Clinical trial results:
Prospective phase IIA multicenter double-blinded randomized placebo-controlled clinical trial evaluating the efficacy and safety of inhaled, aerosolized Tobramycin (TOBI®) b.i.d. in patients with ventilator-associated pneumonia (VAP)

Summary

EudraCT number	2012-003621-21
Trial protocol	DE
Global end of trial date	30 July 2019

Results information

Result version number	v1 (current)
This version publication date	03 April 2022
First version publication date	03 April 2022

Trial information

Trial identification

Sponsor protocol code	CTBM100DDE04T

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Charité University Hospital Berlin
Sponsor organisation address	Charité University Hospital Berlin, Berlin, Germany, 10177
Public contact	Dr. Stefan Angermair, Charité -Campus Benjamin Franklin, Department of Anesthesiology and surgical intensive care medicin, 49 30450551585, stefan.angermair@charite.de
Scientific contact	Dr. Carsten Schwarz, Charité - Campus Mitte, Department of Internal Medicine with a focus on infectiology and pneumology, 49 30450556552, carsten.schwarz@charite.de

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	30 July 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	14 May 2019
Global end of trial reached?	Yes
Global end of trial date	30 July 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective is the reduction and eradication of the endobronchial gram-negative bacteria in the pulmonal system, assessed as eradication of the pathogen at day 6 measured by the decrease in gram-negative pathogen-load in pulmonary infiltrate (either by gram-staining of the pathogen, by measurement of copies of DNA per ml in end-point PCR analysis or by kinetic laser measurement of turbidity increase of particles).

Protection of trial subjects:

The safety of the therapy with TOBI or aerosolized sodium chlorid solution was assessed each day of the sty by physical examination, vital signs, laboratory test and evaluation of adverse events. Furthermore, the patients were monitored for spontaneous complaints after treatments.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 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: 27
Worldwide total number of subjects	27
EEA total number of subjects	27

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)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	9
From 65 to 84 years	18

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 5 study centers at 3 Campi of Charité in Berlin, between 10 February 2014 and 14 May 2019. Each patient fulfilling inclusion criteria (with VAP, between 18-85 ages, treated < 48 h with standard therapy before diagnosis VAP, gram-negativity diagnose within 24 h...) after given written consent by him/legal representative.

Pre-assignment

Screening details:

The originally planned sample size was 90 subjects (45 per treatment group; estimated drop-out rate 10%). After the approved amendment a total of 28 patients suffering from VAP were enrolled. 27 subjects were randomized. Consent withdraw by subject: 1 in the control group.

Period 1

Period 1 title	overall period
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Carer, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	Standard therapy +TOBI

Arm description:

Subjects received a systemic antibiotic standard care therapy (i.e. intravenous penicillin, cephalosporine, carbapenem, chinolone or aminoglycosides) and 300 mg (5ml) inhalative of tobramycin twice daily for 5 days on day 0,1,2,3 and 4 (visit 1-5). The inhalation did not take longer 15 minutes. There were 3 follow-up dates (visit 6-8) . The final investigation was at day of discharge of the patient from ICU (visit 9, at maximum 90 day from enrollment)

Arm type	Experimental
Investigational medicinal product name	Tobramycin
Investigational medicinal product code	32986-56-4
Other name	TOBI
Pharmaceutical forms	Nebuliser solution
Routes of administration	Inhalation use

Dosage and administration details:

Subjects received 300 mg (5ml) tobramycin twice daily for 5 days at Visit (1-5). The inhalation did not take longer than 15 minutes.

Arm title	Standard therapy + Placebo

Arm description:

Subjects received a systemic antibiotic standard care therapy (i.e. intravenous penicillin, cephalosporine, carbapenem, chinolone or aminoglycosides) and 5ml of aerosolized 0,9 % sodium chlorid solution twice daily for 5 days on day 0,1,2,3 and 4 (visit 1-5). The inhalation did not take longer 15 minutes.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Nebuliser solution
Routes of administration	Inhalation use

Dosage and administration details:

Subjects received placebo matched to tobramycin, twice daily for 5 days (Visit 1-5). The inhalation did not take longer than 15 minutes.

Number of subjects in period 1	Standard therapy +TOBI	Standard therapy + Placebo
Started	14	13
Completed	14	12
Not completed	0	1
Adverse event, serious fatal	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Standard therapy +TOBI

Reporting group description:

Subjects received a systemic antibiotic standard care therapy (i.e. intravenous penicillin, cephalosporine, carbapenem, chinolone or aminoglycosides) and 300 mg (5ml) inhalative of tobramycin twice daily for 5 days on day 0,1,2,3 and 4 (visit 1-5). The inhalation did not take longer 15 minutes. There were 3 follow-up dates (visit 6-8) . The final investigation was at day of discharge of the patient from ICU (visit 9, at maximum 90 day from enrollment)

Reporting group title	Standard therapy + Placebo

Reporting group description:

Subjects received a systemic antibiotic standard care therapy (i.e. intravenous penicillin, cephalosporine, carbapenem, chinolone or aminoglycosides) and 5ml of aerosolized 0,9 % sodium chlorid solution twice daily for 5 days on day 0,1,2,3 and 4 (visit 1-5). The inhalation did not take longer 15 minutes.

Reporting group values	Standard therapy +TOBI	Standard therapy + Placebo	Total
Number of subjects	14	13	27
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	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	0	0	0
From 65-84 years	6	5	11
85 years and over	8	8	16
Age continuous Units: years			
arithmetic mean	63.6	62.9	
standard deviation	± 14	± 10.8	-
Gender categorical Units: Subjects			
Female	5	5	10
Male	9	8	17
BMI Units: Kg/m2			
arithmetic mean	26.0	26.0	
standard deviation	± 4.3	± 6.3	-

End points

End points reporting groups

Reporting group title	Standard therapy +TOBI

Reporting group description:

Subjects received a systemic antibiotic standard care therapy (i.e. intravenous penicillin, cephalosporine, carbapenem, chinolone or aminoglycosides) and 300 mg (5ml) inhalative of tobramycin twice daily for 5 days on day 0,1,2,3 and 4 (visit 1-5). The inhalation did not take longer 15 minutes. There were 3 follow-up dates (visit 6-8) . The final investigation was at day of discharge of the patient from ICU (visit 9, at maximum 90 day from enrollment)

Reporting group title	Standard therapy + Placebo

Reporting group description:

Subjects received a systemic antibiotic standard care therapy (i.e. intravenous penicillin, cephalosporine, carbapenem, chinolone or aminoglycosides) and 5ml of aerosolized 0,9 % sodium chlorid solution twice daily for 5 days on day 0,1,2,3 and 4 (visit 1-5). The inhalation did not take longer 15 minutes.

Primary: change eradication of gram-negative pathogens

End point title	change eradication of gram-negative pathogens

End point description:

End point type	Primary

End point timeframe:

from visit 1 up to visit 9

End point values	Standard therapy +TOBI	Standard therapy + Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	12		
Units: patients				
number (not applicable)	14	3		

Statistical analyses

Statistical analysis title	Sensitivity Analysis

Statistical analysis description:

Per protocol analysis
p value was derived via Boschloo-test.
Due to almost perfect separation Firth logistic regression was used
for calculation of the Odds ratio and the 95% confidence interval.

Comparison groups	Standard therapy +TOBI v Standard therapy + Placebo

Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.00003
Method	Boschloo' Exact Test
Parameter estimate	Odds ratio (OR)
Point estimate	4.36
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.97
upper limit	9.32

Secondary: Length of stay in ICU

End point title	Length of stay in ICU

End point description:

End point type	Secondary

End point timeframe:
from visit 1 up to visit 9 (max .90 days)

End point values	Standard therapy +TOBI	Standard therapy + Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	6		
Units: days				
arithmetic mean (standard deviation)	15.7 (± 12.1)	15.8 (± 10.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mortality

End point title	Mortality

End point description:

End point type	Secondary

End point timeframe:
at final visit

End point values	Standard therapy +TOBI	Standard therapy + Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	13		
Units: patients have died				
number (not applicable)				
PP	1	1		
FAS	1	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical cure of pneumonia

End point title	Clinical cure of pneumonia

End point description:

End point type	Secondary

End point timeframe:

From Visit 1 up to Visit 9

End point values	Standard therapy +TOBI	Standard therapy + Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14[1]	13[2]		
Units: number of YES				
V1	0	1		
V2	0	1		
V3	5	2		
V4	10	6		
V5	10	6		
V6	10	7		
V7	8	8		
V8	3	4		
V9	11	8		

Notes:

[1] - for FAS

[2] - for FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of systematic antibiotic treatment for pneumonia

End point title	Duration of systematic antibiotic treatment for pneumonia

End point description: FAS: total n= 13; 7.3 +/- 2.3 days	
End point type	Secondary
End point timeframe: at final visit	

End point values	Standard therapy +TOBI	Standard therapy + Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	6		
Units: days				
arithmetic mean (standard deviation)	8.1 (± 2.0)	6.3 (± 2.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Systemic antibiotic-free days

End point title	Systemic antibiotic-free days
End point description: After the inclusion of the patient into the study	
End point type	Secondary
End point timeframe: at final visit	

End point values	Standard therapy +TOBI	Standard therapy + Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	5		
Units: days				
arithmetic mean (standard deviation)	6.2 (± 6.1)	5.2 (± 5.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of ventilation of pneumonia

End point title	Duration of ventilation of pneumonia
End point description:	

End point type	Secondary

End point timeframe:
at final visit

End point values	Standard therapy +TOBI	Standard therapy + Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	13		
Units: days				
arithmetic mean (standard error)	9.1 (± 5.5)	7.6 (± 3.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Ventilator-free days

End point title	Ventilator-free days

End point description:

End point type	Secondary

End point timeframe:
at day of discharge from ICU

End point values	Standard therapy +TOBI	Standard therapy + Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	6		
Units: days				
arithmetic mean (standard error)	6.7 (± 6.9)	7.0 (± 7.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Reinfection of pneumonia caused by the same pathogen

End point title	Reinfection of pneumonia caused by the same pathogen

End point description:

End point type	Secondary

End point timeframe:
at discharge from ICU

End point values	Standard therapy +TOBI	Standard therapy + Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	8		
Units: number of patients	0	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: from visit 1 up to visit 9 or discharge from the ICU	
Assessment type	Systematic

Dictionary used	
Dictionary name	own
Dictionary version	1

Reporting groups	
Reporting group title	Treatment group
Reporting group description: -	
Reporting group title	Control group
Reporting group description: -	

Serious adverse events	Treatment group	Control group	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 14 (14.29%)	2 / 13 (15.38%)	
number of deaths (all causes)	1	2	
number of deaths resulting from adverse events	1	2	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	1 / 14 (7.14%)	0 / 13 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
tension pneumothorax left side			
subjects affected / exposed	1 / 14 (7.14%)	0 / 13 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Septic shock			
subjects affected / exposed	0 / 14 (0.00%)	2 / 13 (15.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	

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

Non-serious adverse events	Treatment group	Control group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 14 (71.43%)	5 / 13 (38.46%)	
Respiratory, thoracic and mediastinal disorders			
residual pneumothorax left side			
subjects affected / exposed	2 / 14 (14.29%)	0 / 13 (0.00%)	
occurrences (all)	2	0	
Musculoskeletal and connective tissue disorders			
swelling left arm			
subjects affected / exposed	1 / 14 (7.14%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Fever > 38.5 Celsius			
subjects affected / exposed	7 / 14 (50.00%)	5 / 13 (38.46%)	
occurrences (all)	18	19	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 December 2014	Reduction of planned subjects ends based on new findings of the effectiveness of tobramycin, new study protocol V1.2
22 November 2016	Extension of study duration to 3 years an d 9 months
24 April 2019	Extension of study duration to 6 years an 4 months

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported