

Akhmerova YN et al 2023
Akhmerova YN, Shpakova TA, Grammatikati KS, Mitrofanov SI, Kazakova PG, Mkrtchian AA, Zemsky PU, Pilipenko MN, Feliz NV, Frolova LV, Frolovskaya AA, Yudin VS, Keskinov AA, Kraevoy SA, Yudin SM, Skvortsova VI. Genetic Variants Associated with Bronchial Asthma Specific to the Population of the Russian Federation. Acta Naturae. 2023 Jan-Mar;15(1):31-41. doi: 10.32607/actanaturae.11853. PMID: 37153512; PMCID: PMC10154776.

Bonini M et al 2013
Bonini M, Di Mambro C, Calderon MA, Compalati E, Schünemann H, Durham S, et al. Beta2-agonists for exercise-induced asthma. Cochrane Database of Systematic Reviews 2013, Issue 10. Art. No.: CD003564. DOI: 10.1002/14651858.CD003564.pub3.

Chipps BE et al 2023
Chipps BE, Israel E, Beasley R, Panettieri RA Jr, Albers FC, Rees R, Dunsire L, Danilewicz A, Johnsson E, Cappelletti C, Papi A. Albuterol-Budesonide Pressurized Metered Dose Inhaler in Patients With Mild-to-moderate Asthma: Results of the DENALI Double-blind Randomized Controlled Trial. Chest. 2023 Mar 30:S0012-3692(23)00463-4. doi: 10.1016/j.chest.2023.03.035. Epub ahead of print. PMID: 37003355.

Cooper PR et al 2008
Cooper PR, Panettieri RA. Steroids completely reverse albuterol-induced β2-adrenergic receptor tolerance in human small airways. J Allergy Clin Immunol. 2008;122(4):734-740.

Côté A et al 2018
Côté A, Turmel J, Boulet LP. Exercise and Asthma. Semin Respir Crit Care Med. 2018 Feb;39(1):19-28. doi: 10.1055/s-0037-1606215. Epub 2018 Feb 10. PMID: 29427982.

Crapo RO et al 2000
Crapo RO, Casaburi R, Coates AL, Enright PL, Hankinson JL, Irvin CG, et al. Guidelines for methacholine and exercise challenge testing—1999. This official statement of the American Thoracic Society was adopted by the ATS Board of Directors, July 1999. Am J Respir Crit Care Med. 2000;161(1):309-329.

Dockhorn RJ et al 1997
Dockhorn RJ, Wagner DE, Burgess GL, et al. Proventil HFA provides protection from exercise-induced bronchoconstriction comparable to proventil and ventolin. Ann Allergy Asthma Immunol. 1997;79(1):85-88. doi:10.1016/S1081-1206(10)63091-8

EMA Guideline on the clinical investigation of medicinal products for the treatment of asthma 2015
European Medicines Agency. Guideline on the clinical investigation of medicinal products for the treatment of asthma (CHMP/EWP/2922/01 Rev. 1). 2015. Available at https://www.ema.europa.eu/documents/scientific-guideline/guideline-clinical-investigation-medicinal-products-treatment-asthma_en.pdf.

Golam SM et al 2022
Golam SM, Janson C, Beasley R, FitzGerald JM, Harrison T, Chipps B, Hughes R, Müllerová H, Olaguibel JM, Rapsomaniki E, Reddel HK, Sadatsafavi M; NOVELTY study investigators. The burden of mild asthma: Clinical burden and healthcare resource utilisation in the NOVELTY study. Respir Med. 2022 Aug-Sep;200:106863. doi: 10.1016/j.rmed.2022.106863. Epub 2022 May 9. PMID: 35952579.

Graham BL et al 2019
Graham BL, Steenbruggen I, Miller MR, Barjaktarevic IZ, Cooper BG, Hall GL, Hallstrand TS, Kaminsky DA, McCarthy K, McCormack MC, Oropez CE, Rosenfeld M, Stanojevic S, Swanney MP, Thompson BR. Standardization of Spirometry 2019 Update. An Official American Thoracic Society and European Respiratory Society Technical Statement. Am J Respir Crit Care Med. 2019 Oct 15;200(8):e70-e88. doi: 10.1164/rccm.201908-1590ST. PMID: 31613151; PMCID: PMC6794117.

GINA guidelines, 2023
GINA Main Report, Global Strategy for Asthma Management and Prevention, 2023. Available at https://ginasthma.org/2023-gina-main-report/

Halpin DMG et al 2019
Halpin DMG, Meltzer EO, Pisternick-Ruf W, Moroni-Zentgraf P, Engel M, Zaremba-Pechmann L, Casale T, FitzGerald JM. Peak expiratory flow as an endpoint for clinical trials in asthma: a comparison with FEV_1. Respir Res. 2019 Jul 18;20(1):159. doi: 10.1186/s12931-019-1119-6. PMID: 31319851; PMCID: PMC6637596.

Hawksworth RJ et al 2002
Hawksworth RJ, Sykes AP, Faris M, Mant T, Lee TH. Albuterol HFA is as effective as albuterol CFC in preventing exercise-induced bronchoconstriction. Ann Allergy Asthma Immunol. 2002;88(5):473-477. doi:10.1016/S1081-1206(10)62385-X

LaForce C et al 2022
LaForce C, Chipps BE, Albers FC, Reilly L, Johnsson E, Andrews H, Cappelletti C, Maes A, Papi A. Albuterol/budesonide for the treatment of exercise-induced bronchoconstriction in patients with asthma: The TYREE study. Ann Allergy Asthma Immunol. 2022 Feb;128(2):169-177. doi: 10.1016/j.anai.2021.10.020. Epub 2021 Oct 24. PMID: 34699967.

Mendes ES et al 2008
Mendes ES, Horvath G, Campos M, Wanner A. Rapid corticosteroid effect on β(2)- adrenergic airway and airway vascular reactivity in patients with mild asthma. J AllergyClin Immunol. 2008;121(3):700-704.

Mendes ES et al 2015
Mendes ES, Cadet L, Arana J, Wanner A. Acute effect of an inhaled glucocorticosteroidon albuterol-induced bronchodilation in patients with moderately severe asthma. Chest. 2015;147(4):1037-1042.

MoH RF Clinical guidelines, 2021
Clinical guidelines "Bronchial asthma" of the Ministry of Health of the Russian Federation, 2021. Available at https://cr.minzdrav.gov.ru/recomend/359

MoH RF Spirometry (methodological guide) 2023
Ministry of Health of the Russian Federation. Russian Respiratory Society. Spirometry (methodological guide), 2023. Available at https://spulmo.ru/upload/kr/Spirometria_2023.pdf?t=1

Molema J et al 1989
Molema J, van Herwaarden CL, Folgering HT. Effects of long-term treatment with inhaled cromoglycate and budesonide on bronchial hyperresponsiveness in patients with allergic asthma. Eur Respir J. 1989;2(4):308-316.

O'Byrne PM et al 2005
O'Byrne PM, Bisgaard H, Godard PP, Pistolesi M, Palmqvist M, Zhu Y, et al. Budesonide/formoterol combination therapy as both maintenance and reliever medicationin asthma. Am J Respir Crit Care Med. 2005;171(2):129-136.

O'Byrne PM 2007
O'Byrne PM. Acute asthma intervention: insights from the STAY study. J Allergy Clin Immunol. 2007;119(6):1332-1336.

Ostrom NK et al 2015
Ostrom NK, Taveras H, Iverson H, Pearlman DS. Novel albuterol multidose dry powder inhaler in patients with exercise-induced bronchoconstriction: a single-dose, double-blind,randomized, 2-way crossover study. Respir Med. 2015;109(11):1410-1415.

Papi A et al 2022
Papi A, Chipps BE, Beasley R, Panettieri RA Jr, Israel E, Cooper M, Dunsire L, Jeynes-Ellis A, Johnsson E, Rees R, Cappelletti C, Albers FC. Albuterol-Budesonide Fixed-Dose

Combination Rescue Inhaler for Asthma. N Engl J Med. 2022 Jun 2;386(22):2071-2083. doi: 10.1056/NEJMoa2203163. Epub 2022 May 15. PMID: 35569035.

Parsons JP et al 2013
Parsons JP, Hallstrand TS, Mastronarde JG, Kaminsky DA, Rundell KW, Hull JH, et al.An official American Thoracic Society clinical practice guideline: exercise-induced bronchoconstriction. Am J Respir Crit Care Med. 2013;187(9):1016-1027.

Papi A et al 2022
Papi A, Chipps BE, Beasley R, Panettieri RA Jr, Israel E, Cooper M, Dunsire L, Jeynes-Ellis A, Johnsson E, Rees R, Cappelletti C, Albers FC. Albuterol-Budesonide Fixed-Dose Combination Rescue Inhaler for Asthma. N Engl J Med. 2022 Jun 2;386(22):2071-2083. doi: 10.1056/NEJMoa2203163. Epub 2022 May 15. PMID: 35569035.

Reddel HK et al 2009
Reddel HK, Taylor DR, Bateman ED, Boulet LP, Boushey HA, Busse WW, et al. An official American Thoracic Society/European Respiratory Society statement: asthma control and exacerbations: standardizing endpoints for clinical asthma trials and clinical practice. Am J Respir Crit Care Med. 2009;180(1):59–99.

Rabe KF et al 2006
Rabe KF, Atienza T, Magyar P, Larsson P, Jorup C, Lalloo UG. Effect of budesonide in combination with formoterol for reliever therapy in asthma exacerbations: a randomized controlled, double-blind study. Lancet. 2006;368(9537):744-753.

Richter K et al 2002
Richter K, Janicki S, Jörres RA, Magnussen H. Acute protection against exercise-induced bronchoconstriction by formoterol, salmeterol and terbutaline. Eur Respir J. 2002;19(5):865-871.

Senn S 1993
Senn S, Cross-over Trials in Clinical Research. Wiley, Chichester.1993.