Clinical trial results:
A single arm, open-label, multicenter, Phase IV trial to assess long term safety of tobramycin inhalation powder (TIP) in patients with Cystic Fibrosis

Summary

EudraCT number	2011-002000-32
Trial protocol	HU FR ES DE IT
Global end of trial date	13 January 2014

Results information

Result version number	v1 (current)
This version publication date	13 July 2016
First version publication date	07 August 2015

Trial information

Trial identification

Sponsor protocol code	CTBM100C2401

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
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,
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, +41 613241111,

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	13 January 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	13 January 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the study was to assess the safety of tobramycin inhalation powder (TIP) with respect to incidence of treatment emergent adverse events (AEs) over 6 treatment cycles.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were followed. Rescue medications like anti-pseudomonal antibiotics, macrolides (anti-inflammatory regimen), bronchodilators, inhaled hypertonic saline, inhaled corticosteroids were allowed for pulmonary exacerbations as per the discretion of the investigator. If the subject's condition/disease required the medications which potentially affected the systemic tobramycin levels, inhalation of study medication was continued only at the investigator's discretion. The investigator provided followup medical care for all subjects who were prematurely withdrawn from the study, or referred them for appropriate ongoing care.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	16 January 2012
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	Spain: 8
Country: Number of subjects enrolled	France: 19
Country: Number of subjects enrolled	Germany: 12
Country: Number of subjects enrolled	Hungary: 8
Country: Number of subjects enrolled	Italy: 21
Country: Number of subjects enrolled	United States: 50
Country: Number of subjects enrolled	Canada: 2
Country: Number of subjects enrolled	Mexico: 12
Country: Number of subjects enrolled	Argentina: 10
Country: Number of subjects enrolled	Australia: 15
Worldwide total number of subjects	157
EEA total number of subjects	68

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)	5
Adolescents (12-17 years)	21
Adults (18-64 years)	131
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 47 centres in 10 countries.

Pre-assignment

Screening details:

A total of 157 subjects were enrolled in the study.

Period 1

Period 1 title	Overall study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

As the study was an open-label study, this section was not applicable.

Arms

Arm title	Tobramycin inhalation powder

Arm description:

Subjects inhaled four capsules of tobramycin inhalation powder (28 mg) twice daily (bid) via the T-326 inhaler device, for 28 days (treatment phase in each cycle). Each treatment phase therefore consisted of 112 mg tobramycin (4 capsules of 28 mg each) with the total daily dose of 224mg tobramycin (112mg bid). The treatment phase was followed by 28 days of no study treatment (off treatment in each cycle). These 56 days represented 1 cycle of therapy.

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

Dosage and administration details:

Subjects inhaled four capsules of tobramycin inhalation powder (28 mg) bid via the T-326 inhaler device, for 28 days.

Number of subjects in period 1	Tobramycin inhalation powder
Started	157
Completed	96
Not completed	61
Consent withdrawn by subject	17
Adverse event, non-fatal	29
Unsatisfactory therapeutic effect	6
Lost to follow-up	3
Protocol deviation	6

Baseline characteristics

Reporting groups	
Reporting group title	Tobramycin inhalation powder
Reporting group description:	
Subjects inhaled four capsules of tobramycin inhalation powder (28 mg) twice daily (bid) via the T-326 inhaler device, for 28 days (treatment phase in each cycle). Each treatment phase therefore consisted of 112 mg tobramycin (4 capsules of 28 mg each) with the total daily dose of 224mg tobramycin (112mg bid). The treatment phase was followed by 28 days of no study treatment (off treatment in each cycle). These 56 days represented 1 cycle of therapy.	

