Clinical trial results:
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

Summary

EudraCT number	2019-002915-24
Trial protocol	GB
Global end of trial date	03 September 2020

Results information

Result version number	v1 (current)
This version publication date	05 September 2021
First version publication date	05 September 2021

Trial information

Trial identification

Sponsor protocol code	0178

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04150341
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Theravance Biopharma US, Inc
Sponsor organisation address	901 Gateway Boulevard, South San Francisco, CA, United States, 94080
Public contact	Nathan Pfeifer, Theravance Biopharma US, Inc, 001 (650) 808-3711, npfeifer@theravance.com
Scientific contact	Nathan Pfeifer, Theravance Biopharma US, Inc, 001 (650) 808-3711, npfeifer@theravance.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	15 March 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	03 September 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the trial was to characterize the late asthmatic response (LAR) in terms of area under the forced expiratory volume (in 1 second) (FEV1) curve after inhaled allergen challenge in mild asthmatic participants receiving 14 days of TD-8236 or placebo.

Protection of trial subjects:

This study was conducted in accordance with the protocol, the principles of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Guideline for Good Clinical Practice (GCP), the United States (US) Code of Federal Regulations, the principles of the World Medical Association Declaration of Helsinki, Ethical Principles for Medical Research Involving Human Subjects, and all applicable regulatory requirements.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	06 November 2019
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 24
Worldwide total number of subjects	24
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	24
From 65 to 84 years	0

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 24 participants were enrolled at 2 sites in the United Kingdom.

Pre-assignment

Screening details:

Participants were screened with an allergen challenge test within 35 days prior to first dosing. Participants received increasing concentrations of inhaled allergen until a decrease of ≥20% from pre-allergen FEV1 was observed during the 30 minutes following the most recent inhalation, and then monitored for a late asthmatic response (LAR).

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Subject

Arms

Are arms mutually exclusive?	No
Arm title	Placebo

Arm description:

Participants were administered inhaled doses of placebo matching TD-8236 once per day (QD) by dry powder inhaler on Day 1 to Day 14 of the 14 day treatment period. An allergen challenge was performed 1 hour after dosing on Day 14 at the dose of allergen required to achieve a successful response at screening.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Placebo blended capsule(s) for inhalation via a dry powder inhaler.

Arm title	TD-8236 150 mcg

Arm description:

Participants were administered 150 microgram (mcg) inhaled doses of TD-8236 once per day (QD) by dry powder inhaler on Day 1 to Day 14 of the 14 day treatment period. An allergen challenge was performed 1 hour after dosing on Day 14 at the dose of allergen required to achieve a successful response at screening.

Arm type	Experimental
Investigational medicinal product name	TD-8236
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Blended capsules for inhalation via a dry powder inhaler.

Arm title	TD-8236 1500 mcg

Arm description:

Participants were administered 1500 microgram (mcg) inhaled doses of TD-8236 once per day (QD) by dry powder inhaler on Day 1 to Day 14 of the 14 day treatment period. An allergen challenge was

performed 1 hour after dosing on Day 14 at the dose of allergen required to achieve a successful response at screening.

Arm type	Experimental
Investigational medicinal product name	TD-8236
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Blended capsules for inhalation via a dry powder inhaler.

Number of subjects in period 1	Placebo	TD-8236 150 mcg	TD-8236 1500 mcg
Started	24	23	24
Completed	23	22	24
Not completed	1	1	0
Physician decision	-	1	-
Adverse event, non-fatal	1	-	-

Baseline characteristics

Reporting groups	
Reporting group title	Overall Study

Reporting group description: -

Reporting group values	Overall Study	Total	
Number of subjects	24	24	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	24	24	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	42.0		
standard deviation	± 11.21	-	
Gender categorical Units: Subjects			
Female	7	7	
Male	17	17	
Ethnicity Units: Subjects			
Not Hispanic or Latino	24	24	
Race Units: Subjects			
White	19	19	
Black or African American	3	3	
Asian	2	2	

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Participants were administered inhaled doses of placebo matching TD-8236 once per day (QD) by dry powder inhaler on Day 1 to Day 14 of the 14 day treatment period. An allergen challenge was performed 1 hour after dosing on Day 14 at the dose of allergen required to achieve a successful response at screening.	
Reporting group title	TD-8236 150 mcg
Reporting group description:	
Participants were administered 150 microgram (mcg) inhaled doses of TD-8236 once per day (QD) by dry powder inhaler on Day 1 to Day 14 of the 14 day treatment period. An allergen challenge was performed 1 hour after dosing on Day 14 at the dose of allergen required to achieve a successful response at screening.	
Reporting group title	TD-8236 1500 mcg
Reporting group description:	
Participants were administered 1500 microgram (mcg) inhaled doses of TD-8236 once per day (QD) by dry powder inhaler on Day 1 to Day 14 of the 14 day treatment period. An allergen challenge was performed 1 hour after dosing on Day 14 at the dose of allergen required to achieve a successful response at screening.	

Primary: Area Under the Curve of Change from Baseline in Forced Expiratory Volume (in 1 Second) (FEV1) from 3 to 8 Hours After Inhaled Allergen Challenge at Day 14

End point title	Area Under the Curve of Change from Baseline in Forced Expiratory Volume (in 1 Second) (FEV1) from 3 to 8 Hours After Inhaled Allergen Challenge at Day 14
End point description:	
End point type	Primary
End point timeframe:	
Day 14 of treatment period: 3 to 8 hours after allergen challenge	

End point values	Placebo	TD-8236 150 mcg	TD-8236 1500 mcg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	22	22	20	
Units: liters				
least squares mean (standard error)	-0.53 (± 0.077)	-0.54 (± 0.077)	-0.57 (± 0.079)	

Statistical analyses

Statistical analysis title	Placebo v TD-8236 150 mcg
Comparison groups	Placebo v TD-8236 150 mcg

Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.881
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.14
upper limit	0.12

Statistical analysis title	Placebo v TD-8236 1500 mcg
Comparison groups	Placebo v TD-8236 1500 mcg
Number of subjects included in analysis	42
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.575
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-0.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.17
upper limit	0.1

Secondary: Area Under the Curve of Percentage Change from Baseline in Forced Expiratory Volume (in 1 Second) (FEV1) from 3 to 8 Hours After Inhaled Allergen Challenge at Day 14

End point title	Area Under the Curve of Percentage Change from Baseline in Forced Expiratory Volume (in 1 Second) (FEV1) from 3 to 8 Hours After Inhaled Allergen Challenge at Day 14

End point description:

End point type	Secondary

End point timeframe:

Day 14 of treatment period: 3 to 8 hours after allergen challenge

End point values	Placebo	TD-8236 150 mcg	TD-8236 1500 mcg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	22	22	20	
Units: percentage change				
least squares mean (standard error)	-16.92 (± 2.512)	-17.50 (± 2.516)	-17.97 (± 2.562)	

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Decline in Forced Expiratory Volume (in 1 Second) (FEV1) from 3 to 8 Hours After Inhaled Allergen Challenge at Day 14

End point title	Maximum Decline in Forced Expiratory Volume (in 1 Second) (FEV1) from 3 to 8 Hours After Inhaled Allergen Challenge at Day 14

End point description:

End point type	Secondary

End point timeframe:

Day 14 of treatment period: 3 to 8 hours after allergen challenge

End point values	Placebo	TD-8236 150 mcg	TD-8236 1500 mcg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	22	22	20	
Units: liters				
least squares mean (standard error)	-0.83 (± 0.082)	-0.86 (± 0.082)	-0.85 (± 0.084)	

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Percentage Decline in Forced Expiratory Volume (in 1 Second) (FEV1) from 3 to 8 Hours After Inhaled Allergen Challenge at Day 14

End point title	Maximum Percentage Decline in Forced Expiratory Volume (in 1 Second) (FEV1) from 3 to 8 Hours After Inhaled Allergen Challenge at Day 14

End point description:

End point type	Secondary

End point timeframe:

Day 14 of treatment period: 3 to 8 hours after allergen challenge

End point values	Placebo	TD-8236 150 mcg	TD-8236 1500 mcg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	22	22	20	
Units: percentage change				
least squares mean (standard error)	-27.02 (± 2.790)	-28.18 (± 2.794)	-26.88 (± 2.843)	

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Concentration-time Curve Over One 24-hour Dosing Interval (AUC0-24) of TD-8236 in Plasma

End point title	Area Under the Concentration-time Curve Over One 24-hour Dosing Interval (AUC0-24) of TD-8236 in Plasma[1]

End point description:

End point type	Secondary

End point timeframe:

Day 14 of treatment period: Pre-dose and 0.5, 1, 2, 4, 6, 8 and 24 hours post-dose

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No PK data was collected for participants who received the placebo.

End point values	TD-8236 150 mcg	TD-8236 1500 mcg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	20		
Units: nanogram hours per milliliter (h*ng/mL)				
geometric mean (geometric coefficient of variation)	0.482 (± 48.8)	1.54 (± 70.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Observed Plasma Concentration (Cmax) of TD-8236 in Plasma During Dosing Interval

End point title	Maximum Observed Plasma Concentration (Cmax) of TD-8236 in Plasma During Dosing Interval[2]

End point description:

End point type	Secondary

End point timeframe:

Day 14 of treatment period: Pre-dose and 0.5, 1, 2, 4, 6, 8 and 24 hours post-dose

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No PK data was collected for participants who received the placebo.

End point values	TD-8236 150 mcg	TD-8236 1500 mcg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	21		
Units: nanograms per milliliter (ng/mL)				
geometric mean (geometric coefficient of variation)	0.0207 (± 46.4)	0.160 (± 54.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Maximum Observed Concentration (Tmax) of TD-8236 in Plasma Over a Dosing Interval

End point title	Time to Maximum Observed Concentration (Tmax) of TD-8236 in Plasma Over a Dosing Interval[3]

End point description:

End point type	Secondary

End point timeframe:

Day 14 of treatment period: Pre-dose and 0.5, 1, 2, 4, 6, 8 and 24 hours post-dose

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No PK data was collected for participants who received the placebo.

End point values	TD-8236 150 mcg	TD-8236 1500 mcg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	21		
Units: hours				
median (full range (min-max))	0.950 (0.483 to 1.03)	0.550 (0.467 to 1.07)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants who Experienced a Treatment-emergent Adverse Event (TEAE)

End point title	Number of Participants who Experienced a Treatment-emergent Adverse Event (TEAE)

End point description:

A TEAE was defined as any adverse event (AE) that begins on or after the date of first dose of study drug up to the date of last dose of study drug plus the number of days in the follow-up period.

The severity of TEAEs were also assessed and were classified as mild, moderate or severe per the definitions below:
Mild - The AE is noticeable to the participant 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 participant's ability to perform routine activities despite symptomatic therapy.

Clinically significant vital signs, clinical laboratory evaluations and 12-lead electrocardiogram (ECG) changes from baseline were also recorded as TEAEs.

End point type	Secondary

End point timeframe:

Day 1 to end of follow-up (up to approximately 98 days)

End point values	Placebo	TD-8236 150 mcg	TD-8236 1500 mcg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	24	23	24	
Units: participants				
Any TEAE	10	9	9	
Moderate or Severe TEAE	3	3	2	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Day 1 to end of follow-up (up to approximately 98 days)

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

Reporting group title	Placebo

Reporting group description:

Participants were administered inhaled doses of placebo matching TD-8236 once per day (QD) by dry powder inhaler on Day 1 to Day 14 of the 14 day treatment period. An allergen challenge was performed 1 hour after dosing on Day 14 at the dose of allergen required to achieve a successful response at screening.

Reporting group title	TD-8236 150 mcg

Reporting group description:

Participants were administered 150 microgram (mcg) inhaled doses of TD-8236 once per day (QD) by dry powder inhaler on Day 1 to Day 14 of the 14 day treatment period. An allergen challenge was performed 1 hour after dosing on Day 14 at the dose of allergen required to achieve a successful response at screening.

Reporting group title	TD-8236 1500 mcg

Reporting group description:

Participants were administered 1500 microgram (mcg) inhaled doses of TD-8236 once per day (QD) by dry powder inhaler on Day 1 to Day 14 of the 14 day treatment period. An allergen challenge was performed 1 hour after dosing on Day 14 at the dose of allergen required to achieve a successful response at screening.

Serious adverse events	Placebo	TD-8236 150 mcg	TD-8236 1500 mcg
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 24 (0.00%)	0 / 23 (0.00%)	0 / 24 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Placebo	TD-8236 150 mcg	TD-8236 1500 mcg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 24 (41.67%)	9 / 23 (39.13%)	9 / 24 (37.50%)
Investigations			
Blood creatine phosphokinase increased			

subjects affected / exposed	0 / 24 (0.00%)	1 / 23 (4.35%)	0 / 24 (0.00%)
occurrences (all)	0	1	0
Liver function test abnormal			
subjects affected / exposed	0 / 24 (0.00%)	1 / 23 (4.35%)	0 / 24 (0.00%)
occurrences (all)	0	1	0
Forced expiratory volume decreased			
subjects affected / exposed	1 / 24 (4.17%)	1 / 23 (4.35%)	0 / 24 (0.00%)
occurrences (all)	1	2	0
SARS-CoV-2 test positive			
subjects affected / exposed	0 / 24 (0.00%)	0 / 23 (0.00%)	2 / 24 (8.33%)
occurrences (all)	0	0	2
Injury, poisoning and procedural complications			
Exposure to SARS-CoV-2			
subjects affected / exposed	0 / 24 (0.00%)	0 / 23 (0.00%)	1 / 24 (4.17%)
occurrences (all)	0	0	1
Injury			
subjects affected / exposed	1 / 24 (4.17%)	0 / 23 (0.00%)	0 / 24 (0.00%)
occurrences (all)	1	0	0
Joint dislocation			
subjects affected / exposed	1 / 24 (4.17%)	0 / 23 (0.00%)	0 / 24 (0.00%)
occurrences (all)	1	0	0
Joint injury			
subjects affected / exposed	1 / 24 (4.17%)	0 / 23 (0.00%)	0 / 24 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 24 (4.17%)	5 / 23 (21.74%)	4 / 24 (16.67%)
occurrences (all)	1	7	5
Dizziness			
subjects affected / exposed	0 / 24 (0.00%)	1 / 23 (4.35%)	0 / 24 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			
Chest discomfort			
subjects affected / exposed	1 / 24 (4.17%)	1 / 23 (4.35%)	0 / 24 (0.00%)
occurrences (all)	1	1	0
Fatigue			

subjects affected / exposed	0 / 24 (0.00%)	1 / 23 (4.35%)	0 / 24 (0.00%)
occurrences (all)	0	1	0
Pyrexia			
subjects affected / exposed	0 / 24 (0.00%)	0 / 23 (0.00%)	1 / 24 (4.17%)
occurrences (all)	0	0	1
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	1 / 24 (4.17%)	1 / 23 (4.35%)	0 / 24 (0.00%)
occurrences (all)	1	1	0
Eye disorders			
Episcleritis			
subjects affected / exposed	0 / 24 (0.00%)	1 / 23 (4.35%)	0 / 24 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Toothache			
subjects affected / exposed	0 / 24 (0.00%)	1 / 23 (4.35%)	0 / 24 (0.00%)
occurrences (all)	0	1	0
Vomiting			
subjects affected / exposed	0 / 24 (0.00%)	1 / 23 (4.35%)	0 / 24 (0.00%)
occurrences (all)	0	1	0
Nausea			
subjects affected / exposed	1 / 24 (4.17%)	0 / 23 (0.00%)	1 / 24 (4.17%)
occurrences (all)	1	0	1
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 24 (4.17%)	0 / 23 (0.00%)	0 / 24 (0.00%)
occurrences (all)	1	0	0
Nasal congestion			
subjects affected / exposed	1 / 24 (4.17%)	0 / 23 (0.00%)	0 / 24 (0.00%)
occurrences (all)	1	0	0
Asthma			
subjects affected / exposed	0 / 24 (0.00%)	0 / 23 (0.00%)	2 / 24 (8.33%)
occurrences (all)	0	0	2
Cough			
subjects affected / exposed	1 / 24 (4.17%)	0 / 23 (0.00%)	1 / 24 (4.17%)
occurrences (all)	1	0	0

Skin and subcutaneous tissue disorders			
Dermatitis allergic			
subjects affected / exposed	0 / 24 (0.00%)	1 / 23 (4.35%)	0 / 24 (0.00%)
occurrences (all)	0	2	0
Musculoskeletal and connective tissue disorders			
Musculoskeletal chest pain			
subjects affected / exposed	1 / 24 (4.17%)	0 / 23 (0.00%)	0 / 24 (0.00%)
occurrences (all)	1	0	0
Back pain			
subjects affected / exposed	1 / 24 (4.17%)	0 / 23 (0.00%)	1 / 24 (4.17%)
occurrences (all)	1	0	1
Infections and infestations			
Conjunctivitis			
subjects affected / exposed	0 / 24 (0.00%)	1 / 23 (4.35%)	0 / 24 (0.00%)
occurrences (all)	0	1	0
Lower respiratory tract infection			
subjects affected / exposed	1 / 24 (4.17%)	0 / 23 (0.00%)	0 / 24 (0.00%)
occurrences (all)	1	0	0
Suspected COVID-19			
subjects affected / exposed	0 / 24 (0.00%)	0 / 23 (0.00%)	1 / 24 (4.17%)
occurrences (all)	0	0	1
Nasopharyngitis			
subjects affected / exposed	0 / 24 (0.00%)	2 / 23 (8.70%)	1 / 24 (4.17%)
occurrences (all)	0	2	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 October 2019	The following changes were made: • Fasting time before collection of blood samples for serum chemistry was increased from 8 hours to 9 hours due to the addition of fasting lipid profiling to the serum chemistry panel. • Creatine phosphokinase, low density lipoprotein, high density lipoprotein, and triglycerides were added to the serum chemistry panel; these were inadvertently omitted from the original protocol.
05 November 2019	The following changes were made: • Clarification was added that male subjects must use acceptable birth control (i.e., condom with spermicide) only with partners of childbearing potential, and added distinction between requirement for vasectomized vs. non vasectomized subjects. • Exclusion criterion was added regarding exposure to biologic therapies within 6 months before Day 1 of Treatment Period 1 to avoid confounding of results. • Guidance was added for rescreening subjects. • Guidance was added regarding the concomitant receipt of heat-killed/inactive vaccines (e.g., seasonal flu vaccine). • Statement was removed that required subjects returning for Treatment Periods 2 and 3 to have their inclusion and exclusion criteria reevaluated.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported