



Clinical trial results:

A 48 week extension to CTBM100C2401, a single arm open-label, multicenter, phase IV trial, to assess long term safety of tobramycin inhalation powder (TIP) in patients with Cystic Fibrosis

Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use <https://www.novctrd.com/CtrdWeb/home.novfor> complete trial results.

Summary

EudraCT number	2012-003532-23
Trial protocol	HU ES IT DE
Global end of trial date	18 November 2014

Results information

Result version number	v1 (current)
This version publication date	07 July 2018
First version publication date	07 July 2018

Trial information

Trial identification

Sponsor protocol code	CTBM100C2401E1
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01775137
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Novartis Pharma AG, Clinical Disclosure Office, +41 613241111,
Scientific contact	Novartis Pharma AG, Clinical Disclosure Office, +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	18 November 2014
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	18 November 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 12 treatment cycles (6 treatment cycles in the core study and 6 treatment cycles in the extension study).

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 follow-up 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	27 February 2013
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	United States: 6
Country: Number of subjects enrolled	Canada: 1
Country: Number of subjects enrolled	Mexico: 5
Country: Number of subjects enrolled	Argentina: 9
Country: Number of subjects enrolled	Australia: 5
Country: Number of subjects enrolled	Spain: 6
Country: Number of subjects enrolled	Germany: 5
Country: Number of subjects enrolled	Hungary: 1
Country: Number of subjects enrolled	Italy: 7
Worldwide total number of subjects	45
EEA total number of subjects	19

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)	2
Adolescents (12-17 years)	10
Adults (18-64 years)	33
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 22 centres in 9 countries.

Pre-assignment

Screening details:

Of 96 subjects who completed the core study (CTBM100C2401), only 45 subjects were enrolled in the extension 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
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Arm description:

Subjects inhaled four capsules of tobramycin inhalation powder (28 mg) twice daily (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 (112 mg 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:

Four capsules of tobramycin inhalation powder (28 mg) bid via the T 326 inhaler device, for 28 days in each treatment phase.

Number of subjects in period 1	Tobramycin inhalation powder
Started	45
Completed	34
Not completed	11
Consent withdrawn by subject	5
Adverse event, non-fatal	1
Death	1
Unsatisfactory therapeutic effect	2
Protocol deviation	2

Baseline characteristics

Reporting groups

Reporting group title	Tobramycin inhalation powder
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Reporting group description:

Subjects inhaled four capsules of tobramycin inhalation powder (28 mg) twice daily (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 (112 mg 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	45	45	
Age categorical			
Units: Subjects			
6-<13 years	2	2	
13-<20 years	11	11	
≥ 20 years	32	32	
Age continuous			
Units: years			
arithmetic mean	24.5		
standard deviation	± 10.79	-	
Gender categorical			
Units: Subjects			
Female	20	20	
Male	25	25	
Pseudomonas aeruginosa tobramycin minimal inhibitory concentration (MIC)			
Units: Subjects			
> 8 microgram/millilitre(ug/mL)	12	12	
≤ 8 ug/mL	33	33	
Forced expiratory volume in one second (FEV1) percent (%) predicted			
Units: percent			
arithmetic mean	52.2		
standard deviation	± 15.01	-	
Forced vital capacity (FVC) % predicted			
Units: percent			
arithmetic mean	73.2		
standard deviation	± 17.49	-	
Forced expiratory flow from 25 to 75 % (FEF2575%) % predicted			
Units: percent			
arithmetic mean	24.7		
standard deviation	± 14.86	-	

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 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 (112 mg 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.	

Primary: Number of subjects with adverse events (AEs), serious adverse events (SAEs), AEs/SAEs leading to discontinuation of study drug and deaths over 12 treatment cycles

End point title	Number of subjects with adverse events (AEs), serious adverse events (SAEs), AEs/SAEs leading to discontinuation of study drug and deaths over 12 treatment cycles ^[1]
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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. A 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. Death was a fatal event leading to permanent cessations of all vital functions of the body. The analysis was performed in extension safety population, defined as all the subjects who entered the extension study and received at least one dose of study drug within the extension.

End point type	Primary
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End point timeframe:

Baseline (start of study treatment in core study) to Day 673 (end of the extension 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	45			
Units: Number of subjects				
AEs	39			
Mild AEs	10			
Moderate AEs	18			
Severe AEs	11			
SAEs	19			
Discontinued study drug due to AEs	2			
Discontinued study drug due to SAEs	1			
Deaths	1			

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 12 treatment cycles

End point title	Relative change from baseline in forced expiratory volume in one second (FEV1) percent predicted over 12 treatment cycles
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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 extension safety population, defined as all the subjects who entered the extension study and received at least one dose of study drug within the extension 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
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End point timeframe:

Baseline (start of study treatment in core study), Day 29, Day 85, Day 141, Day 197, Day 253, Day 309, Day 337, Day 365, Day 421, Day 477, Day 533, Day 589, Day 645, 673 (end of the extension study)

End point values	Tobramycin inhalation powder			
Subject group type	Reporting group			
Number of subjects analysed	45			
Units: Percent FEV1				
arithmetic mean (standard deviation)				
Core cycle 1, Day 29 (n=44)	5 (± 20.36)			
Core cycle 2, day 85 (n=45)	0.8 (± 19.51)			
Core cycle 3, day 141 (n=45)	1.3 (± 15.32)			
Core cycle 4, day 197 (n=44)	0 (± 17.34)			
Core cycle 5, day 253 (n=43)	-0.5 (± 17.91)			
Core cycle 6, day 309 (n=45)	-1.6 (± 14.19)			
Core study completion, (n=43)	-3.1 (± 19.72)			
Extension Cycle 7, day 337(n=44)	-5.2 (± 14.29)			
Extension Cycle 7, day 365(n=44)	-3.7 (± 14.84)			
Extension Cycle 8, day 421(n=41)	-6.1 (± 14.55)			
Extension Cycle 9, day 477(n=42)	-4.8 (± 14.03)			
Extension Cycle 10, day 533(n=39)	-7.5 (± 13.97)			
Extension Cycle 11, day 589(n=38)	-5.4 (± 19.49)			
Extension Cycle 12, day 645(n=35)	-7.5 (± 14.15)			
Extension completion, (n=33)	-9.3 (± 12.76)			

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change from baseline in Pseudomonas aeruginosa sputum density over 12 treatment cycles

End point title	Absolute change from baseline in Pseudomonas aeruginosa sputum density over 12 treatment cycles
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End point description:

Microbiological data was collected to understand the direct impact of the drug on the pathogens. Sputum samples were cultured for the presence of three Pseudomonas aeruginosa (P. aeruginosa) biotypes measured were mucoid, dry and small colony variant. 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 extension 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
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End point timeframe:

Baseline (start of study treatment in core study), Day 29, Day 85, Day 141, Day 197, Day 253, Day 309, Day 337, Day 365, Day 421, Day 477, Day 533, Day 589, Day 645, 673 (end of the extension study)

End point values	Tobramycin inhalation powder			
Subject group type	Reporting group			
Number of subjects analysed	45			
Units: log10 CFU				
arithmetic mean (standard deviation)				
Core cycle 1, Day 29 (n=42)	-1.9 (± 2.83)			
Core cycle 2, day 85 (n=43)	-1.5 (± 1.6)			
Core cycle 3, day 141 (n=44)	-1.4 (± 2)			
Core cycle 4, day 197 (n=41)	-1.2 (± 1.8)			
Core cycle 5, day 253 (n=40)	-2.2 (± 2.26)			
Core cycle 6, day 309 (n=39)	-1.4 (± 2.02)			
Core study completion, (n=42)	-0.7 (± 2.38)			
Extension Cycle 7, day 337(n=40)	-0.7 (± 2.46)			
Extension Cycle 7, day 365(n=41)	-1.4 (± 2.18)			
Extension Cycle 8, day 421(n=41)	-1.1 (± 2.2)			
Extension Cycle 9, day 477(n=39)	-1.1 (± 2.33)			
Extension Cycle 10, day 533(n=35)	-0.8 (± 1.97)			
Extension Cycle 11, day 589(n=36)	-1 (± 2.38)			
Extension Cycle 12, day 645(n=31)	-0.6 (± 1.96)			
Extension completion, (n=29)	-1 (± 2.7)			

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 over 12 treatment cycles

End point title	Change from baseline in Tobramycin minimum inhibitory concentration (MIC) 50 and MIC 90 values for Pseudomonas
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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 (start of study treatment in core study), Day 29, Day 85, Day 141, Day 197, Day 253, Day 309, Day 337, Day 365, Day 421, Day 477, Day 533, Day 589, Day 645, 673 (end of the extension study)

End point values	Tobramycin inhalation powder			
Subject group type	Reporting group			
Number of subjects analysed	45			
Units: micrograms/millilitres (ug/mL)				
number (not applicable)				
Core cycle 1, day 29- MIC 50 (n=41)	2			
Core cycle 2, day 85- MIC 50 (n=40)	2			
Core cycle 3, day 141- MIC 50 (n=43)	2			
Core cycle 4, day 197- MIC 50 (n=40)	2			
Core cycle 5, day 253- MIC 50 (n=36)	2			
Core cycle 6, day 309- MIC 50 (n=37)	2			
Core study completion, Day 337- MIC 50 (n=40)	2			
Extension cycle 7, day 337- MIC 50 (n=38)	2			
Extension cycle 7, day 365- MIC 50 (n=38)	2			
Extension cycle 8, day 421- MIC 50 (n=39)	2			
Extension cycle 9, day 477- MIC 50 (n=39)	4			
Extension cycle 10, day 533- MIC 50 (n=35)	2			
Extension cycle 11, day 589- MIC 50 (n=36)	2			
Extension cycle 12, day 645- MIC 50 (n=32)	2			
Extension completion, Day 673 - MIC 50 (n=29)	2			
Core cycle 1, day 29- MIC 90 (n=41)	256			
Core cycle 2, day 85- MIC 90 (n=40)	256			
Core cycle 3, day 141- MIC 90 (n=43)	512			
Core cycle 4, day 197- MIC 90 (n=40)	128			
Core cycle 5, day 253- MIC 90 (n=36)	256			
Core cycle 6, day 309- MIC 90 (n=37)	512			
Core study completion, Day 337- MIC 90 (n=40)	512			
Extension cycle 7, day 337- MIC 90 (n=38)	512			

Extension cycle 7, day 365- MIC 90 (n=38)	128			
Extension cycle 8, day 421- MIC 90 (n=39)	128			
Extension cycle 9, day 477- MIC 90 (n=39)	512			
Extension cycle 10, day 533- MIC 90 (n=35)	256			
Extension cycle 11, day 589- MIC 90 (n=36)	512			
Extension cycle 12, day 645- MIC 90 (n=32)	512			
Extension completion, Day 673 - MIC 90 (n=29)	512			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects who used new anti-pseudomonal antibiotics over 12 treatment cycles

End point title	Percentage of subjects who used new anti-pseudomonal antibiotics over 12 treatment cycles
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End point description:

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

End point type	Secondary
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End point timeframe:

Baseline of core study, Day 673 (end of the extension study)

End point values	Tobramycin inhalation powder			
Subject group type	Reporting group			
Number of subjects analysed	45			
Units: Percentage of subjects				
number (not applicable)	77.8			

Statistical analyses

No statistical analyses for this end point

Secondary: Total number of days of new anti-pseudomonal antibiotics use over 12 treatment cycles

End point title	Total number of days of new anti-pseudomonal antibiotics use over 12 treatment cycles
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End point description:

The total number of days with usage of new anti-pseudomonal antibiotic were determined. The analysis

was performed in extension safety population. The 'n' signifies those subjects evaluable for this measure at specified time points for each group, respectively.

End point type	Secondary
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End point timeframe:

Baseline of core study, Day 673 (end of the extension study)

End point values	Tobramycin inhalation powder			
Subject group type	Reporting group			
Number of subjects analysed	45			
Units: Days				
median (full range (min-max))				
Overall route (n=35)	59 (15 to 252)			
Oral use (n=31)	42 (11 to 175)			
i.v use (n=25)	32 (7 to 252)			
Inhaled use (n=1)	9 (9 to 9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to use of new anti-pseudomonal antibiotics over 12 treatment cycles

End point title	Time to use of new anti-pseudomonal antibiotics over 12 treatment cycles
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End point description:

Time to first usage of anti-pseudomonal antibiotic was determined using Kaplan Meier estimate. Subjects without an event were censored at the date of the last available post-baseline measurement. The analysis was performed in extension safety population.

End point type	Secondary
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End point timeframe:

Baseline of core study, Day 673 (end of the extension study)

End point values	Tobramycin inhalation powder			
Subject group type	Reporting group			
Number of subjects analysed	45			
Units: Days				
median (confidence interval 95%)	202 (89 to 336)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects hospitalized due to respiratory related serious adverse events (SAEs) over 12 treatment cycles

End point title	Percentage of subjects hospitalized due to respiratory related serious adverse events (SAEs) over 12 treatment cycles
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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 extension safety population.

