



Clinical trial results:

A single arm, open-label, multicenter, Phase IV trial to assess long term safety of tobramycin inhalation powder (TIP) in patients with Cystic Fibrosis

Summary

| | |
|--------------------------|-----------------|
| EudraCT number | 2011-002000-32 |
| Trial protocol | HU FR ES DE IT |
| Global end of trial date | 13 January 2014 |

Results information

| | |
|--------------------------------|----------------|
| Result version number | v1 (current) |
| This version publication date | 13 July 2016 |
| First version publication date | 07 August 2015 |

Trial information

Trial identification

| | |
|-----------------------|--------------|
| Sponsor protocol code | CTBM100C2401 |
|-----------------------|--------------|

Additional study identifiers

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

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Novartis Pharma AG |
| Sponsor organisation address | CH-4002, Basel, Switzerland, |
| Public contact | Clinical Disclosure Office, Novartis Pharma AG, +41 613241111, |
| Scientific contact | Clinical Disclosure Office, Novartis Pharma AG, +41 613241111, |

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 | 13 January 2014 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 13 January 2014 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The main objective of the study was to assess the safety of tobramycin inhalation powder (TIP) with respect to incidence of treatment emergent adverse events (AEs) over 6 treatment cycles.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were followed. Rescue medications like anti-pseudomonal antibiotics, macrolides (anti-inflammatory regimen), bronchodilators, inhaled hypertonic saline, inhaled corticosteroids were allowed for pulmonary exacerbations as per the discretion of the investigator. If the subject's condition/disease required the medications which potentially affected the systemic tobramycin levels, inhalation of study medication was continued only at the investigator's discretion. The investigator provided followup medical care for all subjects who were prematurely withdrawn from the study, or referred them for appropriate ongoing care.

Background therapy: -

Evidence for comparator: -

| | |
|---|-----------------|
| Actual start date of recruitment | 16 January 2012 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-------------------|
| Country: Number of subjects enrolled | Spain: 8 |
| Country: Number of subjects enrolled | France: 19 |
| Country: Number of subjects enrolled | Germany: 12 |
| Country: Number of subjects enrolled | Hungary: 8 |
| Country: Number of subjects enrolled | Italy: 21 |
| Country: Number of subjects enrolled | United States: 50 |
| Country: Number of subjects enrolled | Canada: 2 |
| Country: Number of subjects enrolled | Mexico: 12 |
| Country: Number of subjects enrolled | Argentina: 10 |
| Country: Number of subjects enrolled | Australia: 15 |
| Worldwide total number of subjects | 157 |
| EEA total number of subjects | 68 |

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) | 5 |
| Adolescents (12-17 years) | 21 |
| Adults (18-64 years) | 131 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 47 centres in 10 countries.

Pre-assignment

Screening details:

A total of 157 subjects were enrolled in the study.

Period 1

| | |
|------------------------------|--------------------------------|
| Period 1 title | Overall study (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

Blinding implementation details:

As the study was an open-label study, this section was not applicable.

Arms

| | |
|-----------|------------------------------|
| Arm title | Tobramycin inhalation powder |
|-----------|------------------------------|

Arm description:

Subjects inhaled four capsules of tobramycin inhalation powder (28 mg) twice daily (bid) via the T-326 inhaler device, for 28 days (treatment phase in each cycle). Each treatment phase therefore consisted of 112 mg tobramycin (4 capsules of 28 mg each) with the total daily dose of 224mg tobramycin (112mg bid). The treatment phase was followed by 28 days of no study treatment (off treatment in each cycle). These 56 days represented 1 cycle of therapy.

| | |
|--|---------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Tobramycin |
| Investigational medicinal product code | TBM100 |
| Other name | |
| Pharmaceutical forms | Inhalation powder, hard capsule |
| Routes of administration | Inhalation use |

Dosage and administration details:

Subjects inhaled four capsules of tobramycin inhalation powder (28 mg) bid via the T-326 inhaler device, for 28 days.

| Number of subjects in period 1 | Tobramycin inhalation powder |
|-----------------------------------|------------------------------|
| Started | 157 |
| Completed | 96 |
| Not completed | 61 |
| Consent withdrawn by subject | 17 |
| Adverse event, non-fatal | 29 |
| Unsatisfactory therapeutic effect | 6 |
| Lost to follow-up | 3 |
| Protocol deviation | 6 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|------------------------------|
| Reporting group title | Tobramycin inhalation powder |
|-----------------------|------------------------------|

Reporting group description:

Subjects inhaled four capsules of tobramycin inhalation powder (28 mg) twice daily (bid) via the T-326 inhaler device, for 28 days (treatment phase in each cycle). Each treatment phase therefore consisted of 112 mg tobramycin (4 capsules of 28 mg each) with the total daily dose of 224mg tobramycin (112mg bid). The treatment phase was followed by 28 days of no study treatment (off treatment in each cycle). These 56 days represented 1 cycle of therapy.

| Reporting group values | Tobramycin inhalation powder | Total | |
|---|------------------------------|-------|--|
| Number of subjects | 157 | 157 | |
| Age categorical | | | |
| Units: Subjects | | | |
| 6-<13 years | 7 | 7 | |
| 13-<20 years | 26 | 26 | |
| >= 20 years | 124 | 124 | |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 27.8 | | |
| standard deviation | ± 10.82 | - | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 60 | 60 | |
| Male | 97 | 97 | |
| Pseudomonas aeruginosa tobramycin minimal inhibitory concentration (MIC) | | | |
| Units: Subjects | | | |
| > 8 microgram/millilitre(ug/mL) | 41 | 41 | |
| <= 8 ug/mL | 115 | 115 | |
| Missing | 1 | 1 | |
| Forced expiratory volume in one second (FEV1) percent (%) predicted | | | |
| Units: percent | | | |
| arithmetic mean | 50.2 | | |
| standard deviation | ± 13.95 | - | |
| Forced vital capacity (FVC) % predicted | | | |
| Units: percent | | | |
| arithmetic mean | 73.9 | | |
| standard deviation | ± 15.88 | - | |
| Forced expiratory flow from 25 to 75 % (FEF25-75%) of the forced vital capacity % predicted | | | |
| Units: percent | | | |
| arithmetic mean | 21.8 | | |
| standard deviation | ± 12.75 | - | |
| Sputum density of Pseudomonas aeruginosa - sum of all biotypes | | | |
| Units: log10 colony forming units (CFU) | | | |
| arithmetic mean | 7.6 | | |

| | | | |
|--------------------|------------|---|--|
| standard deviation | ± 1.65 | - | |
|--------------------|------------|---|--|

End points

End points reporting groups

| | |
|--|--------------------------------|
| Reporting group title | Tobramycin inhalation powder |
| Reporting group description: Subjects inhaled four capsules of tobramycin inhalation powder (28 mg) twice daily (bid) via the T-326 inhaler device, for 28 days (treatment phase in each cycle). Each treatment phase therefore consisted of 112 mg tobramycin (4 capsules of 28 mg each) with the total daily dose of 224mg tobramycin (112mg bid). The treatment phase was followed by 28 days of no study treatment (off treatment in each cycle). These 56 days represented 1 cycle of therapy. | |
| Subject analysis set title | Cycle 1 (Day 29) |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: Subjects inhaled four capsules of tobramycin inhalation powder (28 mg) bid via the T-326 inhaler device, for 28 days. The treatment phase therefore consisted of 112 mg tobramycin (4 capsules of 28 mg each) with the total daily dose of 224 mg tobramycin (112 mg bid). The treatment phase was followed by 28 days of no study treatment (off treatment). | |
| Subject analysis set title | Cycle 2 (Day 85) |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: Subjects inhaled four capsules of tobramycin inhalation powder (28 mg) bid via the T-326 inhaler device, for 28 days. The treatment phase therefore consisted of 112 mg tobramycin (4 capsules of 28 mg each) with the total daily dose of 224 mg tobramycin (112 mg bid). The treatment phase was followed by 28 days of no study treatment (off treatment). These 56 days after Cycle 1 represented Cycle 2 of therapy. | |
| Subject analysis set title | Cycle 3 (Day 141) |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: Subjects inhaled four capsules of tobramycin inhalation powder (28 mg) bid via the T-326 inhaler device, for 28 days. The treatment phase therefore consisted of 112 mg tobramycin (4 capsules of 28 mg each) with the total daily dose of 224 mg tobramycin (112 mg bid). The treatment phase was followed by 28 days of no study treatment (off treatment). These 56 days after Cycle 2 represented Cycle 3 of therapy. | |
| Subject analysis set title | Cycle 4 (Day 197) |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: Subjects inhaled four capsules of tobramycin inhalation powder (28 mg) bid via the T-326 inhaler device, for 28 days. The treatment phase therefore consisted of 112 mg tobramycin (4 capsules of 28 mg each) with the total daily dose of 224 mg tobramycin (112 mg bid). The treatment phase was followed by 28 days of no study treatment (off treatment). These 56 days after Cycle 3 represented Cycle 4 of therapy. | |
| Subject analysis set title | Cycle 5 (Day 253) |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: Subjects inhaled four capsules of tobramycin inhalation powder (28 mg) bid via the T-326 inhaler device, for 28 days. The treatment phase therefore consisted of 112 mg tobramycin (4 capsules of 28 mg each) with the total daily dose of 224 mg tobramycin (112 mg bid). The treatment phase was followed by 28 days of no study treatment (off treatment). These 56 days after Cycle 4 represented Cycle 5 of therapy. | |
| Subject analysis set title | Cycle 6 (Day 309) |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: Subjects inhaled four capsules of tobramycin inhalation powder (28 mg) bid via the T-326 inhaler device, for 28 days. The treatment phase therefore consisted of 112 mg tobramycin (4 capsules of 28 mg each) with the total daily dose of 224 mg tobramycin (112 mg bid). The treatment phase was followed by 28 days of no study treatment (off treatment). These 56 days after Cycle 5 represented Cycle 6 of therapy. | |
| Subject analysis set title | All cycle completion (Day 337) |

| | |
|---------------------------|-----------------|
| Subject analysis set type | Safety analysis |
|---------------------------|-----------------|

Subject analysis set description:

Subjects inhaled four capsules of tobramycin inhalation powder (28 mg) bid via the T-326 inhaler device, for 28 days. The treatment phase therefore consisted of 112 mg tobramycin (4 capsules of 28 mg each) with the total daily dose of 224 mg tobramycin (112 mg bid). The treatment phase was followed by 28 days of no study treatment (off treatment) after Cycle 6 represented as completion of all study cycles.

Primary: Number of subjects with adverse events (AEs), AEs leading to discontinuation and serious adverse events (SAEs) over 6 treatment cycles

| | |
|-----------------|---|
| End point title | Number of subjects with adverse events (AEs), AEs leading to discontinuation and serious adverse events (SAEs) over 6 treatment cycles ^[1] |
|-----------------|---|

End point description:

An AE was defined as any unfavorable and unintended sign, symptom, or disease temporally associated with the use of study drug, whether or not related to study drug. An SAE was defined as an event which was fatal or life threatening, required or prolonged hospitalization, was significantly or permanently disabling or incapacitating, constituted a congenital anomaly or a birth defect, or encompassed any other clinically significant event that could jeopardize the subject or require medical or surgical intervention to prevent one of the aforementioned outcomes. Based on the severity, AEs were categorised into 3 types as mild, moderate and severe. On-treatment AE was defined as the AE occurred during 28 days treatment phase and off-treatment AE was defined as the AE occurred during 28 days no study drug treatment phase. The analysis was performed in safety population, defined as all subjects entered the study and received at least one dose of study drug.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Baseline (start of study treatment) to Day 337 (end of the study)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Only descriptive summary statistics was planned for this outcome measure.

| End point values | Tobramycin inhalation powder | | | |
|------------------------------------|------------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 157 | | | |
| Units: Number of subjects | | | | |
| On-treatment AEs | 121 | | | |
| Off-treatment AEs | 102 | | | |
| Mild AEs | 43 | | | |
| Moderate AEs | 66 | | | |
| Severe AEs | 25 | | | |
| Discontinued study drug due to AE | 66 | | | |
| Discontinued study drug due to SAE | 4 | | | |
| SAE | 49 | | | |
| AE | 134 | | | |
| Deaths | 0 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Relative change from baseline in forced expiratory volume in one second

(FEV1) percent predicted over 6 treatment cycles

| | |
|-----------------|--|
| End point title | Relative change from baseline in forced expiratory volume in one second (FEV1) percent predicted over 6 treatment cycles |
|-----------------|--|

End point description:

FEV1 was defined as the volume of air expired in 1 second. FEV1 was assessed as a pulmonary function by using spirometry tests in accordance with American Thoracic Society/European Respiratory Society (ATS/ERS) criteria. FEV1% predicted is a normalized value of FEV1 calculated using the Knudsen equation, based upon subject's age, gender and height. Relative change in FEV1 % predicted from baseline to pre-dose day X = ((pre-dose day*FEV1% predicted – baseline FEV1% predicted) / baseline FEV1 % predicted) x 100. The analysis was performed in safety set, defined as subjects who received at least one dose of study drug and had FEV1% values at both baseline and the post baseline time points. The 'n' signifies those subjects evaluable for this measure at specified time points for each group, respectively.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Day 29, Day 85, Day 141, Day 197, Day 253, Day 309, Day 337. All study visits (except baseline and Day 337) occurred at the end of a 28-day on-treatment period of a cycle

| End point values | Tobramycin inhalation powder | | | |
|--------------------------------------|------------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 157 | | | |
| Units: Percent FEV1 | | | | |
| arithmetic mean (standard deviation) | | | | |
| Day 29, Cycle 1 (n=149) | 0.8 (± 17.17) | | | |
| Day 85, Cycle 2 (n=146) | 0 (± 17.09) | | | |
| Day 141, Cycle 3 (n=128) | 0.2 (± 15.13) | | | |
| Day 197, Cycle 4 (n=116) | -0.2 (± 15.36) | | | |
| Day 253, Cycle 5 (n=105) | -1.5 (± 17.19) | | | |
| Day 309, Cycle 6 (n=100) | -1.9 (± 14.55) | | | |
| Day 337, Completion (n=93) | -3.5 (± 16.81) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Relative change from baseline in forced vital capacity (FVC) percent predicted over 6 treatment cycles

| | |
|-----------------|--|
| End point title | Relative change from baseline in forced vital capacity (FVC) percent predicted over 6 treatment cycles |
|-----------------|--|

End point description:

FVC was defined as the maximum volume of air exhaled with maximally forced effort from a position of maximal inspiration. FVC was determined from spirometry tests in accordance with ATS/ERS criteria. Relative change in FVC% predicted from baseline to pre-dose day X = ((pre-dose day*FVC% predicted – baseline FVC% predicted) / baseline FVC% predicted) x 100. The analysis was performed in safety population, who had FVC values at both baseline and post baseline time points. The 'n' signifies those subjects evaluable for this measure at specified time points for each group, respectively.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Day 29, Day 85, Day 141, Day 197, Day 253, Day 309, Day 337. All study visits (except baseline and Day 337) occurred at the end of a 28-day on-treatment period of a cycle

| End point values | Tobramycin inhalation powder | | | |
|--------------------------------------|------------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 157 | | | |
| Units: Percent FVC | | | | |
| arithmetic mean (standard deviation) | | | | |
| Day 29, Cycle 1 (n=149) | -2.5 (± 12.95) | | | |
| Day 85, Cycle 2 (n=146) | -2.8 (± 12.81) | | | |
| Day 141, Cycle 3 (n=128) | -2.1 (± 12.25) | | | |
| Day 197, Cycle 4 (n=116) | -1.8 (± 12.64) | | | |
| Day 253, Cycle 5 (n=105) | -3.5 (± 13.11) | | | |
| Day 309, Cycle 6 (n=100) | -3.1 (± 12.17) | | | |
| Day 337, Completion (n=93) | -2.8 (± 13.5) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Relative change from baseline in forced expiratory flow from 25 to 75% (FEF25-75%) of the forced vital capacity percent predicted over 6 treatment cycles

| | |
|-----------------|---|
| End point title | Relative change from baseline in forced expiratory flow from 25 to 75% (FEF25-75%) of the forced vital capacity percent predicted over 6 treatment cycles |
|-----------------|---|

End point description:

FEF25-75% was defined as the forced expiratory flow from 25% to 75% of the FVC. FEF25-75 was determined from spirometry tests in accordance with ATS/ERS criteria. Relative change in FEF25-75% predicted from baseline to pre-dose day X = ((pre-dose day* FEF25-75% predicted-baseline FEF25-75% predicted) / baseline FEF25-75% predicted) x 100. The analysis was performed in safety population, who had FEF values at both baseline and post baseline time points. The 'n' signifies those subjects evaluable for this measure at specified time points for each group, respectively.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Day 29, Day 85, Day 141, Day 197, Day 253, Day 309, Day 337. All study visits (except baseline and Day 337) occurred at the end of a 28-day on-treatment period of a cycle

| End point values | Tobramycin inhalation powder | | | |
|--------------------------------------|------------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 157 | | | |
| Units: Percent FEF | | | | |
| arithmetic mean (standard deviation) | | | | |
| Day 29, Cycle 1 (n=149) | 10.3 (± 36.05) | | | |
| Day 85, Cycle 2 (n=146) | 9.4 (± 55.35) | | | |
| Day 141, Cycle 3 (n=128) | 5.5 (± 31.82) | | | |

| | | | | |
|----------------------------|---------------|--|--|--|
| Day 197, Cycle 4 (n=116) | 6 (± 30.96) | | | |
| Day 253, Cycle 5 (n=105) | 2.9 (± 33.23) | | | |
| Day 309, Cycle 6 (n=100) | 4.3 (± 32.44) | | | |
| Day 337, Completion (n=93) | 0.7 (± 33.78) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change from baseline in Pseudomonas aeruginosa density over 6 treatment cycles

| | |
|-----------------|---|
| End point title | Absolute change from baseline in Pseudomonas aeruginosa density over 6 treatment cycles |
|-----------------|---|

End point description:

Microbiological data was collected to understand the direct impact of the drug on the pathogens. Sputum samples were cultured for the presence of three Pseudomonas aeruginosa (P. aeruginosa) biotypes measured were mucoid, dry and small colony variant. Absolute change was determined using the formula: Post- baseline value - baseline value. If no P. aeruginosa was isolated for a visit, log10 colony forming units (CFU) was imputed with log10 (19) for all biotypes. The analysis was performed in safety population, who had P. aeruginosa sputum density values at both baseline and the given time point. The 'n' signifies those subjects evaluable for this measure at specified time points for each group, respectively.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Day 29, Day 85, Day 141, Day 197, Day 253, Day 309, Day 337. All study visits (except baseline and Day 337) occurred at the end of a 28-day on-treatment period of a cycle

| End point values | Tobramycin inhalation powder | | | |
|---|------------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 157 | | | |
| Units: Base 10 logarithm of CFU (log10 CFU) | | | | |
| arithmetic mean (standard deviation) | | | | |
| Day 29, Cycle 1 (n=141) | -1.6 (± 2.28) | | | |
| Day 85, Cycle 2 (n=135) | -1.1 (± 1.8) | | | |
| Day 141, Cycle 3 (n=119) | -1.2 (± 1.98) | | | |
| Day 197, Cycle 4 (n=107) | -1.1 (± 2.11) | | | |
| Day 253, Cycle 5 (n=98) | -1.3 (± 2.23) | | | |
| Day 309, Cycle 6 (n=89) | -1.2 (± 2.09) | | | |
| Day 337, Study completion (n=85) | -0.4 (± 2.08) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in Tobramycin minimum inhibitory concentration (MIC) 50 and MIC 90 values for Pseudomonas aeruginosa

| | |
|---|---|
| End point title | Change from baseline in Tobramycin minimum inhibitory concentration (MIC) 50 and MIC 90 values for Pseudomonas aeruginosa |
| End point description: MIC was defined as the lowest concentration of an antimicrobial agent required to inhibit the visible growth of a microorganism after overnight incubation. Tobramycin MIC 50 and MIC 90 values were defined as the lowest concentration of tobramycin required to inhibit 50% and 90%, respectively, of the P. aeruginosa strains tested (mucoid, dry and small colony variant biotypes). The analysis was performed in safety population, who had microbiological data at specified time points. The 'n' signifies those subjects evaluable for this measure at specified time points for each group, respectively. | |
| End point type | Secondary |
| End point timeframe: Baseline, Day 29, Day 85, Day 141, Day 197, Day 253, Day 309, Day 337. All study visits (except baseline and Day 337) occurred at the end of a 28-day on-treatment period of a cycle | |

| End point values | Tobramycin inhalation powder | | | |
|---|------------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 157 | | | |
| Units: micrograms/millilitres | | | | |
| number (not applicable) | | | | |
| Cycle 1, day 29 - MIC 50 (n=144) | 2 | | | |
| Cycle 2, day 85 - MIC 50 (n=137) | 2 | | | |
| Cycle 3, day 141 - MIC 50 (n=124) | 2 | | | |
| Cycle 4, day 197 - MIC 50 (n=108) | 2 | | | |
| Cycle 5, day 253 - MIC 50 (n=98) | 2 | | | |
| Cycle 6, day 309 - MIC 50 (n=90) | 4 | | | |
| Study completion, day 337 - MIC 50 (n=89) | 2 | | | |
| Cycle 1, day 29 - MIC 90 (n=144) | 128 | | | |
| Cycle 2, day 85 - MIC 90 (n=137) | 256 | | | |
| Cycle 3, day 141 - MIC 90 (n=124) | 256 | | | |
| Cycle 4, day 197 - MIC 90 (n=108) | 256 | | | |
| Cycle 5, day 253 - MIC 90 (n=98) | 256 | | | |
| Cycle 6, day 309 - MIC 90 (n=90) | 256 | | | |
| Study completion, day 337 - MIC 90 (n=89) | 512 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects hospitalized due to respiratory related serious adverse events (SAEs)

| | |
|-----------------|--|
| End point title | Percentage of subjects hospitalized due to respiratory related serious adverse events (SAEs) |
|-----------------|--|

End point description:

The percentage of the subjects hospitalized due to serious respiratory-related AEs were determined during the study. The analysis was performed in safety population.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Day 337 (End of the study)

| End point values | Tobramycin inhalation powder | | | |
|-------------------------------|------------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 157 | | | |
| Units: Percentage of subjects | | | | |
| number (not applicable) | 26.8 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of hospitalization days due to respiratory related serious adverse events (SAEs)

| | |
|-----------------|---|
| End point title | Number of hospitalization days due to respiratory related serious adverse events (SAEs) |
|-----------------|---|

End point description:

The total number of hospitalization days due to serious respiratory-related adverse events was analyzed using Kaplan-Meier estimate. The analysis was performed in safety population.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Day 337 (End of the study)

| End point values | Tobramycin inhalation powder | | | |
|--------------------------------------|------------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 157 | | | |
| Units: Days | | | | |
| arithmetic mean (standard deviation) | 18.1 (± 17.14) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Time to first hospitalization due to respiratory related serious adverse

events (SAEs)

| | |
|-----------------|--|
| End point title | Time to first hospitalization due to respiratory related serious adverse events (SAEs) |
|-----------------|--|

End point description:

The day of first hospitalization due to serious respiratory-related adverse events was analyzed using Kaplan Meier estimate. The analysis was performed in safety population.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Day 337 (End of the study)

| | | | | |
|----------------------------------|------------------------------|--|--|--|
| End point values | Tobramycin inhalation powder | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 0 ^[2] | | | |
| Units: Days | | | | |
| median (confidence interval 95%) | (to) | | | |

Notes:

[2] - This outcome measure is not estimable due to low number of occurrence for this parameter

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects who used new anti-pseudomonal antibiotics

| | |
|-----------------|--|
| End point title | Percentage of subjects who used new anti-pseudomonal antibiotics |
|-----------------|--|

End point description:

The rate of anti-pseudomonal antibiotic use was determined from the collection of concomitant medication during the study. The analysis was performed in safety population.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Day 337 (End of the study)

| | | | | |
|-------------------------------|------------------------------|--|--|--|
| End point values | Tobramycin inhalation powder | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 157 | | | |
| Units: Percentage of subjects | | | | |
| number (not applicable) | 65.6 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Total number of days of new anti-pseudomonal antibiotics use

| | |
|-----------------|--|
| End point title | Total number of days of new anti-pseudomonal antibiotics use |
|-----------------|--|

End point description:

The total number of days with usage of new anti-pseudomonal antibiotic were determined. The analysis was performed in safety population.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Day 337 (End of the study)

| | | | | |
|--------------------------------------|------------------------------|--|--|--|
| End point values | Tobramycin inhalation powder | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 157 | | | |
| Units: Days | | | | |
| arithmetic mean (standard deviation) | 33.1 (\pm 25.17) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Time to use of new anti-pseudomonal antibiotics

| | |
|-----------------|---|
| End point title | Time to use of new anti-pseudomonal antibiotics |
|-----------------|---|

End point description:

Time to first usage of anti-pseudomonal antibiotic was determined using Kaplan Meier estimate. The analysis was performed in safety population.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Day 337 (End of the study)

| | | | | |
|----------------------------------|------------------------------|--|--|--|
| End point values | Tobramycin inhalation powder | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 157 | | | |
| Units: Days | | | | |
| median (confidence interval 95%) | 136 (97 to 170) | | | |

Statistical analyses

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Serious Adverse Events are monitored from date of First Subject First Visit (FSFV) until Last Subject Last Visit (LSLV). All other adverse events are monitored from First Subject First Treatment until Last Subject Last Visit.

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|--------------------|--------|
| Dictionary name | MedDRA |
| Dictionary version | 17.0 |

Reporting groups

| | |
|-----------------------|------------------------------|
| Reporting group title | Tobramycin inhalation powder |
|-----------------------|------------------------------|

Reporting group description:

Subjects inhaled four capsules of tobramycin inhalation powder (28 mg) bid via the T326 inhaler device, for 28 days (treatment phase in each cycle). Each treatment phase therefore consisted of 112 mg tobramycin (4 capsules of 28 mg each) with the total daily dose of 224 mg tobramycin (112mg bid). The treatment phase was followed by 28 days of no study treatment (off treatment in each cycle). These 56 days represented 1 cycle of therapy.

| Serious adverse events | Tobramycin inhalation powder | | |
|---|------------------------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 49 / 157 (31.21%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | 0 | | |
| Investigations | | | |
| Staphylococcus test positive | | | |
| subjects affected / exposed | 1 / 157 (0.64%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Injury, poisoning and procedural complications | | | |
| Rib fracture | | | |
| subjects affected / exposed | 1 / 157 (0.64%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac disorders | | | |
| Supraventricular tachycardia | | | |
| subjects affected / exposed | 1 / 157 (0.64%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|-----------------|--|--|
| Tachyarrhythmia | | | |
| subjects affected / exposed | 1 / 157 (0.64%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ear and labyrinth disorders | | | |
| Deafness unilateral | | | |
| subjects affected / exposed | 1 / 157 (0.64%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Tinnitus | | | |
| subjects affected / exposed | 1 / 157 (0.64%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| Gastritis | | | |
| subjects affected / exposed | 1 / 157 (0.64%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 1 / 157 (0.64%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pancreatitis | | | |
| subjects affected / exposed | 1 / 157 (0.64%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Subileus | | | |
| subjects affected / exposed | 1 / 157 (0.64%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Reproductive system and breast disorders | | | |
| Ovarian cyst | | | |

| | | | |
|---|-------------------|--|--|
| subjects affected / exposed | 1 / 157 (0.64%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Haemoptysis | | | |
| subjects affected / exposed | 5 / 157 (3.18%) | | |
| occurrences causally related to treatment / all | 2 / 5 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Bronchospasm | | | |
| subjects affected / exposed | 1 / 157 (0.64%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pneumothorax | | | |
| subjects affected / exposed | 1 / 157 (0.64%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 1 / 157 (0.64%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Bronchopneumonia | | | |
| subjects affected / exposed | 1 / 157 (0.64%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infective pulmonary exacerbation of cystic fibrosis | | | |
| subjects affected / exposed | 39 / 157 (24.84%) | | |
| occurrences causally related to treatment / all | 1 / 56 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Influenza | | | |
| subjects affected / exposed | 2 / 157 (1.27%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|-----------------|--|--|
| Pneumonia | | | |
| subjects affected / exposed | 3 / 157 (1.91%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Metabolism and nutrition disorders | | | |
| Hyperamylasaemia | | | |
| subjects affected / exposed | 1 / 157 (0.64%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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

| Non-serious adverse events | Tobramycin inhalation powder | | |
|---|------------------------------|--|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 121 / 157 (77.07%) | | |
| Investigations | | | |
| Forced expiratory volume decreased | | | |
| subjects affected / exposed | 8 / 157 (5.10%) | | |
| occurrences (all) | 8 | | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 11 / 157 (7.01%) | | |
| occurrences (all) | 12 | | |
| General disorders and administration site conditions | | | |
| Chest discomfort | | | |
| subjects affected / exposed | 9 / 157 (5.73%) | | |
| occurrences (all) | 10 | | |
| Fatigue | | | |
| subjects affected / exposed | 9 / 157 (5.73%) | | |
| occurrences (all) | 9 | | |
| Pyrexia | | | |
| subjects affected / exposed | 12 / 157 (7.64%) | | |
| occurrences (all) | 15 | | |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |

| | | | |
|---|-------------------|--|--|
| subjects affected / exposed | 11 / 157 (7.01%) | | |
| occurrences (all) | 16 | | |
| Nausea | | | |
| subjects affected / exposed | 8 / 157 (5.10%) | | |
| occurrences (all) | 15 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 41 / 157 (26.11%) | | |
| occurrences (all) | 69 | | |
| Dyspnoea | | | |
| subjects affected / exposed | 11 / 157 (7.01%) | | |
| occurrences (all) | 16 | | |
| Haemoptysis | | | |
| subjects affected / exposed | 33 / 157 (21.02%) | | |
| occurrences (all) | 64 | | |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 12 / 157 (7.64%) | | |
| occurrences (all) | 12 | | |
| Sputum increased | | | |
| subjects affected / exposed | 16 / 157 (10.19%) | | |
| occurrences (all) | 19 | | |
| Wheezing | | | |
| subjects affected / exposed | 8 / 157 (5.10%) | | |
| occurrences (all) | 11 | | |
| Infections and infestations | | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 21 / 157 (13.38%) | | |
| occurrences (all) | 31 | | |
| Infective pulmonary exacerbation of cystic fibrosis | | | |
| subjects affected / exposed | 67 / 157 (42.68%) | | |
| occurrences (all) | 121 | | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 15 / 157 (9.55%) | | |
| occurrences (all) | 19 | | |

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