Reporting group values	Tobramycin inhalation powder	Total	
Number of subjects	157	157	
Age categorical Units: Subjects			
6-<13 years	7	7	
13-<20 years	26	26	
>= 20 years	124	124	
Age continuous Units: years			
arithmetic mean	27.8		
standard deviation	± 10.82	-	
Gender categorical Units: Subjects			
Female	60	60	
Male	97	97	
Pseudomonas aeruginosa tobramycin minimal inhibitory concentration (MIC) Units: Subjects			
> 8 microgram/millilitre(ug/mL)	41	41	
<= 8 ug/mL	115	115	
Missing	1	1	
Forced expiratory volume in one second (FEV1) percent (%) predicted Units: percent			
arithmetic mean	50.2		
standard deviation	± 13.95	-	
Forced vital capacity (FVC) % predicted Units: percent			
arithmetic mean	73.9		
standard deviation	± 15.88	-	
Forced expiratory flow from 25 to 75 % (FEF25-75%) of the forced vital capacity % predicted Units: percent			
arithmetic mean	21.8		
standard deviation	± 12.75	-	
Sputum density of Pseudomonas aeruginosa - sum of all biotypes Units: log10 colony forming units (CFU)			
arithmetic mean	7.6		

standard deviation	± 1.65	-	

End points

End points reporting groups

Reporting group title	Tobramycin inhalation powder

Reporting group description:

Subjects inhaled four capsules of tobramycin inhalation powder (28 mg) twice daily (bid) via the T-326 inhaler device, for 28 days (treatment phase in each cycle). Each treatment phase therefore consisted of 112 mg tobramycin (4 capsules of 28 mg each) with the total daily dose of 224mg tobramycin (112mg bid). The treatment phase was followed by 28 days of no study treatment (off treatment in each cycle). These 56 days represented 1 cycle of therapy.

Subject analysis set title	Cycle 1 (Day 29)
Subject analysis set type	Safety analysis

Subject analysis set description:

Subjects inhaled four capsules of tobramycin inhalation powder (28 mg) bid via the T-326 inhaler device, for 28 days. The treatment phase therefore consisted of 112 mg tobramycin (4 capsules of 28 mg each) with the total daily dose of 224 mg tobramycin (112 mg bid). The treatment phase was followed by 28 days of no study treatment (off treatment).

Subject analysis set title	Cycle 2 (Day 85)
Subject analysis set type	Safety analysis

Subject analysis set description:

Subjects inhaled four capsules of tobramycin inhalation powder (28 mg) bid via the T-326 inhaler device, for 28 days. The treatment phase therefore consisted of 112 mg tobramycin (4 capsules of 28 mg each) with the total daily dose of 224 mg tobramycin (112 mg bid). The treatment phase was followed by 28 days of no study treatment (off treatment). These 56 days after Cycle 1 represented Cycle 2 of therapy.

Subject analysis set title	Cycle 3 (Day 141)
Subject analysis set type	Safety analysis

Subject analysis set description:

Subjects inhaled four capsules of tobramycin inhalation powder (28 mg) bid via the T-326 inhaler device, for 28 days. The treatment phase therefore consisted of 112 mg tobramycin (4 capsules of 28 mg each) with the total daily dose of 224 mg tobramycin (112 mg bid). The treatment phase was followed by 28 days of no study treatment (off treatment). These 56 days after Cycle 2 represented Cycle 3 of therapy.

Subject analysis set title	Cycle 4 (Day 197)
Subject analysis set type	Safety analysis

Subject analysis set description:

Subjects inhaled four capsules of tobramycin inhalation powder (28 mg) bid via the T-326 inhaler device, for 28 days. The treatment phase therefore consisted of 112 mg tobramycin (4 capsules of 28 mg each) with the total daily dose of 224 mg tobramycin (112 mg bid). The treatment phase was followed by 28 days of no study treatment (off treatment). These 56 days after Cycle 3 represented Cycle 4 of therapy.

Subject analysis set title	Cycle 5 (Day 253)
Subject analysis set type	Safety analysis

Subject analysis set description:

Subjects inhaled four capsules of tobramycin inhalation powder (28 mg) bid via the T-326 inhaler device, for 28 days. The treatment phase therefore consisted of 112 mg tobramycin (4 capsules of 28 mg each) with the total daily dose of 224 mg tobramycin (112 mg bid). The treatment phase was followed by 28 days of no study treatment (off treatment). These 56 days after Cycle 4 represented Cycle 5 of therapy.

Subject analysis set title	Cycle 6 (Day 309)
Subject analysis set type	Safety analysis

Subject analysis set description:

Subjects inhaled four capsules of tobramycin inhalation powder (28 mg) bid via the T-326 inhaler device, for 28 days. The treatment phase therefore consisted of 112 mg tobramycin (4 capsules of 28 mg each) with the total daily dose of 224 mg tobramycin (112 mg bid). The treatment phase was followed by 28 days of no study treatment (off treatment). These 56 days after Cycle 5 represented Cycle 6 of therapy.

Subject analysis set title	All cycle completion (Day 337)

Subject analysis set type	Safety analysis

Subject analysis set description:

Subjects inhaled four capsules of tobramycin inhalation powder (28 mg) bid via the T-326 inhaler device, for 28 days. The treatment phase therefore consisted of 112 mg tobramycin (4 capsules of 28 mg each) with the total daily dose of 224 mg tobramycin (112 mg bid). The treatment phase was followed by 28 days of no study treatment (off treatment) after Cycle 6 represented as completion of all study cycles.

Primary: Number of subjects with adverse events (AEs), AEs leading to discontinuation and serious adverse events (SAEs) over 6 treatment cycles

End point title	Number of subjects with adverse events (AEs), AEs leading to discontinuation and serious adverse events (SAEs) over 6 treatment cycles[1]

End point description:

An AE was defined as any unfavorable and unintended sign, symptom, or disease temporally associated with the use of study drug, whether or not related to study drug. An SAE was defined as an event which was fatal or life threatening, required or prolonged hospitalization, was significantly or permanently disabling or incapacitating, constituted a congenital anomaly or a birth defect, or encompassed any other clinically significant event that could jeopardize the subject or require medical or surgical intervention to prevent one of the aforementioned outcomes. Based on the severity, AEs were categorised into 3 types as mild, moderate and severe. On-treatment AE was defined as the AE occurred during 28 days treatment phase and off-treatment AE was defined as the AE occurred during 28 days no study drug treatment phase. The analysis was performed in safety population, defined as all subjects entered the study and received at least one dose of study drug.

End point type	Primary

End point timeframe:

Baseline (start of study treatment) to Day 337 (end of the study)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive summary statistics was planned for this outcome measure.

End point values	Tobramycin inhalation powder			
Subject group type	Reporting group			
Number of subjects analysed	157			
Units: Number of subjects				
On-treatment AEs	121			
Off-treatment AEs	102			
Mild AEs	43			
Moderate AEs	66			
Severe AEs	25			
Discontinued study drug due to AE	66			
Discontinued study drug due to SAE	4			
SAE	49			
AE	134			
Deaths	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Relative change from baseline in forced expiratory volume in one second

(FEV1) percent predicted over 6 treatment cycles

End point title	Relative change from baseline in forced expiratory volume in one second (FEV1) percent predicted over 6 treatment cycles

End point description:

FEV1 was defined as the volume of air expired in 1 second. FEV1 was assessed as a pulmonary function by using spirometry tests in accordance with American Thoracic Society/European Respiratory Society (ATS/ERS) criteria. FEV1% predicted is a normalized value of FEV1 calculated using the Knudsen equation, based upon subject's age, gender and height. Relative change in FEV1 % predicted from baseline to pre-dose day X = ((pre-dose day*FEV1% predicted – baseline FEV1% predicted) / baseline FEV1 % predicted) x 100. The analysis was performed in safety set, defined as subjects who received at least one dose of study drug and had FEV1% values at both baseline and the post baseline time points. The 'n' signifies those subjects evaluable for this measure at specified time points for each group, respectively.

End point type	Secondary

End point timeframe:

Baseline, Day 29, Day 85, Day 141, Day 197, Day 253, Day 309, Day 337. All study visits (except baseline and Day 337) occurred at the end of a 28-day on-treatment period of a cycle

End point values	Tobramycin inhalation powder			
Subject group type	Reporting group			
Number of subjects analysed	157			
Units: Percent FEV1				
arithmetic mean (standard deviation)				
Day 29, Cycle 1 (n=149)	0.8 (± 17.17)			
Day 85, Cycle 2 (n=146)	0 (± 17.09)			
Day 141, Cycle 3 (n=128)	0.2 (± 15.13)			
Day 197, Cycle 4 (n=116)	-0.2 (± 15.36)			
Day 253, Cycle 5 (n=105)	-1.5 (± 17.19)			
Day 309, Cycle 6 (n=100)	-1.9 (± 14.55)			
Day 337, Completion (n=93)	-3.5 (± 16.81)			

Statistical analyses

No statistical analyses for this end point

Secondary: Relative change from baseline in forced vital capacity (FVC) percent predicted over 6 treatment cycles

End point title	Relative change from baseline in forced vital capacity (FVC) percent predicted over 6 treatment cycles

End point description:

FVC was defined as the maximum volume of air exhaled with maximally forced effort from a position of maximal inspiration. FVC was determined from spirometry tests in accordance with ATS/ERS criteria. Relative change in FVC% predicted from baseline to pre-dose day X = ((pre-dose day*FVC% predicted – baseline FVC% predicted / baseline FVC% predicted) x 100. The analysis was performed in safety population, who had FVC values at both baseline and post baseline time points. The 'n' signifies those subjects evaluable for this measure at specified time points for each group, respectively.

End point type	Secondary

End point timeframe:

Baseline, Day 29, Day 85, Day 141, Day 197, Day 253, Day 309, Day 337. All study visits (except baseline and Day 337) occurred at the end of a 28-day on-treatment period of a cycle

End point values	Tobramycin inhalation powder			
Subject group type	Reporting group			
Number of subjects analysed	157			
Units: Percent FVC				
arithmetic mean (standard deviation)				
Day 29, Cycle 1 (n=149)	-2.5 (± 12.95)			
Day 85, Cycle 2 (n=146)	-2.8 (± 12.81)			
Day 141, Cycle 3 (n=128)	-2.1 (± 12.25)			
Day 197, Cycle 4 (n=116)	-1.8 (± 12.64)			
Day 253, Cycle 5 (n=105)	-3.5 (± 13.11)			
Day 309, Cycle 6 (n=100)	-3.1 (± 12.17)			
Day 337, Completion (n=93)	-2.8 (± 13.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Relative change from baseline in forced expiratory flow from 25 to 75% (FEF25-75%) of the forced vital capacity percent predicted over 6 treatment cycles

End point title	Relative change from baseline in forced expiratory flow from 25 to 75% (FEF25-75%) of the forced vital capacity percent predicted over 6 treatment cycles

End point description:

FEF25-75% was defined as the forced expiatory flow from 25% to 75% of the FVC. FEF25-75 was determined from spirometry tests in accordance with ATS/ERS criteria. Relative change in FEF25-75% predicted from baseline to pre-dose day X = ((pre-dose day* FEF25-75% predicted–baseline FEF25-75% predicted) / baseline FEF25-75% predicted) x 100.The analysis was performed in safety population, who had FEF values at both baseline and post baseline time points. The 'n' signifies those subjects evaluable for this measure at specified time points for each group, respectively.

End point type	Secondary

End point timeframe:

Baseline, Day 29, Day 85, Day 141, Day 197, Day 253, Day 309, Day 337. All study visits (except baseline and Day 337) occurred at the end of a 28-day on-treatment period of a cycle

End point values	Tobramycin inhalation powder			
Subject group type	Reporting group			
Number of subjects analysed	157			
Units: Percent FEF				
arithmetic mean (standard deviation)				
Day 29, Cycle 1 (n=149)	10.3 (± 36.05)			
Day 85, Cycle 2 (n=146)	9.4 (± 55.35)			
Day 141, Cycle 3 (n=128)	5.5 (± 31.82)			

Day 197, Cycle 4 (n=116)	6 (± 30.96)			
Day 253, Cycle 5 (n=105)	2.9 (± 33.23)			
Day 309, Cycle 6 (n=100)	4.3 (± 32.44)			
Day 337, Completion (n=93)	0.7 (± 33.78)			

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change from baseline in Pseudomonas aeruginosa density over 6 treatment cycles

End point title	Absolute change from baseline in Pseudomonas aeruginosa density over 6 treatment cycles

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. Absolute 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. The analysis was performed in safety population, who had P. aeruginosa sputum density values at both baseline and the given time point. The 'n' signifies those subjects evaluable for this measure at specified time points for each group, respectively.

End point type	Secondary

End point timeframe:

Baseline, Day 29, Day 85, Day 141, Day 197, Day 253, Day 309, Day 337. All study visits (except baseline and Day 337) occurred at the end of a 28-day on-treatment period of a cycle

End point values	Tobramycin inhalation powder			
Subject group type	Reporting group			
Number of subjects analysed	157			
Units: Base 10 logarithm of CFU (log10 CFU)				
arithmetic mean (standard deviation)				
Day 29, Cycle 1 (n=141)	-1.6 (± 2.28)			
Day 85, Cycle 2 (n=135)	-1.1 (± 1.8)			
Day 141, Cycle 3 (n=119)	-1.2 (± 1.98)			
Day 197, Cycle 4 (n=107)	-1.1 (± 2.11)			
Day 253, Cycle 5 (n=98)	-1.3 (± 2.23)			
Day 309, Cycle 6 (n=89)	-1.2 (± 2.09)			
Day 337, Study completion (n=85)	-0.4 (± 2.08)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in Tobramycin minimum inhibitory concentration (MIC) 50 and MIC 90 values for Pseudomonas aeruginosa

End point title	Change from baseline in Tobramycin minimum inhibitory concentration (MIC) 50 and MIC 90 values for Pseudomonas aeruginosa

End point description:

MIC was defined as the lowest concentration of an antimicrobial agent required to inhibit the visible growth of a microorganism after overnight incubation. Tobramycin MIC 50 and MIC 90 values were defined as the lowest concentration of tobramycin required to inhibit 50% and 90%, respectively, of the P. aeruginosa strains tested (mucoid,dry and small colony variant biotypes). The analysis was performed in safety population, who had microbiological data at specified time points. The 'n' signifies those subjects evaluable for this measure at specified time points for each group, respectively.

End point type	Secondary

End point timeframe:

Baseline, Day 29, Day 85, Day 141, Day 197, Day 253, Day 309, Day 337. All study visits (except baseline and Day 337) occurred at the end of a 28-day on-treatment period of a cycle

End point values	Tobramycin inhalation powder			
Subject group type	Reporting group			
Number of subjects analysed	157			
Units: micrograms/millilitres				
number (not applicable)				
Cycle 1, day 29 - MIC 50 (n=144)	2			
Cycle 2, day 85 - MIC 50 (n=137)	2			
Cycle 3, day 141 - MIC 50 (n=124)	2			
Cycle 4, day 197 - MIC 50 (n=108)	2			
Cycle 5, day 253 - MIC 50 (n=98)	2			
Cycle 6, day 309 - MIC 50 (n=90)	4			
Study completion, day 337 - MIC 50 (n=89)	2			
Cycle 1, day 29 - MIC 90(n=144)	128			
Cycle 2, day 85 - MIC 90 (n=137)	256			
Cycle 3, day 141 - MIC 90 (n=124)	256			
Cycle 4, day 197 - MIC 90 (n=108)	256			
Cycle 5, day 253 - MIC 90 (n=98)	256			
Cycle 6, day 309 - MIC 90 (n=90)	256			
Study completion, day 337 - MIC 90 (n=89)	512			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects hospitalized due to respiratory related serious adverse events (SAEs)

End point title	Percentage of subjects hospitalized due to respiratory related serious adverse events (SAEs)

End point description:

The percentage of the subjects hospitalized due to serious respiratory-related AEs were determined during the study. The analysis was performed in safety population.

End point type	Secondary

End point timeframe:

Baseline, Day 337 (End of the study)

End point values	Tobramycin inhalation powder			
Subject group type	Reporting group			
Number of subjects analysed	157			
Units: Percentage of subjects				
number (not applicable)	26.8			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of hospitalization days due to respiratory related serious adverse events (SAEs)

End point title	Number of hospitalization days due to respiratory related serious adverse events (SAEs)

End point description:

The total number of hospitalization days due to serious respiratory-related adverse events was analyzed using Kaplan-Meier estimate. The analysis was performed in safety population.

End point type	Secondary

End point timeframe:

Baseline, Day 337 (End of the study)

End point values	Tobramycin inhalation powder			
Subject group type	Reporting group			
Number of subjects analysed	157			
Units: Days				
arithmetic mean (standard deviation)	18.1 (± 17.14)			

Statistical analyses

No statistical analyses for this end point

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

events (SAEs)	
End point title	Time to first hospitalization due to respiratory related serious adverse events (SAEs)

End point description:

The day of first hospitalization due to serious respiratory-related adverse events was analyzed using Kaplan Meier estimate. The analysis was performed in safety population.

End point type	Secondary

End point timeframe:

Baseline, Day 337 (End of the study)

End point values	Tobramycin inhalation powder			
Subject group type	Reporting group			
Number of subjects analysed	0[2]			
Units: Days				
median (confidence interval 95%)	(to)			

Notes:

[2] - This outcome measure is not estimable due to low number of occurrence for this parameter

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects who used new anti-pseudomonal antibiotics

End point title	Percentage of subjects who used new anti-pseudomonal antibiotics

End point description:

The rate of anti-pseudomonal antibiotic use was determined from the collection of concomitant medication during the study. The analysis was performed in safety population.

End point type	Secondary

End point timeframe:

Baseline, Day 337 (End of the study)

End point values	Tobramycin inhalation powder			
Subject group type	Reporting group			
Number of subjects analysed	157			
Units: Percentage of subjects				
number (not applicable)	65.6			

Statistical analyses

No statistical analyses for this end point

Secondary: Total number of days of new anti-pseudomonal antibiotics use

End point title	Total number of days of new anti-pseudomonal antibiotics use

End point description:

The total number of days with usage of new anti-pseudomonal antibiotic were determined. The analysis was performed in safety population.

End point type	Secondary

End point timeframe:

Baseline, Day 337 (End of the study)

End point values	Tobramycin inhalation powder			
Subject group type	Reporting group			
Number of subjects analysed	157			
Units: Days				
arithmetic mean (standard deviation)	33.1 (± 25.17)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to use of new anti-pseudomonal antibiotics

End point title	Time to use of new anti-pseudomonal antibiotics

End point description:

Time to first usage of anti-pseudomonal antibiotic was determined using Kaplan Meier estimate. The analysis was performed in safety population.

End point type	Secondary

End point timeframe:

Baseline, Day 337 (End of the study)

End point values	Tobramycin inhalation powder			
Subject group type	Reporting group			
Number of subjects analysed	157			
Units: Days				
median (confidence interval 95%)	136 (97 to 170)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Serious Adverse Events are monitored from date of First Subject First Visit (FSFV) until Last Subject Last Visit (LSLV). All other adverse events are monitored from First Subject First Treatment until Last Subject Last Visit.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	Tobramycin inhalation powder

Reporting group description:

Subjects inhaled four capsules of tobramycin inhalation powder (28 mg) bid via the T326 inhaler device, for 28 days (treatment phase in each cycle). Each treatment phase therefore consisted of 112 mg tobramycin (4 capsules of 28 mg each) with the total daily dose of 224 mg tobramycin (112mg bid). The treatment phase was followed by 28 days of no study treatment (off treatment in each cycle). These 56 days represented 1 cycle of therapy.

Serious adverse events	Tobramycin inhalation powder		
Total subjects affected by serious adverse events			
subjects affected / exposed	49 / 157 (31.21%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Investigations			
Staphylococcus test positive			
subjects affected / exposed	1 / 157 (0.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Rib fracture			
subjects affected / exposed	1 / 157 (0.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Supraventricular tachycardia			
subjects affected / exposed	1 / 157 (0.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Tachyarrhythmia			
subjects affected / exposed	1 / 157 (0.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ear and labyrinth disorders			
Deafness unilateral			
subjects affected / exposed	1 / 157 (0.64%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Tinnitus			
subjects affected / exposed	1 / 157 (0.64%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Gastritis			
subjects affected / exposed	1 / 157 (0.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 157 (0.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pancreatitis			
subjects affected / exposed	1 / 157 (0.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Subileus			
subjects affected / exposed	1 / 157 (0.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Ovarian cyst			

subjects affected / exposed	1 / 157 (0.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Haemoptysis			
subjects affected / exposed	5 / 157 (3.18%)		
occurrences causally related to treatment / all	2 / 5		
deaths causally related to treatment / all	0 / 0		
Bronchospasm			
subjects affected / exposed	1 / 157 (0.64%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumothorax			
subjects affected / exposed	1 / 157 (0.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary embolism			
subjects affected / exposed	1 / 157 (0.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Bronchopneumonia			
subjects affected / exposed	1 / 157 (0.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infective pulmonary exacerbation of cystic fibrosis			
subjects affected / exposed	39 / 157 (24.84%)		
occurrences causally related to treatment / all	1 / 56		
deaths causally related to treatment / all	0 / 0		
Influenza			
subjects affected / exposed	2 / 157 (1.27%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

Pneumonia			
subjects affected / exposed	3 / 157 (1.91%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hyperamylasaemia			
subjects affected / exposed	1 / 157 (0.64%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Tobramycin inhalation powder		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	121 / 157 (77.07%)		
Investigations			
Forced expiratory volume decreased			
subjects affected / exposed	8 / 157 (5.10%)		
occurrences (all)	8		
Nervous system disorders			
Headache			
subjects affected / exposed	11 / 157 (7.01%)		
occurrences (all)	12		
General disorders and administration site conditions			
Chest discomfort			
subjects affected / exposed	9 / 157 (5.73%)		
occurrences (all)	10		
Fatigue			
subjects affected / exposed	9 / 157 (5.73%)		
occurrences (all)	9		
Pyrexia			
subjects affected / exposed	12 / 157 (7.64%)		
occurrences (all)	15		
Gastrointestinal disorders			
Diarrhoea			

subjects affected / exposed	11 / 157 (7.01%)		
occurrences (all)	16		
Nausea			
subjects affected / exposed	8 / 157 (5.10%)		
occurrences (all)	15		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	41 / 157 (26.11%)		
occurrences (all)	69		
Dyspnoea			
subjects affected / exposed	11 / 157 (7.01%)		
occurrences (all)	16		
Haemoptysis			
subjects affected / exposed	33 / 157 (21.02%)		
occurrences (all)	64		
Oropharyngeal pain			
subjects affected / exposed	12 / 157 (7.64%)		
occurrences (all)	12		
Sputum increased			
subjects affected / exposed	16 / 157 (10.19%)		
occurrences (all)	19		
Wheezing			
subjects affected / exposed	8 / 157 (5.10%)		
occurrences (all)	11		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	21 / 157 (13.38%)		
occurrences (all)	31		
Infective pulmonary exacerbation of cystic fibrosis			
subjects affected / exposed	67 / 157 (42.68%)		
occurrences (all)	121		
Upper respiratory tract infection			
subjects affected / exposed	15 / 157 (9.55%)		
occurrences (all)	19		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported