Clinical trial results:
Pseudomonas aeruginosa eradication in patients with cystic fibrosis: a randomised multicentre study comparing classic treatment protocols with classic treatment together with antibiotic treatment of upper airways.

Summary

EudraCT number	2015-003881-96
Trial protocol	IT
Global end of trial date	08 January 2019

Results information

Result version number	v1 (current)
This version publication date	04 August 2021
First version publication date	04 August 2021

Trial information

Trial identification

Sponsor protocol code	EPAFC

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	AZIENDA OSPEDALIERO UNIVERSITARIA MEYER
Sponsor organisation address	VIALE PIERACCINI 24, FIRENZE, Italy, 50139
Public contact	FIBROSI CISTICA, AZIENDA OSPEDALIERO UNIVERSITARIA MEYER, +39 0555662474, giovanni.taccetti@meyer.it
Scientific contact	FIBROSI CISTICA, AZIENDA OSPEDALIERO UNIVERSITARIA MEYER, +39 0555662474, giovanni.taccetti@meyer.it

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 September 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	08 January 2019
Global end of trial reached?	Yes
Global end of trial date	08 January 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy (P. aeruginosa eradication from the lower airways) of two types of treatment in Cystic Fibrosis (CF) patients: the classic eradication protocol used until now (treatment A), versus the classic protocol together with nasal lavage with colistin (treatment B).

Protection of trial subjects:

No specific risks, pain or distress were expected for the trial subjects. Moreover, risks were comparable to that observed in clinical practice. No specific measures were put in place for trial subjects.

Background therapy:

The following treatments were approved as efficacious standard therapy for the eradication of Pseudomonas Aeruginosa in the lower airways of CF patients:
a) Inhalation of colistin (2.000.000 UI or 1.000.000 UI if I-NEB® is used) b.i.d. (total daily dose 4.000.000 IU) and 30 mg/kg/day of oral ciprofloxacin divided into 2 doses for 4 weeks (maximum daily dose 750 mg x 2);
b) Inhalation of tobramycin, 300 mg twice daily (600 mg total daily dose) for 4 weeks with appropriate nebulizers;
c) Aztreonam lysine for inhalation, 75 mg three times daily (total daily dose 225 mg) for 4 weeks with appropriate nebulizers

Evidence for comparator:

No active comparator or placebo were used in this trial.

Actual start date of recruitment	01 May 2016
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	Italy: 51
Worldwide total number of subjects	51
EEA total number of subjects	51

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)	32
Adolescents (12-17 years)	8
Adults (18-64 years)	11
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The recruitment period lasted 2 years.

Pre-assignment

Screening details:

All the screened patients (n=51) were enrolled in the study.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Standard of care - A

Arm description:

Enrolled patients received the classic eradication therapy as per standard of care

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	Experimental - B

Arm description:

Enrolled patients received the classic eradication therapy as per standard of care with nasal lavage with colistin.

Arm type	Experimental
Investigational medicinal product name	Colistin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for injection
Routes of administration	External use

Dosage and administration details:

Nasal irrigation with colistin 2.000.000 U b.i.d (total daily dose 4.000.000 IU) for a period of 4 weeks.

Number of subjects in period 1	Standard of care - A	Experimental - B
Started	25	26
Completed	21	21
Not completed	4	5
Consent withdrawn by subject	1	3
Physician decision	3	1
Adverse event, non-fatal	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Standard of care - A
Reporting group description:	
Enrolled patients received the classic eradication therapy as per standard of care	
Reporting group title	Experimental - B
Reporting group description:	
Enrolled patients received the classic eradication therapy as per standard of care with nasal lavage with colistin.	

Reporting group values	Standard of care - A	Experimental - B	Total
Number of subjects	25	26	51
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)	14	18	32
Adolescents (12-17 years)	6	2	8
Adults (18-64 years)	5	6	11
From 65-84 years	0	0	0
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	12	14	26
Male	13	12	25

End points

End points reporting groups

Reporting group title	Standard of care - A
Reporting group description:	
Enrolled patients received the classic eradication therapy as per standard of care	
Reporting group title	Experimental - B
Reporting group description:	
Enrolled patients received the classic eradication therapy as per standard of care with nasal lavage with colistin.	

Primary: Difference in P. aeruginosa eradication from the lower airways in the two treatment groups (A and B). Eradication is defined as 3 negative, successive P. aeruginosa cultures within 6 months

End point title	Difference in P. aeruginosa eradication from the lower airways in the two treatment groups (A and B). Eradication is defined as 3 negative, successive P. aeruginosa cultures within 6 months
End point description:	
Difference in P. aeruginosa eradication from the lower airways in the two treatment groups (A and B). Eradication is defined as 3 negative, successive P. aeruginosa cultures within 6 months	
End point type	Primary
End point timeframe:	
6 months	

End point values	Standard of care - A	Experimental - B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25[1]	26[2]		
Units: Number of patients				
Success	16	14		
No success	9	12		

Notes:

[1] - According to the intention to treat analysis dropped-out patients were included

[2] - According to the intention to treat analysis dropped-out patients were included

Statistical analyses

Statistical analysis title	Primary endpoint
Comparison groups	Standard of care - A v Experimental - B
Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	superiority[3]
Parameter estimate	Risk difference (RD)
Point estimate	10.15

Confidence interval	
level	95 %
sides	1-sided
lower limit	-16.7

Notes:

[3] - Intention to treat analysis was conducted and patients dropped-out were considered as treatment failure

Primary: P. Aeruginosa recurrence risk

End point title	P. Aeruginosa recurrence risk

End point description:

We estimated the P. aeruginosa recurrence risk in the two groups and relative risk

End point type	Primary

End point timeframe:

6 months

End point values	Standard of care - A	Experimental - B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25[4]	26[5]		
Units: Number of patients				
Success	16	14		
No success	9	12		

Notes:

[4] - According to the intention to treat analysis dropped-out patients were included

[5] - According to the intention to treat analysis dropped-out patients were included

Statistical analyses

Statistical analysis title	Primary endpoint

Statistical analysis description:

We estimated the risk of recurrence in the Group B and the risk of recurrence in the Group A.

Comparison groups	Standard of care - A v Experimental - B
Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Risk ratio (RR)
Point estimate	1.28
Confidence interval	
level	95 %
sides	1-sided
lower limit	0.7

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Treatment period (28 days) and 6-months follow-up	
Assessment type	Non-systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	22.0
Reporting groups	
Reporting group title	Experimental group - B
Reporting group description: Subjects in the experimental group received the classic eradication therapy as per standard of care with nasal lavage with colistin.	
Reporting group title	Standard of care group - A
Reporting group description: Subjects in the standard of care group received the classic eradication therapy.	

Serious adverse events	Experimental group - B	Standard of care group - A	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 22 (4.55%)	0 / 22 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Respiratory, thoracic and mediastinal disorders			
Haemoptysis	Additional description: Patient experienced haemoptysis (related to cystic fibrosis) and hospitalization occurred in the reporting period.		
subjects affected / exposed	1 / 22 (4.55%)	0 / 22 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Experimental group - B	Standard of care group - A	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 22 (4.55%)	0 / 22 (0.00%)	
Respiratory, thoracic and mediastinal disorders			
Haemoptysis			
subjects affected / exposed	1 / 22 (4.55%)	0 / 22 (0.00%)	
occurrences (all)	1	0	

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.

This study is under-powered as the trial did not enrol the initial estimated sample.

Notes: