Clinical trial results:
Randomized, blinded phase III clinical trial on the use of inhaled tobramycin compared to placebo in mechanically ventilated patients colonized by Gram-negative bacteria to test its efficacy in reducing mechanical ventilation time.

Summary

EudraCT number	2015-001109-15
Trial protocol	ES
Global end of trial date	18 February 2020

Results information

Result version number	v1 (current)
This version publication date	04 February 2022
First version publication date	04 February 2022

Trial information

Trial identification

Sponsor protocol code	BIOTOB

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Instituto de Investigaión Sanitaria La Fe de Valencia
Sponsor organisation address	Avenida Fernando Abril Martorell, Torre 106 A 7 planta , Valencia, Spain, 46026
Public contact	Jose María Millan Salvador, Instituo de Investigación Sanitaria La Fe, Instituto de Investigación Sanitaria La Fe (IIS La Fe), 34 961246611, investigacion_clinica@iislafe.es
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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	11 August 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	18 February 2020
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To reduce by 10% the duration of mechanical ventilation in patients treated with inhaled tobramycin compared to patients treated with placebo.

Protection of trial subjects:

The reference study was conducted in Spain under the legal framework of Royal Decree 1090/2015. It has been performed in accordance with the Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects, adopted by the General Assembly of the World Medical Association (1996). In addition, the study has been conducted in accordance with the protocol, good clinical practice (GCP) in accordance with the guidelines of the international conference on harmonization (ICH) and regulatory requirements for participating institutions.

An appropriately performed informed consent has been used, in compliance with GCP according to ICH guidelines and approved by the CEIm of the Hospital Universitario y Politécnico La Fe. Prior to inclusion of subjects in the study, a copy of the CEIm-approved informed consent has been reviewed with the prospective participant, signed and dated. The investigator has provided a copy of each subject's signed informed consent form and has retained a copy in the subject's study file.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	11 October 2017
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	Spain: 93
Worldwide total number of subjects	93
EEA total number of subjects	93

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	93
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients over 18 years of age, admitted to the ICU, subjected to mechanical ventilation and carriers of artificial airway (endotracheal tube or tracheostomy) for at least 7 days, with persistent respiratory colonization of the airway by Gram-negative bacteria, presenting abundant and purulent bronchorrhea.

Pre-assignment

Screening details:

Scales APACHE II & SOFA, systemic antibiotherapy, use invasive devices, development nosocomial infections. Complete blood analysis, determination of C-reactive protein & procalcitonin. Arterial blood gas analysis. Chest X-ray. Mini-bronchoalveolar lavage (miniBAL) and bronchoaspirate (BAS) for quantitative microbiological culture.

Pre-assignment period milestones

Number of subjects started	93
Number of subjects completed	5

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Physician decision: 88

Period 1

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

Blinding implementation details:

Patients are randomly assigned to receive one of the two treatments, in a 1:1 ratio. The randomization list is generated by a computer program equipped with a random number generator. The randomization codes are inserted into consecutively numbered envelopes which are kept sealed until the time of allocation. If, due to the occurrence of a serious adverse event or accidentally, the code is broken, the incident is noted in the data collection notebook and the sponsor is notified immediately.

Arms

Are arms mutually exclusive?	Yes
Arm title	Experimental treatment

Arm description:

Tobramycin 300 mg/5 ml inhaled every 12h.

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

Dosage and administration details:

300 mg/5 ml inhaled every 12h.

Arm title	Control treatment

Arm description:

Physiological saline 0.9% 5 ml inhaled every 12h

Arm type	Active comparator

Investigational medicinal product name	Physiological saline
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

0.9% 5 ml inhaled every 12h.

Number of subjects in period 1[1]	Experimental treatment	Control treatment
Started	2	3
Completed	1	0
Not completed	1	3
Physician decision	1	3

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Of the 93 patients selected, 88 were selection failures and only 5 were recruited.
Of the 5 recruited, only 1 completed the study, the rest (4) were withdrawn.

Baseline characteristics

Reporting groups

Reporting group title	Treatment assignment

Reporting group description: -

Reporting group values	Treatment assignment	Total	
Number of subjects	5	5	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Adults from 18-85	5	5	
Age continuous Units: years			
median	0		
standard deviation	± 0	-	
Gender categorical Units: Subjects			
Female	3	3	
Male	2	2	

Subject analysis sets

Subject analysis set title	FULL ANALYSIS
Subject analysis set type	Full analysis

Subject analysis set description:

Of the 93 patients selected, 88 were selection failures and only 5 were recruited.
Of the 5 recruited: only 1 completed the study, the rest (4) were withdrawn.
With the sample size of only one patient, it was not possible to perform the statistical analyses reflected in the protocol. Therefore, it was not possible to determine a subgroup of patients who meet the study hypotheses.

Reporting group values	FULL ANALYSIS		
Number of subjects	1		
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)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	0		
From 65-84 years	0		
85 years and over	0		
Adults from 18-85	1		
Age continuous			
Units: years			
median	0		
standard deviation	± 0		
Gender categorical			
Units: Subjects			
Female	1		
Male	0		

End points

End points reporting groups

Reporting group title	Experimental treatment
Reporting group description:	
Tobramycin 300 mg/5 ml inhaled every 12h.	
Reporting group title	Control treatment
Reporting group description:	
Physiological saline 0.9% 5 ml inhaled every 12h	
Subject analysis set title	FULL ANALYSIS
Subject analysis set type	Full analysis
Subject analysis set description:	
Of the 93 patients selected, 88 were selection failures and only 5 were recruited. Of the 5 recruited: only 1 completed the study, the rest (4) were withdrawn. With the sample size of only one patient, it was not possible to perform the statistical analyses reflected in the protocol. Therefore, it was not possible to determine a subgroup of patients who meet the study hypotheses.	

Primary: 10% reduction in mechanical ventilation time in patients treated with inhaled tobramycin compared to patients treated with placebo

End point title	10% reduction in mechanical ventilation time in patients treated with inhaled tobramycin compared to patients treated with placebo[1]
End point description:	
End point type	Primary
End point timeframe:	
Treatment ends on day 8 or at the time of withdrawal of mechanical ventilation (if earlier).	

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: With the sample size finally collected of only one patient, it was not possible to perform the statistical analyses reflected in the protocol. Therefore, it was not possible to determine in any way a subgroup of patients who meet the study hypotheses.

End point values	Experimental treatment	Control treatment	FULL ANALYSIS	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	0[2]	0[3]	0[4]	
Units: Time of mechanical ventilation				

Notes:

[2] - Only one patient completed the study so no data were obtained.

[3] - Only one patient completed the study so no data were obtained.

[4] - Only one patient completed the study so no data were obtained.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

Serious adverse events are reported to the sponsor within 24 hours of becoming aware of the event.

Adverse event reporting additional description:

The investigator follows up on the serious adverse event and notifies the sponsor when the severity/delay or causality changes. A safety assessment form is used to report serious adverse events.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.1

Reporting groups

Reporting group title	Experimental treatment

Reporting group description:

Patients treated with Tobramycin

Reporting group title	Control treatment

Reporting group description: -

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: Only one person completed the study procedures, so no non-serious adverse events have been reported.

Serious adverse events	Experimental treatment	Control treatment	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 3 (33.33%)	0 / 2 (0.00%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events	1	0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	1 / 3 (33.33%)	0 / 2 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	

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

Non-serious adverse events	Experimental treatment	Control treatment	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 March 2018	Changes are made to the CRD and the HIP, eliminating an exclusion criterion and adding a secondary objective. The following text is included in the protocol: "Diagnosis and main inclusion and exclusion criteria: patients over 18 years of age, admitted to the ICU, subjected to mechanical ventilation and carriers of artificial airway (endotracheal tube or tracheostomy) for at least 7 days, with persistent respiratory colonization of the airway by large negative bacteria (regardless of the pattern of antimicrobial resistance), presenting abundant and purulent bronchorrhea that may interfere with the patient's respiratory process, without criteria of respiratory infection associated with mechanical ventilation, will be included in the study. Patients with allergy to aminoglycosides, renal insufficiency or use of renal replacement therapy, pregnant or breastfeeding women, and patients with bronchiectasis or cystic fibrosis will be excluded. The secondary objective is added: To evaluate the effect of inhaled tobramycin on the eradication of gram-negative bacteria that at the time of inclusion in the study are resistant to tobramycin."

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported