



Clinical trial results:

A Randomized, Double-Blind, Placebo-Controlled, Crossover Multi-Center Study to Assess the Efficacy and Safety of Inhaled Tobramycin Nebuliser Solution (TOBI®) for the Treatment of Early Infections of *P. aeruginosa* in Cystic Fibrosis Subjects Aged from 3 Months to less than 7 years

Summary

| | |
|--------------------------|-------------------|
| EudraCT number | 2009-016590-15 |
| Trial protocol | HU FR GR DE IT PL |
| Global end of trial date | 24 June 2015 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 (current) |
| This version publication date | 02 July 2016 |
| First version publication date | 02 July 2016 |

Trial information

Trial identification

| | |
|-----------------------|--------------|
| Sponsor protocol code | CTBM100C2304 |
|-----------------------|--------------|

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 613421111, |
| Scientific contact | Clinical Disclosure Office, Novartis Pharma AG, 41 613421111, |

Notes:

Paediatric regulatory details

| | |
|--|---------------------|
| Is trial part of an agreed paediatric investigation plan (PIP) | Yes |
| EMA paediatric investigation plan number(s) | EMA-000184-PIP02-14 |
| 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? | Yes |

Notes:

Results analysis stage

| | |
|--|--------------|
| Analysis stage | Final |
| Date of interim/final analysis | 24 June 2015 |
| Is this the analysis of the primary completion data? | No |

| | |
|----------------------------------|--------------|
| Global end of trial reached? | Yes |
| Global end of trial date | 24 June 2015 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to estimate the proportion of patients free from any strain of *P. aeruginosa* assessed by sputum/throat swab culture at Day 29, i.e. after completion of a 28-day treatment period with either TOBI or placebo solution inhaled twice daily.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

| | |
|---|---------------|
| Actual start date of recruitment | 28 April 2010 |
| 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 | Canada: 17 |
| Country: Number of subjects enrolled | Egypt: 3 |
| Country: Number of subjects enrolled | France: 2 |
| Country: Number of subjects enrolled | Germany: 1 |
| Country: Number of subjects enrolled | Greece: 1 |
| Country: Number of subjects enrolled | Hungary: 4 |
| Country: Number of subjects enrolled | Italy: 1 |
| Country: Number of subjects enrolled | Russian Federation: 15 |
| Country: Number of subjects enrolled | Switzerland: 7 |
| Worldwide total number of subjects | 51 |
| EEA total number of subjects | 9 |

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) | 16 |
| Children (2-11 years) | 35 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 0 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Participants were randomized 1:1 to TOBI or placebo. After 1 treatment cycle, participants who were P.a positive entered an OL phase. Participants who were P.a negative entered cross-over treatment.

Pre-assignment

Screening details:

The cross-over was optional. At the end of the cross-over or OL phase, participants who were P.a positive terminated the study. P.a negative participants entered follow-up.

Period 1

| | |
|------------------------------|---|
| Period 1 title | Double-blind period |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Monitor, Data analyst, Carer, Assessor |

Arms

| | |
|------------------------------|--|
| Are arms mutually exclusive? | Yes |
| Arm title | TOBI (tobramycin inhaled solution)/Placebo |

Arm description:

Participants randomized to TOBI received the investigational treatment for 28 days twice daily (bid) in the first treatment cycle. At the end of first treatment cycle, participants who were positive for P. aeruginosa entered the open label (OL) phase of the study and received TOBI for 28 days bid. Participants who were negative for P. aeruginosa at the end of first treatment cycle and agreed to participate in the cross-over treatment period received placebo for 28 days bid (second treatment cycle). Eligible participants were followed-up for up to 12-months, having visits every 3 months. If participants were detected P. aeruginosa positive, they received 28-days of OL TOBI. Participants who remained P.aeruginosa positive after TOBI OL treatment discontinued the study. Participants who became P.aeruginosa negative after OL TOBI treatment remained in the study.

| | |
|--|-----------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Tobramycin inhaled solution |
| Investigational medicinal product code | TBM100 |
| Other name | TOBI |
| Pharmaceutical forms | Inhalation solution |
| Routes of administration | Inhalation use |

Dosage and administration details:

Patients received 300mg/5mL TOBI for 28 days bid.

| | |
|------------------|--------------|
| Arm title | Placebo/TOBI |
|------------------|--------------|

Arm description:

Participants randomized to placebo group received 0.9 % saline (NaCl) for 28 days bid in the first treatment cycle. At the end of first treatment cycle, participants who were positive for P. aeruginosa entered the OL phase of the study and received TOBI for 28 days bid. Participants who were negative for P. aeruginosa at the end of first treatment cycle and agreed to participate in the cross-over treatment period received TOBI for 28 days bid (second treatment cycle). Eligible participants were followed-up for up to 12-months, having visits every 3 months. If participants were detected P. aeruginosa positive, they received 28-days of OL TOBI. Participants who remained P.aeruginosa positive after TOBI OL treatment discontinued the study. Participants who became P.aeruginosa negative after OL TOBI treatment remained in the study.

| | |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

| | |
|--|---------------------|
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Inhalation solution |
| Routes of administration | Inhalation use |

Dosage and administration details:

Patients received 0.9 % saline (NaCl) for 28 days bid.

| Number of subjects in period 1 | TOBI (tobramycin inhaled solution)/Placebo | Placebo/TOBI |
|---------------------------------------|---|---------------------|
| Started | 26 | 25 |
| Stage 1:1st treatment (tx) cycle | 26 | 25 |
| Stage 2:no tx | 0 ^[1] | 0 ^[2] |
| Entered OL TOBI | 4 ^[3] | 18 |
| P.a-free,day 29 w/ no cross-over | 9 ^[4] | 0 ^[5] |
| Stage 3: cross-over (co) tx | 13 ^[6] | 6 ^[7] |
| Stage 4:no tx for patients not in co | 0 ^[8] | 0 ^[9] |
| Completed | 21 | 12 |
| Not completed | 5 | 13 |
| Adverse event, non-fatal | - | 1 |
| Administrative problems | - | 1 |
| Lack of efficacy | 5 | 11 |

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: The number of subjects is correct.

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: The number of subjects is correct.

[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: The number of subjects is correct.

[4] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: The number of subjects is correct.

[5] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: The number of subjects is correct.

[6] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: The number of subjects is correct.

[7] - The number of subjects at this milestone seems inconsistent with the number of subjects in the

arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: The number of subjects is correct.

[8] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: The number of subjects is correct.

[9] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: The number of subjects is correct.

Period 2

| | |
|------------------------------|-----------------------------|
| Period 2 title | Follow-up (F-U) period |
| Is this the baseline period? | No |
| Allocation method | Non-randomised - controlled |
| Blinding used | Not blinded |

Arms

| | |
|------------------------------|--|
| Are arms mutually exclusive? | Yes |
| Arm title | TOBI (tobramycin inhaled solution)/Placebo |

Arm description:

Eligible participants were followed-up for up to 12-months, having visits every 3 months. If participants were detected P. aeruginosa positive, they received 28-days of OL TOBI. Participants who remained P.aeruginosa positive after TOBI OL treatment discontinued the study. Participants who became P.aeruginosa negative after OL TOBI treatment remained in the study.

| | |
|--|-----------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Tobramycin inhaled solution |
| Investigational medicinal product code | TBM100C |
| Other name | TOBI |
| Pharmaceutical forms | Inhalation solution |
| Routes of administration | Inhalation use |

Dosage and administration details:

If participants were detected P. aeruginosa positive during follow-up, they received 28-days of OL TOBI 300mg/5mL bid.

| | |
|------------------|--------------|
| Arm title | Placebo/TOBI |
|------------------|--------------|

Arm description:

Eligible participants were followed-up for up to 12-months, having visits every 3 months. If participants were detected P. aeruginosa positive, they received 28-days of OL TOBI. Participants who remained P.aeruginosa positive after TOBI OL treatment discontinued the study. Participants who became P.aeruginosa negative after OL TOBI treatment remained in the study.

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

Dosage and administration details:

If participants were detected P. aeruginosa positive during follow-up, they received 28-days of OL TOBI 300mg/5mL bid.

| Number of subjects in period 2^[10] | TOBI (tobramycin inhaled solution)/Placebo | Placebo/TOBI |
|--|--|-------------------|
| Started | 19 | 10 |
| Treated in F-U | 5 ^[11] | 5 ^[12] |
| Completed | 17 | 9 |
| Not completed | 2 | 1 |
| Adverse event, non-fatal | - | 1 |
| Administrative problems | 1 | - |
| Abnormal lab values | 1 | - |

Notes:

[10] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: The number of subjects is correct.

[11] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: The number of subjects is correct.

[12] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: The number of subjects is correct.

Baseline characteristics

Reporting groups

| | |
|-----------------------|--|
| Reporting group title | TOBI (tobramycin inhaled solution)/Placebo |
|-----------------------|--|

Reporting group description:

Participants randomized to TOBI received the investigational treatment for 28 days twice daily (bid) in the first treatment cycle. At the end of first treatment cycle, participants who were positive for P. aeruginosa entered the open label (OL) phase of the study and received TOBI for 28 days bid. Participants who were negative for P. aeruginosa at the end of first treatment cycle and agreed to participate in the cross-over treatment period received placebo for 28 days bid (second treatment cycle). Eligible participants were followed-up for up to 12-months, having visits every 3 months. If participants were detected P. aeruginosa positive, they received 28-days of OL TOBI. Participants who remained P.aeruginosa positive after TOBI OL treatment discontinued the study. Participants who became P.aeruginosa negative after OL TOBI treatment remained in the study.

| | |
|-----------------------|--------------|
| Reporting group title | Placebo/TOBI |
|-----------------------|--------------|

Reporting group description:

Participants randomized to placebo group received 0.9 % saline (NaCl) for 28 days bid in the first treatment cycle. At the end of first treatment cycle, participants who were positive for P. aeruginosa entered the OL phase of the study and received TOBI for 28 days bid. Participants who were negative for P. aeruginosa at the end of first treatment cycle and agreed to participate in the cross-over treatment period received TOBI for 28 days bid (second treatment cycle). Eligible participants were followed-up for up to 12-months, having visits every 3 months. If participants were detected P. aeruginosa positive, they received 28-days of OL TOBI. Participants who remained P.aeruginosa positive after TOBI OL treatment discontinued the study. Participants who became P.aeruginosa negative after OL TOBI treatment remained in the study.

| Reporting group values | TOBI (tobramycin inhaled solution)/Placebo | Placebo/TOBI | Total |
|--|--|--------------|-------|
| Number of subjects | 26 | 25 | 51 |
| 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) | 8 | 8 | 16 |
| Children (2-11 years) | 18 | 17 | 35 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 0 | 0 | 0 |
| From 65-84 years | 0 | 0 | 0 |
| 85 years and over | 0 | 0 | 0 |
| Age Continuous Units: Years | | | |
| arithmetic mean | 2.9 | 2.7 | |
| standard deviation | ± 1.96 | ± 1.93 | - |
| Gender, Male/Female Units: Participants | | | |
| Female | 15 | 17 | 32 |
| Male | 11 | 8 | 19 |

End points

End points reporting groups

| | |
|--|--|
| Reporting group title | TOBI (tobramycin inhaled solution)/Placebo |
| Reporting group description: Participants randomized to TOBI received the investigational treatment for 28 days twice daily (bid) in the first treatment cycle. At the end of first treatment cycle, participants who were positive for P. aeruginosa entered the open label (OL) phase of the study and received TOBI for 28 days bid. Participants who were negative for P. aeruginosa at the end of first treatment cycle and agreed to participate in the cross-over treatment period received placebo for 28 days bid (second treatment cycle). Eligible participants were followed-up for up to 12-months, having visits every 3 months. If participants were detected P. aeruginosa positive, they received 28-days of OL TOBI. Participants who remained P.aeruginosa positive after TOBI OL treatment discontinued the study. Participants who became P.aeruginosa negative after OL TOBI treatment remained in the study. | |
| Reporting group title | Placebo/TOBI |
| Reporting group description: Participants randomized to placebo group received 0.9 % saline (NaCl) for 28 days bid in the first treatment cycle. At the end of first treatment cycle, participants who were positive for P. aeruginosa entered the OL phase of the study and received TOBI for 28 days bid. Participants who were negative for P. aeruginosa at the end of first treatment cycle and agreed to participate in the cross-over treatment period received TOBI for 28 days bid (second treatment cycle). Eligible participants were followed-up for up to 12-months, having visits every 3 months. If participants were detected P. aeruginosa positive, they received 28-days of OL TOBI. Participants who remained P.aeruginosa positive after TOBI OL treatment discontinued the study. Participants who became P.aeruginosa negative after OL TOBI treatment remained in the study. | |
| Reporting group title | TOBI (tobramycin inhaled solution)/Placebo |
| Reporting group description: Eligible participants were followed-up for up to 12-months, having visits every 3 months. If participants were detected P. aeruginosa positive, they received 28-days of OL TOBI. Participants who remained P.aeruginosa positive after TOBI OL treatment discontinued the study. Participants who became P.aeruginosa negative after OL TOBI treatment remained in the study. | |
| Reporting group title | Placebo/TOBI |
| Reporting group description: Eligible participants were followed-up for up to 12-months, having visits every 3 months. If participants were detected P. aeruginosa positive, they received 28-days of OL TOBI. Participants who remained P.aeruginosa positive after TOBI OL treatment discontinued the study. Participants who became P.aeruginosa negative after OL TOBI treatment remained in the study. | |

Primary: Percentage of participants P aeruginosa-free after completion of the first treatment cycle

| | |
|--|--|
| End point title | Percentage of participants P aeruginosa-free after completion of the first treatment cycle |
| End point description: Sputum/throat swab cultures were assessed. | |
| End point type | Primary |
| End point timeframe: Day 29 | |

| End point values | TOBI (tobramycin inhaled solution)/Place bo | Placebo/TOBI | | |
|-----------------------------------|---|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 26 | 25 | | |
| Units: Percentage of participants | | | | |
| number (not applicable) | 84.6 | 24 | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Analysis of patients free of P. aeruginosa at Day |
| Comparison groups | Placebo/TOBI v TOBI (tobramycin inhaled solution)/Placebo |
| Number of subjects included in analysis | 51 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 21.55 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 4.67 |
| upper limit | 99.52 |

Secondary: Percentage of participants free from P. aeruginosa 28 days after termination of the second treatment cycle

| | |
|--|--|
| End point title | Percentage of participants free from P. aeruginosa 28 days after termination of the second treatment cycle |
| End point description: | |
| Sputum/throat swab cultures were assessed. | |
| End point type | Secondary |
| End point timeframe: | |
| Day 91 | |

| End point values | TOBI (tobramycin inhaled solution)/Place bo | Placebo/TOBI | | |
|-----------------------------------|---|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 13 | 6 | | |
| Units: Percentage of participants | | | | |
| number (not applicable) | 92.3 | 83.3 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants P aeruginosa-free at the termination of the double-blind period

| | |
|-----------------|--|
| End point title | Percentage of participants P aeruginosa-free at the termination of the double-blind period |
|-----------------|--|

End point description:

Sputum/throat swab cultures were assessed.

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

End point timeframe:

Day 91

| End point values | TOBI (tobramycin inhaled solution)/Place bo | Placebo/TOBI | | |
|-----------------------------------|---|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 25 | 22 | | |
| Units: Percentage of participants | | | | |
| number (not applicable) | 76 | 47.8 | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All adverse events reported in this record are from date of First Patient First Treatment until Last Patient Last Visit.

| | |
|---|---------------------------|
| Assessment type | Systematic |
| Dictionary used | |
| Dictionary name | MedDRA |
| Dictionary version | 18.0 |
| Reporting groups | |
| Reporting group title | DB TOBI |
| Reporting group description: DB TOBI | |
| Reporting group title | DB Placebo |
| Reporting group description: DB Placebo | |
| Reporting group title | OL TOBI (core) |
| Reporting group description: OL TOBI (core) | |
| Reporting group title | Off-treatment (core) |
| Reporting group description: Off-treatment (core) | |
| Reporting group title | OL TOBI (follow-up) |
| Reporting group description: OL TOBI (follow-up) | |
| Reporting group title | Off-treatment (follow-up) |
| Reporting group description: Off-treatment (follow-up) | |

| Serious adverse events | DB TOBI | DB Placebo | OL TOBI (core) |
|---|----------------|----------------|----------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 1 / 38 (2.63%) | 0 / 22 (0.00%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Congenital, familial and genetic disorders | | | |
| Glucose-6-phosphate dehydrogenase deficiency | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 0 / 38 (0.00%) | 0 / 22 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |

| | | | |
|---|----------------|----------------|----------------|
| Hypertension | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 0 / 38 (0.00%) | 0 / 22 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| Haemolytic anaemia | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 0 / 38 (0.00%) | 0 / 22 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Stridor | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 0 / 38 (0.00%) | 0 / 22 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Bacterial disease carrier | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 0 / 38 (0.00%) | 0 / 22 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bronchopneumonia | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 0 / 38 (0.00%) | 0 / 22 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Croup infectious | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 0 / 38 (0.00%) | 0 / 22 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infective pulmonary exacerbation of cystic fibrosis | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 0 / 38 (0.00%) | 0 / 22 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Laryngitis | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 32 (0.00%) | 0 / 38 (0.00%) | 0 / 22 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lower respiratory tract infection bacterial | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 0 / 38 (0.00%) | 0 / 22 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pseudomonas infection | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 0 / 38 (0.00%) | 0 / 22 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Staphylococcal infection | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 0 / 38 (0.00%) | 0 / 22 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Upper respiratory tract infection bacterial | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 1 / 38 (2.63%) | 0 / 22 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| Serious adverse events | Off-treatment (core) | OL TOBI (follow-up) | Off-treatment (follow-up) |
|---|----------------------|---------------------|---------------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 2 / 50 (4.00%) | 0 / 10 (0.00%) | 4 / 29 (13.79%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Congenital, familial and genetic disorders | | | |
| Glucose-6-phosphate dehydrogenase deficiency | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 10 (0.00%) | 1 / 29 (3.45%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| Hypertension | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 10 (0.00%) | 1 / 29 (3.45%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| Haemolytic anaemia | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 10 (0.00%) | 1 / 29 (3.45%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Stridor | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 10 (0.00%) | 1 / 29 (3.45%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Bacterial disease carrier | | | |
| subjects affected / exposed | 1 / 50 (2.00%) | 0 / 10 (0.00%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bronchopneumonia | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 10 (0.00%) | 1 / 29 (3.45%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Croup infectious | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 10 (0.00%) | 1 / 29 (3.45%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infective pulmonary exacerbation of cystic fibrosis | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 10 (0.00%) | 1 / 29 (3.45%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Laryngitis | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 10 (0.00%) | 1 / 29 (3.45%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lower respiratory tract infection bacterial | | | |
| subjects affected / exposed | 1 / 50 (2.00%) | 0 / 10 (0.00%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pseudomonas infection | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 10 (0.00%) | 1 / 29 (3.45%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Staphylococcal infection | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 10 (0.00%) | 1 / 29 (3.45%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Upper respiratory tract infection bacterial | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 10 (0.00%) | 0 / 29 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

Frequency threshold for reporting non-serious adverse events: 3 %

| Non-serious adverse events | DB TOBI | DB Placebo | OL TOBI (core) |
|---|------------------|------------------|------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 12 / 32 (37.50%) | 18 / 38 (47.37%) | 10 / 22 (45.45%) |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 0 / 38 (0.00%) | 0 / 22 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pyrexia | | | |
| subjects affected / exposed | 2 / 32 (6.25%) | 3 / 38 (7.89%) | 2 / 22 (9.09%) |
| occurrences (all) | 2 | 3 | 2 |
| Immune system disorders | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| Food allergy | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 0 / 38 (0.00%) | 0 / 22 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Seasonal allergy | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 0 / 38 (0.00%) | 0 / 22 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Bronchospasm | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 0 / 38 (0.00%) | 0 / 22 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Catarrh | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 1 / 38 (2.63%) | 0 / 22 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Cough | | | |
| subjects affected / exposed | 4 / 32 (12.50%) | 6 / 38 (15.79%) | 4 / 22 (18.18%) |
| occurrences (all) | 4 | 6 | 5 |
| Dysphonia | | | |
| subjects affected / exposed | 1 / 32 (3.13%) | 0 / 38 (0.00%) | 0 / 22 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Dyspnoea | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 0 / 38 (0.00%) | 0 / 22 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Increased bronchial secretion | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 0 / 38 (0.00%) | 1 / 22 (4.55%) |
| occurrences (all) | 0 | 0 | 1 |
| Nasal congestion | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 0 / 38 (0.00%) | 0 / 22 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Nasal dryness | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 0 / 38 (0.00%) | 0 / 22 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 0 / 38 (0.00%) | 1 / 22 (4.55%) |
| occurrences (all) | 0 | 0 | 1 |
| Productive cough | | | |

| | | | |
|---|---------------------|---------------------|---------------------|
| subjects affected / exposed occurrences (all) | 0 / 32 (0.00%) 0 | 0 / 38 (0.00%) 0 | 0 / 22 (0.00%) 0 |
| Rhinorrhoea subjects affected / exposed occurrences (all) | 1 / 32 (3.13%) 1 | 1 / 38 (2.63%) 1 | 2 / 22 (9.09%) 2 |
| Snoring subjects affected / exposed occurrences (all) | 0 / 32 (0.00%) 0 | 0 / 38 (0.00%) 0 | 0 / 22 (0.00%) 0 |
| Wheezing subjects affected / exposed occurrences (all) | 1 / 32 (3.13%) 1 | 0 / 38 (0.00%) 0 | 0 / 22 (0.00%) 0 |
| Psychiatric disorders Bruxism subjects affected / exposed occurrences (all) | 0 / 32 (0.00%) 0 | 0 / 38 (0.00%) 0 | 0 / 22 (0.00%) 0 |
| Restlessness subjects affected / exposed occurrences (all) | 0 / 32 (0.00%) 0 | 0 / 38 (0.00%) 0 | 0 / 22 (0.00%) 0 |
| Investigations Acinetobacter test positive subjects affected / exposed occurrences (all) | 0 / 32 (0.00%) 0 | 0 / 38 (0.00%) 0 | 0 / 22 (0.00%) 0 |
| Alanine aminotransferase increased subjects affected / exposed occurrences (all) | 0 / 32 (0.00%) 0 | 2 / 38 (5.26%) 2 | 0 / 22 (0.00%) 0 |
| Aspergillus test positive subjects affected / exposed occurrences (all) | 0 / 32 (0.00%) 0 | 0 / 38 (0.00%) 0 | 0 / 22 (0.00%) 0 |
| Pseudomonas test positive subjects affected / exposed occurrences (all) | 0 / 32 (0.00%) 0 | 1 / 38 (2.63%) 1 | 0 / 22 (0.00%) 0 |
| Streptococcus test positive subjects affected / exposed occurrences (all) | 0 / 32 (0.00%) 0 | 0 / 38 (0.00%) 0 | 1 / 22 (4.55%) 1 |
| Injury, poisoning and procedural complications | | | |

| | | | |
|--|---------------------|---------------------|---------------------|
| Foreign body subjects affected / exposed occurrences (all) | 0 / 32 (0.00%) 0 | 0 / 38 (0.00%) 0 | 0 / 22 (0.00%) 0 |
| Upper limb fracture subjects affected / exposed occurrences (all) | 0 / 32 (0.00%) 0 | 0 / 38 (0.00%) 0 | 0 / 22 (0.00%) 0 |
| Nervous system disorders Headache subjects affected / exposed occurrences (all) | 0 / 32 (0.00%) 0 | 0 / 38 (0.00%) 0 | 0 / 22 (0.00%) 0 |
| Lethargy subjects affected / exposed occurrences (all) | 0 / 32 (0.00%) 0 | 0 / 38 (0.00%) 0 | 1 / 22 (4.55%) 1 |
| Ear and labyrinth disorders Ear pain subjects affected / exposed occurrences (all) | 1 / 32 (3.13%) 1 | 1 / 38 (2.63%) 1 | 0 / 22 (0.00%) 0 |
| Eye disorders Eye discharge subjects affected / exposed occurrences (all) | 0 / 32 (0.00%) 0 | 0 / 38 (0.00%) 0 | 0 / 22 (0.00%) 0 |
| Gastrointestinal disorders Abdominal distension subjects affected / exposed occurrences (all) | 0 / 32 (0.00%) 0 | 1 / 38 (2.63%) 1 | 0 / 22 (0.00%) 0 |
| Abdominal pain subjects affected / exposed occurrences (all) | 0 / 32 (0.00%) 0 | 0 / 38 (0.00%) 0 | 1 / 22 (4.55%) 1 |
| Constipation subjects affected / exposed occurrences (all) | 0 / 32 (0.00%) 0 | 0 / 38 (0.00%) 0 | 0 / 22 (0.00%) 0 |
| Diarrhoea subjects affected / exposed occurrences (all) | 1 / 32 (3.13%) 1 | 0 / 38 (0.00%) 0 | 0 / 22 (0.00%) 0 |
| Faeces soft subjects affected / exposed occurrences (all) | 0 / 32 (0.00%) 0 | 0 / 38 (0.00%) 0 | 0 / 22 (0.00%) 0 |

| | | | |
|---|---------------------|---------------------|---------------------|
| Oral mucosal eruption subjects affected / exposed occurrences (all) | 0 / 32 (0.00%) 0 | 0 / 38 (0.00%) 0 | 1 / 22 (4.55%) 1 |
| Teething subjects affected / exposed occurrences (all) | 2 / 32 (6.25%) 2 | 0 / 38 (0.00%) 0 | 0 / 22 (0.00%) 0 |
| Toothache subjects affected / exposed occurrences (all) | 1 / 32 (3.13%) 1 | 0 / 38 (0.00%) 0 | 0 / 22 (0.00%) 0 |
| Vomiting subjects affected / exposed occurrences (all) | 0 / 32 (0.00%) 0 | 3 / 38 (7.89%) 3 | 0 / 22 (0.00%) 0 |
| Skin and subcutaneous tissue disorders | | | |
| Pruritus subjects affected / exposed occurrences (all) | 0 / 32 (0.00%) 0 | 0 / 38 (0.00%) 0 | 0 / 22 (0.00%) 0 |
| Rash subjects affected / exposed occurrences (all) | 1 / 32 (3.13%) 2 | 1 / 38 (2.63%) 1 | 0 / 22 (0.00%) 0 |
| Rash generalised subjects affected / exposed occurrences (all) | 1 / 32 (3.13%) 1 | 0 / 38 (0.00%) 0 | 0 / 22 (0.00%) 0 |
| Infections and infestations | | | |
| Bronchitis subjects affected / exposed occurrences (all) | 0 / 32 (0.00%) 0 | 0 / 38 (0.00%) 0 | 0 / 22 (0.00%) 0 |
| Conjunctivitis subjects affected / exposed occurrences (all) | 1 / 32 (3.13%) 1 | 0 / 38 (0.00%) 0 | 0 / 22 (0.00%) 0 |
| Ear infection subjects affected / exposed occurrences (all) | 0 / 32 (0.00%) 0 | 1 / 38 (2.63%) 1 | 1 / 22 (4.55%) 1 |
| Eye infection subjects affected / exposed occurrences (all) | 0 / 32 (0.00%) 0 | 0 / 38 (0.00%) 0 | 0 / 22 (0.00%) 0 |
| Gastroenteritis | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 32 (0.00%) | 1 / 38 (2.63%) | 0 / 22 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Lobar pneumonia | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 0 / 38 (0.00%) | 0 / 22 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Lower respiratory tract infection bacterial | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 0 / 38 (0.00%) | 1 / 22 (4.55%) |
| occurrences (all) | 0 | 0 | 1 |
| Lung infection | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 0 / 38 (0.00%) | 0 / 22 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Nasopharyngitis | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 1 / 38 (2.63%) | 1 / 22 (4.55%) |
| occurrences (all) | 0 | 1 | 1 |
| Otitis media | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 0 / 38 (0.00%) | 0 / 22 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Perineal infection | | | |
| subjects affected / exposed | 1 / 32 (3.13%) | 0 / 38 (0.00%) | 0 / 22 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Pharyngitis | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 0 / 38 (0.00%) | 0 / 22 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pseudomonas infection | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 0 / 38 (0.00%) | 0 / 22 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Respiratory tract infection | | | |
| subjects affected / exposed | 1 / 32 (3.13%) | 0 / 38 (0.00%) | 1 / 22 (4.55%) |
| occurrences (all) | 1 | 0 | 1 |
| Respiratory tract infection viral | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 3 / 38 (7.89%) | 0 / 22 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |
| Rhinitis | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 1 / 38 (2.63%) | 0 / 22 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |

| | | | |
|--|---------------------|---------------------|---------------------|
| Staphylococcal infection subjects affected / exposed occurrences (all) | 0 / 32 (0.00%) 0 | 0 / 38 (0.00%) 0 | 0 / 22 (0.00%) 0 |
| Tonsillitis subjects affected / exposed occurrences (all) | 0 / 32 (0.00%) 0 | 0 / 38 (0.00%) 0 | 0 / 22 (0.00%) 0 |
| Urinary tract infection subjects affected / exposed occurrences (all) | 0 / 32 (0.00%) 0 | 0 / 38 (0.00%) 0 | 1 / 22 (4.55%) 1 |
| Varicella subjects affected / exposed occurrences (all) | 0 / 32 (0.00%) 0 | 1 / 38 (2.63%) 1 | 0 / 22 (0.00%) 0 |
| Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all) | 1 / 32 (3.13%) 1 | 1 / 38 (2.63%) 1 | 0 / 22 (0.00%) 0 |

| Non-serious adverse events | Off-treatment (core) | OL TOBI (follow-up) | Off-treatment (follow-up) |
|--|----------------------|---------------------|---------------------------|
| Total subjects affected by non-serious adverse events subjects affected / exposed | 13 / 50 (26.00%) | 2 / 10 (20.00%) | 23 / 29 (79.31%) |
| General disorders and administration site conditions Asthenia subjects affected / exposed occurrences (all) | 0 / 50 (0.00%) 0 | 0 / 10 (0.00%) 0 | 1 / 29 (3.45%) 1 |
| Pyrexia subjects affected / exposed occurrences (all) | 5 / 50 (10.00%) 5 | 0 / 10 (0.00%) 0 | 10 / 29 (34.48%) 16 |
| Immune system disorders Food allergy subjects affected / exposed occurrences (all) | 0 / 50 (0.00%) 0 | 0 / 10 (0.00%) 0 | 1 / 29 (3.45%) 1 |
| Seasonal allergy subjects affected / exposed occurrences (all) | 0 / 50 (0.00%) 0 | 0 / 10 (0.00%) 0 | 1 / 29 (3.45%) 1 |
| Respiratory, thoracic and mediastinal disorders | | | |

| | | | |
|-------------------------------|----------------|-----------------|------------------|
| Bronchospasm | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 10 (0.00%) | 1 / 29 (3.45%) |
| occurrences (all) | 0 | 0 | 1 |
| Catarrh | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 10 (0.00%) | 2 / 29 (6.90%) |
| occurrences (all) | 0 | 0 | 4 |
| Cough | | | |
| subjects affected / exposed | 3 / 50 (6.00%) | 1 / 10 (10.00%) | 12 / 29 (41.38%) |
| occurrences (all) | 3 | 1 | 17 |
| Dysphonia | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 10 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Dyspnoea | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 10 (0.00%) | 2 / 29 (6.90%) |
| occurrences (all) | 0 | 0 | 2 |
| Increased bronchial secretion | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 10 (0.00%) | 1 / 29 (3.45%) |
| occurrences (all) | 0 | 0 | 1 |
| Nasal congestion | | | |
| subjects affected / exposed | 1 / 50 (2.00%) | 1 / 10 (10.00%) | 3 / 29 (10.34%) |
| occurrences (all) | 1 | 1 | 3 |
| Nasal dryness | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 10 (0.00%) | 1 / 29 (3.45%) |
| occurrences (all) | 0 | 0 | 1 |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 10 (0.00%) | 1 / 29 (3.45%) |
| occurrences (all) | 0 | 0 | 1 |
| Productive cough | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 10 (0.00%) | 1 / 29 (3.45%) |
| occurrences (all) | 0 | 0 | 1 |
| Rhinorrhoea | | | |
| subjects affected / exposed | 4 / 50 (8.00%) | 0 / 10 (0.00%) | 7 / 29 (24.14%) |
| occurrences (all) | 5 | 0 | 10 |
| Snoring | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 10 (0.00%) | 1 / 29 (3.45%) |
| occurrences (all) | 0 | 0 | 1 |

| | | | |
|--|---------------------|----------------------|---------------------|
| Wheezing subjects affected / exposed occurrences (all) | 1 / 50 (2.00%) 1 | 1 / 10 (10.00%) 1 | 1 / 29 (3.45%) 1 |
| Psychiatric disorders Bruxism subjects affected / exposed occurrences (all) | 0 / 50 (0.00%) 0 | 0 / 10 (0.00%) 0 | 1 / 29 (3.45%) 1 |
| Restlessness subjects affected / exposed occurrences (all) | 0 / 50 (0.00%) 0 | 0 / 10 (0.00%) 0 | 1 / 29 (3.45%) 1 |
| Investigations Acinetobacter test positive subjects affected / exposed occurrences (all) | 0 / 50 (0.00%) 0 | 0 / 10 (0.00%) 0 | 1 / 29 (3.45%) 1 |
| Alanine aminotransferase increased subjects affected / exposed occurrences (all) | 0 / 50 (0.00%) 0 | 0 / 10 (0.00%) 0 | 0 / 29 (0.00%) 0 |
| Aspergillus test positive subjects affected / exposed occurrences (all) | 0 / 50 (0.00%) 0 | 0 / 10 (0.00%) 0 | 1 / 29 (3.45%) 1 |
| Pseudomonas test positive subjects affected / exposed occurrences (all) | 0 / 50 (0.00%) 0 | 0 / 10 (0.00%) 0 | 2 / 29 (6.90%) 2 |
| Streptococcus test positive subjects affected / exposed occurrences (all) | 0 / 50 (0.00%) 0 | 0 / 10 (0.00%) 0 | 0 / 29 (0.00%) 0 |
| Injury, poisoning and procedural complications Foreign body subjects affected / exposed occurrences (all) | 0 / 50 (0.00%) 0 | 0 / 10 (0.00%) 0 | 1 / 29 (3.45%) 1 |
| Upper limb fracture subjects affected / exposed occurrences (all) | 0 / 50 (0.00%) 0 | 0 / 10 (0.00%) 0 | 1 / 29 (3.45%) 1 |
| Nervous system disorders Headache | | | |

| | | | |
|--|---------------------|---------------------|----------------------|
| subjects affected / exposed occurrences (all) | 0 / 50 (0.00%) 0 | 0 / 10 (0.00%) 0 | 1 / 29 (3.45%) 1 |
| Lethargy subjects affected / exposed occurrences (all) | 0 / 50 (0.00%) 0 | 0 / 10 (0.00%) 0 | 0 / 29 (0.00%) 0 |
| Ear and labyrinth disorders Ear pain subjects affected / exposed occurrences (all) | 0 / 50 (0.00%) 0 | 0 / 10 (0.00%) 0 | 0 / 29 (0.00%) 0 |
| Eye disorders Eye discharge subjects affected / exposed occurrences (all) | 0 / 50 (0.00%) 0 | 0 / 10 (0.00%) 0 | 1 / 29 (3.45%) 1 |
| Gastrointestinal disorders Abdominal distension subjects affected / exposed occurrences (all) | 0 / 50 (0.00%) 0 | 0 / 10 (0.00%) 0 | 1 / 29 (3.45%) 1 |
| Abdominal pain subjects affected / exposed occurrences (all) | 0 / 50 (0.00%) 0 | 0 / 10 (0.00%) 0 | 5 / 29 (17.24%) 5 |
| Constipation subjects affected / exposed occurrences (all) | 1 / 50 (2.00%) 1 | 0 / 10 (0.00%) 0 | 4 / 29 (13.79%) 4 |
| Diarrhoea subjects affected / exposed occurrences (all) | 0 / 50 (0.00%) 0 | 0 / 10 (0.00%) 0 | 1 / 29 (3.45%) 1 |
| Faeces soft subjects affected / exposed occurrences (all) | 0 / 50 (0.00%) 0 | 0 / 10 (0.00%) 0 | 2 / 29 (6.90%) 2 |
| Oral mucosal eruption subjects affected / exposed occurrences (all) | 0 / 50 (0.00%) 0 | 0 / 10 (0.00%) 0 | 0 / 29 (0.00%) 0 |
| Teething subjects affected / exposed occurrences (all) | 1 / 50 (2.00%) 1 | 0 / 10 (0.00%) 0 | 0 / 29 (0.00%) 0 |
| Toothache | | | |

| | | | |
|--|---------------------|---------------------|----------------------|
| subjects affected / exposed occurrences (all) | 0 / 50 (0.00%) 0 | 0 / 10 (0.00%) 0 | 0 / 29 (0.00%) 0 |
| Vomiting subjects affected / exposed occurrences (all) | 1 / 50 (2.00%) 1 | 0 / 10 (0.00%) 0 | 4 / 29 (13.79%) 4 |
| Skin and subcutaneous tissue disorders | | | |
| Pruritus subjects affected / exposed occurrences (all) | 0 / 50 (0.00%) 0 | 0 / 10 (0.00%) 0 | 1 / 29 (3.45%) 1 |
| Rash subjects affected / exposed occurrences (all) | 1 / 50 (2.00%) 1 | 0 / 10 (0.00%) 0 | 1 / 29 (3.45%) 1 |
| Rash generalised subjects affected / exposed occurrences (all) | 0 / 50 (0.00%) 0 | 0 / 10 (0.00%) 0 | 0 / 29 (0.00%) 0 |
| Infections and infestations | | | |
| Bronchitis subjects affected / exposed occurrences (all) | 0 / 50 (0.00%) 0 | 0 / 10 (0.00%) 0 | 2 / 29 (6.90%) 3 |
| Conjunctivitis subjects affected / exposed occurrences (all) | 0 / 50 (0.00%) 0 | 0 / 10 (0.00%) 0 | 0 / 29 (0.00%) 0 |
| Ear infection subjects affected / exposed occurrences (all) | 1 / 50 (2.00%) 1 | 0 / 10 (0.00%) 0 | 4 / 29 (13.79%) 5 |
| Eye infection subjects affected / exposed occurrences (all) | 0 / 50 (0.00%) 0 | 0 / 10 (0.00%) 0 | 1 / 29 (3.45%) 1 |
| Gastroenteritis subjects affected / exposed occurrences (all) | 0 / 50 (0.00%) 0 | 0 / 10 (0.00%) 0 | 1 / 29 (3.45%) 1 |
| Lobar pneumonia subjects affected / exposed occurrences (all) | 0 / 50 (0.00%) 0 | 0 / 10 (0.00%) 0 | 1 / 29 (3.45%) 1 |
| Lower respiratory tract infection bacterial | | | |

| | | | |
|-----------------------------------|----------------|----------------|-----------------|
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 10 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Lung infection | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 10 (0.00%) | 1 / 29 (3.45%) |
| occurrences (all) | 0 | 0 | 1 |
| Nasopharyngitis | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 10 (0.00%) | 5 / 29 (17.24%) |
| occurrences (all) | 0 | 0 | 8 |
| Otitis media | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 10 (0.00%) | 1 / 29 (3.45%) |
| occurrences (all) | 0 | 0 | 1 |
| Perineal infection | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 10 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pharyngitis | | | |
| subjects affected / exposed | 1 / 50 (2.00%) | 0 / 10 (0.00%) | 1 / 29 (3.45%) |
| occurrences (all) | 1 | 0 | 1 |
| Pseudomonas infection | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 10 (0.00%) | 1 / 29 (3.45%) |
| occurrences (all) | 0 | 0 | 1 |
| Respiratory tract infection | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 10 (0.00%) | 2 / 29 (6.90%) |
| occurrences (all) | 0 | 0 | 2 |
| Respiratory tract infection viral | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 10 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Rhinitis | | | |
| subjects affected / exposed | 2 / 50 (4.00%) | 0 / 10 (0.00%) | 0 / 29 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Staphylococcal infection | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 10 (0.00%) | 1 / 29 (3.45%) |
| occurrences (all) | 0 | 0 | 1 |
| Tonsillitis | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 10 (0.00%) | 1 / 29 (3.45%) |
| occurrences (all) | 0 | 0 | 1 |
| Urinary tract infection | | | |

| | | | |
|--|---------------------|---------------------|---------------------|
| subjects affected / exposed occurrences (all) | 0 / 50 (0.00%) 0 | 0 / 10 (0.00%) 0 | 0 / 29 (0.00%) 0 |
| Varicella subjects affected / exposed occurrences (all) | 0 / 50 (0.00%) 0 | 0 / 10 (0.00%) 0 | 1 / 29 (3.45%) 1 |
| Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all) | 1 / 50 (2.00%) 1 | 0 / 10 (0.00%) 0 | 0 / 29 (0.00%) 0 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|--|
| 11 September 2012 | Following are the major changes in amendment-1: 1. Allowing randomization from throat swab, sputum or nasopharyngeal aspiration samples culture tested P. aeruginosa-positive at local site laboratory following local microbiology standard operating procedures. With view to maintain data integrity and primary endpoint robustness, re-identification and susceptibility testing of the P. aeruginosa isolates and the subtypes was to be performed at central laboratory. Hence allowing the screening and randomization visits to occur on the same day and the patient to start study medication immediately. 2. Allowing patients to be randomized from local laboratory safety results. Central safety laboratory results were available to the site within 7 days after samples are taken. The patient was to be discontinued in the event of clinically significant abnormal results as defined in the protocol. 3. Reduction of sample size based on revised realistic active and placebo treatment effects. The initial assumptions for the placebo effect were very conservative, as stated in the protocol. Published data in this population and with placebo-controlled trials are extremely limited; however, in a prospective, randomized, placebo-controlled, double-blind study enrolling 22 patients (Wiesemann et al 1998), 8 out of 10 patients in the placebo arm were still P. aeruginosa-positive after 1 month of treatment. Thus adopting a 30% placebo effect still remained conservative. 4. Performing an analysis and generating a report focusing on the double-blind randomized study results. |
| 11 August 2014 | Amendment 2 included the following changes: 1. It was required to ensure consistency throughout the protocol that audiology assessments were only to be done by the patients at sites which are able to perform this assessment. Therefore the number of patients to have audiology assessments was based on site capabilities. 2. Any reference to the assent form in the protocol was deleted as the assent form was not required by any active site and therefore was not signed by any patient. 3. Exclusion criterion no. 1 was changed in order to clarify that any anti-pseudomonal antibiotic treatment within 1 year prior to randomization was prohibited. 4. The overview of visit paths during the treatment phase was corrected and clarified in order to be in line with the protocol design and text within the protocol. 5. Finally, the statistical section was updated to document that the primary analysis would be performed after all patients had completed the treatment phase of the study as this was missing previously. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported