Sponsor

Novartis

Generic Drug Name

tobramycin

Therapeutic Area of Trial

cystic fibrosis and P. aeruginosa

Approved Indication

investigational

Study Number

CTBM100C2301

Title

A randomized, double-blind, placebo-controlled, multicenter, phase 3 trial to assess the efficacy and safety of tobramycin inhaled powder (TIP) in cystic fibrosis (CF) subjects

Phase of Development

III

Study Start/End Dates

22-Sep-2005 to 28-Feb-2007

Study Design/Methodology

Eligible subjects were randomized to TIP or placebo at a 1:1 ratio for the first cycle using a bi-

ased-coin, adaptive allocation procedure to achieve balance between the two treatment groups with respect to the following covariates: region (Europe, North America, Latin America), age (≥ 6 to < 13 years, ≥ 13 to ≤ 21 years), and baseline FEV_1 (≥ 25 to < 50 % predicted, ≥ 50 to ≤ 80 % predicted).
Upon completion of the first cycle, all subjects received TIP for two additional cycles. Each cycle consisted of 28 days on treatment followed by 28 days off treatment.

Centres

33 centers in 8 countries enrolled patients: Argentina (5), Brazil (3), Bulgaria (2), Chile (3), Lithuania (1), Mexico (2), Serbia (1), United States (16).

Publication

None

Objectives

Primary objective(s)

The primary objective was to demonstrate the efficacy of a 28 day bid dosing regime of TIP versus placebo, as measured by the relative change in FEV_1 percent predicted change from baseline (Week 1/cycle 1, Day 1) to the end of cycle 1 dosing (Week 5/cycle 1, Day 28).

Secondary objective(s)

The secondary objectives were to assess the safety and efficacy of TIP when administered to patients who were dosed for more than one cycle.

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

TIP is a drug-device combination product consisting of TIP in capsules administered by the *T-326* Dry Powder Inhaler. The test product is four capsules of TIP at 28 mg dosage strength (112 mg nominal tobramycin dose) inhaled BID for 28 days (on treatment) followed by 28 days of no study treatment (off treatment).

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

The reference product is four capsules of placebo (DSPC/CaC12) inhaled BID using the T-326 Dry Powder Inhaler for 28 days on treatment followed by 28 days off treatment. Reference product will only be used during the first cycle.

Criteria for Evaluation

Primary efficacy endpoint

Relative change in FEV_1 % predicted from baseline (week 1/cycle 1, day 1) to the end of cycle 1 dosing (week 5/cycle 1, day 28).

Other endpoints

Due to the smaller sample size for the final analysis as a result of the DMC recommendation to terminate the study early, no statistical testing was performed for other efficacy endpoints except for the primary efficacy endpoint (relative change of FEV_1 % predicted). This was pre-specified prior to database lock/unblinding. However, descriptive statistics were generated for these endpoints:

- Incidence of antipseudomonal antibiotics usage and number of days used antipseudomonal antibiotics in Cycle 1 (on and off treatment).
- Incidence of respiratory-related hospitalization and number of days hospitalized in Cycle 1 (on and off treatment).
- Incidence of antipseudomonal antibiotics usage and respiratory-related hospitalization (i.e., % subjects who were both users and hospitalized) in Cycle 1 (on and off treatment).
- Relative change from baseline in FVC % predicted in all cycles.
- Relative change from baseline in FEF_{25-75} % predicted in all cycles.
- Absolute change in P aeruginosa (log10 colony forming units [CFU] per gm sputum) from baseline to each post-baseline time point in cycles 1-3.
- Absolute change in tobramycin minimum inhibitory concentration (MIC) susceptibility from baseline to each post-baseline time point in cycles 1-3.

Safety and tolerability

- Incidence of treatment-emergent adverse events (AE).
- Clinical laboratory test results.
- Serum tobramycin concentrations.
- Audiology test results (at select CF centers).
- Acute change in airway reactivity (FEV_1 % predicted) from predose to 30 minutes after completion of first dose of study drug.

Statistical Methods

General Analysis Plan

The primary efficacy endpoint is the relative change from baseline in FEV_1 % predicted to predose day 28 of Cycle 1. Baseline is defined as the latest measurement prior to the initial dosing of study drug. The primary analysis for claiming superiority is based on the SIA ITT population using an analysis of covariance model with factors of treatment, baseline FEV_1 % predicted, age and region. Due to interim analysis, the statistical significance level is 0.0044 at the SIA (see Interim Analysis Section for more details). All analysis is based on observed data, no imputation for missing data were performed

Interim Analysis

One interim was planned when the 80^{th} randomized subject completed Cycle 1 dosing (day 28) according to protocol. The objectives of the OIA were to (1) estimate the common standard deviation (SD) for sample size re-estimation; (2) evaluate efficacy of TIP versus placebo for potential stopping of study for superior efficacy; and (3) assess safety. Therefore, the OIA is limited to key safety data (adverse events, airway reactivity, bronchospasm), efficacy endpoint (relative change in FEV_1 % predicted from baseline to predose day 28 of Cycle 1), and background data. There are total 79 treated subjects included in the OIA.

The stopping boundary for the interim analysis is based on Gamma spending function. At n=79 subjects with a total of 140 subjects, the information fraction 0.564 (79/140) corresponds to the critical value (Z=2.653) and 2-sided significance level (α=0.0080).

To protect the blinding and scientific integrity of the data, the interim analysis was performed by external DMC CRO (AXIO) with no sponsor involvement. According to the DMC CRO, the Z-statistic was derived as the difference in the mean relative change in FEV1 % predicted from baseline to predose day 28 of cycle 1 (TIP minus placebo), divided by the SD of the difference, where $SD = S_p * \sqrt{(1/n_{TIP} + 1/n_{placebo})}$, and S_p is the pooled SD and the n's are the respective sample sizes for each treatment group. The corresponding p-value was derived via normal distribution.

A sensitivity interim analysis (SIA) was conducted using the sub-population of OIA. The primary objective of the SIA is to re-evaluate the efficacy of TIP versus placebo for potential stopping of study for efficacy, by excluding patients with uncertain quality of spirometry data based on a set of quality criteria pre-defined by an independent Expert Panel of pulmonologists and thereby ensuring the robustness of statistical inference from the original interim analysis of efficacy.

The subjects in the SIA are identical to subjects in the OIA with the exception that some subjects from Latin America sites were excluded due to failure to meet the calibration and/or FEV_1 data quality criteria as assessed blindly by independent external expert review panel. There are 61 subjects (53 from US/Europe and 8 from Latin America) were included in the SIA.

The SIA was performed by the same CRO using the same approach as OIA. At n=61 subjects with a total of 140 subjects, the information fraction 0.436 (61/140) corresponds to the critical value (Z=2.848) and 2-sided significance level (α=0.0044).

Data sets analyzed

- Randomized population (n=102) included all randomized patients.
- All Randomized Safety population (n=95) included all randomized patients who received at least one capsule of study drug.
- All ITT/Safety population (n=69) included patients from SIA population and additional patients from North America and Europe since SIA. The additional Latin American patients since SIA were not included in the All ITT/Safety population since they did not go through quality review of pulmonary function test by independent external expert review panel.
- SIA Safety/ITT population (n=61) included all patients in the sensitivity interim analysis. It included all patients from North America and Europe whose data were available at the interim analysis database lock. In addition, it included 8 patients from Latin America who met the quality review criteria by external review panel.

Rationale for Sample Size

An information-based group sequential procedure with one interim analysis was used for the analysis of the primary efficacy endpoint. Based on this procedure, a preliminary sample size of 140 subjects (70 per group) was needed to provide 90% power to detect a treatment difference of 11% in the mean relative change of FEV_1% predicted from baseline to the end of cycle 1 dosing (visit 5) at the .05 significance level, if the standard deviation of the primary efficacy endpoint was 20%.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion criteria:

Patients were eligible to participate in the study if they met all of the inclusion criteria:

- Confirmed diagnosis of CF by the presence of one or more clinical features of CF in addition to a quantitative pilocarpine iontophoresis sweat chloride test of ≥ 60mEg/L, or identification of well-characterized disease causing mutations in each CFTR gene, or abnormal nasal transepithelial potential difference characteristic of CF.
- Male and female patients aged from ≥ 6 to ≤ 21 years of age at the time of screening.
- FEV_1 at screening must have been ≥ 25% and ≤ 80% of normal predicted values for age, sex and height based upon Knudson criteria.
- *P. aerguinosa* must have been present in a sputum/throat culture (or bronchoalveolar lavage, BAL) within 6 months prior to screening, and in the sputum culture at the screening visit.
- Able to comply with all protocol requirements.
- Clinically stable in the opinion of the investigator.
- Using an effective means of contraception (females of childbearing potential).
- Provided written informed consent and HIPAA authorization (where applicable) prior to the performance of any study-related procedure.

Exclusion criteria:

Patients were excluded who met the following criteria:

- History of sputum culture or throat swab (or BAL) culture yielding *B. cepacia* within 2 years prior to screening and/or sputum sample yielding *B. cepacia* at screening.
- Hemoptysis more than 60 cc at any time within 30 days prior to study drug administration.
- Known local or systemic hypersensitivity to aminoglycosides or inhaled antibiotics.
- Serum creatinine 2 mg/dL or more, BUN 40 mg/dL or more, or an abnormal urinalysis defined as 2+ or greater proteinuria.
- Pregnant, lactating or planning to become pregnant.
- Any use of inhaled antipseudomonal antiobiotics within 4 months prior to screening.
- Use of systemic antipseudomonal antibiotics within 28 days prior to study drug administration.
- Initiation of treatment with macrolide antibiotics within 28 days prior to study drug administration (patients could be taking macrolide antibiotics but they would have had to have been initiated at least 28 days prior to study drug administration).
- Use of loop diuretics within 7 days of study drug administration.
- Initiation of treatment with dornase alpha within 28 days prior to study drug administration (patients could have been taking dornase alpha, but treatment would have had to have started at least 28 days prior to study drug administration).
- Initiation of treatment with inhaled steroids within 28 days prior to study drug administration

(patients could have been taking inhaled steroids, but treatment would have had to have started at least 28 days prior to study drug administration).

Number of Subjects

Patient disposition by treatment group (All Randomized Safety Population)

	TIP N=46	Placebo N=49
Completed	39 (84.8)	40 (81.6)
Discontinuations	7 (15.2)	9 (18.4)
AE or death	0	1 (2.0)
Withdraw consent	0	5 (10.2)
Inappropriate enrollment	2 (4.3)	1 (2.0)
Protocol violation	1 (2.2)	1 (2.0)
Unable to classify	4 (8.7)	1 (2.0)

"Unable to classify" includes move out of area, intolerant of inhaler, non-compliance, self discontinued from study drug, and relapse to participate in study.

Demographic and Background Characteristics

Demographics (All Randomized Safety Population)

		TIP N=46	Placebo N=49
Sex - n(%)	Male	19 (41.3)	23 (46.9)
	Female	27 (58.7)	26 (53.1)
Age (Year)	Mean (SD)	13.4 (4.42)	13.2 (3.91)
	6 to < 13	21 (45.7)	24 (49.0)
	13 to 22	25 (54.3)	25 (51.0)
Region	North America	11 (23.9)	12 (24.5)
	Latin America	17 (37.0)	17 (34.7)
	Europe	18 (39.1)	20 (40.8)

Baseline FEV_1 % predicted (SIA ITT population)

		TIP N=29	Placebo N=32
FEV_1 % predicted	Mean (SD)	55.3 (19.72)	58.7 (18.77)
	<25	1 (3.4)	2 (6.3)
	25 to <50	11 (37.9)	10 (31.3)
	50 to 80	15 (51.7)	16 (50.0)
	> 80	2 (6.9)	4 (12.5)

Primary Objective Result(s)

Relative change in FEV_1 % predicted from baseline to predose Day 28 of Cycle 1 (SIA ITT population)

	TIP N=29	Placebo N=32	Difference (SE)	95% CI of difference	P-value
n	27	31			
Mean[1]	13.21	-0.57	13.79 (3.95)	(5.87, 21.70)	0.0010
LS Mean[2]	13.97	0.68	13.29 (3.98)	(5.31, 21.28)	0.0016

[1] Mean, p-value, mean difference, and its 95% confidence interval are calculated from ANOVA with treatment in the model.

[2] Least square mean, p-value, least square mean difference, and its 95% confidence interval are calculated from ANCOVA with treatment, baseline value, age and region in the model.

SE = standard error, n is number of subjects with value at baseline and Day 28.

The analysis is based on observed data only, no imputation is performed for missing data.

Safety Results

Number (%) of subjects with most frequent AEs (occurring in ≥ 5% subjects in either group, on-treatment and off-treatment) in Cycle 1 (all randomized safety population)

	TIP N=46	Placebo N=49
At least one AE	23 (50.0)	37 (75.5)
Cough	6 (13.0)	13 (26.5)
Lung disorder	5 (10.9)	6 (12.2)
Pharyngolaryngeal pain	5 (10.9)	0
Pyrexia	3 (6.5)	2 (4.1)
Dysgeusia	3 (6.5)	1 (2.0)
Productive cough	1 (2.2)	4 (8.2)
Nasopharyngitis	1 (2.2)	3 (6.1)
Headache	0	3 (6.1)

Number (%) of subjects with SAEs by cycle (all randomized safety population)

	TIP N=46	Placebo N=49
Cycle 1	3/46 (6.5)	7/49 (14.3)
Cycle 2	0/41	3/41 (7.3)
Cycle 3	2/39 (5.1)	3/40 (7.5)

All subjects received TIP in Cycles 2 and 3.

Number (%) of subjects with relative decrease in FEV_1 % predicted from predose to 30-minutes postdose ≥ 20%

Cycle	Day	TIP N=32	Placebo N=37
Cycle 1	Day 1	1/31 (3.2)	2/35 (5.7)
	Day 8	0	0
	Day 28	0	2/34 (5.9)
Cycle 2	Day 1	0	0
	Day 8	0	0
	Day 28	0	1/30 (3.3)
Cycle 3	Day 1	0	0
	Day 8	0	0
	Day 28	0	0

Values from Latin America which failed quality review by external independent panel were excluded.
Subjects on TIP in Cycles 2 and 3.

Other Relevant Findings None
Date of Clinical Trial Report CSR in progress
Date Inclusion on Novartis Clinical Trial Results Database 05-Aug-2008
Date of Latest Update 05-Aug-2008