



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
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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
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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
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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
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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
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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
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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
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End point description:

Sputum/throat swab cultures were assessed.

End point type	Secondary
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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