



## 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 |
|-----------------------|----------|

#### 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:

| <b>Subjects enrolled per age group</b>    |     |
|---|-----|
| 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                         |
| <b>Arm title</b>             | 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.

|                  |         |
|------------------|---------|
| <b>Arm title</b> | Placebo |
|------------------|---------|

---

**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<br>(Colistimethate<br>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<br>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<br>(Colistimethate Sodium) | Placebo | Total |
|---|--------------------------------|---------|-------|
| Number of subjects                                    | 177                            | 200     | 377   |
| Age categorical<br>Units: Subjects                    |                                |         |       |
| In utero  | 0                              | 0       | 0     |
| Preterm newborn infants<br>(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<br>Units: years                        |                                |         |       |
| median  | 64.2                           | 64.3    |       |
| standard deviation                                    | ± 14.78                        | ± 13.03 | -     |
| Gender categorical<br>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<br>(gestational age < 37 wks) | 0        | 0            |  |
| Newborns (0-27 days)                                  | 0        | 0            |  |
| Infants and toddlers (28 days-23<br>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:<br>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:<br>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:<br>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:<br>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:<br>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: <ul style="list-style-type: none"><li>• increased cough;</li><li>• increased sputum volume and/or consistency;</li><li>• increased sputum purulence;</li><li>• new or increased haemoptysis;</li><li>• increased wheezing;</li><li>• increased dyspnoea;</li><li>• increased fatigue/malaise;</li><li>• episodes of fever (temperature <math>\geq 38^{\circ}\text{C}</math>).</li></ul> AND<br>It was clinically determined that the subject required and was prescribed systemic antibiotic therapy.<br>AND<br>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).<br>AND<br>in the opinion of the Investigator, the subject required and started treatment with systemic antibiotics. |   |
| End point type  | Primary   |
| End point timeframe:<br>12 months   |   |



| <b>End point values</b>                      | 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

| <b>Statistical analysis title</b>  | 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 <sup>[1]</sup>             |
| 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 |
|-----------------|------------|

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 22.1 |
|--------------------|------|

### Reporting groups

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

Reporting group description: -

|                       |               |
|-----------------------|---------------|
| Reporting group title | Placebo (SAF) |
|-----------------------|---------------|

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 %

| <b>Non-serious adverse events</b>                     | 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

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported