ALTA -ALbuterol/budesonide Treatment in Acute Airway Obstruction

A randomized, double-blind, 2-period, cross-over study evaluating efficacy and safety of repeated doses of PT027 compared to PT007 in patients with asthma and acute airway obstruction induced by repeated mannitol challenges

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STATISTICAL ANALYSIS PLAN – Part 1	
Study Code	D6930C00017
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LIST OF ABBREVIATIONS

Abbreviation or Specialized Term	Definition
AE	adverse event
AIRQ	Asthma Impairment and Risk Questionnaire
ATC	anatomical therapeutic chemical
AUC	area under the curve
BMI	body mass index
CI	confidence interval
COVID-19	coronavirus disease 2019
CRF	case report form
CSP	clinical study protocol
CSR	clinical study report
ECG	electrocardiogram
FEV_1	forced expiratory volume in 1 second
FVC	forced vital capacity
ICE	intercurrent event
ICF	informed consent form
IPD	important protocol deviation
LLOQ	lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
NAEPP	National Asthma Education and Prevention Program
pMDI	pressurized metered dose inhaler
PT	preferred term
QTCF	QTc interval adjusted for Fridericia's formulae
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SOC	system organ class

AMENDMENT HISTORY

CATEGORY Change refers to:	Date	Description of change	In line with CSP?	Rationale
N/A	Click or tap to enter a date.	Initial approved SAP	N/A	N/A
Choose an item.	Click or tap to enter a date.			
Choose an item.	Click or tap to enter a date.			

1 INTRODUCTION

The purpose of this document is to give details for the Part 1 statistical analysis of study D6930C00017. This study is a Phase 3b, multicenter, randomized, double-blind, 2-period, cross-over study evaluating efficacy and safety of repeated doses of PT027 (albuterol/budesonide) compared to PT007 (albuterol) in patients with asthma and acute airway obstruction, induced by repeated mannitol challenges. Part 1 will comprise of approximately 16 randomized participants and will be used as a pilot study. The data obtained from Part 1 will be assessed by an internal AstraZeneca advisory board, and suggested changes may be made to Part 2 of the study.

The reader is referred to the clinical study protocol (CSP) and the case report form (CRF) for details of study conduct and data collection. This document is written in accordance with CSP Amendment version 3.0 dated 3 Feb 2023 and CRF version 1.0 dated 24 June 2022.

2 CHANGES TO PROTOCOL PLANNED ANALYSES

The linear mixed model described in Section 1.1 Synopsis: Statistical Methods and in Section 9.4.3.1 Primary Endpoint in CSP version 3.0 has been updated to include in the linear predictor also the average of the two periods mannitol baseline FEV_1 values. This approach was undertaken to avoid cross-level bias.

3 DATA ANALYSIS CONSIDERATIONS

3.1 Timing of Analyses

The Part 1 SAP will reference the analyses to cover the adaptations from Part 1 to inform Part 2. There will be a pause in recruitment between Part 1 and Part 2. Following the Part 1 study completion and database lock, Part 1 will be unblinded and analyzed as described in this statistical analysis plan (SAP). Part 1 analysis will be utilized similar to a pilot study to inform the assumptions of the treatment effect size and variability estimates used in sample-size calculations for the primary- and secondary efficacy endpoints in study Part 2 as described in section 5 of this SAP and in line with the CSP section 9.2. Due to the study being double-blind, an independent team, AstraZeneca Internal Advisory Board, will be assigned to evaluate Part 1 data analyses. A detailed description of the remit and the procedures to be followed by the AZ Internal Advisory Board are described in the AZ Internal Advisory Board charter. A separate SAP will define the analysis for Part 2 of the study.

For the primary and secondary objectives, data from Part 1 of the study will not be combined with the data from Part 2. Data describing the study population will not be

addressed within scope of this SAP, but will be described in the SAP for Part 2 as study population data will be pooled for Part 1 and 2, as well as being presented separately. Likewise, safety outputs are planned to be presented for pooled Part 1 and 2 data and this strategy applies also to the exploratory endpoints (except for the exploratory endpoint change from baseline FEV_1 AUC0-15 min post-mannitol challenge 2, which will be reported separately for Part 1 and Part 2, and will be described within scope of this SAP). Biomarkers data will not be described within scope of this SAP. These biomarker analyses are described elsewhere for the combined analysis of Part 1 and Part 2 biomarker data.

3.2 Analysis Populations

Table 1 Populations for Analysis

Population/Analysis Set	Description
Enrolled analysis set (ES)	All participants who sign the ICF.
Randomized analysis set (RS)	All participants who are randomized to any of the 2 treatment sequences, A/B or B/A, where treatments A and B are defined as: Treatment A = PT027 180/160 µg pMDI Treatment B = PT007 180 µg pMDI.
Per Protocol analysis set (PP)	All participants who received all doses of study treatment following mannitol challenge 1, have baseline and post-treatment study evaluation (spirometry tests) and do not have any important protocol deviations.
Safety analysis set (SAF)	All participants randomly assigned to any of the 2 study treatment sequences and who take at least 1 dose of study treatment. Participants will be classified on the basis of treatment they actually received within each treatment period.

Abbreviations: AE' Adverse event(s); pMDI, Pressurized metered dose inhaler.

3.3 General Considerations

All statistical analyses will be performed by Parexel International, under the direction of the Late Stage Respiratory and Immunology Biometrics Group, AstraZeneca. All statistical analyses will be performed using the latest available version of SAS® (SAS Institute Inc., Cary, North Carolina, US), version 9.4 or higher.

The disposition table will be presented by treatment sequence (PT027-PT007, PT007-PT027) and overall for the enrolled analysis set.

Efficacy data will be presented by treatment (PT027 or PT007).

Adverse events will be mapped to treatment periods as described in section 4.6.1.1. A listing for Adverse events occurring during Part 1 will be created based on the enrolled analysis set, where adverse events will be presented by analysis phase and actual treatment.

3.3.1 General Study Level Definitions

Unless stated otherwise, continuous variables will be summarized by descriptive statistics (number of participants [n], minimum, maximum, arithmetic mean, standard deviation (SD), and/or medians and inter-quartile ranges (Q1 - Q3), depending on the distributions of the data. The minimum(s) and maximum(s) will be displayed with the same number of decimal places as the collected data. Mean(s), median(s), SD(s), and quartiles (where applicable) will be displayed with one more decimal place than the collected data. Categorical data will be summarized as the number and percentage among participants with non-missing data. The percentage will be displayed with one decimal place.

The two-sided (2.5% significance level each side) hypothesis test will be presented with the corresponding 95% confidence interval (CI). The presentation of p-values will be to four decimal places unless a p-value is less than 0.0001 (or greater than 0.9999), in which case "<0.0001" (or >0.9999) will be displayed. Confidence intervals will be presented to one more decimal place than the collected data.

A month and a year are operationally defined to be 30.4 and 365.25 days respectively.

Study intervention is defined as any investigational intervention(s) or marketed product(s) intended to be administered to, or medical device(s) utilized by, a study participant according to the CSP. Therefore, the date of first dose of study intervention includes the date of the first dose of PT007 at Visit 1 and is not limited to randomized study drugs at Visits 2 and 3.

3.3.2 Visit Window

All summaries and analysis which are presented by visit and timepoint will use the nominal visit and timepoint labels. For some efficacy endpoints, actual dates and time will be used to derive the endpoint as described in section 4.2.

3.3.3 Handling of unscheduled, incomplete planned and rescheduled Visits

Unscheduled visits will not be included in the by visit summaries for efficacy endpoints, but will be presented in listings.

Incomplete planned visits will not be included in the by visit summaries for efficacy endpoints.

Rescheduled visits will provide to the visit summaries for efficacy endpoints.

3.3.4 Multiplicity/Multiple Comparisons

In order to account for the multiple tests across the primary and secondary endpoints, a hierarchical testing approach will be applied for the primary and secondary efficacy endpoints in the Part 2 analysis.

No adjustment for Part 1 will be performed.

3.3.5 Handling of Protocol Deviations in Study Analysis

Deviations from the protocol will be reviewed prior to the Part 1 database lock, and will be assessed as "important" or "not-important". Only important protocol deviations (IPDs) will be listed, based on Enrolled analysis set. IPDs are defined as protocol deviations which may significantly affect the completeness, accuracy and/or reliability of the study data, or which may significantly affect a participant's rights, safety or well-being. They may include (but not be limited to):

- Participants who were randomized even though they did not meet key inclusion criteria or who met at least one key exclusion criteria
- Participants who met discontinuation criteria for study treatment but were not discontinued from study treatment
- Participants who developed withdrawal criteria during the study but were not withdrawn
- Participants who received wrong IP treatment or incorrect/incomplete IP dosing, or wrong or incomplete mannitol dosing
- Participants who received a restricted or prohibited concomitant treatment
- Written informed consent not obtained prior to mandatory study specific procedures, sampling and analyses.

Prior to the Part 1 database lock and unblinding, IPDs will be assessed for potential impact on the primary endpoint non-inferiority efficacy analysis. Any IPDs determined to potentially impact the accuracy and/or reliability of the study data will lead to exclusion of that participant from the per protocol analysis set.

Any PDs which are not defined as important, except coronavirus disease 2019 (COVID-19) related PDs, will not be reported or discussed in the clinical study report (CSR).

3.3.6 Definition of Baseline and Change from Baseline

Baseline definitions for the primary/secondary forced expiratory volume in 1 second (FEV_1) endpoints and safety parameters are defined in Table 2. The endpoints are further defined in section 4.2.

Change from baseline will be defined as follows, ensuring the correct baseline reference as described in Table 2 is used: (post-baseline value - baseline value). If either the post-baseline value or the baseline value is missing, then the change from baseline will also be missing.

Table 2 Baseline for primary/secondary FEV_1 endpoints and safety parameters

Category/Assessment	Baseline Definition	Endpoints/Parameters
Baseline FEV_1	Baseline FEV_1 is defined as the best FEV_1 value (highest FEV_1 of the acceptable efforts or the highest FEV_1 if no acceptable efforts are obtained) taken pre-mannitol challenge at -30 minutes for Visit 2 and Visit3.	• Fall in FEV_1 from baseline FEV_1 at completion of mannitol challenge 2, pre-dose • Time to return to baseline FEV_1 post-mannitol challenge 2
Mannitol baseline FEV_1	The mannitol baseline is defined as the FEV_1 result where a positive response to mannitol is observed prior to dosing of study drug for challenge 1 in Visit 2 and in Visit 3 (time 0). A positive response is defined as a ≥15% decrease in FEV_1 from the 0 mg mannitol FEV_1 value.	• Change from mannitol baseline FEV_1 to the normalized FEV_1 AUC0-60 min post-mannitol challenge 1 • Change from mannitol baseline FEV_1 to the FEV1 AUC0-15 min post-mannitol challenge 1 • Change from mannitol baseline in FEV_1 at 7 hours post-mannitol challenge 1
Vital signs	Visit 2 and Visit 3 will have separate baseline results utilizing the -30 minutes time point. If the -30 value is missing, baseline will be the latest non-missing value prior to the	Results and change from baseline for: • Pulse • Blood pressure • Pulse oximetry • Respiratory rate

	mannitol challenge ie, prior to time -10.	
12-lead ECG	Visit 2 and Visit 3 will have separate baseline results utilizing the -30 minutes time point. If the -30 value is missing, baseline will be the latest non-missing value prior to the mannitol challenge ie, prior to time -10.	Result and change from baseline for all scheduled timepoints at for all ECG parameters
Laboratory assessments	Visit 2 and Visit 3 will have separate baseline results utilizing the -30 minutes time point. If the -30 value is missing, baseline will be the latest non-missing value prior to the mannitol challenge ie, prior to time -10.	Result and change from baseline for all scheduled timepoints for Laboratory safety variables as listed in Table 6 of the CSP Amendment version 3.0 dated 02 Jan 2023.

4 STATISTICAL ANALYSIS

This section provides information on definitions, derivation and analysis/data presentation per domain.

4.1 Study Population

The domain study population covers participant disposition, analysis sets, protocol deviations, demographics, baseline characteristics medical history, prior and concomitant medication.

4.1.1 Patient Disposition and Completion Status

4.1.1.1 Definitions and Derivations

Screen failures are defined as participants who do consent to participate in the clinical study but are not subsequently randomly assigned to study intervention (ie, at Visit 2).

4.1.1.2 Presentation

Participant disposition will be summarized using the enrolled analysis set. The number of participants screened, screen failures, Participants not randomised, and reason for screen failure will be summarized. The number and percentage of participants within each treatment sequence will be presented by the following categories: randomized, randomized

but not treated (and reason), started any treatment, completed all treatments, discontinued any treatment (and reason), competed study, withdrawn from study (and reason).

4.1.2 Analysis Sets

4.1.2.1 Definitions and Derivations

See section 3.2 for full definitions of the analysis sets.

4.1.2.2 Presentation

The number and percentage of participants in each of the analysis sets will be summarized by treatment sequence, along with reason for exclusion for participants not included in each set.

4.1.3 Protocol Deviations

4.1.3.1 Definitions and Derivations

See section 3.3.5 for definition of IPDs.

4.1.3.2 Presentation

For part 1 a listing of all IPDs (important Protocol Deviations) will be provided based on the enrolled analysis set. **Demographics**

4.1.4.1 Definitions and Derivations

Demographic data will include age, sex, race, and ethnicity. Age will be summarized both continuously and by the following categories: 18 to 64, 65-74, 75-84 and 85 years and older.

4.1.4.2 Presentation

Demographics will be summarized for the pool of Part 1 and Part 2, and for Part 1 and Part 2 separately once part 2 is completed.

4.1.5 Baseline Characteristics

4.1.5.1 Definitions and Derivations

Baseline characteristics (weight [kg], height [cm], and body mass index (BMI) [kg/m2]) are collected at Visit 1.

4.1.5.2 Presentation

Baseline characteristics will be summarized for the pool of Part 1 and Part 2, and for Part 1 and Part 2 separately once Part 2 reads out.

4.1.6 Disease Characteristics

4.1.6.1 Definitions and Derivations

Disease characteristics will include, but is not limited to; smoking status, history of allergy, asthma medications, the number of severe asthma exacerbations in the previous 12 months, number of severe asthma exacerbations requiring hospitalizations in the previous 12 months, Asthma Impairment and Risk Questionnaire (AIRQ), Severity per National Asthma Education and Prevention Program (NAEPP) and spirometry (including FEV_1 (L), forced vital capacity (FVC) (L) and the FEV_1/FVC Ratio – absolute and percent predicted values at Visit 1).

4.1.6.2 Presentation

Disease characteristics will be summarized for the pool of Part 1 and Part 2, and for Part 1 and Part 2 separately once part 2 is completed.

4.1.7 Medical History and Concomitant Disease

4.1.7.1 Definitions and Derivations

Medical and surgical histories are reported at Visit 1.

4.1.7.2 Presentation

Medical and surgical histories will be presented in a listing for the pool of Part 1 and Part 2, and for Part 1 and Part 2 separately once Part 2 is completed.

4.1.8 Prior and Concomitant Medications

4.1.8.1 Definitions and Derivations

A list of permitted, restricted and prohibited medications can be found in section 6.5 of the CSP. Please refer to Appendix A: Imputation Rules for Missing or Partially Missing dates associated with Prior Medications, Concomitant Medications, Procedures and Adverse Events, for the method of imputing missing medication onset/start and end/stop dates. First dose of study intervention is defined in Section 3.3.1.

Medications will be categorized for analysis according to their (imputed) onset and end dates in accordance with Table 3. Note that medications can be assigned to more than one period to reflect the treatment they were prior to, or concomitant with.

Table 3 Classification of Concomitant Medications to Treatment Arm

Period	Participants receiving PT027-PT007	Participants receiving PT007-PT027
Prior - Screening (Visit 1)	**Assign medication to prior medication during Open-label PT007 (Visit 1) if:** end date of medication≥date of first dose of study intervention at visit 1 and the start date of medication < minimum (date of first dose of randomized treatment at Visit 2 [PT027 or PT007], date of death, date of study withdrawal) **Or**	

Period	Participants receiving PT027-PT007	Participants receiving PT007-PT027
	end date of medication is ongoing and start date of medication < minimum (date of first dose of randomized treatment at Visit 2 [PT027 or PT007], date of death, date of study withdrawal)	
Concomitant - Visit 2	**Assign medication To PT027 if:** end date of medication≥date of first dose of PT027 at Visit 2 and start date of medication < minimum (date of first dose of PT007 at Visit 3, date of death, date of study withdrawal) **Or** end date of medication is ongoing and start date of medication < minimum (first dose of PT007 at Visit 3, date of death, date of study withdrawal)	**Assign medication To PT007 if:** end date of medication≥date of first dose of PT007 at Visit 2 and start date of medication < minimum (date of first dose of PT027 at Visit 3, date of death, date of study withdrawal) **Or** end date of medication is ongoing and start date of medication < minimum (first dose of PT027 at Visit 3, date of death, date of study withdrawal)
Concomitant - Visit 3	**Assign medication To PT007 if:** end date of medication≥date of first dose of PT007 at Visit 3 and start date of medication < minimum (date of last dose of PT007 +7 days, date of death, date of study withdrawal) **Or** end date of medication is ongoing and start date of medication ≤ minimum (date of last dose of PT007 +7 days, date of death, date of study withdrawal	**Assign medication To PT027 if:** end date of medication≥date of first dose of PT027 at Visit 3 and start date of medication < minimum (date of last dose of PT027 +7 days, date of death, date of study withdrawal) **Or** end date of medication is ongoing and start date of medication ≤ minimum (date of last dose of PT027 +7 days, date of death, date of study withdrawal

4.1.8.2 Presentation

Prior and concomitant medications will be summarized by their anatomical therapeutic chemical (ATC) classification system codes, generic name and treatment group, using the safety analysis set.

Prior and Concomitant Medications will be summarized by the pool of Part 1 and Part 2, and Part 1 and Part 2 separately once Part 2 reads out.

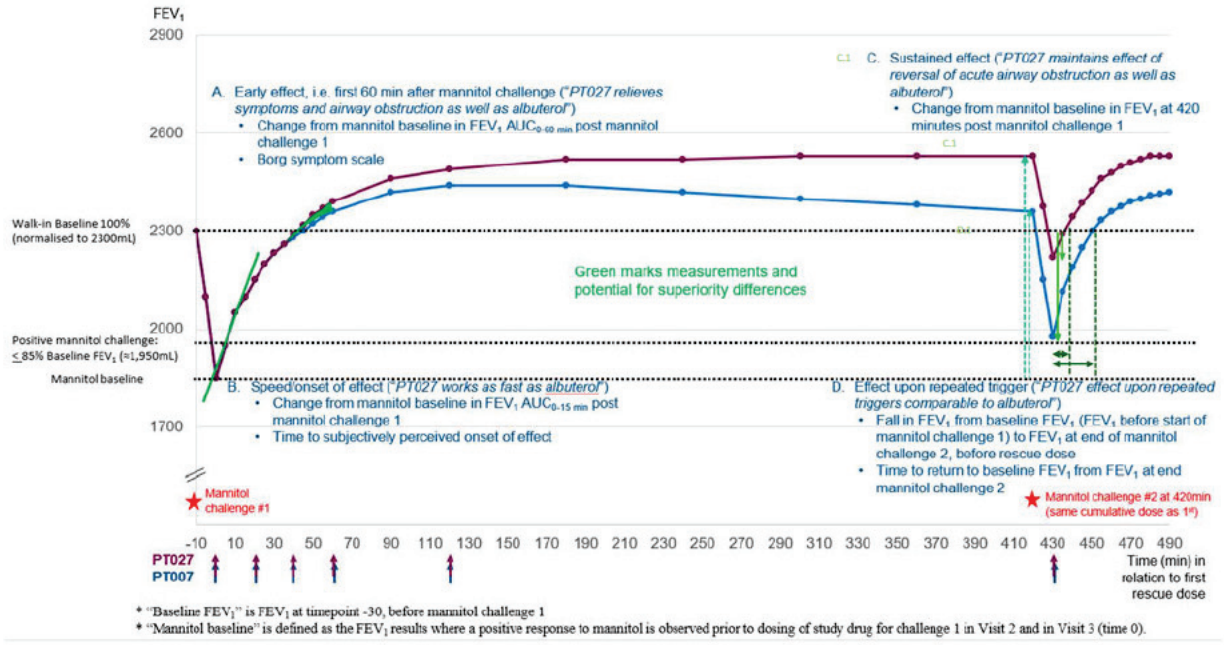
4.2 Endpoint Analyses

This section covers details related to the Part 1 efficacy endpoint analyses (ie, primary and secondary endpoints which may aid design for Part 2). Further exploratory, sensitivity and supportive analyses will be described for Part 2 analyses in the Part 2 SAP. The exception is the exploratory endpoint change from baseline FEV_1 AUC0-15 min post-mannitol challenge 2, which will be reported separately for Part 1 and Part 2 and will be described within scope of this SAP. See Figure 1 for an illustration of some efficacy aspects of FEV_1

and symptoms that will be evaluated during Visits 2 and 3 to support study objectives. Note that the FEV_1 curves in this figure are hypothetical for illustration only.

A descriptive summary of each objective, including the endpoint, population, intercurrent event (ICE) strategy and population level summary is provided below.

Figure 1 Illustration of efficacy endpoints



* "Baseline FEV_1" is FEV_1 at timepoint -30, before mannitol challenge 1
* "Mannitol baseline" is defined as the FEV_1 results where a positive response to mannitol is observed prior to dosing of study drug for challenge 1 in Visit 2 and in Visit 3 (time 0).

Abbreviations: AUC, Area under the curve; FEV_1, Forced expiratory volume in the first second.
Note: FEV_1 Curves are hypothetical, for illustration only.

Statistical category	Endpoint	Population	Intercurrent event (ICE) strategy	Population level summary (analysis)	Details in section
Objective 1: To assess the efficacy of repeated dosing of PT027 relative to PT007, on post-dose lung function, when used by participants with asthma on SABA as-needed treatment only who are experiencing acute airway obstruction.					
Primary	Change from mannitol baseline in FEV_1 $AUC_{0\text{-}60\ min}$ post-mannitol challenge 1.	Adult participants with asthma on SABA as-needed treatment only, and who are sensitive to mannitol.	A hypothetical strategy will be implemented. This estimand targets the hypothetical scenario in which the ICE did not occur and as such outcomes for participants	Difference in the adjusted means of the endpoint for the treatment comparison of PT027 versus PT007.	4.2.1

Statistical category	Endpoint	Population	Intercurrent event (ICE) strategy	Population level summary (analysis)	Details in section
			without an ICE are as observed and for those with an ICE (defined as: discontinuation of study during a treatment period due to an asthma exacerbation or the taking of prohibited medication), will be set to missing from the time-point at which the ICE occurs.		
Objective 2: To establish the efficacy of PT027 after a single dose compared with PT007 in reversal of acute airway obstruction, when used by participants with asthma on SABA as-needed treatment only who are experiencing acute airway obstruction.					
Secondary	Change from mannitol baseline in FEV_1 $AUC_{0\text{-}15\ min}$ post-mannitol challenge 1.	As per primary objective.	As per primary objective.	As per primary objective.	4.2.2
Objective 3: To establish the efficacy of PT027 compared with PT007 in the sustainability of effect of reversal of acute airway obstruction post-mannitol challenge 1 in participants with asthma on SABA as-needed treatment only who are experiencing acute airway obstruction.					
Secondary	Change from mannitol baseline in FEV_1 at 7 hours post-mannitol challenge 1.	As per primary objective.	While-on-treatment.	As per primary objective.	4.2.3
Objective 4: To establish the protective efficacy of prior repetitive doses of PT027 compared with PT007 on lung function fall in response to a recurring trigger of acute airway obstruction in participants with asthma on SABA as-needed treatment only.					
Secondary	Fall in FEV_1 from baseline FEV_1 at completion of mannitol	As per primary objective.	As per primary objective.	As per primary objective.	4.2.4

Statistical category	Endpoint	Population	Intercurrent event (ICE) strategy	Population level summary (analysis)	Details in section
	challenge 2, pre-dose.				
Objective 5: To establish the efficacy of a single dose of PT027 compared with PT007 on post-dose speed of recovery of lung function following a recurring trigger of acute airway obstruction in participants with asthma on SABA as-needed treatment only.					
Secondary	Time to return to baseline FEV_1 (within 5%) post-mannitol challenge 2.	As per primary objective.	While-on-treatment.	Difference in the adjusted medians of the participant-level outcomes for the treatment comparison of PT027 versus PT007	4.2.5
Objective 6: To explore the efficacy after a single dose of PT027 compared with PT007 on post-dose lung function following a recurring trigger of acute airway obstruction in participants with asthma on SABA as needed treatment only.					
Exploratory	Change from baseline FEV_1 $AUC_{0\text{-}15\ min}$ post-mannitol challenge 2.	As per primary objective.	As per primary objective.	As per primary objective.	4.2.6
Objective 7: To assess the perception of relief of dyspnea from PT027 as compared to PT007.					
Exploratory	Change from baseline in Borg dyspnea scale post-mannitol challenge.	As per primary objective.	As per primary objective.	As per primary objective.	4.2.7
Objective 8: To assess the perception of onset of effect of PT027 as compared to PT007.					
Exploratory	Time to perceived onset of effect of study medication working post-mannitol challenge.	As per primary objective.	While-on-treatment.	Difference in the adjusted medians of the participant-level outcomes for the treatment comparison of PT027 versus PT007	4.2.8

4.2.1 Primary Endpoint: Change from mannitol baseline FEV_1 $AUC_{0\text{-}60\ min}$ post-mannitol challenge 1 (in mL)

4.2.1.1 Definition

The primary endpoint is the change from mannitol baseline FEV_1 to normalized FEV_1 calculated using the area under the curve (AUC) 0-60 min for FEV_1 data collected post-mannitol challenge 1.

4.2.1.2 Derivations

AUC 0-60 min (in mL) of the FEV_1 assessments collected 0 to 60 minutes post-mannitol challenge 1 will be calculated using the trapezoidal rule and will be normalized by dividing by the time in minutes from dosing to the last measurement included (typically 60 mins but real assessment times will be used). Only 1 non-missing, post-dose value between 0–30 mins and 1 non-missing, post-dose value between 30-60 mins, is required for the calculation of AUC.

The mannitol baseline for FEV_1 and change from baseline is defined in section 3.3.6.

4.2.1.3 Handling of Dropouts and Missing Data

Discontinuation of study drug during a treatment period due to an asthma exacerbation or the taking of prohibited medication will be considered an ICE. A hypothetical strategy will be implemented. This estimand targets the hypothetical scenario in which the ICE did not occur and as such outcomes for participants without an ICE are as observed and for those with an ICE will be set to missing from the time-point at which the ICE occurs. Participants discontinuing study or starting prohibited medication during a visit with enough data prior to these ICEs, will still have their AUC calculated in line with section 4.2.1.2. However, if they have no post-dose value between 30-60 mins (and no post-dose value between 0-30 mins), then their primary endpoint result will be missing.

ICE defined by study treatment discontinuations due to an asthma exacerbation or the taking of prohibited medications will be identified during the blinded Data Review Meeting (DRM) and documented in the DRM minutes prior to unblinding of Part 1 data. ICEs will be reported by the end of Part 2 for Part 1 and Part 2 separately.

4.2.1.4 Primary Analysis of Primary Endpoint

The primary efficacy comparison of non-inferiority will evaluate the hypothetical estimand in the per protocol analysis set. The hypothetical estimand addresses the treatment effect under the scenario where ICEs in the treatment arms PT027 and PT007 do not occur.

The primary efficacy comparison of non-inferiority will be based on a 1-sided hypothesis testing approach.

To establish non-inferiority of the acute bronchodilatory effect of PT027 compared with PT007, statistical Null hypothesis will be tested: The mean change from mannitol baseline in FEV_1 AUC0-60 min post-mannitol challenge 1 for PT027 is inferior to PT007 by more than −150 mL.

The change from mannitol baseline FEV_1 AUC0-60 min post-mannitol challenge 1 (in mL), will be analyzed using the Per Protocol analysis set and a linear mixed model with a random participant effect. The fixed effects in the model will include center, treatment, treatment sequence, mannitol baseline FEV_1 (as described in section 3.3.6), the average of the two periods mannitol baseline FEV_1 values, and period. Taking the average of the two periods mannitol baseline FEV_1 values, and adding the average as a covariate to the model is to avoid cross-level bias (Kenward et al 2010). See further detail in Appendix B: Linear Mixed Effects Model SAS Code. Point estimates of the estimated adjusted treatment means, standard errors and 95% CIs will be presented. The point estimate of the difference in treatment means for the comparison of PT027 with PT007 with associated 2-sided 95% CI will be used to evaluate non-inferiority, such that non-inferiority of PT027 compared with PT007 is established if the lower 95% confidence limit of the point estimate is greater than the non-inferiority margin of -150 mL.

To establish superiority of the acute bronchodilatory effect between PT027 and PT007, , statistical Null hypothesis 2 will be tested. Hypothesis Null 2: The difference in mean change from mannitol baseline in FEV_1 AUC0-60 min post-mannitol challenge 1 between PT027 and PT007 is equal to 0.

The primary endpoint FEV_1 AUC0-60 min will be analyzed using the specified linear mixed model as detailed above, using the Randomized Set for superiority testing. Point estimates of the estimated adjusted treatment means, standard errors and 95% CIs will be obtained. The estimated mean treatment difference as well as 95% CIs, and 2-sided p-value will be presented. The primary efficacy comparison of superiority will be based on a 2-sided hypothesis testing approach. Superiority will be concluded if the 2-sided p-value is < 0.5.

4.2.1.5 Sensitivity Analyses of the Primary Endpoint

For Part 1 of the study, no sensitivity analysis is planned.

4.2.1.6 Supplementary Analyses of the Primary Endpoint

For Part 1 of the study, no supplementary analysis is planned.

4.2.1.7 Subgroup Analyses

For Part 1 of the study, no subgroup analysis is planned.

4.2.2 Secondary Endpoint: Change from mannitol baseline FEV_1 AUC0-15 min post-mannitol challenge 1 (in mL)

4.2.2.1 Definition

Change from mannitol baseline FEV_1 to normalized FEV_1 calculated using the AUC 0-15 min for FEV_1 data collected post-mannitol challenge 1 is a secondary endpoint for Part 1 data analysis.

4.2.2.2 Derivations

AUC 0-15 min (in mL) of the FEV_1 assessments collected 0 to 15 minutes post mannitol challenge 1 will be calculated using the trapezoidal rule and will be normalized by dividing by the time in minutes from dosing to the last measurement included (typically 15 mins but real assessment times will be used). Only 1 non missing, post-dose value between 0–15 mins is required for the calculation of AUC.

The mannitol baseline for FEV_1 and change from baseline is defined in section 3.3.6.

4.2.2.3 Handling of Dropouts and Missing Data

The ICEs of discontinuation of study during a treatment period due to an asthma exacerbation or the taking of prohibited medication will be handled in the same manner as for the primary endpoint as described in section 4.2.1.3. Participants discontinuing study or starting prohibited medication during a visit with enough data prior to ICE, will still have their AUC calculated in line with section 4.2.2.2. However, if they have no post-dose value between 0-15 mins, then their AUC result will be missing.

ICE defined by study treatment discontinuations due to an asthma exacerbation or the taking of prohibited medications will be identified during the blinded Data Review Meeting (DRM) and documented in the DRM minutes prior to unblinding of Part 1 data. ICE will be reported by the end of Part 2 for Part 1 and Part 2 separately.

4.2.2.4 Primary Analysis of Secondary Endpoint

The efficacy comparison of non-inferiority will evaluate the hypothetical estimand in the per protocol analysis set using the same linear mixed model as described for the primary endpoint in section 4.2.1.4. Non-inferiority will be demonstrated if the upper 95% confidence limit of the point estimate is less than the non-inferiority margin of 150 mL. Superiority of PT027 versus PT007 will evaluate the hypothetical estimand in the randomized analysis set using the same methods as described for the primary endpoint in section 4.2.1.4.

4.2.2.5 Sensitivity Analyses of the Secondary Endpoint

For Part 1 of the study, no sensitivity analysis is planned.

4.2.2.6 Supplementary Analyses of the Secondary Endpoint

For Part 1 of the study, no supplementary analysis is planned .

4.2.2.7 Subgroup Analyses

For Part 1 of the study, no subgroup analysis is planned .

4.2.3 Secondary Endpoint: Change from mannitol baseline in FEV_1 at 7 hours post-mannitol challenge 1 (in mL)

4.2.3.1 Definition

Change from mannitol baseline in FEV_1 at 7 hours post-mannitol challenge 1 is a secondary endpoint for Part 1 data analysis.

4.2.3.2 Derivations

The FEV_1 result (in mL) at 7 hours post-mannitol challenge 1 (ie, at approximately 420 mins following the mannitol challenge 1 and recorded prior to the mannitol challenge 2) will be used.

The mannitol baseline FEV_1 and change from baseline is defined in section 3.3.6.

4.2.3.3 Handling of Dropouts and Missing Data

ICEs are defined as discontinuation of study drug during a treatment period due to an asthma exacerbation or the taking of prohibited medications. A while-on-treatment strategy for addressing ICEs will be implemented. This estimand targets the treatment difference in a scenario, such that outcomes for participants without an ICE are as observed and outcomes for participants with an ICE are treated as MAR in the linear mixed effects model. Discontinuations from study for any other reasons not defined as an ICE will also be treated as MAR in the linear mixed effects model. In other words participants without a FEV_1 result at 7 hours post-mannitol challenge 1 (or with the result set to missing due to it occurring post ICE), will not be imputed.

ICE defined by study treatment discontinuations due to an asthma exacerbation or the taking of prohibited medications will be identified during the blinded Data Review Meeting (DRM) and documented in the DRM minutes prior to unblinding of Part 1 data. ICE will be reported by the end of Part 2 for Part 1 and Part 2 separately.

4.2.3.4 Primary Analysis of Secondary Endpoint

The efficacy comparison of non-inferiority will evaluate the hypothetical estimand in the per protocol analysis set using the same linear mixed model as described for the primary endpoint in section 4.2.1.4. Non-inferiority will be demonstrated if the upper 95% confidence limit of the point estimate is less than the non-inferiority margin of 150 mL. Superiority of PT027 versus PT007 will evaluate the hypothetical estimand in the

randomized analysis set using the same methods as described for the primary endpoint in section 4.2.1.4.

4.2.3.5 Sensitivity Analyses of the Secondary Endpoint

For Part 1 of the study, no sensitivity analysis is planned.

4.2.3.6 Supplementary Analyses of the Secondary Endpoint

For Part 1 of the study, no supplementary analysis is planned .

4.2.3.7 Subgroup Analyses

For Part 1 of the study, no subgroup analysis is planned .

4.2.4 Secondary Endpoint: Peak fall in FEV_1 from baseline at mannitol challenge 2, pre-dose (in mL)

4.2.4.1 Definition

The peak fall in FEV_1 (from FEV_1 baseline to post mannitol challenge 2, pre-dose before IP dose), is a secondary endpoint for Part 1 data analysis.

4.2.4.2 Derivations

FEV_1 baseline is defined in section 3.3.6. The FEV_1 result recorded at the mannitol challenge 2, pre-dose before study intervention treatment, is expected to be at 430 mins following the mannitol challenge 1.

The peak fall in FEV_1 (in mL) is derived as:

FEV_1 baseline - FEV_1 result recorded at mannitol challenge 2 completion, before inititation of the study intervention.

4.2.4.3 Handling of Dropouts and Missing Data

The ICEs of discontinuation of study drug during a treatment period due to an asthma exacerbation or the taking of prohibited medication will be handled in the same manner as for the primary endpoint as described in section 4.2.1.3. Participants discontinuing study or starting prohibited medication prior to the recording of FEV_1 at the mannitol challenge 2, before initiation of the study intervention, will be set to missing in the analysis.

ICE defined by study treatment discontinuations due to an asthma exacerbation or the taking of prohibited medications will be identified during the blinded Data Review Meeting (DRM) and documented in the DRM minutes prior to unblinding of Part 1 data. ICE will be reported by the end of Part 2 for Part 1 and Part 2 separately.

4.2.4.4 Primary Analysis of Secondary Endpoint

The efficacy comparison of non-inferiority will evaluate the hypothetical estimand in the per protocol analysis set using the same linear mixed model as described for the primary endpoint in section 4.2.1.4. with the exception model will adjust for walk-in baseline FEV_1. Non-inferiority will be demonstrated if the upper 95% confidence limit of the point estimate is less than the non-inferiority margin of 150 mL. Superiority of PT027 versus PT007 will evaluate the hypothetical estimand in the randomized analysis set using the same methods as described for the primary endpoint in section 4.2.1.4.

4.2.4.5 Sensitivity Analyses of the Secondary Endpoint

For Part 1 of the study, no sensitivity analysis is planned .

4.2.4.6 Supplementary Analyses of the Secondary Endpoint

For Part 1 of the study, no supplementary analysis is planned .

4.2.4.7 Subgroup Analyses

For Part 1 of the study, no subgroup analysis is planned .

4.2.5 Secondary Endpoint: Time to return to baseline FEV_1 post-mannitol challenge 2 (in mins)

4.2.5.1 Definition

Time to return to baseline FEV_1 post-mannitol challenge 2 is a secondary endpoint for Part 1 data analysis. This is to compare the effect upon repeated trigger therapeutic benefit between PT027 and PT007.

4.2.5.2 Derivations

Return to baseline FEV_1 will be achieved at the first timepoint (post-mannitol challenge 2) where the FEV_1 value is within 5% of baseline FEV_1. FEV_1 baseline is defined in section 3.3.6.

The Time to return in minutes will be calculated as: Datetime of Return to baseline FEV_1 result – Datetime of the Mannitol challenge 2 Study Drug Administration.

The Pairwise treatment difference will be calculated as: Time to return on PT027 - Time to return on PT007

If more than 5% of randomized participants do not have a return to within 5% of baseline FEV_1 post-mannitol challenge 2 for both treatment arms (such that their pairwise difference is non-calculable), then an alternative Kaplan-Meier analysis will be considered. Participants who do return to baseline FEV_1 will be classified as having an event at the time they return to baseline FEV_1. Participants without a return to baseline FEV_1 (or

experiencing an ICE prior to return), will be censored at the time of their latest non missing FEV_1 assessment (prior to ICE occurrence or discontinuation).

4.2.5.3 Handling of Dropouts and Missing Data

ICEs are defined as discontinuation of study during a treatment period due to an asthma exacerbation or the taking of prohibited medications. A while-on-treatment strategy for addressing ICEs will be implemented. This estimand targets the treatment difference in a scenario, such that outcomes for participants without an ICE are as observed and outcomes for participants with an ICE are treated as MAR. Discontinuations from study for any other reasons not defined as an ICE will also be treated as MAR. Therefore, participants without a return to baseline FEV_1 (or with the result set to missing due to it occurring post ICE), will not be imputed. Participants with return to baseline FEV_1 missing in either treatment arm will result in a missing pairwise difference in the primary analysis of this secondary endpoint.

ICE defined by study treatment discontinuations due to an asthma exacerbation or the taking of prohibited medications will be identified during the blinded Data Review Meeting (DRM) and documented in the DRM minutes prior to unblinding of Part 1 data. ICEs will be reported by the end of Part 2 for Part 1 and Part 2 separately.

4.2.5.4 Primary Analysis of Secondary Endpoint

The efficacy comparison of non-inferiority will evaluate the while-on-treatment estimand in the per protocol analysis set. A summary of the number (and percentage) of participants with return to baseline FEV_1 by treatment arm will be provided. The time to return will be summarized using the Median of the pairwise differences and 95% CIs provided using the Hodges-Lehmann estimate based on the Wilcoxon signed-rank statistic.

Non-inferiority will be demonstrated if the upper 95% confidence limit of the point estimate is less than the non-inferiority margin of 3.5 minutes. Superiority of PT027 versus PT007 will evaluate the while-on-treatment estimand in the randomized analysis set using the same methods.

4.2.5.5 Sensitivity Analyses of the Secondary Endpoint

If more than 5% of randomized participants do not have a return to within 5% of baseline FEV_1 for both the PT027 and PT007 treatment arms, then a Kaplan-Meier analysis of time to return (using proc lifetest and the strata option including an identifier for the PT027 or PT007 treatment result) will be performed to investigate the superiority analysis using the randomized analysis set. For the Part 1 study, which is anticipated to have 14 participants in total, this analysis will be conducted if more than 1 participant does not return to baseline.

A non-inferiority comparison will not be presented, due to the small sample size in Part 1 and the likely unreliable estimate of the standard error of the median difference in the time to return, obtained from the Kaplan-Meier estimates.

Events and censoring will be assigned as discussed in Section 4.2.6.2. The product limit survival estimator will used to estimate the median time to return to baseline FEV_1 and associated 95% CI for each treatment arm. A log-rank test will be used to test for a difference between the survival curves for PT027 versus PT007.

A Kaplan-Meier figure will be produced to accompany the summary. The number at risk by time will be shown on the figure.

4.2.5.6 Supplementary Analyses of the Secondary Endpoint

For Part 1 of the study, no supplementary analysis is planned .

4.2.5.7 Subgroup Analyses

For Part 1 of the study, no subgroup analysis is planned.

4.2.6 Other Endpoint: Change from baseline FEV_1 AUC0-15 min post-mannitol challenge 2 (in mL)

4.2.6.1 Definition

Change from baseline FEV_1 AUC during the 0 to 15 mins after the IP dose after mannitol challenge 2, (ie, FEV_1 AUC $_{430\text{-}445\ min}$) is an exploratory endpoint for Part 1 data analysis.

4.2.6.2 Derivations

FEV_1 baseline and change from baseline is defined in section 3.3.6.

The AUC (in mL) of the FEV_1 results 0 to 15 mins after the IP dose after mannitol challenge 2 (ie, between 430-445 minutes post-mannitol challenge 1), will be calculated using the trapezoidal rule and will be normalized by dividing by the time in minutes from dosing to the last measurement included (typically 15 mins but real assessment times will be used). Only 1 non-missing, post-dose value between 0–15 mins, is required for the calculation of AUC.

4.2.6.3 Handling of Dropouts and Missing Data

The ICEs of discontinuation of study during a treatment period due to an asthma exacerbation or the taking of prohibited medication will be handled in the same manner as for the primary endpoint as described in section 4.2.1.3. Participants discontinuing study drug or starting prohibited medication during a visit with enough data prior to ICE, will still have their AUC calculated in line with section 4.2.6.2. However, if they have no post-dose value between 0-15 mins, then the AUC result will be missing.

ICE defined by study treatment discontinuations due to an asthma exacerbation or the taking of prohibited medications will be identified during the blinded Data Review Meeting (DRM) and documented in the DRM minutes prior to unblinding of Part 1 data. ICE will be reported by the end of Part 2 for Part 1 and Part 2 separately.

4.2.6.4 Analysis of Other Endpoint

This endpoint will be analysed fitting the same linear mixed model as described for the primary endpoint in section 4.2.1.4, with the exception model will adjust for each periods walk-in baseline FEV_1, and the average of the two periods walk-in baseline FEV1 values, using both the Per Protocol analysis set and the Randomized analysis set.

4.2.6.5 Sensitivity Analyses of the Other Endpoint

For Part 1 of the study, no sensitivity analysis is planned .

4.2.6.6 Supplementary Analyses of the Other Endpoint

For Part 1 of the study, no supplementary analysis is planned.

4.2.6.7 Subgroup Analyses

For Part 1 of the study, no subgroup analysis is planned .

4.2.7 Other Endpoint: Change from baseline in Borg dyspnea scale post-mannitol challenge.

Change from baseline in Borg dyspnea scale post-mannitol challenge analysis will be presented for pooled Part 1 and 2 data, once Part 2 is completed.

4.2.7.1 Definition

Participants will be asked to report their perceived breathlessness on the modified Borg scale electronically using a handheld device, before spirometry as detailed in the CSP Schedule of Activities in Table 1 and Table 2. This is a 0-10 scale that asks participants to rate the difficulty of breathing, where 0 = breathing is causing no difficulty at all and 10 = where your breathing difficulty is maximal.

Change from baseline in Borg dyspnea scale post-mannitol challenge is an exploratory endpoint for Part 1 data analysis. The visits up to 60-minutes post-mannitol challenges will be used to compare the early effect therapeutic benefit between PT027 and PT007.

4.2.7.2 Derivations

Visit 2 and Visit 3 will have separate Borg dyspnea scale baseline results utilizing the -30 minutes time point.

If the -30 value is missing, baseline will be the latest non-missing value prior to the mannitol challenge ie, prior to time -10.

Change from baseline = (post-baseline value - baseline value).
Note: All scheduled Borg dyspnea scale assessments following the first and second challenges at both Visits 2 and 3 will be included.

4.2.7.3 Primary Analysis of Other Endpoint

Borg Dyspnea scale data at each visit and timepoint will be presented using descriptive statistics by treatment arm. Descriptive statistics of the change from baseline will also be presented by treatment arm. Primary focus will be in timepoints up to 60 minutes following the first mannitol challenges.

4.2.7.4 Additional Analyses of the Other Endpoint

For Part 1 of the study, no additional analysis is planned however these may be explored if required to confirm the design of Part 2 or to aid with decision making.

4.2.7.5 Subgroup Analyses of the Other Endpoint

For Part 1 of the study, no subgroup analysis is planned however these may be explored if required to confirm the design of Part 2 or to aid with decision making.

4.2.8 Other Endpoint: Time to perceived onset of effect of study medication working post-mannitol challenge

Time to perceived onset of effect of study medication working post-mannitol challenge analysis will be presented for pooled Part 1 and 2 data, once Part 2 is completed.

4.2.8.1 Definition

Participants will be asked a single perceived onset effect question “Can you feel your study medication working?” repeatedly (Kaiser et al 2018). The question will be repeated at time-points as specified in the CSP Schedule of Activities in Table 1 and Table 2 and will be repeated after each intervention administration only if the prior response has been “No” (ie, until the participant confirms “yes”).

Time to perceived onset of effect of study medication working post-mannitol challenge is a secondary endpoint for Part 1 data analysis. This is to compare the onset of effect therapeutic benefit between PT027 and PT007.

Time to perceived onset of effect of study medication working post-mannitol challenge will be compared between PT027 and PT007 post challenge 1 and post challenge 2.

4.2.8.2 Derivations

Time to perceived onset of effect will be calculated as the time to the first timepoint where the participant answers “yes” to the question “Can you feel your study medication working?” These will be considered as events in the analysis.

If the participant never answers "yes" to the question, then their time will be set to earliest of (the date of study completion, date of study discontinuation, date of occurrence of ICE) and the participant will be censored in the analysis.

4.2.8.3 Primary Analysis of Other Endpoint

A Kaplan-Meier analysis of time to perceived onset of effect (using proc lifetest and the strata option including an identifier for the PT027 or PT007 treatment) will be performed to investigate the superiority analysis using the randomized analysis set. Events and censoring will be assigned as discussed in Section 4.2.8.2. The product limit survival estimator will used to estimate the median time to perceived onset of effect and associated 95% CI for each treatment arm. A log-rank test will be used to test for a difference between the survival curves for PT027 versus PT007. A Kaplan-Meier figure will be produced to accompany the summary. The number at risk by time will be shown on the figure.

4.2.8.4 Additional Analyses of the Other Endpoint

For Part 1 of the study, no additional analysis is planned however these may be explored if required to confirm the design of Part 2 or to aid with decision making.

4.2.8.5 Subgroup Analyses

For Part 1 of the study, no subgroup analysis is planned however these may be explored if required to confirm the design of Part 2 or to aid with decision making.

4.3 Pharmacodynamic Endpoint(s)

Not applicable.

4.4 Pharmacokinetics

Not applicable.

4.5 Immunogenicity

Not applicable.

4.6 Safety Analyses

The domain safety covers exposure, adverse events, clinical laboratory, vital signs, and ECG.

Safety will be presented for the pool of Part 1 and Part 2 data, once Part 2 reads out. However, within scope of Part 1 reporting, a listing for Adverse events occurring during Part 1 will be created based on the enrolled analysis set, where adverse events will be presented by analysis phase and actual treatment.

4.6.1 Adverse Events

4.6.1.1 Definitions and Derivations

Adverse Events (AEs) will be summarized for analysis according to the treatment arm being taken at the time of the onset date of the AE as shown in Table 4.

Treatment Emergent Adverse Events (TEAE) are defined as all AEs with onset date on or after the date of first dose of randomized study drug at Visit 2, and prior to the minimum of (date of last dose at Visit 3 +7 days, date of death, or date of study withdrawal + 7 days).

Table 4 Classification of AE to Treatment Arm using Onset Date

Phase	Participants receiving PT027-PT007	Participants receiving PT007-PT027
Screening (prior to the open-label)	**Assign AE To Screening Period (prior to receiving PT007) if:** Both AE onset date and Visit 1 date are same and Action Taken with study drug **is "NOT APPLICABLE"**	
Visit 1	**Assign AE To Open-label PT007 if:** Both AE start onset and Visit 1 date are same and Action Taken with study drug **is <u>not</u> "NOT APPLICABLE"** or date of Open-label PT007 administration date < AE onset date < date of first dose of randomized treatment at Visit 2 (PT027 or PT007)	
Visit 2	**Assign AE To PT027 if:** Date of first dose of PT027 at Visit 2 <=AE onset date < minimum (date of first dose of PT007 at Visit 3, date of death, date of study withdrawal)	**Assign AE To PT007 if:** Date of first dose of PT007 at Visit 2<=AE onset date < minimum (date of first dose of PT027 at Visit 3, date of death, date of study withdrawal)
Visit 3	**Assign AE To PT007 if:** Date of first dose of PT007 at Visit 3 <=AE onset date <= minimum of (date of last dose of PT007 +7 days, date of death, date of study withdrawal)	**Assign AE To PT027 if:** Date of first dose of PT027 at Visit 3 <=AE onset date <= minimum of (date of last dose of PT027 +7 days, date of death, date of study withdrawal)

Rules for imputing AE start/stop dates which are partially missing can be found in Appendix A: Imputation Rules for Missing or Partially Missing dates associated with Prior Medications, Concomitant Medications, Procedures and Adverse Events. Partially missing start/stop dates will appear as such in the participant data listings but will be imputed to permit proper tabulation of AE data.

AEs will be coded using the most recent MedDRA version released for execution by AstraZeneca/designee. If an AE still has missing intensity, causality or seriousness after data querying, the following ordering will be used to define "worst" for tabulating participants with more than 1 AE within the category being summarized:

- Intensity: Missing < Mild < Moderate < Severe
- Causality: Missing < No < Yes
- Seriousness: Missing < No < Yes

AEs will be classed as Covid-19 AEs based on the SARS-Cov-2 MedDRA terms.

4.6.1.2 Presentation

All reported AEs will be listed along with the date of onset, date of resolution (if AE is resolved), investigator's assessment of intensity, outcome, action taken with study drug, and possible relationship to study drug.

An overview summary (number and percent of subjects) experiencing AEs in the following categories will be tabulated by treatment arm (Open-label PT007, PT027, PT007 and overall):

- All AEs
- All AEs possibly related to study drug (as determined by the reporting investigator)
- AEs with outcome of death
- All Serious AEs (SAEs)
- All SAEs possibly related to study drug (as determined by the reporting investigator)
- AEs leading to discontinuation of study drug
- AEs leading to withdrawal from the study

The above categories will also be presented by SOC and PT by treatment arm. Multiple events per participant with the same SOC or PT will only be counted once in each row. Events for the same participant reported in both the PT027 and PT007 treatment arms will only be counted once in the overall column within category (SOC or PT).

AEs will also be summarized by SOC, PT and intensity/severity and separately, by causality/ relatedness (as determined by the investigator). Should a participant report the

same PT/SOC within multiple intensity/severity or causality/relatedness categories, the participant's worst occurrence (most severe/related) will be tabulated as described in 4.6.1.1.

Covid-AEs will also be summarized by SOC and PT.

Key participant information (age/sex/race) for participants experiencing SAEs, AEs with outcome of death, AEs leading to discontinuation of study drug and COVID-19 AEs will be presented in a listing.

4.6.2 Other Safety Assessments - Spirometry

4.6.2.1 Definitions and Derivations

Spirometry will be performed at each visit and will capture FEV_1, FVC and FEV_1/FVC. For safety evaluation, the FEV_1 baseline as described in section 3.3.6 will be used for Visit 2 and 3, along with the latest pre-dose measurement at Visit 1 for the Visit 1 baseline. Change from each visits baseline will be calculated as described in section 3.3.6.

4.6.2.2 Presentations

For each scheduled visit and timepoint, descriptive statistics (n, mean, SD, minimum, Q1, median, Q3 and max) will be presented for both the observed values and for the change from baseline at each visit.

5 INTERIM ANALYSIS

No interim analysis has been planned for this study. However, unblinded results obtained after Part 1 of the study will be analyzed and utilized similar to a pilot study to inform the treatment effect size and variability estimates for the secondary efficacy endpoints to be analysed in Part 2.

Part 1 analysis will consist of selected efficacy and safety TFLs.

Due to the study being double-blind, independent teams will be assigned for the analysis of Part 1 data and the discussions of these results. A charter for Part 1 analysis will be created separately.

Sample size re-estimation will be based on the secondary endpoint time to return to baseline FEV_1 (within 5%) post-mannitol challenge 2, since this endpoint has higher variability than the primary endpoint and will be tested using a non-parametric test. The nominal power for other secondary endpoints in Part 2 (and the primary endpoint) of the study may also be re-calculated informed by the treatment effect sizes and variability estimates obtained from the Part 1 data.

Lung function data for the primary and secondary endpoints from Part 1 of the study will not be combined with the data from Part 2 in the final analyses.

6 REFERENCES

Kaiser et al 2018 Kaiser H et al. Onset of effect of budesonide and formoterol administered via one pressurized metered-dose inhaler in patients with asthma previously treated with inhaled corticosteroids. Ann Allergy Asthma Immunol. 2008 Sep;101(3):295-303

Kenward et al 2010 Kenward M.G. and Roger J.H. 2010 The use of baseline covariates in crossover studies. Biostatistics 2010 11(1): 1-17

7 APPENDIX

7.1 Appendix A: Imputation Rules for Missing or Partially Missing dates associated with Prior Medications, Concomitant Medications, Procedures and Adverse Events

The date of first dose of study intervention is defined in section 3.3.1. Prior/Concomitant Medication or Procedures will follow the same rules as described below for AEs.

For missing AE start dates, the following will be applied:

- Missing day only: Impute the 1st of the month unless the month is the same as the month of the first dose of study intervention then impute first dose of study intervention date after randomisation.
- Missing day and month only: Impute 1st January unless the year is the same as the first dose of study intervention then impute first dose of study intervention date.
- Completely missing date: Impute first dose of study intervention date unless the end date of the AE suggests it could have started prior to this, in which case impute the 1st of January of the same year as the end date of the AE.

When imputing a start date, ensure that the new imputed date is sensible e.g., prior to the end date of the AE.

For missing stop dates of AEs, the following will be applied:

- Missing day only: Impute the last day of the month unless the month is the same as month of last dose of study intervention then impute last dose of study intervention date.

- Missing day and month only: Impute 31st December unless year is the same as last dose of study intervention date then impute last dose of study intervention date.

- Completely missing: If an AE has a completely missing end date, then it will be treated as ongoing. Flags will be retained in the database indicating where any programmatic imputation has been applied, and in such cases, any durations would not be calculated.

7.2 Appendix B: Linear Mixed Effects Model SAS Code

```
proc mixed data = inputd;
  class subjid center trtn (ref = 'PT007') trtseq period
  Model chg = center trtn trtseq base avg_base period
  Random subjid(trtseq);
  Lsmeans trtn/ diff cl alpha = 0.05;
run;
quit;
```

Where:
center = center identifier
trtn = PT027 or PT007 representing the treatment arm
trtseq = Treatment sequence (AB or BA corresponding to PT027 followed by PT007 or vice versa)
period = Visit 2 or Visit 3
subjid = participant ID
chg = Change from mannitol baseline FEV_1 AUC0-60 min post-mannitol challenge 1
base = mannitol baseline FEV_1 values as described in section 3.3.6
avg_base = average of the two periods mannitol baseline FEV_1 values

SIGNATURE PAGE

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ALTA - ALbuterol/budesonide Treatment in Acute Airway Obstruction

A randomized, double-blind, 2-period, cross-over study evaluating efficacy and safety of repeated doses of PT027 compared to PT007 in patients with asthma and acute airway obstruction induced by repeated mannitol challenges

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

Abbreviation or Specialized Term	Definition
AE	adverse event
AUC	area under the curve
BMI	body mass index
CI	confidence interval
COVID-19	coronavirus disease 2019
CRF	case report form
CSP	clinical study protocol
CSR	clinical study report
ECG	electrocardiogram
ES	enrolled analysis set
FEV_1	forced expiratory volume in 1 second
FVC	forced vital capacity
ICE	intercurrent event
ICF	informed consent form
IMP	investigational medicinal product
IPD	important protocol deviation
LLOQ	lower limit of quantification
MAR	missing at random
MedDRA	Medical Dictionary for Regulatory Activities
mPP	modified per protocol analysis set
mRS	modified randomized analysis set
NAEPP	National Asthma Education and Prevention Program
pMDI	pressurized metered dose inhaler
PP	per protocol analysis set
PT	preferred term
TEAE	treatment emergent adverse event
TESAE	treatment emergent serious adverse event
SAE	serious adverse event
SAF	Safety analysis set
SAP	statistical analysis plan
SD	standard deviation
SOC	system organ class

AMENDMENT HISTORY

CATEGORY Change refers to:	Date	Description of change	In line with CSP?	Rationale
N/A	Click or tap to enter a date.	Initial approved SAP	CSP v4.0	N/A
Data presentation	12/20/2024	SAP, Part 2, v2.0	CSP v4.0	- Updates following dry-run 1 and dry-run 2 - Adding sensitivity analysis for selected endpoints
Data presentation	03/03/2025	SAP, Part 2, v3.0	CSP v4.0	- Updates to the definition and presentation of actual exposure - Clarification on the censoring approach for the

1 INTRODUCTION

The purpose of this document is to give details for the statistical analysis of the data from Part 2 of study D6930C00017. This study is a Phase 3b, multicenter, randomized, double-blind, 2-period, cross-over study evaluating the efficacy and safety of repeated doses of PT027 (albuterol/budesonide) compared to PT007 (albuterol) in patients with asthma and acute airway obstruction, induced by repeated mannitol challenges.

The Part 2 SAP covers the adaptations from Part 1 to Part 2.

In Part 2, approximately 88 participants will be randomized to the treatment sequences (PT027- PT007, PT007-PT027) to aim for 74 evaluable participants (37 per treatment sequence) to complete the study.

The reader is referred to the clinical study protocol (CSP) and the case report form (CRF) for details of study conduct and data collection. This document is written in accordance with CSP Amendment version 4.0 dated 10 July 2023 and CRF version 2.0.

2 CHANGES TO PROTOCOL PLANNED ANALYSES

Following the Part 1 study completion and database lock, Part 1 was unblinded and analyzed as was described in the statistical analysis plan (SAP) – Part 1. An AstraZeneca Internal Advisory Board was assigned to evaluate the results from Part 1 and the protocol was amended accordingly in version 4.0., This SAP will describe the updated approach to statistical analyses in Part 2 of the study.

This SAP follows the CSP Amendment version 4.0 and incorporates the below changes to the planned analyses:

- The exploratory objective: To assess the perception of relief of dyspnea from PT027 as compared to PT007, was updated to “To assess relief from mannitol challenge induced breathing difficulty following treatment with PT027 as compared to PT007.” And associated endpoint to two separate endpoints: “Change from time 0 min in Borg dyspnea scale post-mannitol challenge 1” and “Change from time 490 min in Borg dyspnea scale post-challenge 2”. Additionally analysis will be presented only for Part 2. See Section 4.2.8 of this document for details.

- The endpoint for the exploratory objective: To assess the perception of onset of effect of PT027 as compared to PT007 was updated to “Time to perceived onset of effect of study medication working post PT027 as compared to PT007 given following mannitol challenge 1 and challenge 2 completion.”

- For the exploratory endpoint: The proportion of participants who are non-responders to mannitol challenge 2, the definition of the non-responder was updated to "A participant who is a non-responder to the mannitol challenge 2 is one who had <15% fall from the 0mg mannitol FEV1 to the last spirometry FEV1 within the respective mannitol challenge". For details, see Section 4.2.11 of this document.

- The secondary endpoint: Time to return to baseline (-30 min) FEV1 post mannitol challenge 2, pre-final dose of rescue/reliever was updated to "Time to return to baseline (-30 min) FEV1 post mannitol challenge 2".

- The secondary endpoint: Peak fall from baseline (-30 min) FEV1 to post mannitol challenge 2, pre-final dose of rescue/reliever was updated to "Peak fall from baseline (-30 min) FEV1 to post mannitol challenge 2".

- The secondary endpoint: Peak fall from 480 min FEV1 to post- mannitol challenge 2, pre-final dose of rescue/reliever was updated to "Peak fall from 480 min FEV1 to post- mannitol challenge 2".

- The exploratory endpoint: Percentage fall in FEV1 from baseline FEV1 to post-mannitol challenge 2, pre-final dose of rescue/reliever was updated to "Percentage fall in FEV1 from baseline (-30 min) FEV1 to post-mannitol challenge 2".

- Selected exploratory endpoints will be presented differently than pooled for Part 1 and 2. For details, see Section 3.3 of this document.

- A Modified per protocol analysis set was defined as an additional population for analysis. This analysis set will include subjects who did not receive the first dose of IMP within 6 minutes of final dose of mannitol challenge 1. For details, see Section 3.2 of this document.

- "Hypothetical" strategy for intercurrent event (ICE) was renamed to "while-on-treatment", to clarify the approach misnamed in the CSP.

3 DATA ANALYSIS CONSIDERATIONS

3.1 Timing of Analyses

Due to the study being double-blind, dry-run 1 and dry-run 2 will be delivered blinded. Following the Part 2 study completion and database lock, Part 2 will be unblinded and analyzed as described in this statistical analysis plan (SAP), High Level Results and Final Analysis will be delivered unblinded.

3.2 Analysis Populations

Table 1 Populations for Analysis

Population/Analysis Set	Description
Enrolled analysis set (ES)	All participants who sign the ICF.
Modified randomized analysis set (mRS)	All participants who are randomized to any of the 2 treatment sequences, A/B or B/A and receive any amount of randomized study treatment. Treatments A and B are defined as: Treatment A = PT027 180/160 µg pMDI Treatment B = PT007 180 µg pMDI.
Per protocol analysis set (PP)	All participants who received all doses of study treatment following mannitol challenge 1, have baseline and post-treatment study evaluation (spirometry tests) and do not have any important protocol deviations.
Modified per protocol analysis set (mPP)	All participants who received all doses of study treatment following mannitol challenge 1, have baseline and post-treatment study evaluation (spirometry tests) and do not have any important protocol deviations, apart from the deviation of not receiving first dose of IMP within 6 minutes of final dose of mannitol challenge 1 (IP03b).
Safety analysis set (SAF)	All participants randomly assigned to any of the 2 study treatment sequences and who take at least 1 dose of study treatment. Participants will be classified on the basis of treatment they actually received within each treatment period.

Abbreviations: AE=Adverse event(s); pMDI=Pressurized metered dose inhaler; IMP investigational medicinal product.

3.3 General Considerations

All statistical analyses will be performed by Parexel International, under the direction of the Late Stage Respiratory and Immunology Biometrics Group, AstraZeneca. All statistical analyses will be performed using the latest available version of SAS® (SAS Institute Inc., Cary, North Carolina, US), version 9.4 or higher and in the StatXact®.

Study population outputs will be presented by treatment sequence (PT027-PT007, PT007-PT027) and overall. These will be presented separately by Part as well as pooled.

Pooled outputs describing the study population will be based on the SAF, while the corresponding study population tables for Part 1 and Part 2 separately, used for the interpretation of efficacy data, should be based on mRS (expect for Disposition summary tables, which will be presented based on the ES).

For the primary and secondary objectives, efficacy outputs will be presented by treatment (PT027 or PT007). Efficacy data from Part 1 of the study will not be combined with the data from Part 2. Outputs will be presented separately for Part 1 and Part 2, except for Peak

fall from 480 min FEV1 to post-mannitol challenge 2 which will be reported only for Part 2.

Safety outputs will be presented by treatment (PT027 or PT007). Outputs will be presented only for pooled Part 1 and Part 2.

Adverse events for Part 2 will be mapped to treatment periods as described in section 4.6.2.1. A listing for Adverse events occurring during Part 1 and Part 2 will be created based on the enrolled analysis set, where adverse events will be presented by analysis phase and actual treatment, where analysis phase is Screening (prior to open-label), Visit 1, Visit 2, Visit 3.

Exploratory endpoint related outputs will be presented by treatment (PT027 or PT007) separately by Part as well as pooled, except for the selected exploratory endpoints, which will be reported only separately for Part 1 and Part 2 or only for Part 2, that is specified in each endpoint section in this document.

All the listings will be presented separately for Part 2 and 1.

3.3.1 General Study Level Definitions

Unless stated otherwise, continuous variables will be summarized by descriptive statistics (number of participants [n], minimum, maximum, arithmetic mean, standard deviation (SD), and/or medians and inter-quartile ranges (Q1 - Q3), depending on the distributions of the data. The minimum(s) and maximum(s) will be displayed with the same number of decimal places as the collected data. Mean(s), median(s), SD(s), and quartiles (where applicable) will be displayed with one more decimal place than the collected data. Categorical data will be summarized as the number and percentage among participants, including those with missing data. The percentage will be displayed with one decimal place.

For analyses, the two-sided (2.5% significance level each side) hypothesis test will be presented with the corresponding 95% confidence interval (CI). The presentation of p-values will be to four decimal places unless a p-value is less than 0.0001, in which case "<0.0001" will be displayed. Confidence intervals will be presented to one more decimal place than the collected data.

A month and a year are operationally defined to be 30.4 and 365.25 days respectively.

Study intervention is defined as any investigational intervention(s) or marketed product(s) intended to be administered to, or medical device(s) utilized by, a study participant according to the CSP. Therefore, the date of first dose of study intervention includes the

date of the first dose of PT007 at Visit 1 and is not limited to randomized study drugs at Visits 2 and 3.

The terms ‘study intervention’, ‘investigational medicinal product (IMP)’ and ‘study drug’ are used interchangeably in this document for PT027 and PT007.

3.3.2 Visit Window

All summaries and analysis which are presented by visit and timepoint will use the nominal visit and timepoint labels. For some efficacy endpoints, actual dates and time will be used to derive the endpoint as described in Section 4.2.

Additionally, a summary table of the actual time of first and final dose post-mannitol challenge will be presented for both Parts separately based on mRS.

3.3.3 Handling of unscheduled, incomplete planned and rescheduled Visits

Unscheduled visits will not be included in the by visit summaries for efficacy endpoints, but will be presented in listings.

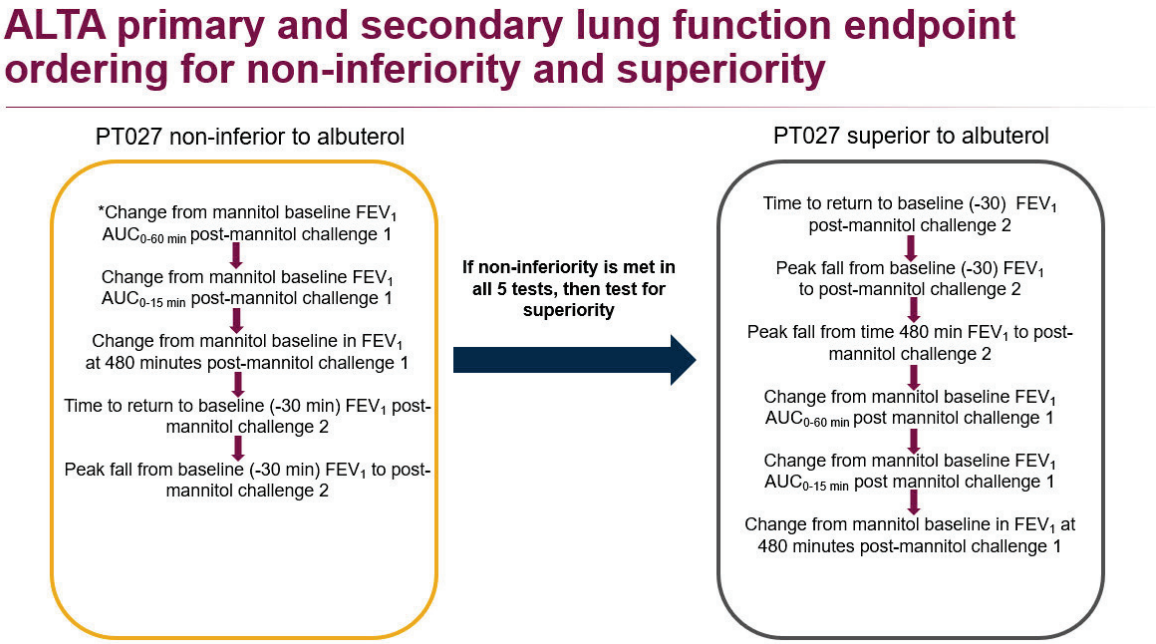
Incomplete planned visits will not be included in the by visit summaries for efficacy endpoints.

Rescheduled visits will provide to the visit summaries for efficacy endpoints.

3.3.4 Multiplicity/Multiple Comparisons

In order to account for the multiple tests across the primary and secondary endpoints, a hierarchical testing approach will be applied for the primary and secondary efficacy endpoints. The adjustments for multiple comparisons will be applied only for the Part 2 outputs. Type 1 error control will be controlled by transferring alpha spending to subsequent endpoints in the testing hierarchy dependent on the statistical significance of the testing.

Figure 1 Hierarchical Testing Structure



For each of the primary and secondary endpoints separately non-inferiority comparisons will be performed as described in Section 4.2.1 and 4.2.2 – 4.2.6.

If the non-inferiority is met in all of the 5 tests, then the superiority will be tested. For each of the primary and secondary endpoints separately superiority comparisons will be performed as described in Section 4.2.1 and 4.2.2 – 4.2.6.

Results of the non-inferiority and superiority comparisons will be presented in separate summary tables.

The non-inferiority limit of -150 mL will be applied for all change from baseline FEV1 endpoints, ie, FEV1 AUC(0-t) normalized by time and those at individual timepoints, with the exception of fall in FEV1 from baseline (-30 min) to post-mannitol challenge 2, for which the non-inferiority limit will be 150 mL.

3.3.5 Handling of Protocol Deviations in Study Analysis

Deviations from the protocol will be reviewed prior to the Part 2 database lock, and will be assessed as “important” or “not-important”. Only important protocol deviations (IPDs) will be listed, for all enrolled subjects. IPDs are defined as protocol deviations which may significantly affect the completeness, accuracy and/or reliability of the study data, or which may significantly affect a participant’s rights, safety or well-being. They may include (but not be limited to):

- Participants who were randomized even though they did not meet key inclusion criteria or who met at least one key exclusion criteria
- Participants who developed withdrawal criteria during the study but were not withdrawn
- Participants who received wrong IMP treatment or incorrect/incomplete IMP dosing, or wrong or incomplete mannitol dosing
- Participants who received a restricted or prohibited concomitant treatment
- Written informed consent not obtained prior to mandatory study specific procedures, sampling and analyses.
- Participant who did not receive first dose of IMP within 6 minutes of final dose of mannitol challenge 1.

Prior to the Part 2 database lock and unblinding, PDs will be assessed during the blinded Planned Analysis Review Meeting (PARM) and documented in the PARM Report. Classification of PD as important/ non-important and their possible impact on the data will be discussed then.

The occurrence of an IPD may result in excluding the effected subject's data from PP analysis set analyses. Subject's data does not need to be excluded from an analysis so long as the IPD does not affect the measurement of that endpoint.

The non-inferiority analysis of the below endpoints will be based on the mPP analysis set, hence subjects with any IPD will be excluded from the analysis apart from whose who did not receive first dose of IMP within 6 minutes of final dose of mannitol challenge 1 (as that IPD does not affect the listed endpoints):

- Time to return to baseline (-30 min) FEV1 post mannitol challenge 2
- Peak fall from baseline (-30 min) FEV1 to post mannitol challenge 2

For the non-inferiority analysis of the endpoints, subjects with any IPD will be excluded from the analysis and PP analysis set will be used.

For the superiority analysis, based on the mRS analysis set, subjects with an IPD will not be excluded from the analysis.

A final list all IPDs for all subjects will be provided. Any that will lead to the above exclusions will be documented by the study team prior to Final Clinical Data Lock (CDL) and treatment unblinding. This will include details of the analysis sets/endpoints that subjects need to be excluded from.

Any PDs which are not defined as important, except coronavirus disease 2019 (COVID-19) related PDs, will not be reported or discussed in the clinical study report (CSR).

3.3.6 Definition of Baseline and Change from Baseline

Baseline definitions for the primary/secondary forced expiratory volume in 1 second (FEV_1) endpoints and safety parameters are defined in Table 2 and Table 3. The endpoints are further defined in section 4.2.

Change from baseline will be defined as follows, ensuring the correct baseline reference as described in Table 2 and Table 3 is used: (post-baseline value - baseline value). If either the post-baseline value or the baseline value is missing, then the change from baseline will also be missing.

Table 2 Baseline for FEV1 endpoints and safety parameters– Visits 1 (screening)

Category/Assessment	Baseline Definition	Endpoints/Parameters
Baseline FEV_1	Baseline (-30 min) FEV_1 is defined as the best FEV_1 value (highest FEV_1 of the acceptable efforts or the highest FEV_1 if no acceptable efforts are obtained) taken premannitol challenge at -30 min for Visit 1.	● Peak fall from baseline (-30 min) FEV_1 to post-mannitol challenge 1 at screening ● FEV_1 results over time at screening
Mannitol baseline FEV_1	The mannitol baseline is defined as the FEV_1 result where a positive response to mannitol is observed prior to dosing of study drug for mannitol challenge in Visit 1 (time 0). A positive response is defined as a ≥15% decrease in FEV_1 from the 0 mg mannitol FEV_1 value.	● FEV_1 results over time at screening
Lung function parameters (FEV_1, FVC)	Study entry is the Walk-in baseline at Visit 1 (-30 min).	● Lung function data at study entry
Asthma characteristics parameters (including FeNO, Blood eosinophils, NAEPP, AIRQ)	Study entry is defined as the latest assessment prior to Visit 2.	● Asthma characteristics at study entry

Table 3 Baseline for primary/secondary FEV1 endpoints and safety parameters– Visits 2 and 3

Category/Assessment	Baseline Definition	Endpoints/Parameters
Baseline (-30 min) FEV1	Baseline (-30 min) FEV1 is defined as the best FEV1 value (highest FEV1 of the acceptable efforts or the highest FEV1 if no acceptable efforts are obtained) taken premannitol challenge at -30 min for Visit 2 and Visit 3.	• Time to return to baseline (-30 min) FEV1 post-mannitol challenge 2 • Peak fall from baseline (-30 min) FEV1 to post-mannitol challenge 2
Mannitol baseline FEV1	The mannitol baseline is defined as the FEV1 result where a positive response to mannitol is observed prior to dosing of study drug for challenge 1 in Visit 2 and in Visit 3 (time 0). A positive response is defined as a ≥15% decrease in FEV1 from the 0 mg mannitol FEV1 value.	• Change from mannitol baseline FEV1 to the normalized FEV1 AUC(0-60 min) post-mannitol challenge 1 • Change from mannitol baseline FEV1 to the normalized FEV1 AUC(0-15 min) post-mannitol challenge 1 • Change from mannitol baseline in FEV1 at 480 min post-mannitol challenge 1
Vital signs	Visit 2 and Visit 3 will have separate baseline results utilizing the -30 min time point. If the -30 min value is missing, baseline will be the latest nonmissing value prior to the mannitol challenge ie, prior to time -10 min.	Results and change from baseline for: • Pulse • Blood pressure • Pulse oximetry • Respiratory rate
12-lead ECG	Visit 2 and Visit 3 will have separate baseline results utilizing the 30 min time point. If the -30 min value is missing, baseline will be the latest non-missing value prior to the mannitol challenge ie, prior to time -10 min.	Result and change from baseline for all scheduled timepoints at for all ECG parameters
Laboratory assessments	Visit 2 and Visit 3 will have separate baseline results utilizing the 30 min time point. If the -30 min value is missing, baseline will be the latest non-missing value prior to the mannitol challenge ie, prior to time -10 min.	Result and change from baseline for all scheduled timepoints for Laboratory safety variables as listed in Table 7 of the protocol

Abbreviations: AUC=area under the curve; ECG=electrocardiogram; FEV1=Forced Expiratory Volume in the first second.

4 STATISTICAL ANALYSIS

This section provides information on definitions, derivation and analysis/data presentation per domain.

4.1 Study Population

The domain study population covers participant disposition, analysis sets, protocol deviations, demographics, baseline characteristics medical history, prior and concomitant medication.

4.1.1 Patient Disposition and Completion Status

4.1.1.1 Definitions and Derivations

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study intervention (ie, at Visit 2).

4.1.1.2 Presentation

Participant disposition will be summarized using the enrolled analysis set. The number of participants enrolled, screen failures and participants who started open-label PT007 treatment will be summarized. The number and percentage of participants within each treatment sequence will be presented by the following categories: randomized, randomized but not treated, started any randomized treatment, completed all randomized treatments, discontinued any randomized treatment (and reason), competed study, withdrawn from study (and reason).

4.1.2 Analysis Sets

4.1.2.1 Definitions and Derivations

See section 3.2 for full definitions of the analysis sets.

4.1.2.2 Presentation

The number and percentage of participants in each of the analysis sets will be summarized by treatment sequence, along with reason for exclusion for participants not included in each set.

4.1.3 Protocol Deviations

4.1.3.1 Definitions and Derivations

See section 3.3.5 for definition of IPDs.

4.1.3.2 Presentation

A listing of all IPDs will be provided based on the mRS for Part 1 and Part 2 separately.

Additionally a summary table of IPDs will be provided, for Part 1 and Part 2 separately.

4.1.4 Demographics

4.1.4.1 Definitions and Derivations

Demographic data will include age, sex, race, and ethnicity. Age will be summarized both continuously and by the following categories: 18-34, 35-64, 65 and older.

4.1.4.2 Presentation

Demographics will be summarized separately for Part 1 and Part 2 as well as pooled.

4.1.5 Baseline Characteristics

4.1.5.1 Definitions and Derivations

Baseline characteristics (weight [kg], height [cm], and body mass index (BMI) [kg/m^2], and number (%) of subjects with BMI $\geq$ 30) are collected at Visit 1.

4.1.5.2 Presentation

Baseline characteristics will be summarized for the pooled Part 1 and Part 2, and for Part 1 and Part 2 separately.

4.1.6 Disease Characteristics

4.1.6.1 Definitions and Derivations

Disease characteristics will include: Asthma characteristics at study entry (including: Time since asthma diagnosis, Time since last severe exacerbation, Total number of severe exacerbations during the past 12 months prior to Visit 1, Total number of hospitalizations due to severe exacerbations during the past 12 months prior to Visit 1, number and percentage of participants with FeNO at Visit 1 separated into categories of 0 to <25ppb, 25 to <50 ppb, and ≥ 50ppb, number and percentage of participants with blood eosinophils at Visit 1 separated into categories of 0 to <150 cells/mm3 Eosinophils, 150 to < 300 cells/mm3 Eosinophils, ≥300 cells/mm3 Eosinophils, Asthma Impairment and Risk Questionnaire (AIRQ), Severity per National Asthma Education and Prevention Program (NAEPP) and Lung function data at study entry (including FEV_1 [L] - absolute and percent predicted values, forced vital capacity [FVC] [L] - absolute and percent predicted values, and the FEV_1/FVC Ratio and number and percentage of participants with FEV1 (% of predicted value) separated into categories of 60 to < 70, 70 to <80 and ≥ 80.

4.1.6.2 Presentation

Disease characteristics will be summarized for the pooled Part 1 and Part 2, and for Part 1 and Part 2 separately.

4.1.7 Medical History and Concomitant Disease

4.1.7.1 Definitions and Derivations

Medical and surgical histories are reported at Visit 1.

4.1.7.2 Presentation

Medical and surgical histories will be summarised in tables. It will be presented for pooled Part 1 and 2 and for Part 1 and Part 2 separately.

4.1.8 Prior and Concomitant Medications

4.1.8.1 Definitions and Derivations

A list of permitted, restricted and prohibited medications can be found in section 6.8 of the CSP. For the method of imputing missing medication onset/start and end/stop dates, please refer to Appendix A: Imputation Rules for Missing or Partially Missing dates associated with Prior Medications, Concomitant Medications, Procedures and Adverse Events. First dose of study intervention is defined in Section 3.3.1.

Medications will be categorized for analysis according to their (imputed) onset and end dates in accordance with Table 4. Note that medications can be assigned to more than one period to reflect the treatment they were prior to, or concomitant with.

Table 4 Classification of Concomitant Medications to Treatment Arm

Period	Participants receiving PT027-PT007	Participants receiving PT007-PT027
Prior - Screening (Visit 1)	Assign medication to prior medication during Open-label PT007 (Visit 1) if: end date of medication ≥ date of first dose of study intervention at visit 1 and the start date of medication < minimum (date of first dose of randomized treatment at Visit 2 [PT027 or PT007], date of death, date of study withdrawal) Or end date of medication is ongoing and start date of medication < minimum (date of first dose of randomized treatment at Visit 2 [PT027 or PT007], date of death, date of study withdrawal)	
Concomitant - Visit 2	Assign medication To PT027 if: end date of medication ≥ date of first dose of PT027 at Visit 2 and start date of medication < minimum (date of first dose of PT007 at Visit 3, date of death, date of study withdrawal) Or end date of medication is ongoing and start date of medication < minimum (first dose of PT007 at Visit 3, date of death, date of study withdrawal)	Assign medication To PT007 if: end date of medication ≥ date of first dose of PT007 at Visit 2 and start date of medication < minimum (date of first dose of PT027 at Visit 3, date of death, date of study withdrawal) Or end date of medication is ongoing and start date of medication < minimum (first dose of PT027 at Visit 3, date of death, date of study withdrawal)

Period	Participants receiving PT027-PT007	Participants receiving PT007-PT027
Concomitant - Visit 3	Assign medication To PT007 if: end date of medication ≥ date of first dose of PT007 at Visit 3 and start date of medication < minimum (date of last dose of PT007 +7 days, date of death, date of study withdrawal) Or end date of medication is ongoing and start date of medication ≤ minimum (date of last dose of PT007 +7 days, date of death, date of study withdrawal	Assign medication To PT027 if: end date of medication ≥ date of first dose of PT027 at Visit 3 and start date of medication < minimum (date of last dose of PT027 +7 days, date of death, date of study withdrawal) Or end date of medication is ongoing and start date of medication ≤ minimum (date of last dose of PT027 +7 days, date of death, date of study withdrawal

4.1.8.2 Presentation

Prior and concomitant medications will be summarized by their anatomical therapeutic chemical (ATC) classification system codes, generic name and treatment group, using the safety analysis set. The highest available coded ATC level will be used in summaries.

Prior and Concomitant Medications will be summarized for the pooled of Part 1 and Part 2, and Part 1 and Part 2 separately. Individual tables for Part 1 and Part 2 will be based on Safety analysis set.

4.1.9 Handling intercurrent events

Intercurrent event (ICE) is defined as discontinuation of study drug during a treatment period due to an asthma exacerbation or the taking of prohibited medications.

Comprehensive list of prohibited medications will be created by the study medical team prior to both blinded Part 2 dry-runs and unblinded Part 2 Final delivery. Based on that, ICEs will be identified programmatically and ADICE dataset will be created and shared for medical team review and approval prior to those deliveries.

ICEs will be summarised in a table only for Part 2 including: number of study discontinuations during a treatment period due to an asthma exacerbation, number of subjects who used prohibited medications, and number of subjects who proceed in visit 2 or 3 despite not meeting study stability criteria or not having positive mannitol challenge 1.

A separate ICE strategy will be implemented for each of the objectives.

4.2 Endpoint Analyses

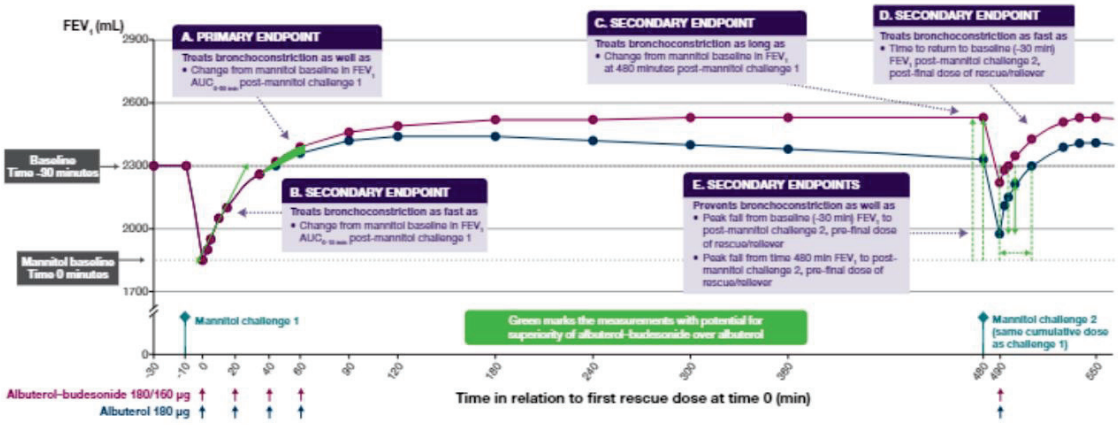
This section covers details related to the Part 2 efficacy endpoint analyses.

For the primary and secondary objectives, efficacy outputs will be presented by treatment (PT027 or PT007). Efficacy data from Part 1 of the study will not be combined with the data from Part 2. Outputs will be presented separately for Part 1 and Part 2.

Exploratory endpoints related outputs will be presented by treatment (PT027 or PT007). Additionally, it will be presented pooled for Part 1 and 2 except for the exploratory endpoint change from baseline FEV_1 AUC(0-15 min) post-mannitol challenge 2, which will be reported separately for Part 1 and Part 2. Endpoints only evaluated in Part 2, percentage fall from baseline (-30 min) FEV_1 to post-mannitol challenge 2, percentage fall in FEV_1 at time 480 min, change from time 0 min in Borg dyspnea scale post-mannitol challenge 1 and change from time 490 min in Borg dyspnea scale post-challenge 2 -, will be reported only for Part 2.

See Figure 2 for an illustration of some efficacy aspects of FEV_1 and symptoms that will be evaluated during Visits 2 and 3 to support study objectives. Note that the FEV_1 curves in this figure are hypothetical for illustration only. Additionally see Table 5 for Schedule of POE and Borg Scale Activities: Mannitol Challenge 1 and Mannitol Challenge 2.

Figure 2 Time course of theoretical lung function changes at treatment visits and associated endpoints (Visits 2 and 3)



Note: FEV1 curves are hypothetical, for illustration only.
Abbreviations: AUC=area under the curve; FEV1=Forced Expiratory Volume in the first second; min=minutes.

Table 4 Schedule of POE and Borg Scale Activities: Mannitol Challenge 1 and Mannitol Challenge 2

Mannitol Challenge 1

Walk-in Baseline		Mannitol Baseline	POST-MANNITOL CHALLENGE 1																			
↓		↓																				
Symptoms and Perception of Effect																						
Minutes	-30	-10	0	3	5	10	15	20	25	30	35	40	45	50	55	60	90	120	180	240	300	360	480
POE				X	X	X	X	X	X	X	X	X	X	X	X	X							
Borg Scale	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Mannitol Challenge 2

Post-treatment Baseline		Mannitol 2 FEV1 response	POST-MANNITOL CHALLENGE 2												
↓		↓													
Symptoms and Perception of Effect															
Minutes	480	490	493	495	500	505	510	515	520	525	530	535	540	545	550
POE			X	X	X	X	X	X	X	X	X	X	X	X	X
Borg Scale	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

A descriptive summary of each objective, including the endpoint, population, intercurrent event (ICE) strategy and population level summary is provided below.

Table 5 Descriptive Summary of Objectives

Statistical category	Endpoint	Population	Intercurrent event (ICE) strategy	Population level summary (analysis)	Details in section
Objective 1: To assess the efficacy of repeated dosing of PT027 relative to PT007, on post-dose lung function, when used by participants with asthma on SABA as needed treatment only who are experiencing acute airway obstruction.					
Primary	Change from mannitol baseline FEV1	Adult participants with asthma on SABA as needed treatment	While-on-treatment.	Difference in the adjusted means of the endpoint for the treatment comparison	4.2.1

Statistical category	Endpoint	Population	Intercurrent event (ICE) strategy	Population level summary (analysis)	Details in section
	AUC(0-60 min) post-mannitol challenge 1.	only, and who are sensitive to mannitol.		of PT027 versus PT007.	
Objective 2: To establish the efficacy of PT027 after a single dose compared with PT007 in reversal of acute airway obstruction, when used by participants with asthma on SABA as needed treatment only who are experiencing acute airway obstruction.					
Secondary	Change from mannitol baseline in FEV_1 AUC(0-15 min) post-mannitol challenge 1.	As per primary objective.	While-on-treatment.	As per primary objective.	4.2.2
Objective 3: To establish the efficacy of PT027 compared with PT007 in the sustainability of effect of reversal of acute airway obstruction post-mannitol challenge 1 in participants with asthma on SABA as needed treatment only who are experiencing acute airway obstruction.					
Secondary	Change from mannitol baseline in FEV_1 at 480 min post mannitol challenge 1.	As per primary objective.	While-on-treatment.	As per primary objective.	4.2.3
Objective 4: To establish the efficacy of a single dose of PT027 compared with PT007 on post-dose speed of recovery of lung function following a recurring trigger of acute airway obstruction in participants with asthma on SABA as needed treatment only.					
Secondary	Time to return to baseline (-30 min) FEV1 post mannitol challenge 2.	As per primary objective.	While-on-treatment.	Difference in the adjusted medians of the participant-level outcomes for the treatment comparison of PT027 versus PT007.	4.2.6
Objective 5: To establish the protective efficacy of prior repetitive doses of PT027 compared with PT007 on lung function fall in response to a recurring trigger of acute airway obstruction in participants with asthma on SABA as needed treatment only.					
Secondary	Peak fall from baseline (-30 min) FEV1 to post mannitol challenge 2.	As per primary objective.	While-on-treatment.	As per primary objective.	4.2.4

Statistical category	Endpoint	Population	Intercurrent event (ICE) strategy	Population level summary (analysis)	Details in section
Objective 6: To assess the protective efficacy of prior repetitive doses of PT027 compared with PT007 on lung function fall in response to a recurring trigger of acute airway obstruction in participants with asthma on SABA as-needed treatment only.					
Secondary	Peak fall from 480 min FEV1 to post- mannitol challenge 2.	As per primary objective.	While-on-treatment.	As per primary objective.	4.2.5
Objective 7: To assess the safety and tolerability of repeated dosing of PT027 as compared to PT007 in participants with asthma on SABA as-needed treatment only.					
Safety	Incidence of AEs and clinical abnormalities related to 12-lead ECG, clinical laboratory tests, and/or vital signs.	Safety analysis set.	N/A	N/A	4.6
Objective 8: To explore the efficacy after a single dose of PT027 compared with PT007 on post-dose lung function following a recurring trigger of acute airway obstruction in participants with asthma on SABA as needed treatment only.					
Exploratory	Change from baseline (-30 min) FEV1 AUC(0-15 min) post-mannitol challenge 2.	As per primary objective.	N/A	As per primary objective.	4.2.7

Statistical category	Endpoint	Population	Intercurrent event (ICE) strategy	Population level summary (analysis)	Details in section
Objective 9: To assess relief from mannitol challenge induced breathing difficulty following treatment with PT027 as compared to PT007.					
Exploratory	Change from time 0 min in Borg dyspnea scale post-mannitol challenge 1, post-dose. Change from time 490 min in Borg dyspnea scale post-mannitol challenge 2, post-dose.	As per primary objective.	N/A	Difference in the means of the endpoint for the treatment comparison of PT027 versus PT007.	4.2.8
Objective 10: To assess the lung function efficacy and sustainability of effect reversal of acute airway obstruction of PT027 compared to PT007.					
Exploratory	Change from mannitol baseline in FEV1 and percentage change from mannitol baseline in FEV1, post-mannitol challenge 1 at each measured timepoint up to and including 480 min.	As per primary objective.	N/A	As per primary objective.	4.2.13
Objective 11: To assess the protective effect of PT027 relative to PT007 in response to a repetitive trigger of bronchoconstriction.					

Statistical category	Endpoint	Population	Intercurrent event (ICE) strategy	Population level summary (analysis)	Details in section
Exploratory	Percentage fall in FEV1 from baseline (-30 min) FEV1 to post-mannitol challenge 2.	As per primary objective.	N/A	As per primary objective.	4.2.12
Objective 12: To assess the perception of onset of effect of PT027 as compared to PT007.					
Exploratory	Time to perceived onset of effect of study medication working post PT027 as compared to PT007 given following mannitol challenge 1 completion. Time to perceived onset of effect of study medication working post PT027 as compared to PT007 given following mannitol challenge 2 completion.	As per primary objective.	N/A	Difference in the means of the endpoint for the treatment comparison of PT027 versus PT007.	4.2.9
Objective 13: To assess the impact of repetitive PT027 as compared to PT007 on airway inflammation.					
Exploratory	Change from baseline FeNO and eosinophils over time, post-mannitol challenge.	As per primary objective.	N/A	Difference in the means of the endpoint for the treatment comparison of PT027 versus PT007.	4.2.10
Objective 14: To assess the protective effect of PT027 relative to PT007					

Statistical category	Endpoint	Population	Intercurrent event (ICE) strategy	Population level summary (analysis)	Details in section
Exploratory	The proportion of participants who are non-responders to mannitol challenge 2. A non-responder is defined as a < 15% fall in FEV_1 relative to baseline FEV_1.	As per primary objective.	N/A	The proportion of participants who are non-responders to mannitol challenge 2.	4.2.11

4.2.1 Primary Endpoint: Change from mannitol baseline FEV_1 AUC(0-60 min) post-mannitol challenge 1 (mL)

4.2.1.1 Definition

The primary endpoint is the change from mannitol baseline FEV_1 AUC(0-60 min) post mannitol challenge 1.

4.2.1.2 Derivations

The mannitol baseline is defined as the FEV_1 result where a positive response to mannitol is observed prior to dosing of study drug for challenge 1 in Visit 2 and in Visit 3 (time 0). A positive response is defined as a $\geq$ 15% decrease in FEV_1 from the 0 mg mannitol FEV_1 value. The change from mannitol baseline FEV_1 AUC(0-60 min) post-mannitol challenge 1, is the area under the curve for the changes from mannitol baseline FEV_1 calculated using the trapezoidal rule. To aid in interpretation, all AUC values will be normalized by dividing by the time in minutes from dosing to the last non-missing measurement included (typically 60 minutes). Only 1 non missing, post- dose value, 0 to 30 minutes and 1 non-missing, post- dose value 30 to 60 minutes, is required for the calculation of AUC. Actual timepoints for spirometry will be used for calculations.

The mannitol baseline for FEV_1 and change from baseline is defined further in Section 3.3.6.

4.2.1.3 Handling of Dropouts and Missing Data

Discontinuation of study drug during a treatment period due to an asthma exacerbation or the taking of prohibited medication will be considered an ICE. A while-on-treatment strategy for addressing ICEs will be implemented. This estimand targets the treatment

difference in a scenario, such that outcomes for participants without an ICE are as observed and outcomes for participants with an ICE are treated as MAR in the linear mixed effects model. Discontinuations from study for any other reasons not defined as an ICE will also be treated as MAR in the linear mixed effects model. Participants discontinuing study or starting prohibited medication during a visit with enough data prior to these ICEs, will still have their AUC calculated in line with Section 4.2.1.2. However, if they have no post-dose value between 30-60 mins (or no post-dose value between 0-30 mins), then their primary endpoint result will be missing.
ICE defined by study treatment discontinuations due to an asthma exacerbation and the taking of prohibited medications will be identified during the blinded Planned Analysis Review Meeting (PARM) and documented in the PARM minutes prior to unblinding of Part 2 data. ICEs will be reported for Part 1 and Part 2 separately.

4.2.1.4 Primary Analysis of Primary Endpoint

The primary efficacy comparison of non-inferiority will evaluate the while-on-treatment estimand in the PP set.

The primary efficacy comparison of non-inferiority will be based on a 1-sided hypothesis testing approach. The statistical null hypothesis for the PT027 versus PT007 comparison will be that the mean treatment difference shows that PT027 is inferior to PT007 by more than -150 mL. The null hypothesis is rejected if the lower limit of the 2–sided 95% CIs for the difference between treatments is greater than the non-inferiority limit of -150 mL.

The change from mannitol baseline FEV_1 AUC(0-60 min) post-mannitol challenge 1, will be analyzed using a linear mixed model with a random participant effect. The fixed effects in the model will include center, treatment, treatment sequence, mannitol baseline FEV1, the average of the two periods mannitol baseline FEV_1 values, and period. Taking the average of the two periods mannitol baseline FEV_1 values (ie, taking the average of the mannitol baseline FEV_1 values at Visit 2 and at Visit 3), and adding the average as a covariate to the model is to avoid cross-level bias (Kenward et al 2010). Contrasts will be used to obtain estimates of the treatment difference. Point estimates of the estimated adjusted treatment means, standard errors and 95% CIs will be presented. The point estimate of the difference in treatment means for the comparison of PT027 with PT007 with associated 2-sided 95% CI will be used to evaluate non-inferiority, such that non-inferiority of PT027 compared with PT007 is established if the lower 95% confidence limit of the point estimate is greater than the non-inferiority margin of -150 mL.

Superiority comparison if first non-inferiority has been demonstrated:

The primary efficacy comparison to establish the superiority of PT027 versus PT007 will evaluate the while-on-treatment estimand in the mRS. Superiority will be concluded if the 2-sided p-value is < 0.05.

The primary endpoint FEV_1 AUC(0-60 min) will be analyzed using the linear mixed model specified above, using the mRS. Point estimates of the estimated adjusted treatment means, standard errors and 95% CIs will be obtained. The estimated mean treatment difference as well as 95% CIs, and 2-sided p-value will be presented.

The primary efficacy comparison of superiority will be based on a 2-sided hypothesis testing approach.

Efficacy data related to the primary endpoint from Part 1 of the study will not be combined with the data from Part 2.

4.2.1.5 Sensitivity Analyses of the Primary Endpoint

For Part 2 of the study, a sensitivity analysis of the superiority comparison will be performed excluding subjects with an IPD for not receiving the first dose of IMP within 6 minutes of the final dose of mannitol challenge 1.

4.2.1.6 Supplementary Analyses of the Primary Endpoint

For Part 2 of the study, no supplementary analysis is planned.

4.2.1.7 Subgroup Analyses

For Part 2 of the study, no subgroup analysis is planned.

4.2.2 Secondary Endpoint: Change from mannitol baseline FEV_1 AUC(0-15) min post-mannitol challenge 1 (in mL)

4.2.2.1 Definition

Change from mannitol baseline FEV_1 (AUC 0-15 min) post-mannitol challenge 1 is a secondary endpoint for Part 2 data analysis.

4.2.2.2 Derivations

AUC (0-15 min) (in mL) of the FEV_1 assessments collected 0 to 15 minutes post mannitol challenge 1 will be calculated using the trapezoidal rule and will be normalized by dividing by the time in minutes from dosing to the last measurement included (typically 15 mins but real assessment times will be used). Only 1 non missing, post-dose value between 0–15 mins is required for the calculation of AUC.

The mannitol baseline for FEV_1 and change from baseline is defined in Section 3.3.6.

4.2.2.3 Handling of Dropouts and Missing Data

The ICEs of discontinuation of study during a treatment period due to an asthma exacerbation and the taking of prohibited medication will be handled in the same manner as for the primary endpoint as described in Section 4.2.1.3. Participants discontinuing study or starting prohibited medication during a visit with enough data prior to ICE, will still have

their AUC calculated in line with section 4.2.2.2. However, if they have no post-dose value between 0-15 mins, then their AUC result will be missing.

4.2.2.4 Primary Analysis of Secondary Endpoint

The efficacy comparison of non-inferiority will evaluate the while-on-treatment estimand in the PP analysis set using the same linear mixed model as described for the primary endpoint in Section 4.2.1.4. Non-inferiority will be demonstrated if the lower 95% confidence limit of the point estimate is less than the non-inferiority margin of -150 mL. Superiority of PT027 versus PT007 will evaluate the while-on-treatment estimand in the mRS using the same methods as described for the primary endpoint in Section 4.2.1.4.

Efficacy data related to the secondary endpoints from Part 1 of the study will not be combined with the data from Part 2.

4.2.2.5 Sensitivity Analyses of the Secondary Endpoint

For Part 2 of the study, a sensitivity analysis of the superiority comparison will be performed excluding subjects with an IPD for not receiving the first dose of IMP within 6 minutes of the final dose of mannitol challenge 1.

4.2.2.6 Supplementary Analyses of the Secondary Endpoint

For Part 2 of the study, no supplementary analysis is planned.

4.2.2.7 Subgroup Analyses

For Part 2 of the study, no subgroup analysis is planned.

4.2.3 Secondary Endpoint: Change from mannitol baseline in FEV_1 at 480 min post-mannitol challenge 1 (in mL)

4.2.3.1 Definition

Change from mannitol baseline in FEV_1 at 480 min post-mannitol challenge 1 is a secondary endpoint for Part 2 data analysis.

4.2.3.2 Derivations

This endpoint is calculated as the absolute difference in FEV_1 result (in mL) at 480 min post-mannitol challenge 1 and the mannitol baseline FEV_1, baseline is defined in Section 3.3.6.

4.2.3.3 Handling of Dropouts and Missing Data

ICEs are defined as discontinuation of study drug during a treatment period due to an asthma exacerbation or the taking of prohibited medications. A while-on-treatment strategy for addressing ICEs will be implemented. This estimand targets the treatment difference in a scenario, such that outcomes for participants without an ICE are as observed and outcomes for participants with an ICE are treated as MAR in the linear mixed effects

model. Discontinuations from study for any other reasons not defined as an ICE will also be treated as MAR in the linear mixed effects model. In other words participants without a FEV_1 result at 480 min post-mannitol challenge 1 (or with the result set to missing due to it occurring post ICE), will not be imputed.

4.2.3.4 Primary Analysis of Secondary Endpoint

The non-inferiority test for the secondary endpoint of change from mannitol baseline in FEV1 at 480 min post-mannitol challenge 1, will evaluate the while-on-treatment estimand in the PP using the same linear mixed model as described for the primary endpoint in Section 4.2.1.4. Non-inferiority will be demonstrated if the upper 95% confidence limit of the point estimate is less than the non-inferiority margin of 150 mL. Efficacy comparisons for superiority will evaluate the while-on-treatment estimand in the mRS population using the same methods as described for the primary endpoint in Section 4.2.1.4.

Efficacy data related to the secondary endpoints from Part 1 of the study will not be combined with the data from Part 2.

4.2.3.5 Sensitivity Analyses of the Secondary Endpoint

For Part 2 of the study, a sensitivity analysis of the superiority comparison will be performed excluding subjects with an IPD for not receiving the first dose of IMP within 6 minutes of the final dose of mannitol challenge 1.

4.2.3.6 Supplementary Analyses of the Secondary Endpoint

For Part 2 of the study, no supplementary analysis is planned.

4.2.3.7 Subgroup Analyses

For Part 2 of the study, no subgroup analysis is planned.

4.2.4 Secondary Endpoint: Peak fall from baseline (-30 min) FEV_1 to post-mannitol challenge 2 (in mL)

4.2.4.1 Definition

Peak fall from baseline (-30 min) FEV1 to post-mannitol challenge 2 is a secondary endpoint for Part 2 data analysis.

4.2.4.2 Derivations

Baseline (-30 min) FEV_1 is the FEV_1 result recorded at -30 minutes. The FEV_1 result recorded at the mannitol challenge 2, i.e. before study intervention treatment, is expected to be at 490 mins following the mannitol challenge 1.

The peak fall in FEV_1 (in mL) is derived as:

Baseline (-30 min) FEV_1 - FEV_1 result recorded at mannitol challenge 2 completion, before initiation of the study intervention (at 490 minutes).

4.2.4.3 Handling of Dropouts and Missing Data

The ICEs of discontinuation of study drug during a treatment period due to an asthma exacerbation or the taking of prohibited medication will be handled in the same manner as for the primary endpoint as described in section 4.2.1.3. Participants discontinuing study or starting prohibited medication prior to the recording of FEV_1 at the mannitol challenge 2, before initiation of the study intervention, will be set to missing in the analysis.

4.2.4.4 Primary Analysis of Secondary Endpoint

The efficacy comparison of non-inferiority will evaluate the while-on-treatment estimand in the mPP analysis set using the same linear mixed model as described for the primary endpoint in Section 4.2.1.4. with the exception model will adjust for walk-in baseline FEV_1. Non-inferiority will be demonstrated if the upper 95% confidence limit of the point estimate is less than the non-inferiority margin of 150 mL. Superiority of PT027 versus PT007 will evaluate the while-on-treatment estimand in the mRS using the same methods as described for the primary endpoint in Section 4.2.1.4.

Efficacy data related to the secondary endpoints from Part 1 of the study will not be combined with the data from Part 2. Outputs will be presented separately for Part 1 and Part 2.

4.2.4.5 Sensitivity Analyses of the Secondary Endpoint

For Part 2 of the study, no sensitivity analysis is planned.

4.2.4.6 Supplementary Analyses of the Secondary Endpoint

For Part 2 of the study, no supplementary analysis is planned.

4.2.4.7 Subgroup Analyses

For Part 2 of the study, no subgroup analysis is planned.

4.2.5 Secondary Endpoint: Peak fall from 480 min FEV1 to post-mannitol challenge 2 (in mL)

4.2.5.1 Definition

Peak fall from 480 min FEV1 to post-mannitol challenge 2 is a secondary endpoint for Part 2 data analysis.

4.2.5.2 Derivations

480 min FEV_1 is the FEV_1 result recorded at 480 minutes. The FEV_1 result recorded at the mannitol challenge 2, i.e. before study intervention treatment, is expected to be at 490 mins following the mannitol challenge 1.

The peak fall in FEV_1 (in mL) is derived as:

480 min FEV_1 - FEV_1 result recorded at mannitol challenge 2 completion, before initiation of the study intervention (at 490 minutes).

4.2.5.3 Handling of Dropouts and Missing Data

The ICEs of discontinuation of study drug during a treatment period due to an asthma exacerbation or the taking of prohibited medication will be handled in the same manner as for the primary endpoint as described in section 4.2.1.3. Participants discontinuing study or starting prohibited medication prior to the recording of FEV_1 at the mannitol challenge 2, before initiation of the study intervention, will be set to missing in the analysis.

4.2.5.4 Primary Analysis of Secondary Endpoint

Superiority of PT027 versus PT007 will evaluate the while-on-treatment estimand in the mRS using the same methods as described for the primary endpoint in section 4.2.1.4.

Outputs related to his endpoint will be presented only for Part 2.

4.2.5.5 Sensitivity Analyses of the Secondary Endpoint

For Part 2 of the study, no sensitivity analysis is planned.

4.2.5.6 Supplementary Analyses of the Secondary Endpoint

For Part 2 of the study, no supplementary analysis is planned.

4.2.5.7 Subgroup Analyses

For Part 2 of the study, no subgroup analysis is planned.

4.2.6 Secondary Endpoint: Time to return to baseline (-30 min) FEV1 post-mannitol challenge 2 (in mins)

4.2.6.1 Definition

Time to return to baseline (-30 min) FEV_1 post-mannitol challenge 2 is a secondary endpoint for Part 2 data analysis. This is to compare the effect upon repeated trigger therapeutic benefit between PT027 and PT007.

4.2.6.2 Derivations

Return to baseline (-30 min) FEV_1 will be achieved at the first timepoint (post-mannitol challenge 2) where the FEV_1 value post-mannitol challenge 2 is within 5% of the baseline (-30 min) FEV_1 value.

The time to return in minutes will be calculated as the time it takes for a subject to return to within 5% of baseline (-30 min) FEV_1 value, post mannitol challenge 2. Time to return to baseline (-30 min) FEV_1 post-mannitol challenge 2, will be calculated using 95% of the baseline obtained prior to the first mannitol challenge and linear interpolation of actual timepoints rather than scheduled timepoints.

The Pairwise treatment difference within a subject will be calculated as: Time to return on PT027 - Time to return on PT007

If more than 5% of randomized participants do not have a return to within 5% of baseline FEV_1 post-mannitol challenge 2 for both treatment arms (such that their pairwise difference is non-calculable), then an alternative Kaplan-Meier analysis will be considered. Participants who do return to baseline FEV_1 will be classified as having an event at the time they return to baseline FEV_1. Participants without a return to baseline FEV_1 (or experiencing an ICE prior to return), will be censored at the time of their latest non missing FEV_1 assessment (prior to ICE occurrence or discontinuation).

4.2.6.3 Handling of Dropouts and Missing Data

ICEs are defined as discontinuation of study during a treatment period due to an asthma exacerbation and the taking of prohibited medications. A while-on-treatment strategy for addressing ICEs will be implemented. This estimand targets the treatment difference in a scenario, such that outcomes for participants without an ICE are as observed and outcomes for participants with an ICE are treated as MAR. Discontinuations from study for any other reasons not defined as an ICE will also be treated as MAR. Therefore, participants without a return to baseline FEV_1 (or with the result set to missing due to it occurring post ICE), will not be imputed. Participants with return to baseline FEV_1 missing in either treatment arm will result in a missing pairwise difference in the primary analysis of this secondary endpoint.

ICE defined by study treatment discontinuations due to an asthma exacerbation or the taking of prohibited medications will be identified during the blinded Data Review Meeting (DRM) and documented in the DRM minutes prior to unblinding of Part 2 data. ICEs will be reported only for Part 2.

4.2.6.4 Primary Analysis of Secondary Endpoint

The efficacy comparison of non-inferiority will evaluate the while-on-treatment estimand in the mPP analysis set. A summary of the number (and percentage) of participants with

return to baseline FEV_1 by treatment arm will be provided. The time to return will be summarized using the median of the pairwise differences and 95% CIs provided using the Hodges-Lehmann estimate based on the Wilcoxon signed-rank statistic.

Non-inferiority will be demonstrated if the upper 95% confidence limit of the point estimate is less than the non-inferiority margin of 3.5 minutes. Superiority of PT027 versus PT007 will evaluate the while-on-treatment estimand in the mRS using the same methods.

4.2.6.5 Sensitivity Analyses of the Secondary Endpoint

If more than 5% of randomized participants do not have a return to within 5% of baseline FEV_1 post-mannitol challenge 2 for both treatment arms (such that their pairwise difference is non-calculable), then an alternative Kaplan-Meier analysis will be considered. Participants who do return to baseline FEV_1 will be classified as having an event at the time they return to baseline FEV_1. Participants without a return to baseline FEV_1 (or experiencing an ICE prior to return), will be censored at the time of their latest non missing FEV_1 assessment (prior to ICE occurrence or discontinuation).

Events and censoring will be assigned as discussed in Section 4.2.6.2. The product limit survival estimator will used to estimate the median time to return to baseline FEV_1 and associated 95% CI for each treatment arm. A log-rank test will be used to test for a difference between the survival curves for PT027 versus PT007.

A Kaplan-Meier figure will be produced to accompany the summary. The number at risk by time will be shown on the figure.

Efficacy data related to the secondary endpoints from Part 1 of the study will not be combined with the data from Part 2. Outputs will be presented separately for Part 1 and Part 2.

4.2.6.6 Supplementary Analyses of the Secondary Endpoint

For Part 2 of the study, no supplementary analysis is planned.

4.2.6.7 Subgroup Analyses

For Part 2 of the study, no subgroup analysis is planned.

4.2.7 Other Endpoint: Change from baseline (-30 min) FEV_1 AUC(0-15 min) post-mannitol challenge 2 (in mL)

4.2.7.1 Definition

Change from baseline (-30min) FEV_1 AUC during the 0 to 15 mins after the IP dose after mannitol challenge 2, (ie, FEV_1 AUC [490-505 min]) is an exploratory endpoint for Part 2 data analysis.

4.2.7.2 Derivations

FEV_1 baseline and change from baseline is defined in section 3.3.6.

The AUC (in mL) of the FEV_1 results 0 to 15 mins after the IP dose after mannitol challenge 2 (ie, between 430-445 minutes post-mannitol challenge 1), will be calculated using the trapezoidal rule and will be normalized by dividing by the time in minutes from dosing to the last measurement included (typically 15 mins but real assessment times will be used). Only 1 non-missing, post-dose value between 0–15 mins, is required for the calculation of AUC.

4.2.7.3 Primary Analysis of Other Endpoint

This endpoint will be analysed fitting the same linear mixed model as described for the primary endpoint in section 4.2.1.4, with the exception model will adjust for each periods walk-in baseline FEV_1, and the average of the two periods walk-in baseline FEV1 values, using both the PP analysis set and the mRS.

Exploratory analysis of Change from baseline FEV_1 AUC(0-15 min) post-mannitol challenge 2 will be reported separately for Part 1 and Part 2.

4.2.7.4 Sensitivity Analyses of the Other Endpoint

For Part 2 of the study, no sensitivity analysis is planned.

4.2.7.5 Supplementary Analyses of the Other Endpoint

For Part 2 of the study, no supplementary analysis is planned.

4.2.7.6 Subgroup Analyses

For Part 2 of the study, no subgroup analysis is planned.

4.2.8 Other Endpoint: Change from time 0 min in Borg dyspnea scale post-mannitol challenge 1, post-dose and Change from time 490 min in Borg dyspnea scale post-mannitol challenge 2, post-dose

4.2.8.1 Definition

Participants will be asked to report their perceived breathlessness on the modified Borg scale electronically using a handheld device, before spirometry as detailed in the CSP Schedule of Activities in Table 1. This is a 0-10 scale that asks participants to rate the difficulty of breathing, where 0 = breathing is causing no difficulty at all and 10 = where your breathing difficulty is maximal.

Change from time 0 min in Borg dyspnea scale post-mannitol challenge 1 and Change from time 490 min in Borg dyspnea scale post-mannitol challenge 2 are two separate exploratory endpoints for Part 2 data analysis.

4.2.8.2 Derivations

Borg dyspnea scale results will utilize 0 minutes time point as the baseline for mannitol challenge 1 and the 490 minutes time point as the baseline for mannitol challenge 2. If the 0 value is missing, baseline will be the earliest, post 0 min non-missing value after the mannitol challenge 1. If the time 490 value is missing, baseline will the earliest post 490 min non-missing value after the mannitol challenge 2. In both cases, that has to be a pre-dosing value.

Change from baseline = (post-baseline value - baseline value).
Note: All scheduled Borg dyspnea scale assessments following the first and second challenges at both Visits 2 and 3 will be included.

4.2.8.3 Primary Analysis of Other Endpoint

Borg Dyspnea scale data at each visit and timepoint will be presented using descriptive statistics by treatment arm. Descriptive statistics the change from baseline will also be presented by treatment arm. Primary focus will be in timepoints up to 480 minutes following the first mannitol challenge, in particular -10, 0, 3, 5, 10, 15, 35, 60, 120 and 480 minutes post-dose will be presented; and in timepoints up to 550 minutes following the second mannitol challenge, in particular 490, 493, 495, 500, 505 and 550 min post-dose. Analysis will be presented for Part 2 data only.

Arithmetic mean (± SD) and mean change from baseline (± SD) of Borg dyspnea scale values versus time will be plotted as well. Plots will be presented by treatment groups, with post-mannitol challenge 1 and 2 combined on one figure. Plots will be provided only for Part 2.

4.2.8.4 Sensitivity Analyses of the Other Endpoint

For Part 2 of the study, a sensitivity analysis of the superiority comparison will be performed excluding subjects with an IPD for not receiving the first dose of IMP within 6 minutes of the final dose of mannitol challenge 1.

4.2.8.5 Additional Analyses of the Other Endpoint

For Part 2 of the study, no additional analysis is planned.

4.2.8.6 Subgroup Analyses of the Other Endpoint

For Part 2 of the study, no subgroup analysis is planned.

4.2.9 Other Endpoint: Time to perceived onset of effect of study medication working post PT027 as compared to PT007 given following mannitol challenge 1 completion and Time to perceived onset of effect of study medication working post PT027 as compared to PT007 given following mannitol challenge 2 completion.

4.2.9.1 Definition

Participants will be asked a single perceived onset effect question "Can you feel your study medication working?" repeatedly (Kaiser et al 2018). The question will be repeated at time-points as specified in the CSP Schedule of Activities in Table 1 and Table 3 and will be repeated after each intervention administration only if the prior response has been "No" (ie, until the participant confirms "yes").

Time to perceived onset of effect of study medication working post-mannitol challenge is an exploratory endpoint for Part 2 data analysis. This is to compare the onset of effect therapeutic benefit between PT027 and PT007.

Time to perceived onset of effect of study medication working post-mannitol challenge will be compared between PT027 and PT007 post challenge 1 and post challenge 2.

4.2.9.2 Derivations

Time to perceived onset of effect will be calculated as the time to the first timepoint where the participant answers "yes" to the question "Can you feel your study medication working?" These will be considered as events in the analysis. Question will be asked first at time 3 minutes and again until the first "yes" is reported post-mannitol challenge 1 and at time 493 minutes post-mannitol challenge 2 and again until the first "yes" is reported.

If the participant never answers "yes" to the question, then their time will be set to time of the last available questionnaire and the participant will be censored in the analysis.

4.2.9.3 Primary Analysis of Other Endpoint

Time to perceived onset of effect of study medication post-mannitol challenge 1 and 2 will be presented using descriptive statistics by treatment arm. Additionally, number of subjects who perceived onset of effect of study medication will be summarised by time and treatment arm. Timepoints 3, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60 min post-mannitol challenge 1 and 493, 495, 500, 515, 520, 525, 530, 535, 540, 545, 550, 555, 560 min post-mannitol challenge 2 will be presented.

A Kaplan-Meier figure will be produced to accompany the summary to assess the difference between the survival curves for PT027 versus PT007. The number at risk by time will be shown on the figure.

Analysis will be presented separately for Part 1 and Part 2.

4.2.9.4 Sensitivity Analyses of the Other Endpoint

For Part 2 of the study, a sensitivity analysis of the superiority comparison will be performed excluding subjects with an IPD for not receiving the first dose of IMP within 6 minutes of the final dose of mannitol challenge 1.

4.2.9.5 Additional Analyses of the Other Endpoint

For Part 2 of the study, no additional analysis is planned.

4.2.9.6 Subgroup Analyses

For Part 2 of the study, no subgroup analysis is planned.

4.2.10 Other Endpoint: Change from baseline FeNO and eosinophils over time, post-mannitol challenge

4.2.10.1 Definition

Change from baseline FeNO and eosinophils over time, post-mannitol challenge is an exploratory endpoint for Part 2 data analysis. This is to assess the impact of repetitive PT027 as compared to PT007 on airway inflammation.

Change from baseline FeNO and eosinophils over time, post-mannitol challenge will be compared between PT027 and PT007 post challenge 1 and post challenge 2.

4.2.10.2 Derivations

Visit 2 and Visit 3 will have separate FeNO and eosinophils baseline results utilizing the – 30 minutes time point.

If the -30 value is missing, baseline will be the latest non-missing value prior to the mannitol challenge ie, prior to time -10.

Change from baseline = (post-baseline value - baseline value).

4.2.10.3 Primary Analysis of Other Endpoint

FeNO and eosinophils data at timepoints -30, 480 and 550 min will be presented using descriptive statistics by treatment arm. Descriptive statistics of the change from baseline will also be presented by treatment arm.

Analysis will be presented for separately for Part 1 and 2 data, based on PP and mRS.

4.2.10.4 Additional Analyses of the Other Endpoint

For Part 2 of the study, no additional analysis is planned.

4.2.10.5 Subgroup Analyses

For Part 2 of the study, no subgroup analysis is planned.

4.2.11 Other Endpoint: The proportion of participants who are non-responders to mannitol challenge 2

4.2.11.1 Definition

The proportion of participants who are non-responders to mannitol challenge 2 is an exploratory endpoint for Part 2 data analysis. This is to assess the protective effect of PT027 relative to PT007.

The proportion of participants who are non-responders to mannitol challenge 2 will be compared between PT027 and PT007.

4.2.11.2 Derivations

At Visit 2 and 3 the proportion of participants who are non-responders to mannitol challenge 2 will be calculated.

A participant who is a non-responder to the mannitol challenge 2 is one who had <15% fall from the 0mg mannitol FEV_1 to the last spirometry FEV_1 within the respective mannitol challenge.

Proportion of participants who are non-responders to mannitol challenge 2 = number of participants who are non-responders to mannitol challenge 2 based on the PP (or mRS) / number of all participants in the PP (or mRS).

4.2.11.3 Primary Analysis of Other Endpoint

Descriptive statistics of proportion of participants who are non-responders to mannitol challenge 2 will be presented by treatment arm.

Additionally, descriptive statistics of the percentage fall from the 0mg mannitol FEV_1 to the last spirometry FEV_1 within the mannitol challenge 2 will also be presented by treatment arm in categories of responders, non-responders and total arm.

Analysis will be presented separately for Part 1 and 2 data, based on PP and mRS.

4.2.11.4 Additional Analyses of the Other Endpoint

For Part 2 of the study, no additional analysis is planned.

4.2.11.5 Subgroup Analyses

For Part 2 of the study, no subgroup analysis is planned.

4.2.12 Other Endpoint: Percentage fall in FEV_1 from baseline (-30 min) FEV_1 to post-mannitol challenge 2

4.2.12.1 Definition

Percentage fall in FEV_1 from baseline (-30 min) FEV_1 to post-mannitol challenge 2 is an exploratory endpoint for Part 2 data analysis. This is to assess the protective effect of PT207 relative to PT007 in response to a repetitive trigger of bronchoconstriction.

4.2.12.2 Derivations

FEV_1 baseline and change from baseline is defined in section 3.3.6.

Percentage fall in FEV_1 from baseline (-30 min) FEV_1 to post-mannitol challenge 2 will be derived as 100*(FEV_1 at baseline – FEV_1 at 490 min)/FEV1 at baseline (-30 min).

4.2.12.3 Primary Analysis of Other Endpoint

Percentage fall from baseline (-30 min) FEV_1 to post-mannitol challenge 2 will be analyzed fitting a linear mixed model adjusting for center, treatment, treatment sequence, baseline FEV_1, the average of the two periods baseline FEV_1 values, and period.

Analysis will be presented only for Part 2 data.

4.2.12.4 Additional Analyses of the Other Endpoint

For Part 2 of the study, no additional analysis is planned.

4.2.12.5 Subgroup Analyses

For Part 2 of the study, no subgroup analysis is planned.

4.2.13 Other Endpoint: Change from mannitol baseline in FEV_1 and percentage change from mannitol baseline in FEV_1, post-mannitol challenge 1 at each measured timepoint up to and including 480 min

4.2.13.1 Definition

Change from mannitol baseline in FEV_1 and percentage change from mannitol baseline in FEV_1, post-mannitol challenge 1 at each measured timepoint up to and including 480 min is an exploratory endpoint for Part 2 data analysis. This is to assess the lung function efficacy and sustainability of effect reversal of acute airway obstruction of PT027 compared to PT007.

4.2.13.2 Derivations

The FEV_1 result (in mL) at each measured timepoint up to and including 480 min post-mannitol challenge 1 will be used.

The mannitol baseline FEV_1 and change from baseline is defined in section 3.3.6.

Change from mannitol baseline in FEV_1 = (post-baseline FEV_1 result (in mL) - mannitol baseline FEV_1).

Percentage change from mannitol baseline in FEV_1 = 100 * (post-baseline FEV_1 result (in mL) - mannitol baseline FEV_1) / mannitol baseline FEV_1.

4.2.13.3 Primary Analysis of Other Endpoint

Descriptive statistics of Change from mannitol baseline in FEV_1 and Percentage change from mannitol baseline in FEV_1 will be presented by treatment arm.

Analysis will be presented for pooled Part 1 and 2 data.

4.2.13.4 Sensitivity Analyses of the Other Endpoint

For Part 2 of the study, a sensitivity analysis of the superiority comparison will be performed excluding subjects with an IPD for not receiving the first dose of IMP within 6 minutes of the final dose of mannitol challenge 1.

4.2.13.5 Additional Analyses of the Other Endpoint

For Part 2 of the study, no additional analysis is planned.

4.2.13.6 Subgroup Analyses

For Part 2 of the study, no subgroup analysis is planned.

4.2.14 Other Endpoint: Urinary leukotrienes, Serum cAMP, cAMP mobilizing analytes, Exploratory blood markers of inflammation, Beta receptor and corticosteroid receptor expression genetics

4.2.14.1 Definition

Urinary leukotrienes, Serum cAMP, cAMP mobilizing analytes, Exploratory blood markers of inflammation, Beta receptor and corticosteroid receptor expression genetics are exploratory endpoints for Part 2 data analysis. This is to assess the lung function efficacy and sustainability of effect reversal of acute airway obstruction of PT027 compared to PT007.

Only urinary leukotrienes are in scope of this SAP. The rest of the biomarkers data analysis will not be described within this document. Those biomarker analyses are described elsewhere (in a separate SAP for exploratory analyses – Part 2).

Urinary leukotrienes will be compared between PT027 and PT007.

4.2.14.2 Primary Analysis of Other Endpoint

Descriptive statistics of urinary leukotrienes results and change baseline will be presented by treatment arm. Timepoints -30, 150, 490 min for Part 1 and 30, 120 and 550 min for Part 2 will be considered.

Analysis will be presented separately for Part 1 and 2.

4.2.14.3 Additional Analyses of the Other Endpoint

For Part 2 of the study, no additional analysis is planned.

4.2.14.4 Subgroup Analyses

For Part 2 of the study, no subgroup analysis is planned.

4.3 Pharmacodynamic Endpoint(s)

Not applicable.

4.4 Pharmacokinetics

Not applicable.

4.5 Immunogenicity

Not applicable.

4.6 Safety Analyses

The domain safety covers exposure, adverse events, clinical laboratory, vital signs, and ECG.

Safety will be presented for the pooled Part 1 and Part 2 data, based on the Safety analysis set.

4.6.1 Exposure

4.6.1.1 Definitions and Derivations

Total actual exposure will be calculated as the number of doses administered of each drug (PT027 or PT007 as per randomization).

4.6.1.2 Presentation

Actual exposure will be listed including visit and timepoint and summarized by visit and treatment arm. Outputs will be presented based on the safety analysis set.

4.6.2 Adverse Events

4.6.2.1 Definitions and Derivations

Adverse Events (AEs) will be summarized for analysis according to the treatment arm being taken at the time of the onset date of the AE as shown in Table 6.

Treatment Emergent Adverse Events (TEAE) are defined as all AEs with onset date on or after the date of first dose of randomized study drug at Visit 2, and prior to the minimum of (date of last dose at Visit 3 +7 days, date of death, or date of study withdrawal + 7 days).

Table 6 Classification of AE to Treatment Arm using Onset Date

Phase	Participants receiving PT027-PT007	Participants receiving PT007-PT027
Screening (prior to the open-label)	Assign AE To Screening Period (prior to receiving PT007) if: Both AE onset date and Visit 1 date are same and Action Taken with study drug is "NOT APPLICABLE"	
Visit 1	Assign AE To Open-label PT007 if: Both AE start onset and Visit 1 date are same and Action Taken with study drug is not "NOT APPLICABLE" or date of Open-label PT007 administration date < AE onset date < date of first dose of randomized treatment at Visit 2 (PT027 or PT007)	
Visit 2	Assign AE To PT027 if: Date of first dose of PT027 at Visit 2 ≤ AE onset date < minimum (date of first dose of PT007 at Visit 3, date of death, date of study withdrawal)	Assign AE To PT007 if: Date of first dose of PT007 at Visit 2 ≤ AE onset date < minimum (date of first dose of PT027 at Visit 3, date of death, date of study withdrawal)
Visit 3	Assign AE To PT007 if: Date of first dose of PT007 at Visit 3 ≤ AE onset date ≤ minimum of (date of last dose of PT007 +7 days, date of death, date of study withdrawal)	Assign AE To PT027 if: Date of first dose of PT027 at Visit 3 ≤ AE onset date ≤ minimum of (date of last dose of PT027 +7 days, date of death, date of study withdrawal)

Rules for imputing AE start/stop dates which are partially missing can be found in Appendix A: Imputation Rules for Missing or Partially Missing dates associated with Prior Medications, Concomitant Medications, Procedures and Adverse Events. Partially missing start/stop dates will appear as such in the participant data listings but will be imputed to permit proper tabulation of AE data.

AEs will be coded using the same MedDRA version as for Part 1, released for execution by AstraZeneca/designee. If an AE still has missing intensity, causality or seriousness after

data querying, the following ordering will be used to define "worst" for tabulating participants with more than 1 AE within the category being summarized:

- Intensity: Missing < Mild < Moderate < Severe
- Causality: Missing < No < Yes
- Seriousness: Missing < No < Yes

4.6.2.2 Presentation

Treatment emergent adverse events will be presented for each treatment group by system organ class and preferred term covering number and percentage of participants reporting at least one event and number of events where appropriate.

An overview of TEAEs will be presented by treatment arm (PT027 and PT007): the number and percentage of participants with any TEAE, TEAEs with outcome of death, treatment-emergent serious adverse events (TESAEs), and TEAEs leading to discontinuation of IMP.

TEAEs will also be summarized by SOC, PT and intensity/severity and separately, by causality/ relatedness (as determined by the investigator). Should a participant report the same PT/SOC within multiple intensity/severity or causality/relatedness categories, the participant's worst occurrence (most severe/related) will be tabulated as described in 4.6.2.1.

Key participant information will be presented for participants with TEAEs with outcome of death, serious TEAEs, and TEAEs leading to discontinuation of IMP.

A listing of all AE for the safety analysis set will cover details for each individual AE.

4.6.3 Laboratory assessment

Laboratory parameters will be presented for each treatment group. Summary statistics for continuous variables cover n, mean, SD, minimum, Q1, median, Q3, and maximum. Frequency tables and shift tables cover number and percentage of participants in the respective category.

For each scheduled post-baseline visit, descriptive statistics for all clinical chemistry and hematology parameters will be presented for observed values and change from baseline. A shift table will present laboratory status including abnormality (eg, low, normal, high) from baseline to worst post-baseline. Elevation in liver parameters for assessment of Hy's Law will be done and reported appropriately if potential cases have been identified during the course of the study.

A frequency table for urinalysis presents number of participants reporting at least one treatment emergent increase in baseline category. A shift table for urinalysis will present the baseline assessment against the maximum on-treatment category.

Supportive laboratory listings will cover observed values and changes from baseline for each individual participant as well as abnormalities.

4.6.4 Vital signs

Vital sign parameters will be presented for each treatment group. Summary statistics for continuous variables cover n, mean, SD, minimum, Q1, median, Q3, and maximum. Frequency tables and shift tables cover number and percentage of participants in the respective category.

Baseline and change from baseline is defined in Section 3.3.6. For each scheduled post-baseline visit, descriptive statistics for all vital sign parameters will be presented for observed values and change from baseline.

A shift table will present vital sign status including abnormality (clinically significant, clinically not significant) from baseline to maximum on-treatment value.

Supportive vital sign listings cover observed values and changes from baseline as well as abnormalities.

For the calculation of the maximum post-baseline result, unscheduled, as well as scheduled post-dose assessments will be considered. Table 7 will be used to define vital sign ranges (low, normal or high).

Table 7 Vital sign ranges

Parameter	Low Range	Normal Range	High Range
Systolic blood pressure (mmHg)	<90	90-140	>140
Diastolic blood pressure (mmHg)	<60	60-90	>90
Sitting pulse (bpm)	<60	60-100	>100
Sitting respiration rate (breaths/min)	<12	12-20	>20
Peripheral Oxygen saturation (%)	<95	95-100	>100

4.6.5 Electrocardiogram

Electrocardiogram parameters will be presented for each treatment group. Summary statistics for continuous variables cover n, mean, SD, minimum, Q1, median, Q3, and maximum. Frequency tables and shift tables cover number and percentage of participants in

the respective category. The (uncorrected) QT interval will be corrected according to the Fridericia's formula.

For each scheduled post-baseline assessment, descriptive statistics for all ECG parameters will be presented for observed values and change from baseline. For QTcF, a frequency table will present number of participants with values exceeding thresholds of 450 ms, 480 ms, and 500 ms at any time during the treatment and number of participants with changes from baseline in QTcF exceeding 30 ms, 60 ms, and 90 ms at any time during the treatment.

A table will present the interpretation of the ECG reading (normal, abnormal - clinically not significant, abnormal – clinically significant) at baseline and for each scheduled post-baseline visit, including shifts in interpretation as compared to baseline.

Supportive ECG listings will cover observed values for each individual participant.

4.6.6 Other Safety Assessments - Spirometry

4.6.6.1 Definitions and Derivations

Spirometry will be performed at each visit and will capture FEV_1, FVC and FEV_1/FVC. For safety evaluation, the FEV_1 baseline as described in section 3.3.6 will be used for Visit 2 and 3, along with the latest pre-dose measurement at Visit 1 for the Visit 1 baseline. Change from each visits baseline will be calculated as described in section 3.3.6.

4.6.6.2 Presentations

For each scheduled visit and timepoint, descriptive statistics (n, mean, SD, minimum, Q1, median, Q3 and max) will be presented for both the observed values and for the change from baseline at each visit.

Additionally, individual combined FEV_1 [L] values will be plotted versus time by treatment groups including all of the assessments. Arithmetic mean (± SD) and mean change from baseline (± SD) versus time will be plotted as well. Plots will be presented by treatment groups, with post-mannitol challenge 1 and 2 combined on one figure, additionally figures post-mannitol challenge 1 only will be presented separately. Plots will be provided only for Part 2.

5 INTERIM ANALYSIS

No interim analysis has been planned for Part 2 of this study.

6 REFERENCES

Kaiser et al 2018 Kaiser H et al. Onset of effect of budesonide and formoterol administered via one pressurized metered-dose inhaler in patients with asthma previously treated with inhaled corticosteroids. Ann Allergy Asthma Immunol. 2008 Sep;101(3):295-303

Kenward et al 2010 Kenward M.G. and Roger J.H. 2010 The use of baseline covariates in crossover studies. Biostatistics 2010 11(1): 1-17

7 APPENDIX

7.1 Appendix A: Imputation Rules for Missing or Partially Missing dates associated with Prior Medications, Concomitant Medications, Procedures and Adverse Events

The date of first dose of study intervention is defined in section 3.3.1. Prior/Concomitant Medication or Procedures will follow the same rules as described below for AEs.

For missing AE start dates, the following will be applied:

- Missing day only: Impute the 1st of the month unless the month is the same as the month of the first dose of study intervention then impute first dose of study intervention date after randomization.
- Missing day and month only: Impute 1st January unless the year is the same as the first dose of study intervention then impute first dose of study intervention date.
- Completely missing date: Impute first dose of study intervention date unless the end date of the AE suggests it could have started prior to this, in which case impute the 1st of January of the same year as the end date of the AE.

When imputing a start date, ensure that the new imputed date is sensible e.g., prior to the end date of the AE.

For missing stop dates of AEs, the following will be applied:

- Missing day only: Impute the last day of the month unless the month is the same as month of last dose of study intervention then impute last dose of study intervention date.

- Missing day and month only: Impute 31st December unless year is the same as last dose of study intervention date then impute last dose of study intervention date.

- Completely missing: If an AE has a completely missing end date, then it will be treated as ongoing. Flags will be retained in the database indicating where any programmatic imputation has been applied, and in such cases, any durations would not be calculated.

7.2 Appendix B: Linear Mixed Effects Model SAS Code

```
proc mixed data = inputd;
  class subjid center trtn (ref = 'PT007') trtseq period
  Model chg = center trtn trtseq base avg_base period
  Random subjid(trtseq);
  Lsmeans trtn/ diff cl alpha = 0.05;
run;
quit;
```

Where:
center = center identifier
trtn = PT027 or PT007 representing the treatment arm
trtseq = Treatment sequence (AB or BA corresponding to PT027 followed by PT007 or vice versa)
period = Visit 2 or Visit 3
subjid = participant ID
chg = Change from mannitol baseline FEV_1 AUC0-60 min post-mannitol challenge 1
base = mannitol baseline FEV_1 values as described in section 3.3.6
avg_base = average of the two periods mannitol baseline FEV_1 values

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