



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 |
|-----------------------|----------|

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 |
|-----------|---------|

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 |
|----------|---------|

| | |
|--|---------------------|
| 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) |
|-----------------------|-----------------------------|

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%.

| | |
|----------------------------|----------|
| 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.

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 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 |
|----------------|---------|

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 |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 24.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|-----------------------------------|
| Reporting group title | CMS (Colistimethate Sodium) (SAF) |
|-----------------------|-----------------------------------|

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) |
|-----------------------|---------------|

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. |

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| 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.

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| 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: