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Sponsor

Novartis Pharmaceuticals Corporation

Generic Drug Name

Tobramycin inhalation powder

Therapeutic Area of Trial

Cystic Fibrosis

Approved Indication

Tobramycin inhalation powder is indicated for the management of pulmonary *Pseudomonas aeruginosa* infection in cystic fibrosis (CF) patients aged 6 years or older.

TOBI® Podhaler™ is registered with this indication in 43 countries.

Protocol Number

CTBM100C2303E2

Title

A Phase III Open-Label Extension Study to Assess the Safety and Efficacy of Tobramycin Inhalation Powder after Manufacturing Process Modifications (TIP_{new}) in Cystic Fibrosis (CF) Patients who successfully Completed Participation in Study CTBM100C2303E1.

Study Phase

Phase III

Study Start/End Dates

Study initiation date: 12-Feb-2010 (first patient first visit)

Study completion date: 19-Mar-2012 (last patient last visit)

Study Design/Methodology

This study of tobramycin inhalation powder at 112 mg b.i.d. dosage was an open-label, single arm (uncontrolled) study in patients suffering from Cystic Fibrosis (CF), who completed their study participation in C2303E1 (all visits) and who were proven infected with *P. aeruginosa* at enrollment in the core study (C2303). Eligible patients were treated with three consecutive cycles of TOBI® Podhaler™ . (Cycles 5, 6 and 7; numbering in continuation from studies C2303 and C2303E1). Each cycle consisted of 28 days on treatment, followed by 28 days off treatment. The study consisted of baseline visit (Visit 12; usually on the same day as Visit 11 (the last visit) of C2303E1, but optionally up to 5 days after that visit), followed by the treatment phase (24 weeks), and the termination visit.

Centers

16 centers in 8 countries: Bulgaria (3), Egypt (1), Estonia (2), India (1), Latvia (1), Lithuania (2), Romania (1) and Russia (5)

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Test Product (s), Dose(s), and Mode(s) of Administration

All patients were assigned to the single treatment arm, using the TOBI® Podhaler™ drug-device combination product consisting of tobramycin dry powder for inhalation in capsules administered by the T-326 inhaler. The study medication consisted of TOBI® Podhaler™ capsules at 28 mg dosage strength. The dose regimen for the study medication was four TOBI® Podhaler™ capsules at 28 mg dosage strength, inhaled twice daily (b.i.d.) in the morning and in the evening, for 28 days (on treatment), followed by 28 days of no study treatment (off treatment). These 56 days represent one cycle of therapy. Each patient was to undergo three cycles of treatment, unless terminated early. Each treatment therefore consisted of 112 mg tobramycin (4 capsules of 28 mg each), the total daily dose corresponds to 224 mg tobramycin (112 mg b.i.d.).

Statistical Methods

There was no primary efficacy objective in this extension 2 study. The primary objective was to evaluate the safety profile of tobramycin inhalation powder after modifications in the manufacturing process (TOBI® Podhaler™) for the treatment of infections with *P. aeruginosa* in patients suffering from CF over three additional treatment cycles.

All safety analyses were performed using the safety population. Baseline for safety analyses was defined as the last measurement prior to the first dose of study drug in the core study.

Appropriate descriptive summary statistics was provided for adverse events, serious adverse events, lab tests, audiology, airway reactivity and vital signs.

Appropriate descriptive summary statistics was provided for the following secondary efficacy endpoints:

- Relative change of Forced Expiratory Volume in 1 second (FEV_1), Forced Vital Capacity (FVC) and Forced Expiratory Flow (FEF_{25-75}) (all as % predicted) from baseline to each post-baseline visit,
- Anti-pseudomonal antibiotic use during the treatment period,
- Microbiology:
  - change from baseline of Sputum *P. aeruginosa* density to each post-baseline visit,
  - change from baseline of *P. aeruginosa* tobramycin minimum inhibitory concentration (MIC) susceptibility to each post-baseline visit

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Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion criteria

Patients eligible for inclusion in this study had to fulfill all of the following criteria:

1. Written informed consent given by adult patients or by the parents/legal guardian on behalf of the patient in combination with the patient's assent, if capable of assenting, before any assessment was performed.
2. Successful completion of all visits in study C2303 and C2303E1 including visit 11, not exceeding more than 5 days before enrollment into this study.
3. Able to comply with all protocol requirements.
4. Use of an effective means of contraception in females of childbearing potential.
5. Clinically stable in the opinion of the investigator for treatment according to this protocol.

Exclusion criteria

Patients fulfilling any of the following criteria were not eligible for inclusion in this study:

1. Any use of inhaled or systemic anti-pseudomonal antibiotics between the termination visit of C2303E1 and enrollment into this study. (Use of inhaled antipseudomonal antibiotics other than study drug was not allowed between start of study drug administration and follow-up/termination. Use of systemic antibiotics between start of study drug administration and follow-up/termination was at the investigator's discretion).
2. Serum creatinine ≥2 mg/dL, BUN ≥40 mg/dL, or an abnormal urinalysis defined as 2+ or greater proteinuria.
3. Known local or systemic hypersensitivity to aminoglycosides or inhaled antibiotics.
4. Signs and symptoms of acute pulmonary disease, e.g., pneumonia, pneumothorax.
5. Administration of any investigational drug within 30 days prior to enrollment (except for study medication in C2303 and C2303E1).
6. Any previous exposure to tobramycin dry powder for inhalation (TOBI® Podhaler™), with the exception of study medication for studies C2303 and C2303E1.
7. Administration of loop diuretics (such as furosemide and bumetanide) within 7 days prior to study drug administration.
8. Initiation of chronic macrolide therapy between the termination visit of C2303E1 and enrollment into this study (the dosage/regimen had to remain stable throughout the study).
9. Initiation of treatment with dornase alfa between the termination visit of C2303E1 and enrollment into this study (the dosage/regimen had to remain stable throughout the study).
10. Initiation of treatment with inhaled steroids (or increased dose) between the termination visit of C2303E1 and enrollment into this study (the dosage/regimen had to remain stable throughout the study).
11. Initiation of treatment with inhaled hypertonic saline (HS) between the termination visit of C2303E1 and enrollment into this study (the dosage/regimen had to remain stable throughout the study). In addition, patients were instructed to inhale their HS at least 30 minutes before their pulmonary function tests (PFT). Patients were to be consistent with the timing of taking their HS at home or clinic, prior to their PFT.

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12. Personal history of abnormal hearing or family history of abnormal hearing other than typical hearing loss associated with the aging process.
13. Abnormal result from any audiology testing (defined as either a unilateral pure-tone audiometry test showing a threshold elevation >20 dB at any frequency across the frequency range 0.25 kHz to 8 kHz or the absence of emission at the evoked otoacoustic emission test).
14. Hemoptysis of more than 60 mL at any time within 30 days prior to study drug administration.
15. History of malignancy of any organ system (other than localized basal cell carcinoma of the skin), treated or untreated, within the past 5 years, regardless of evidence of local recurrence or metastases.
16. Patients with clinically significant laboratory abnormalities (unless expected under the study indication).
17. Patients or caregivers with a history of noncompliance to medical regimens and patients or caregivers who were considered potentially unreliable.
18. Pregnant or nursing (lactating) women, where pregnancy was defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test (> 5 mIU/mL).
19. Women of child-bearing potential unless they were using two birth control methods.

Participant Flow

Patient disposition (All patients)

	Total N=49 n (%)
Completed	46 (93.9)
Discontinued	3 (6.1)
Adverse event(s)	1 (2.0)
Abnormal lab value(s)	0
Abnormal test procedure result(s)	0
Unsatisfactory therapeutic effect	0
Patient’s condition no longer requires study drug	0
Patient withdrew consent	2 (4.1)
Lost to follow-up	0
Administrative problems	0
Death	0
Protocol deviation	0

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Baseline Characteristics

Disease characteristics at baseline and start of extension 2 study (Safety population)

Variable	Total N=49
Baseline FEV_1 % predicted	
n	48
Mean	59.5
SD	16.51
Median	65.4
Min-Max	27.9-86.1
Baseline *P. aeruginosa* sputum density (log10 (CFU))[a]	
n	45
Mean	7.4
SD	1.50
Median	8.0
Min-Max	3.3-9.0
Baseline *P. aeruginosa* tobramycin MIC, n (%)	
> 8 ug/mL	1 (2.0)
<=8 ug/mL	48 (98.0)
Week 33 FEV_1 % predicted	
n	47
Mean	67.2
SD	19.37
Median	71.8
Min-Max	25.9-104.6
Week 33 *P. aeruginosa* sputum density (log10 (CFU))[a]	
n	39
Mean	6.0
SD	3.23
Median	7.6
Min-Max	0.0-8.8
Week 33 *P. aeruginosa* tobramycin MIC, n (%)	
> 8 ug/mL	6 (12.2)
<=8 ug/mL	30 (61.2)
Missing	13 (26.5)

[a] Overall density, defined as the sum of biotypes (mucoid, dry and small colony variant).
MIC = Minimum inhibitory concentration.
Baseline refers to core study C2303.

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Outcome Measures

Primary Outcome Result(s)

Adverse Events by System Organ Class

Adverse events (on and off treatment) regardless of study drug relationship, by primary system organ class (Safety population)

	Total N=49 n (%)
Patients with AE(s)	23 (46.9)
Primary system organ class	
Infections and infestations	17 (34.7)
Respiratory, thoracic and mediastinal disorders	7 (14.3)
General disorders and administration site conditions	3 (6.1)
Ear and labyrinth disorders	2 (4.1)
Gastrointestinal disorders	2 (4.1)
Investigations	2 (4.1)

Primary system organ classes are sorted in descending order of frequency.
A patient with more than one adverse event within a primary system organ class is counted only once for that class.

Most Frequently Reported AEs Overall by Preferred Term n (%)

Adverse events (on and off treatment), regardless of study drug relationship, by preferred term (Safety population)

	Total N=49 n (%)
Patients with AE(s)	23 (46.9)
Preferred term	
Respiratory tract infection	5 (10.2)
Respiratory tract infection viral	4 (8.2)
Bronchitis	3 (6.1)
Cough	3 (6.1)
Infective pulmonary exacerbation of cystic fibrosis	3 (6.1)
Acute sinusitis	2 (4.1)
Dysphonia	2 (4.1)
Hypoacusis	2 (4.1)
Non-cardiac chest pain	2 (4.1)
Alcaligenes infection	1 (2.0)
Antibiotic resistant Staphylococcus test positive	1 (2.0)
Asthenia	1 (2.0)
Bronchospasm	1 (2.0)
Burkholderia cepacia complex infection	1 (2.0)

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	Total N=49 n (%)
Constipation	1 (2.0)
Diarrhoea	1 (2.0)
Haemoptysis	1 (2.0)
Influenza	1 (2.0)
Nasopharyngitis	1 (2.0)
Pneumonia	1 (2.0)
Productive cough	1 (2.0)
Protein urine present	1 (2.0)
Pyrexia	1 (2.0)

Preferred terms are sorted in descending order of frequency.
A patient with multiple occurrences of the same preferred term is counted only once in the preferred term.

Serious Adverse Events and Deaths

Serious adverse events, by preferred term (Safety population)

	Total N=49 n (%)
Patients with SAE(s)	2 (4.1)
Preferred term	
Haemoptysis	1 (2.0)
Infective pulmonary exacerbation of cystic fibrosis	1 (2.0)
Pneumonia	1 (2.0)

Preferred terms are sorted in descending order of frequency.
A patient with multiple occurrences of the same preferred term is counted only once in the preferred term.

Deaths

No patients died during the study.

Shift from baseline in Laboratory parameters to above upper/lower limit of normal at any post-baseline to study completion (safety population).

Hematology values

	Total N=49 n/ N at risk (%)	
Parameter	**Change to low**	**Change to high**
Absolute Basophils	0/ 46 (0.0)	7/ 45 (15.6)
Absolute Eosinophils	0/ 46 (0.0)	16/ 40 (40.0)

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Parameter	Total N=49 n/ N at risk (%) Change to low	Change to high
Absolute Lymphocytes	3/ 42 (7.1)	9/ 35 (25.7)
Absolute Monocytes	0/ 46 (0.0)	8/ 40 (20.0)
Absolute Neutrophils (Seg. + Bands)	9/ 42 (21.4)	13/ 39 (33.3)
Basophils	0/ 46 (0.0)	15/ 24 (62.5)
Eosinophils	0/ 46 (0.0)	15/ 40 (37.5)
Lymphocytes	4/ 42 (9.5)	13/ 40 (32.5)
Monocytes	9/ 43 (20.9)	14/ 35 (40.0)
Neutrophils (Seg. + Bands)	11/ 42 (26.2)	5/ 43 (11.6)
Platelet count (direct)	2/ 44 (4.5)	10/ 22 (45.5)
RBC	0/ 47 (0.0)	9/ 33 (27.3)
WBC (total)	9/ 40 (22.5)	12/ 37 (32.4)
Haematocrit	1/ 47 (2.1)	14/ 41 (34.1)
Haemoglobin	5/ 46 (10.9)	6/ 44 (13.6)

N at risk: Change to low: Number of patients with normal or high values at baseline. Change to high: Number of patients with normal or low values at baseline.
Baseline refers to core study C2303.

Serum chemistry values

Parameter	Total N=49 n/ N at risk (%) Change to low	Change to high
Albumin	0/ 48 (0.0)	8/ 34 (23.5)
Alkaline phosphatase, serum	0/ 48 (0.0)	8/ 37 (21.6)
Bilirubin (direct/conjugated)	0/ 48 (0.0)	7/ 45 (15.6)
Bilirubin (total)	0/ 49 (0.0)	2/ 48 (4.2)
Blood Urea Nitrogen (BUN)	6/ 42 (14.3)	4/ 49 (8.2)
Calcium	8/ 49 (16.3)	3/ 49 (6.1)
Chloride	3/ 49 (6.1)	0/ 49 (0.0)
Creatinine	3/ 11 (27.3)	0/ 48 (0.0)
Gamma Glutamyltransferase	0/ 48 (0.0)	4/ 42 (9.5)
Glucose	13/ 45 (28.9)	12/ 47 (25.5)
Phosphate (Inorganic Phosphorus)	0/ 49 (0.0)	22/ 46 (47.8)
Potassium	1/ 47 (2.1)	5/ 48 (10.4)
SGOT (AST)	0/ 48 (0.0)	14/ 40 (35.0)
SGPT (ALT)	0/ 47 (0.0)	11/ 37 (29.7)
Serum bicarbonate	8/ 33 (24.2)	0/ 49 (0.0)
Sodium	2/ 49 (4.1)	3/ 49 (6.1)
Total Protein (Serum)	1/ 49 (2.0)	9/ 37 (24.3)
Uric Acid	0/ 49 (0.0)	11/ 44 (25.0)

N at risk: Change to low: Number of patients with normal or high values at baseline. Change to high: Number of patients with normal or low values at baseline.
Baseline refers to core study C2303.

Acute Change in Airways Reactivity (FEV1 Percent Predicted): from Pre-dose to 30 Minutes after Completion Dose of Study Drug at D1 and D29 of each cycle.

Relative change = 100 * (30-m-post-dose - pre-dose)/pre-dose assessed by the number and percentage of patients with a decrease of ≥20 % in FEV1 % predicted from pre dose to 30 minutes post dose. Day 1 is the scheduled visit of first study drug administration.

Airway reactivity: >=20% relative decrease in FEV1 % predicted from pre dose to 30 minute post dose (Safety population)

Cycle	Scheduled week - day	Total N=49 n/total (%)
Any		5/ 49 (10.2)
Cycle 5	Week 33 - Day 1	1/ 44 (2.3)
	Week 37 - Day 29	0/ 45 (0.0)
Cycle 6	Week 41 - Day 1	1/ 40 (2.5)
	Week 45 - Day 29	2/ 46 (4.3)
Cycle 7	Week 49 - Day 1	3/ 45 (6.7)
	Week 53 - Day 29	0/ 45 (0.0)

Relative change = 100 * (30-m-post-dose – pre-dose)/pre-dose
n is number of patients with event, total is number patients with values at the visit.

Percentage of Patients with frequency decreases from baseline in the post-baseline audiology tests by normal and abnormal prior to study: from first study drug administration in Extension 2 (Cycle2) to Study Completion (safety population, audiology subgroup)

	Schedule week /day		Total N=49 n	Mean	(SD)	Median	25%-75%	Quantile
Baseline		Value	49	2.2	(9.11)	0.5	0.3	- 1.0
Cycle 5	W33/D1	Value	36	34.2	(118.11)	2.0	1.0	- 8.0
		Change	36	31.4	(117.76)	1.5	0.3	- 7.0
	W37/D29	Value	30	24.7	(92.78)	2.0	1.0	- 16.0
		Change	30	21.6	(92.35)	0.9	0.0	- 6.0
Cycle 6	W41/D1	Value	39	41.9	(137.55)	1.0	0.5	- 4.0
		Change	39	39.3	(138.37)	0.8	0.0	- 3.0
	W45/D29	Value	35	28.2	(94.98)	2.0	0.5	- 8.0
		Change	35	25.5	(94.74)	1.0	0.0	- 6.0
Cycle 7	W49/D1	Value	36	6.4	(21.22)	1.0	0.5	- 4.0
		Change	36	3.7	(22.94)	0.5	-0.1	- 2.4

	W53/D29	Value	38	34.3	(116.02)	2.0	1.0	-	8.0
		Change	38	31.7	(115.97)	1.3	0.4	-	7.5
Follow up	W57/D57	Value	19	5.8	(9.95)	1.0	1.0	-	4.0
		Change	19	1.7	(11.14)	0.8	0.0	-	1.9
Termination		Value	44	47.6	(133.95)	2.0	1.0	-	8.0
		Change	44	45.3	(133.83)	1.0	0.3	-	7.5

Baseline is defined as latest measurement prior to the first dosing of study medication in core study.
Change = Post baseline value - Baseline value. Termination: last available pre-dose post-baseline value.
If sub-isolates exist for MIC biotype mucoid, dry or SCV, then the maximum of sub-isolates is analyzed for a visit. W=Week of study, D=Day of cycle.

Percentage of patients with new anti-pseudomonal antibiotic use and adverse events, by severity: from first administration of study drug in extension 2 to study completion (safety population)

	Total N=49 n (%)	
	Yes	**No**
Total	7 (100.0)	42 (100.0)
Any AE		
Total	6 (85.7)	17 (40.5)
Mild	1 (14.3)	12 (28.6)
Moderate	5 (71.4)	4 (9.5)
Severe	0 (0.0)	1 (2.4)
SAE	2 (28.6)	0 (0.0)

Yes: Patients with a new antibiotic use during study. No: Patients without any new antibiotic use during study. A patient who had several AEs is counted for the highest severity.

Percentage of Death, AE and SAE leading to permanent discontinuation: from first study administration in extension 1 to study completion (safety population)

	Total N=49 n (%)
Patients with AE(s)	23 (46.9)
Serious AEs or AE discontinuations	
Death	0

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	Total N=49 n (%)
SAE(s)	2 (4.1)
Discontinued study due to AE(s)	1 (2.0)
Discontinued study drug due to AE(s)	1 (2.0)
Discontinued study drug due to SAE(s)	0

A patient could have discontinued study drug due to both a SAE and a non SAE.

Secondary Outcome Result(s)

- Relative Change From Baseline to End of Dosing at Each Cycle and Study Completion in Forced Expiratory Volume in One Second (FEV1) Percent Predicted.
- Change From Baseline to End of Dosing at Each Cycle and Study Completion in Forced Vital Capacity (FVC) Percent Predicted.
- Change From Baseline to End of Dosing at Each Cycle and Study Completion in Forced Expiratory Flow Rate Over 25 and 75 Percent. (FEF25-75%) Predicted.

Relative change from baseline to post-baseline in pre-dose spirometry (Safety population)

Cycle	Week/day		n	Mean (SD)	95% CI	P-value
FEV_1 % predicted						
Baseline		Value	48	59.5 (16.51)	[54.7, 64.3]	
Cycle 5	33/1	Rel. change	46	11.4 (21.79)	[4.9, 17.9]	<.001
	37/29	Rel. change	44	12.6 (24.49)	[5.2, 20.1]	0.001
Cycle 6	41/1	Rel. change	44	8.6 (19.73)	[2.6, 14.6]	0.006
	45/29	Rel. change	45	11.9 (24.23)	[4.6, 19.1]	0.002
Cycle 7	49/1	Rel. change	45	9.0 (22.44)	[2.3, 15.8]	0.010
	53/29	Rel. change	44	10.1 (26.37)	[2.0, 18.1]	0.015
Follow up	57/57	Rel. change	42	8.1 (25.79)	[0.0, 16.1]	0.049
FVC % predicted						
Baseline		Value	48	75.0 (17.63)	[69.9, 80.1]	
Cycle 5	33/1	Rel. change	46	5.1 (15.60)	[0.4, 9.7]	0.032
	37/29	Rel. change	44	5.2 (17.87)	[-0.2, 10.6]	0.060
Cycle 6	41/1	Rel. change	44	2.6 (16.36)	[-2.4, 7.6]	0.294
	45/29	Rel. change	45	6.2 (20.01)	[0.2, 12.2]	0.044
Cycle 7	49/1	Rel. change	45	2.3 (19.20)	[-3.4, 8.1]	0.421
	53/29	Rel. change	44	2.9 (20.40)	[-3.3, 9.1]	0.357
Follow up	57/57	Rel. change	42	4.0 (20.37)	[-2.3, 10.4]	0.207
FEF_{25-75} % predicted						
Baseline		Value	48	36.8 (20.30)	[30.9, 42.7]	
Cycle 5	33/1	Rel. change	46	37.7 (57.39)	[20.7, 54.8]	<.001
	37/29	Rel. change	44	43.2 (67.51)	[22.7, 63.8]	<.001

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Cycle	Week/day		n	Mean (SD)	95% CI	P-value
Cycle 6	41/1	Rel. change	44	35.1 (66.39)	[14.9, 55.3]	0.001
	45/29	Rel. change	45	34.3 (63.53)	[15.3, 53.4]	<.001
Cycle 7	49/1	Rel. change	45	44.4 (80.91)	[20.1, 68.7]	<.001
	53/29	Rel. change	44	36.1 (61.75)	[17.4, 54.9]	<.001
Follow up	57/57	Rel. change	42	35.6 (77.34)	[11.5, 59.7]	0.005

P-value calculated from one-sample t-test.
Baseline refers to core study C2303.

Absolute Change From Baseline to End of Dosing at each cycle and Study Completion in Sputum Pseudomonas Aeruginosa Density (log10 Colony Forming Units (CFU) Per Gram Sputum) P. aeruginosa sputum density refers to overall density, defined as the sum of biotypes (mucoid, dry and small colony variant). If sub-isolates exist for CFU biotype mucoid or dry, then the sum of sub-isolates is analyzed

Change from baseline to post-baseline in P. aeruginosa sputum density – log10 CFU (Safety population)

Cycle	Week/day		n	Mean (SD)	95% CI	p-value
Biotype: mucoid						
Baseline		Value	44	7.0 (1.59)	[6.5, 7.5]	
Cycle 5	33/1	Change	35	-1.0 (3.19)	[-2.1, 0.1]	0.075
	37/29	Change	38	-3.3 (3.01)	[-4.3, -2.3]	<.001
Cycle 6	41/1	Change	38	-1.5 (3.34)	[-2.6, -0.4]	0.010
	45/29	Change	37	-3.5 (2.76)	[-4.4, -2.6]	<.001
Cycle 7	49/1	Change	37	-1.6 (3.64)	[-2.8, -0.4]	0.011
	53/29	Change	34	-2.4 (3.13)	[-3.5, -1.3]	<.001
Follow up	57/57	Change	16	-1.6 (3.84)	[-3.7, 0.4]	0.108
Biotype: dry						
Baseline		Value	34	6.8 (1.49)	[6.3, 7.4]	
Cycle 5	33/1	Change	23	-1.1 (2.69)	[-2.3, 0.0]	0.056
	37/29	Change	26	-4.2 (2.77)	[-5.3, -3.1]	<.001
Cycle 6	41/1	Change	25	-1.9 (3.02)	[-3.1, -0.6]	0.005
	45/29	Change	25	-3.8 (2.53)	[-4.8, -2.7]	<.001
Cycle 7	49/1	Change	25	-2.1 (3.36)	[-3.5, -0.7]	0.005
	53/29	Change	25	-2.8 (2.82)	[-3.9, -1.6]	<.001
Follow up	57/57	Change	9	-1.1 (2.92)	[-3.4, 1.1]	0.285
Biotype: small colony variant						
Baseline		Value	10	7.1 (1.09)	[6.3, 7.9]	
Cycle 5	33/1	Change	5	-0.9 (2.31)	[-3.7, 2.0]	0.451
	37/29	Change	7	-5.2 (3.69)	[-8.7, -1.8]	0.010
Cycle 6	41/1	Change	2	-1.4 (2.52)	[-24.0, 21.3]	0.585

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Cycle	Week/day		n	Mean (SD)	95% CI	p-value
	45/29	Change	3	-1.6 (2.78)	[-8.5, 5.3]	0.416
Cycle 7	49/1	Change	6	-1.5 (3.83)	[-5.6, 2.5]	0.371
	53/29	Change	2	-3.2 (2.31)	[-23.9, 17.5]	0.299
Follow up	57/57	Change	0			
Sum of all biotypes						
Baseline		Value	45	7.4 (1.50)	[7.0, 7.9]	
Cycle 5	33/1	Change	37	-1.1 (2.82)	[-2.0, -0.2]	0.023
	37/29	Change	40	-3.7 (2.95)	[-4.7, -2.8]	<.001
Cycle 6	41/1	Change	41	-1.6 (2.95)	[-2.6, -0.7]	<.001
	45/29	Change	41	-3.6 (2.73)	[-4.4, -2.7]	<.001
Cycle 7	49/1	Change	39	-1.5 (3.40)	[-2.6, -0.4]	0.007
	53/29	Change	40	-2.6 (2.92)	[-3.5, -1.6]	<.001
Follow up	57/57	Change	18	-1.8 (3.62)	[-3.6, 0.0]	0.053

P-value calculated from one-sample t-test.
Baseline refers to core study C2303.

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Change From Baseline to End of Dosing at Each Cycle and Study Completion of Pseudomonas Aeruginosa Minimum Inhibitory Concentration (MIC) Maximum MIC values from all biotypes were used (Safety population)

Biotype: Sum of all biotypes

	Scheduled week/day		Total N=49 n	Mean (SD)	Median	25%-75% Quantile
Baseline		Value	49	2.2 (9.11)	0.5	0.3 - 1.0
Cycle 5	W33/D1	Value	36	34.2 (118.11)	2.0	1.0 - 8.0
		Change	36	31.4 (117.76)	1.5	0.3 - 7.0
	W37/D29	Value	30	24.7 (92.78)	2.0	1.0 - 16.0
		Change	30	21.6 (92.35)	0.9	0.0 - 6.0
Cycle 6	W41/D1	Value	39	41.9 (137.55)	1.0	0.5 - 4.0
		Change	39	39.3 (138.37)	0.8	0.0 - 3.0
	W45/D29	Value	35	28.2 (94.98)	2.0	0.5 - 8.0
		Change	35	25.5 (94.74)	1.0	0.0 - 6.0
Cycle 7	W49/D1	Value	36	6.4 (21.22)	1.0	0.5 - 4.0
		Change	36	3.7 (22.94)	0.5	-0.1 - 2.4
	W53/D29	Value	38	34.3 (116.02)	2.0	1.0 - 8.0
		Change	38	31.7 (115.97)	1.3	0.4 - 7.5
Follow up	W57/D57	Value	19	5.8 (9.95)	1.0	1.0 - 4.0
		Change	19	1.7 (11.14)	0.8	0.0 - 1.9
Termination		Value	44	47.6 (133.95)	2.0	1.0 - 8.0
		Change	44	45.3 (133.83)	1.0	0.3 - 7.5

Baseline is defined as latest measurement prior to the first dosing of study medication in core study. Change = Post baseline value - Baseline value.
Termination: last available pre-dose post-baseline value.
If sub-isolates exist for MIC biotype mucoid, dry or SCV, then the maximum of sub-isolates is analyzed for a visit. W=Week of study, D=Day of cycle

Safety Results

Safety outcomes were the primary objective of the study, and the relevant results can be located under the primary outcome results section.

Date of Clinical Trial Report

19-Sep-2012 (pub CSR)

Date Inclusion on Novartis Clinical Trial Results Database

April 1, 2013

Date of Latest Update