CLINICAL STUDY PROTOCOL

Study 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
Study Short Title:	Effect of inhaled TD-8236 on allergen-induced asthmatic response
Sponsor Study No.:	0178
Date:	05 November 2019. [redacted]
Test Product:	TD-8236
EudraCT No.:	2019-002915-24
Sponsor:	Theravance Biopharma Ireland Limited Connaught House 1 Burlington Road Dublin 4 D04 C5Y6 Ireland
Clinical Study Director:	[redacted] Theravance Biopharma US, Inc. Telephone: [redacted] Email: [redacted]

This study will be conducted according to the principles of Good Clinical Practice.

CONFIDENTIAL

PROTOCOL SYNOPSIS

Study Number and Title: Study 0178: 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

Study Short Title: Effect of inhaled TD-8236 on allergen-induced asthmatic response

Estimated Number of Study Centers and Countries or Regions: Up to [redacted] in the United Kingdom

Background and Rationale:

[redacted]

Objectives:

The primary objective of the study is as follows:

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

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 plasma pharmacokinetics (PK) of TD-8236 in subjects with mild asthma
- Evaluate the safety and tolerability of inhaled TD-8236 administered for 14 days in subjects with mild asthma

[redacted]

Study Design: This will be a randomized, double-blind, placebo-controlled, three-period, six-sequence, complete-block, cross-over 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]. Briefly, the challenge at Screening will consist of [redacted] At the investigator's discretion, a subject may be required to stay resident in the research unit the evening following the Screening allergen challenge assessment.

Once a subject meets inclusion and exclusion criteria and following a Screening period of up to 35 days, the subject will be randomized to one of six treatment sequences. Within each treatment sequence, subjects will receive each of three treatments in one of three treatment

periods separated by a washout of at least 21 days 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. Subjects will return to the clinic on Day 7 (±1 day) of each period for safety assessments, trough PK and PD sampling, as well as reconciliation and dispensing of study drug. Subjects will be in-residence at the clinic for Day 14 of each period, including an overnight stay to allow for serial PK sampling through 24 hours after the last dose. 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. The cumulative dose of allergen required to achieve a successful response at Screening will be administered as a bolus during the Treatment Periods. This bolus dose may be modified by the investigator for reasons of subject safety. The modified bolus dose should thereafter remain consistent throughout the Treatment Periods.

Duration of Study Participation:

Individual subject participation will require approximately 20 weeks, as follows:

- up to 35 days for Screening,
- 14 days of treatment in Period 1,
- at least 21 days Washout from Period 1,
- 14 days in Period 2,
- at least 21 days Washout from Period 2,
- 14 days in Period 3,
- and 14 days of Follow-up.

This will include 3 occasions of a one-night- residency in the clinic occurring during screening and on Day 14 of each study period following the allergen challenge procedures. The decision whether a subject remains resident in the clinic on these occasions will be at the discretion of the investigator on a case by case basis. The subjects will be discharged following the Screening allergen challenge and will return the following day for Screening Visit 3 procedures (or if necessary, at investigator discretion, the subject may stay overnight at the research center and the subject will be discharged after Visit 3 procedures are completed). The actual length of individual subject participation will be determined by the length of the Screening and washout periods.

Number of Subjects per Group: Approximately 21 subjects will be enrolled, targeting at least 18 subjects to complete the study, consisting of a crossover design with 3 periods containing 2 active doses of TD-8236 and a matching placebo.

Study Population:

Men and women ages 18 to 65 inclusive who have stable, mild asthma and are a responder to dual inhaled bronchial allergen challenge and who meet other eligibility criteria as described below.

Inclusion Criteria:

1. Male or female, 18 to 65 years of age, inclusive, at Screening.
2. BMI ≥ 18.0 and ≤ 35.0 kg/m^2 at Screening and weighs ≥ 50 kg at Screening.
3. Documented physician-diagnosed asthma for ≥ 4 months prior to Screening.
4. Pre-bronchodilator FEV_1 ≥ 70% predicted at Screening and prior to Day 1 dosing in Treatment Period 1.
5. Documented allergy to at least one common allergen as confirmed by the skin prick test, with wheal diameter ≥3mm greater than the negative control. Historical data up to one year prior to screening, can be used.
6. Subject should be a dual responder to inhaled bronchial allergen challenges as manifested by positive allergen-induced early (EAR) and late airway bronchoconstriction (LAR) at screening, defined as follows:
   - [redacted]
   - [redacted]
7. Able to correctly use the Dry Powder Inhaler (DPI) and to generate sufficient peak inspiratory flow rate (PIFR) (at least 40 L/min) using the [redacted] device at Screening and prior to dosing on Day 1 of Treatment Period 1.
8. Subject has no clinically significant abnormalities as determined by the PI in the results of laboratory evaluations at Screening, including:
   - Liver function tests (i.e., ALT, AST, ALP, GGT, and bilirubin) ≤ upper limit of normal or deemed medically acceptable at the discretion of the PI and Sponsor's Medical Monitor
   - Absolute lymphocyte counts within normal range or should be deemed medically acceptable at the discretion of the PI and Sponsor's Medical Monitor
9. Subject must have a negative [redacted] result at Screening.
10. Pregnancy concerns:
    - Female subjects must be either of non-childbearing potential or if of childbearing potential use a highly effective birth control method (Section 6.3.10) during the study and through 30 days after the last dose of TD-8236.

- Male subjects (with partners of child-bearing potential) must use acceptable contraception (Section 6.3.10) during the study and through 30 days after the last dose of study medication
- Male subjects must agree not to donate semen during the study and for 30 days after the last dose of study medication

11. Understands the study procedures in the ICF and is willing and able to comply with the protocol-defined study procedures and expectations.

Exclusion Criteria:

1. Is mentally or legally incapacitated at the time of the Screening visit, prior to dosing on Day 1 of Treatment Period 1, or expected during the conduct of the study that in the opinion of the PI or designee indicates the subjects is inappropriate for the study.
2. Have abnormal ECG measurements at Screening (any of the three individual ECG measurements) or prior to dosing on Day 1 of Treatment Period 1 indicating:
   - Second or third-degree AV block
   - QRS >120 msec
   - QTcF >450 msec (male) or >460 msec (female)
   - PR interval >220 msec
3. Subject has a known personal or family history of congenital long QT syndrome or known family history of sudden death.
4. Subject has a supine resting bradycardia (pulse <40 bpm) or a supine resting tachycardia (pulse >100 bpm) at Screening or prior to dosing on Day 1 of Treatment Period 1.
5. Lung disease other than stable, mild asthma; worsening of asthma that requires a change in asthma therapy or is deemed clinically significant by the PI or Sponsor Medical Monitor.
6. History of clinically significant hypotensive episodes or symptoms of fainting, dizziness, or light-headedness.
7. History of lymphoma, leukemia, or other types of malignancy (except for completely resected squamous or basal cell cancer.
8. Any signs of respiratory tract infection within 6 weeks of screening or prior to dosing on Day 1 of Treatment Period 1 that are deemed clinically significant by the PI or Sponsor Medical Monitor.
9. Subject who has a current bacterial, parasitic, fungal, or viral infection; any infection requiring hospitalization or intravenous antibiotics within 6 months prior to Screening; any infection requiring oral or topical antimicrobial treatment within 2 weeks prior to Screening or prior to dosing on Day 1 of Treatment Period 1; a history of more than one episode of herpes zoster infection.

10. Any evidence of current or previous clinically significant disease (with the exception of stable, mild asthma): e.g., uncontrolled hyperthyroidism, uncontrolled diabetes mellitus or other endocrine disease; clinically relevant hepatic impairment; clinically relevant renal impairment; cardiovascular disease (e.g., uncontrolled coronary artery disease, uncontrolled hypertension, uncontrolled hypercholesterolemia); uncontrolled gastrointestinal disease (e.g., active peptic ulcer); neurological disease (including transient ischemic attack (TIA), stroke, seizure disorder, or behavioral disturbances); uncontrolled hematological disease; uncontrolled autoimmune disorders, or other which may impact the feasibility of the results of the study according to the judgment of the PI or Sponsor Medical Monitor.
11. History of life-threatening asthma, defined as an asthma episode that required intubation and/or was associated with hypercapnoea, respiratory arrest and/or hypoxic seizures or hospitalization (including emergency room visits) for the treatment of asthma within 3 months of Screening, or have been hospitalized or have attended emergency room visits for asthma more than twice in last 12 months.
12. Subject has any condition of the oro-laryngeal or respiratory tract (including, but not limited to, prior surgery) that could possibly affect drug administration, deposition, or absorption, or ability to perform lung function measurements (spirometry), inhaled allergen challenge, or sputum induction, as determined by the PI or Sponsor Medical Monitor.
13. Positive urine or breath alcohol results at Screening or Day 1 of Treatment Period 1, or history or presence of alcoholism within the past 2 years prior to dosing on Day 1 of Treatment Period 1.
14. Alcohol consumption of >21 units per week for males or >14 units per week for females, with one unit = ½ pint beer, a 25 mL shot of 40% spirit or a 125 mL glass of wine depending on type.
15. Positive urine drugs of abuse test result (unless in the opinion of the investigator this can be explained by the patient's current medications) at Screening or prior to dosing on Day 1 of Treatment Period 1.
16. Positive urine cotinine test result at Screening or prior to dosing on Day 1 in Treatment Period 1.
17. Uses or has used tobacco or nicotine-containing products (e.g., cigarettes, cigars, vaping devices, chewing tobacco, snuff, patches etc.) within 6 months prior to Screening, or has history of >5 pack-years.
18. History of hypersensitivity to drugs, latex allergy, band aids, adhesive dressing, or medical tape, with a clinically significant reaction as determined by the PI or designee.
19. History of serious adverse reaction, severe hypersensitivity or allergy to any drug or in any other circumstance (e.g., anaphylaxis).
20. Female subjects with a positive pregnancy test at Screening or prior to dosing on Day 1 of Treatment Period 1, or who are breastfeeding or lactating.

21. Subjects who have had a live viral vaccine (e.g., MMR, varicella zoster, herpes zoster, oral polio virus, FluMist, attenuated typhoid fever vaccine, or attenuated rotavirus vaccine) within 8 weeks prior to Screening and/or are unwilling to avoid live viral vaccines for until at-least 8 weeks following completion of the final study visit.
22. Positive results at screening for HIV, HAV antibodies (anti-HAV: both IgG and IgM positive, IgG positive in the absence of IgM positive is acceptable), HBsAg, or HCV.
23. Subject who has a history of latent or active tuberculosis.
24. Unable to refrain from or anticipates the use of any drug including prescription and non-prescription medications, herbal remedies, or vitamin supplements beginning 14 days prior to Screening and throughout the study.
    - Paracetamol (up to 1 g per 24 hours) will be allowed from Screening and throughout the study.
    - Hormone replacement therapy will be allowed.
    - Medication listed as part of acceptable birth control methods will be allowed (Section 6.4).
    - Oral and inhaled corticosteroids (ICS) (or ICS/long acting beta agonist) are prohibited for 6 weeks prior to Screening and throughout the study.
    - A short-acting inhaled beta agonist may be used as required, with the exception of 8 hours before lung function assessments.
    - Stable treatment (same medication and dose) of medications for at least 3 months prior to dosing on Day 1 of Treatment Period 1 (other than prohibited medications that the PI and Sponsor consider to neither compromise subject safety or not to affect study data) may be permitted on a case-by-case basis.
25. Subject has dietary restrictions incompatible with the diet that can be provided by the study site, in the opinion of the PI or designee.
26. Donation of blood (≥400 mL) or plasma, or significant blood loss within 56 days prior to dosing on Day 1 of Treatment Period 1.
27. Donation of bone marrow within the last 6 months prior to dosing on Day 1 of Treatment Period 1.
28. Subject has previously received TD-8236.
29. Participation in another clinical study (including medical device study) within 60 days, or < 5.5 half-lives of the last administration of an investigational drug, whichever is longer. The 60-day / 5.5 half-lives window will be derived from the date of the last dosing in the previous study to Day 1 of the current study.
30. Exposure to biologic therapies (approved or experimental, e.g., monoclonal antibodies, allergen immune therapy) within the last 6 months prior to dosing on Day 1 of Treatment Period 1.

Test Product, Dose, and Route of Administration; Regimen; Duration of Treatment:

TD-8236 [redacted] administered by inhalation in the morning daily for 14 days

TD-8236 [redacted] administered by inhalation in the morning daily for 14 days.

Reference Therapy, Dose, and Route of Administration; Regimen; Duration of Treatment:

Placebo [redacted] administered by inhalation in the morning daily for 14 days.

Study Evaluations:

Safety Assessments

Subject safety will be assessed throughout the study using standard measures, including vital signs, 12-lead ECGs, blood and urine safety laboratory tests, physical examinations, concomitant medication usage, and adverse event (AE) monitoring.

Pharmacokinetic Assessments

- Day 14 blood samples for assessment of TD-8236 plasma concentrations will be collected pre-dose, 0.5, 1, 2, 4, 8, 12 and 24 hours post-dose
- Only pre-dose blood samples will be collected on Day 1 and Day 7 for assessment of TD-8236 plasma concentrations
- [redacted]

Pharmacodynamic Assessments

- Inhaled allergen challenge
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]

Statistical Methods:

Sample Size

[redacted]

[redacted]

Study Endpoints

The primary endpoint(s) of this study are:

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

The key secondary endpoint(s) are:

- AUC of percentage change from baseline in FEV_1 from 3 to 8 hours after inhaled allergen challenge at Day 14
- Maximum decline in FEV_1 from 3 to 8 hours after inhaled allergen challenge at Day 14
- Maximum percentage decline in FEV_1 from 3 to 8 hours after inhaled allergen challenge at Day 14
- Day 14 plasma PK parameters of TD-8236 in subjects with mild asthma
- Safety and tolerability of TD-8236 over 14 days of dosing, including frequency and severity of adverse events, vital signs, clinical laboratory evaluations, and 12-lead ECG changes from baseline

[redacted]

[redacted]

Analysis

All safety data will be presented in listings. Descriptive summary tables will be provided for treatment-emergent adverse events, clinical laboratory evaluations, vital signs, 12-lead ECG parameters, and concomitant medications.

[redacted]

SCHEDULE OF STUDY PROCEDURES

Table 1: Schedule of Study Procedures—Daily Assessments Screening through End of Study

Study Procedures [a]	Screening			Treatment Phase (for each Treatment Period [TP])				FU/ ET
Days →	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							
Symptom-driven physical examination [j]		X	X	X	X	X	X	X
12-Lead 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

Table 1: Schedule of Study Procedures—Daily Assessments Screening through End of Study

Study Procedures [a]	**Screening**			**Treatment Phase (for each Treatment Period [TP])**				**FU/ ET**
Days →	**S1 (-35 to -8)**[b]	**S2 (-35 to -8)**[b]	**S3 (S2+1)**	**1**	**7 (±1)**	**14**	**15**	**+14 (±2)**[c]
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
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]								

Table 1: Schedule of Study Procedures—Daily Assessments Screening through End of Study

Study Procedures [a]	Screening			Treatment Phase (for each Treatment Period [TP])				FU/ ET
Days →	S1 (-35 to -8)[b]	S2 (-35 to -8)[b]	S3 (S2+1)	1	7 (±1)	14	15	+14 (±2)[c]
[redacted]								
[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]	

a For details on Procedures, refer to Section 6.

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 a 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 +/- 2 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.

e To be perform prior to dosing

f At Screening and pre-dose on Day 1, Day 7 (± 1 day) and Day 14 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 4.1, item 7).

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 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 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.

r [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.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Description
AE	adverse event
ACQ-5	Asthma control questionnaire – 5 question version
ALP	alkaline phosphatase
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
ATS	American Thoracic Society
AUC	area under the curve
BMI	body mass index
BP	blood pressure
CFR	(United States) Code of Federal Regulations
CS	clinically significant
CRF	case report form
CRU	clinical research unit
DPI	dry powder inhaler
EAR	early asthmatic response
ECG	electrocardiogram
ECP	eosinophilic cationic protein
EDC	electronic data capture
ERS	European Respiratory Society
FEV1	forced expiratory volume in 1 minute
FeNO	fractional exhaled nitric oxide
FVC	forced vital capacity
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
HAV	hepatitis A virus
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HED	human equivalent dose

Abbreviation	Description
HIV	human immunodeficiency virus
HR	heart rate
IB	Investigator's Brochure
IgG	immunoglobulin G
IgM	immunoglobulin M
ICF	informed consent form
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICS	inhaled corticosteriod
IEC	Independent Ethics Committee
IH	inhalation
INR	international normalization ratio
IRB	Institutional Review Board
ITT	Intent-to-treat
IV	intravenous
JAK	Janus kinase
JAK/STAT	Janus kinase and signal transducers and activators of transcription pathway
LAR	late asthmatic response
MAD	multiple ascending dose
MedDRA	Medical Dictionary for Regulatory Activities (MedDRA®)
MMR	measles, mumps and rubella
NCS	not clinically significant
NK	natural killer
NOAEL	no-observed-adverse-effect-level
NSAIDS	non-steroidal anti-inflammatory drugs
OA	oral aspiration
PD	pharmacodynamic(s)
PE	physical examination
PI	principal investigator

Abbreviation	Description
PIFR	peak inspiratory flow rate
PIF	peak inspiratory flow
PK	pharmacokinetic(s)
PO	orally
PRO	patient reported outcome
QD	once a day, daily
QTc	corrected QT interval
REC	Research Ethics Committee
SAD	single ascending dose
SAE	serious adverse event
SC	subcutaneous
SOP	standard operating procedure
STAT	signal transducers and activators of transcription
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
TIA	transient ischemic attack
TYK2	tyrosine kinase 2
WOCBP	woman of child-bearing potential

1. INTRODUCTION

1.1. Background and Rationale

[redacted]

1.2. Nonclinical Profile

A review of the nonclinical profile of TD-8236 can be found in the current version of the TD-8236 Investigator's Brochure (IB).[6] The following is a brief summary of the pertinent findings.

1.2.1. Pharmacology

[redacted]

[redacted]

1.2.2. Toxicology

[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]

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

1.3. Clinical Experience

[redacted]

1.4. Risks and Benefits

TD-8236 is potentially effective for the treatment of asthma. However, since this study will be evaluating multiple doses of limited duration in subjects with well-controlled, mild asthma, no health benefits are anticipated. An indirect health benefit to the subjects enrolled in this study is the free medical tests received at screening and during the study.

Preliminary results from the completed portions of the ongoing Phase 1 study with TD-8236 in healthy subjects and subjects with mild asthma have demonstrated TD-8236 to be generally well tolerated without clinically significant effects on laboratory parameters or adverse event incidence [redacted]

[redacted]

Pregnancy prevention procedures and avoidance of semen donation for 30 days after the last dose of TD-8236 should be followed by all male subjects, based on the same rationale and conservative timeframe required for females prior to obtaining human PK data.

Subjects receiving repeated oral doses of other compounds in this pharmacological class (e.g., tofacitinib, a systemically available JAK inhibitor) on a longer term basis have exhibited alterations in cholesterol, liver function tests, decreased red blood cell and white blood cell subset (neutrophils and lymphocytes) counts, and risk of infection, cancer, intestinal perforation, headache, diarrhea, rhinorrhea, nasopharyngitis, and sore throat.[10] Given the low systemic

exposures of TD-8236 measured in the Phase 1 study relative to the systemic exposure of tofacitinib published in the literature, these risks are anticipated to be minimal with TD-8236. In clinical studies to date, no sign of systemic immunosuppression or adverse effect on lipid parameters has been observed in laboratory evaluation or in adverse events reported in healthy subjects receiving single doses up to 4500 µg or mild asthmatic subjects dosed up to 4000 µg per day for 7 days.

The potential for findings in human subjects will be carefully assessed in this study with an anticipated treatment duration of three periods of 14 days each. Assessments include scheduled and symptom-driven physical exam (including temperature measurements), spirometry testing, and monitoring of complete blood cell counts with differential (including Natural Killer [NK] cells as a marker for systemic immunosuppression). The safety monitoring practices employed by this protocol (i.e., 12-lead ECG, vital signs, spirometry, clinical laboratory tests, AE questioning, and physical examinations) are adequate to protect the subjects' safety and should detect all expected treatment-emergent AEs.

The approximate volume of blood planned for collection from each subject over the course of the study (Section 6.2), presents no undue risk to the subjects nor does the possibility of collection of additional blood in the event an indwelling cannula (for wasting to ensure clean sample) is utilized and the possibility of additional blood for recheck of safety labs if deemed necessary by the PI.

Subjects must consent to four inhaled allergen challenge and eight induced sputum procedures.

1.4.1.1. Risks of Allergen Challenge

When conducted by experienced investigators in the appropriate setting, bronchial allergen challenge is safe and well-tolerated in the patient population proposed for this study. However, because there is a risk of inducing severe, acute bronchoconstriction or anaphylaxis,[11] bronchial allergen challenge will not be performed on subjects with severe or unstable asthma. The procedures produce a reaction that might be similar to a mild asthma attack such as cough, chest tightness and/or wheezing. Many subjects do not have any symptoms at all (typically 70 to 80%). Symptoms (if they occur) are mild, last only a few minutes, and disappear following the inhalation of a bronchodilator medication (e.g., salbutamol), which will be administered to the subject. The test is carried out in such a way that the danger of a severe asthmatic reaction is minimized. However, there is still a rare possibility (less than 1 in 1000) of severe narrowing of the subject's airways. The subject will be carefully monitored and if this occurs, the subject will be immediately treated. The cumulative dose of allergen required to achieve a successful response at Screening will be administered as a bolus during the treatment periods. This bolus dose may be modified by the PI for reasons of subject safety. The "new" bolus dose should thereafter remain consistent throughout the Treatment Periods.

1.4.1.2. Risks of Lung Function Tests Including [redacted]

[redacted]

1.4.1.3. Risks of Skin Prick Testing

The skin prick test is performed at screening. The test is used to confirm the subject' sensitivity to allergen used in the bronchial challenges. The subject may experience discomfort from the skin testing procedures. The discomfort may result from being pricked with a needle and/or from the itching or swelling that may occur at the site of the skin test. This usually goes away within 30 to 60 minutes after the skin test, although it sometimes lasts 24 to 48 hours. Hives (itchy rash) and wheezing may occur in rare cases. Symptoms such as itching all over the body, sneezing, and eyelid swelling occur in 1 per 10,000 people. Any such reaction will be treated if necessary.

2. OBJECTIVES

The primary objective of the study is as follows:

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

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 exploratory objectives of the study are as follows:

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

3. STUDY DESIGN

3.1. Overview

This will be a randomized, double-blind, placebo-controlled, three-period, six-sequence, complete-block, cross-over 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] Briefly, the challenge at Screening will consist of [redacted] administered as a bolus for subsequent challenges during the treatment periods. At the investigator's discretion a subject may be required to stay resident in the research unit the evening following the screening allergen challenge assessment.

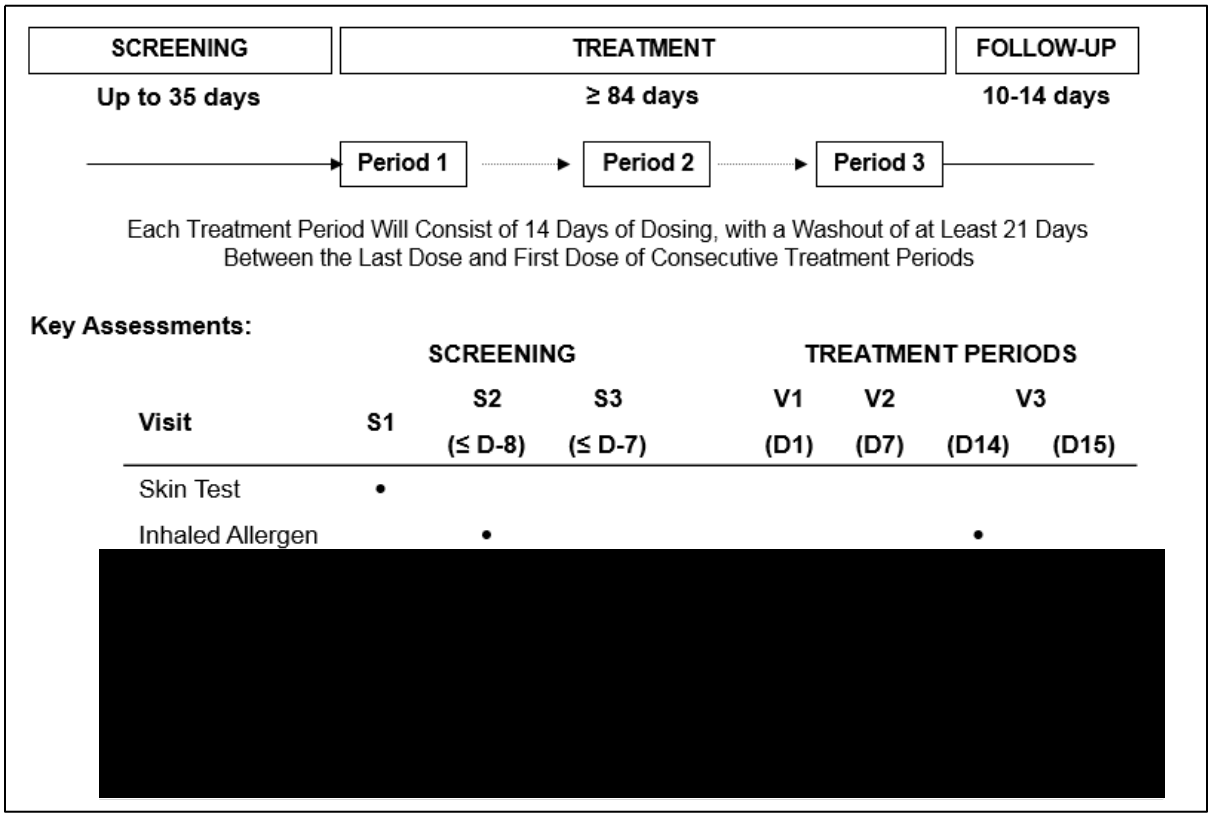
Once a subject meets inclusion and exclusion criteria, and following a Screening period of up to 35 days, the subject will be randomized to one of six treatment sequences. Within each treatment sequence, subjects will receive each of three treatments in one of three treatment periods separated by a washout of at least 21 days 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. Subjects will return to the clinic on Day 7 (±1 day) of each period for safety assessments, trough PK and PD sampling, as well as reconciliation and dispensing of study drug. Subjects will be in-residence at the clinic for Day 14 of each period, including an overnight stay to allow for serial PK sampling through 24 hours after the last dose. 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. The cumulative dose of allergen required to achieve a successful response at Screening will be administered as a bolus during the Treatment Periods. This bolus dose may be modified by the investigator for reasons of subject safety. The modified bolus dose should thereafter remain consistent throughout the Treatment Periods.

Figure 1: Study Design Schematic



3.2. Rationale for Study Design

[redacted]

[redacted]

expected to provide important guidance toward the next stage of TD-8236 development.

3.3. Selection of Doses and Duration of Treatment

[redacted]

3.4. Study Endpoints

The primary endpoint(s) of this study are:

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

The secondary endpoint(s) are:

- AUC of percentage change from baseline in FEV_1 from 3 to 8 hours after inhaled allergen challenge at Day 14
- Maximum decline in FEV_1 from 3 to 8 hours after inhaled allergen challenge at Day 14
- Maximum percentage decline in FEV_1 from 3 to 8 hours after inhaled allergen challenge at Day 14
- Day 14 plasma PK parameters of TD-8236 in subjects with mild asthma
- Safety and tolerability of TD-8236 over 14 days of dosing, including frequency and severity of adverse events, vital signs, clinical laboratory evaluations, and 12-lead ECG changes from baseline

The exploratory endpoint(s) are:

[redacted]

3.5. Minimization of Bias

This study is a randomized, double-blind, placebo-controlled, three-period, six-sequence, complete-block, cross-over study. The study subjects, site investigators, and site study staff will be blinded throughout the duration of the study (except for the unblinded site pharmacist and/or designee[s] and Sponsor's drug supply representative, unblinded pharmacy monitor and PK bioanalyst).

A computerized randomization scheme will be created and shall be considered blinded (as per the following). The randomization is available only to the clinical research unit (CRU) pharmacy staff that is preparing the drug who will not be involved in any other aspect of the study including administration of the drug. It will not be made available to the subjects, site(s) PI(s), or members of the staff responsible for the monitoring and evaluation of safety assessments, except as described in Section 3.5.1.

3.5.1. Blinding

TD-8236 and placebo capsules will be of the same shape, size, and color to ensure that the blind is maintained. Also, subjects who are randomized to receive placebo will receive the equivalent number of capsules as those randomized to receive TD-8236. A subject's treatment assignment will only be unblinded when knowledge of the treatment is essential for the further clinical management of the subject on this study or may potentially impact the safety of subjects currently enrolled or subjects in subsequent enrollment. Unblinding at the study site for any other reason will be considered a protocol deviation. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's treatment assignment is warranted. Participant safety must always be the first consideration in making such a determination.

Sponsor Drug Safety personnel may independently unblind cases for expedited reporting of suspected unexpected serious adverse reactions (SUSARs). With these exceptions, Sponsor personnel involved in the conduct of the study, data cleaning, or data analysis will remain blinded to study treatment assignments until the database has been locked for final analysis. To facilitate PK analysis, the analyst at the PK bioanalytical lab may be unblinded however any PK data provided to the sponsor for analysis will be provided in a blinded fashion (i.e., PK data cannot be linked to an individual subject).

3.5.2. Procedures for Breaking the Blind Prior to Study Completion

One set of sealed envelopes containing the randomization code will be supplied to the PI or designee at each study site at the start of the study.

If breaking the blind is required because of a medical emergency, the treatment identity would be revealed by the PI or designee for that subject only. In the event that the emergency is one in which it appears that the other subjects may be at imminent risk, the blind may be broken for all subjects dosed at that dose level. The unblinding will be properly documented in the study file. The responsibility to break the blind resides solely with the PI (or designee), however, it is requested that the PI or designee will make every effort to contact the Medical Monitor or designee to notify him/her of the medical emergency and the breaking of the blind as soon as it is

practicable, granting that these efforts should not stall or delay the unblinding of trial subject treatment in emergency situations.

In all cases where the code is broken, the PI or designee should record the date and reason for code breaking.

At the end of the study, envelopes will be retained according to site procedures.

3.5.3. Revealing of Randomization

In the absence of a medical emergency, the blinded randomization for this study will not be revealed to any blinded person, as defined in Section 3.5.1, until all data are entered in the database, edits checks are performed, queries closed, eCRFs signed by the PI(s), and the database is officially locked.

3.5.4. Treatment Assignment

Each subject will be assigned a unique subject identification number upon consent. Subjects who complete the study screening assessments and meet all the eligibility criteria will be assigned a unique randomization number prior to the first dose, different from the screening number, and will receive the corresponding product according to a randomization scheme.

[redacted]

4. STUDY POPULATION

Subjects who do not qualify based on a reversible condition or mild concurrent illness may be re-screened after the condition is resolved. Screening procedures 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).

Re-screening will be allowed for a subject who could not be dosed within the permitted screening window for any reason, or as a pre-treatment failure (i.e., subject has not been treated); the reason for failure must be temporary and expected to resolve. If re-screened, the subject must be re-consented.

4.1. Inclusion Criteria

Subjects who meet the following criteria will be eligible for study enrollment:

Inclusion Criteria:

1. Male or female, 18 to 65 years of age, inclusive, at Screening.
2. Body mass index (BMI) ≥ 18.0 and ≤ 35.0 kg/m^2 at Screening and weighs ≥ 50 kg at Screening.
3. Documented physician-diagnosed asthma for ≥ 4 months prior to Screening.
4. Pre-bronchodilator FEV_1 ≥ 70% predicted at Screening and prior to Day 1 dosing in Treatment Period 1.
5. Documented allergy to at least one common allergen as confirmed by the skin prick test, with wheal diameter ≥3mm greater than the negative control. Historical data up to one year can be used.
6. Subject should be a dual responder to inhaled bronchial allergen challenges as manifested by positive allergen-induced early (EAR) and late airway bronchoconstriction (LAR) at screening, defined as follows:
   - [redacted]
   - [redacted]
7. Able to correctly use the dry powder inhaler (DPI) and to generate sufficient peak inspiratory flow rate (PIFR) (at least 40 L/min) using the [redacted] at Screening and prior to dosing on Day 1 of Treatment Period 1.
8. Subject has no clinically significant abnormalities as determined by the PI in the results of laboratory evaluations at Screening, including:
   - Liver function tests (i.e., ALT, AST, ALP, GGT, and bilirubin) ≤ upper limit of normal or deemed medically acceptable at the discretion of the PI and Sponsor's Medical Monitor

- Absolute lymphocyte counts within normal range or should be deemed medically acceptable at the discretion of the PI and Sponsor's Medical Monitor

9. Subject must have a negative [redacted] Test result at Screening.
10. Pregnancy concerns:
    - Female subjects must be either of non-childbearing potential or if of childbearing potential use a highly effective birth control method (Section 6.3.10) during the study and through 30 days after the last dose of TD-8236.
    - Male subjects (with partners of childbearing potential) must use acceptable contraception (Section 6.3.10) during the study and through 30 days after the last dose of study medication
    - Male subjects must agree not to donate semen during the study and for 30 days after the last dose of study medication
11. Understands the study procedures in the ICF and is willing and able to comply with the protocol-defined study procedures and expectations.

4.2. Exclusion Criteria

Subjects who satisfy any of the following criteria are not eligible for study enrollment:

Exclusion Criteria:

1. Is mentally or legally incapacitated at the time of the Screening visit, prior to dosing on Day 1 of Treatment Period 1, or expected during the conduct of the study that in the opinion of the PI or designee indicates the subjects is inappropriate for the study.
2. Have abnormal ECG measurements at Screening (any of the three individual ECG measurements) or prior to dosing on Day 1 of Treatment Period 1 indicating:
    - Second or third-degree AV block
    - QRS >120 msec
    - QTcF >450 msec (male) or >460 msec (female)
    - PR interval >220 msec
3. Subject has a known personal or family history of congenital long QT syndrome or known family history of sudden death.
4. Subject has a supine resting bradycardia (pulse <40 bpm) or a supine resting tachycardia (pulse >100 bpm) at Screening or prior to dosing on Day 1 of Treatment Period 1.
5. Lung disease other than stable, mild asthma; worsening of asthma that requires a change in asthma therapy or is deemed clinically significant by the PI or Sponsor Medical Monitor.
6. History of clinically significant hypotensive episodes or symptoms of fainting, dizziness, or light-headedness.

7. History of lymphoma, leukemia, or other types of malignancy (except for completely resected squamous or basal cell cancer).
8. Any signs of respiratory tract infection within 6 weeks of screening or prior to dosing on Day 1 of Treatment Period 1 that are deemed clinically significant by the PI or Sponsor Medical Monitor.
9. Subject who has a current bacterial, parasitic, fungal, or viral infection; any infection requiring hospitalization or intravenous antibiotics within 6 months prior to Screening; any infection requiring oral or topical antimicrobial treatment within 2 weeks prior to Screening or prior to dosing on Day 1 of Treatment Period 1; a history of more than one episode of herpes zoster infection.
10. Any evidence of current or previous clinically significant disease (with the exception of stable, mild asthma): e.g., uncontrolled hyperthyroidism, uncontrolled diabetes mellitus or other endocrine disease; clinically relevant hepatic impairment; clinically relevant renal impairment; cardiovascular disease (e.g., uncontrolled coronary artery disease, uncontrolled hypertension, uncontrolled hypercholesterolemia); uncontrolled gastrointestinal disease (e.g., active peptic ulcer); neurological disease (including transient ischemic attack (TIA), stroke, seizure disorder, or behavioral disturbances); uncontrolled hematological disease; uncontrolled autoimmune disorders, or other which may impact the feasibility of the results of the study according to the judgment of the PI or Sponsor Medical Monitor.
11. History of life-threatening asthma, defined as an asthma episode that required intubation and/or was associated with hypercapnoea, respiratory arrest and/or hypoxic seizures or hospitalization (including emergency room visits) for the treatment of asthma within 3 months of Screening, or have been hospitalized or have attended emergency room visits for asthma more than twice in last 12 months.
12. Subject has any condition of the oro-laryngeal or respiratory tract (including, but not limited to, prior surgery) that could possibly affect drug administration, deposition, or absorption, or ability to perform lung function measurements (spirometry), inhaled allergen challenge, or sputum induction, as determined by the PI or Sponsor Medical Monitor.
13. Positive urine or breath alcohol results at Screening or Day 1 of Treatment Period 1, or history or presence of alcoholism within the past 2 years prior to dosing on Day 1 of Treatment Period 1.
14. Alcohol consumption of >21 units per week for males or >14 units per week for females, with one unit = ½ pint beer, a 25 mL shot of 40% spirit or a 125 mL glass of wine depending on type.
15. Positive urine drugs of abuse test result (unless in the opinion of the investigator this can be explained by the patient's current medications) at Screening or prior to dosing on Day 1 of Treatment Period 1.
16. Positive urine cotinine test result at Screening or prior to dosing on Day 1 in Treatment Period 1.

17. Uses or has used tobacco or nicotine-containing products (e.g., cigarettes, cigars, vaping devices, chewing tobacco, snuff, patches etc.) within 6 months prior to Screening, or has history of >5 pack-years.
18. History of hypersensitivity to drugs, latex allergy, band aids, adhesive dressing, or medical tape, with a clinically significant reaction as determined by the PI or designee.
19. History of serious adverse reaction, severe hypersensitivity or allergy to any drug or in any other circumstance (e.g., anaphylaxis).
20. Female subjects with a positive pregnancy test at Screening or prior to dosing on Day 1 of Treatment Period 1, or who are breastfeeding or lactating.
21. Subjects who have had a live viral vaccine (e.g., MMR, varicella zoster, herpes zoster, oral polio virus, FluMist, attenuated typhoid fever vaccine, or attenuated rotavirus vaccine) within 8 weeks prior to Screening and/or are unwilling to avoid live viral vaccines for until at-least 8 weeks following completion of the final study visit.
22. Positive results at screening for HIV, HAV antibodies (anti-HAV: both IgG and IgM positive, IgG positive in the absence of IgM positive is acceptable), HBsAg, or HCV.
23. Subject who has a history of latent or active tuberculosis.
24. Unable to refrain from or anticipates the use of any drug including prescription and non-prescription medications, herbal remedies, or vitamin supplements beginning 14 days prior to Screening and throughout the study.
    - Paracetamol (up to 1 g per 24 hours) will be allowed from Screening and throughout the study.
    - Hormone replacement therapy will be allowed.
    - Medication listed as part of acceptable birth control methods will be allowed (Section 6.4).
    - Oral and inhaled corticosteroids (ICS) (or ICS/long acting beta agonist) are prohibited for 6 weeks prior to Screening and throughout the study.
    - A short-acting inhaled beta agonist may be used as required, with the exception of 8 hours before lung function assessments.
    - Stable treatment (same medication and dose) of medications for at least 3 months prior to randomization (other than prohibited medications that the PI and Sponsor consider to neither compromise subject safety or not to affect study data) may be permitted on a case-by-case basis.
25. Subject has dietary restrictions incompatible with the diet that can be provided by the study site, in the opinion of the PI or designee.
26. Donation of blood (≥400 mL) or plasma, or significant blood loss within 56 days prior to dosing on Day 1 of Treatment Period 1.
27. Donation of bone marrow within the last 6 months prior to dosing on Day 1 of Treatment Period 1.

28. Subject has previously received TD-8236.
29. Participation in another clinical study (including medical device study) within 60 days, or < 5.5 half-lives of the last administration of an investigational drug, whichever is longer. The 60-day / 5.5 half-lives window will be derived from the date of the last dosing in the previous study to Day 1 of the current study.
30. Exposure to biologic therapies (approved or experimental, e.g., monoclonal antibodies, allergen immune therapy) within the last 6 months prior to dosing on Day 1 of Treatment Period 1.

5. STUDY DRUGS

All study drug supplied by the Sponsor must be stored in a secure location accessible only to designated study personnel.

5.1. Description of Study Drugs

Investigational materials will be provided by the Sponsor as describe below. In addition, [redacted] dry powder inhaler (DPI) devices will be provided by the Sponsor. Further details are provided in a separate pharmacy manual.

5.1.1. TD-8236

TD-8236 capsules are prepared [redacted].

Doses of TD-8236 to be evaluated include [redacted]

TD-8236 capsules will be packaged in individual-capsule blister packs and prepared as a 7-day, multi-fold blister card with labeling that is blinded to treatment identity.

5.1.2. Placebo

Placebo capsules will match the TD-8236 capsules in size, color and shape, and will contain the same [redacted].

Placebo treatment will be administered as [redacted]

Placebo capsules will be packaged in identical packaging as the TD-8236 active drug product.

5.2. Dosage and Administration

Subjects will receive daily inhaled doses beginning Day 1 at Hour 0 through Day 14 in each period. Following the first dose, subsequent doses will be administered within ± 3 hour of the scheduled dosing time(s). Hour 0 will be defined as the beginning of first capsule inhalation in each dose administration.

The exact clock time for all doses administered in the CRU (i.e., Days 1, 7 and 14) will be recorded.

Additional information regarding study drug dispensing, administration, handling and storage will be provided in a separate pharmacy manual.

Doses may be administered without regard to timing relative to meals.

5.2.1. Training with [redacted]

[redacted]

[redacted]

5.2.2. Training with Empty Capsules

Training will be conducted prior to dosing: at Screening, pre-dose on Day 1, Day 7 (±1 day), and Day 14 (in each period). The correct use of the inhaler will be explained to the subjects and training will be performed using empty capsules identical to the ones used for the study drug administration.

The training kits will be kept at the site by the PI and will not be dispensed to the subjects.

Subject will not be enrolled if the training is not completed with success. Training evidence will be recorded in the eCRF.

5.3. Treatment Compliance

At each return visit to the clinical site, staff will review the returned study medication and will record the number of capsules used and unused in the subject's source records, including checking for any unexpected, unpierced capsules. Any missed doses will be discussed with the subject to understand the reasons for the missed doses and subject retraining will be performed as needed. Missed doses will be recorded in the eCRF.

Subjects will be required to complete a daily dosing diary recording dosing each day.

5.4. Drug Accountability and Reconciliation

The investigator or designee is responsible for maintaining accountability records for all study drug(s) received from the Sponsor, in accordance with applicable government regulations and study procedures. The accountability record will include entries for receipt, distribution or dispensing, and destruction of the material(s). Unused and expired study drugs will be disposed of in accordance with written instructions from the Sponsor.

Subjects will be instructed to return all used and unused study drug containers at each visit. Compliance with the dosing regimen will be assessed by reconciliation of used and unused study drug.

Refer to the separate pharmacy manual for more information.

6. STUDY PROCEDURES

6.1. Schedule of Study Procedures

The schedule of study procedures is summarized in Table 1.

6.2. Total Blood Volume

The total volume of blood to be drawn from each subject for [redacted]

Additional PK and/or PD samples may be added (Sections 6.3.11 and 6.3.12). Additional safety laboratory tests may be drawn, as required for safety assessments.

Sample type	Number of Time Points	Approximate Volume per Time Point * (mL)	Approximate Sample Volume Over Course of Study (mL)
Screening laboratory safety tests (including hematology, serum chemistry, serology, and coagulation), FSH (for postmenopausal female subjects only, if postmenopausal status is in question) and serum pregnancy (for WOCBP only) as applicable.	1	[redacted]	[redacted]
Tuberculosis Test ([redacted]	1	[redacted]	[redacted]
On-study hematology and serum chemistry	12	[redacted]	[redacted]
On-study coagulation	6	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
Blood for TD-8236 PK	30	[redacted]	[redacted]
Follow-up laboratory safety tests (including hematology, serum chemistry, and coagulation) and serum pregnancy (for WOCBP only) as applicable.	1	[redacted]	[redacted]
Total Blood Volume (mL)→			[redacted]

* Represents the largest collection tube that may be used for this (a smaller tube may be used).

** If additional PK analysis is necessary or if larger collection tubes are required to obtain sufficient plasma/serum for analysis, additional blood may be obtained (up to a maximum of 50 mL).

6.3. Description of Study Assessments

The Schedule of Study Procedures (Table 1) summarizes the clinical procedures to be performed at each visit. Individual clinical procedures are described in detail below. Additional evaluations/testing may be deemed necessary by the PI or designee and/or the Sponsor for reasons related to subject safety.

Safety will be determined by evaluating physical examinations, vital signs, safety 12-lead ECGs monitoring, clinical laboratory tests, and AEs as outlined in Table 1.

During the study, every effort should be made to perform study procedures as listed in the Study Schedule of Procedures (Table 1). For procedures scheduled to be performed at common times, collection of TD-8236 PK samples should be collected as close as possible to the designated time unless otherwise noted.

Any nonscheduled procedures required for urgent evaluation of safety concerns take precedence over all routine scheduled procedures.

6.3.1. Informed Consent

Before any study specific procedures or study requirements are conducted on or expected of a subject, the subject must review and sign an IEC/IRB/REC-approved informed consent form.

6.3.2. Allergen Challenge

[redacted]

6.3.3. Spirometry

Spirometry (FEV_1 and FVC) will be assessed as outlined in the Study Schedule of Procedures (Table 1) and measured using a spirometer that meets the American Thoracic Society (ATS)/European Respiratory Society (ERS) recommendations. Spirometry will be performed in accordance with [redacted]

6.3.4. Skin Prick Test

A skin prick test will be performed at screening according to the Schedule of Study Procedures (Table 1), unless historical data is available within one year of screening. Further information regarding the skin prick test and the allergen tests to be used will be covered in a separate study reference manual.

6.3.5. [redacted]

[redacted]

6.3.6. [redacted]

[redacted]

6.3.7. Safety Assessments

6.3.7.1. Physical Examination

A full physical examination will be performed as outlined in the Schedule of Study Procedures (Table 1).

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. Symptom-driven examinations may include the assessment of the following body systems: general appearance; head, ears, eyes, nose, and throat; neck; skin/dermatologic system; cardiovascular system; respiratory system; abdomen/gastrointestinal system; lymphatic system; musculoskeletal system; and nervous system.

6.3.7.2. Vital Signs

Single measurements of body temperature, respiratory rate, blood pressure (BP), and pulse, will be measured as outlined in the Schedule of Study Procedures (Table 1). Additional vital signs may be taken at any other times, if deemed necessary.

Blood pressure and pulse measurements will be performed after subjects have been resting for at least 5 minutes in the supine position. Where possible, subject position, measurement device, and arm (left versus right) should be kept consistent throughout the study, except when subjects are placed in a supine or semi-reclined position because of AEs (e.g., nausea, dizziness) or if deemed necessary by the PI or designee.

Any vital may be repeated at the discretion of the PI or designee. Collection of additional vital sign measurements for routine safety monitoring at additional time points or study days may be performed at the discretion of the PI or designee, or upon request by the Sponsor.

6.3.7.3. 12-Lead ECGs

Electrocardiograms (ECG) will be performed as outlined in the Study Schedule of Procedures (Table 1).

A subject will be withdrawn from the study by the Investigator or his/her designee if, in their medical judgment, safety 12-lead ECG findings are present which make continued study participation not in the subject's best interest.

At the Screening visit, triplicate 12-lead ECG will be performed. Triplicate 12-lead ECG recordings will be taken within a 5-minute time window. Single 12-lead ECGs will be performed at all other times.

ECGs will be taken following resting for at least 10 minutes in the supine position in a quiet environment. Single 12-lead ECGs may be taken at any other times, if deemed necessary.

ECGs will be interpreted and signed and dated by the Investigator or his/her designee. The ECGs will be classified as normal, having a non-clinically significant abnormality (NCS), or having a clinically significant abnormality (CS). In addition, ECG parameters of ventricular heart rate (HR), PQ interval, PR interval, QRS duration, and QT interval (corrected and uncorrected) will be noted on the eCRF. All CS findings will be recorded as AEs.

6.3.7.4. Body Weight

Body weight (kg) will be reported as outlined in the Study Schedule of Procedures (Table 1).

6.3.7.5. Clinical Laboratory Tests

All tests listed below will be performed as outlined in the Schedule of Study Procedures (Table 1). In addition, laboratory safety tests may be performed at various unscheduled time points, if deemed necessary by the PI or designee.

Additional and repeat laboratory safety testing for the evaluation of abnormal results and/or AEs during the study (including after follow up visit) may be performed at the discretion of the PI or upon request of the Sponsor.

6.3.8. Meals

Food and water will be restricted for 1 hour prior to each [redacted] At all other times, water will be allowed ad libitum.

When subjects are confined (Day 14 in each period), meals and snacks will be provided at appropriate times, except when subjects are required to fast. When confined in the CRU, subjects will be required to fast from all food and drink except water between meals and snacks.

6.3.9. Activity

Subjects will be instructed to refrain from strenuous physical activity which could cause muscle aches or injury, including contact sports from 48 hour prior to and during all visits and throughout each treatment period (i.e., 48 hrs prior to Day 1 until discharged on Day 15).

6.3.10. Contraception

Female subjects of childbearing potential must use one of the following highly effective contraceptive measures during the study and for at least 30 days after the last dose of study drug:

- combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - oral
  - intravaginal
  - transdermal
- progestogen-only hormonal contraception associated with inhibition of ovulation:
  - oral
  - injectable
  - implantable
- intrauterine device
- intrauterine hormone-releasing system
- bilateral tubal occlusion
- vasectomised partner *
- sexual abstinence **

* Vasectomised partner is a highly effective birth control method provided that partner is the sole sexual partner of the woman of childbearing potential (WOCBP) trial participant and that the vasectomised partner has documented medical assessment of the surgical success.

** True abstinence is defined as refraining from heterosexual intercourse in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of exposure to study drug, and withdrawal are not acceptable methods of contraception.

To be considered a female of non-childbearing potential, the subject must have undergone one of the following sterilization procedures at least 6 months prior to dosing:

- bilateral salpingectomy;
- hysterectomy;
- bilateral oophorectomy.

or be postmenopausal with amenorrhea for at least 2 years prior to dosing without an alternative medical cause. FSH levels will be measured only in cases when postmenopausal status is in question.

All male subjects (with partners of child-bearing potential) must agree to use a condom with spermicide and also one of the following contraception methods during the study until 30 days after the last dose of study drug:

- vasectomized male subjects with documented medical assessment of the surgical success
- Non-vasectomized male subjects must confirm female partner of childbearing potential is using a highly effective method of contraception as defined above
- be sexually abstinent*

* True abstinence is defined as refraining from heterosexual intercourse in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of exposure to study drug, and withdrawal are not acceptable methods of contraception.

6.3.11. Pharmacokinetic Assessments

Instruction for TD-8236 PK blood sampling, collection, processing, and sample shipment will be provided in a separate PK Laboratory Manual.

6.3.12. [redacted]

[redacted]

6.4. Concomitant Medications

[redacted]

[redacted]

6.5. Restrictions

[redacted]

[redacted]

6.6. Continuation and Discontinuation

Upon return for initiation of subsequent periods of the study (i.e., Periods 2 and 3), the appropriateness for a subject to continue in the study will be decided by the investigator, in consultation with the sponsor medical monitor, where appropriate.

Subjects are free to withdraw from the study at any time for any reason.

Subjects will be withdrawn from the study if they exhibit an SAE and/or any AEs that in the opinion of the PI may jeopardise their safety (Section 7).

In addition, subjects may be withdrawn from the study by the PI or designee for difficulties in blood collection.

A subject may be withdrawn by the PI (or designee) or the Sponsor if enrollment into the study is inappropriate, the study plan is violated, or for administrative and/or other safety reasons.

6.6.1. Subject Discontinuation

Any subject (or his or her legally authorized representative) may withdraw their consent to participate in the study at any time without prejudice. The investigator must withdraw from the study any subject who requests to be withdrawn. A subject's participation in the study may be discontinued at any time at the discretion of the investigator and in accordance with his or her clinical judgment. When possible, the tests and evaluations listed for the termination visit should be carried out. If a subject withdraws before completing the study, the reason for withdrawal is to be documented on the CRF.

The Sponsor will be notified of all subject withdrawals.

Reasons for which the investigator or the Sponsor may withdraw a subject from the study or a subject may choose to terminate participation before completion of the study include, but are not limited to, the following:

- Adverse event
- Subject choice
- Major violation of the protocol
- Termination of the study by the Sponsor
- Other

Subjects who discontinue study drug early because of an adverse reaction should be encouraged to continue their participation in the follow-up safety assessments. If a subject fails to return for scheduled visits, a documented effort must be made to determine the reason.

6.6.2. Subject Replacement

[redacted]

6.6.3. Study Discontinuation

The Sponsor reserves the right to discontinue this study at any time for any reason.

6.6.4. End of Trial

The end of this trial is defined as the date that the last protocol defined study visit occurs for the last subject enrolled in the study.

6.7. Pregnancy

If a female subject becomes pregnant during the study, the Sponsor clinical study director (or designee) must be notified immediately. Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required. Instructions related to contraception are described in Section 6.3.10.

7. ADVERSE EVENTS

7.1. Definitions

The definitions below are based on International Conference on Harmonization (ICH) guideline E2A, "Clinical Safety Data Management: Definitions and Standards for Expedited Reporting".

7.1.1. Adverse Events (AE)

An AE is any untoward medical occurrence in a patient or clinical trial subject administered a pharmaceutical product that does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product.

- AEs may be new events
- Preexisting events that increase in frequency, severity or change in nature or seriousness during or as a consequence of participation in clinical studies.
- Pre- or post-treatment complications that occur as a result of a protocol-mandated procedure (such as a biopsy).
- AEs may be clinically significant changes from baseline in physical examination, laboratory tests, or other diagnostic investigation (e.g., laboratory results, x-ray findings).
- AEs may result from an overdose of the study medication.

Whenever possible, the diagnosis (rather than a series of terms related to a diagnosis) should be recorded as the AE term.

An AE does not include the following:

- Medical or surgical procedures (such as surgery, endoscopy, tooth extraction, or transfusion); the condition that leads to the procedure is an adverse event
- Preexisting diseases or conditions present or detected before signing an informed consent form that do not worsen
- Situations where an untoward medical occurrence has not occurred (such as hospitalization for elective surgery or social and/or convenience admissions)
- Overdose of either study drug or concomitant medication without any signs or symptoms, unless the subject is hospitalized for observation

Any medical condition or clinically significant laboratory abnormality with an onset date prior to the time the subject signed the informed consent form is considered to be preexisting and should be documented in the medical history CRF.

Pregnancy is not an AE; however, if a female subject becomes pregnant during the conduct of the study, Theravance Biopharma, Inc. (TBPH) will be notified according to the procedures for

SAE reporting as outlined in Section 7.4.3. Follow-up information regarding the outcome of the pregnancy and any fetal or neonatal sequelae will be obtained and documented.

7.1.2. Serious Adverse Event (SAE)

A serious adverse event (SAE) is defined as any untoward medical occurrence occurring at any dose that results in any of the following outcomes:

- Death
- Life-threatening situation. "Life-threatening" refers to a situation in which the patient was at risk of death at the time of the event; it does not refer to an event which might have caused death if it were more severe.
- Inpatient hospitalization or prolongation of existing hospitalization

  Note: "Inpatient hospitalization" means the subject has been formally admitted to a hospital for medical reasons, for any length of time. This may or may not be overnight. It does not include presentation and care within an emergency department. A scheduled hospitalization for a pre-existing condition that has not worsened during participation in the study does not meet this criterion. Pre-planned hospitalizations for an elective medical/surgical procedure, scheduled treatments, or routine check-ups do not meet this criterion. Complications that occur during hospitalizations are AEs. If a complication prolongs hospitalization, it is an SAE.
- Congenital anomaly/birth defect in the offspring of a subject who received study drug
- Important medical events that may not result in death, be immediately life-threatening, or require hospitalization, may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such events are as follows:
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias or convulsions that do not result in hospitalization
- Development of drug dependency or drug abuse

7.1.3. Additional Considerations for Serious Adverse Events

- Death is an outcome of an adverse event and not an adverse event in itself. Deaths of unknown cause for which the investigator cannot identify a cause of death will be captured as death of unknown cause or death not otherwise specified.
- All deaths, regardless of cause, must be reported for subjects if the death occurs while the subject is participating in the study.
- "Occurring at any dose" does not imply that the subject is receiving study drug at the time of the event; dosing may have been given as treatment cycles or interrupted temporarily before the onset of the SAE, but may have contributed to the event.

7.2. Clinical Laboratory Abnormalities and Other Abnormal Assessments as Adverse Events or Serious Adverse Events

Abnormal laboratory findings (such as clinical chemistry, hematology, or urinalysis) or other abnormal assessments (such as electrocardiograms [ECGs], X-rays, or vital signs) that are associated with signs and/or symptoms or are considered clinically significant in the judgment of the investigator must be recorded as AEs or SAEs if they meet the definition of an adverse event (or serious adverse event), as described in Section 7.1.1 (Adverse Event) and Section 7.1.2 (Serious Adverse Event).

If there are any AE questions, the investigator is encouraged to contact the Sponsor to discuss.

7.3. Assessment of Adverse Events

All AEs will be assessed by the investigator and recorded in the case report form, including the dates of onset and resolution, severity, relationship to study drug, outcome, and action taken with study medication.

7.3.1. Severity

The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe nausea). This is not the same as "serious," which is based on patient/event outcome or action criteria usually associated with events that pose a threat to a subject's life or functioning. The severity of AEs will be assessed according to the following definitions:

- **Mild**: the AE is noticeable to the patient and/or the Investigator, but does not interfere with routine activity.
- **Moderate**: the AE interferes with routine activity, but responds to symptomatic therapy or rest.
- **Severe**: the AE significantly limits the patient's ability to perform routine activities despite symptomatic therapy.

7.3.2. Causal Relationship to Study Medication

The Investigator's assessment of causality is based on clinical judgment regarding the reasonable possibility that the study medication caused the event and may include consideration of some or all of the following factors:

- Possible alternative causes of the AE, including the disease under treatment, co-morbid conditions, other drugs, and environmental factors.
- The temporal association between drug exposure and onset of the AE.
- Whether the clinical or laboratory manifestations of the AE are consistent with known actions or toxicity of the study medication.

- Whether the AE resolved or improved with decreasing the dose or stopping the study medication ("dechallenge") or recurred or worsened upon re-exposure to the study medication ("rechallenge").

The causal relationship between the study medication and the AE will be described using one of the following categories:

- **Not Related:** Evidence exists that the adverse event has an etiology other than the study drug (such as a preexisting condition, underlying disease, intercurrent illness, or concomitant medication).
- **Related:** A temporal relationship exists between the event onset and administration of the study drug. It cannot be readily explained by the subject's clinical state or concomitant therapies and appears with some degree of certainty to be related based on the known therapeutic and pharmacologic actions of the drug. In case of cessation or reduction of the dose, the event abates or resolves and reappears upon rechallenge. It should be emphasized that ineffective treatment should not be considered as causally related in the context of adverse event reporting.

7.4. AE Reporting and Recording

7.4.1. AE Reporting

Timely, accurate, and complete reporting and analysis of safety information from clinical trials is crucial for the protection of patients and is mandated by regulatory agencies. Sponsor has established standard operating procedures in compliance with regulatory requirements worldwide to ensure appropriate reporting of safety information. All clinical trials sponsored by TBPH will be conducted in accordance with these procedures.

7.4.2. AE and SAE Recording

All AEs, regardless of seriousness, severity, or causal relationship to study medication, will be recorded from signing informed consent through the last study visit (or last subject contact in the case of a follow-up telephone call). AEs will be recorded on the AE page of the CRF. SAEs, regardless of relationship to study medication will be recorded from signing informed consent through the last study visit (or last subject contact in the case of a follow-up telephone call). Additionally, investigators may report SAEs assessed as related to study medication through 30 days following the last study visit (or last subject contact in the case of a follow-up telephone call). All SAEs will be recorded on both the SAE Report Form and the AE page of the CRF and should include the following:

Description of event:

- Signs and symptoms due to a common etiology should be reported as a single diagnosis; for example, cough, runny nose, sneezing, sore throat, and head congestion would be reported as "upper respiratory infection".
- A diagnosis or description must be as specific and as complete as possible (e.g., "lower extremity edema" instead of "edema").

- Hospitalization or surgical procedures should not be used as adverse event terms (e.g., if a subject was hospitalized for cholecystectomy due to cholecystitis, the adverse event term should be recorded as cholecystitis, and not as the procedure, cholecystectomy).
- "Death" should not be used as an adverse event term unless the cause of death is unknown. For events with a fatal outcome, the cause of death should be the adverse event term (e.g., if a subject died of an acute myocardial infarction, the adverse event term should be recorded as "Myocardial Infarction" and the event outcome as fatal).

Relationship to study medication: The Investigator will make an assessment of the causal relationship of the study medication to the AE using the guidelines in Section 7.3.2.

Severity: The severity of the AE will be assessed using the guidelines in Section 7.3.1.

Outcome: The outcome of AEs will be recorded.

Therapeutic measures: Measures taken for the treatment or management of the AEs will be recorded.

7.4.3. SAE Reporting Timeline

SAEs will be reported to Clinical Safety and Pharmacovigilance within 24 hours of the time the Investigator or his/her designee becomes aware that an SAE has occurred, whether or not the event is considered to be related to study medication. If the initial SAE is reported by telephone, a written report signed by the Investigator must be submitted within 24 hours.

The SAE Report Form must be completed in accordance with the SAE Report Form Completion Guidelines. If all information on the SAE Report Form is not available at the time of the initial report, follow-up SAE reports will be completed and submitted.

To report an SAE, complete and fax the Serious Adverse Event Report Form to the following:

Theravance Biopharma Clinical Safety and Pharmacovigilance
[redacted]

For medical questions regarding an SAE, contact the Sponsor medical monitor by telephone as follows:

Sponsor Medical Monitor Contact Information:

[redacted] Clinical Development
Theravance Biopharma US, Inc.
[redacted]

For fatal or life-threatening events, also fax copies of hospital case reports, autopsy reports, and other documents when requested. Additional information may be requested from the investigator to ensure the timely completion of accurate safety reports.

An SAE may qualify for reporting to regulatory authorities if the SAE is possibly attributable to the study drug and is unexpected/unlisted based on the current TD-8236 Investigator's Brochure. In this case, all investigators will receive notification of the event. The investigator is responsible for notifying the Institutional Review Board or Ethics Committee and documenting the notification, as required by local regulatory authorities and in accordance with the local institutional policy.

7.5. Adverse Event Follow-up

A subject experiencing an AE or SAE will be followed by the investigator or his/her trained delegate(s) through the follow-up visit or until the investigator and/or the Sponsor has determined that the AE or SAE has resolved or a stable clinical endpoint is reached, whichever is longer. The Sponsor may request follow-up of certain adverse events until resolution and documentation of assessments made during this period.

The investigator must take all therapeutic measures necessary for resolution of an SAE. Any medications necessary for treatment of the SAE must be recorded in the concomitant medication section of the case report form.

8. STATISTICAL CONSIDERATIONS

8.1. General Considerations

[redacted]

8.2. Sample Size and Power

[redacted]

8.3. Analysis Sets

The Intent-to-Treat (ITT) analysis set will include all randomized subjects who received at least one dose of study drug. The ITT analysis set will be the primary analysis set for the summarization of efficacy analyses.

The Per-protocol (PP) analysis set will include all subjects in the ITT analysis set who completed the study and had no major protocol deviations.

The Safety (Safety) analysis set will include all subjects receiving at least one dose of study drug summarized by actual drug received. The Safety analysis set will be the primary analysis for General and Safety analyses.

The Pharmacokinetic (PK) analysis set will include all randomized subject who received at least one dose of active TD-8236 study drug and have at least one evaluable PK profile.

8.3.1. Examination of Subgroups

Analysis of subgroups will be outlined in the statistical analysis pan (SAP).

8.3.2. Major Protocol Analysis Deviations

The following protocol deviations are defined as major and would be considered to have an impact on the analysis of efficacy data

- [redacted]
- [redacted]
- [redacted]

Additional criteria may be specified in the SAP.

8.4. General Analyses

8.4.1. Demographics Characteristics

Demographics and baseline characteristics including age, sex, race, ethnicity, height, weight, BMI, disease characteristics, previous and current asthma medications, and other medical history will be summarized.

8.4.2. Analysis of Pharmacodynamics/Efficacy

8.4.2.1. Pharmacodynamics/Efficacy endpoints

The primary endpoint(s) of this study are:

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

The key secondary endpoint(s) are:

- AUC of percentage change from baseline in FEV_1 from 3 to 8 hours after inhaled allergen challenge at Day 14
- Maximum decline in FEV_1 from 3 to 8 hours after inhaled allergen challenge at Day 14
- Maximum percentage decline in FEV_1 from 3 to 8 hours after inhaled allergen challenge at Day 14
- Day 14 plasma PK parameters of TD-8236 in subjects with mild asthma
- Safety and tolerability off TD-8236 over 14-days of dosing, including frequency and severity of adverse events, vital signs, clinical laboratory evaluations, and 12-lead ECG changes from baseline

The exploratory endpoint(s) are:

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

8.4.2.2. Primary Pharmacodynamics/Efficacy Evaluation

[redacted]

8.4.3. Secondary and Exploratory Pharmacodynamics/Efficacy Evaluations

[redacted]

8.4.4. Multiplicity Adjustment

[redacted]

8.4.5. Analysis of Pharmacokinetics

[redacted]

8.5. Safety Analyses

For all safety analyses, the safety analysis population will be used.

Safety variables to be summarized include vital signs, adverse events, clinical laboratory results (hematology, chemistry, and urinalysis), and corrected QT interval (QTcF) from standard safety digital ECGs. Vital signs will be summarized in terms of observed values and changes from baseline.

8.5.1. Extent of Exposure

A subject's data for the extent of exposure to study drug will be generated from the study drug administration page of the CRF. Dosing information for individual subjects will be listed. Using drug administration data, compliance for each subject by period will be summarized. Dose discontinuations and reasons for study drug discontinuation will be listed and summarized.

8.5.2. Adverse Event Data

Adverse events will be coded to the preferred terms of the Medical Dictionary for Regulatory Activities (MedDRA®). Summaries will presented by system organ class (SOC), preferred term (PT) and severity, the frequency and percentage of subjects reporting each observed event.

Adverse events observed during the period from obtaining informed consent to the start of administration of study drug will be regarded separately from adverse events observed after study drug administration (i.e., treatment-emergent adverse events [TEAEs]).

A treatment-emergent adverse event (TEAE) will be defined as any AE that begins on or after the subjects first dose in their first treatment period and up to the date of last dose in their final treatment period plus the number of days in the follow-up period. AEs observed during the period from obtaining informed consent to the start of administration of study drug will be regarded separately from TEAEs.

[redacted]

All AEs and all TEAEs will be listed by subject. The frequency of subjects who experience TEAEs will be summarized overall and by treatment group. AEs will also be summarized by relationship to treatment (study drug) and severity.

A listing will be provided for all subjects who experience an SAE. Data listings will also be provided for subjects who discontinued the study due to any AE, as well as for a SAE.

8.5.3. Concomitant Medications

Medications will be summarized both prior and during each the treatment period separately.

8.5.4. Laboratory Data

Laboratory data will be summarized in terms of observed values, changes from baseline, values relative to normal ranges, and changes from baseline relative to normal ranges. Listings will flag laboratory values that are outside of normal range.

Clinical laboratory test results will be listed by subject. Reference ranges provided by the laboratory for each parameter will be used to evaluate the clinical significance of laboratory test results. Values falling outside of the relevant reference range will be flagged, as appropriate, in the data listings. Abnormalities in clinical laboratory test results will be listed in a separate listing.

8.5.5. Vital Signs Data

Vital Signs data will be summarized in terms of observed values (by time point), changes from baseline (by time point), and counts and percentages within appropriately defined categories (Table 4).

Table 4: Outlier Threshold for Vital Signs

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

8.5.6. ECG Data

The QTcF, PR interval, QT interval, QRS duration, and HR from standard digital ECGs will be summarized in terms of observed values, changes from baseline, and counts and percentages within appropriately defined 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]	[redacted]
		[redacted]			[redacted]	
		[redacted]			[redacted]	
		[redacted]			[redacted]	
					[redacted]	
					[redacted]	
					[redacted]	
					[redacted]	
					[redacted]	
					[redacted]	
					[redacted]	

[redacted]

When multiple values exist for the same nominal time point (e.g., triplicate reading), the average of the readings taken for ECG parameters will be used in the data analysis, including the outlier analysis stated below.

There will be no imputation of missing data. Subjects without post-baseline measurement for a given treatment period will be excluded from the summary statistic (e.g., denominator of the summary statistic) for that time point.

All recorded values for the ECG parameters will be presented in a by-subject listing. A separate listing of subjects with values of QTcF > 500 msec or an increase > 60 msec will be provided, as necessary.

Cumulative distribution plots will be provided for maximum change in QTcF by day.

8.6. Missing Data Handling

[redacted]

8.7. Interim Analysis

[redacted]

8.8. Data Monitoring Committee

No data monitoring committee is planned for this study.

9. STUDY ADMINISTRATION

This study will be conducted in compliance with all applicable regulations.

9.1. Principal Investigator Responsibilities

Before beginning the study, the principal investigator (PI) at each site must provide to the Sponsor or its designee a fully executed and signed Form FDA 1572 and, if applicable, a financial disclosure form. For applicable studies, financial disclosure forms must also be completed for all subinvestigators who will be directly involved in the treatment or evaluation of research subjects in this study. (A subinvestigator is defined in ICH E6 as any individual member of the clinical study team designated and supervised by the investigator at a study site to perform critical study-related procedures and/or to make important study-related decisions [e.g., associates, residents, research fellows].)

The PI will ensure the following:

- He or she will conduct the study in accordance with the relevant, current protocol and will only make changes in a protocol after notifying the sponsor, except when necessary to protect the safety, rights, or welfare of subjects.
- He or she will personally conduct or supervise the study.
- He or she will inform any potential subjects, or any persons used as controls, that the drugs are being used for investigational purposes and he or she will ensure that the requirements relating to obtaining informed consent in 21 CFR Part 50 and institutional review board (IRB) review and approval in 21 CFR Part 56 are met.
- He or she will report to the sponsor adverse experiences that occur in the course of the investigation in accordance with 21 CFR 312.64.
- He or she has read and understands the information in the TD-8236 Investigator's Brochure, including potential risks and side effects of the drug.
- His or her staff and all persons who assist in the conduct of the study are informed about their obligations in meeting the above commitments
- He or she will ensure that adequate and accurate records in accordance with 21 CFR 312.62 and to make those records available for inspection in accordance with 21 CFR 312.68.
- He or she will ensure that the IRB/IEC complies with the requirements of 21 CFR Part 56, and other applicable regulations, and conducts initial and ongoing reviews and approvals of the study. He or she will also ensure that any change in research activity and all problems involving risks to human subjects or others are reported to the IRB/IEC. Additionally, he or she will not make any changes in the research without IRB/IEC approval, except where necessary to eliminate apparent immediate hazards to human subjects.
- He or she agrees to comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements in 21 CFR Part 312.

9.2. Institutional Review Board/Independent Ethics Committee

Before beginning study-specific research, the investigator will obtain written confirmation that the IRB, IEC, or Research Ethics Board (REB) is properly constituted and compliant with ICH and GCP requirements, applicable laws, and local regulations. A copy of the confirmation from the IRB/IEC/REB will be provided to the Sponsor or its designee. The protocol, informed consent form (ICF), IB, and any other appropriate written information provided to the subjects that the IRB/IEC/REB may require to fulfill its responsibilities will be submitted to the IRB/IEC/REB in advance of the study. The Sponsor or its designee must approve the ICF and all subject recruitment materials before they are submitted to the IRB/IEC/REB. The study will not proceed until appropriate documents from the IRB/IEC/REB confirming unconditional approval of the protocol and the ICF are obtained by the investigator and copies are received by the Sponsor or its designee. If possible, the approval document should refer to the study by study protocol title and the Sponsor study number, identify the documents reviewed, and include the date of the review and approval. The written approval of the IRB/IEC/REB will be retained as part of the study file. The study may proceed before approval of consent forms and other study documents translated to a language other than the native language of the clinical site, provided that written IRB/IEC/REB approval of the translated documents is obtained before they are used. Any amendments to the protocol should be reviewed promptly.

The investigator must provide the appropriate periodic reports on the progress of the study to the IRB/IEC/REB and the Sponsor in accordance with local IRB/IEC/REB requirements and applicable governmental regulations, whichever is strictest.

9.3. Informed Consent

A properly written and executed ICF, in compliance with-ICH E6 (GCP Guideline, Section 4.8), 21 CFR §50, and other applicable local regulations, will be obtained for each subject before enrollment of the subject into the study. The investigator will prepare the ICF or revise the template ICF and provide the documents to the Sponsor (or designee) for approval before submission to the IRB/IEC/REB. The Sponsor and the IRB/IEC/REB must approve the documents before they are implemented.

The investigator will provide copies of the signed ICF to each subject and will maintain the original in the subject's record file.

9.4. Data Recording and Quality Assurance

As used in this protocol, the term case report form (CRF) should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used.

Electronic data capture (EDC) technology will be used for this study. All clinical information requested in this protocol will be recorded on the electronic case report forms approved by the Sponsor, or via other data collection methods, e.g., electronic laboratory data transfer. Study site personnel will enter (in English) study data into the CRFs for each randomized subject. Training on the EDC application will be completed and documented before access to the EDC system is given.

In the event of a CRF data change (e.g., correction of an error or addition of new information), corrections will be made to the CRF. Corrections to the CRFs, including the reason for change, will be automatically documented through the EDC system's audit trail.

The investigator is responsible for reviewing all CRFs, verifying them for accuracy, and approving them via an electronic signature. The investigator is designated as the signatory coordinating investigator.

An electronic copy of the CRF casebooks will be sent to the site for retention with other study documents after full completion of the study, i.e., after database lock.

The investigator is responsible for maintaining accurate, authentic, complete, and up-to-date records for each subject. The investigator is also responsible for ensuring the availability of any original source documentation related to the study (including any films, tracings, computer discs, tapes, and worksheets). In most cases the source is the subject's medical record. Data collected on the CRFs must match the source documents.

In some cases, the CRF may also serve as the source document. In these cases, a document should be available at the investigator's site and clearly identify those data that will be recorded in the CRF and for which the CRF will stand as the source document.

9.5. Document Retention

Until otherwise notified by the Sponsor, an investigative site must retain in a controlled manner all study documents required by the Sponsor and by the applicable regulations. The investigative site must take measures to prevent accidental or premature destruction of essential documents, that is, documents that individually and collectively permit evaluation of the conduct of a study and the quality of the data produced, including paper copies of study records (e.g., subject charts) and any original source documents that are electronic, as required by applicable regulations.

The investigator must consult the Sponsor representative before disposal of any study records and must notify the Sponsor of any change in the location or disposition of the study files. If an investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study documents, custody must be transferred to a person who will accept the responsibility. The Sponsor must be notified in writing of the name and address of the new custodian and must approve this transfer of responsibility.

9.6. Confidentiality

The investigator or designee must explain to each subject, before enrollment into the study, that, for evaluation of study results, the subject's confidential medical information obtained during the study may be shared with the study sponsor, the study sponsor's affiliated companies, the study sponsor's designated service providers, regulatory agencies, and the institutional review board (IRB) or independent ethics committee (IEC). The investigator (or designee) is responsible for obtaining written permission to use confidential medical information in accordance with country-specific regulations (such as the Health Insurance Portability and Accountability Act in the United States) from each subject or, if appropriate, the subject's legally authorized representative. If permission to use confidential medical information is withdrawn, the

investigator is responsible for documenting that no further data from the subject will be collected.

Subject medical information obtained during this study is confidential, and disclosure to unauthorized third parties is prohibited. The pertinent sections of data protection laws will be complied with in full. Study records containing subject information will only be identified by the subject identification number, subject initials, date of birth, and study number, and not by the subject's full name, except the subject consent form, which is archived at the study center only. The subject's name will not be used in any public report of the study.

During the course of the study, a confidential subject identification list will be maintained by the investigator and archived at the investigative site.

Before and during the conduct of the study, no study-related details may be disclosed, i.e., placed on the internet, published, or otherwise publicized, or provided to a third party without prior written permission from the Sponsor. The policy for publication of data after completion of the study is described in Section 9.9 (Publication).

9.7. Access to Data and Documents

Upon receipt of the subject's permission, medical information may be given to his or her personal physician or other appropriate medical personnel responsible for his or her welfare.

Study data recorded on the CRFs must be verifiable to the source data. All original recordings, laboratory reports, and subject records generated by this study must be available to the Sponsor, representatives of the Sponsor, the IRB/IEC/REB, and applicable regulatory authorities, and they may be used for submission to regulatory authorities. In addition, all source data should be attributable (signed and dated), consistent with local medical practice. The investigator must therefore agree to allow direct access to all source data. Subjects (or their legally authorized representatives) must also allow access to their medical records, and subjects will be informed of this and will confirm their agreement when giving informed consent.

9.8. Quality Control: Study Monitoring and Auditing

Qualified individuals designated by the Sponsor will monitor all aspects of the study according to GCP and standard operating procedures (SOPs) for compliance with applicable government regulations. The investigator agrees to allow these monitors direct access to the clinical data and supplies, dispensing, and storage areas and, if requested, agrees to assist the monitors. The investigator and staff are responsible for being present or available for consultation during routinely scheduled site visits conducted by the Sponsor or its designees.

Members of the Sponsor's GCP Quality Assurance Department or designees may conduct an audit of a clinical site at any time during or after completion of the study. The investigator will be informed if an audit is to take place and advised as to the scope of the audit. Inspections and audits are typically carried out during the clinical and reporting phases of this study to ensure that the study is conducted and data are generated, documented, and reported in compliance with the protocol, GCP, written SOPs and applicable laws, rules, and regulations.

Representatives of the FDA or other Regulatory Agencies, including IRB/IEC representatives may also conduct an audit of the study. If informed of such an inspection, the investigator should notify the Sponsor immediately. The investigator will ensure that the auditors have access to the clinical supplies, study site facilities, laboratory and all data (including original source documentation) and all study files are available, if requested.

Noncompliance with the protocol, ICH, GCP, or local regulatory requirements by an investigator, institution, institution staff, or representatives of the Sponsor will lead to prompt action by the Sponsor to secure compliance. Continued noncompliance may result in termination of the investigator's involvement in the study. The IRB/IEC/REB and relevant regulatory authority will be informed.

9.9. Publication

The Sponsor recognizes the importance of communicating medical study data and therefore encourages their publication in reputable scientific journals and presentation at seminars or conferences. The Sponsor will retain the ownership of the data collected in this study. The investigator will provide any proposed manuscript or abstract to the Sponsor before submission for publication or presentation of any results or data obtained in this study.

Additional details of the processes of producing and reviewing reports, manuscripts, and presentations based on the data from this study will be described in the Clinical Study Agreement between the Sponsor and the investigator.

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APPENDIX 2. PROTOCOL SIGNATURE FORM

Protocol Signature Form

Protocol #:	TD-8236 Study 0178
Protocol Title:	A Randomized, Double-blind, Placebo-controlled, 3-period Crossover Study to Evaluate the Safety of Repeated Doses of Inhaled TD-8236 and Impact on Airway Responses Following Allergen Challenge in Patients with Asthma
Version:	[redacted]
Version Date:	05 November 2019

I have read the protocol described above and agree to conduct this study in accordance with procedures described therein. I also agree to conduct the study in compliance with all applicable regulations.

Investigator's Name (print)

Investigator's Signature Date