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Novartis Clinical Trial Results

Sponsor

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Generic Drug Name

Tobramycin inhalation powder (TIP)

Trial Indication(s)

CTBM100C2303E1

Protocol Number

CTBM100C2303E1

Protocol 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) Subjects who Completed Participation in Study CTBM100C2303

Clinical Trial Phase

Phase III

Phase of Drug Development

Phase III

Study Start/End Dates

12-Aug-2009 to 06-Oct-2011

Reason for Termination

Not applicable.

Study Design/Methodology

Multi-center, open-label, single arm (uncontrolled) extension to core study (C2303).

Centers

16 centers in 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)

Objectives:

Primary objective(s)

Primary Objective: The primary objective of the study was to evaluate the safety profile of tobramycin inhalation powder after modifications in the manufacturing process (TIP_{new}) for the treatment of infections with P. aeruginosa in patients suffering from cystic fibrosis, over three additional treatment cycles.

Secondary objective(s)

The secondary objectives were to:

- Evaluate the efficacy of TIP_{new} assessed by FEV_1, FVC and FEF_{25-75}.
- Assess the effect of TIP_{new} on the density of microorganisms and on tobramycin minimum inhibitory concentration (MIC) in sputum samples.
- Investigate anti-pseudomonal antibiotic use and days of hospitalization due to respiratory events.

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

All patients started treatment with tobramycin inhalation powder (TIP_{new}) 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

There was no primary efficacy objective in this extension to core study (C2303). The primary objective was to evaluate the safety profile of TIP_{new} 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 TIP_{new}, the % predicted values of FEV_1, FVC and FEF_{25-75} were calculated based on the Knudson criteria. Relative and absolute changes from baseline for FEV_1 % predicted, FVC % predicted and FEF_{25-75} % 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 (core study) ≤8 and >8, sex, any cough AE (yes/no), any new anti-pseudomonal antibiotic use (yes/no), baseline domase alfa use (yes/no), baseline bronchodilator use (yes/no) and baseline macrolide use (yes/no). Relative and absolute change 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 core study treatment groups were analyzed by a two-sample t-test.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria:

• Completed all visits in study CTBM100C2303 and visit 4 took place not more than 5 days before enrollment into this study.
• Confirmed diagnosis of cystic fibrosis participants with P. aeruginosa infection.
• Forced Expiratory Volume in One Second (FEV_1) at screening (study CTBM100C2303) must be between 25% and 80% of normal predicted values.

Exclusion Criteria:

• Any use of inhaled anti-pseudomonal antibiotics between the termination of the core trial CTMB100C2303 and the enrollment into this study.
• Known local or systemic hypersensitivity to aminoglycosides or inhaled antibiotics.

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Participant Flow Table

Patient disposition - All patients

Disposition Reason	Total N=55 n (%)
Completed	51 (92.7)
Discontinued	4 (7.3)
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	2 (3.6)
Death	0 (0.0)
Protocol deviation	0 (0.0)

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Baseline Characteristics

Demographic summary (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	26 (47.3)
>=13	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

Body mass index: weight (kg) / [height $(m)^2$]
Demographics are taken over from core study (C2303)

Primary Outcome Result(s)

	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

Hematology values shift from baseline to above upper/below lower limit of normal at any time post-baseline (Safety population)

	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

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Serum chemistry values shift from baseline to above upper/below lower limit of normal at any time post-baseline (Safety population)

Any time post-baseline

Parameter	Total N=55 n/ N at Risk (%) 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)	6/ 55 (10.9)
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)

Low/Normal/High categories were defined by normal ranges.
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 latest measurement prior to the first dosing of study medication in core study.
Only patients with at least one post-baseline value are included.

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Airway reactivity: Acute relative change from pre-dose to 30-minute post-dose in FEV_1 % predicted, by cycle and visit
Safety population

	Scheduled week/day	Value	Total N=55 n	Mean (SD)	Min	Median	Max
Cycle 2	W9/D1	Pre-dose value	48	66.6 (21.01)	18.3	70.4	113.8
		30 min post-dose value	48	63.3 (20.93)	23.7	66.0	101.3
		Relative change	44	0.0 (12.07)	-18.9	0.1	50.0
	W13/D29	Pre-dose value	48	67.7 (21.11)	25.1	73.3	110.2
		30 min post-dose value	46	65.5 (20.48)	25.0	71.8	100.2
		Relative change	43	-3.0 (7.21)	-20.2	-2.0	13.8
Cycle 3	W17/D1	Pre-dose value	49	66.6 (21.40)	21.6	69.8	112.0
		30 min post-dose value	49	66.1 (21.23)	22.1	68.5	100.9
		Relative change	46	-1.4 (13.33)	-32.2	-2.9	73.7
	W21/D29	Pre-dose value	50	69.5 (21.65)	20.2	72.5	106.9
		30 min post-dose value	49	67.9 (20.37)	27.0	71.9	107.6
		Relative change	46	-1.8 (6.67)	-21.5	-1.6	14.0
Cycle 4	W25/D1	Pre-dose value	51	68.9 (22.54)	21.1	71.8	116.8
		30 min post-dose value	47	67.7 (21.08)	23.6	69.3	101.6
		Relative change	46	-3.0 (11.01)	-30.8	-2.5	44.1
	W29/D29	Pre-dose value	49	71.4 (21.60)	28.7	72.2	110.9
		30 min post-dose value	50	69.9 (22.00)	24.6	73.8	105.6
		Relative change	49	-0.6 (6.82)	-19.5	-0.1	23.8

Relative change = 100 * (30-min post-dose value - pre-dose value) / pre-dose value.
W-Week of study, D-Day of cycle.

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Number (%) of patients with frequency decreases from baseline in the post-baseline audiology tests, by normal or abnormal hearing prior to study Safety population (Audiology subgroup)

	Scheduled week/day	Criterion	Normal hearing at baseline N=22 n (%)	Abnormal hearing at baseline N=0 n (%)
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)

	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)

Scheduled week/day	Criterion	Normal hearing at baseline N=22 n (%)	Abnormal hearing at baseline N=0 n (%)
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)

12 frequencies were tested.
Baseline is defined as the visit 2 result in core study.
Results could occur in either ear.
A patient can be counted in more than one category.
W-Week of study, D-Day of cycle.

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.

Secondary Outcome Result(s)

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)

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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 (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

Cycle	Week/day		n	Mean (SD)	95 % CI	P-value
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 (C2303)

Microbiology MIC: Change in tobramycin MIC for P. aeruginosa from baseline, by biotype Safety population

Biotype: Maximum of all biotypes

	Scheduled week/day		Total N=55 n	Mean (SD)	Median	25%-75% Quantile
Baseline		Value	55	4.6 (14.60)	0.5	0.3 - 1.0
Cycle 2	W9/D1	Value	45	14.0 (76.52)	0.5	0.3 - 1.0
		Change	45	8.8 (77.70)	0.0	-0.1 - 0.5
	W13/D29	Value	39	18.1 (82.01)	1.0	0.5 - 2.0
		Change	39	15.1 (82.45)	0.0	-0.3 - 1.0
Cycle 3	W17/D1	Value	45	7.9 (16.78)	1.0	0.5 - 4.0
		Change	45	2.4 (20.10)	0.3	0.0 - 3.8
	W21/D29	Value	41	35.1 (111.93)	2.0	0.5 - 8.0
		Change	41	30.7 (112.32)	0.9	0.0 - 6.0
Cycle 4	W25/D1	Value	43	43.7 (132.55)	1.0	0.5 - 4.0
		Change	43	38.3 (127.74)	0.5	0.0 - 1.5

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.

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New anti-pseudomonal antibiotic use and hospitalization due to respiratory serious adverse events during study (Safety population)

Variable	Total N=55
Use of antipseudomonal antibiotics	
Any patients, n (%)	
Overall use	5 (9.1)
Oral use	3 (5.5)
IV use	3 (5.5)
Inhaled use	0
Total days used	
Overall use	
Mean	22.6
SD	14.77
Median	15.0
Oral use	
Mean	25.3
SD	18.77
Median	15.0
IV use	
Mean	17.3
SD	7.77
Median	15.0
Inhaled use	
Mean	-
SD	-
Median	-
Hospitalization due to respiratory events	
Any patients, n (%)	2 (3.6)
Total days in hospitalization	
Mean	13.0
SD	7.07
Median	13.0

n (%) number an percentage of patients with events
A patient could use more than one antibiotic and would be counted in each single category, but just once for overall
The overall category include as well any other and missing routes

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Safety Results

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

Preferred terms	Total N=55 n (%)
Patients with AE(s)	**26 (47.3)**
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)

Preferred terms	Total N=55 n (%)
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

Death, other serious adverse events and adverse events leading to permanent discontinuation of study drug (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

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Serious adverse events, by preferred term (Safety population)

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

Conclusion:

- Treatment with TIP is safe and well tolerated
- No new safety signals were identified
- Efficacy was sustained for lung function assessments (FEV_1, FEF_{25-75} and FVC)
- Sustained bacterial suppression

Date of Clinical Trial Report

31-Jan-2012