Clinical trial results:
An open-label, crossover, interventional Phase IV study to compare the ease of use of tobramycin inhalation powder with tobramycin inhalation solution and nebulized colistimethate for the treatment of pulmonary Pseudomonas aeruginosa in patients with cystic fibrosis

Due to EudraCT system limitations, which EMA is aware of, results of crossover studies and data using 999 as data points are not accurately represented in this record. Please go to https://www.novctrd.com/CtrdWeb/home.nov for complete trial results

Summary

EudraCT number	2012-001565-33
Trial protocol	GB DE ES IE
Global end of trial date	20 October 2015
Results information	
Result version number	v1 (current)
This version publication date	06 July 2018
First version publication date	06 July 2018

Trial information

Trial identification	
Sponsor protocol code	CTBM100C2403
Additional study identifiers	
ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01844778
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	20 October 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	20 October 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare as a primary indicator for ease of use the mean cumulative time required to set up the delivery device (including preparation of the treatment), administer the drug, and clean the delivery device for TIP administered with the T-326 Inhaler, with the mean cumulative time to perform the same activities (including disinfection of the device, where applicable) for the patient’s usual (pre-study prescribed) inhaled antibiotic treatment for P. aeruginosa.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.
Rescue medication for pulmonary exacerbations was allowed in this study.If a patient experienced a pulmonary exacerbation and/or worsening of the disease condition, he/she was to be treated as deemed appropriate by the investigator.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 August 2013
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	Germany: 19
Country: Number of subjects enrolled	United Kingdom: 25
Country: Number of subjects enrolled	Ireland: 2
Country: Number of subjects enrolled	Spain: 6
Country: Number of subjects enrolled	Switzerland: 8
Worldwide total number of subjects	60
EEA total number of subjects	52

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)	1
Adolescents (12-17 years)	3
Adults (18-64 years)	56
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Each participant was assigned to 1 of 3 treatment arms, TIS/TIP, COLI/TIP, or TIP/TIP with the first treatment cycle based on the participant's usual antibiotic treatment. Then all participants were crossed-over to receive TIP for the second cycle of treatment.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	TIS/TIP

Arm description:

During the first cycle of treatment, participants received nebulized TIS, 300 mg twice per day for 28 days followed by 28 days off-treatment. During the second cycle, participants received TIP 112 mg (four 28 mg capsules) twice per day for 28 days followed by 28 days off-treatment.

Arm type	Active comparator
Investigational medicinal product name	Tobramycin inhalation solution (TIS)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Nebuliser solution
Routes of administration	Inhalation use

Dosage and administration details:

nebulized TIS, 300 mg twice per day for 28 days followed by 28 days off-treatment

Arm title	COLI/TIP

Arm description:

During the first cycle, participants received nebulized COLI, 1 million or 2 million units twice or thrice per day (or the participant\'s usual dose and regimen) for 56 days (no off-treatment period) or 28 days on-treatment followed by 28 days off-treatment (cycling regimen), depending on local treatment guidelines. During the second cycle, participants received TIP 112 mg (four 28 mg capsules) twice per day for 28 days followed by 28 days off-treatment.

Arm type	Active comparator
Investigational medicinal product name	Colistimethate (COLI)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Nebuliser solution
Routes of administration	Inhalation use

Dosage and administration details:

nebulized COLI, 1 million or 2 million units twice or thrice per day (or the participant's usual dose andregimen) for 56 days (no off-treatment period) or 28 days on-treatment followed by 28 days off treatment (cycling regimen), depending on local treatment guidelines

Arm title	TIP/TIP

Arm description:

During the first and second cycles, participants received TIP 112 mg (four 28 mg capsules) twice per day for 28 days followed by 28 days off-treatment.

Arm type	Active comparator

Investigational medicinal product name	Tobramycin inhaltion powder
Investigational medicinal product code	TBM100
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Inhalation use

Dosage and administration details:

112 mg (four 28 mg capsules) twice per day for 28 days followed by 28 days off-treatment.

Number of subjects in period 1	TIS/TIP	COLI/TIP	TIP/TIP
Started	14	28	18
Safety Set 1 (at least 1 dose, cycle 1)	14	28	18
Safety Set 2 (at least 1 dose, cycle 2)	12	25	15
Completed	12	25	14
Not completed	2	3	4
Consent withdrawn by subject	2	-	-
Adverse event, non-fatal	-	2	2
Protocol deviation	-	1	2

Baseline characteristics

Reporting groups	
Reporting group title	TIS/TIP
Reporting group description:	
During the first cycle of treatment, participants received nebulized TIS, 300 mg twice per day for 28 days followed by 28 days off-treatment. During the second cycle, participants received TIP 112 mg (four 28 mg capsules) twice per day for 28 days followed by 28 days off-treatment.	
Reporting group title	COLI/TIP
Reporting group description:	
During the first cycle, participants received nebulized COLI, 1 million or 2 million units twice or thrice per day (or the participant\'s usual dose and regimen) for 56 days (no off-treatment period) or 28 days on-treatment followed by 28 days off-treatment (cycling regimen), depending on local treatment guidelines. During the second cycle, participants received TIP 112 mg (four 28 mg capsules) twice per day for 28 days followed by 28 days off-treatment.	
Reporting group title	TIP/TIP
Reporting group description:	
During the first and second cycles, participants received TIP 112 mg (four 28 mg capsules) twice per day for 28 days followed by 28 days off-treatment.	

Reporting group values	TIS/TIP	COLI/TIP	TIP/TIP
Number of subjects	14	28	18
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	1
Adolescents (12-17 years)	1	1	1
Adults (18-64 years)	13	27	16
From 65-84 years	0	0	0
85 years and over	0	0	0
Age Continuous Units: Years			
arithmetic mean	27.4	28.4	26.6
standard deviation	± 6.82	± 9.86	± 7.25
Gender, Male/Female Units: Participants			
Female	4	10	7
Male	10	18	11

Reporting group values	Total		
Number of subjects	60		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		

Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	1		
Adolescents (12-17 years)	3		
Adults (18-64 years)	56		
From 65-84 years	0		
85 years and over	0		
Age Continuous			
Units: Years			
arithmetic mean			
standard deviation	-		
Gender, Male/Female			
Units: Participants			
Female	21		
Male	39		

End points

End points reporting groups

Reporting group title	TIS/TIP

Reporting group description:

During the first cycle of treatment, participants received nebulized TIS, 300 mg twice per day for 28 days followed by 28 days off-treatment. During the second cycle, participants received TIP 112 mg (four 28 mg capsules) twice per day for 28 days followed by 28 days off-treatment.

Reporting group title	COLI/TIP

Reporting group description:

During the first cycle, participants received nebulized COLI, 1 million or 2 million units twice or thrice per day (or the participant\'s usual dose and regimen) for 56 days (no off-treatment period) or 28 days on-treatment followed by 28 days off-treatment (cycling regimen), depending on local treatment guidelines. During the second cycle, participants received TIP 112 mg (four 28 mg capsules) twice per day for 28 days followed by 28 days off-treatment.

Reporting group title	TIP/TIP

Reporting group description:

During the first and second cycles, participants received TIP 112 mg (four 28 mg capsules) twice per day for 28 days followed by 28 days off-treatment.

Primary: Mean total administration time

End point title	Mean total administration time[1]

End point description:

The mean total time for administration of TIP via T-326 inhaler versus the total time for administration of COLI or TIS was assessed from information entered by participants into an ediary during the last 7 days prior to the last dose of a cycle. The total time included the setup, preparation, administration and cleaning/disinfection time.

End point type	Primary

End point timeframe:

days 22 through 28 (cycle 1), days 78 through 84 (cycle 2)

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: Statistical analysis was not done on the primary outcome measure.

End point values	TIS/TIP	COLI/TIP	TIP/TIP	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	14	28	18	
Units: minutes				
arithmetic mean (standard deviation)				
Cycle 1 (n=8,17,14)	37 (± 22.06)	16.4 (± 9.54)	4.2 (± 2.02)	
Cycle 2 (n=10,16,11)	5 (± 2.04)	3.8 (± 1.7)	3.4 (± 2.06)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change in P. aeruginosa sputum density

End point title	Change in P. aeruginosa sputum density

End point description:

Sputum samples were sent to a central laboratory at the start and end of 2 treatment periods. The absolute change in the number of colony forming units (CFU) of Pseudomonas aeruginosa in sputum = the value of end of on/off treatment period of the cycle minus the pre-dose value at the start of that cycle. A negative change from baseline indicates improvement.

End point type	Secondary

End point timeframe:

days 1, 28 (cycle 1); 57, 84, 112 (cycle 2)

End point values	TIS/TIP	COLI/TIP	TIP/TIP	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	14	28	18	
Units: log10 CFU/mL				
arithmetic mean (standard deviation)				
Cycle 1, on-treatment change (n=11,22,9)	-1.4 (± 1.85)	-0.6 (± 1.88)	-1.7 (± 2.87)	
Cycle 1, off-treatment change (n=10,20,8)	0.2 (± 1.98)	-0.6 (± 2.36)	-0.2 (± 1.56)	
Cycle 2, on-treatment (n=9,16,5)	-0.9 (± 1.66)	-0.5 (± 1.65)	-1.6 (± 1.53)	
Cycle 2, off-treatment (n=9,18,5)	0 (± 0.95)	0.5 (± 2.55)	0 (± 0.91)	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with any contaminated delivery device

End point title	Number of participants with any contaminated delivery device

End point description:

Devices used to administer the drugs (the T-326 inhaler and nebulisers) were swabbed for contamination testing at the start and end of each treatment cycle (or discontinuation visit if the participant withdrew). No assessments were required from the T-326 inhaler when participants started the treatment period (days 1 and 57). Microbial contamination was measured according to device type and the frequency of organism growth (light/ moderate/ heavy). All nebulisers (neb) used by the participants were analyzed, including those for inhaling other medications, like mucolytics.

End point type	Secondary

End point timeframe:

days (d) 1, 28, 57, 84

End point values	TIS/TIP	COLI/TIP	TIP/TIP	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	14	28	18	
Units: Participants				
P. a biotype 2 - dry,d1,neb, moderate,(n=0,0,1)	9999	9999	1	
A. baumannii,d1,neb,heavy,n=0,7,0	9999	1	9999	
A. junii,d1,neb,moderate,n=0,7,0	9999	1	9999	

A.lwoffi,d1,neb,light,n=0,7,0	9999	2	9999	
H. parainfluenza,d1,neb,light,n=0,7,0	9999	1	9999	
O. anthropic,d1,neb,heavy,n=0,7,0	9999	1	9999	
P. fluorescens,d1,neb,light,n=0,7,0	9999	1	9999	
P. putida,d1,neb,light,n=0,7,0	9999	1	9999	
P. stutzeri,d1,neb,moderate,n=0,7,0	9999	1	9999	
S.liquefaciens,d1,neb,light,n=0,7,0	9999	1	9999	
S. multivorum,d1,neb,light,n=0,7,0	9999	1	9999	
S. maltophilia,d1,neb,light,n=0,7,0	9999	1	9999	
Acinetobacter species,d28,neb,light,n=0,6,0	9999	1	9999	
C. indologenes,d28,neb,moderate,n=0,6,0	9999	1	9999	
D. acidovorans,d 28,neb,light,n=0,6,0	9999	1	9999	
P. fluorescens,d28,neb,light,n=0,6,0	9999	2	9999	
S. paucimobilis,d28,neb,heavy,n=0,6,0	9999	1	9999	
S. aureus,d28,neb,light,n=0,6,0	9999	1	9999	
P. a biotype 2 - dry,d57,neb,light,n=1,0,0	1	9999	9999	
S. aureus,d84,T-326,light,n=1,0,0	1	9999	9999	

Statistical analyses

No statistical analyses for this end point

Secondary: Minimum inhibitory concentration (MIC) - MIC50 and MIC90 tobramycin values

End point title	Minimum inhibitory concentration (MIC) - MIC50 and MIC90 tobramycin values

End point description:

MIC50/90 is the lowest concentration required to inhibit 50%/90% of the isolates tested. The MIC50/90 of a range of antibiotics for P.aeruginosa was determined at the start and end of each treatment cycle, and at the end of the off-treatment period of the second cycle.

End point type	Secondary

End point timeframe:

days 1, 28, 57, 84, 112

End point values	TIS/TIP	COLI/TIP	TIP/TIP	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	14	28	18	
Units: ug/mL				
MIC50: Day 1, n=14,27,18; m=27,51,29	2	2	2	
MIC50: Day 28, n=13,23,13; m=25,46,21	2	2	2	
MIC50: Day 57, n=11,19,15; m=23,34,24	4	4	2	
MIC50: Day 84, n=12,17,11; m=25,29,18	4	4	2	

MIC50: Day 112, n=12,19,12; m=24,33,19	2	2	1	
MIC90: Day 1, n=14,27,18; m=27,51,29	256	16	64	
MIC90: Day 28, n=13,23,13; m=25,46,21	256	16	64	
MIC90: Day 57, n=11,19,15; m=23,34,24	64	16	64	
MIC90: Day 84, n=12,17,11; m=25,29,18	512	32	64	
MIC90: Day 112, n=12,19,12; m=24,33,19	32	32	32	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with post-inhalation bronchospasm

End point title	Number of participants with post-inhalation bronchospasm

End point description:

Bronchospasm was defined as the relative decrease of 20% or more in forced expiratory volume in 1 second (FEV1) percent predicted from pre-dose to 15 to 45 minutes post-dose.

End point type	Secondary

End point timeframe:

days 1, 28, 57, 84

End point values	TIS/TIP	COLI/TIP	TIP/TIP	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	14	28	18	
Units: Participants				
Day 1, n=8,17,14	0	1	0	
Day 28, n=6,19,14	0	1	0	
Day 57, n=10,22,13	0	0	1	
Day 84, n=8,14,10	0	0	0	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All adverse events reported in this record are from date of First Patient First Treatment until Last Patient Last Visit.

Adverse event reporting additional description:

AE additional description

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	Cycle 1 TIS/TIP

Reporting group description:

Cycle 1 TIS/TIP

Reporting group title	Cycle 1 COLI/TIP

Reporting group description:

Cycle 1 COLI/TIP

Reporting group title	Cycle 2 COLI/TIP

Reporting group description:

Cycle 2 COLI/TIP

Reporting group title	Cycle 2 TIS/TIP

Reporting group description:

Cycle 2 TIS/TIP

Reporting group title	Cycle 2 TIP/TIP

Reporting group description:

Cycle 2 TIP/TIP

Reporting group title	Cycle 1 TIP/TIP

Reporting group description:

Cycle 1 TIP/TIP

Serious adverse events	Cycle 1 TIS/TIP	Cycle 1 COLI/TIP	Cycle 2 COLI/TIP
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 14 (21.43%)	9 / 28 (32.14%)	3 / 25 (12.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Acoustic stimulation tests abnormal			
subjects affected / exposed	0 / 14 (0.00%)	0 / 28 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Forced expiratory volume decreased			

subjects affected / exposed	0 / 14 (0.00%)	0 / 28 (0.00%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary function test decreased			
subjects affected / exposed	0 / 14 (0.00%)	1 / 28 (3.57%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 14 (0.00%)	0 / 28 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	0 / 14 (0.00%)	0 / 28 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Faecaloma			
subjects affected / exposed	0 / 14 (0.00%)	1 / 28 (3.57%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Bile duct stenosis			
subjects affected / exposed	0 / 14 (0.00%)	1 / 28 (3.57%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Biliary tract disorder			
subjects affected / exposed	0 / 14 (0.00%)	1 / 28 (3.57%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			

subjects affected / exposed	0 / 14 (0.00%)	1 / 28 (3.57%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Haemoptysis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 28 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sputum increased			
subjects affected / exposed	0 / 14 (0.00%)	0 / 28 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Fungal infection			
subjects affected / exposed	0 / 14 (0.00%)	0 / 28 (0.00%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infective pulmonary exacerbation of cystic fibrosis			
subjects affected / exposed	3 / 14 (21.43%)	6 / 28 (21.43%)	3 / 25 (12.00%)
occurrences causally related to treatment / all	0 / 3	0 / 8	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	0 / 14 (0.00%)	0 / 28 (0.00%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection			
subjects affected / exposed	0 / 14 (0.00%)	0 / 28 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinusitis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 28 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Upper respiratory tract infection			
subjects affected / exposed	0 / 14 (0.00%)	0 / 28 (0.00%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Cycle 2 TIS/TIP	Cycle 2 TIP/TIP	Cycle 1 TIP/TIP
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 12 (25.00%)	2 / 15 (13.33%)	3 / 18 (16.67%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Acoustic stimulation tests abnormal			
subjects affected / exposed	0 / 12 (0.00%)	1 / 15 (6.67%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Forced expiratory volume decreased			
subjects affected / exposed	0 / 12 (0.00%)	0 / 15 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary function test decreased			
subjects affected / exposed	0 / 12 (0.00%)	0 / 15 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 15 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	0 / 12 (0.00%)	1 / 15 (6.67%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Faecaloma			

subjects affected / exposed	0 / 12 (0.00%)	0 / 15 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Bile duct stenosis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 15 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Biliary tract disorder			
subjects affected / exposed	0 / 12 (0.00%)	0 / 15 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 15 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Haemoptysis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 15 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sputum increased			
subjects affected / exposed	0 / 12 (0.00%)	1 / 15 (6.67%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Fungal infection			
subjects affected / exposed	0 / 12 (0.00%)	0 / 15 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infective pulmonary exacerbation of cystic fibrosis			

subjects affected / exposed	3 / 12 (25.00%)	0 / 15 (0.00%)	2 / 18 (11.11%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	0 / 12 (0.00%)	0 / 15 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection			
subjects affected / exposed	0 / 12 (0.00%)	1 / 15 (6.67%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinusitis			
subjects affected / exposed	1 / 12 (8.33%)	0 / 15 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	0 / 12 (0.00%)	0 / 15 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Cycle 1 TIS/TIP	Cycle 1 COLI/TIP	Cycle 2 COLI/TIP
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 14 (35.71%)	12 / 28 (42.86%)	7 / 25 (28.00%)
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 14 (0.00%)	0 / 28 (0.00%)	0 / 25 (0.00%)
occurrences (all)	0	0	0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 14 (0.00%)	0 / 28 (0.00%)	0 / 25 (0.00%)
occurrences (all)	0	0	0
Forced expiratory volume decreased			

subjects affected / exposed	0 / 14 (0.00%)	0 / 28 (0.00%)	0 / 25 (0.00%)
occurrences (all)	0	0	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 14 (0.00%)	0 / 28 (0.00%)	0 / 25 (0.00%)
occurrences (all)	0	0	0
Glucose urine present			
subjects affected / exposed	0 / 14 (0.00%)	0 / 28 (0.00%)	0 / 25 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Aphonia			
subjects affected / exposed	0 / 14 (0.00%)	0 / 28 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	2
Dizziness			
subjects affected / exposed	1 / 14 (7.14%)	0 / 28 (0.00%)	0 / 25 (0.00%)
occurrences (all)	1	0	0
Headache			
subjects affected / exposed	1 / 14 (7.14%)	0 / 28 (0.00%)	0 / 25 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 14 (0.00%)	0 / 28 (0.00%)	0 / 25 (0.00%)
occurrences (all)	0	0	0
Non-cardiac chest pain			
subjects affected / exposed	0 / 14 (0.00%)	0 / 28 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1
Pyrexia			
subjects affected / exposed	0 / 14 (0.00%)	0 / 28 (0.00%)	0 / 25 (0.00%)
occurrences (all)	0	0	0
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	0 / 14 (0.00%)	0 / 28 (0.00%)	0 / 25 (0.00%)
occurrences (all)	0	0	0
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 14 (0.00%)	0 / 28 (0.00%)	0 / 25 (0.00%)
occurrences (all)	0	0	0

Seasonal allergy			
subjects affected / exposed	0 / 14 (0.00%)	0 / 28 (0.00%)	0 / 25 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	0 / 14 (0.00%)	1 / 28 (3.57%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Diarrhoea			
subjects affected / exposed	0 / 14 (0.00%)	0 / 28 (0.00%)	0 / 25 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 14 (14.29%)	2 / 28 (7.14%)	0 / 25 (0.00%)
occurrences (all)	2	2	0
Epistaxis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 28 (0.00%)	0 / 25 (0.00%)
occurrences (all)	0	0	0
Haemoptysis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 28 (0.00%)	2 / 25 (8.00%)
occurrences (all)	0	0	2
Oropharyngeal pain			
subjects affected / exposed	0 / 14 (0.00%)	0 / 28 (0.00%)	0 / 25 (0.00%)
occurrences (all)	0	0	0
Prolonged expiration			
subjects affected / exposed	0 / 14 (0.00%)	0 / 28 (0.00%)	0 / 25 (0.00%)
occurrences (all)	0	0	0
Rales			
subjects affected / exposed	0 / 14 (0.00%)	0 / 28 (0.00%)	0 / 25 (0.00%)
occurrences (all)	0	0	0
Respiratory arrest			
subjects affected / exposed	0 / 14 (0.00%)	0 / 28 (0.00%)	0 / 25 (0.00%)
occurrences (all)	0	0	0
Respiratory tract congestion			
subjects affected / exposed	1 / 14 (7.14%)	0 / 28 (0.00%)	0 / 25 (0.00%)
occurrences (all)	1	0	0
Sputum increased			

subjects affected / exposed	1 / 14 (7.14%)	0 / 28 (0.00%)	0 / 25 (0.00%)
occurrences (all)	1	0	0
Wheezing			
subjects affected / exposed	1 / 14 (7.14%)	0 / 28 (0.00%)	1 / 25 (4.00%)
occurrences (all)	1	0	1
Skin and subcutaneous tissue disorders			
Night sweats			
subjects affected / exposed	0 / 14 (0.00%)	0 / 28 (0.00%)	0 / 25 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Insomnia			
subjects affected / exposed	0 / 14 (0.00%)	0 / 28 (0.00%)	0 / 25 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 14 (0.00%)	1 / 28 (3.57%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal pain			
subjects affected / exposed	0 / 14 (0.00%)	0 / 28 (0.00%)	0 / 25 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Cystitis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 28 (0.00%)	0 / 25 (0.00%)
occurrences (all)	0	0	0
Infective pulmonary exacerbation of cystic fibrosis			
subjects affected / exposed	2 / 14 (14.29%)	5 / 28 (17.86%)	6 / 25 (24.00%)
occurrences (all)	2	5	6
Nasopharyngitis			
subjects affected / exposed	0 / 14 (0.00%)	3 / 28 (10.71%)	0 / 25 (0.00%)
occurrences (all)	0	3	0
Tongue fungal infection			
subjects affected / exposed	0 / 14 (0.00%)	0 / 28 (0.00%)	0 / 25 (0.00%)
occurrences (all)	0	0	0
Urinary tract infection			
subjects affected / exposed	0 / 14 (0.00%)	0 / 28 (0.00%)	0 / 25 (0.00%)
occurrences (all)	0	0	0

Vulvovaginal candidiasis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 28 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1
Vulvovaginal mycotic infection			
subjects affected / exposed	0 / 14 (0.00%)	0 / 28 (0.00%)	0 / 25 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	0 / 14 (0.00%)	0 / 28 (0.00%)	0 / 25 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Cycle 2 TIS/TIP	Cycle 2 TIP/TIP	Cycle 1 TIP/TIP
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 12 (50.00%)	10 / 15 (66.67%)	10 / 18 (55.56%)
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 12 (0.00%)	1 / 15 (6.67%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 12 (0.00%)	1 / 15 (6.67%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Forced expiratory volume decreased			
subjects affected / exposed	0 / 12 (0.00%)	0 / 15 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 12 (0.00%)	1 / 15 (6.67%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Glucose urine present			
subjects affected / exposed	1 / 12 (8.33%)	0 / 15 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			
Aphonia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 15 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Dizziness			

subjects affected / exposed	0 / 12 (0.00%)	0 / 15 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Headache			
subjects affected / exposed	0 / 12 (0.00%)	3 / 15 (20.00%)	3 / 18 (16.67%)
occurrences (all)	0	4	10
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 12 (0.00%)	1 / 15 (6.67%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Non-cardiac chest pain			
subjects affected / exposed	1 / 12 (8.33%)	0 / 15 (0.00%)	0 / 18 (0.00%)
occurrences (all)	2	0	0
Pyrexia			
subjects affected / exposed	0 / 12 (0.00%)	1 / 15 (6.67%)	1 / 18 (5.56%)
occurrences (all)	0	1	1
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	0 / 12 (0.00%)	1 / 15 (6.67%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 12 (0.00%)	1 / 15 (6.67%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Seasonal allergy			
subjects affected / exposed	0 / 12 (0.00%)	0 / 15 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	1 / 12 (8.33%)	1 / 15 (6.67%)	0 / 18 (0.00%)
occurrences (all)	1	1	0
Diarrhoea			
subjects affected / exposed	0 / 12 (0.00%)	1 / 15 (6.67%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Cough			

subjects affected / exposed	1 / 12 (8.33%)	2 / 15 (13.33%)	2 / 18 (11.11%)
occurrences (all)	2	2	2
Epistaxis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 15 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Haemoptysis			
subjects affected / exposed	1 / 12 (8.33%)	0 / 15 (0.00%)	2 / 18 (11.11%)
occurrences (all)	1	0	2
Oropharyngeal pain			
subjects affected / exposed	0 / 12 (0.00%)	1 / 15 (6.67%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Prolonged expiration			
subjects affected / exposed	0 / 12 (0.00%)	0 / 15 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Rales			
subjects affected / exposed	0 / 12 (0.00%)	0 / 15 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Respiratory arrest			
subjects affected / exposed	0 / 12 (0.00%)	1 / 15 (6.67%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Respiratory tract congestion			
subjects affected / exposed	0 / 12 (0.00%)	0 / 15 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Sputum increased			
subjects affected / exposed	0 / 12 (0.00%)	2 / 15 (13.33%)	3 / 18 (16.67%)
occurrences (all)	0	2	3
Wheezing			
subjects affected / exposed	1 / 12 (8.33%)	0 / 15 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Skin and subcutaneous tissue disorders			
Night sweats			
subjects affected / exposed	0 / 12 (0.00%)	1 / 15 (6.67%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Psychiatric disorders			
Insomnia			

subjects affected / exposed	0 / 12 (0.00%)	0 / 15 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 12 (0.00%)	0 / 15 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Musculoskeletal pain			
subjects affected / exposed	1 / 12 (8.33%)	0 / 15 (0.00%)	1 / 18 (5.56%)
occurrences (all)	1	0	1
Infections and infestations			
Cystitis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 15 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Infective pulmonary exacerbation of cystic fibrosis			
subjects affected / exposed	1 / 12 (8.33%)	1 / 15 (6.67%)	0 / 18 (0.00%)
occurrences (all)	1	1	0
Nasopharyngitis			
subjects affected / exposed	0 / 12 (0.00%)	3 / 15 (20.00%)	2 / 18 (11.11%)
occurrences (all)	0	3	2
Tongue fungal infection			
subjects affected / exposed	0 / 12 (0.00%)	1 / 15 (6.67%)	1 / 18 (5.56%)
occurrences (all)	0	1	1
Urinary tract infection			
subjects affected / exposed	0 / 12 (0.00%)	0 / 15 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	2
Vulvovaginal candidiasis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 15 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Vulvovaginal mycotic infection			
subjects affected / exposed	0 / 12 (0.00%)	0 / 15 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	0 / 12 (0.00%)	1 / 15 (6.67%)	0 / 18 (0.00%)
occurrences (all)	0	1	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 May 2014	Threshold values for BUN (from ≥5.7 µmol/L to ≥14.28 mmol/L [≥40 mg/dL]) and serum creatinine (≥89 µmol/L to ≥176.8 µmol/L [≥2 mg/dL]) exclusion criteria were corrected for consistency with the Summary of Product Characteristics (SmPC)/ PI and to avoid unnecessary screening failures. The threshold value for serum creatinine in the treatment discontinuation criteria was corrected. The threshold value for BUN in the discontinuation criteria was deleted as not considered medically relevant. Creatinine clearance as an exclusion criterion was deleted due to the threshold value being updated to cover the detection of potential renal AEs. Audiology testing requirements at baseline and/or at the subsequent visits were updated to be in line with the SmPC and PI. They were at the discretion of the investigator. Audiology assessments were not required from a subset of patients at selected sites, but from all patients who had a medical history of hearing loss or who experience AEs related to hearing loss during the study. The wording for the primary objective was updated to clarify that the cumulative times required to a) set up the delivery device (including preparation of the treatment), b) administer the drug and c) clean the device (including disinfecting the nebulizers where applicable) are being compared between the T-326 Inhaler and the nebulizers. The wordings for the study purpose and for one secondary objective were updated to clarify that the testing of the inhalation devices for microbiological contamination relates to all nebulizers used by the patients, including those for inhaling other medications (e.g. mucolytics). Clarified that semi-quantitative culture data for non-P. aeruginosa pathogens was collected and analyzed for this study. Clarified that re-screening of patients was allowed.

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.

Due to EudraCT system limitations, which EMA is aware of, results of crossover studies and data using 999 as data points are not accurately represented in this record. Please go to https://www.novctrd.com/CtrdWeb/home.nov for complete trial results

Notes: