Clinical trial results:
A multicentre, multinational, open-label, randomised, parallel group clinical trial of Tobrineb®/Actitob®/ Bramitob® (Tobramycin solution for nebulisation, 300 mg twice daily in 4 ml unit dose vials) compared to Tobi® in the treatment of patients with cystic fibrosis and chronic infection with Pseudomonas Aeruginosa.

Summary

EudraCT number	2006-006215-68
Trial protocol	CZ HU ES DE FR
Global end of trial date	24 May 2010

Results information

Result version number	v1 (current)
This version publication date	09 July 2017
First version publication date	09 July 2017

Trial information

Trial identification

Sponsor protocol code	CMA-0631-PR-0010

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00885365
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Chiesi Farmaceutici S.p.A.
Sponsor organisation address	Via Palermo, 26/A, Parma, Italy, 43126
Public contact	Clinical Trial Transparency, , Chiesi Farmaceutici S.p.A., 0521 2791, ClinicalTrials_info@chiesi.com
Scientific contact	Clinical Trial Transparency, , Chiesi Farmaceutici S.p.A., 0521 2791, ClinicalTrials_info@chiesi.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000184-PIP02-14
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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	24 May 2010
Is this the analysis of the primary completion data?	Yes
Primary completion date	24 May 2010
Global end of trial reached?	Yes
Global end of trial date	24 May 2010
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to demonstrate that CHF 1538 is non-inferior to TOBI in the primary efficacy variable forced expiratory volume in one second (FEV1) percent predicted in patients with cystic fibrosis (CF) and chronic infection of the lungs with Pseudomonas aeruginosa (P. aeruginosa) at the end of the treatment phase.

Protection of trial subjects:

The study was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice (GCP) guidelines and local law requirements. Other than routine care, no specific measures for protection of trial subjects were implemented..

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	27 April 2009
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Russian Federation: 69
Country: Number of subjects enrolled	Ukraine: 80
Country: Number of subjects enrolled	Spain: 5
Country: Number of subjects enrolled	Poland: 131
Country: Number of subjects enrolled	Czech Republic: 8
Country: Number of subjects enrolled	France: 10
Country: Number of subjects enrolled	Germany: 4
Country: Number of subjects enrolled	Hungary: 17
Worldwide total number of subjects	324
EEA total number of subjects	175

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0

Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	84
Adolescents (12-17 years)	131
Adults (18-64 years)	109
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 406 patients were screened for the study of whom 82 (20.2%) failed screening and 324 patients were randomized; 159 to the CHF 1538 group and 165 to the TOBI group.

Pre-assignment period milestones

Number of subjects started	406[1]
Number of subjects completed	324

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Failure to meet Inclusion/Exclusion criteria: 80
Reason: Number of subjects	Patient withdrew consent: 2

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: There were 82 screen failures.

Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

Blind conditions could not be applied to this study due to the different volumes of the tobramycin solutions to be tested (CHF 1538 4 mL and TOBI 5 mL).

Arms

Are arms mutually exclusive?	Yes
Arm title	CHF 1538

Arm description:

Tobramycin 300 mg/4 mL inhalation solution for nebulization, administered 300mg twice a day for 4 weeks

Arm type	Experimental
Investigational medicinal product name	Bramitob
Investigational medicinal product code	
Other name	Tobrineb, Actitob, tobramycin
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

300mg administered twice a day for 4 weeks via the Pari LC Plus nebulizer

Arm title	TOBI

Arm description:

Tobramycin 300 mg/5 mL inhalation solution for nebulization, administered 300mg twice a day for 4 weeks.

Arm type	Active comparator

Investigational medicinal product name	TOBI
Investigational medicinal product code	
Other name	tobramycin
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

300mg administered twice a day for 4 weeks via Pari LC Plus Nebulizer

Number of subjects in period 1	CHF 1538	TOBI
Started	159	165
Week 4 - End of "ON" Treatment	155	159
Week 8 - End of "OFF" Treatment	155	159
Completed	155	159
Not completed	4	6
Consent withdrawn by subject	1	-
Adverse event, non-fatal	2	4
Protocol deviation	1	2

Baseline characteristics

Reporting groups	
Reporting group title	CHF 1538
Reporting group description:	
Tobramycin 300 mg/4 mL inhalation solution for nebulization, administered 300mg twice a day for 4 weeks	
Reporting group title	TOBI
Reporting group description:	
Tobramycin 300 mg/5 mL inhalation solution for nebulization, administered 300mg twice a day for 4 weeks.	

Reporting group values	CHF 1538	TOBI	Total
Number of subjects	159	165	324
Age categorical			
Age in years calculated as integer ((date of Screening - date of birth/365.25))			
Units: Subjects			
Children (6-12 years)	47	56	103
Adolescents (13-17 years)	54	58	112
Adults (> 17 years)	58	51	109
Gender categorical Units: Subjects			
Male	72	85	157
Female	87	80	167

Subject analysis sets	
Subject analysis set title	CHF 1538 - ITT Population
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All randomized patients who took at least one dose of study medication (Bramitob), with available baseline FEV1 value and with at least one available post-baseline FEV1 value during treatment period.	
Subject analysis set title	TOBI - ITT Population
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All randomized patients who took at least one dose of study medication (TOBI), with available baseline FEV1 value and with at least one available post-baseline FEV1 value during treatment period.	
Subject analysis set title	CHF1538 - Safety Population
Subject analysis set type	Safety analysis
Subject analysis set description:	
All randomized patients who took at least one dose of study medication - Bramitob.	
Subject analysis set title	TOBI - Safety Population
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All randomized patients who took at least one dose of study medication - TOBI.	

Reporting group values	CHF 1538 - ITT Population	TOBI - ITT Population	CHF1538 - Safety Population
Number of subjects	158	163	156

Age categorical			
Age in years calculated as integer ((date of Screening - date of birth/365.25))			
Units: Subjects			
Children (6-12 years)	47	56	49
Adolescents (13-17 years)	54	57	50
Adults (> 17 years)	57	50	57
Gender categorical Units: Subjects			
Male	72	84	72
Female	86	79	84

Reporting group values	TOBI - Safety Population		
Number of subjects	168		
Age categorical			
Age in years calculated as integer ((date of Screening - date of birth/365.25))			
Units: Subjects			
Children (6-12 years)	54		
Adolescents (13-17 years)	62		
Adults (> 17 years)	52		
Gender categorical Units: Subjects			
Male	85		
Female	83		

End points

End points reporting groups

Reporting group title	CHF 1538
Reporting group description:	
Tobramycin 300 mg/4 mL inhalation solution for nebulization, administered 300mg twice a day for 4 weeks	
Reporting group title	TOBI
Reporting group description:	
Tobramycin 300 mg/5 mL inhalation solution for nebulization, administered 300mg twice a day for 4 weeks.	
Subject analysis set title	CHF 1538 - ITT Population
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All randomized patients who took at least one dose of study medication (Bramitob), with available baseline FEV1 value and with at least one available post-baseline FEV1 value during treatment period.	
Subject analysis set title	TOBI - ITT Population
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All randomized patients who took at least one dose of study medication (TOBI), with available baseline FEV1 value and with at least one available post-baseline FEV1 value during treatment period.	
Subject analysis set title	CHF1538 - Safety Population
Subject analysis set type	Safety analysis
Subject analysis set description:	
All randomized patients who took at least one dose of study medication - Bramitob.	
Subject analysis set title	TOBI - Safety Population
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All randomized patients who took at least one dose of study medication - TOBI.	

Primary: Change from Baseline to End of the Treatment Period of FEV1, expressed as Percentage of Predicted Normal

End point title	Change from Baseline to End of the Treatment Period of FEV1, expressed as Percentage of Predicted Normal
End point description:	
Pulmonary function measurements were performed by using a self-calibrated computer-operated pneumotochographic spirometer at all clinic visits. Because this study included both adults and children and lung volume is an age-dependent variable, reference normal FEV1 values for children were different than the reference normal values used with adult participants. Three measurements were collected and the greatest FEV1 value was recorded in the CRF. Values reported in the system are "last observation carried forward" (LOCF).	
End point type	Primary
End point timeframe:	
Baseline (Visit 2), Week 4 (Visit 4)	

End point values	CHF 1538 - ITT Population	TOBI - ITT Population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	158	163		
Units: percentage predicted FEV1				
arithmetic mean (standard deviation)				
Week 4	6.99 (± 9.52)	7.51 (± 9.63)		

Statistical analyses

Statistical analysis title	CHF 1538 vs TOBI

Statistical analysis description:

This statistical analysis is based on last observation carried forward (LOCF).

Comparison groups	CHF 1538 - ITT Population v TOBI - ITT Population
Number of subjects included in analysis	321
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
P-value	= 0.64 [2]
Method	ANCOVA
Parameter estimate	Least Square Means Difference
Point estimate	-0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.58
upper limit	1.59

Notes:

[1] - Non-inferiority was evaluated for the primary efficacy variable (change from baseline in FEV1 % predicted normal at Visit 4) by calculating the two-sided 95% CI for the difference in the LSMEANS between CHF 1538 and TOBI, from an analysis of covariance (ANCOVA) model including treatment and country as effects and baseline value as covariate.

[2] - the p value reported here refers to the "treatment" as effect/factor

Secondary: Change From Baseline to End of Week 2 of FEV1, Expressed as Percentage of Predicted Normal

End point title	Change From Baseline to End of Week 2 of FEV1, Expressed as Percentage of Predicted Normal

End point description:

Pulmonary function measurements were performed by using a self-calibrated computer-operated pneumotochographic spirometer at all clinic visits. Because this study included both adults and children and lung volume is an age-dependent variable, reference normal FEV1 values for children were different than the reference normal values used with adult participants. Three measurements were collected and the greatest FEV1 value was recorded in the CRF.

End point type	Secondary

End point timeframe:

Baseline (Visit 2), Week 2 (Visit 3)

End point values	CHF 1538 - ITT Population	TOBI - ITT Population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	158	163		
Units: percent				
arithmetic mean (standard deviation)	6.7 (± 9.99)	6.93 (± 9.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline to End of Week 8 of FEV1, Expressed as Percentage of Predicted Normal

End point title	Change From Baseline to End of Week 8 of FEV1, Expressed as Percentage of Predicted Normal

End point description:

Pulmonary function measurements were performed by using a self-calibrated computer-operated pneumotochographic spirometer at all clinic visits. Because this study included both adults and children and lung volume is an age-dependent variable, reference normal FEV1 values for children were different than the reference normal values used with adult participants. Three measurements were collected and the greatest FEV1 value was recorded in the CRF.

End point type	Secondary

End point timeframe:

Baseline (Visit 2), Week 8 (Visit 5)

End point values	CHF 1538 - ITT Population	TOBI - ITT Population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	155[3]	159[4]		
Units: percent				
arithmetic mean (standard deviation)	5.47 (± 11.88)	5.37 (± 11.11)		

Notes:

[3] - this is the actual number of the patients analyzed

[4] - this is the actual number of the patients analyzed

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline to End of Week 2 of FEV1, Expressed as liters

End point title	Change From Baseline to End of Week 2 of FEV1, Expressed as liters

End point description:

Pulmonary function measurements were performed by using a self-calibrated computer-operated pneumotochographic spirometer at all clinic visits. Because this study included both adults and children and lung volume is an age-dependent variable, reference normal FEV1 values for children were different than the reference normal values used with adult participants. Three measurements were collected and the greatest FEV1 value was recorded in the CRF.

End point type	Secondary

End point timeframe:

Baseline (Visit 2), Week 2 (Visit 3)

End point values	CHF 1538 - ITT Population	TOBI - ITT Population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	158	163		
Units: LIters				
arithmetic mean (standard deviation)	0.18 (± 0.27)	0.19 (± 0.27)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline to End of Week 4 of FEV1, Expressed as liters

End point title	Change From Baseline to End of Week 4 of FEV1, Expressed as liters

End point description:

Pulmonary function measurements were performed by using a self-calibrated computer-operated pneumotochographic spirometer at all clinic visits. Because this study included both adults and children and lung volume is an age-dependent variable, reference normal FEV1 values for children were different than the reference normal values used with adult participants. Three measurements were collected and the greatest FEV1 value was recorded in the CRF.

End point type	Secondary

End point timeframe:

Baseline (Visit 2), Week 4 (Visit 4). For Visit 4, LOCF values are reported.

End point values	CHF 1538 - ITT Population	TOBI - ITT Population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	155[5]	161[6]		
Units: Liters				
arithmetic mean (standard deviation)	0.2 (± 0.29)	0.21 (± 0.29)		

Notes:

[5] - this is the actual number of the patients analyzed

[6] - this is the actual number of the patients analyzed

Statistical analyses

Statistical analysis title	CHF1538 vs TOBI

Statistical analysis description:

This statistical analysis is based on last observation carried forward (LOCF) values.

Comparison groups	CHF 1538 - ITT Population v TOBI - ITT Population

Number of subjects included in analysis	316
Analysis specification	Pre-specified
Analysis type	other[7]
P-value	= 0.634 [8]
Method	ANCOVA
Parameter estimate	least Square Means Difference
Point estimate	-0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.08
upper limit	0.05

Notes:

[7] - Comparisons between treatment groups were made at Visit 4 by using the same ANCOVA model as for the primary variable. This model included the effects of treatment group and country as factors and baseline value as covariate.

[8] - the p value reported here refers to the "treatment" as factor

Secondary: Change From Baseline to End of Week 8 of FEV1, Expressed as liters

End point title	Change From Baseline to End of Week 8 of FEV1, Expressed as liters

End point description:

Pulmonary function measurements were performed by using a self-calibrated computer-operated pneumotochographic spirometer at all clinic visits. Because this study included both adults and children and lung volume is an age-dependent variable, reference normal FEV1 values for children were different than the reference normal values used with adult participants. Three measurements were collected and the greatest FEV1 value was recorded in the CRF.

End point type	Secondary

End point timeframe:

Baseline (Visit 2), Week 8 (Visit 5)

End point values	CHF 1538 - ITT Population	TOBI - ITT Population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	155[9]	159[10]		
Units: Liters				
arithmetic mean (standard deviation)	0.16 (± 0.33)	0.16 (± 0.32)		

Notes:

[9] - this is the actual number of the patients analyzed

[10] - this is the actual number of the patients analyzed

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline to End of Week 2 of FVC, Expressed as Percentage of Predicted Normal

End point title	Change From Baseline to End of Week 2 of FVC, Expressed as Percentage of Predicted Normal

End point description:

FVC was measured via spirometry. Because this study included both adults and children and lung volume is an age-dependent variable, reference normal FVC values for children were different than the reference normal values used with adult participants.

End point type	Secondary

End point timeframe:

Baseline (Visit 2), Week 2 (Visit 3)

End point values	CHF 1538 - ITT Population	TOBI - ITT Population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	156[11]	163		
Units: percent				
arithmetic mean (standard deviation)	4.36 (± 10.81)	5.36 (± 10.03)		

Notes:

[11] - this is the actual number of the patients analyzed

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline to End of Week 4 of FVC, Expressed as Percentage of Predicted Normal

End point title	Change From Baseline to End of Week 4 of FVC, Expressed as Percentage of Predicted Normal

End point description:

FVC was measured via spirometry. Because this study included both adults and children and lung volume is an age-dependent variable, reference normal FVC values for children were different than the reference normal values used with adult participants.

End point type	Secondary

End point timeframe:

Baseline (Visit 2), Week 4 (Visit 4). For Visit 4, LOCF values are reported.

End point values	CHF 1538 - ITT Population	TOBI - ITT Population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	156[12]	163		
Units: Percent				
arithmetic mean (standard deviation)	4.8 (± 9.96)	5.48 (± 10.83)		

Notes:

[12] - this is the actual number of the patients analyzed

Statistical analyses

Statistical analysis title	CHF1538 vs TOBI

Statistical analysis description:

This statistical analysis is based on last observation carried forward (LOCF) values.

Comparison groups	TOBI - ITT Population v CHF 1538 - ITT Population

Number of subjects included in analysis	319
Analysis specification	Pre-specified
Analysis type	other[13]
P-value	= 0.63 [14]
Method	ANCOVA
Parameter estimate	least Square Means Difference
Point estimate	-0.55
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.78
upper limit	1.69

Notes:

[13] - Comparisons between treatment groups were made at Visit 4 by using the same ANCOVA model as for the primary variable. This model included the effects of treatment group and country as factors and baseline value as covariate.

[14] - the p value reported here refers to the "treatment" as factor.

Secondary: Change From Baseline to End of Week 8 of FVC, Expressed as Percentage of Predicted Normal

End point title	Change From Baseline to End of Week 8 of FVC, Expressed as Percentage of Predicted Normal

End point description:

FVC was measured via spirometry. Because this study included both adults and children and lung volume is an age-dependent variable, reference normal FVC values for children were different than the reference normal values used with adult participants.

End point type	Secondary

End point timeframe:

Baseline (Visit 2), Week 8 (Visit 5).

End point values	CHF 1538 - ITT Population	TOBI - ITT Population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	153[15]	159[16]		
Units: percent				
arithmetic mean (standard deviation)	2.7 (± 12.3)	5.04 (± 12.21)		

Notes:

[15] - this is the actual number of the patients analyzed

[16] - this is the actual number of the patients analyzed

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline to End of Week 2 of FVC, Expressed as liters

End point title	Change From Baseline to End of Week 2 of FVC, Expressed as liters

End point description:

FVC was measured via spirometry. Because this study included both adults and children and lung volume is an age-dependent variable, reference normal FVC values for children were different than the reference normal values used with adult participants.

End point type	Secondary

End point timeframe:

Baseline (Visit 2), Week 2 (Visit 3)

End point values	CHF 1538 - ITT Population	TOBI - ITT Population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	156[17]	163		
Units: LIters				
arithmetic mean (standard deviation)	0.14 (± 0.34)	0.16 (± 0.32)		

Notes:

[17] - this is the actual number of the patients analyzed

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline to End of Week 4 of FVC, Expressed as liters

End point title	Change From Baseline to End of Week 4 of FVC, Expressed as liters

End point description:

FVC was measured via spirometry. Because this study included both adults and children and lung volume is an age-dependent variable, reference normal FVC values for children were different than the reference normal values used with adult participants.

End point type	Secondary

End point timeframe:

Baseline (Visit 2), Week 4 (Visit 4). For Visit 4, LOCF values are reported.

End point values	CHF 1538 - ITT Population	TOBI - ITT Population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	156[18]	163		
Units: Liters				
arithmetic mean (standard deviation)	0.16 (± 0.34)	0.17 (± 0.36)		

Notes:

[18] - this is the actual number of the patients analyzed

Statistical analyses

Statistical analysis title	CHF1538 vs TOBI

Statistical analysis description:

This statistical analysis is based on last observation carried forward (LOCF) values.

Comparison groups	CHF 1538 - ITT Population v TOBI - ITT Population

Number of subjects included in analysis	319
Analysis specification	Pre-specified
Analysis type	other[19]
P-value	= 0.693 [20]
Method	ANCOVA
Parameter estimate	least Square Means Difference
Point estimate	-0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.09
upper limit	0.06

Notes:

[19] - Comparisons between treatment groups were made at Visit 4 by using the same ANCOVA model as for the primary variable. This model included the effects of treatment group and country as factors and baseline value as covariate.

[20] - the p value reported here refers to the "treatment" as effect/factor

Secondary: Change From Baseline to End of Week 8 of FVC, Expressed as liters

End point title	Change From Baseline to End of Week 8 of FVC, Expressed as liters

End point description:

FVC was measured via spirometry. Because this study included both adults and children and lung volume is an age-dependent variable, reference normal FVC values for children were different than the reference normal values used with adult participants.

End point type	Secondary

End point timeframe:

at Week 2 (Visit 3) and Week 8 (Visit 5)

End point values	CHF 1538 - ITT Population	TOBI - ITT Population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	153[21]	159[22]		
Units: Liters				
arithmetic mean (standard deviation)	0.1 (± 0.38)	0.16 (± 0.39)		

Notes:

[21] - this is the actual number of the patients analyzed

[22] - this is the actual number of the patients analyzed

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline to End of Week 2 of FEF25-75%, Expressed as Percentage of Predicted Normal

End point title	Change From Baseline to End of Week 2 of FEF25-75%, Expressed as Percentage of Predicted Normal

End point description:

Difference in FEF25-75% was measured from baseline to weeks 2 (Visit 3), 4 (Visit 4), and 8 (Visit 5). Because this study included both adults and children and lung volume is an age-dependent variable, reference normal FEF 25-75% values for children were different than the reference normal values used with adult participants.

End point type	Secondary

End point timeframe:

Baseline (Visit 2), Week 2 (Visit 3)

End point values	CHF 1538 - ITT Population	TOBI - ITT Population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	156[23]	162[24]		
Units: Percent				
arithmetic mean (standard deviation)	10.3 (± 17.07)	8.57 (± 19)		

Notes:

[23] - this is the actual number of the patients analyzed

[24] - this is the actual number of the patients analyzed

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline to End of Week 4 of FEF25-75%, Expressed as Percentage of Predicted Normal

End point title	Change From Baseline to End of Week 4 of FEF25-75%, Expressed as Percentage of Predicted Normal

End point description:

Difference in FEF25-75% was measured from baseline to weeks 2 (Visit 3), 4 (Visit 4), and 8 (Visit 5). Because this study included both adults and children and lung volume is an age-dependent variable, reference normal FEF 25-75% values for children were different than the reference normal values used with adult participants.

End point type	Secondary

End point timeframe:

Baseline (Visit 2), Week 4 (Visit 4). For Visit 4, LOCF values are reported.

End point values	CHF 1538 - ITT Population	TOBI - ITT Population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	157[25]	162[26]		
Units: Percent				
arithmetic mean (standard deviation)	10.22 (± 15.11)	9.25 (± 17.85)		

Notes:

[25] - this is the actual number of the patients analyzed

[26] - this is the actual number of the patients analyzed

Statistical analyses

Statistical analysis title	CHF1538 vs TOBI

Statistical analysis description:

This statistical analysis is based on last observation carried forward (LOCF) values.

Comparison groups	CHF 1538 - ITT Population v TOBI - ITT Population

Number of subjects included in analysis	319
Analysis specification	Pre-specified
Analysis type	other[27]
P-value	= 0.777 [28]
Method	ANCOVA
Parameter estimate	least Square Means Difference
Point estimate	0.51
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.06
upper limit	4.09

Notes:

[27] - Comparisons between treatment groups were made at Visit 4 by using the same ANCOVA model as for the primary variable. This model included the effects of treatment group and country as factors and baseline value as covariate.

[28] - the p value reported here refers to the "treatment" as effect/factor

Secondary: Change From Baseline to End of Week 8 of FEF25-75%, Expressed as Percentage of Predicted Normal

End point title	Change From Baseline to End of Week 8 of FEF25-75%, Expressed as Percentage of Predicted Normal

End point description:

Difference in FEF25-75% was measured from baseline to weeks 2 (Visit 3), 4 (Visit 4), and 8 (Visit 5). Because this study included both adults and children and lung volume is an age-dependent variable, reference normal FEF 25-75% values for children were different than the reference normal values used with adult participants.

End point type	Secondary

End point timeframe:

Baseline (Visit 2), Week 8 (Visit 5)

End point values	CHF 1538 - ITT Population	TOBI - ITT Population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	154[29]	158[30]		
Units: Percent				
arithmetic mean (standard deviation)	9.05 (± 19.59)	6.41 (± 20.46)		

Notes:

[29] - this is the actual number of the patients analyzed

[30] - this is the actual number of the patients analyzed

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline to End of Week 2 of FEF25-75%, Expressed as liters/sec

End point title	Change From Baseline to End of Week 2 of FEF25-75%, Expressed as liters/sec

End point description:

Difference in FEF25-75% was measured from baseline to weeks 2 (Visit 3), 4 (Visit 4), and 8 (Visit 5). Because this study included both adults and children and lung volume is an age-dependent variable, reference normal FEF 25-75% values for children were different than the reference normal values used

with adult participants.

End point type	Secondary

End point timeframe:

Baseline (Visit 2), Week 2 (Visit 3)

End point values	CHF 1538 - ITT Population	TOBI - ITT Population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	156[31]	162[32]		
Units: Liters/sec				
arithmetic mean (standard deviation)	0.32 (± 0.5)	0.28 (± 0.56)		

Notes:

[31] - this is the actual number of the patients analyzed

[32] - this is the actual number of the patients analyzed

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline to End of Week 4 of FEF25-75%, Expressed as liters/sec

End point title	Change From Baseline to End of Week 4 of FEF25-75%, Expressed as liters/sec

End point description:

Difference in FEF25-75% was measured from baseline to weeks 2 (Visit 3), 4 (Visit 4), and 8 (Visit 5). Because this study included both adults and children and lung volume is an age-dependent variable, reference normal FEF 25-75% values for children were different than the reference normal values used with adult participants.

End point type	Secondary

End point timeframe:

Baseline (Visit 2), Week 4 (Visit 4). For Visit 4, LOCF values are reported.

End point values	CHF 1538 - ITT Population	TOBI - ITT Population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	157[33]	162[34]		
Units: Liters/sec				
arithmetic mean (standard deviation)	0.33 (± 0.48)	0.29 (± 0.56)		

Notes:

[33] - this is the actual number of the patients analyzed

[34] - this is the actual number of the patients analyzed

Statistical analyses

Statistical analysis title	CHF1538 vs TOBI

Statistical analysis description:

This statistical analysis is based on last observation carried forward (LOCF) values.

Comparison groups	CHF 1538 - ITT Population v TOBI - ITT Population
Number of subjects included in analysis	319
Analysis specification	Pre-specified
Analysis type	other[35]
P-value	= 0.505 [36]
Method	ANCOVA
Parameter estimate	least Square Means Difference
Point estimate	0.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.08
upper limit	0.15

Notes:

[35] - Comparisons between treatment groups were made at Visit 4 by using the same ANCOVA model as for the primary variable. This model included the effects of treatment group and country as factors and baseline value as covariate.

[36] - the p value reported here refers to the "treatment" as effect/factor

Secondary: Change From Baseline to End of Week 8 of FEF25-75%, Expressed as liters/sec

End point title	Change From Baseline to End of Week 8 of FEF25-75%, Expressed as liters/sec

End point description:

Difference in FEF25-75% was measured from baseline to weeks 2 (Visit 3), 4 (Visit 4), and 8 (Visit 5). Because this study included both adults and children and lung volume is an age-dependent variable, reference normal FEF 25-75% values for children were different than the reference normal values used with adult participants.

End point type	Secondary

End point timeframe:

Baseline (Visit 2), Week 8 (Visit 5)

End point values	CHF 1538 - ITT Population	TOBI - ITT Population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	154[37]	158[38]		
Units: liters/sec				
arithmetic mean (standard deviation)	0.28 (± 0.57)	0.21 (± 0.67)		

Notes:

[37] - this is the actual number of the patients analyzed

[38] - this is the actual number of the patients analyzed

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline to End of Week 4 in Pseudomonas Log10 bacterial load in sputum

End point title	Change from baseline to End of Week 4 in Pseudomonas Log10 bacterial load in sputum

End point description:

If a participant had more than one Pseudomonas aeruginosa (PA) morphotype at a given visit, and therefore more than one bacterial load value, then the bacterial load value corresponding to the highest tobramycin minimal inhibitory concentration (MIC) value regardless of the PA morphotype was used. If the tobramycin MIC value was the same for different PA morphotypes, then the bacterial load value corresponding to morphotype 1 (mucoid colony) was used. If morphotype 1 was not available, bacterial load value corresponding to morphotype 2 (dry colony) was used.

End point type	Secondary

End point timeframe:

Baseline (Visit 2), Week 4 (Visit 4).

End point values	CHF 1538 - ITT Population	TOBI - ITT Population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	152[39]	156[40]		
Units: CFU/gram				
arithmetic mean (standard deviation)	-2.14 (± 2.41)	-2.07 (± 2.2)		

Notes:

[39] - this is the actual number of the patients analyzed

[40] - this is the actual number of the patients analyzed

Statistical analyses

Statistical analysis title	CHF 1538 vs TOBI
Comparison groups	TOBI - ITT Population v CHF 1538 - ITT Population
Number of subjects included in analysis	308
Analysis specification	Pre-specified
Analysis type	other[41]
P-value	= 0.82 [42]
Method	ANCOVA
Parameter estimate	Least Square Means Difference
Point estimate	0.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.31
upper limit	0.39

Notes:

[41] - Comparisons between treatment groups were made at Visit 4 by using the same ANCOVA model as for the primary variable. This model included the effects of treatment group and country as factors and baseline value as covariate

[42] - the p value reported here refers to the "treatment" as effect/factor

Secondary: Change from baseline to End of Week 8 in Pseudomonas Log10 bacterial load in sputum

End point title	Change from baseline to End of Week 8 in Pseudomonas Log10 bacterial load in sputum

End point description:

If a participant had more than one Pseudomonas aeruginosa (PA) morphotype at a given visit, and therefore more than one bacterial load value, then the bacterial load value corresponding to the highest tobramycin minimal inhibitory concentration (MIC) value regardless of the PA morphotype was used. If the tobramycin MIC value was the same for different PA morphotypes, then the bacterial load value corresponding to morphotype 1 (mucoid colony) was used. If morphotype 1 was not available, bacterial load value corresponding to morphotype 2 (dry colony) was used.

End point type	Secondary

End point timeframe:

Baseline (Visit 2), Week 8 (Visit 5)

End point values	CHF 1538 - ITT Population	TOBI - ITT Population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	147[43]	147[44]		
Units: CFU/gram				
arithmetic mean (standard deviation)	-0.72 (± 2.17)	-0.87 (± 2.23)		

Notes:

[43] - this is the actual number of the patients analyzed

[44] - this is the actual number of the patients analyzed

Statistical analyses

No statistical analyses for this end point

Secondary: Tobramicyn MIC50 of Pseudomonas aeruginosa at week 4

End point title	Tobramicyn MIC50 of Pseudomonas aeruginosa at week 4

End point description:

MIC50 values were calculated for three different Pseudomonas aeruginosa (PA) strains:
- Morphotype 1: mucoid
- Morphotype 2: dry
- Morphotype 3: variant

Overall MIC50 values are reported. If a participant has more than one PA morphotype at a given visit, then the highest tobramycin MIC value was used, regardless of PA morphotype. If a participant has more than one available result for each morphotype then the highest tobramycin MIC value was used. If the tobramycin MIC values are equal, then the MIC value for the isolate with the highest bacterial load value was used.

End point type	Secondary

End point timeframe:

Week 4 (Visit 4).

End point values	CHF 1538 - ITT Population	TOBI - ITT Population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	126[45]	134[46]		
Units: micrograms/mL				
number (not applicable)	1	0.5		

Notes:

[45] - this is the actual number of the patients analyzed

[46] - this is the actual number of the patients analyzed

Statistical analyses

No statistical analyses for this end point

Secondary: Tobramicyn MIC50 of Pseudomonas aeruginosa at week 8

End point title	Tobramicyn MIC50 of Pseudomonas aeruginosa at week 8

End point description:

MIC50 values were calculated for three different Pseudomonas aeruginosa (PA) strains:
- Morphotype 1: mucoid
- Morphotype 2: dry
- Morphotype 3: variant

Overall MIC50 values are reported. If a participant has more than one PA morphotype at a given visit, then the highest tobramycin MIC value was used, regardless of PA morphotype. If a participant has more than one available result for each morphotype then the highest tobramycin MIC value was used. If the tobramycin MIC values are equal, then the MIC value for the isolate with the highest bacterial load value was used.

End point type	Secondary

End point timeframe:

Baseline (Visit 2), Week 8 (Visit 5).

End point values	CHF 1538 - ITT Population	TOBI - ITT Population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	129[47]	128[48]		
Units: micrograms(mL				
number (not applicable)	1	1		

Notes:

[47] - this is the actual number of the patients analyzed

[48] - this is the actual number of the patients analyzed

Statistical analyses

No statistical analyses for this end point

Secondary: Tobramicyn MIC90 of Pseudomonas aeruginosa at week 4

End point title	Tobramicyn MIC90 of Pseudomonas aeruginosa at week 4

End point description:

MIC values were calculated for three different Pseudomonas aeruginosa (PA) strains:
- Morphotype 1: mucoid
- Morphotype 2: dry
- Morphotype 3: variant

Overall MIC90 values are reported. If a participant has more than one PA morphotype at a given visit, then the highest tobramycin MIC value was used, regardless of PA morphotype. If a participant has more than one available result for each morphotype then the highest tobramycin MIC value was used. If the tobramycin MIC values are equal then the MIC value for the isolate with the highest bacterial load value was used.

End point type	Secondary

End point timeframe:

Baseline (Visit 2), Week 4 (Visit 4).

End point values	CHF 1538 - ITT Population	TOBI - ITT Population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	126[49]	134[50]		
Units: micrograms/mL				
number (not applicable)	32	32		

Notes:

[49] - this is the actual number of the patients analyzed

[50] - this is the actual number of the patients analyzed

Statistical analyses

No statistical analyses for this end point

Secondary: Tobramicyn MIC90 of Pseudomonas aeruginosa at week 8

End point title	Tobramicyn MIC90 of Pseudomonas aeruginosa at week 8

End point description:

MIC values were calculated for three different Pseudomonas aeruginosa (PA) strains:
- Morphotype 1: mucoid
- Morphotype 2: dry
- Morphotype 3: variant

Overall MIC90 values are reported. If a participant has more than one PA morphotype at a given visit, then the highest tobramycin MIC value was used, regardless of PA morphotype. If a participant has more than one available result for each morphotype then the highest tobramycin MIC value was used. If the tobramycin MIC values are equal then the MIC value for the isolate with the highest bacterial load value was used.

End point type	Secondary

End point timeframe:

Baseline (Visit 2), Week 8 (Visit 5).

End point values	CHF 1538 - ITT Population	TOBI - ITT Population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	129[51]	128[52]		
Units: micrograms/mL				
number (not applicable)	32	32		

Notes:

[51] - this is the actual number of the patients analyzed

[52] - this is the actual number of the patients analyzed

Statistical analyses

No statistical analyses for this end point

Secondary: Microbiological outcome by visit

End point title	Microbiological outcome by visit

End point description:

Microbiological outcomes are derived considering all P. aeruginosa (PA) morphotypes together.
Week 4 and Week 8 microbiological outcomes:
Eradication = elimination of PA
Persistence = persistence of PA detected at previous visit
Superinfection = appearance of a pathogen (other than PA) not detected at previous visit
Re-infection (week 8 only) = re-appearance of PA detected at Screening and eradicated at Week 4

Superinfection supersedes eradication. Persistence for P. aeruginosa supersedes superinfection. Re-infection for P. aeruginosa supersedes superinfection.

End point type	Secondary

End point timeframe:

Week 4 and Week 8

End point values	CHF 1538 - ITT Population	TOBI - ITT Population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	158	162[53]		
Units: percentage of participants				
number (not applicable)				
Screening presence of P aeruginosa	100	100		
Week 4 - Eradication	9.2	7.1		
Week 4 - Persistence	82.9	85.3		
Week 4 - Superinfection	7.9	7.7		
Week 8 - Eradication	2.7	3.4		
Week 8 - Persistence	78.9	83		
Week 8 - Superinfection	9.5	9.5		
Week 8 - Reinfection	8.8	4.1		

Notes:

[53] - this is the actual number of the patients analyzed

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline to End of Week 2 in Body Weight

End point title	Change From Baseline to End of Week 2 in Body Weight

End point description:

Body weight was measured at all study visits as part of the physical examination

End point type	Secondary

End point timeframe:

Baseline (Visit 2), Weeks 2 (Visit 3).

End point values	CHF 1538 - ITT Population	TOBI - ITT Population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	158	163		
Units: kilograms				
arithmetic mean (standard deviation)	0.24 (± 0.68)	0.22 (± 0.72)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline to End of Week 4 in Body Weight	
End point title	Change From Baseline to End of Week 4 in Body Weight
End point description:	
Body weight was measured at all study visits as part of the physical examination.	
End point type	Secondary
End point timeframe:	
Baseline (Visit 2), Weeks 4 (Visit 4). For Visit 4, LOCF values are reported.	

End point values	CHF 1538 - ITT Population	TOBI - ITT Population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	158	163		
Units: kilograms				
arithmetic mean (standard deviation)	0.4 (± 0.9)	0.39 (± 1.01)		

Statistical analyses

Statistical analysis title	CHF1538 vs TOBI
Statistical analysis description:	
This statistical analysis is based on last observation carried forward (LOCF) values.	
Comparison groups	TOBI - ITT Population v CHF 1538 - ITT Population
Number of subjects included in analysis	321
Analysis specification	Pre-specified
Analysis type	other[54]
P-value	= 0.886 [55]
Method	ANCOVA
Parameter estimate	least Square Means Difference
Point estimate	0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2
upper limit	0.23

Notes:

[54] - Change from baseline in weight was analyzed at Visit 4 by an ANCOVA model including treatment, country, sex and age in classes (6-12 years, 13-17 years,
> 17 years) as factors and baseline value as covariate.

[55] - the p value reported here refers to the "treatment" as effect/factor.

Secondary: Change From Baseline to End of Week 8 in Body Weight	
End point title	Change From Baseline to End of Week 8 in Body Weight
End point description:	
Body weight was measured at all study visits as part of the physical examination.	
End point type	Secondary

End point timeframe:

Baseline (Visit 2), Weeks 8 (Visit 5),

End point values	CHF 1538 - ITT Population	TOBI - ITT Population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	155[56]	159		
Units: KIlograms				
arithmetic mean (standard deviation)	0.6 (± 1.14)	0.53 (± 1.27)		

Notes:

[56] - this is the actual number of the patients analyzed

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline to End of Week 2 in Body Mass Index (BMI)

End point title	Change From Baseline to End of Week 2 in Body Mass Index (BMI)

End point description:

BMI was measured at all study visits as part of the physical examination.

End point type	Secondary

End point timeframe:

Baseline (Visit 2), Weeks 2 (Visit 3),

End point values	CHF 1538 - ITT Population	TOBI - ITT Population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	158	163		
Units: kilograms/meters^2				
arithmetic mean (standard deviation)	0.1 (± 0.28)	0.1 (± 0.29)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline to End of Week 4 in Body Mass Index (BMI)

End point title	Change From Baseline to End of Week 4 in Body Mass Index (BMI)

End point description:

BMI was measured at all study visits as part of the physical examination.

End point type	Secondary

End point timeframe:

Baseline (Visit 2), Weeks 4 (Visit 4). For Visit 4, LOCF values are reported.

End point values	CHF 1538 - ITT Population	TOBI - ITT Population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	158	163		
Units: kilograms/meters^2				
arithmetic mean (standard deviation)	0.12 (± 0.37)	0.12 (± 0.39)		

Statistical analyses

Statistical analysis title	CHF1538 vs TOBI
Statistical analysis description:	
This statistical analysis is based on last observation carried forward (LOCF) values.	
Comparison groups	CHF 1538 - ITT Population v TOBI - ITT Population
Number of subjects included in analysis	321
Analysis specification	Pre-specified
Analysis type	other[57]
P-value	= 0.856 [58]
Method	ANCOVA
Parameter estimate	least Square Means Difference
Point estimate	-0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.09
upper limit	0.08

Notes:

[57] - Change from baseline in BMI was analyzed at Visit 4 by an ANCOVA model including treatment, country, sex and age in classes (6-12 years, 13-17 years,
> 17 years) as factors and baseline value as covariate.

[58] - the p value reported here refers to the "treatment" as effect/factor.

Secondary: Change From Baseline to End of Week 8 in Body Mass Index (BMI)

End point title	Change From Baseline to End of Week 8 in Body Mass Index (BMI)
End point description:	
BMI was measured at all study visits as part of the physical examination.	
End point type	Secondary
End point timeframe:	
Baseline (Visit 2), Weeks 8 (Visit 5),	

End point values	CHF 1538 - ITT Population	TOBI - ITT Population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	155[59]	159[60]		
Units: kilograms/meters^2				
arithmetic mean (standard deviation)	0.16 (± 0.48)	0.14 (± 0.49)		

Notes:

[59] - this is the actual number of the patients analyzed

[60] - this is the actual number of the patients analyzed

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Day 0 to Week 8	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	13.0

Reporting groups	
Reporting group title	CHF1538
Reporting group description: tobramycin / Bramitob administered 300mg twice a day for 4 weeks	
Reporting group title	TOBI
Reporting group description: tobramycin / TOBI administered 300mg twice a day for 4 weeks	

Serious adverse events	CHF1538	TOBI	
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 156 (3.85%)	2 / 168 (1.19%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Head injury			
subjects affected / exposed	1 / 156 (0.64%)	0 / 168 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Cystic fibrosis lung			
subjects affected / exposed	1 / 156 (0.64%)	1 / 168 (0.60%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Syncope			
subjects affected / exposed	1 / 156 (0.64%)	0 / 168 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			

Appendicitis			
subjects affected / exposed	1 / 156 (0.64%)	0 / 168 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 156 (0.64%)	1 / 168 (0.60%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngitis			
subjects affected / exposed	1 / 156 (0.64%)	0 / 168 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung Infection			
subjects affected / exposed	1 / 156 (0.64%)	0 / 168 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0.6 %

Non-serious adverse events	CHF1538	TOBI	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	44 / 156 (28.21%)	47 / 168 (27.98%)	
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 156 (0.64%)	0 / 168 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 156 (0.64%)	0 / 168 (0.00%)	
occurrences (all)	1	0	
Catheter site phlebitis			
subjects affected / exposed	0 / 156 (0.00%)	1 / 168 (0.60%)	
occurrences (all)	0	1	
Chest discomfort			

subjects affected / exposed	1 / 156 (0.64%)	0 / 168 (0.00%)	
occurrences (all)	1	0	
Chest pain			
subjects affected / exposed	1 / 156 (0.64%)	0 / 168 (0.00%)	
occurrences (all)	1	0	
Face oedema			
subjects affected / exposed	0 / 156 (0.00%)	1 / 168 (0.60%)	
occurrences (all)	0	1	
Fatigue			
subjects affected / exposed	2 / 156 (1.28%)	0 / 168 (0.00%)	
occurrences (all)	6	0	
Mucosal dryness			
subjects affected / exposed	1 / 156 (0.64%)	0 / 168 (0.00%)	
occurrences (all)	1	0	
Pyrexia			
subjects affected / exposed	5 / 156 (3.21%)	5 / 168 (2.98%)	
occurrences (all)	5	5	
Respiratory, thoracic and mediastinal disorders			
Bronchospasm			
subjects affected / exposed	0 / 156 (0.00%)	1 / 168 (0.60%)	
occurrences (all)	0	1	
Cough			
subjects affected / exposed	10 / 156 (6.41%)	10 / 168 (5.95%)	
occurrences (all)	12	11	
Dysphonia			
subjects affected / exposed	1 / 156 (0.64%)	2 / 168 (1.19%)	
occurrences (all)	2	2	
Haemoptysis			
subjects affected / exposed	3 / 156 (1.92%)	2 / 168 (1.19%)	
occurrences (all)	3	2	
Nasal congestion			
subjects affected / exposed	1 / 156 (0.64%)	0 / 168 (0.00%)	
occurrences (all)	1	0	
Obstructive airways disorder			

subjects affected / exposed	0 / 156 (0.00%)	1 / 168 (0.60%)	
occurrences (all)	0	1	
Oropharyngeal pain			
subjects affected / exposed	3 / 156 (1.92%)	1 / 168 (0.60%)	
occurrences (all)	3	1	
Productive cough			
subjects affected / exposed	0 / 156 (0.00%)	1 / 168 (0.60%)	
occurrences (all)	0	1	
Rales			
subjects affected / exposed	1 / 156 (0.64%)	0 / 168 (0.00%)	
occurrences (all)	1	0	
Rhinorrhoea			
subjects affected / exposed	0 / 156 (0.00%)	1 / 168 (0.60%)	
occurrences (all)	0	1	
Sputum increased			
subjects affected / exposed	1 / 156 (0.64%)	0 / 168 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 156 (0.64%)	0 / 168 (0.00%)	
occurrences (all)	1	0	
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 156 (0.64%)	0 / 168 (0.00%)	
occurrences (all)	1	0	
Audiogram abnormal			
subjects affected / exposed	1 / 156 (0.64%)	1 / 168 (0.60%)	
occurrences (all)	1	1	
Blood glucose increased			
subjects affected / exposed	0 / 156 (0.00%)	1 / 168 (0.60%)	
occurrences (all)	0	1	
Forced expiratory volume decreased			
subjects affected / exposed	2 / 156 (1.28%)	1 / 168 (0.60%)	
occurrences (all)	2	1	
Neutrophil count increased			

subjects affected / exposed	0 / 156 (0.00%)	1 / 168 (0.60%)	
occurrences (all)	0	1	
Pulmonary function test decreased			
subjects affected / exposed	0 / 156 (0.00%)	2 / 168 (1.19%)	
occurrences (all)	0	2	
Red blood cell sedimentation rate increased			
subjects affected / exposed	1 / 156 (0.64%)	3 / 168 (1.79%)	
occurrences (all)	1	3	
Injury, poisoning and procedural complications			
Skin injury			
subjects affected / exposed	0 / 156 (0.00%)	1 / 168 (0.60%)	
occurrences (all)	0	1	
Congenital, familial and genetic disorders			
Cystic fibrosis lung			
subjects affected / exposed	5 / 156 (3.21%)	4 / 168 (2.38%)	
occurrences (all)	5	4	
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 156 (0.64%)	0 / 168 (0.00%)	
occurrences (all)	1	0	
Headache			
subjects affected / exposed	5 / 156 (3.21%)	0 / 168 (0.00%)	
occurrences (all)	6	0	
Somnolence			
subjects affected / exposed	0 / 156 (0.00%)	1 / 168 (0.60%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Eosinophilia			
subjects affected / exposed	1 / 156 (0.64%)	0 / 168 (0.00%)	
occurrences (all)	1	0	
Leukopenia			
subjects affected / exposed	1 / 156 (0.64%)	0 / 168 (0.00%)	
occurrences (all)	1	0	
Thrombocytopenia			

subjects affected / exposed	1 / 156 (0.64%)	0 / 168 (0.00%)	
occurrences (all)	1	0	
Ear and labyrinth disorders			
Deafness neurosensory			
subjects affected / exposed	1 / 156 (0.64%)	0 / 168 (0.00%)	
occurrences (all)	1	0	
Hypoacusis			
subjects affected / exposed	1 / 156 (0.64%)	1 / 168 (0.60%)	
occurrences (all)	1	1	
Otosalpingitis			
subjects affected / exposed	0 / 156 (0.00%)	1 / 168 (0.60%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	2 / 156 (1.28%)	0 / 168 (0.00%)	
occurrences (all)	2	0	
Abdominal pain			
subjects affected / exposed	1 / 156 (0.64%)	0 / 168 (0.00%)	
occurrences (all)	1	0	
Diarrhoea			
subjects affected / exposed	0 / 156 (0.00%)	1 / 168 (0.60%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Urticaria			
subjects affected / exposed	0 / 156 (0.00%)	1 / 168 (0.60%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 156 (0.64%)	0 / 168 (0.00%)	
occurrences (all)	1	0	
Back pain			
subjects affected / exposed	1 / 156 (0.64%)	0 / 168 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal pain			
subjects affected / exposed	1 / 156 (0.64%)	0 / 168 (0.00%)	
occurrences (all)	1	0	

Infections and infestations			
acute tonsillitis			
subjects affected / exposed	0 / 156 (0.00%)	1 / 168 (0.60%)	
occurrences (all)	0	1	
Bronchitis			
subjects affected / exposed	3 / 156 (1.92%)	3 / 168 (1.79%)	
occurrences (all)	3	3	
Gastrointestinal viral infection			
subjects affected / exposed	1 / 156 (0.64%)	0 / 168 (0.00%)	
occurrences (all)	1	0	
Influenza			
subjects affected / exposed	1 / 156 (0.64%)	0 / 168 (0.00%)	
occurrences (all)	1	0	
Lung infection			
subjects affected / exposed	0 / 156 (0.00%)	1 / 168 (0.60%)	
occurrences (all)	0	1	
Nasopharyngitis			
subjects affected / exposed	6 / 156 (3.85%)	2 / 168 (1.19%)	
occurrences (all)	6	2	
Pharyngitis			
subjects affected / exposed	6 / 156 (3.85%)	2 / 168 (1.19%)	
occurrences (all)	6	2	
Pneumonia			
subjects affected / exposed	0 / 156 (0.00%)	1 / 168 (0.60%)	
occurrences (all)	0	1	
Respiratory tract infection viral			
subjects affected / exposed	1 / 156 (0.64%)	1 / 168 (0.60%)	
occurrences (all)	1	1	
Respiratory tract infection			
subjects affected / exposed	1 / 156 (0.64%)	3 / 168 (1.79%)	
occurrences (all)	1	4	
Rhinitis			
subjects affected / exposed	7 / 156 (4.49%)	5 / 168 (2.98%)	
occurrences (all)	7	5	
Sinusitis			

subjects affected / exposed	0 / 156 (0.00%)	1 / 168 (0.60%)	
occurrences (all)	0	1	
Tracheitis			
subjects affected / exposed	0 / 156 (0.00%)	1 / 168 (0.60%)	
occurrences (all)	0	1	
Tracheobronchitis			
subjects affected / exposed	1 / 156 (0.64%)	0 / 168 (0.00%)	
occurrences (all)	1	0	
Upper respiratory tract infection			
subjects affected / exposed	2 / 156 (1.28%)	3 / 168 (1.79%)	
occurrences (all)	2	3	
Varicella			
subjects affected / exposed	0 / 156 (0.00%)	1 / 168 (0.60%)	
occurrences (all)	0	1	
Viral pharyngitis			
subjects affected / exposed	0 / 156 (0.00%)	1 / 168 (0.60%)	
occurrences (all)	0	1	
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 156 (0.64%)	0 / 168 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	0 / 156 (0.00%)	1 / 168 (0.60%)	
occurrences (all)	0	1	
Hyponatraemia			
subjects affected / exposed	0 / 156 (0.00%)	1 / 168 (0.60%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 December 2008	Version 3 of the Protocol incorporates Version 2 and the amendment (substantial general amendment 1.0) which contains substantial changes to the trial conduct and design.

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.

There are no limitation or caveats to this summary of results.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/24464974