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Novartis Clinical Trial Results

Sponsor

Novartis

Generic Drug Name

Tobramycin inhalation powder/TBM100

Trial Indication(s)

Pseudomonas aeruginosa infection in patients with cystic fibrosis

Protocol Number

CTBM100C2303E2

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) Patients who successfully Completed Participation in Study CTBM100C2303E1

Clinical Trial Phase

Phase III

Phase of Drug Development

Phase III

Study Start/End Dates

12-Feb-2010 to 19-Mar-2012

Reason for Termination

Not applicable.

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 Tobramycin inhalation powder (TIP), 28 mg hard capsules. TIP (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)

Objectives:

Primary objective(s)

Primary Objective: 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)

- Evaluate the efficacy of tobramycin inhalation powder after modifications in the manufacturing process (TIPnew) for the treatment of infections with P. aeruginosa in patients suffering from cystic fibrosis, assessed by forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC) and forced expiratory flow rate over 25% to 75% of vital capacity (FEF 25-75%) profile.
- Assess the effect of tobramycin inhalation powder after modifications in the manufacturing process (TIPnew) on the density of microorganisms in sputum samples of patients.
- Number (%) of patients with frequency decreases from baseline in the post-baseline audiology tests, by normal or abnormal hearing prior to study Safety population

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

At Visit 12, all patients completing study CTBM100C2303E1 continued their 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

The primary objective in this second extension study was safety. The primary objective 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 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 was 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 presented as well for the subgroups screening FEV_1 % predicted (core study) < 50% and ≥50%, age < 13 and ≥ 13, baseline MIC status (core study) ≤8 and > 8 µg/mL, 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). The relative and absolute change from Day 1 (treatment start) to Day 29 (treatment end) for each of the three cycles was analyzed with descriptive statistics. Means together with 95 % CIs of the relative change from baseline was graphically displayed over time. FEV_1 % predicted was also summarized by the core treatment groups TIP and Placebo. Treatment differences between core treatment groups were analyzed by a two-sample t-test.

Study Population: Key Inclusion/Exclusion Criteria

Key Inclusion Criteria:

- Completed all visits in study CTBM100C2303 and CTBM100C2303E1 and visit 11 of study CTBM100C2303E1 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 (at start of study CTBM100C2303) must be between 25% and 80% of normal predicted values.

Key Exclusion Criteria:

- Any use of inhaled anti-pseudomonal antibiotics between the termination of the trial CTMB100C2303E1 and the enrollment into this study.
- Known local or systemic hypersensitivity to aminoglycosides or inhaled antibiotics.

Participant Flow Table

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

Demographic summary (Safety population)

Variable	Total N=49
Age (years)	
n	49
Mean	13.3
SD	4.31
Median	14.0
Min-Max	6- 21
Age category (years), n (%)	
< 13 years	21 (42.9)
>= 13 years	28 (57.1)
Sex, n (%)	
Male	17 (34.7)
Female	32 (65.3)
Race, n (%)	
Caucasian	48 (98.0)
Asian	1 (2.0)
Weight (kg)	
n	49
Mean	36.7
SD	15.06
Median	33.0
Min-Max	11.0-70.0
Height (cm)	
n	49
Mean	146.7
SD	19.78
Median	153.0
Min-Max	106-184
Body mass index (kg/m^2)	
n	49
Mean	16.2
SD	3.55
Median	16.1
Min-Max	8.6-25.4

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

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Primary Outcome Result(s)

Number of Participants With Adverse Events (AEs)
Number of Participants With Serious Adverse Events (SAEs)

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

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.

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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=19 n (%)	Abnormal hearing at baseline N=0 n (%)
Cycle 5	W33/D1	Test performed	13 (100.0)	0 (0.0)
		Any frequencies decreased	3 (23.1)	0 (0.0)
		2 consec. frequencies decreased	1 (7.7)	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)
	W37/D29	Test performed	19 (100.0)	0 (0.0)
		Any frequencies decreased	7 (36.8)	0 (0.0)
		2 consec. frequencies decreased	3 (15.8)	0 (0.0)
		>=3 consec. frequencies decreased	1 (5.3)	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)	1 (5.3)	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 (5.3)	0 (0.0)

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	Scheduled week/day	Criterion	Normal hearing at baseline N=19 n (%)	Abnormal hearing at baseline N=0 n (%)
Cycle 6	W45/D29	Test performed	19 (100.0)	0 (0.0)
		Any frequencies decreased	5 (26.3)	0 (0.0)
		2 consec. frequencies decreased	3 (15.8)	0 (0.0)
		>=3 consec. frequencies decreased	1 (5.3)	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)	1 (5.3)	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 (5.3)	0 (0.0)
Cycle 7	W53/D29	Test performed	19 (100.0)	0 (0.0)
		Any frequencies decreased	5 (26.3)	0 (0.0)
		2 consec. frequencies decreased	2 (10.5)	0 (0.0)
		>=3 consec. frequencies decreased	3 (15.8)	0 (0.0)
		>= 10dB decrease in 3 consecutive frequencies in either ear (1)	2 (10.5)	0 (0.0)
		>= 15dB decrease in 2 consecutive frequencies in either ear (2)	1 (5.3)	0 (0.0)
		>= 20dB decrease in at least one frequency in either ear (3)	1 (5.3)	0 (0.0)
		(1), (2) or (3)	3 (15.8)	0 (0.0)

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	Scheduled week/day	Criterion	Normal hearing at baseline N=19 n (%)	Abnormal hearing at baseline N=0 n (%)
Follow up	W57/D57	Test performed	5 (100.0)	0 (0.0)
		Any frequencies decreased	2 (40.0)	0 (0.0)
		2 consec. frequencies decreased	2 (40.0)	0 (0.0)
		>=3 consec. frequencies decreased	1 (20.0)	0 (0.0)
		>= 10dB decrease in 3 consecutive frequencies in either ear (1)	1 (20.0)	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 (20.0)	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.

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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		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
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.

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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

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.

Percentage of Participants With Hospitalization Due to Respiratory Serious Adverse Events (SAEs)

	Tobramycin Inhalation Powder (TIPnew)
Overall Number of Participants Analyzed	49
Percentage of Participants With Hospitalization Due to Respiratory Serious Adverse Events (SAEs) Measure Type: Number Unit of measure: percentage of participants	4.1

Number of Days of Hospitalization Due to Respiratory Serious Adverse Events (SAEs)

	Tobramycin Inhalation Powder (TIPnew)
Overall Number of Participants Analyzed	49
Number of Days of Hospitalization Due to Respiratory Serious Adverse Events (SAEs) Mean (Standard Deviation) Unit of measure: days	16.5(2.12)

Safety Results

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.

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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)
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.

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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.

Conclusion:

- Treatment with TIP is safe and well tolerated
- No new safety signals were identified
- Efficacy was well maintained for lung function assessments of FEV_1
- Sustained bacterial suppression

Date of Clinical Trial Report

19-Sep-2012