



Clinical trial results:

A double-blind, placebo controlled, multicentre, clinical trial to investigate the efficacy and safety of 12 months of therapy with inhaled Promixin® (colistimethate sodium) in the treatment of subjects with non-cystic fibrosis bronchiectasis chronically infected with Pseudomonas aeruginosa (P. aeruginosa)

Summary

EudraCT number	2016-004558-13
Trial protocol	FR PL DE PT GR IT
Global end of trial date	15 March 2022

Results information

Result version number	v1 (current)
This version publication date	23 February 2024
First version publication date	23 February 2024

Trial information

Trial identification

Sponsor protocol code	Z7224L02
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03460704
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Zambon S.p.A.
Sponsor organisation address	Via Lillo Del Duca, 10, Bresso (MI), Italy, 20091
Public contact	Clinical Trial Manager, Zambon S.p.A. , +39 02 665241, clinicaltrials@zambongroup.com
Scientific contact	Clinical Trial Manager, Zambon S.p.A. , +39 02 665241, clinicaltrials@zambongroup.com

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	15 March 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 March 2022
Global end of trial reached?	Yes
Global end of trial date	15 March 2022
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the trial was to investigate the effect of the use of inhaled colistimethate sodium (CMS), administered twice a day (b.i.d.) via a specific nebulizer for 12 month, compared to placebo in subjects with non-cystic fibrosis bronchiectasis (NCFB) chronically infected with *P. aeruginosa* on the annualised frequency of pulmonary exacerbations.

Protection of trial subjects:

This trial was conducted in compliance with the latest version of the Declaration of Helsinki, with International Council for Harmonisation (ICH) Good Clinical Practice (GCP), in particular E6 (R2), with the applicable regulatory requirements and with Zambon and contract research organisation (CRO) standard operating procedures (SOPs).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	29 January 2018
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	Poland: 48
Country: Number of subjects enrolled	France: 30
Country: Number of subjects enrolled	Germany: 3
Country: Number of subjects enrolled	Greece: 3
Country: Number of subjects enrolled	Italy: 1
Country: Number of subjects enrolled	New Zealand: 6
Country: Number of subjects enrolled	Canada: 19
Country: Number of subjects enrolled	Argentina: 108
Country: Number of subjects enrolled	United States: 50
Country: Number of subjects enrolled	Australia: 13
Country: Number of subjects enrolled	Israel: 4
Country: Number of subjects enrolled	Portugal: 2
Worldwide total number of subjects	287
EEA total number of subjects	87

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)	158
From 65 to 84 years	127
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

A total of 428 subjects were screened, of whom 287 were randomised, 141 were screen failures and 135 did not meet the inclusion/exclusion criteria.

Pre-assignment

Screening details:

In total, 287 subjects were randomised 1:1 to CMS or placebo, with slightly more assignment to the CSM group. Of the 287 subjects randomised there were 152 subjects randomised to CMS and 135 randomised to placebo.

Period 1

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

Blinding implementation details:

Investigational site staff including the Investigator and all personnel involved in study procedures were blinded to treatment allocation. All CRO and Zambon study staff involved in monitoring, data management or other aspects of the study were also blinded.

Arms

Are arms mutually exclusive?	Yes
Arm title	CMS (Colistimethate Sodium)

Arm description:

Inhaled CMS twice daily. The active pharmaceutical ingredient consisting of pure CMS one million international units (MIU) / 80 mg of CMS / 33 mg colistin base activity (CBA) was provided as a powder for nebuliser solution in 10R International Organization for Standardization (ISO) glass vials.
CMS: 1 MIU equivalent to 80 mg colistimethate sodium diluted in 1 mL saline solution 0.45%.

Arm type	Experimental
Investigational medicinal product name	Colistimethate sodium
Investigational medicinal product code	
Other name	Promixin
Pharmaceutical forms	Powder for nebuliser solution
Routes of administration	Inhalation use

Dosage and administration details:

1 MIU equivalent to 80 mg colistimethate sodium diluted in 1 mL saline solution 0.45%. Investigational Medicinal Product (IMP) glass vials were shrink wrapped in opaque white plastic and provided in boxes of 30 vials (two weeks of b.i.d. dosing).

The 1 MIU/mL CMS/0.45% saline solution was transferred from the glass vial into a specific nebuliser system fitted with a 0.3 mL medication chamber, for administration by inhalation. This delivered a nominal dose of 0.3 MIU/24 mg CMS (11 mg CBA) from the device.

The first dose of the IMP was administered at the site under the supervision of the site staff and subjects were instructed how to prepare and self-administer the IMP at home via a specific nebuliser system, b.i.d. (morning and evening) over a period of 12 months.

At least 10 minutes (min) before each administration, an inhaled short-acting bronchodilator (e.g. salbutamol/albuterol), supplied by the Sponsor, could be taken to improve tolerability.

Arm title	Placebo
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Arm description:

Saline solution inhaled twice daily, provided and administered at the same way of the IMP.
Placebo: 1 mL saline solution 0.45%.

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

Dosage and administration details:

1 mL saline solution 0.45%. The placebo was made up of identical empty glass vials to which the same saline solution diluent was added in exactly the same way as the reconstitution of the active treatment by injecting the diluent through the rubber stopper. The glass vials were shrink wrapped with opaque white plastic to maintain the blind.

Number of subjects in period 1	CMS (Colistimethate Sodium)	Placebo
Started	152	135
Completed	94	89
Not completed	58	46
Protocol-specified withdrawal criterion met	-	5
Adverse event, non-fatal	10	5
Death	3	2
Unknown	2	1
Study terminated by the sponsor	29	19
Non compliance with study drug	3	-
Withdrawal by subject	11	14

Baseline characteristics

Reporting groups

Reporting group title	CMS (Colistimethate Sodium)
Reporting group description: Inhaled CMS twice daily. The active pharmaceutical ingredient consisting of pure CMS one million international units (MIU) / 80 mg of CMS / 33 mg colistin base activity (CBA) was provided as a powder for nebuliser solution in 10R International Organization for Standardization (ISO) glass vials. CMS: 1 MIU equivalent to 80 mg colistimethate sodium diluted in 1 mL saline solution 0.45%.	
Reporting group title	Placebo
Reporting group description: Saline solution inhaled twice daily, provided and administered at the same way of the IMP. Placebo: 1 mL saline solution 0.45%.	

Reporting group values	CMS (Colistimethate Sodium)	Placebo	Total
Number of subjects	152	135	287
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)	85	73	158
From 65-84 years	66	61	127
85 years and over	1	1	2
Age continuous Units: years			
arithmetic mean	59.9	59.6	-
standard deviation	± 15.19	± 14.73	-
Gender categorical Units: Subjects			
Female	104	94	198
Male	48	41	89

Subject analysis sets

Subject analysis set title	CMS mITT
Subject analysis set type	Modified intention-to-treat
Subject analysis set description: The modified Intention-To-Treat (mITT) Population is the Full Analysis Set and comprised all subjects who provided informed consent, were randomised and received at least 1 dose or partial dose of the IMP.	
Subject analysis set title	Placebo mITT
Subject analysis set type	Modified intention-to-treat
Subject analysis set description: The modified Intention-To-Treat (mITT) Population is the Full Analysis Set and comprised all subjects	

who provided informed consent, were randomised and received at least 1 dose or partial dose of the IMP.

Reporting group values	CMS mITT	Placebo mITT	
Number of subjects	152	135	
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)	85	73	
From 65-84 years	66	61	
85 years and over	1	1	
Age continuous			
Units: years			
arithmetic mean	59.9	59.6	
standard deviation	± 15.19	± 14.73	
Gender categorical			
Units: Subjects			
Female	104	94	
Male	48	41	

End points

End points reporting groups

Reporting group title	CMS (Colistimethate Sodium)
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Reporting group description:

Inhaled CMS twice daily. The active pharmaceutical ingredient consisting of pure CMS one million international units (MIU) / 80 mg of CMS / 33 mg colistin base activity (CBA) was provided as a powder for nebuliser solution in 10R International Organization for Standardization (ISO) glass vials.

CMS: 1 MIU equivalent to 80 mg colistimethate sodium diluted in 1 mL saline solution 0.45%.

Reporting group title	Placebo
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Reporting group description:

Saline solution inhaled twice daily, provided and administered at the same way of the IMP.

Placebo: 1 mL saline solution 0.45%.

Subject analysis set title	CMS mITT
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Subject analysis set type	Modified intention-to-treat
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Subject analysis set description:

The modified Intention-To-Treat (mITT) Population is the Full Analysis Set and comprised all subjects who provided informed consent, were randomised and received at least 1 dose or partial dose of the IMP.

Subject analysis set title	Placebo mITT
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Subject analysis set type	Modified intention-to-treat
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Subject analysis set description:

The modified Intention-To-Treat (mITT) Population is the Full Analysis Set and comprised all subjects who provided informed consent, were randomised and received at least 1 dose or partial dose of the IMP.

Primary: Mean Annual Non-cystic Fibrosis Bronchiectasis (NCFB) Pulmonary Exacerbation Rate

End point title	Mean Annual Non-cystic Fibrosis Bronchiectasis (NCFB) Pulmonary Exacerbation Rate
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End point description:

The primary efficacy assessment for an individual subject was the frequency of pulmonary exacerbations (exacerbation rate). A pulmonary exacerbation was defined as the presence concurrently of at least three of the following eight symptoms/signs for at least 24 hours:

- increased cough;
- increased sputum volume and/or consistency;
- increased sputum purulence;
- new or increased haemoptysis;
- increased wheezing;
- increased dyspnoea;
- increased fatigue/malaise and
- episodes of fever (temperature $\geq 38^{\circ}\text{C}$).

AND

It was clinically determined that the subject required and was prescribed systemic antibiotic therapy.

AND

The episode of exacerbation lasted for at least 24 hours. The overall episode of exacerbation needs to last at least 24 hours, but individual symptoms/signs can last less than 24 hours (e.g, a temperature).

End point type	Primary
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End point timeframe:

12 month

End point values	CMS mITT	Placebo mITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	152	135		
Units: Number of pulmonary exacerbations				
least squares mean (confidence interval 95%)	0.889 (0.722 to 1.093)	0.885 (0.710 to 1.103)		

Statistical analyses

Statistical analysis title	CMS (Colistimethate Sodium) vs Placebo
Statistical analysis description:	
The number of NCFB pulmonary exacerbations was compared between treatment groups using a negative binomial model including treatment, country, and baseline use of stable concomitant therapy with oral macrolides as fixed effects and log-exposure time on treatment as an offset.	
Comparison groups	Placebo mITT v CMS mITT
Number of subjects included in analysis	287
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.97889
Method	negative binomial model
Parameter estimate	LS Mean rate ratio
Point estimate	1.004
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.747
upper limit	1.349

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All AEs occurring from Visit 2 (day 0 = first IMP administration) until the follow-up phone call (2 weeks +/- 3 days after the end of treatment = totally up to 54 weeks +/- 3 days from the study Day 0.

Adverse event reporting additional description:

Adverse events were recorded by the Investigator in the appropriate CRF section starting with the date of informed consent until the follow-up phone call. At each contact (i.e., clinical visit or phone call), subjects were asked in a non-leading manner if they experienced any AEs.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	24.1
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Reporting groups

Reporting group title	CMS (Colistimethate Sodium) (SAF)
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Reporting group description:

The Safety Population comprised all subjects who provided informed consent, were randomised and received at least 1 dose or partial dose of IMP.

Subjects were analysed according to the treatment they actually received.

Reporting group title	Placebo (SAF)
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Reporting group description:

The Safety Population comprised all subjects who provided informed consent, were randomised and received at least 1 dose or partial dose of IMP.

Subjects were analysed according to the treatment they actually received.

Serious adverse events	CMS (Colistimethate Sodium) (SAF)	Placebo (SAF)	
Total subjects affected by serious adverse events			
subjects affected / exposed	27 / 152 (17.76%)	17 / 135 (12.59%)	
number of deaths (all causes)	3	2	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Endometrial cancer			
subjects affected / exposed	0 / 152 (0.00%)	1 / 135 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritoneal neoplasm			
subjects affected / exposed	0 / 152 (0.00%)	1 / 135 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			

Forearm fracture			
subjects affected / exposed	1 / 152 (0.66%)	0 / 135 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Head injury			
subjects affected / exposed	0 / 152 (0.00%)	1 / 135 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal compression fracture			
subjects affected / exposed	1 / 152 (0.66%)	0 / 135 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wrist fracture			
subjects affected / exposed	0 / 152 (0.00%)	1 / 135 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Adam-Strokes syndrome			
subjects affected / exposed	1 / 152 (0.66%)	0 / 135 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	0 / 152 (0.00%)	1 / 135 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	1 / 152 (0.66%)	0 / 135 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus arrest			
subjects affected / exposed	1 / 152 (0.66%)	0 / 135 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus node dysfunction			

subjects affected / exposed	1 / 152 (0.66%)	0 / 135 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Haemorrhagic stroke			
subjects affected / exposed	1 / 152 (0.66%)	0 / 135 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Death			
subjects affected / exposed	1 / 152 (0.66%)	0 / 135 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	1 / 152 (0.66%)	1 / 135 (0.74%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	1 / 152 (0.66%)	0 / 135 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	0 / 152 (0.00%)	1 / 135 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal perforation			
subjects affected / exposed	0 / 152 (0.00%)	1 / 135 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Asthma			

subjects affected / exposed	2 / 152 (1.32%)	0 / 135 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	2 / 152 (1.32%)	0 / 135 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory failure			
subjects affected / exposed	1 / 152 (0.66%)	0 / 135 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchial disorder			
subjects affected / exposed	1 / 152 (0.66%)	0 / 135 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 152 (0.00%)	1 / 135 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	0 / 152 (0.00%)	1 / 135 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Osteoarthritis			
subjects affected / exposed	1 / 152 (0.66%)	0 / 135 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Infective exacerbation of bronchiectasis			

subjects affected / exposed	12 / 152 (7.89%)	10 / 135 (7.41%)	
occurrences causally related to treatment / all	0 / 12	1 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19			
subjects affected / exposed	3 / 152 (1.97%)	0 / 135 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain abscess			
subjects affected / exposed	1 / 152 (0.66%)	0 / 135 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19 pneumonia			
subjects affected / exposed	1 / 152 (0.66%)	0 / 135 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 152 (0.66%)	1 / 135 (0.74%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudomonas infection			
subjects affected / exposed	0 / 152 (0.00%)	1 / 135 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory syncytial virus infection			
subjects affected / exposed	1 / 152 (0.66%)	0 / 135 (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: 2 %

Non-serious adverse events	CMS (Colistimethate Sodium) (SAF)	Placebo (SAF)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	39 / 152 (25.66%)	30 / 135 (22.22%)	
Investigations			
Weight decreased			
subjects affected / exposed	0 / 152 (0.00%)	3 / 135 (2.22%)	
occurrences (all)	0	3	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	1 / 152 (0.66%)	3 / 135 (2.22%)	
occurrences (all)	1	3	
Exposure to contaminated device			
subjects affected / exposed	0 / 152 (0.00%)	3 / 135 (2.22%)	
occurrences (all)	0	3	
Nervous system disorders			
Syncope			
subjects affected / exposed	3 / 152 (1.97%)	0 / 135 (0.00%)	
occurrences (all)	3	0	
General disorders and administration site conditions			
Non-cardiac chest pain			
subjects affected / exposed	1 / 152 (0.66%)	3 / 135 (2.22%)	
occurrences (all)	1	3	
Pyrexia			
subjects affected / exposed	1 / 152 (0.66%)	3 / 135 (2.22%)	
occurrences (all)	1	3	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	4 / 152 (2.63%)	1 / 135 (0.74%)	
occurrences (all)	5	1	
Dyspepsia			
subjects affected / exposed	3 / 152 (1.97%)	1 / 135 (0.74%)	
occurrences (all)	3	1	
Dry mouth			
subjects affected / exposed	3 / 152 (1.97%)	1 / 135 (0.74%)	
occurrences (all)	3	1	
Respiratory, thoracic and mediastinal disorders			

Asthma			
subjects affected / exposed	5 / 152 (3.29%)	0 / 135 (0.00%)	
occurrences (all)	5	0	
Sputum increased			
subjects affected / exposed	3 / 152 (1.97%)	2 / 135 (1.48%)	
occurrences (all)	3	2	
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 152 (0.66%)	3 / 135 (2.22%)	
occurrences (all)	1	3	
Epistaxis			
subjects affected / exposed	3 / 152 (1.97%)	1 / 135 (0.74%)	
occurrences (all)	4	1	
Oropharyngeal pain			
subjects affected / exposed	3 / 152 (1.97%)	1 / 135 (0.74%)	
occurrences (all)	3	1	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 152 (1.32%)	3 / 135 (2.22%)	
occurrences (all)	4	4	
Musculoskeletal chest pain			
subjects affected / exposed	3 / 152 (1.97%)	2 / 135 (1.48%)	
occurrences (all)	3	2	
Infections and infestations			
Chronic sinusitis			
subjects affected / exposed	3 / 152 (1.97%)	0 / 135 (0.00%)	
occurrences (all)	6	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 February 2018	<ul style="list-style-type: none">• The CTP was harmonised globally following further comments received from the FDA after the opening of the IND. The treatment phase was extended to a 24-month, placebo-controlled period, and the co-primary endpoints were amended from time to first exacerbation to FOE and exacerbation-free days.• The sample size was recalculated based on the revised primary endpoint and study duration (previously 330, now 374 subjects).• Extensive revisions were made to the inclusion and exclusion criteria to clarify the subject selection criteria and avoid cases of duplication and/or ambiguities in the previous protocol version. The changes did not materially alter the population being studied.• Screen failure criteria previously referred to as "Withdrawal Criteria" were deleted.• Safety variables were amended to include additional information regarding anti-microbial resistance (additional sputum sample analyses) and renal function tests.• Secondary study objectives were included (previously not explicitly stated).• Details regarding the optional open-label extension period (previously introduced for US sites only) were removed.
12 December 2018	<ul style="list-style-type: none">• The CTP was modified following agreement with the FDA during a type C meeting held on 31 October 2018 to revert to a single primary endpoint of FOE, with exacerbation-free days being included as a secondary endpoint and reducing the duration of the treatment period to 12 months. The study objective was amended accordingly to have 1 single primary objective of frequency of exacerbations in the 12-month treatment period. The number of patients to be randomised was amended in light of the revised study duration and single primary efficacy endpoint and resulting sample size re-calculation.• Inclusion criterion #5 was amended from "had 1 positive sputum culture for P. aeruginosa in the 12 months preceding the Screening Visit (but performed at least 30 days before the Screening Visit)" to "have a documented history of P. aeruginosa infection".• Exclusion criterion #2 was expanded to specify "known history of hypogammaglobulinaemia requiring treatment with immunoglobulin, unless fully replaced and considered immuno-competent by the Investigator".• Exclusion criterion #9 was amended from "receiving long-term domiciliary oxygen therapy or non-invasive ventilation for the management of respiratory failure" to "respiratory failure requiring long-term domiciliary oxygen therapy or non-invasive ventilation".• Exclusion criterion #17 was amended to include examples of chronic macrolides.• The duration for excluding pregnancy or breast-feeding in exclusion criterion #19 was amended to 1 year.

22 October 2019	<ul style="list-style-type: none"> • The CTP was amended to reflect the transition in contract research organisation from Chiltern International Ltd. (a Covance Company) to Syneos Health. • Inclusion criterion #3 was amended from "diagnosed with NCFB by computerised tomography (CT) or high resolution CT (HRCT) as recorded in the subject's notes" to "are diagnosed with NCFB by computerised tomography (CT) or high resolution CT (HRCT) as recorded in the subject's notes and this was their predominant condition being treated". • Inclusion criterion #4 was amended to allow patients experiencing 2 NCFB pulmonary exacerbations requiring inhaled antibiotics to be enrolled. • Inclusion criterion #7 was amended to allow patients with a pre-bronchodilator FEV1 $\geq 25\%$ (as opposed to $\geq 30\%$). • Inclusion criterion #8 was amended to reflect the fact that any positive result for 1 of the 3 potential sputum samples collected during the periods between Visit 1 and Visit 2 allowed for patient inclusion. • Exclusion criterion #14 ("known to be intolerant to inhaled beta-2 agonists (bronchodilators)") was deleted. Zambon removed this requirement due to feedback that, as many patients could tolerate the IMP without it, the mandated use was an unnecessary burden on patients who would prefer not to use it. The use of the bronchodilator was to aid tolerability, not to improve efficacy. In addition, a statement was added to allow subject to continue in the study without pre-bronchodilator use prior to IMP administration. • Exclusion criterion #13 (as re-numbered) was amended from "known or suspected to be allergic or unable to tolerate colistimethate sodium or other polymyxins (IV or inhaled) including evidence of bronchial hyperreactivity" to "known or suspected to be allergic or unable to tolerate colistimethate sodium (IV or inhaled) or other polymyxins, including evidence of bronchial hyper-reactivity following inhaled colistimethate sodium".
22 October 2019	<ul style="list-style-type: none"> • The wording regarding the definition of the resolution of pulmonary exacerbations was re-phrased, and the following statement was added: "The occurrence of a pulmonary exacerbation does not mandate the discontinuation of the subject from the study, unless it occurs between Visit 1 and Visit 2 and/or the Investigator believes discontinuation is in the subject's best interest." • Acute and/or short-term administration of oxygen therapy/ventilator assistance was included as an acceptable rescue medication.
22 July 2021	<ul style="list-style-type: none"> • Country-specific amendments of CTP version 4.0 were incorporated. • Changes to the conduct and duration of the study required due to the COVID-19 pandemic were made including inclusion of a contingency plans for remote visits during the COVID-19 pandemic. • Provisions were included for the original sample size to be recalculated at a later date to take into consideration: a) treatment exposure for withdrawn subjects and b) a planned blinded review of the exacerbation rate. • Clarification was added to specify that subjects not using the recommended bronchodilator prior to IMP administration needed to be clinically assessed to determine whether this was appropriate. • The Screening period (between Visits 1 and 2) was extended from 30 days to 45 days to allow for sufficient time for the processing of sputum samples for the analysis of <i>P. aeruginosa</i>. A clarification was added that re-screening for subjects who screen failed for reasons other than a negative result for <i>P. aeruginosa</i> was permitted at any time. For subjects with a negative result for <i>P. aeruginosa</i>, re-screening was also permitted after approximately 3 months from the last Screening test. • The units for <i>P. aeruginosa</i> were corrected to CFU/mL. • Provisions were included for the use of paper quality of life questionnaires when the electronic tablet supplied to sites malfunctioned or there were other technical issues. • The reporting of episodes of pneumonia as pulmonary exacerbations was clarified. • A Data Assessment Committee was established for the assessment of the impact of COVID-19 on the study, and blinded review of pulmonary exacerbation data, and details were included.

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.

The study was brought to an early close primarily due to the difficulty of recruiting subjects in the context of the COVID pandemic, but also due to the potential for loss of scientific equipoise.
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Notes: