Sponsor

Novartis Pharmaceuticals Corporation

Generic Drug Name

Tobramycin inhaled powder

Therapeutic Area of Trial

Cystic Fibrosis

Approved Indication

Tobramycin Inhalation Powder (TIP) is approved for:

- Long term management of chronic infection due to Pseudomonas aeruginosa in cystic fibrosis patients aged 6 years and older

Approved in all EU members states , Norway and Iceland via centralized procedure, Switzerland and Canada

Protocol Number

CTBM100C2303E1

Title

A Phase III Open-Label Extension Study to Assess the Safety and Efficacy of Tobramycin Inhalation Powder after Manufacturing Process Modifications (TIPnew) in Cystic Fibrosis (CF) Subjects Who Completed Participation in Study CTBM100C2303

Phase of Development

Phase III

Study Start/End Dates

First patient first visit 12 Aug 2009
Last patient last visit 06 Oct 2011

Study Design/Methodology

This single arm (uncontrolled), safety study of Tobramycin Inhalation Powder at 112mg b.i.d dosage was an open-label, extension 1 to CTBM100C2303 study, conducted in patients suffering from cystic fibrosis and infected with P. aeruginosa. Patient who had completed their study participation in CTBM100C2303 (all visits) were eligible. The patient had received one cycle of either Tobramycin Inhalation Powder or matching placebo at 112mg b.i.d dosage in the CTBM100C2303 study entered into this study and received 3 additional TIP cycles. Each cycle are defined as 28 days on treatment followed by 28 days off treatment which is similar to Tobramycin nebulizer solution. This study consisted of a baseline visit (Visit 5; usually on the same day as Visit 4 of the core study (C2303), but optionally up to 5 days after that visit), followed by the treatment phase (24 weeks), and the termination visit.

Centres

The study was conducted at 16 centers in the following 8 countries: Bulgaria (3 centers), Egypt (1 center), Estonia (2 centers), India (1 center), Latvia (1 center), Lithuania (2 centers), Romania (1 center) and Russia (5 centers)

Publication

None

Outcome measures

Primary outcome measures(s)

- Percentage of Patients With Adverse Events (AEs) : from first administration of study drug in extension 1 to study completion Adverse Events (AEs) (on and off treatment) regardless of study relationship by primary system organ and treatment group. A patient with more than one AE within a primary system organ class is counted only once for that class.
- Percentage of Patients With Serious Adverse Events (SAEs) : from Time of consent to 4 weeks after study completion Serious Adverse Events (on and off treatment) by preferred term and treatment group. A patient with multiple occurrences of the same preferred term is counted only once in the preferred term.
- Percentage of death cases: from time of consent to 4 weeks after study completion
- Percentage of AE and SAE leading to permanent discontinuation: from first study administration in extension 1 to study completion
- Shift From Baseline to in Laboratory Parameters to Above Upper/Lower Limit of Normal: from baseline (CTBM100C2303) to Study completion

  Hematology values shift from baseline to above upper/below lower limit of normal at any time post-baseline. Biochemistry values shift from baseline to above upper/below lower limit of normal at any time post-baseline.
- Acute Change in Airways Reactivity (FEV_1 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 $\geq$20 % in FEV_1 % predicted from pre dose to 30 minutes post dose. Day 1 is the scheduled visit of first study drug administration.
- Percentage of Patients with hearing loss at different frequencies: from first administration of study drug in extension 1 to Study Completion
- Percentage of patients with new anti-pseudomonal antibiotic use and adverse event: from first administration of study drug in extension 1 to Study Completion

Secondary outcome measures(s)

- Relative Change From Baseline to End of Dosing at Each Cycle and Study Completion in Forced Expiratory Volume in One Second (FEV_1) 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
- 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 End of Dosing at Each Cycle and Study Completion of Pseudomonas Aeruginosa Minimum Inhibitory Concentration (MIC) Maximum MIC

values from all biotypes were used.

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

Tobramycin inhalation powder (TIPnew) administered by the T-326 Inhaler. The dose regimen for the test product was four capsules of TIP at 28 mg dosage strength, inhaled b.i.d. (in the morning and in the evening) for 28 days.

Statistical Methods

The primary objective was to evaluate the safety profile of TIPnew 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.
For efficacy evaluation of TIPnew, the % predicted values of FEV_1, FVC and FEF25-75 were calculated based on the Knudson criteria. Relative and absolute changes from baseline for FEV_1 % predicted, FVC % predicted and FEF25-75 % predicted were calculated for each post-baseline visit.
Relative change from baseline was defined as: Relative change = 100 * (Post-baseline – baseline) / baseline.
Absolute change from baseline was defined as: Absolute change = Post-baseline – baseline.
Post-baseline measurements together with the relative and absolute change from baseline were summarized with standard descriptive statistics (number, mean, SD, minimum, median, maximum and the 95 % confidence interval [CI]) for each post baseline visit (including termination) and for each efficacy variable. A one sample t-test was calculated as a supportive analysis for the relative and absolute change from baseline to test the hypothesis if change equals zero. Summary statistics (including number, mean, SD, minimum, median and maximum) were derived for the subgroups screening FEV_1 % predicted (core study) <50% and ≥50%, age <13 and ≥13, baseline MIC status (CTBM100C2303 study) ≤8 and >8, sex, any cough AE (yes/no), any new anti-pseudomonal antibiotic use (yes/no), baseline dornase alfa use (yes/no), baseline bronchodilator use (yes/no) and baseline macrolide use (yes/no).
Relative and absolute changes from Day 1 (treatment start) to Day 29 (treatment end) for each of the three cycles were analyzed with the same descriptive statistics as before. Means together with 95 % CIs of the relative change from baseline were graphically displayed over time. FEV_1 % predicted was also summarized by the core treatment groups TIP and placebo.
Treatment differences between CTBM100C2303 study treatment groups were analyzed by a two sample t-test.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion 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. Completed all visits in core study (C2303), and Visit 4 of Study C2303 took place not 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 women of childbearing potential
5. Clinically stable in the opinion of the investigator to be treated according to this protocol.

Exclusion criteria

1. Any use of inhaled anti-pseudomonal antibiotics between the termination of the core study (C2303) and the enrollment into this study
2. Any use of systemic anti-pseudomonal antibiotics between the termination of the core study (C2303) and the enrollment into this study
3. Serum creatinine 2 mg/dL or above, blood urea nitrogen (BUN) 40 mg/dL or above, or an abnormal urinalysis defined as 2+ or greater proteinuria
4. Known local or systemic hypersensitivity to aminoglycosides or inhaled antibiotics
5. Signs and symptoms of acute pulmonary disease, e.g., pneumonia, pneumothorax
6. Administration of any investigational drug within 30 days prior to enrollment (except for study drug in Study C2303)
7. Any previous exposure to tobramycin dry powder for inhalation (TIP), with the exception of study drug for Study C2303
8. Administration of loop diuretics within 7 days prior to study drug administration
9. Initiation of treatment with chronic macrolide therapy between the termination of the core study (C2303) and the enrollment into this study
10. Initiation of treatment with dornase alfa between the termination of the core study (C2303) and the enrollment into this study
11. Initiation of treatment with inhaled steroids (or increased dose) between the termination of the core study (C2303) and the enrollment into this study
12. Initiation of treatment with inhaled hypertonic saline (HS) between the termination of the core study (C2303) and the enrollment into this study
13. Personal history of abnormal hearing or family history of abnormal hearing other than typical hearing loss associated with the aging process
14. Abnormal result from any audiology testing (defined as either a unilateral pure-tone audiometry test showing a threshold elevation >20 decibel [dB] at any frequency across the frequency range 0.25 kilohertz [kHz] to 8 kHz or the absence of emission at the evoked otoacoustic emission test)
15. History of sputum culture or throat swab (or bronchoalveolar lavage) culture yielding *Burkholderia cepacia* (*B. cepacia*) within 2 years prior to screening for Study C2303 and/or sputum culture yielding *B. cepacia* at screening for Study C2303 or at enrollment into this study Hemoptysis of more than 60 mL at any time within 30 days prior to study drug administration
17. 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 whether there was evidence of local recurrence or metastases
18. Patients with clinically significant laboratory abnormalities (unless expected under the study indication) at the termination of Study C2303 /Visit 4, especially if meeting the relevant criteria for premature withdrawal
19. Patients or caregivers with a history of non-compliance to medical regimens and patients or caregivers who are considered potentially unreliable
20. Pregnant or nursing (lactating) women
21. Women of child-bearing potential unless they were using two birth control methods.

Participant Flow

Patient disposition (All patients)

	Total N=55 n (%)
Completed	52 (94.5)
Discontinued	3 (5.5)
Adverse event(s)	1 (1.8)
Abnormal laboratory value(s)	0 (0.0)
Abnormal test procedure result(s)	0 (0.0)
Unsatisfactory therapeutic effect	0 (0.0)
Subject's condition no longer requires study drug	0 (0.0)
Subject withdrew consent	1 (1.8)
Lost to follow-up	0 (0.0)
Administrative problems	1 (1.8)
Death	0 (0.0)
Protocol deviation	0 (0.0)

Baseline Characteristics (safety population)

Variable	Total N=55
Age (years)	
n	55
Mean	12.9
SD	4.44
Median	13.0
Min-Max	6- 21
Age category (years), n (%)	
< 13 years	26 (47.3)
>= 13 years	29 (52.7)
Sex, n (%)	
Male	20 (36.4)
Female	35 (63.6)
Race, n (%)	
Caucasian	54 (98.2)
Asian	1 (1.8)
Weight (kg)	
n	55
Mean	35.8

SD	14.85
Median	32.8
Min-Max	11.0- 70.0
Height (cm)	
n	55
Mean	145.1
SD	20.05
Median	152.0
Min-Max	106- 184
Body mass index (kg/m^2)	
n	55
Mean	16.2
SD	3.44
Median	16.1
Min-Max	8.6- 25.4

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

Variable	Total N=55
Baseline FEV_1 % predicted	
n	52
Mean	59.9
SD	16.24
Median	65.4
Min - Max	27.9 - 86.1
Baseline P.aeruginosa sputum density (log10(CFU))[a]	
n	50
Mean	7.3
SD	1.81
Median	7.9
Min - Max	0.0 - 9.1
Baseline P.aeruginosa tobramycin MIC, n (%)	
> 8 ug/mL	4 (7.3)
<= 8 ug/mL	51 (92.7)
Week 9 FEV_1 % predicted	
n	48
Mean	66.6
SD	21.01
Median	70.4
Min - Max	18.3 - 113.8
Week 9 P.aeruginosa sputum density (log10(CFU))[a]	

n	46
Mean	5.9
SD	3.29
Median	7.1
Min - Max	0.0 - 9.1
Week 9 P.aeruginosa tobramycin MIC, n (%)	
> 8 ug/mL	2 (3.6)
<= 8 ug/mL	43 (78.2)
Missing	10 (18.2)

Outcome measures

Primary Outcome Result(s)

Refer to Safety outcome measures and Other relevant findings

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 (FEV_1) 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 (core study)		Value	52	59.9 (16.24)	[55.4, 64.4]	
Cycle 2	9/1	Rel. change	46	8.0 (19.71)	[2.1, 13.8]	0.009
	13/29	Rel. change	47	13.5 (23.42)	[6.6, 20.4]	<0.001
Cycle 3	17/1	Rel. change	47	11.5 (22.74)	[4.8, 18.2]	0.001
	21/29	Rel. change	49	14.8 (22.40)	[8.4, 21.3]	<0.001
Cycle 4	25/1	Rel. change	49	13.9 (23.73)	[7.1, 20.7]	<0.001
	29/29	Rel. change	48	17.3 (23.56)	[10.5, 24.2]	<0.001
Follow up	33/57	Rel. change	47	13.5 (20.62)	[7.4, 19.5]	<0.001
FVC % predicted						
Baseline (core study)		Value	52	75.2 (17.05)	[70.4, 79.9]	
Cycle 2	9/1	Rel. change	46	4.2 (16.18)	[-0.6, 9.0]	0.085
	13/29	Rel. change	47	7.0 (17.46)	[1.9, 12.2]	0.008
Cycle 3	17/1	Rel. change	47	7.7 (16.18)	[3.0, 12.5]	0.002
	21/29	Rel. change	49	7.2 (16.89)	[2.3, 12.0]	0.005
Cycle 4	25/1	Rel. change	49	9.6 (17.77)	[4.5, 14.7]	<0.001
	29/29	Rel. change	48	9.6 (16.87)	[4.7, 14.5]	<0.001
Follow up	33/57	Rel. change	47	7.4 (14.99)	[3.0, 11.8]	0.001
FEF_{25-75} % predicted						
Baseline (core study)		Value	52	37.2 (20.19)	[31.6, 42.8]	
Cycle 2	9/1	Rel. change	46	23.3 (37.49)	[12.2, 34.4]	<0.001
	13/29	Rel. change	47	35.2 (55.86)	[18.8, 51.6]	<0.001
Cycle 3	17/1	Rel. change	47	33.2 (60.81)	[15.4, 51.1]	<0.001
	21/29	Rel. change	49	44.7 (58.17)	[27.9, 61.4]	<0.001
Cycle 4	25/1	Rel. change	49	33.6 (59.13)	[16.6, 50.6]	<0.001
	29/29	Rel. change	48	40.5 (59.21)	[23.3, 57.7]	<0.001
Follow up	33/57	Rel. change	47	35.9 (58.08)	[18.9, 53.0]	<0.001

P-value calculated from one-sample t-test- Baseline refers to the 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 – log_{10} CFU (Safety population)

Cycle	Week/day		n	Mean (SD)	95 % CI	P-value
Biotype: mucoid						
Baseline (core study)		Value	47	6.8 (2.04)	[6.2, 7.4]	
Cycle 2	9/1	Change	40	-0.8 (2.69)	[-1.6, 0.1]	0.082
	13/29	Change	41	-3.3 (2.79)	[-4.2, -2.4]	<0.001
Cycle 3	17/1	Change	38	-1.1 (3.04)	[-2.1, -0.1]	0.037
	21/29	Change	44	-3.3 (3.12)	[-4.2, -2.3]	<0.001
Cycle 4	25/1	Change	41	-1.3 (3.06)	[-2.3, -0.4]	0.009
	29/29	Change	40	-3.8 (2.72)	[-4.7, -3.0]	<0.001
Follow up	33/57	Change	21	-1.1 (3.24)	[-2.6, 0.4]	0.141
Bioype: dry						
Baseline (core study)		Value	39	6.5 (1.91)	[5.8, 7.1]	
Cycle 2	9/1	Change	26	-1.4 (2.91)	[-2.5, -0.2]	0.026
	13/29	Change	24	-3.3 (2.56)	[-4.4, -2.2]	<0.001
Cycle 3	17/1	Change	29	-1.1 (2.64)	[-2.1, -0.1]	0.033
	21/29	Change	27	-3.5 (2.92)	[-4.7, -2.4]	<0.001
Cycle 4	25/1	Change	28	-1.4 (2.69)	[-2.5, -0.4]	0.010
	29/29	Change	25	-4.0 (2.68)	[-5.1, -2.9]	<0.001
Follow up	33/57	Change	14	-0.9 (2.47)	[-2.3, 0.5]	0.205
Biotype: small colony						
Baseline (core study)		Value	15	6.7 (2.17)	[5.5, 7.9]	
Cycle 2	9/1	Change	3	-3.3 (2.89)	[-10.5, 3.8]	0.184
	13/29	Change	6	-4.7 (2.97)	[-7.8, -1.6]	0.012
Cycle 3	17/1	Change	5	-2.3 (2.82)	[-5.8, 1.2]	0.144
	21/29	Change	5	-3.4 (3.03)	[-7.2, 0.3]	0.063
Cycle 4	25/1	Change	4	-1.9 (2.35)	[-5.6, 1.9]	0.208
	29/29	Change	5	-6.1 (1.59)	[-8.1, -4.1]	0.001
Follow up	33/57	Change	3	-0.1 (1.18)	[-3.1, 2.8]	0.856
Sum of all biotypes						
Baseline (core study)		Value	50	7.3 (1.81)	[6.8, 7.8]	
Cycle 2	9/1	Change	45	-1.3 (2.76)	[-2.1, -0.4]	0.004
	13/29	Change	46	-3.7 (2.76)	[-4.5, -2.8]	<0.001
Cycle 3	17/1	Change	46	-1.3 (2.70)	[-2.1, -0.5]	0.003
	21/29	Change	49	-3.5 (3.04)	[-4.4, -2.6]	<0.001
Cycle 4	25/1	Change	44	-1.4 (2.74)	[-2.2, -0.6]	0.001
	29/29	Change	44	-3.9 (2.82)	[-4.7, -3.0]	<0.001
Follow up	33/57	Change	24	-1.1 (2.76)	[-2.3, 0.1]	0.063

P-value calculated from one-sample t-test
Baseline refers to the core study (CTBM100C2303)

- 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=55 n	Mean (SD)	Min	Median	Max	95% CI	p-value
Baseline		Value	50	7.3 (1.81)	0.0	7.9	9.1	[6.8, 7.8]	
Cycle 2	W9/D1	Value	46	5.9 (3.29)	0.0	7.1	9.1	[4.9, 6.8]	
		Change	45	-1.3 (2.76)	-9.0	-0.2	3.3	[-2.1, -0.4]	0.004
	W13/D29	Value	49	3.5 (2.88)	0.0	3.7	8.8	[2.6, 4.3]	
		Change	46	-3.7 (2.76)	-9.0	-3.6	2.0	[-4.5, -2.8]	<.001
Cycle 3	W17/D1	Value	49	5.7 (3.32)	0.0	7.4	8.8	[4.7, 6.7]	
		Change	46	-1.3 (2.70)	-9.0	-0.6	4.4	[-2.1, -0.5]	0.003
	W21/D29	Value	50	3.7 (2.97)	0.0	3.3	8.8	[2.8, 4.5]	
		Change	49	-3.5 (3.04)	-9.0	-3.6	4.0	[-4.4, -2.6]	<.001

	Scheduled week/day		Total N=55 n	Mean (SD)	Min	Median	Max	95% CI	p-value
Cycle 4	W25/D1	Value	48	5.6 (3.05)	0.0	6.6	9.1	[4.8, 6.5]	
		Change	45	-1.4 (2.71)	-9.0	-1.1	3.8	[-2.2, -0.6]	0.001
	W29/D29	Value	46	3.4 (3.07)	0.0	3.7	8.6	[2.5, 4.3]	
		Change	44	-3.9 (2.82)	-9.0	-3.9	1.5	[-4.7, -3.0]	<.001
Follow up	W33/D57	Value	24	6.1 (3.02)	0.0	7.2	8.8	[4.9, 7.4]	
		Change	23	-1.1 (2.82)	-9.0	-0.3	2.5	[-2.3, 0.1]	0.079
Termination		Value	54	4.0 (3.44)	0.0	4.9	8.8	[3.1, 5.0]	
		Change	50	-2.9 (3.16)	-9.0	-2.3	2.5	[-3.8, -2.0]	<.001

SD = Standard deviation.
Change = Post baseline value - baseline value.
Baseline, defined as the lastest measurement prior to the first dosing of study medication in core study.
Termination: last available pre-dose post-baseline measurement.
P-value calculated from one sample t-test.
If no P. aeruginosa is isolated for a visit, log10 CFU is imputed with 0 for all biotypes.
If sub-isolates exist for CFU biotype mucoid, dry or SCV, then the sum of sub-isolates is analyzed.
W=Week of study, D=Day of cycle.

Safety Results

Adverse Events by System Organ Class

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

Primary system organ class	Total N=55 n (%)
Patients with AE(s)	26 (47.3)
Infections and infestations	15 (27.3)
Respiratory, thoracic and mediastinal disorders	9 (16.4)
Gastrointestinal disorders	4 (7.3)
Investigations	4 (7.3)
Ear and labyrinth disorders	3 (5.5)
General disorders and administration site conditions	2 (3.6)
Nervous system disorders	2 (3.6)
Injury, poisoning and procedural complications	1 (1.8)
Metabolism and nutrition disorders	1 (1.8)
Musculoskeletal and connective tissue disorders	1 (1.8)
Skin and subcutaneous tissue disorders	1 (1.8)

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, regardless of study drug relationship, by preferred term (Safety population)

	Total N=55 n (%)
Patients with AE(s)	26 (47.3)
Preferred term	
Cough	5 (9.1)
Respiratory tract infection	5 (9.1)
Dysphonia	3 (5.5)
Hypoacusis	3 (5.5)
Abdominal pain	2 (3.6)
Bronchopulmonary aspergillosis	2 (3.6)
Diarrhoea	2 (3.6)
Headache	2 (3.6)
Protein urine present	2 (3.6)
Pyrexia	2 (3.6)
Sinus polyp	2 (3.6)
Arthralgia	1 (1.8)
Ascariasis	1 (1.8)
Aspergillosis	1 (1.8)
Blood calcium decreased	1 (1.8)
Bronchitis	1 (1.8)
Dyspnoea	1 (1.8)
Gastrointestinal candidiasis	1 (1.8)
Hepatic enzyme increased	1 (1.8)
Hypoglycaemia	1 (1.8)
Lung infection	1 (1.8)
Middle ear effusion	1 (1.8)
Nasopharyngitis	1 (1.8)
Pneumonia	1 (1.8)
Productive cough	1 (1.8)
Protein urine	1 (1.8)
Rash	1 (1.8)
Respiratory tract infection viral	1 (1.8)
Sinusitis	1 (1.8)
Stenotrophomonas infection	1 (1.8)
Upper respiratory tract infection	1 (1.8)
Vaccination complication	1 (1.8)
Viral rhinitis	1 (1.8)
White blood cell count increased	1 (1.8)

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=55 n (%)
Patients with SAE(s)	3 (5.5)
Preferred term	
Aspergillosis	1 (1.8)
Lung infection	1 (1.8)
Pneumonia	1 (1.8)

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

Other Relevant Findings

- Shift From Baseline to in Laboratory Parameters to Above Upper/Lower Limit of Normal at any post-baseline to Study Completion (safety population)

Hematology values

	Total N=55 n/ N at risk (%)	
Parameter	**Change to low**	**Change to high**
Absolute Basophils	0/ 51 (0.0)	8/ 50 (16.0)
Absolute Eosinophils	0/ 51 (0.0)	15/ 45 (33.3)
Absolute Lymphocytes	5/ 47 (10.6)	12/ 37 (32.4)
Absolute Monocytes	0/ 51 (0.0)	9/ 43 (20.9)
Absolute Neutrophils (Seg. + Bands)	13/ 46 (28.3)	15/ 42 (35.7)
Basophils	0/ 51 (0.0)	19/ 27 (70.4)
Eosinophils	0/ 51 (0.0)	17/ 45 (37.8)
Lymphocytes	6/ 47 (12.8)	17/ 43 (39.5)
Monocytes	7/ 47 (14.9)	17/ 40 (42.5)
Neutrophils (Seg. + Bands)	17/ 45 (37.8)	5/ 48 (10.4)
Platelet count (direct)	1/ 49 (2.0)	6/ 25 (24.0)
RBC	0/ 53 (0.0)	10/ 36 (27.8)
WBC (total)	9/ 44 (20.5)	13/ 41 (31.7)
Haematocrit	0/ 53 (0.0)	13/ 44 (29.5)
Haemoglobin	3/ 52 (5.8)	3/ 50 (6.0)

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 is defined as the last measurement prior to study drug in core study

Serum chemistry values

	TIP N=55 n/ N at risk (%)	
Parameter	**Change to low**	**Change to high**
Albumin	0/ 54 (0.0)	12/ 37 (32.4)
Alkaline phosphatase, serum	0/ 54 (0.0)	9/ 41 (22.0)
Bilirubin (direct/conjugated)	0/ 54 (0.0)	6/ 51 (11.8)
Bilirubin (total)	0/ 55 (0.0)	4/ 54 (7.4)
Blood Urea Nitrogen (BUN)	8/ 48 (16.7)	5/ 55 (9.1)
Calcium	7/ 55 (12.7)	6/ 54 (11.1)
Chloride	5/ 55 (9.1)	1/ 55 (1.8)
Creatinine	4/ 11 (36.4)	1/ 54 (1.9)
Gamma Glutamyltransferase	1/ 54 (1.9)	5/ 48 (10.4)
Glucose	12/ 50 (24.0)	8/ 53 (15.1)
Phosphate (Inorganic Phosphorus)	1/ 55 (1.8)	24/ 51 (47.1)
Potassium	2/ 53 (3.8)	4/ 54 (7.4)

SGOT (AST)	2/ 54 (3.7)	14/ 46 (30.4)
SGPT (ALT)	0/ 53 (0.0)	16/ 41 (39.0)
Serum bicarbonate	17/ 37 (45.9)	0/ 55 (0.0)
Sodium	6/ 55 (10.9)	3/ 55 (5.5)
Total Protein (Serum)	1/ 55 (1.8)	12/ 43 (27.9)
Uric Acid	1/ 55 (1.8)	8/ 50 (16.0)

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 is defined as the last measurement prior to study drug in core study

- Acute Change in Airways Reactivity (FEV_1 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 FEV_1 % 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 FEV_1 % predicted from pre dose to 30 minute post dose (Safety population)

Cycle	Scheduled week - day	Total N=55 n/total (%)
2	Week 9 - Day 1	0/ 44 (0.0)
	Week 13 - Day 29	1/ 43 (2.3)
3	Week 17 - Day 1	1/ 46 (2.2)
	Week 21 - Day 29	1/ 46 (2.2)
4	Week 25 - Day 1	3/ 46 (6.5)
	Week 29 - Day 29	0/ 49 (0.0)

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

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

	Scheduled week/day	Criterion	Normal hearing at baseline N=22 n (%)	Abnormal hearing at baseline N=0 n (%)
Cycle 2	W9/D1	Test performed	18 (100.0)	0 (0.0)
		Any frequencies decreased	2 (11.1)	0 (0.0)
		2 consec. frequencies decreased	2 (11.1)	0 (0.0)
		>=3 consec. frequencies decreased	2 (11.1)	0 (0.0)
		>= 10dB decrease in 3 consecutive frequencies in either ear (1)	1 (5.6)	0 (0.0)
		>= 15dB decrease in 2 consecutive frequencies in either ear (2)	0 (0.0)	0 (0.0)
		>= 20dB decrease in at least one frequency in either ear (3)	0 (0.0)	0 (0.0)
		(1), (2) or (3)	1 (5.6)	0 (0.0)
	W13/D29	Test performed	20 (100.0)	0 (0.0)
		Any frequencies decreased	9 (45.0)	0 (0.0)
		2 consec. frequencies decreased	3 (15.0)	0 (0.0)
		>=3 consec. frequencies decreased	2 (10.0)	0 (0.0)
		>= 10dB decrease in 3 consecutive frequencies in either ear (1)	1 (5.0)	0 (0.0)
		>= 15dB decrease in 2 consecutive frequencies in either ear (2)	0 (0.0)	0 (0.0)
		>= 20dB decrease in at least one frequency in either ear (3)	0 (0.0)	0 (0.0)
		(1), (2) or (3)	1 (5.0)	0 (0.0)
Cycle 3	W21/D29	Test performed	22 (100.0)	0 (0.0)
		Any frequencies decreased	7 (31.8)	0 (0.0)
		2 consec. frequencies decreased	5 (22.7)	0 (0.0)
		>=3 consec. frequencies decreased	3 (13.6)	0 (0.0)
		>= 10dB decrease in 3 consecutive frequencies in either ear (1)	2 (9.1)	0 (0.0)
		>= 15dB decrease in 2 consecutive frequencies in either ear (2)	1 (4.5)	0 (0.0)
		>= 20dB decrease in at least one frequency in either ear (3)	1 (4.5)	0 (0.0)
		(1), (2) or (3)	2 (9.1)	0 (0.0)
Cycle 4	W29/D29	Test performed	22 (100.0)	0 (0.0)
		Any frequencies decreased	11 (50.0)	0 (0.0)
		2 consec. frequencies decreased	6 (27.3)	0 (0.0)
		>=3 consec. frequencies decreased	1 (4.5)	0 (0.0)
		>= 10dB decrease in 3 consecutive frequencies in either ear (1)	1 (4.5)	0 (0.0)
		>= 15dB decrease in 2 consecutive frequencies in either ear (2)	0 (0.0)	0 (0.0)
		>= 20dB decrease in at least one frequency in either ear (3)	0 (0.0)	0 (0.0)
		(1), (2) or (3)	1 (4.5)	0 (0.0)
Follow up	W33/D57	Test performed	8 (100.0)	0 (0.0)
		Any frequencies decreased	5 (62.5)	0 (0.0)
		2 consec. frequencies decreased	2 (25.0)	0 (0.0)
		>=3 consec. frequencies decreased	0 (0.0)	0 (0.0)
		>= 10dB decrease in 3 consecutive frequencies in either ear (1)	0 (0.0)	0 (0.0)
		>= 15dB decrease in 2 consecutive frequencies in either ear (2)	0 (0.0)	0 (0.0)
		>= 20dB decrease in at least one frequency in either ear (3)	0 (0.0)	0 (0.0)
		(1), (2) or (3)	0 (0.0)	0 (0.0)

- Percentage of patients with new anti-pseudomonal antibiotic use and adverse events, by severity: from first administration of study drug in extension 1 to study completion

Table 14.3-4.7 (Page 1 of 1)
Number (%) of patients with new anti-pseudomonal antibiotic use and adverse events, by severity
Safety population

	Total N=55 n (%)	
	Yes	No
Total	5 (100.0)	50 (100.0)
Any AE		
Total	4 (80.0)	22 (44.0)
Mild	1 (20.0)	13 (26.0)
Moderate	3 (60.0)	9 (18.0)
Severe	0 (0.0)	0 (0.0)
SAE	2 (40.0)	1 (2.0)

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 cases: from time of consent to 4 weeks after study completion**

  No patients died during the study.

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

	Total N=55 n (%)
Patients with AE(s)	**26 (47.3)**
Serious AEs or AE discontinuations	
Death	0
SAE(s)	3 (5.5)
Discontinued study due to AE(s)	1 (1.8)
Discontinued study drug due to AE(s)	1 (1.8)
Discontinued study drug due to SAE(s)	0

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

Date of Clinical Trial Report **31 Jan 2012**
Date Inclusion on Novartis Clinical Trial Results Database 6 Oct 2012
Date of Latest Update