End point type	Secondary
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End point timeframe:

Baseline of core study, Day 673 (end of the extension study)

End point values	Tobramycin inhalation powder			
Subject group type	Reporting group			
Number of subjects analysed	45			
Units: Percentage of subjects				
number (not applicable)	40			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of hospitalization days due to respiratory related serious adverse events (SAEs) over 12 treatment cycles

End point title	Number of hospitalization days due to respiratory related serious adverse events (SAEs) over 12 treatment cycles
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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 extension safety population.

End point type	Secondary
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End point timeframe:

Baseline of core study, Day 673 (end of the extension study)

End point values	Tobramycin inhalation powder			
Subject group type	Reporting group			
Number of subjects analysed	45			
Units: Days				
median (full range (min-max))	17 (4 to 129)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to first hospitalization due to respiratory related serious adverse events (SAEs) over 12 treatment cycles

End point title	Time to first hospitalization due to respiratory related serious adverse events (SAEs) over 12 treatment cycles
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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 extension safety population. Here, 99999.9 represents not estimable data due to an insufficient number of events.

End point type	Secondary
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End point timeframe:

Baseline of core study, Day 673 (end of the extension study)

End point values	Tobramycin inhalation powder			
Subject group type	Reporting group			
Number of subjects analysed	45			
Units: Days				
median (confidence interval 95%)	99999.9 (99999.9 to 99999.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Acute relative change from pre-dose to 30-minute post-dose in forced expiratory volume in one second (FEV1) percent predicted over 12 treatment cycles

End point title	Acute relative change from pre-dose to 30-minute post-dose in forced expiratory volume in one second (FEV1) percent predicted over 12 treatment cycles
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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. Relative change in FEV1 % predicted was calculated by using the formula = $100 * (30\text{-min post-dose value} - \text{pre-dose value}) / \text{pre-dose value}$. The analysis was performed in extension safety population. The 'n' signifies those subjects evaluable for this measure at specified time points for each group, respectively

End point type	Secondary
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End point timeframe:

Baseline (start of study treatment in core study), Day 29, Day 85, Day 141, Day 197, Day 253, Day 309, Day 337, Day 365, Day 421, Day 477, Day 533, Day 589, Day 645, 673 (end of the extension study)

End point values	Tobramycin inhalation powder			
Subject group type	Reporting group			
Number of subjects analysed	45			
Units: Percent FEV1				
arithmetic mean (standard deviation)				
Core cycle 1, day 1 (n=44)	-4.9 (± 6.72)			
Core cycle 1, day 29 (n=41)	-3.5 (± 4.25)			
Core cycle 2, day 85 (n=39)	-3.5 (± 6.19)			
Core cycle 3, day 141 (n=42)	-2.6 (± 6.06)			
Core cycle 4, day 197 (n=40)	-3.2 (± 5.41)			
Core cycle 5, day 253 (n=41)	-3.8 (± 5.47)			
Core cycle 6, day 309 (n=39)	-2.5 (± 5.94)			
Extension cycle 7, day 365(n=37)	-0.1 (± 7.79)			
Extension cycle 8, day 421(n=36)	-3.7 (± 5.1)			
Extension cycle 9, day 477(n=37)	-3.5 (± 4.78)			
Extension cycle 10, day 533(n=36)	-1 (± 12.54)			
Extension cycle 11, day 589(n=35)	-3.3 (± 6.73)			
Extension cycle 12, day 645(n=30)	-3.1 (± 4.01)			

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 in extension study

End point title	Relative change from baseline in forced expiratory volume in one second (FEV1) percent predicted over 6 treatment cycles in extension study
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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 extension safety population, defined as all the subjects who entered the extension study and received at least one dose of study drug within the extension 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
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End point timeframe:

Baseline (start of study treatment in extension study), Day 365, Day 421, Day 477, Day 533, Day 589, Day 645, 673 (end of the extension study)

End point values	Tobramycin inhalation powder			
Subject group type	Reporting group			
Number of subjects analysed	45			
Units: Percent FEV1				
arithmetic mean (standard deviation)				
Extension Cycle 7, day 365(n=44)	4 (± 16.93)			
Extension Cycle 8, day 421(n=41)	2.4 (± 13.71)			
Extension Cycle 9, day 477(n=42)	2.4 (± 16.18)			
Extension Cycle 10, day 533(n=39)	-1.4 (± 13.75)			
Extension Cycle 11, day 589(n=38)	0.3 (± 14.76)			
Extension Cycle 12, day 645(n=35)	-0.6 (± 13.95)			
Extension completion, (n=33)	-3.5 (± 10.74)			

Statistical analyses

No statistical analyses for this end point

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

End point title	Absolute change from baseline in Pseudomonas aeruginosa density over 6 treatment cycles in extension study
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End point description:

Microbiological data was collected to understand the direct impact of the drug on the pathogens. Sputum samples were cultured for the presence of three Pseudomonas aeruginosa (P. aeruginosa) biotypes measured were mucoid, dry and small colony variant. If no P. aeruginosa was isolated for a visit, log10 colony forming units (CFU) was imputed with log10 (19) for all biotypes. Absolute change was calculated by using the formula = (Value at actual time point - start of extension value). The analysis was performed in extension 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
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End point timeframe:

Baseline (start of study treatment in extension study), Day 365, Day 421, Day 477, Day 533, Day 589, Day 645, 673 (end of the extension study)

End point values	Tobramycin inhalation powder			
Subject group type	Reporting group			
Number of subjects analysed	45			
Units: log10 CFU				
arithmetic mean (standard deviation)				
Extension Cycle 7, day 365(n=41)	-0.7 (± 2.77)			
Extension Cycle 8, day 421(n=41)	-0.2 (± 2.6)			

Extension Cycle 9, day 477(n=39)	-0.2 (± 2.51)			
Extension Cycle 10, day 533(n=35)	0.2 (± 2.89)			
Extension Cycle 11, day 589(n=36)	0 (± 2.49)			
Extension Cycle 12, day 645(n=31)	0.4 (± 2.75)			
Extension completion, (n=29)	0.3 (± 2.48)			

Statistical analyses

No statistical analyses for this end point

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

End point title	Percentage of subjects who used new anti-pseudomonal antibiotics in extension study
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End point description:

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

End point type	Secondary
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End point timeframe:

Baseline of extension study, Day 673 (end of extension study)

End point values	Tobramycin inhalation powder			
Subject group type	Reporting group			
Number of subjects analysed	45			
Units: Percentage of subjects				
number (not applicable)	68.9			

Statistical analyses

No statistical analyses for this end point

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

End point title	Total number of days of new anti-pseudomonal antibiotics use in extension study
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End point description:

The total number of days with usage of new anti-pseudomonal antibiotic were determined. The analysis was performed in extension safety population. The 'n' signifies those subjects evaluable for this measure at specified time points for each group, respectively.

End point type	Secondary
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End point timeframe:

Baseline of extension study, Day 673 (end of extension study)

End point values	Tobramycin inhalation powder			
Subject group type	Reporting group			
Number of subjects analysed	45			
Units: Days				
median (full range (min-max))				
Overall route (n=31)	33 (1 to 252)			
Oral use (n=23)	28 (1 to 44)			
i.v use (n=20)	16 (7 to 252)			
Inhaled use (n=1)	9 (9 to 9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to use of new anti-pseudomonal antibiotics in extension study

End point title	Time to use of new anti-pseudomonal antibiotics in extension study
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End point description:

Time to first usage of anti-pseudomonal antibiotic was determined using Kaplan Meier estimate. Subjects without an event were censored at the date of the last available post-baseline measurement. The analysis was performed in extension safety population.

End point type	Secondary
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End point timeframe:

Baseline of extension study, Day 673 (end of extension study)

End point values	Tobramycin inhalation powder			
Subject group type	Reporting group			
Number of subjects analysed	45			
Units: Days				
median (confidence interval 95%)	139 (86 to 271)			

Statistical analyses

No statistical analyses for this end point

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

End point title	Percentage of subjects hospitalized due to respiratory related serious adverse events (SAEs) in extension study
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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 extension safety population.

End point type	Secondary
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End point timeframe:

Baseline of extension study, Day 673 (end of extension study)

End point values	Tobramycin inhalation powder			
Subject group type	Reporting group			
Number of subjects analysed	45			
Units: Percentage of subjects				
number (not applicable)	35.6			

Statistical analyses

No statistical analyses for this end point

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

End point title	Number of hospitalization days due to respiratory related serious adverse events (SAEs) in extension study
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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 extension safety population.

End point type	Secondary
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End point timeframe:

Baseline of extension study, Day 673 (end of extension study)

End point values	Tobramycin inhalation powder			
Subject group type	Reporting group			
Number of subjects analysed	45			
Units: Days				
median (full range (min-max))	16 (5 to 64)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to first hospitalization due to respiratory related serious adverse events (SAEs) in extension study

End point title	Time to first hospitalization due to respiratory related serious adverse events (SAEs) in extension study
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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 extension safety population.

End point type	Secondary
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End point timeframe:

Baseline of extension study, Day 673 (end of extension 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] - End point is not estimable due to low occurrences of the event

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with adverse events (AEs), serious adverse events (SAEs), AEs/SAEs leading to discontinuation of study drug and deaths over 6 treatment cycles in extension study

End point title	Number of subjects with adverse events (AEs), serious adverse events (SAEs), AEs/SAEs leading to discontinuation of study drug and deaths over 6 treatment cycles in extension study
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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. A 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. Death was a fatal event leading to permanent cessations of all vital functions of the body. The analysis was performed in extension safety population, defined as all the subjects who entered the extension study and received at least one dose of study drug within the extension.

End point type	Secondary
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End point timeframe:

Baseline (start of study treatment in extension study) to Day 673 (end of the extension study)

End point values	Tobramycin inhalation powder			
Subject group type	Reporting group			
Number of subjects analysed	45			
Units: Number of subjects				
AEs	36			
SAEs	16			
Discontinued study drug due to AEs	1			
Discontinued study drug due to SAEs	0			
Deaths	1			

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.

Adverse event reporting additional description:

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

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	17.0
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Reporting groups

Reporting group title	Tobramycin inhalation powder
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Reporting group description:

Subjects inhaled four capsules of tobramycin inhalation powder (28 mg) twice daily (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 (112 mg 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	16 / 45 (35.56%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	0		
Investigations			
Forced expiratory volume decreased			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Haemodynamic instability			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Cardiac failure			

subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiogenic shock			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Syncope			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Distal intestinal obstruction syndrome			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Prostatitis			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea exertional			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Haemoptysis			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory acidosis			

subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory failure			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Infective pulmonary exacerbation of cystic fibrosis			
subjects affected / exposed	14 / 45 (31.11%)		
occurrences causally related to treatment / all	0 / 18		
deaths causally related to treatment / all	0 / 1		
Influenza			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	1 / 45 (2.22%)		
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	32 / 45 (71.11%)		
Investigations			
Forced expiratory volume decreased			
subjects affected / exposed	5 / 45 (11.11%)		
occurrences (all)	6		
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 45 (8.89%)		
occurrences (all)	5		

General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	2 / 45 (4.44%)		
occurrences (all)	3		
Fatigue			
subjects affected / exposed	3 / 45 (6.67%)		
occurrences (all)	3		
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	3 / 45 (6.67%)		
occurrences (all)	3		
Abdominal pain			
subjects affected / exposed	4 / 45 (8.89%)		
occurrences (all)	4		
Vomiting			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Diarrhoea			
subjects affected / exposed	5 / 45 (11.11%)		
occurrences (all)	8		
Respiratory, thoracic and mediastinal disorders			
Sputum increased			
subjects affected / exposed	5 / 45 (11.11%)		
occurrences (all)	9		
Oropharyngeal pain			
subjects affected / exposed	3 / 45 (6.67%)		
occurrences (all)	3		
Rhinorrhoea			
subjects affected / exposed	3 / 45 (6.67%)		
occurrences (all)	3		
Dysphonia			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	2		
Haemoptysis			
subjects affected / exposed	10 / 45 (22.22%)		
occurrences (all)	25		

Cough subjects affected / exposed occurrences (all)	8 / 45 (17.78%) 15		
Infections and infestations			
Sinusitis subjects affected / exposed occurrences (all)	3 / 45 (6.67%) 4		
Nasopharyngitis subjects affected / exposed occurrences (all)	9 / 45 (20.00%) 14		
Infective pulmonary exacerbation of cystic fibrosis subjects affected / exposed occurrences (all)	16 / 45 (35.56%) 21		
Bacterial disease carrier subjects affected / exposed occurrences (all)	3 / 45 (6.67%) 4		
Upper respiratory tract infection subjects affected / exposed occurrences (all)	2 / 45 (4.44%) 2		

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

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, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use https://www.novctrd.com/CtrdWeb/home.nov for complete trial results.

Notes: