



Clinical trial results:

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

Summary

EudraCT number	2015-002743-33
Trial protocol	GB ES DE PT NL GR IT
Global end of trial date	09 April 2021

Results information

Result version number	v1 (current)
This version publication date	02 February 2023
First version publication date	02 February 2023

Trial information

Trial identification

Sponsor protocol code	Z7224L01
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03093974
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Zambon SPA
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	09 April 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	09 April 2021
Global end of trial reached?	Yes
Global end of trial date	09 April 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the trial is to investigate the effect of the use of inhaled colistimethate sodium, administered twice daily via a specific nebuliser for 12 months, compared to placebo in subjects with NCFB chronically infected with *P. aeruginosa* on the 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	28 February 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	Australia: 63
Country: Number of subjects enrolled	New Zealand: 19
Country: Number of subjects enrolled	Israel: 41
Country: Number of subjects enrolled	Switzerland: 1
Country: Number of subjects enrolled	Netherlands: 1
Country: Number of subjects enrolled	Portugal: 48
Country: Number of subjects enrolled	Spain: 34
Country: Number of subjects enrolled	United Kingdom: 33
Country: Number of subjects enrolled	Belgium: 2
Country: Number of subjects enrolled	Germany: 65
Country: Number of subjects enrolled	Greece: 17
Country: Number of subjects enrolled	Italy: 53
Worldwide total number of subjects	377
EEA total number of subjects	220

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	211
85 years and over	8

Subject disposition

Recruitment

Recruitment details:

A total of 538 subjects were screened, of whom 377 (~70%) were randomised and 161 (~30%) were screen failures.

Pre-assignment

Screening details:

In total, 377 subjects were randomised 1:1 to CMS or placebo, with slightly more assigned to the placebo group (53.1% compared to 46.9% CMS). Of the 377 subjects randomized there were 177 randomized to CMS and 200 randomised to placebo. Four subjects (one randomised to CMS and three to placebo) did not receive any study medication.

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. The allocation to treatment was stored within the IWRS database until unblinding of the trial was requested.

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 CMS 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 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 b.i.d. for 12 months.

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

Dosage and administration details:

Inhaled colistimethate sodium twice daily.

CMS: 1 MIU equivalent to 80 mg CMS 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 fitted with a 0.3 mL medication chamber, for administration by inhalation. This delivered a nominal dose of 0.3 MIU/24 mg CMS (~10 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 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.

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

Dosage and administration details:

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

Placebo: 1 ml saline solution 0.45%. the placebo was made up of identical empty glass vials to which the same saline 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	177	200
Completed	123	129
Not completed	54	71
Adverse event, serious fatal	-	1
Consent withdrawn by subject	32	27
Adverse event, non-fatal	17	24
Protocol-specified withdrawal criterion met	3	16
Unknown	1	2
Non-compliance with study drug	1	-
Lost to follow-up	-	1

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 CMS 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 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 b.i.d. for 12 months.	
Reporting group title	Placebo
Reporting group description:	
Saline solution inhaled twice daily, provided and administered at the same way of the IMP.	

Reporting group values	CMS (Colistimethate Sodium)	Placebo	Total
Number of subjects	177	200	377
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)	70	88	158
From 65-84 years	103	108	211
85 years and over	4	4	8
Age continuous Units: years			
median	64.2	64.3	
standard deviation	± 14.78	± 13.03	-
Gender categorical Units: Subjects			
Female	124	129	253
Male	53	71	124

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 one 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 one dose or partial dose of the IMP.

Reporting group values	CMS mITT	Placebo mITT	
Number of subjects	176	197	
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)			
From 65-84 years			
85 years and over			
Age continuous			
Units: years			
median	64.2	64.2	
standard deviation	± 14.86	± 13.06	
Gender categorical			
Units: Subjects			
Female	123	126	
Male	53	71	

End points

End points 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 CMS 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 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 b.i.d. for 12 months.	
Reporting group title	Placebo
Reporting group description:	
Saline solution inhaled twice daily, provided and administered at the same way of the IMP.	
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 one 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 one 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
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; • 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).	
AND	
in the opinion of the Investigator, the subject required and started treatment with systemic antibiotics.	
End point type	Primary
End point timeframe:	
12 months	

End point values	CMS mITT	Placebo mITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	176	194		
Units: Number of pulmonary exacerbations				
least squares mean (confidence interval 95%)	0.580 (0.001 to 9999.999)	0.948 (0.001 to 9999.999)		

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, pooled site (country) and baseline use of stable concomitant therapy with oral macrolides as fixed effects and log-time on treatment as an offset.	
Comparison groups	CMS mITT v Placebo mITT
Number of subjects included in analysis	370
Analysis specification	Pre-specified
Analysis type	superiority ^[1]
P-value	= 0.00101
Method	Two sided Wald chi-square test
Parameter estimate	LS Mean rate ratio
Point estimate	0.612
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.457
upper limit	0.82

Notes:

[1] - The number of NCFB pulmonary exacerbations was compared between treatment groups using a negative binomial model including treatment, pooled site (country) and baseline use of stable concomitant therapy with oral macrolides as fixed effects and log-time on treatment as an offset.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All AEs occurring from the day of the first IMP administration, i.e. Visit 2 (day 0), up to the follow-up (54 weeks after the beginning of the trial), when follow-up phone call took place.

Adverse event reporting additional description:

AEs will be recorded by the Investigator in the appropriate eCRF 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 will be asked in a non-leading manner if they experienced any AE.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	22.1
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Reporting groups

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

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 one 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	31 / 176 (17.61%)	46 / 197 (23.35%)	
number of deaths (all causes)	1	1	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	0 / 176 (0.00%)	1 / 197 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatocellular carcinoma			
subjects affected / exposed	1 / 176 (0.57%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngeal cancer			

subjects affected / exposed	0 / 176 (0.00%)	1 / 197 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Aortic stenosis			
subjects affected / exposed	0 / 176 (0.00%)	1 / 197 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
General physical health deterioration			
subjects affected / exposed	1 / 176 (0.57%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	1 / 176 (0.57%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute pulmonary oedema			
subjects affected / exposed	0 / 176 (0.00%)	1 / 197 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthma			
subjects affected / exposed	1 / 176 (0.57%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cough			
subjects affected / exposed	0 / 176 (0.00%)	1 / 197 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			

subjects affected / exposed	1 / 176 (0.57%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	0 / 176 (0.00%)	1 / 197 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infiltration			
subjects affected / exposed	1 / 176 (0.57%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	1 / 176 (0.57%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 176 (0.57%)	1 / 197 (0.51%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
C-reactive protein increased			
subjects affected / exposed	1 / 176 (0.57%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 176 (0.57%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar vertebral fracture			
subjects affected / exposed	0 / 176 (0.00%)	1 / 197 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Rib fracture			
subjects affected / exposed	0 / 176 (0.00%)	1 / 197 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			
subjects affected / exposed	0 / 176 (0.00%)	1 / 197 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thoracic vertebral fracture			
subjects affected / exposed	0 / 176 (0.00%)	1 / 197 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 176 (0.57%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	1 / 176 (0.57%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	0 / 176 (0.00%)	1 / 197 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	0 / 176 (0.00%)	1 / 197 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiogenic shock			
subjects affected / exposed	1 / 176 (0.57%)	0 / 197 (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	1 / 176 (0.57%)	1 / 197 (0.51%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	1 / 176 (0.57%)	0 / 197 (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			
Cognitive disorder			
subjects affected / exposed	0 / 176 (0.00%)	1 / 197 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 176 (0.57%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Gallbladder polyp			
subjects affected / exposed	1 / 176 (0.57%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 176 (0.00%)	1 / 197 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urethral stenosis			
subjects affected / exposed	0 / 176 (0.00%)	1 / 197 (0.51%)	
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			
Arthropathy			

subjects affected / exposed	0 / 176 (0.00%)	1 / 197 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemarthrosis			
subjects affected / exposed	0 / 176 (0.00%)	1 / 197 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc protrusion			
subjects affected / exposed	1 / 176 (0.57%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal chest pain			
subjects affected / exposed	0 / 176 (0.00%)	1 / 197 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Empyema			
subjects affected / exposed	0 / 176 (0.00%)	1 / 197 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Extradural abscess			
subjects affected / exposed	1 / 176 (0.57%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infective exacerbation of bronchiectasis			
subjects affected / exposed	15 / 176 (8.52%)	29 / 197 (14.72%)	
occurrences causally related to treatment / all	0 / 17	1 / 36	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	1 / 176 (0.57%)	1 / 197 (0.51%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumocystis jirovecii infection			

subjects affected / exposed	1 / 176 (0.57%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	4 / 176 (2.27%)	5 / 197 (2.54%)	
occurrences causally related to treatment / all	0 / 4	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	1 / 176 (0.57%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	1 / 176 (0.57%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinusitis			
subjects affected / exposed	0 / 176 (0.00%)	1 / 197 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord infection			
subjects affected / exposed	1 / 176 (0.57%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Varicella zoster virus infection			
subjects affected / exposed	0 / 176 (0.00%)	1 / 197 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	0 / 176 (0.00%)	1 / 197 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Fluid overload			

subjects affected / exposed	0 / 176 (0.00%)	1 / 197 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	CMS (Colistimethate Sodium) (SAF)	Placebo (SAF)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	142 / 176 (80.68%)	159 / 197 (80.71%)	
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 176 (2.27%)	11 / 197 (5.58%)	
occurrences (all)	4	13	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	12 / 176 (6.82%)	5 / 197 (2.54%)	
occurrences (all)	12	5	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	21 / 176 (11.93%)	19 / 197 (9.64%)	
occurrences (all)	24	19	
Dyspnoea			
subjects affected / exposed	22 / 176 (12.50%)	16 / 197 (8.12%)	
occurrences (all)	34	19	
Haemoptysis			
subjects affected / exposed	9 / 176 (5.11%)	19 / 197 (9.64%)	
occurrences (all)	19	33	
Sputum increased			
subjects affected / exposed	13 / 176 (7.39%)	7 / 197 (3.55%)	
occurrences (all)	13	9	
Infections and infestations			
Infective exacerbation of bronchiectasis			
subjects affected / exposed	67 / 176 (38.07%)	110 / 197 (55.84%)	
occurrences (all)	110	196	

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

None reported