STATISTICAL ANALYSIS PLAN
Clinical Study Report

Protocol Title:	A Randomized, Double-blind, Placebo-controlled, 3-period Crossover Study to Evaluate the Effects of Repeated Doses of Inhaled TD-8236 and Impact on Airway Responses Following Allergen Challenge in Patients with Asthma
Protocol Number:	0178
Compound Number:	TD-8236
Short Title:	Effect of inhaled TD-8236 on allergen-induced asthmatic response
Sponsor Name:	Theravance Biopharma Ireland Limited
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Regulatory Agency Identifier Number(s)

EuDraCT No.	2019-002915-24

This study will be conducted in compliance with Good Clinical Practice.

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SIGNATURE PAGE

TD-8236

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LIST OF ABBREVIATIONS

Table 1: List of Abbreviations

Abbreviation	Term
AE	adverse event
AUC	area under curve
AUC(3-))H	AUC 3 to 8 Hours
AUC(0-2)H	AUC 0 to 2 Hours
AU(0-8)H	AUC 0 to 8 hours
ACQ	Asthma Control Questionnaire
BMI	body mass index
CSR	clinical study report
EAR	Early asthmatic response
ECG	electrocardiogram
FEV	Forced expiratory volume
ITT	intent-to-treat
HR	heart rate
LAR	Late asthmatic response
LOD	Limit of detection
LS	Least Squares
LSM	Least Squares Mean
MedDRA	Medical Dictionary For Regulatory Activities Terminology
NA	Not Applicable
PP	Per Protocol Population
SD	Standard Deviation
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SOC	System Organ Class
TEAE	Treatment-emergent adverse event

SAP VERSION HISTORY

[redacted]

1. INTRODUCTION

This statistical analysis plan (SAP) provides comprehensive and detailed descriptions of the statistical analyses of the efficacy and safety data as outlined and specified in the final protocol of study 0178 for TD-8236.

This study is a randomized, double-blind, placebo-controlled, three-period, six-sequence, complete-block, crossover study to characterize two doses of inhaled TD-8236 compared to placebo in subjects with mild asthma and a known response to an allergen challenge.

The SAPs for [redacted] will be prepared separately.

Specifications of tables, figures, and data listings are contained in a separate document.

1.1. Objectives and Endpoints

1.1.1. Primary Objective(s) and Endpoint(s)

As stated in the protocol, the primary objective of the study is as follows:

- Characterize the late asthmatic response (LAR) in terms of area under the Forced Expiratory Volume (FEV_1) curve after inhaled allergen challenge in mild asthmatic subjects receiving 14 days of TD-8236 or placebo

The primary endpoint is:

- Area under the curve (AUC) of change from baseline FEV_1 from 3 to 8 hours after inhaled allergen challenge (FEV_1 AUC Change (3-8)H) at Day 14

1.1.2. Secondary Objective(s) and Endpoint(s)

The secondary objectives of the study are as follows:

- Characterize the late asthmatic response (LAR) in terms of maximum decline in FEV_1 and area under the percent change FEV_1 curve after inhaled allergen challenge in mild asthmatic subjects receiving 14 days of TD-8236 or placebo
- Assess the pharmacokinetics (PK) of TD-8236 in subjects with asthma
- Evaluate the safety and tolerability of inhaled TD-8236 administered for 14 days in subjects with mild asthma

The secondary endpoint(s) are:

- AUC of percent change from baseline in FEV_1 from 3 to 8 hours after inhaled allergen challenge (FEV_1 AUC % Change (3-8)H) at Day 14
- Maximum (Max) decline in FEV_1 from 3 to 8 hours after inhaled allergen challenge (FEV_1 Max Decline(3-8)H) at Day 14
- Max percent decline in FEV_1 from 3 to 8 hours after inhaled allergen challenge at (FEV_1 Max % Decline(3-8)H) at Day 14

- Safety and tolerability of TD-8236 over 14 days of dosing, including frequency and severity of adverse events (AEs) vital signs, clinical laboratory evaluations, and 12-lead electrocardiogram (ECG) changes from baseline

1.1.3. Exploratory Objective(s) and Endpoint(s)

[redacted]

[redacted]

1.2. Study Design

This is a randomized, double-blind, placebo-controlled, three-period, six-sequence, complete-block, crossover study to characterize two doses of inhaled TD-8236 compared to placebo in subjects with mild asthma and a known response to an allergen challenge.

Subjects will undergo an allergen challenge test at Screening as described by [redacted] Following a Screening period of up to 35 days, subjects who meet inclusion and exclusion criteria will be randomized to receive each of three treatments (TD-8236 [redacted] TD-8236 [redacted] or placebo) in one of the three treatment periods separated by a washout [redacted] between the last dose of the previous period and first dose of the next period.

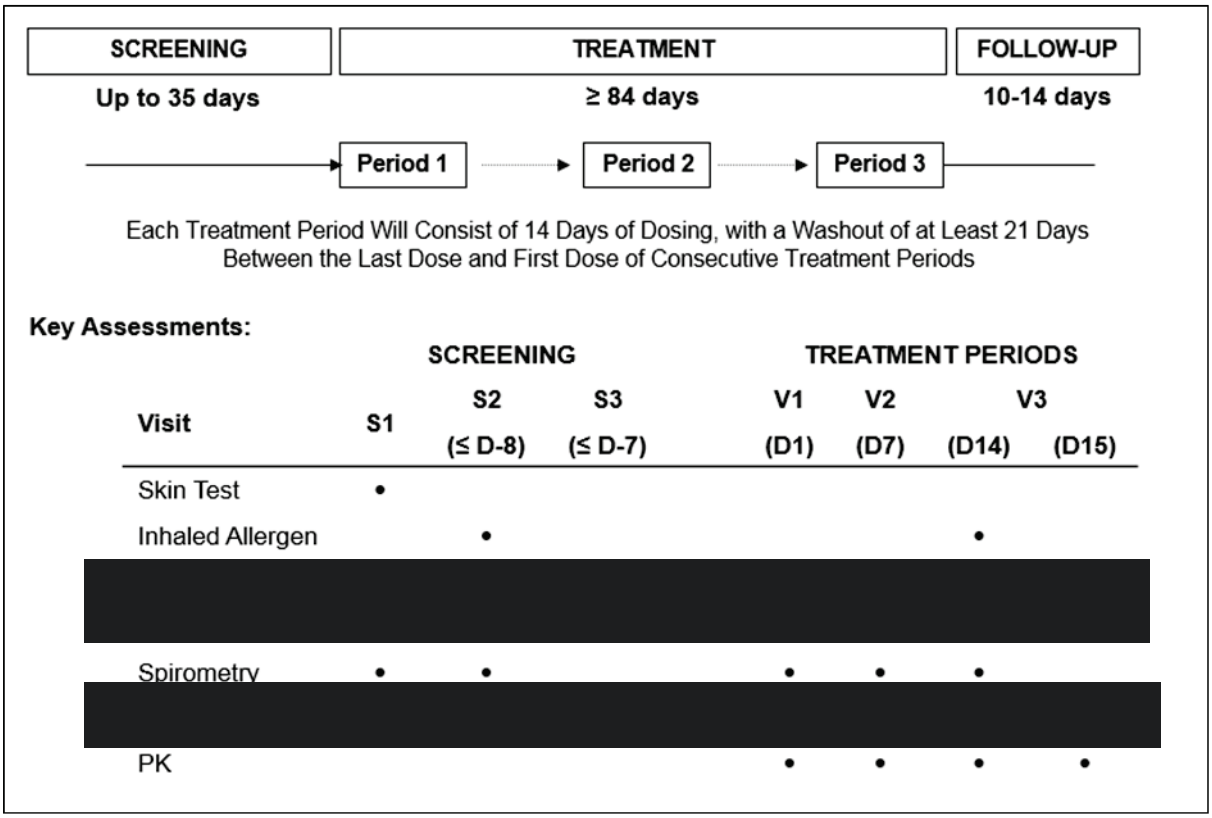
Each treatment period will consist of 14 days of treatment with one dose level of TD-8236 or placebo (Figure 1). Subjects will return to the clinic on Day 7 (±1 day) of each period for safety and pharmacodynamic (PD) assessments as well as reconciliation and dispensing of study drug. Subjects will be in-residence at the clinic for Day 14 of each period. At the investigator's discretion subjects may be discharged the evening of Day 14 and return to the clinic the morning of Day 15.

[redacted]

Subjects will undergo an allergen challenge test 1 hour after the last dose (Day 14) in each period.

[redacted] and LAR will be assessed between 3 and 8 hours after allergen challenge.

Figure 1: Study Schema



Note: S = Screening. For Spirometry, the assessment for entry criteria is done on S1 and pre-dose before the allergen challenge on S2. [redacted]
PK = Pharmacokinetics.

1.3. Treatment Assignment

Study drug refers to placebo and 2 doses of TD-8236, as follows:

- TD-8236 [redacted]
- TD-8236 [redacted]
- Placebo [redacted]

[redacted]

Table 3: Dosing Regimens

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

1.4. Schedule of Assessments

The schedule of assessments is presented in Table 4.

Table 4: Schedule of Study Procedures

Study Procedures [a] Days →	Screening			Treatment Phase (for each Treatment Period (TP))				FU/ ET
	S1 (-35 to -8)[b]	S2 (-35 to -8)[b]	S3 (S2+1)	1	7 (±1)	14	15	+14 (±2)[c]
General Procedures								
Informed consent	X							
Inclusion/exclusion criteria	X	X		X [d]				
Demographics and Medical history	X							
Height	X							
Weight	X			X [e]				X
Inhaler training and PIF testing with In-check [f]	X			X [e]	X [e]	X [e]		
Study drug reconciliation					X	X		
Study drug dispensing				X	X			
TD-8236 administration[g]				X	X	X		
Subject Dosing Diary [h]				X	X	X		
Safety Evaluations								
Physical examination [i]	X							X
Symptom-driven physical examination [j]		X	X	X	X	X	X	
12Lead safety ECG [k]	X			X [e]	X [e]	X [e]		X
Vital Signs (pulse, BP, temp, RR)	X			X [e]	X [e]	X [e]		X
Hematology, serum chemistry, and urinalysis [l]	X			X [e]	X [e]	X [e]	X	X
Immunophenotyping (NK, T, and B cell counts)				X [e]		X [e]		X
Coagulation	X			X		X		X
Serum FSH (postmenopausal females only) [m]	X							
Urine or serum pregnancy test (WOCBP only) [n]	X	X		X		X		X
Urine drug test	X			X				
Urine cotinine test	X			X				
Breath or urine alcohol screen	X			X				
HIV/Hepatitis test	X							
Tuberculosis (Quantiferon) test	X							
AE monitoring	X	X	X	X	X	X	X	X
Concomitant medication monitoring	X	X	X	X	X	X	X	X

Study Procedures [a] Days →	Screening			Treatment Phase (for each Treatment Period (TP))				FU/ ET
	S1 (-35 to -8)[b]	S2 (-35 to -8)[b]	S3 (S2+1)	1	7 (±1)	14	15	+14 (±2)[c]
Salbutamol dispensing [o]	X	X	X	X	X	X	X	
Pharmacokinetics / Pharmacodynamics								
Allergen skin test	X							
Inhaled allergen challenge		X				X [p]		
Spirometry [q]	X			X	X	X		X
[redacted]								
[redacted]								
[redacted]								
[redacted]								
[redacted]								
[redacted]								
Other Procedures								
Study visits	X	X [v]	X [v]	X	X			X
Residence in the CRU						X [w]	X [w]	

S = Screening.

a. For details on Procedures, refer to Section 6 of protocol.

b. Screening procedures (including informed consent) may be performed over more than 1 day. Repeats of study procedures are permitted on the day and/or on another day during screening or treatment period (as appropriate) at the discretion of the PI(s). Additionally. screening visits S1 and S2 may be combined into 1 visit day and in such case procedures scheduled for both visits are only needed to be performed once (e.g., FeNO, pregnancy test).

c. The followup visit is performed 14 days + following the last dose of study medication in Treatment Period 3 only

d. Inclusion & exclusion criteria for initial study entry are evaluated only in Treatment Period 1; for subsequent periods assessment for study continuation should be evaluated as described in Section 6.6 of protocol.

e. To be perform prior to dosing

f. At Screening and pre-dose on Day 1 of each Treatment Period, the correct use of the inhaler will be explained to the subject and each subject will train with an empty capsule, and PIF will be measured using an [redacted] Generation of sufficient PIF at all sessions will be considered a requirement for participation/continuation in the study (Section 4, item 7 of protocol).

g. Study drug will be administered at the CRU by study staff following any pre-dose procedures associated with the Study Visit.

h. Subject will be provided a daily dosing diary on Day 1 and will be reviewed by study staff and reissued to the subject on Day 7 and reviewed again and collected by study staff on Day 14 of each period. Any deviations or missed doses will be noted in the source documents.

i. Full PE is required at the Screening Visit. A symptom-driven PE will be conducted at other scheduled time points as described below.

j. Symptom-driven physical examinations will be performed at the PI's or designee's discretion, as needed, and at other times to focus on evaluation of AEs throughout the study, if any, including any emergence of symptoms or worsening of any abnormalities identified, but found by the PI to be non-clinically significant, on the screening or check-in examination(s) since the last study day or physical exam. Symptom-driven examinations should be performed for any AE or existing AE that increases in severity or frequency. Refer to Section 7 of the protocol for more information.

k. At screening, triplicate 12-lead ECG will be conducted. At all other scheduled time points, safety 12-lead ECGs will be conducted as a single 12-lead ECG.

l. Samples for serum chemistry (screening and Day 1 of each period only) will be obtained following a fast of at least 9 hours (water permitted), however, in case of dropouts or rechecks, subjects are not required to have fasted for 9 hours ahead of the serum chemistry sample draw.

m. To be conducted for postmenopausal women who did not undergo any sterilization procedures as detailed in Section 6.3.10 of protocol and where postmenopausal state is in question.

n. Serum pregnancy test will be conducted at Screening and at the follow-up visit. Urine pregnancy test will be conducted prior to each allergen challenge, and predose on Days 1 and 14 of each Treatment Period.

o. Salbutamol will be dispensed at screening and can be dispensed at other times during the study as required.

p. The inhaled allergen challenge will be performed 1-hour post-dose on Day 14.

q. Spirometry testing will be performed prior to the dose, as applicable. Spirometry that is conducted as part of other study procedures, e.g., bronchial challenges and sputum induction, will be covered in a separate Allergen Challenge Study manual.

[redacted]

u. Blood for PK assessments will be collected predose and 0.5, 1, 2, 4, 6, 8, and 24 hours following the dose on Day 14 in each Treatment Period. Note Day 14 Post dose PK samples are to be taken on the timepoint with the exception that if a post-allergen FEV_1 coincides with a PK collection (e.g., 1 hr sample) the FEV_1 measurement will be prioritized; blood sample collection for PK analysis will be performed at the earliest convenience either before or after the FEV_1 (within allowed permitted windows).

v. Subjects will be discharged home after the screening allergen challenge and will return the following day for S3 procedures. Subjects may be required to stay overnight on S2 visit if required to do so for reasons of safety at the discretion of the investigator.

w. Subjects will be resident overnight on Day 14 and will be discharged on Day 15. Subjects may be allowed to be discharged on the evening of Day 14 and return to the clinic on the morning of Day 15 at the discretion of the investigator.

1.5. Sample Size Determination

[redacted]

2. ANALYSIS SETS

The analysis sets and the treatment assignments that will be used for each type of analysis are shown in Table 5.

Table 5: Analysis Sets

Analysis Set	Definition	Treatment Assignment
Randomized	Subjects who are randomized to study treatments	Randomized treatment
Intent-to-Treat (ITT)	Subjects who are randomized to study treatments and who received at least one dose of study drug.	Randomized treatment
Safety	All treated subjects	Treatment received
Pharmacodynamic (PD)	Subjects who are randomized to study treatment, who received at least one dose of study drug, and who have at least one baseline and postbaseline PD measurement (e.g., [redacted],	Treatment received
Per-Protocol (PP; membership to be determined before unblinding)	Intent-to-Treat subjects with no protocol deviations during the study that would affect the primary efficacy analyses.	Treatment received

3. STATISTICAL ANALYSES

3.1. General Considerations

- The primary analysis will be performed after the database is locked and the randomization schedule is released.
- All efficacy analyses will be performed using the ITT analysis set. Safety analyses will be performed using the Safety analysis set. Analysis for [redacted]
- Primary and secondary efficacy analyses will also be performed using the PP analysis set.
- Change from baseline will be computed as the postbaseline value minus the baseline value, unless otherwise indicated.
- [redacted]

3.1.1. Visit Windows

No visit window will be used in summaries of efficacy points. The analyses will be based on the nominal CRF visits.

Safety events (AEs, Concomitant Medications) occurring in washout periods are assigned to the previous treatment period as follows:

Table 6: Safety Analysis Windows

Actual Period	Nominal Period	Start Date/Time	Stop Date/time
	Screening	Informed consent	Period 1 first dose/time
1	Treatment 1	Period 1 first dose date/time	Period 2 first dose date/time
2	Washout 1	Included with Period 1	
3	Treatment 2	Period 2 first dose date/time	Period 3 first dose date/time
4	Washout 2	Included with Period 2	
5	Treatment 3	Period 3 first dose date/time	Last Follow-up
6	Follow-Up	Included with Period 3	

3.2. Study Subjects

3.2.1. Enrollment

Number and percentage of subjects enrolled in the study will be summarized by treatment group and total for each investigator by frequency distributions, sorted by highest enroller first. The randomized analysis set is used for this summary.

3.2.2. Subject Disposition and Completion Status

For subject study status, number and percentage of subjects in each of the following categories will be presented by treatment group and total.

- Randomized subjects
- Randomized and treated
- Completed the study
- Discontinued from the study
- Reasons discontinued from the study

For all categories, the percentages will be calculated using the number of randomized patients as the denominator.

Reasons for not completing the study will be presented based on eCRF categories, including AEs, lost to follow-up, physician decision, pregnancy, protocol violation, study termination by sponsor, withdrawal by subject, other.

A listing of subject disposition will include analysis set flags (ITT, Safety (Yes/No)), date the informed consent form was signed, dates of first and last dose of study drug, primary reason for discontinuation of study treatment, study completion status, and date of last contact.

A listing of subject eligibility (inclusion or exclusion criteria exceptions) will be provided.

3.2.3. Demographic and Baseline Characteristics

Demographic and baseline characteristics including age, sex, race, ethnicity, height, weight and body mass index (BMI) will be summarized in total and by treatment group. Age will be analyzed with descriptive statistics. Sex, race and ethnicity will be analyzed with frequency distribution. The analyses will be based on ITT and Safety populations, separately.

Subject listings for demographic and baseline characteristics will be provided.

3.2.4. Protocol Deviations

Unique subjects reporting major protocol deviations that have significant impact on primary efficacy analyses (major analysis protocol deviations) will be summarized overall and by treatment group for the ITT analysis set.

Major analysis protocol deviations that will exclude subjects from the PP analysis set include:

[redacted]

A summary of protocol deviations by site and treatment group based on randomized analysis set will be provided.

A subject listing with all protocol deviations identified prior to database lock will be provided. In addition, a subject listing with newly identified nonmajor protocol deviations identified during site closeout visits following database lock will be provided as applicable. Moreover, a listing of all major analysis protocol deviations will be provided. All subject listings will be based on the randomized analysis set.

Subjects with major analysis protocol deviations will be identified before unblinding.

3.2.5. Medical History

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 23 or newer.

The number and percentage of subjects with medical history in each system organ class and preferred term will be summarized by treatment group using the Safety analysis set.

3.2.6. Prior/Concomitant Medications

Prior medications include all medications taken prior to the first dose of study drug in treatment period 1, regardless of medication end date. Concomitant medications, prescribed and over-the-counter, encompass all nonstudy medicinal products that the subject was taking prior to the Day 1 visit of each respective treatment period that are ongoing at the visit, in addition to all medications that have a start date on or after the first dose of study drug of each respective treatment period.

Recorded prior and concomitant medication names will be mapped according to the World Health Organization Drug Dictionary (WHODD) for this study with Theravance review and approval of the mappings. The 1Q2020 C3 or later version of the WHODD will be used.

Prior and concomitant medication will be tabulated by major drug class, minor drug class, and generic name for treatment group and for all safety subjects, separately. The frequency (number and percentages) of subjects who have taken each medication will be tabulated for each treatment regimen.

3.2.7. Allergen Skin Test

A subject listing displaying the allergen solution received ([redacted]) and test results (i.e., positive, negative, Not Applicable (NA)) will be provided.

3.3. Primary Endpoint(s) Analysis

3.3.1. Definition of Primary Endpoint

[redacted]

3.3.2. Statistical Hypotheses

[redacted]

[redacted]

3.3.3. Main Analysis Methods

[redacted]

3.3.3.1. Missing Data Handling

3.3.3.1.1. AUC and Weighted Mean Spirometry Endpoints

[redacted]

3.3.4. Sensitivity Analyses

[redacted]

3.3.5. Supplementary Analyses

[redacted]

[redacted]

Line Graphs

[redacted]

3.3.5.1. Carryover Effect

[redacted]

[redacted]

3.4. Secondary Endpoint(s) Analyses

3.4.1. Definition of Secondary Endpoint(s)

Table 7: Definition of Secondary Endpoints

Secondary Endpoints	Definition
AUC of percent change from baseline in FEV_1 from 3 to 8 hours after inhaled allergen challenge at Day 14	[redacted]
Max decline in FEV_1 from 3 to 8 hours after inhaled allergen challenge at Day 14	[redacted]
Max percent decline in FEV_1 from 3 to 8 hours after inhaled allergen challenge at Day 14	[redacted]

Note: AUC: Area under curve, WM: Weighted Mean, Max: Maximum.

3.4.2. Statistical Hypotheses

[redacted]

3.4.3. Main Analysis Methods

[redacted]

3.4.3.1. Missing Data Handling

[redacted]

3.4.4. Sensitivity Analyses

3.4.5. Supplementary Analyses

[redacted]

3.5. Exploratory Endpoint(s) Analyses

3.5.1. Definition of Exploratory Endpoints

Table 8: Definition of Exploratory Endpoints

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

Table 8: Definition of Exploratory Endpoints (Continued)

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

[redacted]

3.5.2. Main Analytical Approach

3.5.2.1. [redacted]

[redacted]

3.5.2.2. [redacted]

[redacted]

3.5.2.3. [redacted]

[redacted]

3.5.2.4. Missing Data Handling

[redacted]

3.5.3. Other Analyses

[redacted]

3.6. Safety Analyses

For all safety analyses, the safety analysis population will be used. Safety variables to be summarized include vital signs, AEs, clinical laboratory results (hematology, chemistry, and urinalysis), and Fridericia's-corrected QT interval (QTcF) from standard safety digital ECGs. Vital signs will be summarized in terms of observed values and changes from baseline.

Safety events (labs and AEs) occurring in washout periods are assigned to the previous treatment periods.

3.6.1. Extent of Exposure

A subject's data for the extent of exposure (i.e., duration of study medication within each period) to study drug will be summarized by treatment using the 8-point descriptive summary.

Dosing information for individual subjects will be listed.

3.6.2. Treatment Compliance

The rate of study drug compliance within each period is calculated as 0[((total number of capsules dispense within each period – total number of capsules returned within each period)/(Days of exposure in each period x 3)]x 100.

The rate of study drug compliance will be summarized with descriptive statistics as well as the categories of ≥ 120%, 100% to < 120%, ≥ 90% to < 100%, ≥ 80% to <90% and < 80%, and will be presented by treatment groups for the Safety Set using frequency distributions.

3.6.3. Adverse Events

Recorded adverse events will be mapped according to the MedDRA thesaurus with Theravance review and approval of the mappings. MedDRA version 23.0 or later will be used.

An AE will be considered a treatment-emergent adverse event (TEAE) if the AE began or worsened (increased in severity or became serious) on or after the date (and time, if known) of the first dose of study drug in each period.

- Adverse events with a start date/time after the follow-up period are nontreatment-emergent.
- If more than one AE with the same preferred term is reported before the first dose of investigational product, the AE with the greatest severity will be used as the

benchmark for comparison with the AEs occurring during the study coded to that preferred term.

An AE will be considered a treatment-emergent serious AE (TESAE) if it is a TEAE that additionally meets any SAE criteria.

The following TEAE summaries will be generated:

- Overall Summary of Adverse Events
  - The overall summary of adverse events will include the following summary lines: (any AE, any AE related to Study Drug, Moderate or severe AEs, Moderate or severe AEs related to Study Drug, Serious AEs, Serious AEs related to Study Drug, AEs leading to discontinuation, Deaths during Study).
- TEAEs by primary System Organ Class (SOC) and Preferred Term (PT)
- Drug-Related TEAEs by SOC and PT
- TEAEs by SOC, PT and Severity
- Drug-related TEAEs by SOC, PT and Severity
- Moderate or Severe TEAEs by SOC and PT
- Moderate or Severe Drug-Related TEAEs by SOC and PT
- Serious TEAEs by SOC and PT
- Drug-related Serious TEAEs by SOC and PT
- Adverse events leading to premature study drug discontinuation
- TEAEs by PT with Overall Frequency ≥ 10% of overall population

3.6.3.1. Adverse Events of Special Interest

Not applicable.

3.6.4. Additional Safety Assessments

3.6.4.1. Clinical Laboratory Parameters

Laboratory data (hematology, serum chemistry, immunophenotyping and coagulation) will be summarized in terms of observed values, changes from baseline for each period, and changes from baseline for each period relative to normal ranges (e.g., shifts from normal to abnormal high/low). Listings will flag laboratory values that are outside of normal range.

3.6.4.2. Vital Signs

Descriptive statistics for vital signs (systolic and diastolic blood pressures, heart rate, respiratory rate, temperature and weight) and changes from baseline values (predose of each period) at each visit by treatment group.

Vital signs data will be summarized in terms of counts and percentages within appropriately defined categories (Table 9). For each nominal time point, vital signs will be summarized in

terms of observed values and changes from baseline (predose) for each period. Marked abnormalities as defined in Table 9 will be flagged in the listing.

Table 9: Outlier Threshold in Vital Signs

Heart Rate (bpm)	Systolic Blood Pressure (mm Hg)	Diastolic Blood Pressure (mm Hg)
< 40	< 85	< 45
> 110	> 160	> 100

3.6.4.3. Electrocardiogram

Descriptive statistics for ECG parameters (heart rate, PR interval, QRS interval, QT interval, and QTcF) and changes from baseline values at each assessment time point to the end of study will be presented by treatment group.

Subjects without a postbaseline measurement for a given treatment period will be excluded from the summary statistics (i.e., denominator of the summary statistic) for that time point.

All recorded values by central reader at ECG core lab for the standard 12-lead ECG parameters will be presented in a by-subject listing.

Categorical Analyses

The number (percentage) of subjects with ECG values in the ranges shown in Table 10 will be presented in a by-visit categorical summary.

Table 10: ECG Interval Categories

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

Table 10: ECG Interval Categories (Continued)

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

[redacted]

[redacted]

3.7. Other Analyses

3.7.1. FEV_1 at Screening

Subject listings displaying FEV_1 endpoints at Screening will be provided as described in Table 11.

In addition, the time course of FEV_1 change from prechallenge baseline during the 8-hour serial measurements postchallenge will be presented using line graphs. LS mean with 95% confidence intervals (CIs) will be shown on the y-axis and scheduled time points following allergen inhalation (in hours) will be shown on the x-axis.

Table 11: Definition of FEV_1 Endpoints at Screening

Endpoints at Screening	Definition
AUC of change from baseline FEV_1 3 to 8 hours after inhaled allergen challenge at Screening	[redacted]
AUC of percent change from baseline in FEV_1 3 to 8 hours after inhaled allergen challenge at Screening	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

3.7.2. Subgroup Analyses

The following efficacy endpoints will be analyzed by study site and type of allergen used [redacted] using descriptive statistics.

Table 12: Endpoints for Subgroup Analyses

Endpoints
WM AUC of change from baseline FEV_1 3 to 8 hours after inhaled allergen challenge at Day 14
WM AUC of percent change from baseline in FEV_1 3 to 8 hours after inhaled allergen challenge at Day 14
Maximum decline from baseline in FEV_1 3 to 8 hours after inhaled allergen challenge at Day 14
Maximum percent decline from baseline in FEV_1 3 to 8 hours after inhaled allergen challenge at Day 14
[redacted]
[redacted]
[redacted]
[redacted]
[redacted]
[redacted]

Note: AUC: Area under curve, WM: Weighted Mean, Max: Maximum.

3.7.3. COVID-19 Data

A subject listing with results of COVID-19 testing will be provided.

3.7.4. Screening Laboratory Data

Subject listings for screening laboratory data related to eligibility (i.e., urine drug test, breath or urine alcohol screen, HIV/Hepatitis test, Tuberculosis Test) will be provided.

3.7.5. Pregnancy Test Results

The screening laboratory data related to eligibility (i.e., serum follicle-stimulating hormone (for postmenopausal female subjects only, if postmenopausal status is in question)), urine or serum pregnancy (for Women of childbearing potential only) will be provided.

3.8. Interim Analyses

[redacted]

3.8.1. Data Monitoring Committee

Not applicable.

4. REFERENCES

1. Taylor DA, Harris JG, O'Connor BJ. Comparison of incremental and bolus dose inhaled allergen challenge in asthmatic patients. Clin Exp Allergy. 2000 Jan; 30(1):56-63.

5. SUPPORTING DOCUMENTATION

5.1. Appendix 1: Changes to Protocol-Planned Analyses

- [redacted]

5.2. Appendix 2: Data Conventions and Transformations

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