Clinical trial results:
A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Parallel-group, Multi-center Study of an Inhaled Pan-Janus Kinase Inhibitor, TD-0903, to Treat Symptomatic Acute Lung Injury Associated with COVID-19

Summary

EudraCT number	2020-001807-18
Trial protocol	GB RO FI
Global end of trial date	21 April 2021

Results information

Result version number	v1 (current)
This version publication date	13 March 2022
First version publication date	13 March 2022

Trial information

Trial identification

Sponsor protocol code	TD-0903-0188

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04402866
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Theravance Biopharma
Sponsor organisation address	Connaught House, 1 Burlington Road, Dublin, Ireland, D04 C5Y6
Public contact	Medical Monitor, Theravance Biopharma, 1 855-633-8479 , medinfo@theravance.com
Scientific contact	Medical Monitor, Theravance Biopharma, 1 855-633-8479 , medinfo@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	21 April 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	21 April 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to characterize the efficacy of TD-0903 as measured by respiratory failure-free days (RFDs) through Day 28.

Protection of trial subjects:

This trial was designed and monitored in accordance with Sponsor procedures, which comply with the ethical principles of good clinical practice as required by the major regulatory authorities, and in accordance with the Declaration of Helsinki.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	24 June 2020
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 States: 20
Country: Number of subjects enrolled	Brazil: 26
Country: Number of subjects enrolled	Finland: 5
Country: Number of subjects enrolled	Moldova, Republic of: 72
Country: Number of subjects enrolled	Ukraine: 108
Country: Number of subjects enrolled	United Kingdom: 4
Worldwide total number of subjects	235
EEA total number of subjects	5

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)	155
From 65 to 84 years	80
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

235 participants were enrolled across 18 sites in the United States, Brazil, Finland, the Republic of Moldova, Ukraine and the United Kingdom.

Pre-assignment

Screening details:

235 participants were enrolled and 230 participants were randomized and treated with study drug. Within each cohort in Part 1 (multiple-ascending dose design), participants were randomized 3:1, TD-0903 to placebo. During Part 2 (parallel-group design), participants were randomized 1:1, TD-0903 to placebo.

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	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Part 1: Matching Placebo

Arm description:

Matching placebo inhalation solution (1 mL) was administered once daily for up to 7 days via oral inhalation using the Aerogen Solo nebulizer system.

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

Dosage and administration details:

Matching placebo was administered by oral inhalation.

Arm title	Part 1: TD-0903 - 1 mg

Arm description:

TD-0903 inhalation solution (1 mL) was administered once daily for up to 7 days via oral inhalation using the Aerogen Solo nebulizer system at a dose of 1 mg. Participants were administered a 2 mg loading dose as the total dose on Day 1.

Arm type	Experimental
Investigational medicinal product name	TD-0903
Investigational medicinal product code	
Other name	nezulcitinib
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

TD-0903 was administered by oral inhalation.

Arm title	Part 1: TD-0903 - 3 mg

Arm description:

TD-0903 inhalation solution (1 mL) was administered once daily for up to 7 days via oral inhalation using the Aerogen Solo nebulizer system at a dose of 3 mg. Participants were administered a 6 mg loading dose as the total dose on Day 1.

Arm type	Experimental

Investigational medicinal product name	TD-0903
Investigational medicinal product code	
Other name	nezulcitinib
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

TD-0903 was administered by oral inhalation.

Arm title	Part 1: TD-0903 - 10 mg

Arm description:

TD-0903 inhalation solution (1 mL) was administered once daily for up to 7 days via oral inhalation using the Aerogen Solo nebulizer system at a dose of 10 mg.

Arm type	Experimental
Investigational medicinal product name	TD-0903
Investigational medicinal product code	
Other name	nezulcitinib
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

TD-0903 was administered by oral inhalation.

Arm title	Part 2: Matching Placebo

Arm description:

Matching placebo inhalation solution (1 mL) was administered once daily for up to 7 days via oral inhalation using the Aerogen Solo nebulizer system.

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

Dosage and administration details:

Matching placebo was administered by oral inhalation.

Arm title	Part 2: TD-0903 - 3 mg

Arm description:

TD-0903 inhalation solution (1 mL) was administered once daily for up to 7 days via oral inhalation using the Aerogen Solo nebulizer system at a dose of 3 mg. Participants were administered a 6 mg loading dose as the total dose on Day 1.

Arm type	Experimental
Investigational medicinal product name	TD-0903
Investigational medicinal product code	
Other name	nezulcitinib
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

TD-0903 was administered by oral inhalation.

Number of subjects in period 1	Part 1: Matching Placebo	Part 1: TD-0903 - 1 mg	Part 1: TD-0903 - 3 mg
Started	6	6	7
Randomized and Treated With Study Drug	6	6	7
Completed	4	5	6
Not completed	2	1	1
Consent withdrawn by subject	-	-	-
Adverse event, non-fatal	2	1	-
Discontinued Prior to Treatment	-	-	-
Miscellaneous	-	-	1
Lost to follow-up	-	-	-

Number of subjects in period 1	Part 1: TD-0903 - 10 mg	Part 2: Matching Placebo	Part 2: TD-0903 - 3 mg
Started	6	104	106
Randomized and Treated With Study Drug	6	102	103
Completed	6	89	92
Not completed	0	15	14
Consent withdrawn by subject	-	-	2
Adverse event, non-fatal	-	13	8
Discontinued Prior to Treatment	-	2	3
Miscellaneous	-	-	-
Lost to follow-up	-	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Part 1: Matching Placebo
Reporting group description:	
Matching placebo inhalation solution (1 mL) was administered once daily for up to 7 days via oral inhalation using the Aerogen Solo nebulizer system.	
Reporting group title	Part 1: TD-0903 - 1 mg
Reporting group description:	
TD-0903 inhalation solution (1 mL) was administered once daily for up to 7 days via oral inhalation using the Aerogen Solo nebulizer system at a dose of 1 mg. Participants were administered a 2 mg loading dose as the total dose on Day 1.	
Reporting group title	Part 1: TD-0903 - 3 mg
Reporting group description:	
TD-0903 inhalation solution (1 mL) was administered once daily for up to 7 days via oral inhalation using the Aerogen Solo nebulizer system at a dose of 3 mg. Participants were administered a 6 mg loading dose as the total dose on Day 1.	
Reporting group title	Part 1: TD-0903 - 10 mg
Reporting group description:	
TD-0903 inhalation solution (1 mL) was administered once daily for up to 7 days via oral inhalation using the Aerogen Solo nebulizer system at a dose of 10 mg.	
Reporting group title	Part 2: Matching Placebo
Reporting group description:	
Matching placebo inhalation solution (1 mL) was administered once daily for up to 7 days via oral inhalation using the Aerogen Solo nebulizer system.	
Reporting group title	Part 2: TD-0903 - 3 mg
Reporting group description:	
TD-0903 inhalation solution (1 mL) was administered once daily for up to 7 days via oral inhalation using the Aerogen Solo nebulizer system at a dose of 3 mg. Participants were administered a 6 mg loading dose as the total dose on Day 1.	

Reporting group values	Part 1: Matching Placebo	Part 1: TD-0903 - 1 mg	Part 1: TD-0903 - 3 mg
Number of subjects	6	6	7
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	54.2	59.5	62.0
standard deviation	± 16.94	± 15.49	± 3.27
Gender categorical			
Units: Subjects			
Female	3	1	3
Male	3	5	4
Ethnicity			
Units: Subjects			
Hispanic or Latino	0	0	0
Not Hispanic or Latino	6	6	7
Unknown or Not Reported	0	0	0
Race			
Units: Subjects			

Asian	1	0	0
Black or African American	0	0	0
White	5	6	7
More Than One Race	0	0	0
Other	0	0	0

Reporting group values	Part 1: TD-0903 - 10 mg	Part 2: Matching Placebo	Part 2: TD-0903 - 3 mg
Number of subjects	6	104	106
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	52.8	58.1	58.3
standard deviation	± 13.41	± 12.54	± 12.42
Gender categorical Units: Subjects			
Female	1	41	41
Male	5	63	65
Ethnicity Units: Subjects			
Hispanic or Latino	0	10	14
Not Hispanic or Latino	6	90	89
Unknown or Not Reported	0	4	3
Race Units: Subjects			
Asian	0	0	0
Black or African American	0	0	2
White	6	102	104
More Than One Race	0	1	0
Other	0	1	0

Reporting group values	Total		
Number of subjects	235		
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical Units: Subjects			
Female	90		
Male	145		
Ethnicity Units: Subjects			
Hispanic or Latino	24		
Not Hispanic or Latino	204		
Unknown or Not Reported	7		

Race Units: Subjects			
Asian	1		
Black or African American	2		
White	230		
More Than One Race	1		
Other	1		

End points

End points reporting groups

Reporting group title	Part 1: Matching Placebo
Reporting group description:	
Matching placebo inhalation solution (1 mL) was administered once daily for up to 7 days via oral inhalation using the Aerogen Solo nebulizer system.	
Reporting group title	Part 1: TD-0903 - 1 mg
Reporting group description:	
TD-0903 inhalation solution (1 mL) was administered once daily for up to 7 days via oral inhalation using the Aerogen Solo nebulizer system at a dose of 1 mg. Participants were administered a 2 mg loading dose as the total dose on Day 1.	
Reporting group title	Part 1: TD-0903 - 3 mg
Reporting group description:	
TD-0903 inhalation solution (1 mL) was administered once daily for up to 7 days via oral inhalation using the Aerogen Solo nebulizer system at a dose of 3 mg. Participants were administered a 6 mg loading dose as the total dose on Day 1.	
Reporting group title	Part 1: TD-0903 - 10 mg
Reporting group description:	
TD-0903 inhalation solution (1 mL) was administered once daily for up to 7 days via oral inhalation using the Aerogen Solo nebulizer system at a dose of 10 mg.	
Reporting group title	Part 2: Matching Placebo
Reporting group description:	
Matching placebo inhalation solution (1 mL) was administered once daily for up to 7 days via oral inhalation using the Aerogen Solo nebulizer system.	
Reporting group title	Part 2: TD-0903 - 3 mg
Reporting group description:	
TD-0903 inhalation solution (1 mL) was administered once daily for up to 7 days via oral inhalation using the Aerogen Solo nebulizer system at a dose of 3 mg. Participants were administered a 6 mg loading dose as the total dose on Day 1.	

Primary: Part 2: Number of RFDs From Randomization to Day 28

End point title	Part 2: Number of RFDs From Randomization to Day 28[1]
End point description:	
An RFD was defined as a day that a participant was alive and did not require the use of any respiratory support (invasive mechanical ventilation, non-invasive positive pressure ventilation, high-flow oxygen devices, or oxygen supplementation) from randomization through Day 28. The number of RFDs was 0 for participants who used respiratory support for 28 days or longer or for participants who died on or before Day 28. A clinical status score of ≤ 4 on a given day was equivalent to an RFD. The clinical status categories and associated scores ranged from 1-8 where a higher score represented a worse outcome. A clinical status score of 4 was defined as a participant who was hospitalized, not requiring supplemental oxygen, but requiring ongoing medical care (whether or not related to COVID-19). Intent-to-Treat (ITT) analysis set (Part 2) - all participants with analyzable data who were randomized into the study.	
End point type	Primary
End point timeframe:	
Randomization to Day 28	

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: Statistical analysis was pre-specified for Part 2 only.

End point values	Part 2: Matching Placebo	Part 2: TD-0903 - 3 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	102	100		
Units: days				
median (inter-quartile range (Q1-Q3))	21.0 (15.0 to 23.0)	21.0 (17.5 to 23.0)		

Statistical analyses

Statistical analysis title	Part 2: Matching Placebo versus (vs) TD-0903 3 mg

Statistical analysis description:

Common Odds Ratio (TD-0903 vs placebo) and corresponding 95% Wald confidence interval were obtained from the proportional odds regression model of RFD adjusting for baseline age strata (≤ 60 years vs > 60 years).

Comparison groups	Part 2: Matching Placebo v Part 2: TD-0903 - 3 mg
Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6137
Method	Van Elteren test
Parameter estimate	Common Odds Ratio
Point estimate	1.142
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.706
upper limit	1.846

Secondary: Part 2: Change From Baseline in SaO2/FiO2 Ratio on Day 7

End point title	Part 2: Change From Baseline in SaO2/FiO2 Ratio on Day 7[2]

End point description:

SaO2/FiO2 ratio was calculated as SaO2 divided by FiO2.

ITT analysis set (Part 2) - all participants with analyzable data who were randomized into the study.

End point type	Secondary

End point timeframe:

Baseline and Day 7

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: Statistical analysis was pre-specified for Part 2 only.

End point values	Part 2: Matching Placebo	Part 2: TD-0903 - 3 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	86	90		
Units: ratio measure				
least squares mean (standard error)	88.97 (± 7.769)	88.46 (± 7.654)		

Statistical analyses

Statistical analysis title	Part 2: Matching Placebo vs TD-0903 3 mg
Comparison groups	Part 2: Matching Placebo v Part 2: TD-0903 - 3 mg
Number of subjects included in analysis	176
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	= 0.962
Method	Mixed model repeated measures model
Parameter estimate	LS mean difference
Point estimate	-0.51
Confidence interval	
level	95 %
sides	2-sided
lower limit	-21.95
upper limit	20.92

Notes:

[3] - Since this was a Phase 2 study, it was not powered for any of the secondary endpoints.

Secondary: Part 2: Number of Participants in Each Category of the 8-point Ordinal Clinical Status Scale on Days 7, 14, 21, and 28

End point title	Part 2: Number of Participants in Each Category of the 8-point Ordinal Clinical Status Scale on Days 7, 14, 21, and 28[4]

End point description:

The clinical status categories and associated scores ranged from 1-8 where a higher score represented a worse outcome. The scale was as follows:
• Score 1: Not hospitalized, no limitations on activities
• Score 2: Not hospitalized, but with limitations on activities and/or requiring home oxygen
• Score 3: Hospitalized, not requiring supplemental oxygen, and no longer requiring ongoing medical care
• Score 4: Hospitalized, not requiring supplemental oxygen, but requiring ongoing medical care (whether or not related to COVID-19)
• Score 5: Hospitalized, requiring supplemental oxygen
• Score 6: Hospitalized, on non-invasive ventilation or high-flow oxygen devices
• Score 7: Hospitalized, on invasive mechanical ventilation or extracorporeal membrane oxygenation
• Score 8: Death.

ITT analysis set (Part 2) - all participants with analyzable data who were randomized into the study.

End point type	Secondary

End point timeframe:

Days 7, 14, 21 and 28

Notes:

[4] - 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: Statistical analysis was pre-specified for Part 2 only.

End point values	Part 2: Matching Placebo	Part 2: TD-0903 - 3 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	102[5]	100[6]		
Units: participants				
Day 7: Score 1	6	8		
Day 7: Score 2	12	9		
Day 7: Score 3	1	1		
Day 7: Score 4	25	23		
Day 7: Score 5	42	48		
Day 7: Score 6	7	7		
Day 7: Score 7	7	2		
Day 7: Score 8	2	1		
Day 14: Score 1	57	52		
Day 14: Score 2	6	11		
Day 14: Score 3	2	7		
Day 14: Score 4	14	13		
Day 14: Score 5	10	7		
Day 14: Score 6	1	2		
Day 14: Score 7	6	5		
Day 14: Score 8	6	2		
Day 21: Score 1	72	72		
Day 21: Score 2	4	9		
Day 21: Score 3	4	6		
Day 21: Score 4	4	0		
Day 21: Score 5	3	4		
Day 21: Score 6	1	0		
Day 21: Score 7	2	3		
Day 21: Score 8	12	5		
Day 28: Score 1	79	78		
Day 28: Score 2	5	11		
Day 28: Score 3	0	1		
Day 28: Score 4	1	1		
Day 28: Score 5	3	1		
Day 28: Score 6	0	0		
Day 28: Score 7	1	2		
Day 28: Score 8	13	6		

Notes:

[5] - Day 7: n = 102
Day 14: n = 102
Day 21: n = 102
Day 28: n = 102
[6] - Day 7: n = 99
Day 14: n = 99
Day 21: n = 99
Day 28: n = 100

Statistical analyses

Statistical analysis title	Part 2: Matching Placebo vs TD-0903 3 mg on Day 7

Statistical analysis description:

Between-group comparisons analyzed using a proportional odds model adjusting for baseline age strata (≤ 60 years vs > 60 years).

Comparison groups	Part 2: Matching Placebo v Part 2: TD-0903 - 3 mg

Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	other[7]
P-value	= 0.5918
Method	Van Elteren test
Parameter estimate	Odds ratio (OR)
Point estimate	1.153
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.692
upper limit	1.922

Notes:

[7] - Since this was a Phase 2 study, it was not powered for any of the secondary endpoints.

Statistical analysis title	Part 2: Matching Placebo vs TD-0903 3 mg on Day 14

Statistical analysis description:

Between-group comparisons analyzed using a proportional odds model adjusting for baseline age strata (≤ 60 years vs > 60 years).

Comparison groups	Part 2: Matching Placebo v Part 2: TD-0903 - 3 mg
Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	other[8]
P-value	= 0.6978
Method	Van Elteren test
Parameter estimate	Odds ratio (OR)
Point estimate	1.105
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.651
upper limit	1.878

Notes:

[8] - Since this was a Phase 2 study, it was not powered for any of the secondary endpoints.

Statistical analysis title	Part 2: Matching Placebo vs TD-0903 3 mg on Day 21

Statistical analysis description:

Between-group comparisons analyzed using a proportional odds model adjusting for baseline age strata (≤ 60 years vs > 60 years).

Comparison groups	Part 2: Matching Placebo v Part 2: TD-0903 - 3 mg
Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	other[9]
P-value	= 0.399
Method	Van Elteren test
Parameter estimate	Odds ratio (OR)
Point estimate	1.295

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.702
upper limit	2.388

Notes:

[9] - Since this was a Phase 2 study, it was not powered for any of the secondary endpoints.

Statistical analysis title	Part 2: Matching Placebo vs TD-0903 3 mg on Day 28

Statistical analysis description:

Between-group comparisons analyzed using a proportional odds model adjusting for baseline age strata (≤ 60 years vs > 60 years).

Comparison groups	Part 2: Matching Placebo v Part 2: TD-0903 - 3 mg
Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	other[10]
P-value	= 0.6445
Method	Van Elteren test
Parameter estimate	Odds ratio (OR)
Point estimate	1.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.605
upper limit	2.299

Notes:

[10] - Since this was a Phase 2 study, it was not powered for any of the secondary endpoints.

Secondary: Part 2: Number of Participants Alive and Respiratory Failure-free on Day 28

End point title	Part 2: Number of Participants Alive and Respiratory Failure-free on Day 28[11]

End point description:

Defined as participants who were alive and did not require the use of any respiratory support (invasive mechanical ventilation, non-invasive positive pressure ventilation, high-flow oxygen devices, or oxygen supplementation) on Day 28.

ITT analysis set (Part 2) - all participants with analyzable data who were randomized into the study.

End point type	Secondary

End point timeframe:

Day 28

Notes:

[11] - 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: Statistical analysis was pre-specified for Part 2 only.

End point values	Part 2: Matching Placebo	Part 2: TD-0903 - 3 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	104	106		
Units: participants	85	92		

Statistical analyses

Statistical analysis title	Part 2: Matching Placebo vs TD-0903 3 mg
Comparison groups	Part 2: Matching Placebo v Part 2: TD-0903 - 3 mg
Number of subjects included in analysis	210
Analysis specification	Pre-specified
Analysis type	other[12]
P-value	= 0.3005 [13]
Method	Cochran-Mantel-Haenszel chi-square test
Parameter estimate	Risk difference (RD)
Point estimate	5.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.5
upper limit	14.63

Notes:

[12] - Since this was a Phase 2 study, it was not powered for any of the secondary endpoints.

[13] - The p-value was calculated using the Cochran-Mantel-Haenszel chi-square test stratified by baseline age group (≤ 60 years vs > 60 years).

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Day 1 to Day 28

Adverse event reporting additional description:

Safety analysis set - all participants who received at least one dose of study drug.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.1

Reporting groups

Reporting group title	Part 1: Matching Placebo

Reporting group description:

Matching placebo inhalation solution (1 mL) was administered once daily for up to 7 days via oral inhalation using the Aerogen Solo nebulizer system.

Reporting group title	Part 1: TD-0903 - 1 mg

Reporting group description:

TD-0903 inhalation solution (1 mL) was administered once daily for up to 7 days via oral inhalation using the Aerogen Solo nebulizer system at a dose of 1 mg. Participants were administered a 2 mg loading dose as the total dose on Day 1.

Reporting group title	Part 1: TD-0903 - 3 mg

Reporting group description:

TD-0903 inhalation solution (1 mL) was administered once daily for up to 7 days via oral inhalation using the Aerogen Solo nebulizer system at a dose of 3 mg. Participants were administered a 6 mg loading dose as the total dose on Day 1.

Reporting group title	Part 1: TD-0903 - 10 mg

Reporting group description:

TD-0903 inhalation solution (1 mL) was administered once daily for up to 7 days via oral inhalation using the Aerogen Solo nebulizer system at a dose of 10 mg.

Reporting group title	Part 2: Matching Placebo

Reporting group description:

Matching placebo inhalation solution (1 mL) was administered once daily for up to 7 days via oral inhalation using the Aerogen Solo nebulizer system.

Reporting group title	Part 2: TD-0903 - 3 mg

Reporting group description:

TD-0903 inhalation solution (1 mL) was administered once daily for up to 7 days via oral inhalation using the Aerogen Solo nebulizer system at a dose of 3 mg. Participants were administered a 6 mg loading dose as the total dose on Day 1.

Serious adverse events	Part 1: Matching Placebo	Part 1: TD-0903 - 1 mg	Part 1: TD-0903 - 3 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 6 (50.00%)	1 / 6 (16.67%)	1 / 7 (14.29%)
number of deaths (all causes)	2	1	0
number of deaths resulting from adverse events			
Investigations			
Alanine aminotransferase increased			

subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Shock			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Ventricular fibrillation			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Ischaemic stroke			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 7 (14.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Multiple organ dysfunction syndrome			

subjects affected / exposed	1 / 6 (16.67%)	1 / 6 (16.67%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Sudden death			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	2 / 6 (33.33%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute respiratory failure			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Infections and infestations			
Bacterial sepsis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COVID-19			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Systemic bacterial infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Part 1: TD-0903 - 10 mg	Part 2: Matching Placebo	Part 2: TD-0903 - 3 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 6 (0.00%)	16 / 102 (15.69%)	10 / 103 (9.71%)
number of deaths (all causes)	0	13	6
number of deaths resulting from adverse events			
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 102 (0.00%)	1 / 103 (0.97%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 102 (0.00%)	1 / 103 (0.97%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Shock			

subjects affected / exposed	0 / 6 (0.00%)	2 / 102 (1.96%)	1 / 103 (0.97%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	0 / 6 (0.00%)	2 / 102 (1.96%)	0 / 103 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 0
Ventricular fibrillation			
subjects affected / exposed	0 / 6 (0.00%)	0 / 102 (0.00%)	0 / 103 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Ischaemic stroke			
subjects affected / exposed	0 / 6 (0.00%)	0 / 102 (0.00%)	1 / 103 (0.97%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	0 / 6 (0.00%)	1 / 102 (0.98%)	0 / 103 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Multiple organ dysfunction syndrome			
subjects affected / exposed	0 / 6 (0.00%)	1 / 102 (0.98%)	3 / 103 (2.91%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 3
Sudden death			
subjects affected / exposed	0 / 6 (0.00%)	1 / 102 (0.98%)	0 / 103 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			

subjects affected / exposed	0 / 6 (0.00%)	0 / 102 (0.00%)	3 / 103 (2.91%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute respiratory failure			
subjects affected / exposed	0 / 6 (0.00%)	3 / 102 (2.94%)	0 / 103 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 0
Pneumothorax			
subjects affected / exposed	0 / 6 (0.00%)	1 / 102 (0.98%)	1 / 103 (0.97%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Pulmonary embolism			
subjects affected / exposed	0 / 6 (0.00%)	4 / 102 (3.92%)	0 / 103 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 4	0 / 0
Respiratory failure			
subjects affected / exposed	0 / 6 (0.00%)	5 / 102 (4.90%)	3 / 103 (2.91%)
occurrences causally related to treatment / all	0 / 0	0 / 5	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 3	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 6 (0.00%)	3 / 102 (2.94%)	0 / 103 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Bacterial sepsis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 102 (0.98%)	1 / 103 (0.97%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
COVID-19			
subjects affected / exposed	0 / 6 (0.00%)	0 / 102 (0.00%)	0 / 103 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			

subjects affected / exposed	0 / 6 (0.00%)	1 / 102 (0.98%)	0 / 103 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Systemic bacterial infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 102 (0.00%)	1 / 103 (0.97%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Part 1: Matching Placebo	Part 1: TD-0903 - 1 mg	Part 1: TD-0903 - 3 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 6 (100.00%)	4 / 6 (66.67%)	1 / 7 (14.29%)
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Hypotension			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Oropharyngeal pain			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Pulmonary hypertension			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Upper-airway cough syndrome			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			

Depressed mood			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Depression			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Insomnia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Bradycardia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 7 (0.00%)
occurrences (all)	0	2	0
Sinus tachycardia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Headache			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Tremor			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Blood and lymphatic system disorders			
Lymphopenia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Abdominal pain			

subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Diarrhoea			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Nausea			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	3	0	0
Vomiting			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Pyrexia			
subjects affected / exposed	1 / 6 (16.67%)	1 / 6 (16.67%)	0 / 7 (0.00%)
occurrences (all)	1	1	0
Hepatobiliary disorders			
Hepatic failure			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Hypertransaminasaemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Renal and urinary disorders			
Chronic kidney disease			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
Oropharyngeal candidiasis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Vascular device infection			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Metabolism and nutrition disorders			

Hyperglycaemia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Hypokalaemia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0

Non-serious adverse events	Part 1: TD-0903 - 10 mg	Part 2: Matching Placebo	Part 2: TD-0903 - 3 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 6 (83.33%)	18 / 102 (17.65%)	15 / 103 (14.56%)
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 6 (0.00%)	0 / 102 (0.00%)	4 / 103 (3.88%)
occurrences (all)	0	0	4
Hypotension			
subjects affected / exposed	1 / 6 (16.67%)	1 / 102 (0.98%)	1 / 103 (0.97%)
occurrences (all)	1	1	2
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	3 / 6 (50.00%)	1 / 102 (0.98%)	3 / 103 (2.91%)
occurrences (all)	4	1	3
Oropharyngeal pain			
subjects affected / exposed	1 / 6 (16.67%)	1 / 102 (0.98%)	0 / 103 (0.00%)
occurrences (all)	1	1	0
Pulmonary hypertension			
subjects affected / exposed	0 / 6 (0.00%)	0 / 102 (0.00%)	0 / 103 (0.00%)
occurrences (all)	0	0	0
Upper-airway cough syndrome			
subjects affected / exposed	1 / 6 (16.67%)	0 / 102 (0.00%)	0 / 103 (0.00%)
occurrences (all)	1	0	0
Psychiatric disorders			
Depressed mood			
subjects affected / exposed	0 / 6 (0.00%)	0 / 102 (0.00%)	0 / 103 (0.00%)
occurrences (all)	0	0	0
Depression			

subjects affected / exposed	0 / 6 (0.00%)	0 / 102 (0.00%)	0 / 103 (0.00%)
occurrences (all)	0	0	0
Insomnia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 102 (0.00%)	1 / 103 (0.97%)
occurrences (all)	0	0	1
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 6 (16.67%)	6 / 102 (5.88%)	5 / 103 (4.85%)
occurrences (all)	1	6	5
Cardiac disorders			
Bradycardia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 102 (0.00%)	0 / 103 (0.00%)
occurrences (all)	0	0	0
Sinus tachycardia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 102 (0.00%)	1 / 103 (0.97%)
occurrences (all)	0	0	1
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	1 / 6 (16.67%)	1 / 102 (0.98%)	1 / 103 (0.97%)
occurrences (all)	1	2	1
Headache			
subjects affected / exposed	0 / 6 (0.00%)	0 / 102 (0.00%)	1 / 103 (0.97%)
occurrences (all)	0	0	1
Tremor			
subjects affected / exposed	0 / 6 (0.00%)	0 / 102 (0.00%)	0 / 103 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
Lymphopenia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 102 (0.00%)	0 / 103 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 102 (0.00%)	0 / 103 (0.00%)
occurrences (all)	0	0	0
Diarrhoea			
subjects affected / exposed	0 / 6 (0.00%)	7 / 102 (6.86%)	3 / 103 (2.91%)
occurrences (all)	0	7	3

Nausea			
subjects affected / exposed	0 / 6 (0.00%)	1 / 102 (0.98%)	0 / 103 (0.00%)
occurrences (all)	0	1	0
Vomiting			
subjects affected / exposed	0 / 6 (0.00%)	0 / 102 (0.00%)	0 / 103 (0.00%)
occurrences (all)	0	0	0
Pyrexia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 102 (0.00%)	0 / 103 (0.00%)
occurrences (all)	0	0	0
Hepatobiliary disorders			
Hepatic failure			
subjects affected / exposed	0 / 6 (0.00%)	2 / 102 (1.96%)	1 / 103 (0.97%)
occurrences (all)	0	2	1
Hypertransaminasaemia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 102 (0.00%)	0 / 103 (0.00%)
occurrences (all)	1	0	0
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	0 / 6 (0.00%)	0 / 102 (0.00%)	0 / 103 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
Chronic kidney disease			
subjects affected / exposed	0 / 6 (0.00%)	0 / 102 (0.00%)	0 / 103 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Oropharyngeal candidiasis			
subjects affected / exposed	1 / 6 (16.67%)	0 / 102 (0.00%)	0 / 103 (0.00%)
occurrences (all)	1	0	0
Vascular device infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 102 (0.00%)	0 / 103 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	0 / 6 (0.00%)	2 / 102 (1.96%)	3 / 103 (2.91%)
occurrences (all)	0	2	3
Hypokalaemia			

subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 102 (0.00%) 0	0 / 103 (0.00%) 0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 May 2020	Amendment 2, dated 16 May 2020, was classified as a substantial amendment, and included the following non-administrative changes to Amendment 1: - Revisions to the secondary and exploratory objectives. - Reduction in enrollment. - Revisions to blood oxygenation measurements. - Revisions to inclusion and exclusion criteria. - Revisions to dose escalation stopping rules. - Specification that a major violation of the protocol was grounds for study withdrawal by the investigator.
18 May 2020	Amendment 2, Revision 1, dated 18 May 2020, was classified as a substantial amendment, and included all of the non-administrative changes listed for Amendment 2, and the following non-administrative changes: - Clarifications on the informed consent procedure. - Revisions to inclusion criteria.
25 June 2020	Amendment 3, dated 25 June 2020, was classified as a substantial amendment, and included the following non-administrative changes to Amendment 2, Revision 1: - Revisions to inclusion and exclusion criteria. - Revisions to the clinical status scale based on feedback from the United States Food and Drug Administration. - Removal of nasal swab restrictions for COVID-19 testing. - Revisions to the primary, secondary and exploratory objectives. - Revisions to the blinding details. - Removal of discharge criteria language. - Revisions to the informed consent procedure. - Safety Assessment Committee were added. - Revisions to the pharmacokinetic sampling time intervals. - Revision of the assumptions associated with the sample size. - Potential of pooling data from Parts 1 and 2 was removed. - Additional collection, analysis, and storage of plasma samples. - Revisions to the withdrawal criteria.
18 September 2020	Amendment 4, dated 18 September 2020, was a substantial amendment that consolidated changes from Amendment 3 and Amendment 3.1, and included the following non-administrative changes: - Introduction updated. - Revisions to the primary, secondary and exploratory objectives. - Revisions to the study design. - Modified randomization schedule. - Revisions to the inclusion and exclusion criteria. - Clarification of loading doses. - Revisions to the schedule of study procedures. - Revisions to the assessments associated with clinical outcomes. - Revisions to the list of biomarkers. - Revisions to the list of prohibited concomitant medications. - Clarification of renal disease study equation. - Added language regarding partners of study participants reporting pregnancy. - Clarification that the Safety Assessment Committee was no longer independent of the Sponsor. - Revisions of the assumptions associated with the sample size. - Revisions to the analysis sets.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported