



Clinical trial results:

A randomized, blinded, parallel group, multi-center dose-finding study, to assess the efficacy, safety and tolerability of different doses of tobramycin inhalation powder in patients with Non Cystic Fibrosis Bronchiectasis and pulmonary P. aeruginosa infection

Summary

EudraCT number	2015-003040-39
Trial protocol	ES BE DE IE NL GB FR IT
Global end of trial date	20 March 2019

Results information

Result version number	v2
This version publication date	02 July 2020
First version publication date	03 April 2020
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	CTBM100G2202
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02712983
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@novartis.com
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@novartis.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	20 March 2019
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	20 March 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objectives were to: • Evaluate the change in colony forming units (CFUs) in *P. aeruginosa* bacterial load in sputum, from baseline to Day 29 of treatment, for different doses of tobramycin inhalation powder (TIP) administered once daily (o.d.) and twice daily (b.i.d.), each compared to placebo. • Assess safety and tolerability during the treatment epoch (112 days) and during the follow-up epoch (56 days) for each of the different doses of TIP, as compared to placebo. Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use <https://www.novctrd.com/CtrdWeb/home.novfor> complete trial results.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	28 February 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 6
Country: Number of subjects enrolled	France: 16
Country: Number of subjects enrolled	Germany: 16
Country: Number of subjects enrolled	United Kingdom: 26
Country: Number of subjects enrolled	Italy: 17
Country: Number of subjects enrolled	Spain: 26
Worldwide total number of subjects	107
EEA total number of subjects	107

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
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)	45
From 65 to 84 years	61
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

A total of 107 subjects were enrolled in the trial from 6 countries (Belgium [2 sites], France [4 sites], Germany [5 sites], Italy [6 sites], Spain [8 sites] and United Kingdom [9 sites]).

Pre-assignment

Screening details:

This study planned to recruit approximately 180 subjects to one of the 3 cohorts in a ratio of 1:1:1. The subjects within each cohort were randomized to blinded TIP or placebo with the following randomization scheme: TIP:TIP/Placebo cyclical:Placebo, in a 2:2:1 ratio.

Period 1

Period 1 title	Treatment Phase
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort A (3 capsules o.d.): TIP

Arm description:

Cohort A (3 capsules o.d.): Tobramycin inhalation powder (TIP)

Arm type	Experimental
Investigational medicinal product name	tobramycin dry powder
Investigational medicinal product code	TBM100
Other name	
Pharmaceutical forms	Inhalation powder, hard capsule
Routes of administration	Inhalation use

Dosage and administration details:

Three capsules of blinded TIP at 28 mg dosage strength, inhaled o.d. via the T 326 inhaler, for 112 days (on treatment). The total daily dose and each treatment therefore consisted of 84 mg tobramycin (3 capsules of 28 mg each).

Arm title	Cohort A (3 capsules o.d.): TIP/PBO
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Arm description:

Cohort A (3 capsules o.d.): Tobramycin inhalation powder (TIP) and inhaled placebo (PBO) cyclical

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

Dosage and administration details:

Three capsules of matching placebo to blinded TIP at 28 mg dosage strength, inhaled o.d. via the T 326 inhaler, by alternating TIP 28-days with placebo 28-days for two cycles for a total of 112 days.

Investigational medicinal product name	tobramycin dry powder
Investigational medicinal product code	TBM100
Other name	
Pharmaceutical forms	Inhalation powder, hard capsule
Routes of administration	Inhalation use

Dosage and administration details:

Three capsules of blinded TIP at 28 mg dosage strength, inhaled o.d. via the T 326 inhaler, by alternating TIP 28-days with placebo 28-days for two cycles for a total of 112 days.

Arm title	Cohort A (3 capsules o.d.): PBO
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Arm description:

Cohort A (3 capsules o.d.): Inhaled placebo (PBO)

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

Dosage and administration details:

The reference product consisted of placebo capsules (1,2 distearoyl-sn-glycero-3-phosphocholine /CaCl₂). The dose regimen for the reference product was 3 capsules blinded, inhaled o.d. via the T 326 inhaler, for 112 days (on treatment).

Arm title	Cohort B (5 capsules o.d.): TIP
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Arm description:

Cohort B (5 capsules o.d.): Tobramycin inhalation powder (TIP)

Arm type	Experimental
Investigational medicinal product name	tobramycin dry powder
Investigational medicinal product code	TBM100
Other name	
Pharmaceutical forms	Inhalation powder, hard capsule
Routes of administration	Inhalation use

Dosage and administration details:

Five capsules of blinded TIP at 28 mg dosage strength, inhaled o.d. via the T 326 inhaler, for 112 days (on treatment). The total daily dose and each treatment therefore consisted of 140 mg tobramycin (5 capsules of 28 mg each).

Arm title	Cohort B (5 capsules o.d.): TIP/PBO
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Arm description:

Cohort B (5 capsules o.d.): Tobramycin inhalation powder (TIP) and inhaled placebo (PBO) cyclical

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

Dosage and administration details:

Five capsules of matching placebo to blinded TIP at 28 mg dosage strength, inhaled o.d. via the T 326 inhaler, by alternating TIP 28-days with placebo 28-days for two cycles for a total of 112 days.

Investigational medicinal product name	tobramycin dry powder
Investigational medicinal product code	TBM100
Other name	
Pharmaceutical forms	Inhalation powder, hard capsule
Routes of administration	Inhalation use

Dosage and administration details:

Five capsules of blinded TIP at 28 mg dosage strength, inhaled o.d. via the T 326 inhaler, by alternating TIP 28-days with placebo 28-days for two cycles for a total of 112 days.

Arm title	Cohort B (5 capsules o.d.): PBO
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Arm description:	
Cohort B (5 capsules o.d.): inhaled placebo (PBO)	
Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder, hard capsule
Routes of administration	Inhalation use
Dosage and administration details:	
The reference product consisted of placebo capsules. The dose regimen for the reference product was 5 capsules blinded, inhaled o.d. via the T-326 inhaler, for 112 days (on treatment).	
Arm title	Cohort C (4 capsules b.i.d.): TIP
Arm description:	
Cohort C (4 capsules b.i.d.): Tobramycin inhalation powder (TIP)	
Arm type	Experimental
Investigational medicinal product name	tobramycin dry powder
Investigational medicinal product code	TBM100
Other name	
Pharmaceutical forms	Inhalation powder, hard capsule
Routes of administration	Inhalation use
Dosage and administration details:	
Four capsules of blinded TIP at 28 mg dosage strength, inhaled b.i.d. in the morning and in the evening via the T-326 inhaler, for 112 days of treatment. Each dose therefore consisted of 112 mg tobramycin (4 capsules of 28 mg each), the total daily dose corresponds to 224 mg tobramycin (112 mg b.i.d.).	
Arm title	Cohort C (4 capsules b.i.d.): TIP/PBO
Arm description:	
Cohort C (4 capsules b.i.d.): Tobramycin inhalation powder (TIP) and inhaled placebo (PBO) cyclical	
Arm type	Experimental
Investigational medicinal product name	tobramycin dry powder
Investigational medicinal product code	TBM100
Other name	
Pharmaceutical forms	Inhalation powder, hard capsule
Routes of administration	Inhalation use
Dosage and administration details:	
Four capsules of blinded TIP at 28 mg dosage strength, inhaled b.i.d. in the morning and in the evening via the T-326 inhaler, by alternating TIP 28-days with placebo 28-days for two cycles for a total of 112 days.	
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder, hard capsule
Routes of administration	Inhalation use
Dosage and administration details:	
Four capsules of matching placebo to blinded TIP at 28 mg dosage strength, inhaled b.i.d. in the morning and in the evening via the T-326 inhaler, by alternating TIP 28-days with placebo 28-days for two cycles for a total of 112 days.	
Arm title	Cohort C (4 capsules b.i.d.): PBO
Arm description:	
Cohort C (4 capsules b.i.d.): inhaled placebo (PBO)	
Arm type	Placebo

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder, hard capsule
Routes of administration	Inhalation use

Dosage and administration details:

The reference product consisted of placebo capsules. The dose regimen for the reference product was four capsules blinded, inhaled b.i.d. via the T-326 inhaler, for 112 days (on treatment).

Number of subjects in period 1	Cohort A (3 capsules o.d.): TIP	Cohort A (3 capsules o.d.): TIP/PBO	Cohort A (3 capsules o.d.): PBO
Started	14	13	7
Pharmacokinetic Analysis Set	14	13	0 ^[1]
Completed	9	12	6
Not completed	5	1	1
Consent withdrawn by subject	2	-	-
Physician decision	-	-	-
Adverse event, non-fatal	3	1	1
Technical Problems	-	-	-
Protocol deviation	-	-	-

Number of subjects in period 1	Cohort B (5 capsules o.d.): TIP	Cohort B (5 capsules o.d.): TIP/PBO	Cohort B (5 capsules o.d.): PBO
Started	15	14	7
Pharmacokinetic Analysis Set	15	14	0 ^[2]
Completed	7	10	7
Not completed	8	4	0
Consent withdrawn by subject	2	1	-
Physician decision	-	-	-
Adverse event, non-fatal	4	3	-
Technical Problems	-	-	-
Protocol deviation	2	-	-

Number of subjects in period 1	Cohort C (4 capsules b.i.d.): TIP	Cohort C (4 capsules b.i.d.): TIP/PBO	Cohort C (4 capsules b.i.d.): PBO
Started	15	15	7
Pharmacokinetic Analysis Set	15	14	0 ^[3]
Completed	6	6	5
Not completed	9	9	2
Consent withdrawn by subject	1	2	-
Physician decision	-	1	1
Adverse event, non-fatal	6	6	1
Technical Problems	1	-	-
Protocol deviation	1	-	-

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: PK assessments were done for placebo groups per protocol but they might have not considered in Analysis set for placebo group

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: PK assessments were done for placebo groups per protocol but they might have not considered in Analysis set for placebo group

[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: PK assessments were done for placebo groups per protocol but they might have not considered in Analysis set for placebo group

Period 2

Period 2 title	Post-Treatment Efficacy Follow-Up Phase
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	No
Arm title	Cohort A (3 capsules o.d.): TIP/PBO

Arm description:

Cohort A (3 capsules o.d.): Tobramycin inhalation powder (TIP) and inhaled placebo (PBO) cyclical

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

Dosage and administration details:

Three capsules of matching placebo to blinded TIP at 28 mg dosage strength, inhaled o.d. via the T 326 inhaler, by alternating TIP 28-days with placebo 28-days for two cycles for a total of 112 days.

Investigational medicinal product name	tobramycin dry powder
Investigational medicinal product code	TBM100
Other name	
Pharmaceutical forms	Inhalation powder, hard capsule
Routes of administration	Inhalation use

Dosage and administration details:

Three capsules of blinded TIP at 28 mg dosage strength, inhaled o.d. via the T 326 inhaler, by alternating TIP 28-days with placebo 28-days for two cycles for a total of 112 days.

Arm title	Cohort B (5 capsules o.d.): TIP
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Arm description:

Cohort B (5 capsules o.d.): Tobramycin inhalation powder (TIP)

Arm type	Experimental
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Investigational medicinal product name	tobramycin dry powder
Investigational medicinal product code	TBM100
Other name	
Pharmaceutical forms	Inhalation powder, hard capsule
Routes of administration	Inhalation use

Dosage and administration details:

Five capsules of blinded TIP at 28 mg dosage strength, inhaled o.d. via the T 326 inhaler, for 112 days (on treatment). The total daily dose and each treatment therefore consisted of 140 mg tobramycin (5 capsules of 28 mg each).

Arm title	Cohort B (5 capsules o.d.): TIP/PBO
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Arm description:

Cohort B (5 capsules o.d.): Tobramycin inhalation powder (TIP) and inhaled placebo (PBO) cyclical

Arm type	Experimental
Investigational medicinal product name	tobramycin dry powder
Investigational medicinal product code	TBM100
Other name	
Pharmaceutical forms	Inhalation powder, hard capsule
Routes of administration	Inhalation use

Dosage and administration details:

Five capsules of blinded TIP at 28 mg dosage strength, inhaled o.d. via the T 326 inhaler, by alternating TIP 28-days with placebo 28-days for two cycles for a total of 112 days.

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder, hard capsule
Routes of administration	Inhalation use

Dosage and administration details:

Five capsules of matching placebo to blinded TIP at 28 mg dosage strength, inhaled o.d. via the T 326 inhaler, by alternating TIP 28-days with placebo 28-days for two cycles for a total of 112 days.

Arm title	Cohort B (5 capsules o.d.): PBO
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Arm description:

Cohort B (5 capsules o.d.): inhaled placebo (PBO)

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

Dosage and administration details:

The reference product consisted of placebo capsules. The dose regimen for the reference product was 5 capsules blinded, inhaled o.d. via the T-326 inhaler, for 112 days (on treatment).

Arm title	Cohort C (4 capsules b.i.d.): TIP
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Arm description:

Cohort C (4 capsules b.i.d.): Tobramycin inhalation powder (TIP)

Arm type	Experimental
Investigational medicinal product name	tobramycin dry powder
Investigational medicinal product code	TBM100
Other name	
Pharmaceutical forms	Inhalation powder, hard capsule
Routes of administration	Inhalation use

Dosage and administration details:

Four capsules of blinded TIP at 28 mg dosage strength, inhaled b.i.d. in the morning and in the evening via the T-326 inhaler, for 112 days of treatment. Each dose therefore consisted of 112 mg tobramycin

(4 capsules of 28 mg each), the total daily dose corresponds to 224 mg tobramycin (112 mg b.i.d.).

Arm title	Cohort C (4 capsules b.i.d.): TIP/PBO
Arm description: Cohort C (4 capsules b.i.d.): Tobramycin inhalation powder (TIP) and inhaled placebo (PBO) cyclical	
Arm type	Experimental
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder, hard capsule
Routes of administration	Inhalation use

Dosage and administration details:

Four capsules of matching placebo to blinded TIP at 28 mg dosage strength, inhaled b.i.d. in the morning and in the evening via the T-326 inhaler, by alternating TIP 28-days with placebo 28-days for two cycles for a total of 112 days.

Investigational medicinal product name	tobramycin dry powder
Investigational medicinal product code	TBM100
Other name	
Pharmaceutical forms	Inhalation powder, hard capsule
Routes of administration	Inhalation use

Dosage and administration details:

Four capsules of blinded TIP at 28 mg dosage strength, inhaled b.i.d. in the morning and in the evening via the T-326 inhaler, by alternating TIP 28-days with placebo 28-days for two cycles for a total of 112 days.

Number of subjects in period 2	Cohort A (3 capsules o.d.): TIP/PBO	Cohort B (5 capsules o.d.): TIP	Cohort B (5 capsules o.d.): TIP/PBO
Started	1	1	2
Completed	0	0	0
Not completed	1	1	2
Consent withdrawn by subject	-	-	2
Adverse event, non-fatal	1	-	-
Lost to follow-up	-	1	-

Number of subjects in period 2	Cohort B (5 capsules o.d.): PBO	Cohort C (4 capsules b.i.d.): TIP	Cohort C (4 capsules b.i.d.): TIP/PBO
Started	1	2	3
Completed	0	0	0
Not completed	1	2	3
Consent withdrawn by subject	1	1	2
Adverse event, non-fatal	-	1	1
Lost to follow-up	-	-	-

Baseline characteristics

Reporting groups	
Reporting group title	Cohort A (3 capsules o.d.): TIP
Reporting group description:	
Cohort A (3 capsules o.d.): Tobramycin inhalation powder (TIP)	
Reporting group title	Cohort A (3 capsules o.d.): TIP/PBO
Reporting group description:	
Cohort A (3 capsules o.d.): Tobramycin inhalation powder (TIP) and inhaled placebo (PBO) cyclical	
Reporting group title	Cohort A (3 capsules o.d.): PBO
Reporting group description:	
Cohort A (3 capsules o.d.): Inhaled placebo (PBO)	
Reporting group title	Cohort B (5 capsules o.d.): TIP
Reporting group description:	
Cohort B (5 capsules o.d.): Tobramycin inhalation powder (TIP)	
Reporting group title	Cohort B (5 capsules o.d.): TIP/PBO
Reporting group description:	
Cohort B (5 capsules o.d.): Tobramycin inhalation powder (TIP) and inhaled placebo (PBO) cyclical	
Reporting group title	Cohort B (5 capsules o.d.): PBO
Reporting group description:	
Cohort B (5 capsules o.d.): inhaled placebo (PBO)	
Reporting group title	Cohort C (4 capsules b.i.d.): TIP
Reporting group description:	
Cohort C (4 capsules b.i.d.): Tobramycin inhalation powder (TIP)	
Reporting group title	Cohort C (4 capsules b.i.d.): TIP/PBO
Reporting group description:	
Cohort C (4 capsules b.i.d.): Tobramycin inhalation powder (TIP) and inhaled placebo (PBO) cyclical	
Reporting group title	Cohort C (4 capsules b.i.d.): PBO
Reporting group description:	
Cohort C (4 capsules b.i.d.): inhaled placebo (PBO)	

Reporting group values	Cohort A (3 capsules o.d.): TIP	Cohort A (3 capsules o.d.): TIP/PBO	Cohort A (3 capsules o.d.): PBO
Number of subjects	14	13	7
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	6	10	4
From 65-84 years	8	3	3
85 years and over	0	0	0
Age Continuous			
Units: Years			
arithmetic mean	63.4	57.5	61.3

standard deviation	± 12.66	± 11.83	± 7.45
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Sex: Female, Male			
Units: Participants			
Female	9	10	3
Male	5	3	4
Race/Ethnicity, Customized			
Units: Subjects			
Caucasian	12	11	7
Asian	1	0	0
Pacific Islander	0	0	0
Other	1	2	0

Reporting group values	Cohort B (5 capsules o.d.): TIP	Cohort B (5 capsules o.d.): TIP/PBO	Cohort B (5 capsules o.d.): PBO
Number of subjects	15	14	7
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	6	6	1
From 65-84 years	9	8	6
85 years and over	0	0	0
Age Continuous			
Units: Years			
arithmetic mean	64.3	62.4	69.1
standard deviation	± 17.86	± 16.71	± 13.21
Sex: Female, Male			
Units: Participants			
Female	10	7	6
Male	5	7	1
Race/Ethnicity, Customized			
Units: Subjects			
Caucasian	13	11	5
Asian	0	0	1
Pacific Islander	1	0	0
Other	1	3	1

Reporting group values	Cohort C (4 capsules b.i.d.): TIP	Cohort C (4 capsules b.i.d.): TIP/PBO	Cohort C (4 capsules b.i.d.): PBO
Number of subjects	15	15	7
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0

Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	5	6	1
From 65-84 years	9	9	6
85 years and over	1	0	0
Age Continuous			
Units: Years			
arithmetic mean	66.1	60.8	71.3
standard deviation	± 12.23	± 12.94	± 10.39
Sex: Female, Male			
Units: Participants			
Female	9	8	4
Male	6	7	3
Race/Ethnicity, Customized			
Units: Subjects			
Caucasian	15	15	7
Asian	0	0	0
Pacific Islander	0	0	0
Other	0	0	0

Reporting group values	Total		
Number of subjects	107		
Age categorical			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	45		
From 65-84 years	61		
85 years and over	1		
Age Continuous			
Units: Years			
arithmetic mean	-		
standard deviation	-		
Sex: Female, Male			
Units: Participants			
Female	66		
Male	41		
Race/Ethnicity, Customized			
Units: Subjects			
Caucasian	96		
Asian	2		
Pacific Islander	1		
Other	8		

Subject analysis sets

Subject analysis set title	Pooled TIP
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Pooled Tobramycin inhalation powder (TIP): For efficacy analysis, subjects assigned to TIP groups were pooled across the 3 cohorts.

Subject analysis set title	Pooled TIP/PBO
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Pooled Tobramycin inhalation powder (TIP) and inhaled placebo (PBO) cyclical: For efficacy analysis, subjects assigned to TIP/PBO groups were pooled across the 3 cohorts.

Subject analysis set title	Pooled PBO
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Pooled inhaled placebo (PBO): For efficacy analysis, subjects assigned to Placebo groups were pooled across the 3 cohorts, as the number of placebo capsules was not expected to impact the efficacy assessments.

Subject analysis set title	Pooled TIP
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Pooled Tobramycin inhalation powder (TIP): For efficacy analysis, subjects assigned to TIP groups were pooled across the 3 cohorts.

Subject analysis set title	Pooled TIP
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Pooled Tobramycin inhalation powder (TIP): For efficacy analysis, subjects assigned to TIP groups were pooled across the 3 cohorts.

Subject analysis set title	Pooled TIP
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Pooled Tobramycin inhalation powder (TIP): For efficacy analysis, subjects assigned to TIP groups were pooled across the 3 cohorts.

Subject analysis set title	Pooled TIP/PBO
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Pooled Tobramycin inhalation powder (TIP) and inhaled placebo (PBO) cyclical: For efficacy analysis, subjects assigned to TIP/PBO groups were pooled across the 3 cohorts.

Subject analysis set title	Pooled TIP
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Pooled Tobramycin inhalation powder (TIP): For efficacy analysis, subjects assigned to TIP groups were pooled across the 3 cohorts.

Subject analysis set title	Pooled TIP/PBO
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Pooled Tobramycin inhalation powder (TIP) and inhaled placebo (PBO) cyclical: For efficacy analysis, subjects assigned to TIP/PBO groups were pooled across the 3 cohorts.

Subject analysis set title	Pooled PBO
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Pooled inhaled placebo (PBO): For efficacy analysis, subjects assigned to Placebo groups were pooled across the 3 cohorts, as the number of placebo capsules was not expected to impact the efficacy assessments.

Reporting group values	Pooled TIP	Pooled TIP/PBO	Pooled PBO
Number of subjects	44	42	21
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age Continuous Units: Years arithmetic mean standard deviation	±	±	±
Sex: Female, Male Units: Participants			
Female Male			
Race/Ethnicity, Customized Units: Subjects			
Caucasian Asian Pacific Islander Other			

Reporting group values	Pooled TIP	Pooled TIP	Pooled TIP
Number of subjects	43	42	38
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age Continuous Units: Years arithmetic mean			

standard deviation	±	±	±
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Sex: Female, Male Units: Participants			
Female			
Male			
Race/Ethnicity, Customized Units: Subjects			
Caucasian			
Asian			
Pacific Islander			
Other			

Reporting group values	Pooled TIP/PBO	Pooled TIP	Pooled TIP/PBO
Number of subjects	33	7	6
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age Continuous Units: Years arithmetic mean standard deviation		16.2 ± 7.05	15.2 ± 6.44
Sex: Female, Male Units: Participants			
Female			
Male			
Race/Ethnicity, Customized Units: Subjects			
Caucasian			
Asian			
Pacific Islander			
Other			

Reporting group values	Pooled PBO		
Number of subjects	2		
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days)			

Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age Continuous Units: Years arithmetic mean standard deviation	10.5 ± 0.71		
Sex: Female, Male Units: Participants			
Female Male			
Race/Ethnicity, Customized Units: Subjects			
Caucasian Asian Pacific Islander Other			

End points

End points reporting groups

Reporting group title	Cohort A (3 capsules o.d.): TIP
Reporting group description:	
Cohort A (3 capsules o.d.): Tobramycin inhalation powder (TIP)	
Reporting group title	Cohort A (3 capsules o.d.): TIP/PBO
Reporting group description:	
Cohort A (3 capsules o.d.): Tobramycin inhalation powder (TIP) and inhaled placebo (PBO) cyclical	
Reporting group title	Cohort A (3 capsules o.d.): PBO
Reporting group description:	
Cohort A (3 capsules o.d.): Inhaled placebo (PBO)	
Reporting group title	Cohort B (5 capsules o.d.): TIP
Reporting group description:	
Cohort B (5 capsules o.d.): Tobramycin inhalation powder (TIP)	
Reporting group title	Cohort B (5 capsules o.d.): TIP/PBO
Reporting group description:	
Cohort B (5 capsules o.d.): Tobramycin inhalation powder (TIP) and inhaled placebo (PBO) cyclical	
Reporting group title	Cohort B (5 capsules o.d.): PBO
Reporting group description:	
Cohort B (5 capsules o.d.): inhaled placebo (PBO)	
Reporting group title	Cohort C (4 capsules b.i.d.): TIP
Reporting group description:	
Cohort C (4 capsules b.i.d.): Tobramycin inhalation powder (TIP)	
Reporting group title	Cohort C (4 capsules b.i.d.): TIP/PBO
Reporting group description:	
Cohort C (4 capsules b.i.d.): Tobramycin inhalation powder (TIP) and inhaled placebo (PBO) cyclical	
Reporting group title	Cohort C (4 capsules b.i.d.): PBO
Reporting group description:	
Cohort C (4 capsules b.i.d.): inhaled placebo (PBO)	
Reporting group title	Cohort A (3 capsules o.d.): TIP/PBO
Reporting group description:	
Cohort A (3 capsules o.d.): Tobramycin inhalation powder (TIP) and inhaled placebo (PBO) cyclical	
Reporting group title	Cohort B (5 capsules o.d.): TIP
Reporting group description:	
Cohort B (5 capsules o.d.): Tobramycin inhalation powder (TIP)	
Reporting group title	Cohort B (5 capsules o.d.): TIP/PBO
Reporting group description:	
Cohort B (5 capsules o.d.): Tobramycin inhalation powder (TIP) and inhaled placebo (PBO) cyclical	
Reporting group title	Cohort B (5 capsules o.d.): PBO
Reporting group description:	
Cohort B (5 capsules o.d.): inhaled placebo (PBO)	
Reporting group title	Cohort C (4 capsules b.i.d.): TIP
Reporting group description:	
Cohort C (4 capsules b.i.d.): Tobramycin inhalation powder (TIP)	
Reporting group title	Cohort C (4 capsules b.i.d.): TIP/PBO
Reporting group description:	
Cohort C (4 capsules b.i.d.): Tobramycin inhalation powder (TIP) and inhaled placebo (PBO) cyclical	
Subject analysis set title	Pooled TIP
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Pooled Tobramycin inhalation powder (TIP): For efficacy analysis, subjects assigned to TIP groups were pooled across the 3 cohorts.

Subject analysis set title	Pooled TIP/PBO
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Pooled Tobramycin inhalation powder (TIP) and inhaled placebo (PBO) cyclical: For efficacy analysis, subjects assigned to TIP/PBO groups were pooled across the 3 cohorts.

Subject analysis set title	Pooled PBO
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Pooled inhaled placebo (PBO): For efficacy analysis, subjects assigned to Placebo groups were pooled across the 3 cohorts, as the number of placebo capsules was not expected to impact the efficacy assessments.

Subject analysis set title	Pooled TIP
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Pooled Tobramycin inhalation powder (TIP): For efficacy analysis, subjects assigned to TIP groups were pooled across the 3 cohorts.

Subject analysis set title	Pooled TIP
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Pooled Tobramycin inhalation powder (TIP): For efficacy analysis, subjects assigned to TIP groups were pooled across the 3 cohorts.

Subject analysis set title	Pooled TIP
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Pooled Tobramycin inhalation powder (TIP): For efficacy analysis, subjects assigned to TIP groups were pooled across the 3 cohorts.

Subject analysis set title	Pooled TIP/PBO
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Pooled Tobramycin inhalation powder (TIP) and inhaled placebo (PBO) cyclical: For efficacy analysis, subjects assigned to TIP/PBO groups were pooled across the 3 cohorts.

Subject analysis set title	Pooled TIP
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Pooled Tobramycin inhalation powder (TIP): For efficacy analysis, subjects assigned to TIP groups were pooled across the 3 cohorts.

Subject analysis set title	Pooled TIP/PBO
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Pooled Tobramycin inhalation powder (TIP) and inhaled placebo (PBO) cyclical: For efficacy analysis, subjects assigned to TIP/PBO groups were pooled across the 3 cohorts.

Subject analysis set title	Pooled PBO
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Pooled inhaled placebo (PBO): For efficacy analysis, subjects assigned to Placebo groups were pooled across the 3 cohorts, as the number of placebo capsules was not expected to impact the efficacy assessments.

Primary: Change From Baseline to Day 29 in Pseudomonas Aeruginosa (P. aeruginosa) density in sputum (log10 CFUs)

End point title	Change From Baseline to Day 29 in Pseudomonas Aeruginosa (P. aeruginosa) density in sputum (log10 CFUs) ^[1]
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End point description:

Microbiological data was collected to understand the direct impact of the drug on the pathogens. Sputum samples were cultured for the presence of three Pseudomonas aeruginosa (P. aeruginosa) biotypes measured were mucoid, dry and small colony variant. Change was determined using the formula = (Post-baseline value - baseline value). If no P. aeruginosa was isolated for a visit, log10 colony forming units (CFU) was imputed with log10 (19) for all biotypes. Only values for all morphotypes presented.

End point type	Primary
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End point timeframe:

Baseline (Visit 101/Day 1), Visit 102 (Day 8), Visit 103 (Day 29)

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: For efficacy analysis, subjects assigned to: Placebo groups were pooled across the 3 cohorts, as the number of placebo capsules was not expected to impact the efficacy assessments (Pooled inhaled placebo (PBO)); TIP groups were pooled across the 3 cohorts (Pooled TIP) and TIP/PBO groups were pooled across the 3 cohorts (Pooled TIP/PBO).

End point values	Cohort A (3 capsules o.d.): TIP	Cohort A (3 capsules o.d.): TIP/PBO	Cohort B (5 capsules o.d.): TIP	Cohort B (5 capsules o.d.): TIP/PBO
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	14	13	15	14
Units: log10 CFUs				
arithmetic mean (standard deviation)				
Baseline	6.80 (± 1.202)	7.67 (± 1.507)	6.10 (± 2.419)	6.98 (± 1.804)
Change from BL at Day 8	-2.82 (± 1.440)	-3.23 (± 2.204)	-2.04 (± 2.274)	-3.98 (± 1.865)
Change from BL at Day 29	-2.61 (± 2.600)	-2.80 (± 2.823)	-1.56 (± 2.885)	-3.57 (± 2.218)

End point values	Cohort C (4 capsules b.i.d.): TIP	Cohort C (4 capsules b.i.d.): TIP/PBO	Pooled TIP	Pooled TIP/PBO
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	15	15	44	42
Units: log10 CFUs				
arithmetic mean (standard deviation)				
Baseline	6.79 (± 0.908)	5.73 (± 1.885)	6.57 (± 1.625)	6.74 (± 1.892)
Change from BL at Day 8	-4.54 (± 1.283)	-3.47 (± 1.583)	-3.30 (± 1.937)	-3.58 (± 1.878)
Change from BL at Day 29	-4.36 (± 1.101)	-2.58 (± 2.871)	-2.98 (± 2.474)	-2.96 (± 2.618)

End point values	Pooled PBO			
Subject group type	Subject analysis set			
Number of subjects analysed	21			
Units: log10 CFUs				

arithmetic mean (standard deviation)				
Baseline	7.09 (\pm 2.012)			
Change from BL at Day 8	-0.72 (\pm 1.765)			
Change from BL at Day 29	0.05 (\pm 1.518)			

Statistical analyses

Statistical analysis title	Day 8 Cohort A: TIP, Pooled PBO
Comparison groups	Cohort A (3 capsules o.d.): TIP v Pooled PBO
Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	LS Mean Diff (SE) vs pooled placebo
Point estimate	-2.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.62
upper limit	-1.22
Variability estimate	Standard error of the mean
Dispersion value	0.6

Statistical analysis title	Day 8 Cohort A: TIP/PBO, Pooled PBO
Comparison groups	Cohort A (3 capsules o.d.): TIP/PBO v Pooled PBO
Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	LS Mean Diff (SE) vs pooled placebo
Point estimate	-2.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.3
upper limit	-0.98
Variability estimate	Standard error of the mean
Dispersion value	0.58

Statistical analysis title	Day 8 Cohort B: TIP, Pooled PBO
Comparison groups	Cohort B (5 capsules o.d.): TIP v Pooled PBO

Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	LS Mean Diff (SE) vs pooled placebo
Point estimate	-1.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.2
upper limit	-0.68
Variability estimate	Standard error of the mean
Dispersion value	0.63

Statistical analysis title	Day 8 Cohort B: TIP/PBO, Pooled PBO
Comparison groups	Cohort B (5 capsules o.d.): TIP/PBO v Pooled PBO
Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	LS Mean Diff (SE) vs pooled placebo
Point estimate	-3.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.38
upper limit	-2.15
Variability estimate	Standard error of the mean
Dispersion value	0.56

Statistical analysis title	Day 8 Cohort C: TIP, Pooled PBO
Comparison groups	Cohort C (4 capsules b.i.d.): TIP v Pooled PBO
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	LS Mean Diff (SE) vs pooled placebo
Point estimate	-4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.06
upper limit	-2.88
Variability estimate	Standard error of the mean
Dispersion value	0.55

Statistical analysis title	Day 8 Cohort C: TIP/PBO, Pooled PBO
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Comparison groups	Cohort C (4 capsules b.i.d.): TIP/PBO v Pooled PBO
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	LS Mean Diff (SE) vs pooled placebo
Point estimate	-3.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.57
upper limit	-2.14
Variability estimate	Standard error of the mean
Dispersion value	0.61

Statistical analysis title	Day 8: Pooled TIP, Pooled PBO
Comparison groups	Pooled TIP v Pooled PBO
Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	LS Mean Diff (SE) vs pooled placebo
Point estimate	-2.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.66
upper limit	-1.89
Variability estimate	Standard error of the mean
Dispersion value	0.44

Statistical analysis title	Day 8: Pooled TIP/PBO, Pooled PBO
Comparison groups	Pooled TIP/PBO v Pooled PBO
Number of subjects included in analysis	63
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	LS Mean Diff (SE) vs pooled placebo
Point estimate	-2.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.79
upper limit	-2.05
Variability estimate	Standard error of the mean
Dispersion value	0.43

Statistical analysis title	Day 29 Cohort A: TIP, Pooled PBO
Comparison groups	Cohort A (3 capsules o.d.): TIP v Pooled PBO
Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	LS Mean Diff (SE) vs pooled placebo
Point estimate	-2.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.28
upper limit	-1.31
Variability estimate	Standard error of the mean
Dispersion value	0.75

Statistical analysis title	Day 29 Cohort A: TIP/PBO, Pooled PBO
Comparison groups	Cohort A (3 capsules o.d.): TIP/PBO v Pooled PBO
Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	LS Mean Diff (SE) vs pooled placebo
Point estimate	-2.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.03
upper limit	-0.67
Variability estimate	Standard error of the mean
Dispersion value	0.84

Statistical analysis title	Day 29 Cohort B: TIP, Pooled PBO
Comparison groups	Cohort B (5 capsules o.d.): TIP v Pooled PBO
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	LS Mean Diff (SE) vs pooled placebo
Point estimate	-2.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.04
upper limit	-0.52
Variability estimate	Standard error of the mean
Dispersion value	0.88

Statistical analysis title	Day 29 Cohort B: TIP/PBO, Pooled PBO
Comparison groups	Cohort B (5 capsules o.d.): TIP/PBO v Pooled PBO
Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	LS Mean Diff (SE) vs pooled placebo
Point estimate	-3.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.16
upper limit	-1.85
Variability estimate	Standard error of the mean
Dispersion value	0.83

Statistical analysis title	Day 29 Cohort C: TIP, Pooled PBO
Comparison groups	Cohort C (4 capsules b.i.d.): TIP v Pooled PBO
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	LS Mean Diff (SE) vs pooled placebo
Point estimate	-4.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.13
upper limit	-3.09
Variability estimate	Standard error of the mean
Dispersion value	0.76

Statistical analysis title	Day 29 Cohort C: TIP/PBO, Pooled PBO
Comparison groups	Cohort C (4 capsules b.i.d.): TIP/PBO v Pooled PBO
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	LS Mean Diff (SE) vs pooled placebo
Point estimate	-3.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.68
upper limit	-1.52

Variability estimate	Standard error of the mean
Dispersion value	0.79

Statistical analysis title	Day 29: Pooled TIP, Pooled PBO
Comparison groups	Pooled TIP v Pooled PBO
Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	LS Mean Diff (SE) vs pooled placebo
Point estimate	-3.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.43
upper limit	-2.02
Variability estimate	Standard error of the mean
Dispersion value	0.61

Statistical analysis title	Day 29: Pooled TIP/PBO, Pooled PBO
Comparison groups	Pooled TIP/PBO v Pooled PBO
Number of subjects included in analysis	63
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	LS Mean Diff (SE) vs pooled placebo
Point estimate	-3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.19
upper limit	-1.78
Variability estimate	Standard error of the mean
Dispersion value	0.61

Secondary: Change From Baseline to each post-baseline visit in *Pseudomonas aeruginosa* (P. aeruginosa) density in sputum (log10 CFUs)

End point title	Change From Baseline to each post-baseline visit in <i>Pseudomonas aeruginosa</i> (P. aeruginosa) density in sputum (log10 CFUs) ^[2]
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End point description:

Microbiological data was collected to understand the direct impact of the drug on the pathogens. Sputum samples were cultured for the presence of three *Pseudomonas aeruginosa* (P. aeruginosa) biotypes measured were mucoid, dry and small colony variant. Change was determined using the formula = (Post-baseline value - baseline value). If no P. aeruginosa was isolated for a visit, log10 colony forming units (CFU) was imputed with log10 (19) for all biotypes. Only values for all morphotypes are presented.

End point type	Secondary
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End point timeframe:

Baseline (Visit 101/Day 1), Visit 104 (Day 57), Visit 105 (Day 85), Visit 106 (Day 113), End of Treatment (EOT), Visit 201 (Day 141), Visit 202 (Day 169)

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: For efficacy analysis, subjects assigned to: Placebo groups were pooled across the 3 cohorts, as the number of placebo capsules was not expected to impact the efficacy assessments (Pooled inhaled placebo (PBO)); TIP groups were pooled across the 3 cohorts (Pooled TIP) and TIP/PBO groups were pooled across the 3 cohorts (Pooled TIP/PBO).

End point values	Cohort A (3 capsules o.d.): TIP	Cohort A (3 capsules o.d.): TIP/PBO	Cohort B (5 capsules o.d.): TIP	Cohort B (5 capsules o.d.): TIP/PBO
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	14	13	15	14
Units: log ₁₀ CFUs				
arithmetic mean (standard deviation)				
Baseline (BL)	6.80 (± 1.202)	7.67 (± 1.507)	6.10 (± 2.419)	6.98 (± 1.804)
Change from BL at Day 57	-1.72 (± 3.066)	-0.72 (± 2.677)	-0.90 (± 1.894)	-1.62 (± 2.804)
Change from BL at Day 85	-2.47 (± 2.446)	-2.94 (± 2.492)	-2.81 (± 3.653)	-3.88 (± 2.470)
Change from BL at Day 113	-2.94 (± 1.977)	-1.03 (± 2.002)	-1.82 (± 2.331)	-1.99 (± 3.020)
Change from BL at EOT	-2.49 (± 1.896)	-1.08 (± 1.907)	-0.84 (± 1.766)	-1.86 (± 2.607)
Change from BL at Day 141	-0.90 (± 2.113)	-0.82 (± 2.117)	0.10 (± 1.551)	-2.17 (± 2.863)
Change from BL at Day 169	-0.62 (± 2.324)	-1.19 (± 1.885)	0.46 (± 1.651)	-1.27 (± 2.684)

End point values	Cohort C (4 capsules b.i.d.): TIP	Cohort C (4 capsules b.i.d.): TIP/PBO	Pooled TIP	Pooled TIP/PBO
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	15	15	44	42
Units: log ₁₀ CFUs				
arithmetic mean (standard deviation)				
Baseline (BL)	6.79 (± 0.908)	5.73 (± 1.885)	6.57 (± 1.625)	6.74 (± 1.892)
Change from BL at Day 57	-3.53 (± 2.220)	-0.49 (± 2.305)	-2.25 (± 2.646)	-0.96 (± 2.576)
Change from BL at Day 85	-3.08 (± 1.624)	-2.00 (± 2.951)	-2.76 (± 2.446)	-3.01 (± 2.641)
Change from BL at Day 113	-3.17 (± 2.378)	-1.54 (± 3.534)	-2.79 (± 2.141)	-1.50 (± 2.707)
Change from BL at EOT	-2.60 (± 2.531)	-1.29 (± 3.300)	-2.01 (± 2.192)	-1.42 (± 2.650)
Change from BL at Day 141	-0.92 (± 2.385)	-0.87 (± 3.640)	-0.68 (± 2.067)	-1.34 (± 2.793)
Change from BL at Day 169	0.62 (± 1.038)	1.33 (± 4.219)	0.03 (± 1.882)	-0.51 (± 3.036)

End point values	Pooled PBO			
Subject group type	Subject analysis set			
Number of subjects analysed	21			
Units: log10 CFUs				
arithmetic mean (standard deviation)				
Baseline (BL)	7.09 (± 2.012)			
Change from BL at Day 57	0.20 (± 1.408)			
Change from BL at Day 85	-0.36 (± 2.238)			
Change from BL at Day 113	-0.20 (± 1.513)			
Change from BL at EOT	-0.34 (± 1.445)			
Change from BL at Day 141	-0.06 (± 2.191)			
Change from BL at Day 169	0.62 (± 2.694)			

Statistical analyses

Statistical analysis title	Day 57 Cohort A: TIP, Pooled PBO
Comparison groups	Cohort A (3 capsules o.d.): TIP v Pooled PBO
Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	LS Mean Diff (SE) vs pooled placebo
Point estimate	-2.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.82
upper limit	-0.36
Variability estimate	Standard error of the mean
Dispersion value	0.87

Statistical analysis title	Day 57 Cohort A: TIP/PBO, Pooled PBO
Comparison groups	Cohort A (3 capsules o.d.): TIP/PBO v Pooled PBO
Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	LS Mean Diff (SE) vs pooled placebo
Point estimate	-0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.21
upper limit	1.29
Variability estimate	Standard error of the mean
Dispersion value	0.88

Statistical analysis title	Day 57 Cohort B: TIP, Pooled PBO
Comparison groups	Cohort B (5 capsules o.d.): TIP v Pooled PBO
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	LS Mean Diff (SE) vs pooled placebo
Point estimate	-1.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.87
upper limit	0.08
Variability estimate	Standard error of the mean
Dispersion value	0.99

Statistical analysis title	Day 57 Cohort B: TIP/PBO, Pooled PBO
Comparison groups	Cohort B (5 capsules o.d.): TIP/PBO v Pooled PBO
Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	LS Mean Diff (SE) vs pooled placebo
Point estimate	-1.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.34
upper limit	0.16
Variability estimate	Standard error of the mean
Dispersion value	0.88

Statistical analysis title	Day 57 Cohort C: TIP, Pooled PBO
Comparison groups	Cohort C (4 capsules b.i.d.): TIP v Pooled PBO
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	LS Mean Diff (SE) vs pooled placebo
Point estimate	-3.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.5
upper limit	-2.22

Variability estimate	Standard error of the mean
Dispersion value	0.82

Statistical analysis title	Day 57 Cohort C: TIP/PBO, Pooled PBO
Comparison groups	Cohort C (4 capsules b.i.d.): TIP/PBO v Pooled PBO
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	LS Mean Diff (SE) vs pooled placebo
Point estimate	-1.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.26
upper limit	0.41
Variability estimate	Standard error of the mean
Dispersion value	0.92

Statistical analysis title	Day 57: Pooled TIP, Pooled PBO
Comparison groups	Pooled TIP v Pooled PBO
Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	LS Mean Diff (SE) vs pooled placebo
Point estimate	-2.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.98
upper limit	-1.25
Variability estimate	Standard error of the mean
Dispersion value	0.68

Statistical analysis title	Day 57: Pooled TIP/PBO, Pooled PBO
Comparison groups	Pooled TIP/PBO v Pooled PBO
Number of subjects included in analysis	63
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	LS Mean Diff (SE) vs pooled placebo
Point estimate	-1.2

Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.5
upper limit	0.19
Variability estimate	Standard error of the mean
Dispersion value	0.67

Statistical analysis title	Day 85 Cohort A: TIP, Pooled PBO
Comparison groups	Cohort A (3 capsules o.d.): TIP v Pooled PBO
Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	LS Mean Diff (SE) vs pooled placebo
Point estimate	-2.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4
upper limit	-0.38
Variability estimate	Standard error of the mean
Dispersion value	0.9

Statistical analysis title	Day 85 Cohort A: TIP/PBO, Pooled PBO
Comparison groups	Cohort A (3 capsules o.d.): TIP/PBO v Pooled PBO
Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	LS Mean Diff (SE) vs pooled placebo
Point estimate	-1.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.81
upper limit	0.13
Variability estimate	Standard error of the mean
Dispersion value	0.99

Statistical analysis title	Day 85 Cohort B: TIP, Pooled PBO
Comparison groups	Cohort B (5 capsules o.d.): TIP v Pooled PBO

Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	LS Mean Diff (SE) vs pooled placebo
Point estimate	-2.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.96
upper limit	-0.53
Variability estimate	Standard error of the mean
Dispersion value	1.11

Statistical analysis title	Day 85 Cohort B: TIP/PBO, Pooled PBO
Comparison groups	Cohort B (5 capsules o.d.): TIP/PBO v Pooled PBO
Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	LS Mean Diff (SE) vs pooled placebo
Point estimate	-3.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.44
upper limit	-1.73
Variability estimate	Standard error of the mean
Dispersion value	0.93

Statistical analysis title	Day 85 Cohort C: TIP, Pooled PBO
Comparison groups	Cohort C (4 capsules b.i.d.): TIP v Pooled PBO
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	LS Mean Diff (SE) vs pooled placebo
Point estimate	-3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.9
upper limit	-1.07
Variability estimate	Standard error of the mean
Dispersion value	0.96

Statistical analysis title	Day 85 Cohort C: TIP/PBO, Pooled PBO
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Comparison groups	Cohort C (4 capsules b.i.d.): TIP/PBO v Pooled PBO
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	LS Mean Diff (SE) vs pooled placebo
Point estimate	-2.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.66
upper limit	-0.53
Variability estimate	Standard error of the mean
Dispersion value	1.03

Statistical analysis title	Day 85: Pooled TIP, Pooled PBO
Comparison groups	Pooled TIP v Pooled PBO
Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	LS Mean Diff (SE) vs pooled placebo
Point estimate	-2.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.11
upper limit	-1.17
Variability estimate	Standard error of the mean
Dispersion value	0.74

Statistical analysis title	Day 85: Pooled TIP/PBO, Pooled PBO
Comparison groups	Pooled TIP/PBO v Pooled PBO
Number of subjects included in analysis	63
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	LS Mean Diff (SE) vs pooled placebo
Point estimate	-2.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.12
upper limit	-1.23
Variability estimate	Standard error of the mean
Dispersion value	0.72

Statistical analysis title	Day 113 Cohort A: TIP, Pooled PBO
Comparison groups	Cohort A (3 capsules o.d.): TIP v Pooled PBO
Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	LS Mean Diff (SE) vs pooled placebo
Point estimate	-2.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.55
upper limit	-1.08
Variability estimate	Standard error of the mean
Dispersion value	0.87

Statistical analysis title	Day 113 Cohort A: TIP/PBO, Pooled PBO
Comparison groups	Cohort A (3 capsules o.d.): TIP/PBO v Pooled PBO
Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	LS Mean Diff (SE) vs pooled placebo
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.61
upper limit	1.71
Variability estimate	Standard error of the mean
Dispersion value	0.83

Statistical analysis title	Day 113 Cohort B: TIP, Pooled PBO
Comparison groups	Cohort B (5 capsules o.d.): TIP v Pooled PBO
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	LS Mean Diff (SE) vs pooled placebo
Point estimate	-2.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.93
upper limit	-0.29
Variability estimate	Standard error of the mean
Dispersion value	1.16

Statistical analysis title	Day 113 Cohort B: TIP/PBO, Pooled PBO
Comparison groups	Cohort B (5 capsules o.d.): TIP/PBO v Pooled PBO
Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	LS Mean Diff (SE) vs pooled placebo
Point estimate	-1.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.62
upper limit	-0.25
Variability estimate	Standard error of the mean
Dispersion value	0.84

Statistical analysis title	Day 113 Cohort C: TIP, Pooled PBO
Comparison groups	Cohort C (4 capsules b.i.d.): TIP v Pooled PBO
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	LS Mean Diff (SE) vs pooled placebo
Point estimate	-3.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.94
upper limit	-1.3
Variability estimate	Standard error of the mean
Dispersion value	0.91

Statistical analysis title	Day 113 Cohort C: TIP/PBO, Pooled PBO
Comparison groups	Cohort C (4 capsules b.i.d.): TIP/PBO v Pooled PBO
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	LS Mean Diff (SE) vs pooled placebo
Point estimate	-2.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.37
upper limit	-0.43

Variability estimate	Standard error of the mean
Dispersion value	0.98

Statistical analysis title	Day 113: Pooled TIP, Pooled PBO
Comparison groups	Pooled TIP v Pooled PBO
Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	LS Mean Diff (SE) vs pooled placebo
Point estimate	-2.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.24
upper limit	-1.45
Variability estimate	Standard error of the mean
Dispersion value	0.7

Statistical analysis title	Day 113: Pooled TIP/PBO, Pooled PBO
Comparison groups	Pooled TIP/PBO v Pooled PBO
Number of subjects included in analysis	63
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	LS Mean Diff (SE) vs pooled placebo
Point estimate	-1.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.73
upper limit	-0.13
Variability estimate	Standard error of the mean
Dispersion value	0.65

Statistical analysis title	EoT Cohort A: TIP, Pooled PBO
Comparison groups	Cohort A (3 capsules o.d.): TIP v Pooled PBO
Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	LS Mean Diff (SE) vs pooled placebo
Point estimate	-2.2

Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.64
upper limit	-0.73
Variability estimate	Standard error of the mean
Dispersion value	0.73

Statistical analysis title	EoT Cohort A: TIP/PBO, Pooled PBO
Comparison groups	Cohort A (3 capsules o.d.): TIP/PBO v Pooled PBO
Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	LS Mean Diff (SE) vs pooled placebo
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.61
upper limit	1.43
Variability estimate	Standard error of the mean
Dispersion value	0.76

Statistical analysis title	EoT Cohort B: TIP, Pooled PBO
Comparison groups	Cohort B (5 capsules o.d.): TIP v Pooled PBO
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	LS Mean Diff (SE) vs pooled placebo
Point estimate	-1.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.81
upper limit	0.25
Variability estimate	Standard error of the mean
Dispersion value	0.77

Statistical analysis title	EoT Cohort B: TIP/PBO, Pooled PBO
Comparison groups	Cohort B (5 capsules o.d.): TIP/PBO v Pooled PBO

Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	LS Mean Diff (SE) vs pooled placebo
Point estimate	-1.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.14
upper limit	-0.22
Variability estimate	Standard error of the mean
Dispersion value	0.73

Statistical analysis title	EoT Cohort C: TIP, Pooled PBO
Comparison groups	Cohort C (4 capsules b.i.d.): TIP v Pooled PBO
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	LS Mean Diff (SE) vs pooled placebo
Point estimate	-2.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.89
upper limit	-0.98
Variability estimate	Standard error of the mean
Dispersion value	0.73

Statistical analysis title	EoT Cohort C: TIP/PBO, Pooled PBO
Comparison groups	Cohort C (4 capsules b.i.d.): TIP/PBO v Pooled PBO
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	LS Mean Diff (SE) vs pooled placebo
Point estimate	-1.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.12
upper limit	-0.22
Variability estimate	Standard error of the mean
Dispersion value	0.73

Statistical analysis title	EOT Pooled TIP, Pooled PBO
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Comparison groups	Pooled TIP v Pooled PBO
Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	LS Mean Diff (SE) vs pooled placebo
Point estimate	-2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.08
upper limit	-0.85
Variability estimate	Standard error of the mean
Dispersion value	0.56

Statistical analysis title	EOT PBO, Pooled PBO
Comparison groups	Pooled TIP/PBO v Pooled PBO
Number of subjects included in analysis	63
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	LS Mean Diff (SE) vs pooled placebo
Point estimate	-1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.25
upper limit	-0.04
Variability estimate	Standard error of the mean
Dispersion value	0.56

Statistical analysis title	Day 141 Cohort A: TIP, Pooled PBO
Comparison groups	Cohort A (3 capsules o.d.): TIP v Pooled PBO
Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	LS Mean Diff (SE) vs pooled placebo
Point estimate	-0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.63
upper limit	0.99
Variability estimate	Standard error of the mean
Dispersion value	0.91

Statistical analysis title	Day 141 Cohort A: TIP/PBO, Pooled PBO
Comparison groups	Cohort A (3 capsules o.d.): TIP/PBO v Pooled PBO
Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	LS Mean Diff (SE) vs pooled placebo
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.83
upper limit	1.98
Variability estimate	Standard error of the mean
Dispersion value	0.95

Statistical analysis title	Day 141 Cohort B: TIP, Pooled PBO
Comparison groups	Cohort B (5 capsules o.d.): TIP v Pooled PBO
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	LS Mean Diff (SE) vs pooled placebo
Point estimate	0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.03
upper limit	2.41
Variability estimate	Standard error of the mean
Dispersion value	1.11

Statistical analysis title	Day 141 Cohort B: TIP/PBO, Pooled PBO
Comparison groups	Cohort B (5 capsules o.d.): TIP/PBO v Pooled PBO
Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	LS Mean Diff (SE) vs pooled placebo
Point estimate	-1.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.68
upper limit	-0.01
Variability estimate	Standard error of the mean
Dispersion value	0.92

Statistical analysis title	Day 141 Cohort C: TIP, Pooled PBO
Comparison groups	Cohort C (4 capsules b.i.d.): TIP v Pooled PBO
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	LS Mean Diff (SE) vs pooled placebo
Point estimate	-0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.78
upper limit	1.07
Variability estimate	Standard error of the mean
Dispersion value	0.96

Statistical analysis title	Day 141 Cohort C: TIP/PBO, Pooled PBO
Comparison groups	Cohort C (4 capsules b.i.d.): TIP/PBO v Pooled PBO
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	LS Mean Diff (SE) vs pooled placebo
Point estimate	-1.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.36
upper limit	0.89
Variability estimate	Standard error of the mean
Dispersion value	1.06

Statistical analysis title	Day 141: Pooled TIP, Pooled PBO
Comparison groups	Pooled TIP v Pooled PBO
Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	LS Mean Diff (SE) vs pooled placebo
Point estimate	-0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.97
upper limit	0.98

Variability estimate	Standard error of the mean
Dispersion value	0.74

Statistical analysis title	Day 141: Pooled TIP/PBO, Pooled PBO
Comparison groups	Pooled TIP/PBO v Pooled PBO
Number of subjects included in analysis	63
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	LS Mean Diff (SE) vs pooled placebo
Point estimate	-1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.45
upper limit	0.45
Variability estimate	Standard error of the mean
Dispersion value	0.73

Statistical analysis title	Day 169 Cohort A: TIP, Pooled PBO
Comparison groups	Cohort A (3 capsules o.d.): TIP v Pooled PBO
Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	LS Mean Diff (SE) vs pooled placebo
Point estimate	-1.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.24
upper limit	0.61
Variability estimate	Standard error of the mean
Dispersion value	0.96

Statistical analysis title	Day 169 Cohort A: TIP/PBO, Pooled PBO
Comparison groups	Cohort A (3 capsules o.d.): TIP/PBO v Pooled PBO
Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	LS Mean Diff (SE) vs pooled placebo
Point estimate	-1.1

Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.05
upper limit	0.91
Variability estimate	Standard error of the mean
Dispersion value	0.99

Statistical analysis title	Day 169 Cohort B: TIP, Pooled PBO
Comparison groups	Cohort B (5 capsules o.d.): TIP v Pooled PBO
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	LS Mean Diff (SE) vs pooled placebo
Point estimate	-0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.73
upper limit	1.62
Variability estimate	Standard error of the mean
Dispersion value	1.09

Statistical analysis title	Day 169 Cohort B: TIP/PBO, Pooled PBO
Comparison groups	Cohort B (5 capsules o.d.): TIP/PBO v Pooled PBO
Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	LS Mean Diff (SE) vs pooled placebo
Point estimate	-2.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.22
upper limit	-0.08
Variability estimate	Standard error of the mean
Dispersion value	1.03

Statistical analysis title	Day 169 Cohort C: TIP, Pooled PBO
Comparison groups	Cohort C (4 capsules b.i.d.): TIP v Pooled PBO

Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	LS Mean Diff (SE) vs pooled placebo
Point estimate	-0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.48
upper limit	2.1
Variability estimate	Standard error of the mean
Dispersion value	1.14

Statistical analysis title	Day 169 Cohort C: TIP/PBO, Pooled PBO
Comparison groups	Cohort C (4 capsules b.i.d.): TIP/PBO v Pooled PBO
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	LS Mean Diff (SE) vs pooled placebo
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.33
upper limit	2.13
Variability estimate	Standard error of the mean
Dispersion value	1.12

Statistical analysis title	Day 169: Pooled TIP, Pooled PBO
Comparison groups	Pooled TIP v Pooled PBO
Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	LS Mean Diff (SE) vs pooled placebo
Point estimate	-0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.24
upper limit	0.86
Variability estimate	Standard error of the mean
Dispersion value	0.77

Statistical analysis title	Day 169: Pooled TIP/PBO, Pooled PBO
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Comparison groups	Pooled TIP/PBO v Pooled PBO
Number of subjects included in analysis	63
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	LS Mean Diff (SE) vs pooled placebo
Point estimate	-1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.61
upper limit	0.4
Variability estimate	Standard error of the mean
Dispersion value	0.75

Secondary: Time to first onset of pulmonary exacerbation by exacerbation category

End point title	Time to first onset of pulmonary exacerbation by exacerbation category ^[3]
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End point description:

The time to first onset of pulmonary exacerbation compared to placebo was analyzed. Participants with pulmonary exacerbation were categorized as: a) Overall, b) Category 1 (Oral): treated with oral antibiotics only and c) Category 2 (Parenteral): treated with parenteral Antibiotics and/or requiring hospitalization. Participants were censored at the time of completion of study or early discontinuation if they did not have a pulmonary exacerbation during the study period.

End point type	Secondary
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End point timeframe:

Baseline (Visit 101/Day 1) to Visit 202 (Day 169)

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: For efficacy analysis, subjects assigned to: Placebo groups were pooled across the 3 cohorts, as the number of placebo capsules was not expected to impact the efficacy assessments (Pooled inhaled placebo (PBO)); TIP groups were pooled across the 3 cohorts (Pooled TIP) and TIP/PBO groups were pooled across the 3 cohorts (Pooled TIP/PBO).

End point values	Cohort A (3 capsules o.d.): TIP	Cohort A (3 capsules o.d.): TIP/PBO	Cohort B (5 capsules o.d.): TIP	Cohort B (5 capsules o.d.): TIP/PBO
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	14	13	15	14
Units: Days				
median (full range (min-max))				
Overall	999 (39.00 to 999)	999 (48.00 to 999)	999 (15.00 to 999)	999 (85.00 to 999)
Oral	999 (999 to 999)	999 (48.00 to 999)	999 (22.00 to 999)	999 (85.00 to 999)
Parenteral	999 (110.00 to 999)	999 (999 to 999)	999 (60.00 to 999)	999 (154.00 to 999)

End point values	Cohort C (4 capsules b.i.d.): TIP	Cohort C (4 capsules b.i.d.):	Pooled TIP	Pooled TIP/PBO
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Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	15	15	44	42
Units: Days				
median (full range (min-max))				
Overall	999 (127.00 to 999)	999 (24.00 to 999)	999 (127.00 to 999)	999 (85.00 to 999)
Oral	999 (999 to 999)	999 (84.00 to 999)	999 (999 to 999)	999 (999 to 999)
Parenteral	999 (999 to 999)	999 (33.00 to 999)	999 (999 to 999)	999 (999 to 999)

End point values	Pooled PBO			
Subject group type	Subject analysis set			
Number of subjects analysed	21			
Units: Days				
median (full range (min-max))				
Overall	173.00 (77.00 to 999)			
Oral	173.00 (106.00 to 999)			
Parenteral	999 (999 to 999)			

Statistical analyses

Statistical analysis title	Overall Cohort A: TIP, Pooled PBO
Comparison groups	Cohort A (3 capsules o.d.): TIP v Pooled PBO
Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	1.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.14
upper limit	3.18

Statistical analysis title	Overall Cohort A: TIP/PBO, Pooled PBO
Comparison groups	Cohort A (3 capsules o.d.): TIP/PBO v Pooled PBO

Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	0.57
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.18
upper limit	1.85

Statistical analysis title	Overall Cohort B: TIP, Pooled PBO
Comparison groups	Cohort B (5 capsules o.d.): TIP v Pooled PBO
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	1.26
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.42
upper limit	3.77

Statistical analysis title	Overall Cohort B: TIP/PBO, Pooled PBO
Comparison groups	Cohort B (5 capsules o.d.): TIP/PBO v Pooled PBO
Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	0.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.2
upper limit	1.83

Statistical analysis title	Overall Cohort C: TIP, Pooled PBO
Comparison groups	Cohort C (4 capsules b.i.d.): TIP v Pooled PBO

Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	0.67
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.21
upper limit	2.17

Statistical analysis title	Overall Cohort C: TIP/PBO, Pooled PBO
Comparison groups	Cohort C (4 capsules b.i.d.): TIP/PBO v Pooled PBO
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	1.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.44
upper limit	3.62

Statistical analysis title	Overall Pooled TIP, Pooled PBO
Comparison groups	Pooled TIP v Pooled PBO
Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	0.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.44
upper limit	2.23

Statistical analysis title	Overall Pooled TIP/PBO, Pooled PBO
Comparison groups	Pooled TIP/PBO v Pooled PBO

Number of subjects included in analysis	63
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	0.76
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.34
upper limit	1.71

Statistical analysis title	Oral Cohort A: TIP, Pooled PBO
Comparison groups	Cohort A (3 capsules o.d.): TIP v Pooled PBO
Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	0.39
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.08
upper limit	1.83

Statistical analysis title	Oral Cohort A: TIP/PBO, Pooled PBO
Comparison groups	Cohort A (3 capsules o.d.): TIP/PBO v Pooled PBO
Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	0.85
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.25
upper limit	2.89

Statistical analysis title	Oral Cohort B: TIP, Pooled PBO
Comparison groups	Cohort B (5 capsules o.d.): TIP v Pooled PBO

Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	0.98
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.25
upper limit	3.93

Statistical analysis title	Oral Cohort B: TIP/PBO, Pooled PBO
Comparison groups	Cohort B (5 capsules o.d.): TIP/PBO v Pooled PBO
Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	0.67
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.19
upper limit	2.36

Statistical analysis title	Oral Cohort C: TIP, Pooled PBO
Comparison groups	Cohort C (4 capsules b.i.d.): TIP v Pooled PBO
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	0.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.02
upper limit	1.57

Statistical analysis title	Oral Cohort C: TIP/PBO, Pooled PBO
Comparison groups	Cohort C (4 capsules b.i.d.): TIP/PBO v Pooled PBO

Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	0.62
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.16
upper limit	2.41

Statistical analysis title	Oral Pooled TIP, Pooled PBO
Comparison groups	Pooled TIP v Pooled PBO
Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	0.42
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.13
upper limit	1.31

Statistical analysis title	Oral Pooled TIP/PBO, Pooled PBO
Comparison groups	Pooled TIP/PBO v Pooled PBO
Number of subjects included in analysis	63
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	0.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.28
upper limit	1.8

Statistical analysis title	Parenteral Cohort A: TIP, Pooled PBO
Comparison groups	Cohort A (3 capsules o.d.): TIP v Pooled PBO

Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	10.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.1
upper limit	104.19

Statistical analysis title	Parenteral Cohort B: TIP, Pooled PBO
Comparison groups	Cohort B (5 capsules o.d.): TIP v Pooled PBO
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	4.62
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.41
upper limit	52.29

Statistical analysis title	Parenteral Cohort B: TIP/PBO, Pooled PBO
Comparison groups	Cohort B (5 capsules o.d.): TIP/PBO v Pooled PBO
Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	3.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.28
upper limit	37.06

Statistical analysis title	Parenteral Cohort C: TIP, Pooled PBO
Comparison groups	Cohort C (4 capsules b.i.d.): TIP v Pooled PBO

Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	1.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.1
upper limit	25.94

Statistical analysis title	Parenteral Cohort C: TIP/PBO, Pooled PBO
Comparison groups	Cohort C (4 capsules b.i.d.): TIP/PBO v Pooled PBO
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	11.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.09
upper limit	117.34

Statistical analysis title	Parenteral Pooled TIP, Pooled PBO
Comparison groups	Pooled TIP v Pooled PBO
Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	4.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5
upper limit	37.32

Secondary: Duration of pulmonary exacerbation by exacerbation category

End point title	Duration of pulmonary exacerbation by exacerbation
End point description:	
The duration of pulmonary exacerbation compared to placebo was analyzed. Participants with pulmonary exacerbation were categorized as: a) Overall, b) Category 1 (Oral): treated with oral antibiotics only and c) Category 2 (Parenteral): treated with parenteral Antibiotics and/or requiring hospitalization.	
End point type	Secondary

End point timeframe:

Baseline (Visit 101/Day 1) to Visit 202 (Day 169)

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: For efficacy analysis, subjects assigned to: Placebo groups were pooled across the 3 cohorts, as the number of placebo capsules was not expected to impact the efficacy assessments (Pooled inhaled placebo (PBO)); TIP groups were pooled across the 3 cohorts (Pooled TIP) and TIP/PBO groups were pooled across the 3 cohorts (Pooled TIP/PBO).

End point values	Cohort A (3 capsules o.d.): TIP	Cohort A (3 capsules o.d.): TIP/PBO	Cohort B (5 capsules o.d.): TIP	Cohort B (5 capsules o.d.): TIP/PBO
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	14	13	15	14
Units: Days				
arithmetic mean (standard deviation)				
Overall	15.7 (± 6.22)	18.0 (± 8.26)	20.2 (± 6.37)	10.3 (± 5.12)
Oral	19.5 (± 12.02)	15.4 (± 4.24)	19.3 (± 3.20)	8.3 (± 4.16)
Parenteral	15.0 (± 5.52)	999 (± 999)	22.0 (± 12.73)	16.0 (± 999)

End point values	Cohort C (4 capsules b.i.d.): TIP	Cohort C (4 capsules b.i.d.): TIP/PBO	Pooled TIP	Pooled TIP/PBO
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	15	15	44	42
Units: Days				
arithmetic mean (standard deviation)				
Overall	25.5 (± 27.09)	14.8 (± 6.73)	19.0 (± 12.64)	15.2 (± 7.39)
Oral	14.0 (± 999)	16.3 (± 5.51)	18.6 (± 5.77)	14.0 (± 5.24)
Parenteral	66.0 (± 999)	16.8 (± 4.86)	23.1 (± 18.73)	16.6 (± 4.22)

End point values	Pooled PBO			
Subject group type	Subject analysis set			
Number of subjects analysed	21			
Units: Days				
arithmetic mean (standard deviation)				
Overall	14.5 (± 5.61)			
Oral	15.6 (± 5.75)			
Parenteral	10.0 (± 999)			

Statistical analyses

Statistical analysis title	Overall Cohort A: TIP, Pooled PBO
Comparison groups	Cohort A (3 capsules o.d.): TIP v Pooled PBO

Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	LS Mean Diff (SE) vs pooled placebo
Point estimate	9.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-27.15
upper limit	46.81
Variability estimate	Standard error of the mean
Dispersion value	18.15

Statistical analysis title	Overall Cohort A: TIP/PBO, Pooled PBO
Comparison groups	Cohort A (3 capsules o.d.): TIP/PBO v Pooled PBO
Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	LS Mean Diff (SE) vs pooled placebo
Point estimate	19.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-22.63
upper limit	62.14
Variability estimate	Standard error of the mean
Dispersion value	20.81

Statistical analysis title	Overall Cohort B: TIP, Pooled PBO
Comparison groups	Cohort B (5 capsules o.d.): TIP v Pooled PBO
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	LS Mean Diff (SE) vs pooled placebo
Point estimate	8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-31.32
upper limit	47.26
Variability estimate	Standard error of the mean
Dispersion value	19.29

Statistical analysis title	Overall Cohort B: TIP/PBO, Pooled PBO
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Comparison groups	Cohort B (5 capsules o.d.): TIP/PBO v Pooled PBO
Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	LS Mean Diff (SE) vs pooled placebo
Point estimate	12.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-26.49
upper limit	51.89
Variability estimate	Standard error of the mean
Dispersion value	19.24

Statistical analysis title	Overall Cohort C: TIP, Pooled PBO
Comparison groups	Cohort C (4 capsules b.i.d.): TIP v Pooled PBO
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	LS Mean Diff (SE) vs pooled placebo
Point estimate	46.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.37
upper limit	89.61
Variability estimate	Standard error of the mean
Dispersion value	21.17

Statistical analysis title	Overall Cohort C: TIP/PBO, Pooled PBO
Comparison groups	Cohort C (4 capsules b.i.d.): TIP/PBO v Pooled PBO
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	LS Mean Diff (SE) vs pooled placebo
Point estimate	3.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-34.21
upper limit	40.64
Variability estimate	Standard error of the mean
Dispersion value	18.37

Statistical analysis title	Overall Pooled TIP, Pooled PBO
Comparison groups	Pooled TIP v Pooled PBO
Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	LS Mean Diff (SE) vs pooled placebo
Point estimate	21.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.03
upper limit	50.89
Variability estimate	Standard error of the mean
Dispersion value	14.46

Statistical analysis title	Overall Pooled TIP/PBO, Pooled PBO
Comparison groups	Pooled TIP/PBO v Pooled PBO
Number of subjects included in analysis	63
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	LS Mean Diff (SE) vs pooled placebo
Point estimate	11.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-17.52
upper limit	41.29
Variability estimate	Standard error of the mean
Dispersion value	14.44

Secondary: Exposure adjusted rate of pulmonary exacerbations (PE) over the entire study period

End point title	Exposure adjusted rate of pulmonary exacerbations (PE) over the entire study period ^[5]
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End point description:

The exposure adjusted rate of pulmonary exacerbation compared to placebo was analyzed. Participants with pulmonary exacerbation were categorized as: a) Overall, b) Category 1 (Oral): treated with oral antibiotics only and c) Category 2 (Parenteral): treated with parenteral Antibiotics and/or requiring hospitalization. The Exposure adjusted rate = (Number of pulmonary exacerbations reported during the study period) / (sum of study duration in days for all participants/ 365.25). Only descriptive analysis performed.

End point type	Secondary
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End point timeframe:

Baseline (Visit 101/Day 1) to Visit 202 (Day 169)

Notes:

[5] - 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: For efficacy analysis, subjects assigned to: Placebo groups were pooled across the 3 cohorts, as the number of placebo capsules was not expected to impact the efficacy assessments

(Pooled inhaled placebo (PBO)); TIP groups were pooled across the 3 cohorts (Pooled TIP) and TIP/PBO groups were pooled across the 3 cohorts (Pooled TIP/PBO).

End point values	Cohort A (3 capsules o.d.): TIP	Cohort A (3 capsules o.d.): TIP/PBO	Cohort B (5 capsules o.d.): TIP	Cohort B (5 capsules o.d.): TIP/PBO
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	14	13	15	14
Units: pulmonary exacerbation per study years				
number (confidence interval 95%)				
Overall	1.71 (0.92 to 3.17)	1.39 (0.70 to 2.78)	1.29 (0.58 to 2.87)	1.20 (0.57 to 2.51)
Oral	0.34 (0.09 to 1.37)	1.22 (0.58 to 2.56)	0.86 (0.32 to 2.29)	0.85 (0.36 to 2.05)
Parenteral	0.85 (0.36 to 2.05)	999 (999 to 999)	0.43 (0.11 to 1.72)	0.34 (0.09 to 1.37)

End point values	Cohort C (4 capsules b.i.d.): TIP	Cohort C (4 capsules b.i.d.):	Pooled TIP	Pooled TIP/PBO
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	15	15	44	42
Units: pulmonary exacerbation per study years				
number (confidence interval 95%)				
Overall	0.66 (0.25 to 1.76)	1.46 (0.73 to 2.93)	1.21 (0.78 to 1.87)	1.35 (0.90 to 2.03)
Oral	0.16 (0.02 to 1.17)	0.55 (0.18 to 1.70)	0.42 (0.20 to 0.89)	0.88 (0.53 to 1.46)
Parenteral	0.16 (0.02 to 1.17)	0.73 (0.27 to 1.95)	0.48 (0.24 to 0.96)	0.35 (0.16 to 0.78)

End point values	Pooled PBO			
Subject group type	Subject analysis set			
Number of subjects analysed	21			
Units: pulmonary exacerbation per study years				
number (confidence interval 95%)				
Overall	1.41 (0.82 to 2.42)			
Oral	1.19 (0.66 to 2.15)			
Parenteral	0.11 (0.02 to 0.77)			

Statistical analyses

Secondary: Number of participants with at least one pulmonary exacerbation by exacerbation category

End point title	Number of participants with at least one pulmonary exacerbation by exacerbation category ^[6]
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End point description:

Pulmonary exacerbations are defined as events requiring antibiotic therapy AND for which at least 3 of the following 6 symptoms, signs, or findings were present outside of normal variation: 1. Increased sputum volume, or change in viscosity/consistency or purulence for more than 24 hours; 2. Increased shortness of breath at rest or on exercise for more than 24 hours; 3. Increased cough for more than 24 hours; 4. Fever of $\geq 38^{\circ}$ Celsius within the last 24 hours; 5. Increased malaise/fatigue/lethargy for more than 24 hours; 6. A reduction in forced expiratory volume in the first second of expiration (FEV1) or forced vital capacity (FVC) of least 10% from screening.

Participants were categorized as: a) Overall, b) Category 1: treated with oral antibiotics only and c) Category 2: treated with parenteral Antibiotics and/or requiring hospitalization.

Only descriptive analysis performed.

End point type	Secondary
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End point timeframe:

Baseline (Visit 101/Day 1) to Visit 202 (Day 169)

Notes:

[6] - 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: For efficacy analysis, subjects assigned to: Placebo groups were pooled across the 3 cohorts, as the number of placebo capsules was not expected to impact the efficacy assessments (Pooled inhaled placebo (PBO)); TIP groups were pooled across the 3 cohorts (Pooled TIP) and TIP/PBO groups were pooled across the 3 cohorts (Pooled TIP/PBO).

End point values	Cohort A (3 capsules o.d.): TIP	Cohort A (3 capsules o.d.): TIP/PBO	Cohort B (5 capsules o.d.): TIP	Cohort B (5 capsules o.d.): TIP/PBO
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	14	13	15	14
Units: Participants				
Overall No of participants with no events	8	9	10	9
Oral No of participants with no events	12	9	12	10
Parenteral No of participants with no events	10	13	13	12
Overall No. of participants with 1 event	3	1	4	3
Oral No. of participants with 1 event	2	2	2	3
Parenteral No. of participants with 1 event	3	0	2	2
Overall No. of participants with 2 events	2	2	1	2
Oral No. of participants with 2 events	0	1	1	1
Parenteral No. of participants with 2 events	1	0	0	0
Overall No. of participants with 3 events	1	1	0	0
Oral No. of participants with 3 events	0	1	0	0
Parenteral No. of participants with 3 events	0	0	0	0

End point values	Cohort C (4 capsules b.i.d.): TIP	Cohort C (4 capsules b.i.d.):	Pooled TIP	Pooled TIP/PBO
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Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	15	15	44	42
Units: Participants				
Overall No of participants with no events	11	9	29	27
Oral No of participants with no events	14	12	38	31
Parenteral No of participants with no events	14	11	37	36
Overall No. of participants with 1 event	4	4	11	8
Oral No. of participants with 1 event	1	3	5	8
Parenteral No. of participants with 1 event	1	4	6	6
Overall No. of participants with 2 events	0	2	3	6
Oral No. of participants with 2 events	0	0	1	2
Parenteral No. of participants with 2 events	0	0	1	0
Overall No. of participants with 3 events	0	0	1	1
Oral No. of participants with 3 events	0	0	0	1
Parenteral No. of participants with 3 events	0	0	0	0

End point values	Pooled PBO			
Subject group type	Subject analysis set			
Number of subjects analysed	21			
Units: Participants				
Overall No of participants with no events	11			
Oral No of participants with no events	13			
Parenteral No of participants with no events	20			
Overall No. of participants with 1 event	7			
Oral No. of participants with 1 event	5			
Parenteral No. of participants with 1 event	1			
Overall No. of participants with 2 events	3			
Oral No. of participants with 2 events	3			
Parenteral No. of participants with 2 events	0			
Overall No. of participants with 3 events	0			
Oral No. of participants with 3 events	0			
Parenteral No. of participants with 3 events	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants who permanently discontinued study drug due to pulmonary exacerbation

End point title	Number of participants who permanently discontinued study
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End point description:

The number of participants who permanently discontinued study drug due to pulmonary exacerbation compared to placebo was analyzed.

End point type	Secondary
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End point timeframe:

Baseline (Visit 101/Day 1) to Visit 202 (Day 169)

Notes:

[7] - 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: For efficacy analysis, subjects assigned to: Placebo groups were pooled across the 3 cohorts, as the number of placebo capsules was not expected to impact the efficacy assessments (Pooled inhaled placebo (PBO)); TIP groups were pooled across the 3 cohorts (Pooled TIP) and TIP/PBO groups were pooled across the 3 cohorts (Pooled TIP/PBO).

End point values	Cohort A (3 capsules o.d.): TIP	Cohort A (3 capsules o.d.): TIP/PBO	Cohort B (5 capsules o.d.): TIP	Cohort B (5 capsules o.d.): TIP/PBO
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	14	13	15	14
Units: Participants	2	0	1	0

End point values	Cohort C (4 capsules b.i.d.): TIP	Cohort C (4 capsules b.i.d.): TIP/PBO	Pooled TIP	Pooled TIP/PBO
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	15	15	44	42
Units: Participants	0	2	41	40

End point values	Pooled PBO			
Subject group type	Subject analysis set			
Number of subjects analysed	21			
Units: Participants	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to permanent study drug discontinuation due to Pulmonary exacerbation

End point title	Time to permanent study drug discontinuation due to Pulmonary exacerbation ^[8]
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End point description:

The time to permanent study drug discontinuation due to Pulmonary exacerbation. Participants were censored at the time of last contact if they did not permanently discontinue study drug due to pulmonary exacerbation requiring during the study period. Only descriptive analysis performed.

End point type	Secondary
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End point timeframe:

Baseline (Visit 101/Day 1) to Visit 202 (Day 169)

Notes:

[8] - 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: For efficacy analysis, subjects assigned to: Placebo groups were pooled across the 3 cohorts, as the number of placebo capsules was not expected to impact the efficacy assessments (Pooled inhaled placebo (PBO)); TIP groups were pooled across the 3 cohorts (Pooled TIP) and TIP/PBO groups were pooled across the 3 cohorts (Pooled TIP/PBO).

End point values	Cohort A (3 capsules o.d.): TIP	Cohort A (3 capsules o.d.): TIP/PBO	Cohort B (5 capsules o.d.): TIP	Cohort B (5 capsules o.d.): TIP/PBO
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	14	13	15	14
Units: Days				
median (confidence interval 95%)	999 (94.00 to 999)	999 (999 to 999)	999 (999 to 999)	999 (999 to 999)

End point values	Cohort C (4 capsules b.i.d.): TIP	Cohort C (4 capsules b.i.d.): TIP/PBO	Pooled TIP	Pooled TIP/PBO
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	15	15	44	42
Units: Days				
median (confidence interval 95%)	999 (999 to 999)	999 (84.00 to 999)	999 (999 to 999)	999 (999 to 999)

End point values	Pooled PBO			
Subject group type	Subject analysis set			
Number of subjects analysed	21			
Units: Days				
median (confidence interval 95%)	999 (999 to 999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to first use (overall, oral, and parenteral) of anti-pseudomonal antibiotics usage

End point title	Time to first use (overall, oral, and parenteral) of anti-pseudomonal antibiotics usage ^[9]
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End point description:

The time to first use of anti-pseudomonal antibiotics administered compared to placebo was analyzed. Participants were censored at the time of last contact if they did not have anti-pseudomonal antibiotics over the entire study period.

End point type	Secondary
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End point timeframe:

From Baseline (Visit 101/Day 1) up to approximately Day 173

Notes:

[9] - 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: For efficacy analysis, subjects assigned to: Placebo groups were pooled across the 3 cohorts, as the number of placebo capsules was not expected to impact the efficacy assessments (Pooled inhaled placebo (PBO)); TIP groups were pooled across the 3 cohorts (Pooled TIP) and TIP/PBO groups were pooled across the 3 cohorts (Pooled TIP/PBO).

End point values	Cohort A (3 capsules o.d.): TIP	Cohort A (3 capsules o.d.): TIP/PBO	Cohort B (5 capsules o.d.): TIP	Cohort B (5 capsules o.d.): TIP/PBO
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	14	13	15	14
Units: Days				
median (full range (min-max))				
Overall	122.00 (29.00 to 999)	999 (50.00 to 999)	116.00 (17.00 to 999)	161.00 (58.00 to 999)
Oral	999 (43.00 to 999)	999 (50.00 to 999)	999 (17.00 to 999)	999 (85.00 to 999)
Parenteral	999 (105.0 to 999)	999 (999 to 999)	999 (63.00 to 999)	999 (95.00 to 999)

End point values	Cohort C (4 capsules b.i.d.): TIP	Cohort C (4 capsules b.i.d.):	Pooled TIP	Pooled TIP/PBO
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	15	15	44	42
Units: Days				
median (full range (min-max))				
Overall	999 (127.00 to 999)	999 (11.00 to 999)	999 (110.00 to 999)	999 (84.00 to 999)
Oral	999 (999 to 999)	999 (11.00 to 999)	999 (999 to 999)	999 (85.00 to 999)
Parenteral	999 (999 to 999)	999 (37.00 to 999)	999 (999 to 999)	999 (999 to 999)

End point values	Pooled PBO			
Subject group type	Subject analysis set			
Number of subjects analysed	21			
Units: Days				
median (full range (min-max))				
Overall	141.00 (57.00 to 999)			
Oral	173.00 (106.00 to 999)			
Parenteral	999 (999 to 999)			

Statistical analyses

Statistical analysis title	Overall Cohort A: TIP, Pooled PBO
Comparison groups	Cohort A (3 capsules o.d.): TIP v Pooled PBO
Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	1.26
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.51
upper limit	3.13

Statistical analysis title	Overall Cohort A: TIP/PBO, Pooled PBO
Comparison groups	Cohort A (3 capsules o.d.): TIP/PBO v Pooled PBO
Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	0.47
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.15
upper limit	1.46

Statistical analysis title	Overall Cohort B: TIP, Pooled PBO
Comparison groups	Cohort B (5 capsules o.d.): TIP v Pooled PBO
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	1.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.44
upper limit	3.21

Statistical analysis title	Overall Cohort B: TIP/PBO, Pooled PBO
Comparison groups	Cohort B (5 capsules o.d.): TIP/PBO v Pooled PBO
Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	0.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.32
upper limit	2.18

Statistical analysis title	Overall Cohort C: TIP, Pooled PBO
Comparison groups	Cohort C (4 capsules b.i.d.): TIP v Pooled PBO
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	0.35
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.1
upper limit	1.27

Statistical analysis title	Overall Cohort C: TIP/PBO, Pooled PBO
Comparison groups	Cohort C (4 capsules b.i.d.): TIP/PBO v Pooled PBO
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	1.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.43
upper limit	2.99

Statistical analysis title	Overall Pooled TIP, Pooled PBO
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Comparison groups	Pooled TIP v Pooled PBO
Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	0.81
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.37
upper limit	1.76

Statistical analysis title	Overall Pooled TIP/PBO, Pooled PBO
Comparison groups	Pooled TIP/PBO v Pooled PBO
Number of subjects included in analysis	63
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	0.76
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.36
upper limit	1.61

Statistical analysis title	Oral Cohort A: TIP, Pooled PBO
Comparison groups	Cohort A (3 capsules o.d.): TIP v Pooled PBO
Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	0.87
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.3
upper limit	2.55

Statistical analysis title	Oral Cohort A: TIP/PBO, Pooled PBO
Comparison groups	Cohort A (3 capsules o.d.): TIP/PBO v Pooled PBO

Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	0.63
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.2
upper limit	2.03

Statistical analysis title	Oral Cohort B: TIP, Pooled PBO
Comparison groups	Cohort B (5 capsules o.d.): TIP v Pooled PBO
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	1.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4
upper limit	3.6

Statistical analysis title	Oral Cohort B: TIP/PBO, Pooled PBO
Comparison groups	Cohort B (5 capsules o.d.): TIP/PBO v Pooled PBO
Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	0.89
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.31
upper limit	2.55

Statistical analysis title	Oral Cohort C: TIP, Pooled PBO
Comparison groups	Cohort C (4 capsules b.i.d.): TIP v Pooled PBO

Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	0.28
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.06
upper limit	1.27

Statistical analysis title	Oral Cohort C: TIP/PBO, Pooled PBO
Comparison groups	Cohort C (4 capsules b.i.d.): TIP/PBO v Pooled PBO
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	1.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.45
upper limit	3.73

Statistical analysis title	Oral Pooled TIP, Pooled PBO
Comparison groups	Pooled TIP v Pooled PBO
Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	0.66
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.27
upper limit	1.6

Statistical analysis title	Oral Pooled TIP/PBO, Pooled PBO
Comparison groups	Pooled TIP/PBO v Pooled PBO

Number of subjects included in analysis	63
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4
upper limit	2.02

Statistical analysis title	Parenteral Cohort A: TIP, Pooled PBO
Comparison groups	Cohort A (3 capsules o.d.): TIP v Pooled PBO
Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	3.72
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.84
upper limit	16.52

Statistical analysis title	Parenteral Cohort B: TIP, Pooled PBO
Comparison groups	Cohort B (5 capsules o.d.): TIP v Pooled PBO
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	1.34
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.22
upper limit	8.16

Statistical analysis title	Parenteral Cohort B: TIP/PBO, Pooled PBO
Comparison groups	Cohort B (5 capsules o.d.): TIP/PBO v Pooled PBO

Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	2.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.46
upper limit	10.05

Statistical analysis title	Parenteral Cohort C: TIP, Pooled PBO
Comparison groups	Cohort C (4 capsules b.i.d.): TIP v Pooled PBO
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.05
upper limit	4.87

Statistical analysis title	Parenteral Cohort C: TIP/PBO, Pooled PBO
Comparison groups	Cohort C (4 capsules b.i.d.): TIP/PBO v Pooled PBO
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	2.56
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.53
upper limit	12.49

Statistical analysis title	Parenteral Pooled TIP, Pooled PBO
Comparison groups	Pooled TIP v Pooled PBO

Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	1.36
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.33
upper limit	5.68

Secondary: Number of participants requiring anti-pseudomonal antibiotics

End point title	Number of participants requiring anti-pseudomonal
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End point description:

The number of participants requiring anti-pseudomonal antibiotics compared to placebo was analyzed. Only descriptive analysis performed.

End point type	Secondary
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End point timeframe:

Baseline (Visit 101/Day 1) to Visit 202 (Day 169)

Notes:

[10] - 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: For efficacy analysis, subjects assigned to: Placebo groups were pooled across the 3 cohorts, as the number of placebo capsules was not expected to impact the efficacy assessments (Pooled inhaled placebo (PBO)); TIP groups were pooled across the 3 cohorts (Pooled TIP) and TIP/PBO groups were pooled across the 3 cohorts (Pooled TIP/PBO).

End point values	Cohort A (3 capsules o.d.): TIP	Cohort A (3 capsules o.d.): TIP/PBO	Cohort B (5 capsules o.d.): TIP	Cohort B (5 capsules o.d.): TIP/PBO
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	14	13	15	14
Units: Participants				
Overall Any antipseudomonal antibiotic use?=Yes	8	4	6	7
Oral Any antipseudomonal antibiotic use?=Yes	5	4	5	6
Parenteral Any antipseudomonal antibiotic use?=Yes	5	0	2	4
Overall Any antipseudomonal antibiotic use?=No	6	9	9	7
Oral Any antipseudomonal antibiotic use?=No	9	9	10	8
Parenteral Any antipseudomonal antibiotic use?=No	9	13	13	10

End point values	Cohort C (4 capsules b.i.d.): TIP	Cohort C (4 capsules b.i.d.):	Pooled TIP	Pooled TIP/PBO
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Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	15	15	44	42
Units: Participants				
Overall Any antipseudomonal antibiotic use?=Yes	3	7	17	18
Oral Any antipseudomonal antibiotic use?=Yes	2	6	12	16
Parenteral Any antipseudomonal antibiotic use?=Yes	1	4	8	8
Overall Any antipseudomonal antibiotic use?=No	12	8	27	24
Oral Any antipseudomonal antibiotic use?=No	13	9	32	26
Parenteral Any antipseudomonal antibiotic use?=No	14	11	36	34

End point values	Pooled PBO			
Subject group type	Subject analysis set			
Number of subjects analysed	21			
Units: Participants				
Overall Any antipseudomonal antibiotic use?=Yes	12			
Oral Any antipseudomonal antibiotic use?=Yes	10			
Parenteral Any antipseudomonal antibiotic use?=Yes	3			
Overall Any antipseudomonal antibiotic use?=No	9			
Oral Any antipseudomonal antibiotic use?=No	11			
Parenteral Any antipseudomonal antibiotic use?=No	18			

Statistical analyses

Statistical analysis title	Overall Cohort A: TIP, Pooled PBO
Comparison groups	Cohort A (3 capsules o.d.): TIP v Pooled PBO
Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Anti-pseudomonal antibiotics rate
Point estimate	3.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.71
upper limit	6.4

Statistical analysis title	Overall Cohort A: TIP/PBO, Pooled PBO
Comparison groups	Cohort A (3 capsules o.d.): TIP/PBO v Pooled PBO
Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Anti-pseudomonal antibiotics rate
Point estimate	1.41
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.62
upper limit	3.24

Statistical analysis title	Overall Cohort B: TIP, Pooled PBO
Comparison groups	Cohort B (5 capsules o.d.): TIP v Pooled PBO
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Anti-pseudomonal antibiotics rate
Point estimate	2.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.05
upper limit	5.15

Statistical analysis title	Overall Cohort B: TIP/PBO, Pooled PBO
Comparison groups	Cohort B (5 capsules o.d.): TIP/PBO v Pooled PBO
Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Anti-pseudomonal antibiotics rate
Point estimate	2.43
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.23
upper limit	4.8

Statistical analysis title	Overall Cohort C: TIP, Pooled PBO
Comparison groups	Cohort C (4 capsules b.i.d.): TIP v Pooled PBO

Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Anti-pseudomonal antibiotics rate
Point estimate	0.49
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.14
upper limit	1.64

Statistical analysis title	Overall Cohort C: TIP/PBO, Pooled PBO
Comparison groups	Cohort C (4 capsules b.i.d.): TIP/PBO v Pooled PBO
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Anti-pseudomonal antibiotics rate
Point estimate	2.31
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.11
upper limit	4.8

Statistical analysis title	Oral Cohort A: TIP, Pooled PBO
Comparison groups	Cohort A (3 capsules o.d.): TIP v Pooled PBO
Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Anti-pseudomonal antibiotics rate
Point estimate	1.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.54
upper limit	2.44

Statistical analysis title	Oral Cohort A: TIP/PBO, Pooled PBO
Comparison groups	Cohort A (3 capsules o.d.): TIP/PBO v Pooled PBO

Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Anti-pseudomonal antibiotics rate
Point estimate	1.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.58
upper limit	2.56

Statistical analysis title	Oral Cohort B: TIP, Pooled PBO
Comparison groups	Cohort B (5 capsules o.d.): TIP v Pooled PBO
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Anti-pseudomonal antibiotics rate
Point estimate	1.42
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.66
upper limit	3.06

Statistical analysis title	Oral Cohort B: TIP/PBO, Pooled PBO
Comparison groups	Cohort B (5 capsules o.d.): TIP/PBO v Pooled PBO
Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Anti-pseudomonal antibiotics rate
Point estimate	1.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.58
upper limit	2.55

Statistical analysis title	Oral Cohort C: TIP, Pooled PBO
Comparison groups	Cohort C (4 capsules b.i.d.): TIP v Pooled PBO

Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Anti-pseudomonal antibiotics rate
Point estimate	0.31
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.08
upper limit	1.27

Statistical analysis title	Oral Cohort C: TIP/PBO, Pooled PBO
Comparison groups	Cohort C (4 capsules b.i.d.): TIP/PBO v Pooled PBO
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Anti-pseudomonal antibiotics rate
Point estimate	1.36
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.64
upper limit	2.91

Statistical analysis title	Parenteral Cohort A: TIP, Pooled PBO
Comparison groups	Cohort A (3 capsules o.d.): TIP v Pooled PBO
Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Anti-pseudomonal antibiotics rate
Point estimate	1.58
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.61
upper limit	4.09

Statistical analysis title	Parenteral Cohort B: TIP, Pooled PBO
Comparison groups	Cohort B (5 capsules o.d.): TIP v Pooled PBO

Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Anti-pseudomonal antibiotics rate
Point estimate	0.67
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.17
upper limit	2.69

Statistical analysis title	Parenteral Cohort B: TIP/PBO, Pooled PBO
Comparison groups	Cohort B (5 capsules o.d.): TIP/PBO v Pooled PBO
Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Anti-pseudomonal antibiotics rate
Point estimate	1.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.37
upper limit	2.86

Statistical analysis title	Parenteral Cohort C: TIP, Pooled PBO
Comparison groups	Cohort C (4 capsules b.i.d.): TIP v Pooled PBO
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Anti-pseudomonal antibiotics rate
Point estimate	0.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.02
upper limit	1.12

Statistical analysis title	Parenteral Cohort C: TIP/PBO, Pooled PBO
Comparison groups	Cohort C (4 capsules b.i.d.): TIP/PBO v Pooled PBO

Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Anti-pseudomonal antibiotics rate
Point estimate	0.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.26
upper limit	2.58

Secondary: Duration of anti-pseudomonal antibiotics usage

End point title	Duration of anti-pseudomonal antibiotics usage ^[11]
End point description: The total number of days of new anti-pseudomonal antibiotic use compared to placebo was analyzed. Only descriptive analysis	
End point type	Secondary
End point timeframe: Baseline (Visit 101/Day 1) to Visit 202 (Day 169)	

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: For efficacy analysis, subjects assigned to: Placebo groups were pooled across the 3 cohorts, as the number of placebo capsules was not expected to impact the efficacy assessments (Pooled inhaled placebo (PBO)); TIP groups were pooled across the 3 cohorts (Pooled TIP) and TIP/PBO groups were pooled across the 3 cohorts (Pooled TIP/PBO).

End point values	Cohort A (3 capsules o.d.): TIP	Cohort A (3 capsules o.d.): TIP/PBO	Cohort B (5 capsules o.d.): TIP	Cohort B (5 capsules o.d.): TIP/PBO
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	14	13	15	14
Units: Days				
arithmetic mean (standard deviation)				
Overall	18.4 (± 10.39)	20.0 (± 12.03)	19.2 (± 14.84)	25.7 (± 13.21)
Oral	14.2 (± 7.79)	19.8 (± 12.34)	15.0 (± 7.42)	14.0 (± 10.92)
Parenteral	15.0 (± 10.02)	999 (± 999)	20.0 (± 14.14)	23.8 (± 15.20)

End point values	Cohort C (4 capsules b.i.d.): TIP	Cohort C (4 capsules b.i.d.):	Pooled TIP	Pooled TIP/PBO
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	15	15	44	42
Units: Days				
arithmetic mean (standard deviation)				
Overall	15.3 (± 10.07)	15.7 (± 10.90)	18.1 (± 11.43)	20.6 (± 12.24)
Oral	20.0 (± 8.49)	10.8 (± 6.24)	15.5 (± 7.29)	14.3 (± 9.79)
Parenteral	6.0 (± 999)	11.3 (± 2.75)	15.1 (± 10.23)	17.5 (± 12.12)

End point values	Pooled PBO			
Subject group type	Subject analysis set			
Number of subjects analysed	21			
Units: Days				
arithmetic mean (standard deviation)				
Overall	14.6 (± 8.27)			
Oral	13.7 (± 7.41)			
Parenteral	12.7 (± 7.64)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants requiring hospitalization due to serious respiratory-related adverse events

End point title	Number of participants requiring hospitalization due to serious respiratory-related adverse events ^[12]
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End point description:

The number of participants requiring hospitalization due to serious respiratory-related adverse events (other than those regularly scheduled hospitalization that were planned prior to study start) was analyzed to define severity of pulmonary exacerbations compared to placebo. Only descriptive analysis performed.

End point type	Secondary
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End point timeframe:

Baseline (Visit 101/Day 1) to Visit 202 (Day 169)

Notes:

[12] - 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: For efficacy analysis, subjects assigned to: Placebo groups were pooled across the 3 cohorts, as the number of placebo capsules was not expected to impact the efficacy assessments (Pooled inhaled placebo (PBO)); TIP groups were pooled across the 3 cohorts (Pooled TIP) and TIP/PBO groups were pooled across the 3 cohorts (Pooled TIP/PBO).

End point values	Cohort A (3 capsules o.d.): TIP	Cohort A (3 capsules o.d.): TIP/PBO	Cohort B (5 capsules o.d.): TIP	Cohort B (5 capsules o.d.): TIP/PBO
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	14	13	15	14
Units: Participants				
No of participants with 0 event	10	13	13	12
No. of participants with 1 event	3	0	2	1
No. of participants with 2 events	0	0	0	0
No. of participants with > 2 events	1	0	0	1

End point values	Cohort C (4	Cohort C (4	Pooled TIP	Pooled TIP/PBO
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	capsules b.i.d.): TIP	capsules b.i.d.):		
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	15	15	44	42
Units: Participants				
No of participants with 0 event	14	11	37	36
No. of participants with 1 event	0	4	5	5
No. of participants with 2 events	1	0	1	0
No. of participants with > 2 events	0	0	1	1

End point values	Pooled PBO			
Subject group type	Subject analysis set			
Number of subjects analysed	21			
Units: Participants				
No of participants with 0 event	19			
No. of participants with 1 event	2			
No. of participants with 2 events	0			
No. of participants with > 2 events	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of hospitalization due to serious respiratory-related adverse events

End point title	Duration of hospitalization due to serious respiratory-related adverse events ^[13]
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End point description:

The duration of hospitalization due to serious respiratory-related adverse events (other than those regularly scheduled hospitalization that were planned prior to study start) was analyzed to define severity of pulmonary exacerbations compared to placebo. Only descriptive analysis performed.

End point type	Secondary
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End point timeframe:

Baseline (Visit 101/Day 1) to Visit 202 (Day 169)

Notes:

[13] - 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: For efficacy analysis, subjects assigned to: Placebo groups were pooled across the 3 cohorts, as the number of placebo capsules was not expected to impact the efficacy assessments (Pooled inhaled placebo (PBO)); TIP groups were pooled across the 3 cohorts (Pooled TIP) and TIP/PBO groups were pooled across the 3 cohorts (Pooled TIP/PBO).

End point values	Cohort A (3 capsules o.d.): TIP	Cohort A (3 capsules o.d.): TIP/PBO	Cohort B (5 capsules o.d.): TIP	Cohort B (5 capsules o.d.): TIP/PBO
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	0 ^[14]	2	2
Units: Days				
arithmetic mean (standard deviation)	15.2 (± 5.19)	()	22.0 (± 12.73)	12.2 (± 6.06)

Notes:

[14] - No participants with at least one hospitalization

End point values	Cohort C (4 capsules b.i.d.): TIP	Cohort C (4 capsules b.i.d.):	Pooled TIP	Pooled TIP/PBO
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	1	4	7	6
Units: Days				
arithmetic mean (standard deviation)	11.0 (± 999)	19.0 (± 5.23)	16.2 (± 7.05)	15.2 (± 6.44)

End point values	Pooled PBO			
Subject group type	Subject analysis set			
Number of subjects analysed	2			
Units: Days				
arithmetic mean (standard deviation)	10.5 (± 0.71)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of hospitalization due to serious respiratory-related adverse events

End point title	Number of hospitalization due to serious respiratory-related adverse events ^[15]
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End point description:

The number of hospitalization due to serious respiratory-related AEs was analyzed to define severity of pulmonary exacerbations compared to placebo. Respiratory related adverse events were identified using the AEs captured under system organ class 'Respiratory, thoracic and mediastinal disorders' and 'Infections and infestations'.

End point type	Secondary
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End point timeframe:

Baseline (Visit 101/Day 1) to Visit 202 (Day 169)

Notes:

[15] - 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: For efficacy analysis, subjects assigned to: Placebo groups were pooled across the 3 cohorts, as the number of placebo capsules was not expected to impact the efficacy assessments (Pooled inhaled placebo (PBO)); TIP groups were pooled across the 3 cohorts (Pooled TIP) and TIP/PBO groups were pooled across the 3 cohorts (Pooled TIP/PBO).

End point values	Cohort A (3 capsules o.d.): TIP	Cohort A (3 capsules o.d.): TIP/PBO	Cohort B (5 capsules o.d.): TIP	Cohort B (5 capsules o.d.): TIP/PBO
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	14	13	15	14
Units: Hospitalization	6	0	2	5

End point values	Cohort C (4 capsules b.i.d.): TIP	Cohort C (4 capsules b.i.d.):	Pooled TIP	Pooled TIP/PBO
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	15	15	44	42
Units: Hospitalization	2	4	10	9

End point values	Pooled PBO			
Subject group type	Subject analysis set			
Number of subjects analysed	21			
Units: Hospitalization	2			

Statistical analyses

Statistical analysis title	Cohort A (3 capsules o.d.): TIP, Pooled PBO
Comparison groups	Cohort A (3 capsules o.d.): TIP v Pooled PBO
Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Log odds ratio
Point estimate	5.62
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.83
upper limit	38.18

Statistical analysis title	Cohort B (5 capsules o.d.): TIP, Pooled PBO
Comparison groups	Cohort B (5 capsules o.d.): TIP v Pooled PBO
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Log odds ratio
Point estimate	2
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.21
upper limit	19.16

Statistical analysis title	Cohort B (5 capsules o.d.): TIP/PBO, Pooled PBO
Comparison groups	Cohort B (5 capsules o.d.): TIP/PBO v Pooled PBO
Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Log odds ratio
Point estimate	3.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.43
upper limit	21.8

Statistical analysis title	Cohort C (4 capsules b.i.d.): TIP, Pooled PBO
Comparison groups	Cohort C (4 capsules b.i.d.): TIP v Pooled PBO
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Log odds ratio
Point estimate	1.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.19
upper limit	17.42

Statistical analysis title	Cohort C (4 capsules b.i.d.): TIP/PBO, Pooled PBO
Comparison groups	Cohort C (4 capsules b.i.d.): TIP/PBO v Pooled PBO
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Log odds ratio
Point estimate	3.41
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.47
upper limit	25.03

Statistical analysis title	Pooled TIP_Pooled PBO
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Comparison groups	Pooled TIP v Pooled PBO
Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Log odds ratio
Point estimate	2.74
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.47
upper limit	16.07

Secondary: Time to first hospitalization due to serious respiratory-related adverse events

End point title	Time to first hospitalization due to serious respiratory-related adverse events ^[16]
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End point description:

Time to first hospitalization due to serious respiratory-related AEs was analyzed to define severity of pulmonary exacerbations compared to placebo. Participants were censored at the time of last contact if they did not have a hospitalization due to serious respiratory-related adverse events over the entire study period.

End point type	Secondary
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End point timeframe:

Baseline (Visit 101/Day 1) to Visit 202 (Day 169)

Notes:

[16] - 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: For efficacy analysis, subjects assigned to: Placebo groups were pooled across the 3 cohorts, as the number of placebo capsules was not expected to impact the efficacy assessments (Pooled inhaled placebo (PBO)); TIP groups were pooled across the 3 cohorts (Pooled TIP) and TIP/PBO groups were pooled across the 3 cohorts (Pooled TIP/PBO).

End point values	Cohort A (3 capsules o.d.): TIP	Cohort A (3 capsules o.d.): TIP/PBO	Cohort B (5 capsules o.d.): TIP	Cohort B (5 capsules o.d.): TIP/PBO
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	14	13	15	14
Units: Day				
median (confidence interval 95%)	999 (93.00 to 999)	999 (999 to 999)	999 (60.00 to 999)	999 (999 to 999)

End point values	Cohort C (4 capsules b.i.d.): TIP	Cohort C (4 capsules b.i.d.): TIP/PBO	Pooled TIP	Pooled TIP/PBO
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	15	15	44	42
Units: Day				
median (confidence interval 95%)	999 (999 to 999)	999 (65.00 to 999)	999 (999 to 999)	999 (999 to 999)

End point values	Pooled PBO			
Subject group type	Subject analysis set			
Number of subjects analysed	21			
Units: Day				
median (confidence interval 95%)	999 (999 to 999)			

Statistical analyses

Statistical analysis title	Cohort A (3 capsules o.d.): TIP, Pooled PBO
Comparison groups	Cohort A (3 capsules o.d.): TIP v Pooled PBO
Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	4.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.77
upper limit	26.42

Statistical analysis title	Cohort B (5 capsules o.d.): TIP, Pooled PBO
Comparison groups	Cohort B (5 capsules o.d.): TIP v Pooled PBO
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	2
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.28
upper limit	14.47

Statistical analysis title	Cohort B (5 capsules o.d.): TIP/PBO, Pooled PBO
Comparison groups	Cohort B (5 capsules o.d.): TIP/PBO v Pooled PBO

Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	1.54
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.2
upper limit	11.6

Statistical analysis title	Cohort C (4 capsules b.i.d.): TIP, Pooled PBO
Comparison groups	Cohort C (4 capsules b.i.d.): TIP v Pooled PBO
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	0.67
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.06
upper limit	7.49

Statistical analysis title	Cohort C (4 capsules b.i.d.): TIP/PBO, Pooled PBO
Comparison groups	Cohort C (4 capsules b.i.d.): TIP/PBO v Pooled PBO
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	3.81
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.62
upper limit	23.29

Statistical analysis title	Pooled TIP, Pooled PBO
Comparison groups	Pooled TIP v Pooled PBO

Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	1.82
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.35
upper limit	9.45

Secondary: Serum tobramycin concentration

End point title	Serum tobramycin concentration ^[17]
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End point description:

The serum pharmacokinetic (PK) properties of tobramycin were assessed by evaluating tobramycin concentrations in serum collected from the non-cystic fibrosis bronchiectasis population post administration of o.d. or b.i.d. doses of TIP. Serum specimens for PK tobramycin concentration were assessed at Visit 101 (Day 1/start of treatment) 0 to 1 and 1 to 2 hours post-dose and Visit 102 (Day 8) 0 to 1 and 1 to 2 hours post-dose. Prior to protocol amendment #2, PK samples were assessed on Visits 103 (Day 29) rather than Visit 102. Only descriptive analysis performed.

End point type	Secondary
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End point timeframe:

Baseline (Visit 101/Day 1), Visit 102 (Day 8) and Visits 103 (Day 29): 0-1 hours and 1-2 hours post-dose.

Notes:

[17] - 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: For efficacy analysis, subjects assigned to: Placebo groups were pooled across the 3 cohorts, as the number of placebo capsules was not expected to impact the efficacy assessments (Pooled inhaled placebo (PBO)); TIP groups were pooled across the 3 cohorts (Pooled TIP) and TIP/PBO groups were pooled across the 3 cohorts (Pooled TIP/PBO).

End point values	Cohort A (3 capsules o.d.): TIP	Cohort A (3 capsules o.d.): TIP/PBO	Cohort B (5 capsules o.d.): TIP	Cohort B (5 capsules o.d.): TIP/PBO
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	14	13	15	14
Units: microgram/milliliter				
arithmetic mean (standard deviation)				
Visit 101 (Day 1)/0-1 hr post dose	0.256 (± 0.144)	0.479 (± 0.47)	0.4 (± 0.259)	0.441 (± 0.273)
Visit 101 (Day 1)/1-2 hr post dose	0.481 (± 0.287)	0.571 (± 0.349)	0.517 (± 0.392)	0.624 (± 0.322)
Visit 102 (Day 8)/0-1 hr post dose	999 (± 999)	0 (± 999)	1.81 (± 999)	0.258 (± 999)
Visit 102 (Day 8)/1-2 hr post dose	999 (± 999)	0.18 (± 999)	1.67 (± 999)	0.588 (± 999)
Visit 103 (Day 29)/0-1 hr post dose	0.607 (± 0.455)	0.0718 (± 0.0498)	1.23 (± 1.08)	0.103 (± 0.0983)
Visit 103 (Day 29)/1-2 hr post dose	0.768 (± 0.477)	0.0818 (± 0.0972)	1.37 (± 0.647)	0.104 (± 0.096)

End point values	Cohort C (4 capsules b.i.d.): TIP	Cohort C (4 capsules b.i.d.):		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	15		
Units: microgram/milliliter				
arithmetic mean (standard deviation)				
Visit 101 (Day 1)/0-1 hr post dose	0.59 (± 0.37)	0.321 (± 0.21)		
Visit 101 (Day 1)/1-2 hr post dose	0.64 (± 0.338)	0.476 (± 0.295)		
Visit 102 (Day 8)/0-1 hr post dose	1.4 (± 999)	0.489 (± 0.257)		
Visit 102 (Day 8)/1-2 hr post dose	1.48 (± 999)	0.447 (± 999)		
Visit 103 (Day 29)/0-1 hr post dose	1.05 (± 0.603)	0.339 (± 0.274)		
Visit 103 (Day 29)/1-2 hr post dose	1.05 (± 0.622)	0.307 (± 0.24)		

Statistical analyses

No statistical analyses for this end point

Secondary: Sputum tobramycin concentration

End point title	Sputum tobramycin concentration ^[18]
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End point description:

The sputum pharmacokinetic (PK) properties of tobramycin were assessed by evaluating tobramycin concentrations in sputum collected from the non-cystic fibrosis bronchiectasis population post administration of o.d. or b.i.d. doses of TIP. Only descriptive analysis performed.

End point type	Secondary
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End point timeframe:

Baseline (Visit 101/Day 1): 0-1 hours and 1-2 hours post-dose; Visit 102 (Day 8):0-2 hours and 5-6 hours post-dose; Visits 103 (Day 29): 5 to 6 hours post-dose, Visit 4 (Day 57) and Visit 5 (Day 85): 3-4 hours post-dose.

Notes:

[18] - 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: For efficacy analysis, subjects assigned to: Placebo groups were pooled across the 3 cohorts, as the number of placebo capsules was not expected to impact the efficacy assessments (Pooled inhaled placebo (PBO)); TIP groups were pooled across the 3 cohorts (Pooled TIP) and TIP/PBO groups were pooled across the 3 cohorts (Pooled TIP/PBO).

End point values	Cohort A (3 capsules o.d.): TIP	Cohort A (3 capsules o.d.): TIP/PBO	Cohort B (5 capsules o.d.): TIP	Cohort B (5 capsules o.d.): TIP/PBO
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	14	13	15	14
Units: microgram/milliliter				
arithmetic mean (standard deviation)				
Visit 101 (Day 1)/0-1 hr post dose	1750 (± 2160)	637 (± 608)	2640 (± 2680)	2020 (± 2360)
Visit 101 (Day 1)/1-2 hr post dose	1100 (± 2480)	204 (± 445)	1650 (± 2340)	1100 (± 2310)
Visit 102 (Day 8)/0-2 hr post dose	1440 (± 1470)	2390 (± 2730)	2460 (± 761)	4290 (± 3730)
Visit 102 (Day 8)/5-6 hr post dose	999 (± 999)	32.4 (± 999)	999 (± 999)	4460 (± 999)
Visit 103 (Day 29)/5-6 hr post dose	389 (± 554)	136 (± 258)	915 (± 1450)	16.3 (± 28.6)
Visit 104 (Day 57)/3-4 hr post dose	198 (± 138)	0 (± 999)	96.4 (± 999)	4540 (± 999)

Visit 105 (Day 85)/3-4 hr post dose	791 (± 883)	45.7 (± 75.8)	101 (± 100)	61 (± 108)
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End point values	Cohort C (4 capsules b.i.d.): TIP	Cohort C (4 capsules b.i.d.):		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	15		
Units: microgram/milliliter				
arithmetic mean (standard deviation)				
Visit 101 (Day 1)/0-1 hr post dose	2820 (± 2250)	2060 (± 1840)		
Visit 101 (Day 1)/1-2 hr post dose	631 (± 441)	610 (± 463)		
Visit 102 (Day 8)/0-2 hr post dose	1980 (± 2060)	2290 (± 1560)		
Visit 102 (Day 8)/5-6 hr post dose	999 (± 999)	1200 (± 51.6)		
Visit 103 (Day 29)/5-6 hr post dose	620 (± 513)	134 (± 175)		
Visit 104 (Day 57)/3-4 hr post dose	999 (± 999)	0 (± 0)		
Visit 105 (Day 85)/3-4 hr post dose	2810 (± 2200)	121 (± 166)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Quality of Life Questionnaire for Bronchiectasis (QOL-B)-Physical Functioning

End point title	Change from Baseline in Quality of Life Questionnaire for Bronchiectasis (QOL-B)-Physical Functioning ^[19]
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End point description:

The QoL-B consists of 37 items across 8 domains: Physical Functioning (PF), Role Functioning (RF), Vitality, Emotional Function (EF), Social Functioning (SF), Treatment Burden (TB), Health Perception (HP) and Respiratory Symptoms (RS). Each of the 37 items is scored from 1 to 4, and each of the 8 scale scores is standardized on a 0-100 point scale, with higher scores representing fewer symptoms or better functioning and HRQoL. A total score is not calculated since functioning can vary greatly from one domain to another. Only descriptive analysis performed.

End point type	Secondary
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End point timeframe:

Baseline, Visit 102 (Day 8), Visit 103 (Day 29), End of Treatment (Day 113) and Visit 202 (Day 169)

Notes:

[19] - 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: For efficacy analysis, subjects assigned to: Placebo groups were pooled across the 3 cohorts, as the number of placebo capsules was not expected to impact the efficacy assessments (Pooled inhaled placebo (PBO)); TIP groups were pooled across the 3 cohorts (Pooled TIP) and TIP/PBO groups were pooled across the 3 cohorts (Pooled TIP/PBO).

End point values	Cohort A (3 capsules o.d.): TIP	Cohort A (3 capsules o.d.): TIP/PBO	Cohort B (5 capsules o.d.): TIP	Cohort B (5 capsules o.d.): TIP/PBO
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	14	13	15	14
Units: Score on Scale				
arithmetic mean (standard deviation)				

Baseline (BL)	51.33 (± 38.33)	60.5 (± 28.60)	45.8 (± 19.98)	50.5 (± 33.04)
Change from BL at Day 8	5.6 (± 18.83)	-2.8 (± 14.35)	-6.7 (± 22.02)	-2.9 (± 18.06)
Change from BL at Day 29	-2.1 (± 24.40)	-7.2 (± 16.44)	-5.3 (± 27.90)	-2.6 (± 8.41)
Change from BL at EoT	-6.7 (± 18.66)	-6.1 (± 18.53)	-19.4 (± 23.00)	-6.7 (± 23.39)
Change from BL at Day 169	5.5 (± 25.27)	-3.3 (± 18.09)	0.0 (± 22.44)	-1.3 (± 16.27)

End point values	Cohort C (4 capsules b.i.d.): TIP	Cohort C (4 capsules b.i.d.):	Pooled TIP/PBO	Pooled PBO
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	15	15	42	21
Units: Score on Scale				
arithmetic mean (standard deviation)				
Baseline (BL)	46.2 (± 30.29)	53.8 (± 26.72)	54.8 (± 29.10)	49.8 (± 27.97)
Change from BL at Day 8	0.9 (± 11.51)	3.1 (± 14.44)	-0.7 (± 15.62)	-7.4 (± 17.76)
Change from BL at Day 29	-0.4 (± 16.23)	-6.2 (± 27.48)	-5.3 (± 19.05)	-1.1 (± 17.68)
Change from BL at EoT	-5.8 (± 31.36)	-9.8 (± 30.43)	-7.6 (± 24.47)	0.4 (± 20.30)
Change from BL at Day 169	-3.9 (± 26.43)	7.3 (± 22.54)	0.6 (± 19.04)	-4.8 (± 16.77)

End point values	Pooled TIP			
Subject group type	Subject analysis set			
Number of subjects analysed	43			
Units: Score on Scale				
arithmetic mean (standard deviation)				
Baseline (BL)	47.6 (± 29.41)			
Change from BL at Day 8	0.2 (± 17.83)			
Change from BL at Day 29	-2.3 (± 22.04)			
Change from BL at EoT	-10.2 (± 25.44)			
Change from BL at Day 169	0.4 (± 24.43)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Quality of Life Questionnaire for Bronchiectasis (QOL-B)-Role Functioning

End point title	Change from Baseline in Quality of Life Questionnaire for Bronchiectasis (QOL-B)-Role Functioning ^[20]
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End point description:

The QoL-B consists of 37 items across 8 domains: Physical Functioning (PF), Role Functioning (RF), Vitality, Emotional Function (EF), Social Functioning (SF), Treatment Burden (TB), Health Perception (HP) and Respiratory Symptoms (RS). Each of the 37 items is scored from 1 to 4, and each of the 8 scale scores is standardized on a 0-100 point scale, with higher scores representing fewer symptoms or better functioning and HRQoL. A total score is not calculated since functioning can vary greatly from one

domain to another. Only descriptive analysis performed.

End point type	Secondary
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End point timeframe:

Baseline, Visit 102 (Day 8), Visit 103 (Day 29), End of Treatment (Day 113) and Visit 202 (Day 169)

Notes:

[20] - 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: For efficacy analysis, subjects assigned to: Placebo groups were pooled across the 3 cohorts, as the number of placebo capsules was not expected to impact the efficacy assessments (Pooled inhaled placebo (PBO)); TIP groups were pooled across the 3 cohorts (Pooled TIP) and TIP/PBO groups were pooled across the 3 cohorts (Pooled TIP/PBO).

End point values	Cohort A (3 capsules o.d.): TIP	Cohort A (3 capsules o.d.): TIP/PBO	Cohort B (5 capsules o.d.): TIP	Cohort B (5 capsules o.d.): TIP/PBO
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	14	13	15	14
Units: Score on Scale				
arithmetic mean (standard deviation)				
Baseline (BL)	63.1 (± 24.28)	67.2 (± 14.26)	53.3 (± 21.68)	64.3 (± 29.77)
Change from BL at Day 8	5.6 (± 14.36)	-2.2 (± 19.76)	2.2 (± 20.17)	-1.4 (± 13.88)
Change from BL at Day 29	1.5 (± 19.66)	-1.1 (± 18.17)	2.0 (± 21.33)	-1.0 (± 14.87)
Change from BL at EoT	-0.5 (± 23.95)	-5.0 (± 24.47)	-0.4 (± 23.79)	-9.0 (± 25.30)
Change from BL at Day 169	10.3 (± 16.96)	-7.2 (± 17.17)	10.7 (± 13.41)	-2.7 (± 21.82)

End point values	Cohort C (4 capsules b.i.d.): TIP	Cohort C (4 capsules b.i.d.):	Pooled TIP/PBO	Pooled PBO
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	15	15	42	21
Units: Score on Scale				
arithmetic mean (standard deviation)				
Baseline (BL)	57.8 (± 26.86)	67.6 (± 24.67)	66.3 (± 23.46)	63.9 (± 19.79)
Change from BL at Day 8	3.6 (± 17.43)	-4.2 (± 20.95)	-2.7 (± 18.03)	-1.4 (± 14.67)
Change from BL at Day 29	-0.9 (± 19.82)	-4.5 (± 23.88)	-2.3 (± 19.06)	1.8 (± 16.00)
Change from BL at EoT	0.9 (± 20.30)	-4.0 (± 24.27)	-6.0 (± 24.17)	1.0 (± 19.70)
Change from BL at Day 169	-6.1 (± 15.94)	6.7 (± 16.92)	-1.5 (± 18.99)	-4.4 (± 15.51)

End point values	Pooled TIP			
Subject group type	Subject analysis set			
Number of subjects analysed	43			
Units: Score on Scale				
arithmetic mean (standard deviation)				
Baseline (BL)	57.8 (± 24.11)			
Change from BL at Day 8	3.8 (± 17.01)			
Change from BL at Day 29	0.7 (± 19.65)			
Change from BL at EoT	0.0 (± 22.01)			
Change from BL at Day 169	4.4 (± 17.13)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Quality of Life Questionnaire for Bronchiectasis (QOL-B)-Vitality

End point title	Change from Baseline in Quality of Life Questionnaire for Bronchiectasis (QOL-B)-Vitality ^[21]
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End point description:

The QoL-B consists of 37 items across 8 domains: Physical Functioning (PF), Role Functioning (RF), Vitality, Emotional Function (EF), Social Functioning (SF), Treatment Burden (TB), Health Perception (HP) and Respiratory Symptoms (RS). Each of the 37 items is scored from 1 to 4, and each of the 8 scale scores is standardized on a 0-100 point scale, with higher scores representing fewer symptoms or better functioning and HRQoL. A total score is not calculated since functioning can vary greatly from one domain to another. Only descriptive analysis performed.

End point type	Secondary
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End point timeframe:

Baseline, Visit 102 (Day 8), Visit 103 (Day 29), End of Treatment (Day 113) and Visit 202 (Day 169)

Notes:

[21] - 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: For efficacy analysis, subjects assigned to: Placebo groups were pooled across the 3 cohorts, as the number of placebo capsules was not expected to impact the efficacy assessments (Pooled inhaled placebo (PBO)); TIP groups were pooled across the 3 cohorts (Pooled TIP) and TIP/PBO groups were pooled across the 3 cohorts (Pooled TIP/PBO).

End point values	Cohort A (3 capsules o.d.): TIP	Cohort A (3 capsules o.d.): TIP/PBO	Cohort B (5 capsules o.d.): TIP	Cohort B (5 capsules o.d.): TIP/PBO
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	14	13	15	14
Units: Score on Scale				
arithmetic mean (standard deviation)				
Baseline (BL)	56.4 (± 22.89)	47.9 (± 17.21)	52.4 (± 21.54)	44.4 (± 26.51)
Change from BL at Day 8	6.8 (± 18.45)	1.9 (± 24.54)	-6.1 (± 31.18)	4.8 (± 17.27)
Change from BL at Day 29	-4.3 (± 30.95)	4.6 (± 15.23)	-9.9 (± 28.57)	3.4 (± 18.36)
Change from BL at EoT	-5.6 (± 25.26)	2.8 (± 24.22)	-12.1 (± 26.04)	3.2 (± 28.05)
Change from BL at Day 169	8.1 (± 20.55)	3.7 (± 22.89)	3.7 (± 24.22)	2.2 (± 21.47)

End point values	Cohort C (4 capsules b.i.d.): TIP	Cohort C (4 capsules b.i.d.):	Pooled TIP/PBO	Pooled PBO
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	15	15	42	21
Units: Score on Scale				
arithmetic mean (standard deviation)				

Baseline (BL)	47.4 (± 25.36)	51.9 (± 18.63)	48.1 (± 20.92)	46.2 (± 25.46)
Change from BL at Day 8	5.2 (± 20.52)	2.2 (± 11.27)	3.0 (± 17.57)	-2.9 (± 16.08)
Change from BL at Day 29	-0.7 (± 24.66)	-5.6 (± 23.77)	80.6 (± 19.74)	1.8 (± 19.69)
Change from BL at EoT	-0.7 (± 29.24)	2.2 (± 30.35)	2.7 (± 27.19)	-1.2 (± 23.97)
Change from BL at Day 169	-2.8 (± 22.78)	1.1 (± 19.21)	2.4 (± 20.69)	-2.5 (± 20.36)

End point values	Pooled TIP			
Subject group type	Subject analysis set			
Number of subjects analysed	42			
Units: Score on Scale				
arithmetic mean (standard deviation)				
Baseline (BL)	51.9 (± 23.11)			
Change from BL at Day 8	2.6 (± 23.43)			
Change from BL at Day 29	-4.2 (± 27.39)			
Change from BL at EoT	-5.6 (± 26.77)			
Change from BL at Day 169	2.8 (± 22.22)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Quality of Life Questionnaire for Bronchiectasis (QOL-B)-Emotional Functioning

End point title	Change from Baseline in Quality of Life Questionnaire for Bronchiectasis (QOL-B)-Emotional Functioning ^[22]
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End point description:

The QoL-B consists of 37 items across 8 domains: Physical Functioning (PF), Role Functioning (RF), Vitality, Emotional Function (EF), Social Functioning (SF), Treatment Burden (TB), Health Perception (HP) and Respiratory Symptoms (RS). Each of the 37 items is scored from 1 to 4, and each of the 8 scale scores is standardized on a 0-100 point scale, with higher scores representing fewer symptoms or better functioning and HRQoL. A total score is not calculated since functioning can vary greatly from one domain to another. Only descriptive analysis performed.

End point type	Secondary
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End point timeframe:

Baseline, Visit 102 (Day 8), Visit 103 (Day 29), End of Treatment (Day 113) and Visit 202 (Day 169)

Notes:

[22] - 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: For efficacy analysis, subjects assigned to: Placebo groups were pooled across the 3 cohorts, as the number of placebo capsules was not expected to impact the efficacy assessments (Pooled inhaled placebo (PBO)); TIP groups were pooled across the 3 cohorts (Pooled TIP) and TIP/PBO groups were pooled across the 3 cohorts (Pooled TIP/PBO).

End point values	Cohort A (3 capsules o.d.): TIP	Cohort A (3 capsules o.d.): TIP/PBO	Cohort B (5 capsules o.d.): TIP	Cohort B (5 capsules o.d.): TIP/PBO
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	14	13	15	14
Units: Score on Scale				
arithmetic mean (standard deviation)				
Baseline (BL)	79.5 (± 14.28)	71.2 (± 18.51)	77.4 (± 17.73)	74.4 (± 29.50)
Change from BL at Day 8	2.6 (± 11.48)	-4.2 (± 12.05)	-0.8 (± 13.67)	2.4 (± 11.52)
Change from BL at Day 29	1.9 (± 11.36)	-4.9 (± 12.03)	2.8 (± 13.18)	3.8 (± 16.53)
Change from BL at EoT	1.3 (± 17.63)	-8.3 (± 22.19)	-9.1 (± 18.43)	2.4 (± 32.26)
Change from BL at Day 169	6.1 (± 21.44)	-6.9 (± 15.00)	7.4 (± 17.40)	5.0 (± 18.51)

End point values	Cohort C (4 capsules b.i.d.): TIP	Cohort C (4 capsules b.i.d.):	Pooled TIP/PBO	Pooled PBO
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	15	15	42	21
Units: Score on Scale				
arithmetic mean (standard deviation)				
Baseline (BL)	71.1 (± 18.86)	76.1 (± 23.54)	74.0 (± 23.87)	79.6 (± 16.96)
Change from BL at Day 8	4.4 (± 18.33)	4.4 (± 6.19)	1.2 (± 10.47)	-1.4 (± 11.87)
Change from BL at Day 29	5.6 (± 13.24)	-1.2 (± 14.93)	-0.6 (± 14.73)	-1.9 (± 12.31)
Change from BL at EoT	1.1 (± 15.06)	-3.3 (± 14.36)	-2.8 (± 23.76)	-2.3 (± 15.60)
Change from BL at Day 169	0.0 (± 7.11)	6.7 (± 21.45)	1.0 (± 18.78)	3.9 (± 13.85)

End point values	Pooled TIP			
Subject group type	Subject analysis set			
Number of subjects analysed	42			
Units: Score on Scale				
arithmetic mean (standard deviation)				
Baseline (BL)	75.8 (± 17.15)			
Change from BL at Day 8	2.4 (± 14.80)			
Change from BL at Day 29	3.6 (± 12.35)			
Change from BL at EoT	-1.7 (± 17.12)			
Change from BL at Day 169	4.2 (± 15.98)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Quality of Life Questionnaire for Bronchiectasis (QOL-B)-Social Functioning

End point title	Change from Baseline in Quality of Life Questionnaire for Bronchiectasis (QOL-B)-Social Functioning ^[23]
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End point description:

The QoL-B consists of 37 items across 8 domains: Physical Functioning (PF), Role Functioning (RF), Vitality, Emotional Function (EF), Social Functioning (SF), Treatment Burden (TB), Health Perception (HP) and Respiratory Symptoms (RS). Each of the 37 items is scored from 1 to 4, and each of the 8 scale scores is standardized on a 0-100 point scale, with higher scores representing fewer symptoms or better functioning and HRQoL. A total score is not calculated since functioning can vary greatly from one domain to another. Only descriptive analysis performed.

End point type	Secondary
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End point timeframe:

Baseline, Visit 102 (Day 8), Visit 103 (Day 29), End of Treatment (Day 113) and Visit 202 (Day 169)

Notes:

[23] - 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: For efficacy analysis, subjects assigned to: Placebo groups were pooled across the 3 cohorts, as the number of placebo capsules was not expected to impact the efficacy assessments (Pooled inhaled placebo (PBO)); TIP groups were pooled across the 3 cohorts (Pooled TIP) and TIP/PBO groups were pooled across the 3 cohorts (Pooled TIP/PBO).

End point values	Cohort A (3 capsules o.d.): TIP	Cohort A (3 capsules o.d.): TIP/PBO	Cohort B (5 capsules o.d.): TIP	Cohort B (5 capsules o.d.): TIP/PBO
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	14	13	15	14
Units: Score on Scale				
arithmetic mean (standard deviation)				
Baseline (BL)	66.2 (± 19.21)	51.3 (± 22.53)	36.5 (± 21.18)	63.5 (± 26.17)
Change from BL at Day 8	3.0 (± 13.49)	2.1 (± 23.61)	29.6 (± 23.67)	-2.6 (± 12.49)
Change from BL at Day 29	4.9 (± 15.51)	-2.5 (± 26.05)	22.8 (± 18.14)	-1.5 (± 24.50)
Change from BL at EoT	3.0 (± 21.71)	2.1 (± 26.14)	17.8 (± 27.89)	-5.6 (± 26.73)
Change from BL at Day 169	3.3 (± 24.27)	-5.1 (± 20.41)	25.3 (± 21.73)	-4.2 (± 28.43)

End point values	Cohort C (4 capsules b.i.d.): TIP	Cohort C (4 capsules b.i.d.):	Pooled TIP/PBO	Pooled PBO
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	15	15	42	21
Units: Score on Scale				
arithmetic mean (standard deviation)				
Baseline (BL)	48.5 (± 19.95)	55.7 (± 26.80)	56.9 (± 25.22)	51.9 (± 25.24)
Change from BL at Day 8	-0.7 (± 21.91)	8.5 (± 15.66)	2.8 (± 17.67)	5.0 (± 14.18)
Change from BL at Day 29	2.6 (± 23.95)	4.8 (± 19.89)	0.4 (± 23.07)	-1.2 (± 15.72)
Change from BL at EoT	1.5 (± 30.10)	5.7 (± 15.38)	0.8 (± 22.95)	-0.6 (± 18.04)
Change from BL at Day 169	-4.2 (± 25.42)	11.9 (± 21.91)	0.5 (± 24.15)	-0.5 (± 19.37)

End point values	Pooled TIP			
Subject group type	Subject analysis set			
Number of subjects analysed	43			
Units: Score on Scale				
arithmetic mean (standard deviation)				

Baseline (BL)	49.7 (± 23.13)			
Change from BL at Day 8	9.6 (± 23.78)			
Change from BL at Day 29	8.7 (± 21.19)			
Change from BL at EoT	6.9 (± 27.25)			
Change from BL at Day 169	7.2 (± 26.36)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Quality of Life Questionnaire for Bronchiectasis (QOL-B)-Treatment Burden

End point title	Change from Baseline in Quality of Life Questionnaire for Bronchiectasis (QOL-B)-Treatment Burden ^[24]
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End point description:

The QoL-B consists of 37 items across 8 domains: Physical Functioning (PF), Role Functioning (RF), Vitality, Emotional Function (EF), Social Functioning (SF), Treatment Burden (TB), Health Perception (HP) and Respiratory Symptoms (RS). Each of the 37 items is scored from 1 to 4, and each of the 8 scale scores is standardized on a 0-100 point scale, with higher scores representing fewer symptoms or better functioning and HRQoL. A total score is not calculated since functioning can vary greatly from one domain to another. Only descriptive analysis performed.

End point type	Secondary
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End point timeframe:

Baseline, Visit 102 (Day 8), Visit 103 (Day 29), End of Treatment (Day 113) and Visit 202 (Day 169)

Notes:

[24] - 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: For efficacy analysis, subjects assigned to: Placebo groups were pooled across the 3 cohorts, as the number of placebo capsules was not expected to impact the efficacy assessments (Pooled inhaled placebo (PBO)); TIP groups were pooled across the 3 cohorts (Pooled TIP) and TIP/PBO groups were pooled across the 3 cohorts (Pooled TIP/PBO).

End point values	Cohort A (3 capsules o.d.): TIP	Cohort A (3 capsules o.d.): TIP/PBO	Cohort B (5 capsules o.d.): TIP	Cohort B (5 capsules o.d.): TIP/PBO
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	14	13	15	14
Units: Score on Scale				
arithmetic mean (standard deviation)				
Baseline (BL)	67.7 (± 25.56)	68.9 (± 26.09)	64.3 (± 29.29)	73.1 (± 18.63)
Change from BL at Day 8	-2.2 (± 19.46)	-8.6 (± 29.28)	0.0 (± 15.71)	-9.3 (± 17.62)
Change from BL at Day 29	-9.1 (± 28.03)	-8.3 (± 27.70)	8.3 (± 30.14)	-10.0 (± 22.50)
Change from BL at EoT	-7.1 (± 21.81)	-8.6 (± 31.32)	-10.1 (± 16.07)	-14.8 (± 23.37)
Change from BL at Day 169	1.4 (± 26.19)	-3.7 (± 31.92)	0.0 (± 13.28)	-4.2 (± 24.44)

End point values	Cohort C (4 capsules b.i.d.): TIP	Cohort C (4 capsules b.i.d.):	Pooled PBO	Pooled TIP
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Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	15	15	21	38
Units: Score on Scale				
arithmetic mean (standard deviation)				
Baseline (BL)	56.4 (± 27.76)	54.5 (± 27.42)	64.6 (± 30.69)	62.6 (± 27.39)
Change from BL at Day 8	4.3 (± 14.01)	4.0 (± 7.49)	-2.6 (± 19.33)	1.0 (± 16.04)
Change from BL at Day 29	1.9 (± 13.26)	-3.7 (± 25.46)	-5.1 (± 25.91)	-0.4 (± 24.26)
Change from BL at EoT	6.8 (± 26.66)	1.0 (± 9.23)	-3.0 (± 30.13)	-2.9 (± 22.92)
Change from BL at Day 169	0.0 (± 17.37)	12.7 (± 11.88)	-5.1 (± 18.16)	0.4 (± 18.72)

End point values	Pooled TIP/PBO			
Subject group type	Subject analysis set			
Number of subjects analysed	33			
Units: Score on Scale				
arithmetic mean (standard deviation)				
Baseline (BL)	65.7 (± 24.75)			
Change from BL at Day 8	-4.5 (± 19.73)			
Change from BL at Day 29	-7.4 (± 24.27)			
Change from BL at EoT	-7.6 (± 22.83)			
Change from BL at Day 169	0.9 (± 25.15)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Quality of Life Questionnaire for Bronchiectasis (QOL-B)-Health Perceptions

End point title	Change from Baseline in Quality of Life Questionnaire for Bronchiectasis (QOL-B)-Health Perceptions ^[25]
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End point description:

The QoL-B consists of 37 items across 8 domains: Physical Functioning (PF), Role Functioning (RF), Vitality, Emotional Function (EF), Social Functioning (SF), Treatment Burden (TB), Health Perception (HP) and Respiratory Symptoms (RS). Each of the 37 items is scored from 1 to 4, and each of the 8 scale scores is standardized on a 0-100 point scale, with higher scores representing fewer symptoms or better functioning and HRQoL. A total score is not calculated since functioning can vary greatly from one domain to another. Only descriptive analysis performed.

End point type	Secondary
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End point timeframe:

Baseline, Visit 102 (Day 8), Visit 103 (Day 29), End of Treatment (Day 113) and Visit 202 (Day 169)

Notes:

[25] - 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: For efficacy analysis, subjects assigned to: Placebo groups were pooled across the 3 cohorts, as the number of placebo capsules was not expected to impact the efficacy assessments (Pooled inhaled placebo (PBO)); TIP groups were pooled across the 3 cohorts (Pooled TIP) and TIP/PBO groups were pooled across the 3 cohorts (Pooled TIP/PBO).

End point values	Cohort A (3 capsules o.d.): TIP	Cohort A (3 capsules o.d.): TIP/PBO	Cohort B (5 capsules o.d.): TIP	Cohort B (5 capsules o.d.): TIP/PBO
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	14	13	15	14
Units: Score on Scale				
arithmetic mean (standard deviation)				
Baseline (BL)	41.0 (± 17.83)	35.3 (± 19.29)	33.1 (± 20.26)	41.1 (± 27.83)
Change from BL at Day 8	7.1 (± 23.28)	4.9 (± 20.24)	10.0 (± 11.87)	-2.4 (± 13.25)
Change from BL at Day 29	7.1 (± 26.54)	4.9 (± 20.24)	12.8 (± 16.26)	3.8 (± 19.73)
Change from BL at EoT	-3.2 (± 25.35)	0.7 (± 17.93)	-2.5 (± 15.28)	-3.6 (± 23.51)
Change from BL at Day 169	10.6 (± 13.99)	0.0 (± 21.32)	14.4 (± 19.72)	6.7 (± 17.91)

End point values	Cohort C (4 capsules b.i.d.): TIP	Cohort C (4 capsules b.i.d.):	Pooled TIP/PBO	Pooled PBO
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	15	15	42	21
Units: Score on Scale				
arithmetic mean (standard deviation)				
Baseline (BL)	39.4 (± 21.70)	40.0 (± 20.70)	38.9 (± 22.52)	41.7 (± 16.67)
Change from BL at Day 8	5.6 (± 13.24)	5.6 (± 15.96)	2.6 (± 16.50)	0.0 (± 16.43)
Change from BL at Day 29	-1.1 (± 18.06)	-1.8 (± 26.19)	2.1 (± 22.02)	3.1 (± 14.49)
Change from BL at EoT	1.1 (± 23.12)	-0.6 (± 23.46)	-1.2 (± 21.53)	1.6 (± 16.67)
Change from BL at Day 169	-1.4 (± 11.70)	9.2 (± 14.93)	4.9 (± 18.31)	0.9 (± 19.57)

End point values	Pooled TIP			
Subject group type	Subject analysis set			
Number of subjects analysed	43			
Units: Score on Scale				
arithmetic mean (standard deviation)				
Baseline (BL)	37.7 (± 19.91)			
Change from BL at Day 8	7.4 (± 16.52)			
Change from BL at Day 29	5.3 (± 21.19)			
Change from BL at EoT	-1.4 (± 21.43)			
Change from BL at Day 169	7.4 (± 16.30)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Quality of Life Questionnaire for Bronchiectasis (QOL-B)-Respiratory Symptoms

End point title	Change from Baseline in Quality of Life Questionnaire for Bronchiectasis (QOL-B)-Respiratory Symptoms ^[26]
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End point description:

The QoL-B consists of 37 items across 8 domains: Physical Functioning (PF), Role Functioning (RF), Vitality, Emotional Function (EF), Social Functioning (SF), Treatment Burden (TB), Health Perception (HP) and Respiratory Symptoms (RS). Each of the 37 items is scored from 1 to 4, and each of the 8 scale scores is standardized on a 0-100 point scale, with higher scores representing fewer symptoms or better functioning and HRQoL. A total score is not calculated since functioning can vary greatly from one domain to another. Only descriptive analysis performed.

End point type	Secondary
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End point timeframe:

Baseline, Visit 102 (Day 8), Visit 103 (Day 29), End of Treatment (Day 113) and Visit 202 (Day 169)

Notes:

[26] - 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: For efficacy analysis, subjects assigned to: Placebo groups were pooled across the 3 cohorts, as the number of placebo capsules was not expected to impact the efficacy assessments (Pooled inhaled placebo (PBO)); TIP groups were pooled across the 3 cohorts (Pooled TIP) and TIP/PBO groups were pooled across the 3 cohorts (Pooled TIP/PBO).

End point values	Cohort A (3 capsules o.d.): TIP	Cohort A (3 capsules o.d.): TIP/PBO	Cohort B (5 capsules o.d.): TIP	Cohort B (5 capsules o.d.): TIP/PBO
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	14	13	15	14
Units: Score on Scale				
arithmetic mean (standard deviation)				
Baseline (BL)	56.0 (± 13.05)	53.8 (± 18.12)	56.8 (± 17.63)	55.9 (± 21.69)
Change from BL at Day 8	10.3 (± 6.83)	6.5 (± 14.66)	13.9 (± 16.12)	3.3 (± 9.99)
Change from BL at Day 29	7.0 (± 11.94)	0.6 (± 19.97)	6.3 (± 24.57)	3.6 (± 14.69)
Change from BL at EoT	-0.4 (± 11.21)	4.1 (± 15.65)	1.9 (± 18.52)	-0.6 (± 20.73)
Change from BL at Day 169	7.1 (± 11.76)	0.9 (± 16.42)	10.7 (± 8.63)	-2.7 (± 24.33)

End point values	Cohort C (4 capsules b.i.d.): TIP	Cohort C (4 capsules b.i.d.):	Pooled TIP/PBO	Pooled PBO
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	15	15	42	21
Units: Score on Scale				
arithmetic mean (standard deviation)				
Baseline (BL)	52.3 (± 22.39)	61.9 (± 13.31)	57.4 (± 17.83)	53.8 (± 14.42)
Change from BL at Day 8	9.8 (± 12.30)	-0.6 (± 16.20)	2.8 (± 13.85)	1.0 (± 12.09)
Change from BL at Day 29	6.9 (± 22.57)	-5.7 (± 25.58)	-0.7 (± 20.58)	2.3 (± 13.48)
Change from BL at EoT	6.7 (± 16.52)	-6.5 (± 26.18)	-1.4 (± 21.59)	4.0 (± 12.12)
Change from BL at Day 169	5.6 (± 16.53)	10.7 (± 12.52)	2.8 (± 18.57)	1.6 (± 19.98)

End point values	Pooled TIP			
Subject group type	Subject analysis set			
Number of subjects analysed	43			
Units: Score on Scale				
arithmetic mean (standard deviation)				

Baseline (BL)	55.0 (± 17.98)			
Change from BL at Day 8	11.2 (± 12.05)			
Change from BL at Day 29	6.8 (± 19.65)			
Change from BL at EoT	2.9 (± 15.58)			
Change from BL at Day 169	7.6 (± 12.76)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected from first dose of study drug treatment until end of study treatment plus 30 days post treatment, up to a maximum duration of 134 days.

Adverse event reporting additional description:

Consistent with EudraCT disclosure specifications, Novartis has reported under the Serious adverse events field "number of deaths resulting from adverse events" all those deaths, resulting from serious adverse events that are deemed to be causally related to treatment by the investigator.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	21.1
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Reporting groups

Reporting group title	Cohort A:3 capsules o.d. TIP
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Reporting group description:

Cohort A:3 capsules o.d. TIP

Reporting group title	Cohort A:3 capsules o.d. TIP/PBO
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Reporting group description:

Cohort A:3 capsules o.d. TIP/PBO

Reporting group title	Cohort A:3 capsules o.d. PBO
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Reporting group description:

Cohort A:3 capsules o.d. PBO

Reporting group title	Cohort B:5 capsules o.d. TIP
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Reporting group description:

Cohort B:5 capsules o.d. TIP

Reporting group title	Cohort B:5 capsules o.d. TIP/PBO
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Reporting group description:

Cohort B:5 capsules o.d. TIP/PBO

Reporting group title	Cohort B:5 capsules o.d. PBO
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Reporting group description:

Cohort B:5 capsules o.d. PBO

Reporting group title	Cohort C:4 capsules b.i.d. TIP
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Reporting group description:

Cohort C:4 capsules b.i.d. TIP

Reporting group title	Cohort C:4 capsules b.i.d. TIP/PBO
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Reporting group description:

Cohort C:4 capsules b.i.d. TIP/PBO

Reporting group title	Cohort C:4 capsules b.i.d. PBO
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Reporting group description:

Cohort C:4 capsules b.i.d. PBO

Serious adverse events	Cohort A:3 capsules o.d. TIP	Cohort A:3 capsules o.d. TIP/PBO	Cohort A:3 capsules o.d. PBO
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 14 (28.57%)	2 / 13 (15.38%)	0 / 7 (0.00%)
number of deaths (all causes)	0	0	0

number of deaths resulting from adverse events	0	0	0
Investigations			
Blood creatinine abnormal			
subjects affected / exposed	0 / 14 (0.00%)	0 / 13 (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
Glomerular filtration rate decreased			
subjects affected / exposed	0 / 14 (0.00%)	0 / 13 (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			
Orthostatic hypotension			
subjects affected / exposed	0 / 14 (0.00%)	0 / 13 (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			
Acute myocardial infarction			
subjects affected / exposed	0 / 14 (0.00%)	0 / 13 (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
Atrial fibrillation			
subjects affected / exposed	0 / 14 (0.00%)	0 / 13 (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
Nervous system disorders			
Syncope			
subjects affected / exposed	0 / 14 (0.00%)	1 / 13 (7.69%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 14 (0.00%)	0 / 13 (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
Gastrointestinal disorders			

Intestinal obstruction			
subjects affected / exposed	0 / 14 (0.00%)	0 / 13 (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
Hepatobiliary disorders			
Bile duct stone			
subjects affected / exposed	0 / 14 (0.00%)	0 / 13 (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
Cholecystitis acute			
subjects affected / exposed	0 / 14 (0.00%)	1 / 13 (7.69%)	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
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 14 (0.00%)	0 / 13 (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
Dyspnoea			
subjects affected / exposed	0 / 14 (0.00%)	0 / 13 (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
Haemoptysis			
subjects affected / exposed	1 / 14 (7.14%)	0 / 13 (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
Respiratory failure			
subjects affected / exposed	1 / 14 (7.14%)	0 / 13 (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
Infections and infestations			
Bacterial disease carrier			

subjects affected / exposed	0 / 14 (0.00%)	0 / 13 (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
Infective exacerbation of bronchiectasis			
subjects affected / exposed	3 / 14 (21.43%)	0 / 13 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 14 (0.00%)	0 / 13 (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	Cohort B:5 capsules o.d. TIP	Cohort B:5 capsules o.d. TIP/PBO	Cohort B:5 capsules o.d. PBO
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 15 (26.67%)	3 / 14 (21.43%)	2 / 7 (28.57%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Blood creatinine abnormal			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (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
Glomerular filtration rate decreased			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (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			
Orthostatic hypotension			
subjects affected / exposed	1 / 15 (6.67%)	0 / 14 (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
Cardiac disorders			
Acute myocardial infarction			

subjects affected / exposed	0 / 15 (0.00%)	1 / 14 (7.14%)	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
Atrial fibrillation			
subjects affected / exposed	1 / 15 (6.67%)	0 / 14 (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
Nervous system disorders			
Syncope			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (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			
Asthenia			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (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
Gastrointestinal disorders			
Intestinal obstruction			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (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
Hepatobiliary disorders			
Bile duct stone			
subjects affected / exposed	1 / 15 (6.67%)	0 / 14 (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
Cholecystitis acute			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (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			
Chronic obstructive pulmonary disease			

subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (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
Dyspnoea			
subjects affected / exposed	0 / 15 (0.00%)	1 / 14 (7.14%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoptysis			
subjects affected / exposed	0 / 15 (0.00%)	1 / 14 (7.14%)	1 / 7 (14.29%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	0 / 15 (0.00%)	1 / 14 (7.14%)	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
Infections and infestations			
Bacterial disease carrier			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (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
Infective exacerbation of bronchiectasis			
subjects affected / exposed	2 / 15 (13.33%)	1 / 14 (7.14%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 2	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (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	Cohort C:4 capsules b.i.d. TIP	Cohort C:4 capsules b.i.d. TIP/PBO	Cohort C:4 capsules b.i.d. PBO
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 15 (13.33%)	4 / 15 (26.67%)	1 / 7 (14.29%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Investigations			
Blood creatinine abnormal			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Glomerular filtration rate decreased			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Orthostatic hypotension			
subjects affected / exposed	0 / 15 (0.00%)	0 / 15 (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			
Acute myocardial infarction			
subjects affected / exposed	0 / 15 (0.00%)	0 / 15 (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
Atrial fibrillation			
subjects affected / exposed	0 / 15 (0.00%)	0 / 15 (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
Nervous system disorders			
Syncope			
subjects affected / exposed	0 / 15 (0.00%)	0 / 15 (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			
Asthenia			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (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
Gastrointestinal disorders			
Intestinal obstruction			

subjects affected / exposed	0 / 15 (0.00%)	0 / 15 (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
Hepatobiliary disorders			
Bile duct stone			
subjects affected / exposed	0 / 15 (0.00%)	0 / 15 (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
Cholecystitis acute			
subjects affected / exposed	0 / 15 (0.00%)	0 / 15 (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			
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (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
Dyspnoea			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (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
Haemoptysis			
subjects affected / exposed	0 / 15 (0.00%)	0 / 15 (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 / 15 (0.00%)	1 / 15 (6.67%)	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
Infections and infestations			
Bacterial disease carrier			

subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (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
Infective exacerbation of bronchiectasis			
subjects affected / exposed	0 / 15 (0.00%)	3 / 15 (20.00%)	0 / 7 (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
Pneumonia			
subjects affected / exposed	0 / 15 (0.00%)	0 / 15 (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

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

Non-serious adverse events	Cohort A:3 capsules o.d. TIP	Cohort A:3 capsules o.d. TIP/PBO	Cohort A:3 capsules o.d. PBO
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 14 (85.71%)	12 / 13 (92.31%)	6 / 7 (85.71%)
Vascular disorders			
Hot flush			
subjects affected / exposed	1 / 14 (7.14%)	0 / 13 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Hypertension			
subjects affected / exposed	0 / 14 (0.00%)	0 / 13 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 14 (0.00%)	0 / 13 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Chest discomfort			
subjects affected / exposed	0 / 14 (0.00%)	0 / 13 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Chest pain			
subjects affected / exposed	1 / 14 (7.14%)	2 / 13 (15.38%)	0 / 7 (0.00%)
occurrences (all)	1	2	0

Discomfort			
subjects affected / exposed	1 / 14 (7.14%)	0 / 13 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Exercise tolerance decreased			
subjects affected / exposed	0 / 14 (0.00%)	0 / 13 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Fatigue			
subjects affected / exposed	1 / 14 (7.14%)	2 / 13 (15.38%)	0 / 7 (0.00%)
occurrences (all)	1	2	0
Influenza like illness			
subjects affected / exposed	0 / 14 (0.00%)	1 / 13 (7.69%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Oedema peripheral			
subjects affected / exposed	0 / 14 (0.00%)	0 / 13 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Peripheral swelling			
subjects affected / exposed	0 / 14 (0.00%)	0 / 13 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Pyrexia			
subjects affected / exposed	0 / 14 (0.00%)	0 / 13 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Immune system disorders			
Food allergy			
subjects affected / exposed	0 / 14 (0.00%)	0 / 13 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 14 (0.00%)	0 / 13 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Prostatitis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 13 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 14 (0.00%)	0 / 13 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0

Bronchiectasis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 13 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Bronchospasm			
subjects affected / exposed	0 / 14 (0.00%)	0 / 13 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Cough			
subjects affected / exposed	2 / 14 (14.29%)	3 / 13 (23.08%)	1 / 7 (14.29%)
occurrences (all)	8	4	1
Dry throat			
subjects affected / exposed	0 / 14 (0.00%)	0 / 13 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Dysphonia			
subjects affected / exposed	0 / 14 (0.00%)	1 / 13 (7.69%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Dyspnoea			
subjects affected / exposed	2 / 14 (14.29%)	2 / 13 (15.38%)	1 / 7 (14.29%)
occurrences (all)	2	2	1
Dyspnoea exertional			
subjects affected / exposed	0 / 14 (0.00%)	1 / 13 (7.69%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Dyspnoea paroxysmal nocturnal			
subjects affected / exposed	0 / 14 (0.00%)	0 / 13 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Epistaxis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 13 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Haemoptysis			
subjects affected / exposed	1 / 14 (7.14%)	1 / 13 (7.69%)	0 / 7 (0.00%)
occurrences (all)	1	3	0
Increased bronchial secretion			
subjects affected / exposed	0 / 14 (0.00%)	0 / 13 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	2
Increased viscosity of bronchial secretion			

subjects affected / exposed	0 / 14 (0.00%)	1 / 13 (7.69%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Nasal discomfort			
subjects affected / exposed	0 / 14 (0.00%)	0 / 13 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Oropharyngeal pain			
subjects affected / exposed	0 / 14 (0.00%)	1 / 13 (7.69%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Pulmonary pain			
subjects affected / exposed	0 / 14 (0.00%)	0 / 13 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Rales			
subjects affected / exposed	1 / 14 (7.14%)	0 / 13 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Respiratory symptom			
subjects affected / exposed	0 / 14 (0.00%)	0 / 13 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Rhinorrhoea			
subjects affected / exposed	0 / 14 (0.00%)	0 / 13 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Sputum discoloured			
subjects affected / exposed	0 / 14 (0.00%)	0 / 13 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	3
Sputum increased			
subjects affected / exposed	3 / 14 (21.43%)	1 / 13 (7.69%)	1 / 7 (14.29%)
occurrences (all)	3	1	1
Throat irritation			
subjects affected / exposed	0 / 14 (0.00%)	0 / 13 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Wheezing			
subjects affected / exposed	1 / 14 (7.14%)	0 / 13 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 14 (0.00%)	1 / 13 (7.69%)	0 / 7 (0.00%)
occurrences (all)	0	1	0

Investigations			
Blood cholesterol increased			
subjects affected / exposed	0 / 14 (0.00%)	0 / 13 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 14 (0.00%)	0 / 13 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Blood creatinine increased			
subjects affected / exposed	1 / 14 (7.14%)	1 / 13 (7.69%)	0 / 7 (0.00%)
occurrences (all)	1	1	0
Blood electrolytes decreased			
subjects affected / exposed	0 / 14 (0.00%)	1 / 13 (7.69%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Blood urea increased			
subjects affected / exposed	0 / 14 (0.00%)	0 / 13 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
C-reactive protein increased			
subjects affected / exposed	1 / 14 (7.14%)	0 / 13 (0.00%)	1 / 7 (14.29%)
occurrences (all)	1	0	1
Eosinophil count abnormal			
subjects affected / exposed	0 / 14 (0.00%)	0 / 13 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Forced expiratory volume decreased			
subjects affected / exposed	0 / 14 (0.00%)	1 / 13 (7.69%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Forced vital capacity decreased			
subjects affected / exposed	1 / 14 (7.14%)	1 / 13 (7.69%)	0 / 7 (0.00%)
occurrences (all)	1	1	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 14 (0.00%)	0 / 13 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Glomerular filtration rate decreased			
subjects affected / exposed	0 / 14 (0.00%)	0 / 13 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Haemoglobin decreased			

subjects affected / exposed	0 / 14 (0.00%)	0 / 13 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Liver function test abnormal			
subjects affected / exposed	0 / 14 (0.00%)	0 / 13 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Neutrophil count increased			
subjects affected / exposed	0 / 14 (0.00%)	0 / 13 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Protein urine present			
subjects affected / exposed	0 / 14 (0.00%)	0 / 13 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Sputum abnormal			
subjects affected / exposed	0 / 14 (0.00%)	0 / 13 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Urine albumin/creatinine ratio increased			
subjects affected / exposed	1 / 14 (7.14%)	1 / 13 (7.69%)	0 / 7 (0.00%)
occurrences (all)	2	1	0
Urine protein/creatinine ratio increased			
subjects affected / exposed	1 / 14 (7.14%)	1 / 13 (7.69%)	0 / 7 (0.00%)
occurrences (all)	1	1	0
Weight decreased			
subjects affected / exposed	0 / 14 (0.00%)	1 / 13 (7.69%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
White blood cell count increased			
subjects affected / exposed	0 / 14 (0.00%)	0 / 13 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Airway complication of anaesthesia			
subjects affected / exposed	0 / 14 (0.00%)	1 / 13 (7.69%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Arthropod bite			
subjects affected / exposed	0 / 14 (0.00%)	0 / 13 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Fall			

subjects affected / exposed	1 / 14 (7.14%)	0 / 13 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Hypobarism			
subjects affected / exposed	0 / 14 (0.00%)	0 / 13 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Ligament sprain			
subjects affected / exposed	0 / 14 (0.00%)	1 / 13 (7.69%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Procedural pain			
subjects affected / exposed	0 / 14 (0.00%)	0 / 13 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Road traffic accident			
subjects affected / exposed	0 / 14 (0.00%)	1 / 13 (7.69%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
Ageusia			
subjects affected / exposed	0 / 14 (0.00%)	0 / 13 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Anosmia			
subjects affected / exposed	0 / 14 (0.00%)	0 / 13 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Dizziness			
subjects affected / exposed	1 / 14 (7.14%)	0 / 13 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Headache			
subjects affected / exposed	2 / 14 (14.29%)	4 / 13 (30.77%)	0 / 7 (0.00%)
occurrences (all)	4	5	0
Hypoaesthesia			
subjects affected / exposed	0 / 14 (0.00%)	1 / 13 (7.69%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Migraine			
subjects affected / exposed	0 / 14 (0.00%)	1 / 13 (7.69%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Muscle spasticity			
subjects affected / exposed	0 / 14 (0.00%)	0 / 13 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0

Paraesthesia subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	1 / 13 (7.69%) 1	0 / 7 (0.00%) 0
Sciatica subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	0 / 13 (0.00%) 0	0 / 7 (0.00%) 0
Tremor subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1	0 / 13 (0.00%) 0	0 / 7 (0.00%) 0
Blood and lymphatic system disorders			
Anaemia subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	0 / 13 (0.00%) 0	0 / 7 (0.00%) 0
Eosinophilia subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	0 / 13 (0.00%) 0	0 / 7 (0.00%) 0
Iron deficiency anaemia subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	0 / 13 (0.00%) 0	0 / 7 (0.00%) 0
Thrombocytopenia subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	0 / 13 (0.00%) 0	0 / 7 (0.00%) 0
Ear and labyrinth disorders			
Cerumen impaction subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	0 / 13 (0.00%) 0	0 / 7 (0.00%) 0
Deafness subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	0 / 13 (0.00%) 0	0 / 7 (0.00%) 0
Eustachian tube dysfunction subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	0 / 13 (0.00%) 0	0 / 7 (0.00%) 0
Middle ear effusion subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	1 / 13 (7.69%) 1	0 / 7 (0.00%) 0
Tinnitus			

subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1	0 / 13 (0.00%) 0	0 / 7 (0.00%) 0
Eye disorders			
Eye pain			
subjects affected / exposed	0 / 14 (0.00%)	0 / 13 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 14 (7.14%)	1 / 13 (7.69%)	0 / 7 (0.00%)
occurrences (all)	1	1	0
Abdominal pain upper			
subjects affected / exposed	0 / 14 (0.00%)	0 / 13 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Aerophagia			
subjects affected / exposed	0 / 14 (0.00%)	0 / 13 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Cheilitis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 13 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Constipation			
subjects affected / exposed	0 / 14 (0.00%)	0 / 13 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Dental caries			
subjects affected / exposed	0 / 14 (0.00%)	1 / 13 (7.69%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Diarrhoea			
subjects affected / exposed	0 / 14 (0.00%)	3 / 13 (23.08%)	2 / 7 (28.57%)
occurrences (all)	0	3	3
Dry mouth			
subjects affected / exposed	0 / 14 (0.00%)	1 / 13 (7.69%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Dyspepsia			
subjects affected / exposed	0 / 14 (0.00%)	1 / 13 (7.69%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Gastric polyps			

subjects affected / exposed	0 / 14 (0.00%)	1 / 13 (7.69%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorder			
subjects affected / exposed	0 / 14 (0.00%)	0 / 13 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Glossodynia			
subjects affected / exposed	0 / 14 (0.00%)	0 / 13 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Inguinal hernia			
subjects affected / exposed	0 / 14 (0.00%)	0 / 13 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Lip swelling			
subjects affected / exposed	0 / 14 (0.00%)	1 / 13 (7.69%)	1 / 7 (14.29%)
occurrences (all)	0	1	1
Mouth ulceration			
subjects affected / exposed	0 / 14 (0.00%)	0 / 13 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Nausea			
subjects affected / exposed	1 / 14 (7.14%)	1 / 13 (7.69%)	0 / 7 (0.00%)
occurrences (all)	1	1	0
Oral pain			
subjects affected / exposed	1 / 14 (7.14%)	0 / 13 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Paraesthesia oral			
subjects affected / exposed	0 / 14 (0.00%)	1 / 13 (7.69%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Rectal haemorrhage			
subjects affected / exposed	0 / 14 (0.00%)	1 / 13 (7.69%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Vomiting			
subjects affected / exposed	1 / 14 (7.14%)	1 / 13 (7.69%)	1 / 7 (14.29%)
occurrences (all)	1	1	1
Hepatobiliary disorders			
Hepatic function abnormal			
subjects affected / exposed	0 / 14 (0.00%)	0 / 13 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0

Hepatotoxicity subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	0 / 13 (0.00%) 0	0 / 7 (0.00%) 0
Skin and subcutaneous tissue disorders			
Alopecia subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	1 / 13 (7.69%) 1	0 / 7 (0.00%) 0
Dermatitis allergic subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	0 / 13 (0.00%) 0	0 / 7 (0.00%) 0
Night sweats subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	0 / 13 (0.00%) 0	0 / 7 (0.00%) 0
Rash subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1	0 / 13 (0.00%) 0	0 / 7 (0.00%) 0
Rash papular subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	0 / 13 (0.00%) 0	0 / 7 (0.00%) 0
Skin exfoliation subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	0 / 13 (0.00%) 0	0 / 7 (0.00%) 0
Swelling face subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	0 / 13 (0.00%) 0	1 / 7 (14.29%) 1
Urticaria subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	0 / 13 (0.00%) 0	0 / 7 (0.00%) 0
Renal and urinary disorders			
Calculus urinary subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	1 / 13 (7.69%) 1	0 / 7 (0.00%) 0
Glycosuria subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	0 / 13 (0.00%) 0	0 / 7 (0.00%) 0
Haematuria			

subjects affected / exposed	0 / 14 (0.00%)	0 / 13 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Proteinuria			
subjects affected / exposed	1 / 14 (7.14%)	1 / 13 (7.69%)	0 / 7 (0.00%)
occurrences (all)	2	1	0
Renal cyst			
subjects affected / exposed	0 / 14 (0.00%)	1 / 13 (7.69%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Renal failure			
subjects affected / exposed	0 / 14 (0.00%)	0 / 13 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Renal impairment			
subjects affected / exposed	0 / 14 (0.00%)	0 / 13 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Urinary incontinence			
subjects affected / exposed	0 / 14 (0.00%)	1 / 13 (7.69%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 14 (0.00%)	0 / 13 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Joint contracture			
subjects affected / exposed	0 / 14 (0.00%)	0 / 13 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Joint swelling			
subjects affected / exposed	1 / 14 (7.14%)	0 / 13 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Limb discomfort			
subjects affected / exposed	0 / 14 (0.00%)	0 / 13 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Muscle contracture			
subjects affected / exposed	1 / 14 (7.14%)	0 / 13 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Muscle spasms			

subjects affected / exposed	0 / 14 (0.00%)	0 / 13 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Muscle tightness			
subjects affected / exposed	0 / 14 (0.00%)	0 / 13 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Musculoskeletal chest pain			
subjects affected / exposed	0 / 14 (0.00%)	0 / 13 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Myalgia			
subjects affected / exposed	0 / 14 (0.00%)	0 / 13 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Pain in extremity			
subjects affected / exposed	0 / 14 (0.00%)	0 / 13 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Periarthritis			
subjects affected / exposed	0 / 14 (0.00%)	1 / 13 (7.69%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 14 (7.14%)	0 / 13 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Candida infection			
subjects affected / exposed	1 / 14 (7.14%)	0 / 13 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Cystitis			
subjects affected / exposed	1 / 14 (7.14%)	0 / 13 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Ear infection			
subjects affected / exposed	0 / 14 (0.00%)	0 / 13 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Gastroenteritis viral			
subjects affected / exposed	0 / 14 (0.00%)	0 / 13 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Herpes simplex			
subjects affected / exposed	0 / 14 (0.00%)	0 / 13 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0

Hordeolum			
subjects affected / exposed	1 / 14 (7.14%)	0 / 13 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Infective exacerbation of bronchiectasis			
subjects affected / exposed	4 / 14 (28.57%)	4 / 13 (30.77%)	6 / 7 (85.71%)
occurrences (all)	6	8	6
Influenza			
subjects affected / exposed	0 / 14 (0.00%)	0 / 13 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Joint abscess			
subjects affected / exposed	0 / 14 (0.00%)	0 / 13 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Labyrinthitis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 13 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Lower respiratory tract infection			
subjects affected / exposed	0 / 14 (0.00%)	0 / 13 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Nasopharyngitis			
subjects affected / exposed	1 / 14 (7.14%)	1 / 13 (7.69%)	0 / 7 (0.00%)
occurrences (all)	1	1	0
Oral candidiasis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 13 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Oral fungal infection			
subjects affected / exposed	0 / 14 (0.00%)	0 / 13 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Oral herpes			
subjects affected / exposed	0 / 14 (0.00%)	0 / 13 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Respiratory tract infection viral			
subjects affected / exposed	0 / 14 (0.00%)	0 / 13 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Rhinitis			

subjects affected / exposed	1 / 14 (7.14%)	1 / 13 (7.69%)	0 / 7 (0.00%)
occurrences (all)	1	1	0
Sinusitis			
subjects affected / exposed	0 / 14 (0.00%)	1 / 13 (7.69%)	1 / 7 (14.29%)
occurrences (all)	0	1	2
Sputum purulent			
subjects affected / exposed	1 / 14 (7.14%)	1 / 13 (7.69%)	0 / 7 (0.00%)
occurrences (all)	1	1	0
Tooth infection			
subjects affected / exposed	0 / 14 (0.00%)	0 / 13 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Upper respiratory tract infection			
subjects affected / exposed	0 / 14 (0.00%)	0 / 13 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Urinary tract infection			
subjects affected / exposed	0 / 14 (0.00%)	1 / 13 (7.69%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Viral infection			
subjects affected / exposed	0 / 14 (0.00%)	0 / 13 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 14 (0.00%)	0 / 13 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	2
Vulvovaginal candidiasis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 13 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Metabolism and nutrition disorders			
Acidosis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 13 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Decreased appetite			
subjects affected / exposed	0 / 14 (0.00%)	1 / 13 (7.69%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Hyperglycaemia			
subjects affected / exposed	0 / 14 (0.00%)	0 / 13 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0

Hyponatraemia			
subjects affected / exposed	0 / 14 (0.00%)	1 / 13 (7.69%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 14 (0.00%)	0 / 13 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Cohort B:5 capsules o.d. TIP	Cohort B:5 capsules o.d. TIP/PBO	Cohort B:5 capsules o.d. PBO
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 15 (66.67%)	10 / 14 (71.43%)	7 / 7 (100.00%)
Vascular disorders			
Hot flush			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Hypertension			
subjects affected / exposed	1 / 15 (6.67%)	0 / 14 (0.00%)	1 / 7 (14.29%)
occurrences (all)	1	0	1
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 15 (0.00%)	1 / 14 (7.14%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Chest discomfort			
subjects affected / exposed	0 / 15 (0.00%)	1 / 14 (7.14%)	1 / 7 (14.29%)
occurrences (all)	0	1	3
Chest pain			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Discomfort			
subjects affected / exposed	2 / 15 (13.33%)	0 / 14 (0.00%)	0 / 7 (0.00%)
occurrences (all)	2	0	0
Exercise tolerance decreased			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Fatigue			
subjects affected / exposed	1 / 15 (6.67%)	3 / 14 (21.43%)	2 / 7 (28.57%)
occurrences (all)	1	5	3

Influenza like illness subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 14 (0.00%) 0	0 / 7 (0.00%) 0
Oedema peripheral subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 14 (0.00%) 0	0 / 7 (0.00%) 0
Peripheral swelling subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 14 (0.00%) 0	1 / 7 (14.29%) 1
Pyrexia subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	1 / 14 (7.14%) 2	0 / 7 (0.00%) 0
Immune system disorders Food allergy subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 14 (0.00%) 0	0 / 7 (0.00%) 0
Reproductive system and breast disorders Benign prostatic hyperplasia subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 14 (0.00%) 0	0 / 7 (0.00%) 0
Prostatitis subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	1 / 14 (7.14%) 1	0 / 7 (0.00%) 0
Respiratory, thoracic and mediastinal disorders Asthma subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 14 (0.00%) 0	0 / 7 (0.00%) 0
Bronchiectasis subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 14 (0.00%) 0	0 / 7 (0.00%) 0
Bronchospasm subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 14 (0.00%) 0	0 / 7 (0.00%) 0
Cough subjects affected / exposed occurrences (all)	4 / 15 (26.67%) 10	2 / 14 (14.29%) 3	1 / 7 (14.29%) 1

Dry throat			
subjects affected / exposed	0 / 15 (0.00%)	1 / 14 (7.14%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Dysphonia			
subjects affected / exposed	1 / 15 (6.67%)	0 / 14 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Dyspnoea			
subjects affected / exposed	3 / 15 (20.00%)	2 / 14 (14.29%)	2 / 7 (28.57%)
occurrences (all)	4	2	2
Dyspnoea exertional			
subjects affected / exposed	0 / 15 (0.00%)	1 / 14 (7.14%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Dyspnoea paroxysmal nocturnal			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Epistaxis			
subjects affected / exposed	1 / 15 (6.67%)	0 / 14 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Haemoptysis			
subjects affected / exposed	0 / 15 (0.00%)	2 / 14 (14.29%)	3 / 7 (42.86%)
occurrences (all)	0	2	8
Increased bronchial secretion			
subjects affected / exposed	1 / 15 (6.67%)	0 / 14 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Increased viscosity of bronchial secretion			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Nasal discomfort			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Oropharyngeal pain			
subjects affected / exposed	0 / 15 (0.00%)	2 / 14 (14.29%)	1 / 7 (14.29%)
occurrences (all)	0	2	1
Pulmonary pain			

subjects affected / exposed	0 / 15 (0.00%)	1 / 14 (7.14%)	1 / 7 (14.29%)
occurrences (all)	0	1	1
Rales			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Respiratory symptom			
subjects affected / exposed	0 / 15 (0.00%)	1 / 14 (7.14%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Rhinorrhoea			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Sputum discoloured			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Sputum increased			
subjects affected / exposed	0 / 15 (0.00%)	1 / 14 (7.14%)	0 / 7 (0.00%)
occurrences (all)	0	2	0
Throat irritation			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Wheezing			
subjects affected / exposed	1 / 15 (6.67%)	0 / 14 (0.00%)	1 / 7 (14.29%)
occurrences (all)	1	0	1
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Investigations			
Blood cholesterol increased			
subjects affected / exposed	0 / 15 (0.00%)	1 / 14 (7.14%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 15 (6.67%)	0 / 14 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Blood creatinine increased			

subjects affected / exposed	1 / 15 (6.67%)	1 / 14 (7.14%)	0 / 7 (0.00%)
occurrences (all)	1	1	0
Blood electrolytes decreased			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Blood urea increased			
subjects affected / exposed	1 / 15 (6.67%)	0 / 14 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
C-reactive protein increased			
subjects affected / exposed	2 / 15 (13.33%)	0 / 14 (0.00%)	0 / 7 (0.00%)
occurrences (all)	2	0	0
Eosinophil count abnormal			
subjects affected / exposed	0 / 15 (0.00%)	1 / 14 (7.14%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Forced expiratory volume decreased			
subjects affected / exposed	0 / 15 (0.00%)	1 / 14 (7.14%)	0 / 7 (0.00%)
occurrences (all)	0	3	0
Forced vital capacity decreased			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Glomerular filtration rate decreased			
subjects affected / exposed	1 / 15 (6.67%)	1 / 14 (7.14%)	0 / 7 (0.00%)
occurrences (all)	1	1	0
Haemoglobin decreased			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Liver function test abnormal			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Neutrophil count increased			
subjects affected / exposed	1 / 15 (6.67%)	0 / 14 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0

Protein urine present subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1	0 / 14 (0.00%) 0	0 / 7 (0.00%) 0
Sputum abnormal subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 14 (0.00%) 0	0 / 7 (0.00%) 0
Urine albumin/creatinine ratio increased subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 14 (0.00%) 0	0 / 7 (0.00%) 0
Urine protein/creatinine ratio increased subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 14 (0.00%) 0	0 / 7 (0.00%) 0
Weight decreased subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 14 (0.00%) 0	0 / 7 (0.00%) 0
White blood cell count increased subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1	0 / 14 (0.00%) 0	0 / 7 (0.00%) 0
Injury, poisoning and procedural complications			
Airway complication of anaesthesia subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 14 (0.00%) 0	0 / 7 (0.00%) 0
Arthropod bite subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 14 (0.00%) 0	0 / 7 (0.00%) 0
Fall subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 14 (0.00%) 0	0 / 7 (0.00%) 0
Hypobarism subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 14 (0.00%) 0	0 / 7 (0.00%) 0
Ligament sprain subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 14 (0.00%) 0	0 / 7 (0.00%) 0
Procedural pain			

subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 14 (0.00%) 0	0 / 7 (0.00%) 0
Road traffic accident subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 14 (0.00%) 0	0 / 7 (0.00%) 0
Nervous system disorders			
Ageusia subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 14 (0.00%) 0	0 / 7 (0.00%) 0
Anosmia subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 14 (0.00%) 0	0 / 7 (0.00%) 0
Dizziness subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 14 (0.00%) 0	0 / 7 (0.00%) 0
Headache subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1	2 / 14 (14.29%) 3	1 / 7 (14.29%) 1
Hypoaesthesia subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 14 (0.00%) 0	0 / 7 (0.00%) 0
Migraine subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 14 (0.00%) 0	0 / 7 (0.00%) 0
Muscle spasticity subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1	0 / 14 (0.00%) 0	0 / 7 (0.00%) 0
Paraesthesia subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 14 (0.00%) 0	0 / 7 (0.00%) 0
Sciatica subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 14 (0.00%) 0	1 / 7 (14.29%) 1
Tremor subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 14 (0.00%) 0	0 / 7 (0.00%) 0

Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 15 (0.00%)	1 / 14 (7.14%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Eosinophilia			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Iron deficiency anaemia			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Thrombocytopenia			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Ear and labyrinth disorders			
Cerumen impaction			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Deafness			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Eustachian tube dysfunction			
subjects affected / exposed	1 / 15 (6.67%)	0 / 14 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Middle ear effusion			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Tinnitus			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Eye disorders			
Eye pain			
subjects affected / exposed	1 / 15 (6.67%)	0 / 14 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 15 (6.67%)	0 / 14 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0

Abdominal pain upper			
subjects affected / exposed	0 / 15 (0.00%)	1 / 14 (7.14%)	1 / 7 (14.29%)
occurrences (all)	0	1	1
Aerophagia			
subjects affected / exposed	1 / 15 (6.67%)	0 / 14 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Cheilitis			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Constipation			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Dental caries			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Diarrhoea			
subjects affected / exposed	1 / 15 (6.67%)	1 / 14 (7.14%)	0 / 7 (0.00%)
occurrences (all)	1	1	0
Dry mouth			
subjects affected / exposed	0 / 15 (0.00%)	2 / 14 (14.29%)	1 / 7 (14.29%)
occurrences (all)	0	3	1
Dyspepsia			
subjects affected / exposed	1 / 15 (6.67%)	0 / 14 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Gastric polyps			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorder			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Glossodynia			
subjects affected / exposed	1 / 15 (6.67%)	0 / 14 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Inguinal hernia			
subjects affected / exposed	0 / 15 (0.00%)	1 / 14 (7.14%)	0 / 7 (0.00%)
occurrences (all)	0	1	0

Lip swelling subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 14 (0.00%) 0	0 / 7 (0.00%) 0
Mouth ulceration subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 14 (0.00%) 0	0 / 7 (0.00%) 0
Nausea subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 14 (0.00%) 0	1 / 7 (14.29%) 1
Oral pain subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 14 (0.00%) 0	0 / 7 (0.00%) 0
Paraesthesia oral subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 14 (0.00%) 0	0 / 7 (0.00%) 0
Rectal haemorrhage subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 14 (0.00%) 0	0 / 7 (0.00%) 0
Vomiting subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 14 (0.00%) 0	0 / 7 (0.00%) 0
Hepatobiliary disorders Hepatic function abnormal subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 14 (0.00%) 0	0 / 7 (0.00%) 0
Hepatotoxicity subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	1 / 14 (7.14%) 1	0 / 7 (0.00%) 0
Skin and subcutaneous tissue disorders Alopecia subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 14 (0.00%) 0	0 / 7 (0.00%) 0
Dermatitis allergic subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	1 / 14 (7.14%) 1	0 / 7 (0.00%) 0
Night sweats			

subjects affected / exposed	1 / 15 (6.67%)	0 / 14 (0.00%)	1 / 7 (14.29%)
occurrences (all)	1	0	1
Rash			
subjects affected / exposed	0 / 15 (0.00%)	1 / 14 (7.14%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Rash papular			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Skin exfoliation			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Swelling face			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Urticaria			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
Calculus urinary			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Glycosuria			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Haematuria			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Proteinuria			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Renal cyst			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Renal failure			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0

Renal impairment subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1	0 / 14 (0.00%) 0	0 / 7 (0.00%) 0
Urinary incontinence subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 14 (0.00%) 0	0 / 7 (0.00%) 0
Musculoskeletal and connective tissue disorders			
Back pain subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	1 / 14 (7.14%) 1	0 / 7 (0.00%) 0
Joint contracture subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 14 (0.00%) 0	0 / 7 (0.00%) 0
Joint swelling subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 14 (0.00%) 0	0 / 7 (0.00%) 0
Limb discomfort subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 14 (0.00%) 0	1 / 7 (14.29%) 1
Muscle contracture subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 14 (0.00%) 0	0 / 7 (0.00%) 0
Muscle spasms subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 14 (0.00%) 0	0 / 7 (0.00%) 0
Muscle tightness subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 14 (0.00%) 0	0 / 7 (0.00%) 0
Musculoskeletal chest pain subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	1 / 14 (7.14%) 1	0 / 7 (0.00%) 0
Myalgia subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 14 (0.00%) 0	0 / 7 (0.00%) 0
Pain in extremity			

subjects affected / exposed	0 / 15 (0.00%)	1 / 14 (7.14%)	2 / 7 (28.57%)
occurrences (all)	0	1	2
Periarthritis			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 15 (6.67%)	0 / 14 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Candida infection			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Cystitis			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Ear infection			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Gastroenteritis viral			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Herpes simplex			
subjects affected / exposed	1 / 15 (6.67%)	0 / 14 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Hordeolum			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Infective exacerbation of bronchiectasis			
subjects affected / exposed	3 / 15 (20.00%)	5 / 14 (35.71%)	2 / 7 (28.57%)
occurrences (all)	4	6	4
Influenza			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Joint abscess			

subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Labyrinthitis			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Lower respiratory tract infection			
subjects affected / exposed	1 / 15 (6.67%)	0 / 14 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Nasopharyngitis			
subjects affected / exposed	1 / 15 (6.67%)	2 / 14 (14.29%)	1 / 7 (14.29%)
occurrences (all)	1	2	1
Oral candidiasis			
subjects affected / exposed	0 / 15 (0.00%)	1 / 14 (7.14%)	1 / 7 (14.29%)
occurrences (all)	0	2	1
Oral fungal infection			
subjects affected / exposed	0 / 15 (0.00%)	1 / 14 (7.14%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Oral herpes			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Respiratory tract infection viral			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Rhinitis			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Sinusitis			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Sputum purulent			
subjects affected / exposed	0 / 15 (0.00%)	1 / 14 (7.14%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Tooth infection			
subjects affected / exposed	1 / 15 (6.67%)	0 / 14 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Upper respiratory tract infection			

subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Urinary tract infection			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Viral infection			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Vulvovaginal candidiasis			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Metabolism and nutrition disorders			
Acidosis			
subjects affected / exposed	0 / 15 (0.00%)	1 / 14 (7.14%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Decreased appetite			
subjects affected / exposed	0 / 15 (0.00%)	1 / 14 (7.14%)	1 / 7 (14.29%)
occurrences (all)	0	1	1
Hyperglycaemia			
subjects affected / exposed	1 / 15 (6.67%)	0 / 14 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Hyponatraemia			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Cohort C:4 capsules b.i.d. TIP	Cohort C:4 capsules b.i.d. TIP/PBO	Cohort C:4 capsules b.i.d. PBO
Total subjects affected by non-serious adverse events			
subjects affected / exposed	13 / 15 (86.67%)	14 / 15 (93.33%)	5 / 7 (71.43%)
Vascular disorders			

Hot flush			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Hypertension			
subjects affected / exposed	0 / 15 (0.00%)	0 / 15 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 15 (0.00%)	0 / 15 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Chest discomfort			
subjects affected / exposed	2 / 15 (13.33%)	0 / 15 (0.00%)	0 / 7 (0.00%)
occurrences (all)	2	0	0
Chest pain			
subjects affected / exposed	0 / 15 (0.00%)	2 / 15 (13.33%)	0 / 7 (0.00%)
occurrences (all)	0	2	0
Discomfort			
subjects affected / exposed	0 / 15 (0.00%)	0 / 15 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Exercise tolerance decreased			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Fatigue			
subjects affected / exposed	2 / 15 (13.33%)	0 / 15 (0.00%)	1 / 7 (14.29%)
occurrences (all)	2	0	1
Influenza like illness			
subjects affected / exposed	0 / 15 (0.00%)	0 / 15 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Oedema peripheral			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Peripheral swelling			
subjects affected / exposed	0 / 15 (0.00%)	0 / 15 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Pyrexia			

subjects affected / exposed occurrences (all)	2 / 15 (13.33%) 2	0 / 15 (0.00%) 0	0 / 7 (0.00%) 0
Immune system disorders Food allergy subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 15 (0.00%) 0	0 / 7 (0.00%) 0
Reproductive system and breast disorders Benign prostatic hyperplasia subjects affected / exposed occurrences (all) Prostatitis subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0 0 / 15 (0.00%) 0	0 / 15 (0.00%) 0 0 / 15 (0.00%) 0	1 / 7 (14.29%) 1 0 / 7 (0.00%) 0
Respiratory, thoracic and mediastinal disorders Asthma subjects affected / exposed occurrences (all) Bronchiectasis subjects affected / exposed occurrences (all) Bronchospasm subjects affected / exposed occurrences (all) Cough subjects affected / exposed occurrences (all) Dry throat subjects affected / exposed occurrences (all) Dysphonia subjects affected / exposed occurrences (all) Dyspnoea subjects affected / exposed occurrences (all) Dyspnoea exertional	0 / 15 (0.00%) 0 0 / 15 (0.00%) 0 1 / 15 (6.67%) 1 2 / 15 (13.33%) 2 3 / 15 (20.00%) 3 1 / 15 (6.67%) 1 4 / 15 (26.67%) 4	1 / 15 (6.67%) 2 1 / 15 (6.67%) 1 3 / 15 (20.00%) 3 2 / 15 (13.33%) 2 0 / 15 (0.00%) 0 2 / 15 (13.33%) 2	0 / 7 (0.00%) 0 0 / 7 (0.00%) 0 0 / 7 (0.00%) 0 3 / 7 (42.86%) 3 0 / 7 (0.00%) 0 0 / 7 (0.00%) 0 0 / 7 (0.00%) 0

subjects affected / exposed	0 / 15 (0.00%)	0 / 15 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Dyspnoea paroxysmal nocturnal			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Epistaxis			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Haemoptysis			
subjects affected / exposed	0 / 15 (0.00%)	2 / 15 (13.33%)	1 / 7 (14.29%)
occurrences (all)	0	2	1
Increased bronchial secretion			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Increased viscosity of bronchial secretion			
subjects affected / exposed	0 / 15 (0.00%)	0 / 15 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Nasal discomfort			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Oropharyngeal pain			
subjects affected / exposed	2 / 15 (13.33%)	0 / 15 (0.00%)	1 / 7 (14.29%)
occurrences (all)	2	0	1
Pulmonary pain			
subjects affected / exposed	0 / 15 (0.00%)	0 / 15 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Rales			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Respiratory symptom			
subjects affected / exposed	0 / 15 (0.00%)	0 / 15 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Rhinorrhoea			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0

Sputum discoloured subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 15 (0.00%) 0	0 / 7 (0.00%) 0
Sputum increased subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	3 / 15 (20.00%) 3	1 / 7 (14.29%) 1
Throat irritation subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	1 / 15 (6.67%) 1	0 / 7 (0.00%) 0
Wheezing subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1	2 / 15 (13.33%) 2	0 / 7 (0.00%) 0
Psychiatric disorders Anxiety subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 15 (0.00%) 0	1 / 7 (14.29%) 1
Investigations Blood cholesterol increased subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 15 (0.00%) 0	0 / 7 (0.00%) 0
Blood creatine phosphokinase increased subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1	0 / 15 (0.00%) 0	0 / 7 (0.00%) 0
Blood creatinine increased subjects affected / exposed occurrences (all)	6 / 15 (40.00%) 6	1 / 15 (6.67%) 1	0 / 7 (0.00%) 0
Blood electrolytes decreased subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 15 (0.00%) 0	0 / 7 (0.00%) 0
Blood urea increased subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 15 (0.00%) 0	0 / 7 (0.00%) 0
C-reactive protein increased subjects affected / exposed occurrences (all)	2 / 15 (13.33%) 2	0 / 15 (0.00%) 0	0 / 7 (0.00%) 0
Eosinophil count abnormal			

subjects affected / exposed	0 / 15 (0.00%)	0 / 15 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Forced expiratory volume decreased			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Forced vital capacity decreased			
subjects affected / exposed	0 / 15 (0.00%)	0 / 15 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Glomerular filtration rate decreased			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Haemoglobin decreased			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Liver function test abnormal			
subjects affected / exposed	0 / 15 (0.00%)	0 / 15 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Neutrophil count increased			
subjects affected / exposed	0 / 15 (0.00%)	0 / 15 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Protein urine present			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Sputum abnormal			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Urine albumin/creatinine ratio increased			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Urine protein/creatinine ratio increased			

subjects affected / exposed occurrences (all)	2 / 15 (13.33%) 2	0 / 15 (0.00%) 0	0 / 7 (0.00%) 0
Weight decreased subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 15 (0.00%) 0	1 / 7 (14.29%) 1
White blood cell count increased subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 15 (0.00%) 0	0 / 7 (0.00%) 0
Injury, poisoning and procedural complications			
Airway complication of anaesthesia subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 15 (0.00%) 0	0 / 7 (0.00%) 0
Arthropod bite subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	1 / 15 (6.67%) 1	0 / 7 (0.00%) 0
Fall subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 15 (0.00%) 0	0 / 7 (0.00%) 0
Hypobarism subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	1 / 15 (6.67%) 1	0 / 7 (0.00%) 0
Ligament sprain subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 15 (0.00%) 0	0 / 7 (0.00%) 0
Procedural pain subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	1 / 15 (6.67%) 1	0 / 7 (0.00%) 0
Road traffic accident subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 15 (0.00%) 0	0 / 7 (0.00%) 0
Nervous system disorders			
Ageusia subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 15 (0.00%) 0	0 / 7 (0.00%) 0
Anosmia			

subjects affected / exposed	0 / 15 (0.00%)	0 / 15 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Dizziness			
subjects affected / exposed	0 / 15 (0.00%)	0 / 15 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Headache			
subjects affected / exposed	2 / 15 (13.33%)	0 / 15 (0.00%)	0 / 7 (0.00%)
occurrences (all)	3	0	0
Hypoaesthesia			
subjects affected / exposed	0 / 15 (0.00%)	0 / 15 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Migraine			
subjects affected / exposed	0 / 15 (0.00%)	0 / 15 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Muscle spasticity			
subjects affected / exposed	0 / 15 (0.00%)	0 / 15 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Paraesthesia			
subjects affected / exposed	0 / 15 (0.00%)	0 / 15 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Sciatica			
subjects affected / exposed	0 / 15 (0.00%)	0 / 15 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Tremor			
subjects affected / exposed	0 / 15 (0.00%)	0 / 15 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 15 (0.00%)	0 / 15 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Eosinophilia			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Iron deficiency anaemia			
subjects affected / exposed	0 / 15 (0.00%)	0 / 15 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1

Thrombocytopenia subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1	0 / 15 (0.00%) 0	0 / 7 (0.00%) 0
Ear and labyrinth disorders			
Cerumen impaction subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1	0 / 15 (0.00%) 0	0 / 7 (0.00%) 0
Deafness subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 15 (0.00%) 0	1 / 7 (14.29%) 1
Eustachian tube dysfunction subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 15 (0.00%) 0	0 / 7 (0.00%) 0
Middle ear effusion subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 15 (0.00%) 0	0 / 7 (0.00%) 0
Tinnitus subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1	0 / 15 (0.00%) 0	0 / 7 (0.00%) 0
Eye disorders			
Eye pain subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 15 (0.00%) 0	0 / 7 (0.00%) 0
Gastrointestinal disorders			
Abdominal pain subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 15 (0.00%) 0	0 / 7 (0.00%) 0
Abdominal pain upper subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 15 (0.00%) 0	1 / 7 (14.29%) 1
Aerophagia subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 15 (0.00%) 0	0 / 7 (0.00%) 0
Cheilitis subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	1 / 15 (6.67%) 1	0 / 7 (0.00%) 0
Constipation			

subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Dental caries			
subjects affected / exposed	0 / 15 (0.00%)	0 / 15 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Diarrhoea			
subjects affected / exposed	2 / 15 (13.33%)	0 / 15 (0.00%)	0 / 7 (0.00%)
occurrences (all)	3	0	0
Dry mouth			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	1 / 7 (14.29%)
occurrences (all)	1	0	1
Dyspepsia			
subjects affected / exposed	0 / 15 (0.00%)	0 / 15 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Gastric polyps			
subjects affected / exposed	0 / 15 (0.00%)	0 / 15 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorder			
subjects affected / exposed	0 / 15 (0.00%)	0 / 15 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Glossodynia			
subjects affected / exposed	0 / 15 (0.00%)	0 / 15 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Inguinal hernia			
subjects affected / exposed	0 / 15 (0.00%)	0 / 15 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Lip swelling			
subjects affected / exposed	0 / 15 (0.00%)	0 / 15 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Mouth ulceration			
subjects affected / exposed	0 / 15 (0.00%)	0 / 15 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Nausea			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Oral pain			

subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 15 (0.00%) 0	0 / 7 (0.00%) 0
Paraesthesia oral subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 15 (0.00%) 0	0 / 7 (0.00%) 0
Rectal haemorrhage subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	1 / 15 (6.67%) 1	0 / 7 (0.00%) 0
Vomiting subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 15 (0.00%) 0	0 / 7 (0.00%) 0
Hepatobiliary disorders Hepatic function abnormal subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1	0 / 15 (0.00%) 0	0 / 7 (0.00%) 0
Hepatotoxicity subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 15 (0.00%) 0	0 / 7 (0.00%) 0
Skin and subcutaneous tissue disorders Alopecia subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 15 (0.00%) 0	0 / 7 (0.00%) 0
Dermatitis allergic subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 15 (0.00%) 0	0 / 7 (0.00%) 0
Night sweats subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 15 (0.00%) 0	0 / 7 (0.00%) 0
Rash subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 15 (0.00%) 0	0 / 7 (0.00%) 0
Rash papular subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1	0 / 15 (0.00%) 0	0 / 7 (0.00%) 0
Skin exfoliation			

subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	1 / 15 (6.67%) 1	0 / 7 (0.00%) 0
Swelling face subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 15 (0.00%) 0	0 / 7 (0.00%) 0
Urticaria subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	1 / 15 (6.67%) 1	0 / 7 (0.00%) 0
Renal and urinary disorders Calculus urinary subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 15 (0.00%) 0	0 / 7 (0.00%) 0
Glycosuria subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 15 (0.00%) 0	1 / 7 (14.29%) 1
Haematuria subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 15 (0.00%) 0	1 / 7 (14.29%) 1
Proteinuria subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 15 (0.00%) 0	1 / 7 (14.29%) 1
Renal cyst subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 15 (0.00%) 0	0 / 7 (0.00%) 0
Renal failure subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	1 / 15 (6.67%) 1	0 / 7 (0.00%) 0
Renal impairment subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	1 / 15 (6.67%) 1	0 / 7 (0.00%) 0
Urinary incontinence subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 15 (0.00%) 0	0 / 7 (0.00%) 0
Musculoskeletal and connective tissue disorders			

Back pain			
subjects affected / exposed	0 / 15 (0.00%)	0 / 15 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Joint contracture			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Joint swelling			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Limb discomfort			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Muscle contracture			
subjects affected / exposed	0 / 15 (0.00%)	0 / 15 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Muscle spasms			
subjects affected / exposed	2 / 15 (13.33%)	0 / 15 (0.00%)	1 / 7 (14.29%)
occurrences (all)	2	0	1
Muscle tightness			
subjects affected / exposed	0 / 15 (0.00%)	0 / 15 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal chest pain			
subjects affected / exposed	1 / 15 (6.67%)	1 / 15 (6.67%)	1 / 7 (14.29%)
occurrences (all)	1	1	1
Myalgia			
subjects affected / exposed	0 / 15 (0.00%)	0 / 15 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Pain in extremity			
subjects affected / exposed	0 / 15 (0.00%)	0 / 15 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Periarthritis			
subjects affected / exposed	0 / 15 (0.00%)	0 / 15 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Bronchitis			

subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Candida infection			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Cystitis			
subjects affected / exposed	0 / 15 (0.00%)	0 / 15 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Ear infection			
subjects affected / exposed	0 / 15 (0.00%)	0 / 15 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Gastroenteritis viral			
subjects affected / exposed	0 / 15 (0.00%)	0 / 15 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Herpes simplex			
subjects affected / exposed	0 / 15 (0.00%)	0 / 15 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Hordeolum			
subjects affected / exposed	0 / 15 (0.00%)	0 / 15 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Infective exacerbation of bronchiectasis			
subjects affected / exposed	4 / 15 (26.67%)	5 / 15 (33.33%)	2 / 7 (28.57%)
occurrences (all)	4	5	3
Influenza			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	1 / 7 (14.29%)
occurrences (all)	1	0	1
Joint abscess			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Labyrinthitis			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Lower respiratory tract infection			
subjects affected / exposed	0 / 15 (0.00%)	0 / 15 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0

Nasopharyngitis			
subjects affected / exposed	0 / 15 (0.00%)	0 / 15 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Oral candidiasis			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	1 / 7 (14.29%)
occurrences (all)	0	1	1
Oral fungal infection			
subjects affected / exposed	0 / 15 (0.00%)	0 / 15 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Oral herpes			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Respiratory tract infection viral			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Rhinitis			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Sinusitis			
subjects affected / exposed	0 / 15 (0.00%)	0 / 15 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Sputum purulent			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Tooth infection			
subjects affected / exposed	0 / 15 (0.00%)	0 / 15 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Upper respiratory tract infection			
subjects affected / exposed	0 / 15 (0.00%)	1 / 15 (6.67%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Urinary tract infection			
subjects affected / exposed	0 / 15 (0.00%)	2 / 15 (13.33%)	0 / 7 (0.00%)
occurrences (all)	0	2	0
Viral infection			
subjects affected / exposed	1 / 15 (6.67%)	0 / 15 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0

Viral upper respiratory tract infection subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 15 (0.00%) 0	0 / 7 (0.00%) 0
Vulvovaginal candidiasis subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 15 (0.00%) 0	0 / 7 (0.00%) 0
Metabolism and nutrition disorders			
Acidosis subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 15 (0.00%) 0	0 / 7 (0.00%) 0
Decreased appetite subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 15 (0.00%) 0	0 / 7 (0.00%) 0
Hyperglycaemia subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 15 (0.00%) 0	0 / 7 (0.00%) 0
Hyponatraemia subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 15 (0.00%) 0	0 / 7 (0.00%) 0
Type 2 diabetes mellitus subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	1 / 15 (6.67%) 1	0 / 7 (0.00%) 0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 September 2017	Amendment 1: The purpose of this protocol amendment was to clarify specific elements in the protocol. First, the timing of the Data Monitoring Committee (DMC) interim review was removed, as this was detailed in the DMC charter. Furthermore, the amendment clarified that for the signs and symptoms characterizing the pulmonary exacerbations and which were required to last for more than 24 hours, additional information regarding duration were collected to document if the reported signs and symptoms were present for more than 48 hours. The additional information was collected in line with the recently published consensus definition of pulmonary exacerbations for clinical research (Hill et al 2017). In addition, thresholds and criteria for renal event monitoring were revised in accordance with the updated Novartis renal safety guideline and the safety profile of Tobramycin Inhalation Powder (TIP) obtained from clinical and post-marketing experience in cystic fibrosis (CF) patients. Based on the review of the most recent data cumulatively (until 30-June-2017), there was no evidence to suggest a causal relationship between use of TIP and the potential risk of nephrotoxicity. The risk for nephrotoxicity was expected to be very low considering the systemic levels of tobramycin after TIP administration (C_{max} is $1.02 \pm 0.53 \mu\text{g/mL}$) compared to the maximum systemic levels recommended for avoidance of the toxicity associated with intravenous tobramycin therapy (C_{max} greater than $12 \mu\text{g/mL}$) (Sweetman 2011). The revised renal safety alert criteria were designed to facilitate the early detection of a renal event. Moreover, corrections on minor inconsistencies or clarifications were incorporated in this protocol amendment.
09 February 2018	Amendment 2: The purpose of this protocol amendment is to revise the following enrolment criteria (9a, 10a, 18a, 21a and 33a). Furthermore, the renal alert criteria and follow-up actions and the discontinuation criteria were amended in order to focus on the relevant renal function markers. To improve the renal function monitoring distinction was made between renal findings and confirmed renal events. Instructions for study treatment interruption/discontinuation were clarified to distinguish events that mandate permanent study drug discontinuation as per protocol from those that are at investigators' discretion. The pharmacokinetics (PK) sampling scheme was revised in order to maximize the number of samples for tobramycin exposure in particular in patients who are on alternating TIP/placebo treatment. Changing PK sampling from Day 29 to Day 8 is acceptable to assess the exposure. This is based on the short estimated terminal half-life of tobramycin in serum after inhalation of a single 112 mg dose of TIP which was approximately 3 hours (Ting 2014).
21 June 2018	Amendment 3: The purpose of this protocol amendment was to revise: a) Exclusion criterion 33b: To clarify the assessment of total abstinence as highly effective contraception method. Total abstinence was to be in line with the preferred and usual lifestyle of the subject. For consistency with the "Recommendations related to contraception and pregnancy testing" of the Clinical Trials Facilitation Group the wording was reverted to the initial protocol wording. In addition, this amendment included the definition of personal data and modified withdrawal of study consent definition in accordance with the European Economic Area General Data Protection Regulation requirements. This amendment also included the following changes in planned statistical analysis: • removing the cohort from the models due to confounding with treatment, • including the multiple imputation technique as a sensitivity analysis and, • dropping some exploratory analyses due to small sample size as outlined below.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Novartis decided to close the recruitment of new subjects into this study earlier than scheduled. The early recruitment halt of the study was not due to safety or lack of efficacy.
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Notes: