Clinical trial results:
An 8 week open-label interventional multicenter study to evaluate the lung clearance index as endpoint for clinical trials in cystic fibrosis patients 6 years of age, chronically infected with Pseudomonas aeruginosa

Summary

EudraCT number	2014-001204-21
Trial protocol	DE
Global end of trial date	10 April 2017

Results information

Result version number	v1 (current)
This version publication date	25 October 2017
First version publication date	25 October 2017

Trial information

Trial identification

Sponsor protocol code	CTBM100CDE02

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02248922
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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	10 April 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	10 April 2017
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to assess the change of LCI after 4 weeks following onset of study drug inhalation versus Baseline.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	27 January 2015
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: 17
Worldwide total number of subjects	17
EEA total number of subjects	17

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)	2
Adults (18-64 years)	14
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

At least 35 patients were planned to be recruited in the study. However, in total, 17 patients entered into the study and completed.
Reason for termination was challenge with enrollment and recruitment. A significant decrease in the eligible patient population was main driver.

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	Tobramycin inhalation solution(TIS)

Arm description:

300mg nebulized Tobramycin (Tobramycin inhalation solution(TIS)) twice a day (BID) 28days on / 28 days off

Arm type	Experimental
Investigational medicinal product name	Tobramycin
Investigational medicinal product code	TBM100
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

Tobramycin inhalation solution(TIS) 300mg nebulized inhalation twice a day 28 days on and 28 days off

Arm title	Tobramycin inhalation powder (TIP)

Arm description:

TOBI Podhaler (Tobramycin inhalation powder(TIP), equivalent dry powder)twice a day (BID) 28days on / 28 days off

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:

Tobramycin inhalation powder (TIP) 112 mg inhalation twice a day 28 days on and 28 days off

Number of subjects in period 1	Tobramycin inhalation solution(TIS)	Tobramycin inhalation powder (TIP)
Started	5	12
Completed	5	12

Baseline characteristics

Reporting groups	
Reporting group title	Tobramycin inhalation solution(TIS)
Reporting group description:	
300mg nebulized Tobramycin (Tobramycin inhalation solution(TIS)) twice a day (BID) 28days on / 28 days off	
Reporting group title	Tobramycin inhalation powder (TIP)
Reporting group description:	
TOBI Podhaler (Tobramycin inhalation powder(TIP), equivalent dry powder)twice a day (BID) 28days on / 28 days off	

Reporting group values	Tobramycin inhalation solution(TIS)	Tobramycin inhalation powder (TIP)	Total
Number of subjects	5	12	17
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)	1	0	1
Adolescents (12-17 years)	1	1	2
Adults (18-64 years)	3	11	14
From 65-84 years	0	0	0
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	20.2	28.9	
standard deviation	± 8.26	± 9.79	-
Gender, Male/Female Units: Subjects			
Female	3	3	6
Male	2	9	11
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	0
White	5	12	17
More than one race	0	0	0
Unknown or Not Reported	0	0	0

Subject analysis sets

Subject analysis set title	Tobramycin ALL
Subject analysis set type	Safety analysis

Subject analysis set description:

300mg nebulized Tobramycin (Tobramycin inhalation solution(TIS)) or TOBI Podhaler (Tobramycin inhalation powder(TIP), equivalent dry powder)twice a day (BID) 28days on / 28 days off

Reporting group values	Tobramycin ALL		
Number of subjects	17		
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)	2		
Adults (18-64 years)	14		
From 65-84 years	0		
85 years and over	0		
Age Continuous Units: years			
arithmetic mean	26.4		
standard deviation	± 9.99		
Gender, Male/Female Units: Subjects			
Female	6		
Male	11		
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0		
Asian	0		
Native Hawaiian or Other Pacific Islander	0		
Black or African American	0		
White	17		
More than one race	0		
Unknown or Not Reported	0		

End points

End points reporting groups

Reporting group title	Tobramycin inhalation solution(TIS)
Reporting group description:	
300mg nebulized Tobramycin (Tobramycin inhalation solution(TIS)) twice a day (BID) 28days on / 28 days off	
Reporting group title	Tobramycin inhalation powder (TIP)
Reporting group description:	
TOBI Podhaler (Tobramycin inhalation powder(TIP), equivalent dry powder)twice a day (BID) 28days on / 28 days off	
Subject analysis set title	Tobramycin ALL
Subject analysis set type	Safety analysis
Subject analysis set description:	
300mg nebulized Tobramycin (Tobramycin inhalation solution(TIS)) or TOBI Podhaler (Tobramycin inhalation powder(TIP), equivalent dry powder)twice a day (BID) 28days on / 28 days off	

Primary: Change from Baseline in Lung Clearance Index (LCI) after 4 weeks following onset of study

End point title	Change from Baseline in Lung Clearance Index (LCI) after 4 weeks following onset of study[1]
End point description:	
The Lung Clearance Index (LCI), measured by Multiple Breath Washout of a tracer gas reflects the obstruction of airways in the lung. A LCI of 7.5 and below is normal. No statistical analysis as there was no comparison and only one reporting group. No statistical analysis as there was no comparison and only one reporting group.	
End point type	Primary
End point timeframe:	
Baseline, week 4	

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: No statistical analysis as there was no comparison and only one reporting group.

End point values	Tobramycin ALL			
Subject group type	Subject analysis set			
Number of subjects analysed	17			
Units: score				
least squares mean (standard error)				
Baseline	17.985 (± 1.1494)			
Week 4	17.101 (± 0.8409)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline of forced expiratory volume at 1 second (FEV1) after 4 weeks following onset of study

End point title	Change from Baseline of forced expiratory volume at 1 second

	(FEV1) after 4 weeks following onset of study
End point description:	
Change of FEV1 (Forced expiry volume in the first second) measured by Spirometry	
End point type	Secondary
End point timeframe:	
Baseline, week 4	

End point values	Tobramycin ALL			
Subject group type	Subject analysis set			
Number of subjects analysed	17			
Units: % Predicted				
least squares mean (standard error)				
Baseline	76.964 (± 4.5121)			
Week 4	77.481 (± 4.9877)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline of colony-forming units (CFU) after 4 weeks following onset of study

End point title	Change from Baseline of colony-forming units (CFU) after 4 weeks following onset of study
End point description:	
Microbacterial density of Pseudomonas aeruginosa in Sputum-Samples in CFU (Colony Forming Units) per gram sputum.	
End point type	Secondary
End point timeframe:	
Baseline, week 4	

End point values	Tobramycin ALL			
Subject group type	Subject analysis set			
Number of subjects analysed	17			
Units: 1/mL				
least squares mean (standard error)				
Baseline n=15	56594.3 (± 28018.89)			
Week 4 n=10	26113.0 (± 27280.98)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Lung Clearance Index (LCI) after 1 week

End point title	Change from Baseline in Lung Clearance Index (LCI) after 1 week

End point description:

The Lung Clearance Index (LCI), measured by Multiple Breath Washout of a tracer gas reflects the obstruction of airways in the lung. A LCI of 7.5 and below is normal,

End point type	Secondary

End point timeframe:

Baseline, week 1

End point values	Tobramycin ALL			
Subject group type	Subject analysis set			
Number of subjects analysed	17			
Units: score				
least squares mean (standard error)				
Baseline	17.985 (± 1.1494)			
Week 1	17.506 (± 1.0002)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change of Lung Clearance Index (LCI) between week 4 (end of study drug inhalation in the current treatment cycle) and week 8 (prior to start of study drug inhalation in the following treatment cycle)

End point title	Change of Lung Clearance Index (LCI) between week 4 (end of study drug inhalation in the current treatment cycle) and week 8 (prior to start of study drug inhalation in the following treatment cycle)

End point description:

The Lung Clearance Index (LCI), measured by Multiple Breath Washout of a tracer gas reflects the obstruction of airways in the lung. A LCI of 7.5 and below is normal,

End point type	Secondary

End point timeframe:

week 4, week 8

End point values	Tobramycin ALL			
Subject group type	Subject analysis set			
Number of subjects analysed	17			
Units: score				
least squares mean (standard error)				
Week 4	17.101 (± 0.8409)			
Week 8	16.489 (± 1.1473)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change of forced expiratory volume at 1 second(FEV1) between week 4 (end of study drug inhalation in the current treatment cycle) and week 8 (prior to start of study drug inhalation in the following treatment cycle)

End point title	Change of forced expiratory volume at 1 second(FEV1) between week 4 (end of study drug inhalation in the current treatment cycle) and week 8 (prior to start of study drug inhalation in the following treatment cycle)

End point description:

Change of FEV1 (Forced expiry volume in the first second) measured by Spirometry

End point type	Secondary

End point timeframe:

week 4, week 8

End point values	Tobramycin ALL			
Subject group type	Subject analysis set			
Number of subjects analysed	17			
Units: % Predicted				
least squares mean (standard error)				
Week 4	77.481 (± 4.9877)			
Week 8	78.705 (± 5.4782)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change of colony-forming units (CFU) between week 4 (end of study drug inhalation in the current treatment cycle) and week 8 (prior to start of study drug inhalation in the following treatment cycle)

End point title	Change of colony-forming units (CFU) between week 4 (end of study drug inhalation in the current treatment cycle) and week

	8 (prior to start of study drug inhalation in the following treatment cycle)

End point description:

Microbacterial density of Pseudomonas aeruginosa in Sputum-Samples in CFU (Colony Forming Units) per gram sputum.

End point type	Secondary

End point timeframe:

week 4, week 8

End point values	Tobramycin ALL			
Subject group type	Subject analysis set			
Number of subjects analysed	17			
Units: 1/mL				
least squares mean (standard error)				
Week 4 n=10	26113.0 (± 27280.98)			
Week 8 n=15	56285.0 (± 28022.28)			

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

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	Tobramycin@Inhalation@Solution
Reporting group description: Tobramycin@Inhalation@Solution	
Reporting group title	Tobramycin@Inhalation@Powder
Reporting group description: Tobramycin@Inhalation@Powder	

Serious adverse events	Tobramycin@Inhalation@Solution	Tobramycin@Inhalation@Powder	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 5 (0.00%)	0 / 12 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	Tobramycin@Inhalation@Solution	Tobramycin@Inhalation@Powder	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 5 (40.00%)	3 / 12 (25.00%)	
Investigations			
Forced expiratory volume decreased			
subjects affected / exposed	0 / 5 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Sunburn			
subjects affected / exposed	1 / 5 (20.00%)	0 / 12 (0.00%)	
occurrences (all)	1	0	

Gastrointestinal disorders Abdominal pain upper subjects affected / exposed occurrences (all)	 0 / 5 (0.00%) 0	 1 / 12 (8.33%) 1	
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Haemoptysis subjects affected / exposed occurrences (all) Obstructive airways disorder subjects affected / exposed occurrences (all)	 0 / 5 (0.00%) 0 1 / 5 (20.00%) 1 0 / 5 (0.00%) 0	 1 / 12 (8.33%) 1 0 / 12 (0.00%) 0 1 / 12 (8.33%) 1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 May 2015	Amendment 1: The rationale for changes in protocol amendment 1 were as follows: 1. To clarify the LCI assessment, and to align the protocol with the standard assessment approach for LCI of the device manufacturer. The revised section 7.4.1 reflects now the workflow implemented in the Exhalyzer D device by the actual "Spiroware" software version. Following Investigator-feedback, the upper limit for the FRC coefficient of variation had been increased from 10% to 25% to help reducing the number of MBW measurements needed in pediatric CF patients with moderate lung disease. In addition, this change allowed for the documentation of values for LCI and FRC which had been automatically calculated by the device-software. A more detailed and step-by-step description for the LCI assessment made it easier for the study team to follow the protocol. 2. To add the change of pulmonary air trapping after 1 week, 4 weeks, and 8 weeks versus baseline to the protocol as an explorative objective. Air trapping was assessed by the difference in FRC measured by bodyplethysmography (FRCples) and FRC measured by MBW (FRCMBW). In this study, spirometry was done by bodyplethysmography. Thus,FRCples was already documented in the source documents. Beneficial effects of treatment with inhaled tobramycin could include a reduction of air trapping by recruitment of lung units previously not contributing to ventilation. If the time constant in newly recruited units was slower, ventilation inhomogeneity, and therefore LCI, could increase despite the positive treatment effect 3. Following feedback of investigators, the guidance for the spirometric timeframe had been updated to allow for a more flexible assessment planning.
03 August 2015	Amendment 2: The rationale for changes in protocol amendment 2 was to allow for a more clear and detailed documentation of screening failures with a following re-screening of the patient. In order to limit eCRF page numbers per patient and to optimize the database structure and thus the usability of the data capturing system, a change of the individual number for patients who were re-screened were permitted. Furthermore, the change of patient no. in re-screened patients allowed for a unique and well matched visit numbering in the data capturing and the study management system.

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.

Reason for termination was challenge with enrollment and recruitment. A significant decrease in the eligible patient population was main driver.

Notes: