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Trial record **3 of 3** for: CTBM100C2303

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A Study of Tobramycin Inhalation Powder From a Modified Manufacturing Process Versus Placebo (EDIT)

This study has been completed.

Sponsor:
Novartis Pharmaceuticals

Information provided by (Responsible Party):
Novartis (Novartis Pharmaceuticals)

ClinicalTrials.gov Identifier:
NCT00918957

First received: June 4, 2009
Last updated: October 1, 2012
Last verified: October 2012
History of Changes

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Results First Received: May 5, 2012

Study Type:	Interventional
Study Design:	Allocation: Randomized; Intervention Model: Parallel Assignment; Masking: Double Blind (Subject, Caregiver, Investigator); Primary Purpose: Treatment
Condition:	Cystic Fibrosis
Interventions:	Drug: Tobramycin Inhalation Powder Drug: Placebo

Participant Flow

Hide Participant Flow

Recruitment Details

Key information relevant to the recruitment process for the overall study, such as dates of the recruitment period and locations
No text entered.

Pre-Assignment Details

Significant events and approaches for the overall study following participant enrollment, but prior to group assignment
Although 32 patients were randomized to the TIP group and 30 to the Placebo group, the ITT population included 2 patients allocated to the TIP group but received placebo due to Investigator error during the drug dispensation process. The safety population contained 30 patients who were treated with TIP and 32 patients who were treated with placebo.

Reporting Groups

	Description
TIP (Tobramycin Inhalation Powder)	Tobramycin 28 mg powder. The TIP dose of 112 mg twice a day (bis in diem = b.i.d.), given in a cycle of 28 days on treatment followed by 28 days off treatment.
Placebo	Placebo 20 mg powder capsules. The dose regimen for the reference product was inhaling the contents of four capsules twice a day (bis in diem = 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).

Participant Flow: Overall Study

	TIP (Tobramycin Inhalation Powder)	Placebo
STARTED	**32**	**30**
COMPLETED	**29**	**30**
NOT COMPLETED	**3**	**0**
Adverse Event	**2**	**0**
Withdrawal by Subject	**1**	**0**

Baseline Characteristics

Hide Baseline Characteristics

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.
No text entered.

Reporting Groups

	Description
TIP (Tobramycin Inhalation Powder)	Tobramycin 28 mg powder. The TIP dose of 112 mg twice a day (bis in diem = b.i.d.), given in a cycle of 28 days on treatment followed by 28 days off treatment.
Placebo	Placebo 20 mg powder capsules. The dose regimen for the reference product was inhaling the contents of four capsules twice a day (bis in diem = 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).
Total	Total of all reporting groups

Baseline Measures

	TIP (Tobramycin Inhalation Powder)	**Placebo**	**Total**
Number of Participants [units: participants]	**30**	**32**	**62**
Age [units: years] Mean (Standard Deviation)	**12.9 (4.25)**	**12.9 (4.68)**	**12.9 (4.44)**
Age, Customized [units: participants]			
<13 years	**15**	**15**	**30**

>= 13 years	15	17	32
Gender [units: participants]			
Female	21	19	40
Male	9	13	22
Baseline Forced Expiratory Volume in one second (FEV1) percentage predicted [1] **[units: Percentage] Mean (Standard Deviation)**	59.1 (18.18)	59.3 (16.61)	59.2 (17.25)
Baseline P. aeruginosa sputum density [2] **[units: Log10 CFU (colony forming unit)] Mean (Standard Deviation)**	7.4 (1.53)	7.4 (1.55)	7.4 (1.52)

[1]
- Any spirometry values that are listed as missing at Screening and/or Baseline FEV1 % predicted can include data that was captured but identified as technically unacceptable.
- Baseline is defined as the latest measurement prior to first dosing of study medication.

[2]
- Overall density, defined as the sum of biotypes (mucoid, dry and small colony variant).
- Baseline is defined as the latest measurement prior to first dosing of study medication.
  - If sub-isolates existed for CFU biotype mucoid or dry, then the sum of sub-isolates is analyzed.

Outcome Measures

Hide All Outcome Measures

1. Primary: Relative Change From Baseline of Forced Expiratory Volume in One Second (FEV1) Percent Predicted to End of Dosing (Day 29) [Time Frame: Baseline, Day 29]

Measure Type	Primary

Measure Title	Relative Change From Baseline of Forced Expiratory Volume in One Second (FEV1) Percent Predicted to End of Dosing (Day 29)
Measure Description	Relative change in percentage predicted FEV1 in the Intent-to-treat (ITT), modified ITT (mITT) and Observed cases in the ITT populations were calculated from an adjusted analysis ANOVA model. ITT Patients with missing or unacceptable Day 29 spirometry measurements had their primary endpoint data imputed with zero. BSL = Baseline, defined as the latest measurement prior to the first dosing of study medication - Relative change = 100 * (value - baseline) / baseline There were 3 patients who had no screening nor baseline values (due to inadequate spirometry) and so were excluded from all change from baseline analyses.
Time Frame	Baseline, Day 29
Safety Issue	No

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.
ITT: All randomized patients (pts) received at least one dose of study drug. Missing or unacceptable Day 29 spirometry test -change from baseline FEV1 % predicted imputed using last available post-baseline value or 0. mITT: Pts with unacceptable FEV1 measurements excluded. Observed cases: Pts with missing or unacceptable FEV1 measurements excluded.

Reporting Groups

	Description
TIP (Tobramycin Inhalation Powder)	Tobramycin 28 mg powder. The TIP dose of 112 mg twice a day (bis in diem = b.i.d.), given in a cycle of 28 days on treatment followed by 28 days off treatment.
Placebo	Placebo 20 mg powder capsules. The dose regimen for the reference product was inhaling the contents of four capsules twice a day (bis in diem = 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).

Measured Values

	TIP (Tobramycin Inhalation	

	Powder)	Placebo
Number of Participants Analyzed [units: participants]	**31**	**28**
Relative Change From Baseline of Forced Expiratory Volume in One Second (FEV1) Percent Predicted to End of Dosing (Day 29) [units: change in percentage] Least Squares Mean (Standard Error)		
Participants analyzed: ITT Population (31, 28)	**8.2 (2.93)**	**2.3 (3.13)**
Parts. analyzed: Modified ITT Pop (27, 27)	**9.7 (3.30)**	**2.5 (3.30)**
Parts analyzed: Observed Cases in ITT Pop (25, 27)	**10.3 (3.42)**	**2.4 (3.35)**

No statistical analysis provided for Relative Change From Baseline of Forced Expiratory Volume in One Second (FEV1) Percent Predicted to End of Dosing (Day 29)

2. Primary: Pre-planned Sensitivity Analysis: Absolute Change From Baseline of Forced Expiratory Volume in One Second (FEV1) Percent (%) Predicted to End of Dosing (Day 29) [Time Frame: Baseline, Day 29]

Measure Type	Primary
Measure Title	Pre-planned Sensitivity Analysis: Absolute Change From Baseline of Forced Expiratory Volume in One Second (FEV1) Percent (%) Predicted to End of Dosing (Day 29)
Measure Description	Absolute change in percentage predicted FEV1 in the Intent-to-treat (ITT), modified ITT (mITT) and Observed cases in the ITT populations were calculated from an adjusted analysis ANOVA model. In the adjusted analysis model: response = treatment + screening FEV1 % predicted (<50 and >=50) + age (<13 and >=13) + error. Significance for the FEV1 % predicted is reached for p-values <= 0.05. There were 3 patients who had no screening

	nor baseline values (due to inadequate spirometry) and so were excluded from all change from baseline analyses.
Time Frame	Baseline, Day 29
Safety Issue	No

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.
ITT: All randomized patients (pts) received at least one dose of study drug. Missing or unacceptable Day 29 spirometry test -change from baseline FEV1 % predicted imputed using last available post-baseline value or 0. mITT: Pts with unacceptable FEV1 measurements excluded. Observed cases: Pts with missing or unacceptable FEV1 measurements excluded.

Reporting Groups

	Description
TIP (Tobramycin Inhalation Powder)	Tobramycin 28 mg powder. The TIP dose of 112 mg twice a day (bis in diem = b.i.d.), given in a cycle of 28 days on treatment followed by 28 days off treatment.
Placebo	Placebo 20 mg powder capsules. The dose regimen for the reference product was inhaling the contents of four capsules twice a day (bis in diem = 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).

Measured Values

	TIP (Tobramycin Inhalation Powder)	**Placebo**
Number of Participants Analyzed [units: participants]	**31**	**28**
Pre-planned Sensitivity Analysis: Absolute Change From Baseline of Forced Expiratory Volume in One Second (FEV1) Percent (%) Predicted to End of Dosing (Day 29) [units: change in percentage] Least Squares Mean (Standard Error)		

Participants analyzed: ITT Population (31, 28)	**4.9 (1.59)**	**0.5 (1.70)**
Parts. analyzed: Modified ITT Pop (25, 27)	**5.7 (1.78)**	**0.6 (1.79)**
Parts. analyzed: Observed Cases, ITT Pop (27, 27)	**6.1 (1.84)**	**0.5 (1.80)**

No statistical analysis provided for Pre-planned Sensitivity Analysis: Absolute Change From Baseline of Forced Expiratory Volume in One Second (FEV1) Percent (%) Predicted to End of Dosing (Day 29)

3. Primary: Post-hoc: Relative Change From Baseline of Forced Expiratory Volume in One Second (FEV1) Percent Predicted to End of Dosing (Day 29) Without Outlier [Time Frame: Baseline, Day 29]

Measure Type	Primary
Measure Title	Post-hoc: Relative Change From Baseline of Forced Expiratory Volume in One Second (FEV1) Percent Predicted to End of Dosing (Day 29) Without Outlier
Measure Description	Relative change in percentage predicted FEV1 without outlier (outliers with respect to FEV1 values and PK data), in the Intent-to-treat (ITT), modified ITT (mITT) and Observed cases in the ITT populations were calculated from an adjusted analysis ANOVA model.
Time Frame	Baseline, Day 29
Safety Issue	No

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.
ITT: All randomized patients (pts) received at least one dose of study drug. Missing or unacceptable Day 29 spirometry test -change from baseline FEV1 % predicted imputed using last available post-baseline value or 0. mITT: Pts with unacceptable FEV1 measurements excluded. Observed cases: Pts with missing or unacceptable FEV1 measurements excluded.

Reporting Groups

	Description
TIP (Tobramycin Inhalation Powder)	Tobramycin 28 mg powder. The TIP dose of 112 mg twice a day (bis in diem = b.i.d.), given in a cycle of 28 days on treatment followed by 28 days off treatment.
Placebo	Placebo 20 mg powder capsules. The dose regimen for the reference product was inhaling the contents of four capsules twice a day (bis in diem = 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).

Measured Values

	TIP (Tobramycin Inhalation Powder)	Placebo
Number of Participants Analyzed [units: participants]	**31**	**28**
Post-hoc: Relative Change From Baseline of Forced Expiratory Volume in One Second (FEV1) Percent Predicted to End of Dosing (Day 29) Without Outlier [units: change in percentage] Least Squares Mean (Standard Error)		
Participants analyzed: ITT Population (30, 28)	**10.4 (2.81)**	**3.1 (2.92)**
Parts. analyzed: Modified ITT Pop (24, 27)	**12.4 (3.14)**	**3.5 (3.05)**
Parts. analyzed: Observed Cases, ITT Pop (26, 27)	**13.1 (3.25)**	**3.4 (3.08)**

No statistical analysis provided for Post-hoc: Relative Change From Baseline of Forced Expiratory Volume in One Second (FEV1) Percent Predicted to End of Dosing (Day 29) Without Outlier

4. Secondary: Change From Baseline of Forced Vital Capacity (FVC) Percent Predicted to End of Dosing (Day 29) and to the End of Off-cycle

Period (Day 57) [Time Frame: Baseline, Day 29, Day 57]

Measure Type	Secondary
Measure Title	Change From Baseline of Forced Vital Capacity (FVC) Percent Predicted to End of Dosing (Day 29) and to the End of Off-cycle Period (Day 57)
Measure Description	Results of statistical analysis were calculated from an ANOVA model. Baseline is defined as the latest measurement prior to the first dosing of study medication. Response (percentage change) = treatment + Screening FEV1 percentage predicted (<50 and >=50) + age (<13 and >=13) + error
Time Frame	Baseline, Day 29, Day 57
Safety Issue	No

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.
Intent-to-treat (ITT) population: All randomized patients who received at least one dose of study drug. Following the intent-to-treat principle, patients were analyzed according to the treatment they were assigned to at randomization.

Reporting Groups

	Description
TIP (Tobramycin Inhalation Powder)	Tobramycin 28 mg powder. The TIP dose of 112 mg twice a day (bis in diem = b.i.d.), given in a cycle of 28 days on treatment followed by 28 days off treatment.
Placebo	Placebo 20 mg powder capsules. The dose regimen for the reference product was inhaling the contents of four capsules twice a day (bis in diem = 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).

Measured Values

	TIP (Tobramycin Inhalation Powder)	**Placebo**

Number of Participants Analyzed [units: participants]	**31**	**28**
Change From Baseline of Forced Vital Capacity (FVC) Percent Predicted to End of Dosing (Day 29) and to the End of Off-cycle Period (Day 57) [units: percentage change] Mean (Standard Error)		
Number of participants analyzed (31, 28): Baseline	**73.3 (19.19)**	**76.9 (15.16)**
Number of participants analyzed (25, 27): Day 29	**7.2 (9.94)**	**1.6 (14.74)**
Number of participants analyzed (28, 23): Day 57	**5.2 (16.99)**	**3.1 (15.05)**

No statistical analysis provided for Change From Baseline of Forced Vital Capacity (FVC) Percent Predicted to End of Dosing (Day 29) and to the End of Off-cycle Period (Day 57)

5. Secondary: Change From Baseline of Forced Expiratory Flow Rate Over 25 and 75 Percent. (FEF25-75%) Predicted to End of Dosing (Day 29) and End of Off-cycle Period (Day 57) [Time Frame: Baseline, Day 29, Day 57]

Measure Type	Secondary
Measure Title	Change From Baseline of Forced Expiratory Flow Rate Over 25 and 75 Percent. (FEF25-75%) Predicted to End of Dosing (Day 29) and End of Off-cycle Period (Day 57)
Measure Description	FEF25-75: Forced expiratory flow rate over 25% to 75% of vital capacity For FEF25-75 percentage predicted the relative change is analyzed. If screening FEV1 percentage predicted is missing, it will be imputed by the baseline value.
Time Frame	Baseline, Day 29, Day 57
Safety Issue	No

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.
Intent-to-treat (ITT) population: All randomized patients who received at least one dose of study drug. Following the intent-to-treat principle, patients were analyzed according to the treatment they were assigned to at randomization.

Reporting Groups

	Description
TIP (Tobramycin Inhalation Powder)	Tobramycin 28 mg powder. The TIP dose of 112 mg twice a day (bis in diem = b.i.d.), given in a cycle of 28 days on treatment followed by 28 days off treatment.
Placebo	Placebo 20 mg powder capsules. The dose regimen for the reference product was inhaling the contents of four capsules twice a day (bis in diem = 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).

Measured Values

	TIP (Tobramycin Inhalation Powder)	**Placebo**
Number of Participants Analyzed [units: participants]	**31**	**28**
Change From Baseline of Forced Expiratory Flow Rate Over 25 and 75 Percent. (FEF25-75%) Predicted to End of Dosing (Day 29) and End of Off-cycle Period (Day 57) [units: percentage change] Least Squares Mean (Standard Error)		
Number of participants analyzed (31, 28): Baseline	**36.2 (20.15)**	**35.9 (20.67)**
Number of participants analyzed (25, 27): Day 29	**21.00 (36.55)**	**7.8 (29.65)**

Number of participants analyzed (28, 23): Day 57	**23.9 (35.57)**	**17.7 (37.40)**

No statistical analysis provided for Change From Baseline of Forced Expiratory Flow Rate Over 25 and 75 Percent. (FEF25-75%) Predicted to End of Dosing (Day 29) and End of Off-cycle Period (Day 57)

6. Secondary: Absolute Change From Baseline to End of Dosing (Day 29) and End of Off-cycle Period (Day 57) in Sputum Pseudomonas Aeruginosa Density (log10 Colony Forming Units(CFU) Per Gram Sputum) [Time Frame: Baseline, Day 29, Day 57]

Measure Type	Secondary
Measure Title	Absolute Change From Baseline to End of Dosing (Day 29) and End of Off-cycle Period (Day 57) in Sputum Pseudomonas Aeruginosa Density (log10 Colony Forming Units(CFU) Per Gram Sputum)
Measure Description	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.
Time Frame	Baseline, Day 29, Day 57
Safety Issue	No

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.
Intent-to-treat (ITT) population: All randomized patients who received at least one dose of study drug. Following the intent-to-treat principle, patients were analyzed according to the treatment they were assigned to at randomization.

Reporting Groups

	Description
TIP (Tobramycin Inhalation Powder)	Tobramycin 28 mg powder. The TIP dose of 112 mg twice a day (bis in diem = b.i.d.), given in a cycle

	of 28 days on treatment followed by 28 days off treatment.
Placebo	Placebo 20 mg powder capsules. The dose regimen for the reference product was inhaling the contents of four capsules twice a day (bis in diem = 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).

Measured Values

	TIP (Tobramycin Inhalation Powder)	Placebo
Number of Participants Analyzed [units: participants]	**31**	**28**
Absolute Change From Baseline to End of Dosing (Day 29) and End of Off-cycle Period (Day 57) in Sputum Pseudomonas Aeruginosa Density (log10 Colony Forming Units(CFU) Per Gram Sputum) [units: Log10 CFU (colony forming unit)] Mean (Standard Error)		
Number of participants analyzed (29, 28): Baseline	**7.5 (1.49)**	**7.3 (1.58)**
Number of participants analyzed (14, 27): Day 29	**-2.4 (1.54)**	**0.0 (0.89)**
Number of participants analyzed (19, 24): Day 57	**-0.9 (2.09)**	**-0.2 (1.20)**

No statistical analysis provided for Absolute Change From Baseline to End of Dosing (Day 29) and End of Off-cycle Period (Day 57) in Sputum Pseudomonas Aeruginosa Density (log10 Colony Forming Units(CFU) Per Gram Sputum)

7. Secondary: Change From Baseline to End of Dosing (Day 29) and End of Off-cycle Period (Day 57) of Pseudomonas Aeruginosa Minimum Inhibitory Concentration (MIC) [Time Frame: Baseline, Day 29, Day 57]

Measure Type	Secondary

Measure Title	Change From Baseline to End of Dosing (Day 29) and End of Off-cycle Period (Day 57) of Pseudomonas Aeruginosa Minimum Inhibitory Concentration (MIC)
Measure Description	Maximum MIC values from all biotypes were used. Absolute values and changes in tobramycin MIC for P. aeruginosa from baseline are summarized by biotype. Overall, a high variability of MIC was observed within each treatment group. For the maximum of all biotypes, large differences in mean changes from baseline at Day 29 were observed between the TIP group and the placebo group.
Time Frame	Baseline, Day 29, Day 57
Safety Issue	No

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.
Intent-to-treat (ITT) population: All randomized patients who received at least one dose of study drug. Following the intent-to-treat principle, patients were analyzed according to the treatment they were assigned to at randomization.

Reporting Groups

	Description
TIP (Tobramycin Inhalation Powder)	Tobramycin 28 mg powder. The TIP dose of 112 mg twice a day (bis in diem = b.i.d.), given in a cycle of 28 days on treatment followed by 28 days off treatment.
Placebo	Placebo 20 mg powder capsules. The dose regimen for the reference product was inhaling the contents of four capsules twice a day (bis in diem = 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).

Measured Values

	TIP (Tobramycin Inhalation Powder)	**Placebo**
Number of Participants Analyzed [units: participants]	**31**	**28**

Change From Baseline to End of Dosing (Day 29) and End of Off-cycle Period (Day 57) of Pseudomonas Aeruginosa Minimum Inhibitory Concentration (MIC) **[units: µg/mL]** **Mean (Standard Deviation)**		
Number of participants analyzed (28, 29):Baseline	**0.8 (1.49)**	**2.7 (11.81)**
Number of participants analyzed (13, 27): Day 29	**0.1 (0.73)**	**10.0 (38.32)**
Number of participants analyzed (19, 24): Day 57	**0.5 (1.49)**	**1.4 (6.58)**

No statistical analysis provided for Change From Baseline to End of Dosing (Day 29) and End of Off-cycle Period (Day 57) of Pseudomonas Aeruginosa Minimum Inhibitory Concentration (MIC)

8. Secondary: Shift From Baseline in Laboratory Parameters to Above Upper/Lower Limit of Normal [Time Frame: Baseline, Study completion]

Measure Type	Secondary
Measure Title	Shift From Baseline in Laboratory Parameters to Above Upper/Lower Limit of Normal
Measure Description	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.
Time Frame	Baseline, Study completion
Safety Issue	No

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.
Safety population: All randomized patients who received at least one dose of study drug. In all safety analyses patients were analyzed

according to the treatment received.

Reporting Groups

	Description
TIP (Tobramycin Inhalation Powder)	Tobramycin 28 mg powder. The TIP dose of 112 mg twice a day (bis in diem = b.i.d.), given in a cycle of 28 days on treatment followed by 28 days off treatment.
Placebo	Placebo 20 mg powder capsules. The dose regimen for the reference product was inhaling the contents of four capsules twice a day (bis in diem = 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).

Measured Values

	TIP (Tobramycin Inhalation Powder)	Placebo
Number of Participants Analyzed [units: participants]	**30**	**32**
Shift From Baseline in Laboratory Parameters to Above Upper/Lower Limit of Normal [units: percentage of participants at risk]		
Hematology (Hem): Absolute Basophilis- low - low	**0.0**	**0.0**
Hem: Absolute Basophilis - high	**8.3**	**10.0**
Hem: Absolute Eosinophils - low	**0.0**	**0.0**
Hem: Absolute Eosinophils - high	**14.3**	**7.4**
Hem: Absolute Lymphocytes - low	**4.2**	**3.7**
Hem: Absolute Lymphocytes - high	**11.1**	**9.5**
Hem: Absolute Monocytes - low	**0.0**	**0.0**
Hem: Absolute Monocytes - high	**9.5**	**19.2**
Hem: Absolute Neutrophils (Seg. + Bands) - low	**9.5**	**10.3**
Hem: Absolute Neutrophils (Seg. + Bands) - high	**11.1**	**25.0**

Hem: Basophils - low	**0.0**	**0.0**
Hem: Basophils - high	**60.0**	**40.0**
Hem: Eosinophils - low	**0.0**	**0.0**
Hem: Eosinophils - high	**28.6**	**14.8**
Hem: Lymphocytes -low	**4.3**	**14.3**
Hem: Lymphocytes - high	**14.3**	**7.7**
Hem: Monocytes - low	**8.3**	**0.0**
Hem: Monocytes - high	**27.8**	**24.0**
Hem: Neutrophils (Seg. + Bands) - low	**13.6**	**11.1**
Hem: Neutrophils (Seg. + Bands) - high	**4.3**	**6.9**
Hem: Platelet count (direct) - low	**4.5**	**0.0**
Hem: Platelet count (direct) - high	**7.7**	**13.3**
Hem: RBC- low	**0.0**	**0.0**
Hem: RBC- high	**16.7**	**9.1**
Hem: WBC (total)- low	**9.5**	**3.7**
Hem: WBC (total) - high	**5.3**	**26.1**
Hem: Hematocrit - low	**0.0**	**0.0**
Hem: Hematocrit - high	**14.3**	**14.8**
Hem: Hemoglobin - low	**3.8**	**0.0**
Hem: Hemoglobin - high	**4.2**	**3.3**
Biochemistry (Bio): Album - low	**0.0**	**0.0**
Bio: Album - high	**20.0**	**10.0**
Bio: Alkaline phosphatase, serum - low	**0.0**	**0.0**

Bio: Alkaline phosphatase, serum - high	**14.3**	**4.3**
Bio: Bilirubin (direct/conjugated) -low	**0.0**	**0.0**
Bio: Bilirubin (direct/conjugated) -high	**7.7**	**7.1**
Bio: Bilirubin (total) - low	**0.0**	**0.0**
Bio: Bilirubin (total) - high	**3.4**	**3.3**
Bio: Blood Urea Nitrogen (BUN) - low	**0.0**	**13.8**
Bio: Blood Urea Nitrogen (BUN) - high	**3.4**	**3.2**
Bio: Calcium -low	**0.0**	**12.9**
Bio: Calcium -high	**6.9**	**6.7**
Bio: Chloride - low	**0.0**	**6.5**
Bio: Chloride - high	**10.3**	**0.0**
Bio: Creatinine - low	**0.0**	**50.0**
Bio: Creatinine - high	**0.0**	**0.0**
Bio: Gamma Glutamyltransferase - low	**0.0**	**3.2**
Bio: Gamma Glutamyltransferase - high	**4.2**	**3.8**
Bio: Glucose - low	**12.0**	**20.0**
Bio: Glucose - high	**11.1**	**6.7**
Bio: Phosphate (Inorganic Phosphorus) - low	**0.0**	**0.0**
Bio: Phosphate (Inorganic Phosphorus) - high	**19.2**	**13.8**
Bio: Potassioum - low	**0.0**	**3.2**
Bio: Potassioum - high	**7.1**	**0.0**
Bio: SGOT (AST) - low	**0.0**	**3.2**
Bio: SGOT (AST) - high	**12.5**	**12.0**

Bio: SGPT (ALT) - low	**0.0**	**0.0**
Bio: SGPT (ALT) - high	**9.5**	**13.0**
Bio: Serum bicarbonate - low	**47.6**	**23.8**
Bio: Serum bicarbonate - high	**0.0**	**0.0**
Bio: Sodium - low	**0.0**	**6.5**
Bio: Sodium - high	**10.3**	**0.0**
Bio: Total Protein (Serum) - low	**0.0**	**3.2**
Bio: Total Protein (Serum) - high	**4.2**	**29.2**
Bio: Uric Acid - low	**3.6**	**3.2**
Bio: Uric Acid - high	**10.7**	**19.2**

No statistical analysis provided for Shift From Baseline in Laboratory Parameters to Above Upper/Lower Limit of Normal

9. Secondary: Percentage of Participants With Adverse Events (AEs) [Time Frame: First administration of study drug, study completion]

Measure Type	Secondary
Measure Title	Percentage of Participants With Adverse Events (AEs)
Measure Description	Adverse Events (AEs) (on and off treatment) regardless of study relationship by primary system organ and treatment group. Primary system organ classes are sorted in descending order of frequency in the TIP treatment group. A patient with more than one AE within a primary system organ class is counted only once for that class.
Time Frame	First administration of study drug, study completion
Safety Issue	Yes

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.
Safety population: All randomized patients who received at least one dose of study drug.In all safety analyses patients were analyzed according to the treatment received

Reporting Groups

	Description
TIP (Tobramycin Inhalation Powder)	Tobramycin 28 mg powder. The TIP dose of 112 mg twice a day (bis in diem = b.i.d.), given in a cycle of 28 days on treatment followed by 28 days off treatment.
Placebo	Placebo 20 mg powder capsules. The dose regimen for the reference product was inhaling the contents of four capsules twice a day (bis in diem = 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).

Measured Values

	TIP (Tobramycin Inhalation Powder)	**Placebo**
Number of Participants Analyzed [units: participants]	**30**	**32**
Percentage of Participants With Adverse Events (AEs) [units: Percentage of participants]		
Respiratory, thoracic & mediastinal disorders	**13.3**	**3.1**
Ear and labyrinth disorders	**10.0**	**6.3**
Infections and infestations	**10.0**	**25.0**
Gastrointestinal disorders	**3.3**	**3.1**
Metabolism and nutrition disorders	**3.3**	**3.1**
Nervous system disorders	**3.3**	**0.0**
Renal and urinary disorders	**3.3**	**0.0**

Skin and subcutaneous tissue disorder	**3.3**	**0.0**
Blood and lymphatic system disorder	**0.0**	**3.1**
Injury, poisoning and procedural complications	**0.0**	**3.1**
Investigation	**0.0**	**3.1**

No statistical analysis provided for Percentage of Participants With Adverse Events (AEs)

10. Secondary: Percentage of Participants With Serious Adverse Events (SAEs) [Time Frame: Time of consent, 4 weeks after study completion]

Measure Type	Secondary
Measure Title	Percentage of Participants With Serious Adverse Events (SAEs)
Measure Description	Serious Adverse Events (on and off treatment) by preferred term and treatment group. Preferred terms are sorted in descending order of frequency in the TIP treatment group. A patient with multiple occurrences of the same preferred term is counted only once in the preferred term.
Time Frame	Time of consent, 4 weeks after study completion
Safety Issue	Yes

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.
Safety population: All randomized patients who received at least one dose of study drug. In all safety analyses patients were analyzed according to the treatment received.

Reporting Groups

	Description

TIP (Tobramycin Inhalation Powder)	Tobramycin 28 mg powder. The TIP dose of 112 mg twice a day (bis in diem = b.i.d.), given in a cycle of 28 days on treatment followed by 28 days off treatment.
Placebo	Placebo 20 mg powder capsules. The dose regimen for the reference product was inhaling the contents of four capsules twice a day (bis in diem = 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).

Measured Values

	TIP (Tobramycin Inhalation Powder)	Placebo
Number of Participants Analyzed [units: participants]	**30**	**32**
Percentage of Participants With Serious Adverse Events (SAEs) [units: percentage of participants]		
Lower limb fracture	**0.0**	**3.1**
Pneumonia	**0.0**	**3.1**

No statistical analysis provided for Percentage of Participants With Serious Adverse Events (SAEs)

11. Secondary: Acute Change in Airways Reactivity (FEV1 Percent Predicted) From Pre-dose to 30 Minutes After Completion of First Dose of Study Drug [Time Frame: Day 1, Day 29]

Measure Type	Secondary
Measure Title	Acute Change in Airways Reactivity (FEV1 Percent Predicted) From Pre-dose to 30 Minutes After Completion of First Dose of Study Drug
Measure Description	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.
Time Frame	Day 1, Day 29

Safety Issue	No

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.
Safety population: All randomized patients who received at least one dose of study drug.In all safety analyses patients were analyzed according to the treatment received.

Reporting Groups

	Description
TIP (Tobramycin Inhalation Powder)	Tobramycin 28 mg powder. The TIP dose of 112 mg twice a day (bis in diem = b.i.d.), given in a cycle of 28 days on treatment followed by 28 days off treatment.
Placebo	Placebo 20 mg powder capsules. The dose regimen for the reference product was inhaling the contents of four capsules twice a day (bis in diem = 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).

Measured Values

	TIP (Tobramycin Inhalation Powder)	**Placebo**
Number of Participants Analyzed [units: participants]	**30**	**32**
Acute Change in Airways Reactivity (FEV1 Percent Predicted) From Pre-dose to 30 Minutes After Completion of First Dose of Study Drug [units: Percentage of participants]		
Day 1	**4.8**	**0.0**
Day 29	**0.0**	**8.0**

No statistical analysis provided for Acute Change in Airways Reactivity (FEV1 Percent Predicted) From Pre-dose to 30 Minutes After Completion of First Dose of Study Drug

12. Secondary: Tobramycin Serum Concentration [Time Frame: Pre-dose, 0 - 1 hour post-dose, 1 -2 hours post-dose, 2 - 6 hours post-dose]

Measure Type	Secondary
Measure Title	Tobramycin Serum Concentration
Measure Description	Descriptive statistics of serum and sputum concentrations per scheduled sampling time. Detectable concentration values at pre-dose on Day 1 were excluded from the analysis.
Time Frame	Pre-dose, 0 - 1 hour post-dose, 1 -2 hours post-dose, 2 - 6 hours post-dose
Safety Issue	No

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.
Safety population: All randomized patients who received at least one dose of study drug. In all safety analyses patients were analyzed according to the treatment received. This measures the concentration of active substance in the body at different time-point to evaluate there is abnormal accumulation of active substance. Not for Placebo Patients.

Reporting Groups

	Description
TIP (Tobramycin Inhalation Powder)	Tobramycin 28 mg powder. The TIP dose of 112 mg twice a day (bis in diem = b.i.d.), given in a cycle of 28 days on treatment followed by 28 days off treatment.

Measured Values

	TIP (Tobramycin Inhalation Powder)
Number of Participants Analyzed	**30**

[units: participants]	
Tobramycin Serum Concentration [units: µg/mL] Mean (Standard Deviation)	
Day1: 0 -1 hour (hr) post dose (28, 0)	**0.83 (0.40)**
Day 1: 1 -2 hours (hr) post dose (28, 0)	**0.93 (0.44)**
Day 1: 2 -6 hours (hr) post dose (29, 0)	**0.73 (0.39)**
Day 29: Pre-dose (27, 0)	**0.41 (0.51)**
Day 29: 0 -1 hr post dose (28, 0)	**1.48 (0.69)**
Day 29: 1 -2 hrs post dose (29, 0)	**1.37 (0.64)**
Day 29: 2 -6 hrs post dose (27, 0)	**1.14 (0.65)**

No statistical analysis provided for Tobramycin Serum Concentration

Serious Adverse Events

Hide Serious Adverse Events

Time Frame	No text entered.
Additional Description	No text entered.

Reporting Groups

	Description
TIP (Tobramycin Inhalation Powder)	Tobramycin 28 mg powder. The TIP dose of 112 mg twice a day (bis in diem = b.i.d.), given in a cycle of 28 days on treatment followed by 28 days off treatment.
Placebo	Placebo 20 mg powder capsules. The dose regimen for the reference product was inhaling the

	contents of four capsules twice a day (bis in diem = 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).

Serious Adverse Events

	TIP (Tobramycin Inhalation Powder)	Placebo
Total, serious adverse events		
# participants affected / at risk	**0/30 (0.00%)**	**2/32 (6.25%)**
Infections and infestations		
Pneumonia † 1		
# participants affected / at risk	**0/30 (0.00%)**	**1/32 (3.13%)**
Injury, poisoning and procedural complications		
Lower limb fracture † 1		
# participants affected / at risk	**0/30 (0.00%)**	**1/32 (3.13%)**

† Events were collected by systematic assessment
1 Term from vocabulary, MedDRA 10.X

Other Adverse Events

Hide Other Adverse Events

Time Frame	No text entered.
Additional Description	No text entered.

Frequency Threshold

Threshold above which other adverse events are reported	5%

Reporting Groups

	Description
TIP (Tobramycin Inhalation Powder)	Tobramycin 28 mg powder. The TIP dose of 112 mg twice a day (bis in diem = b.i.d.), given in a cycle of 28 days on treatment followed by 28 days off treatment.
Placebo	Placebo 20 mg powder capsules. The dose regimen for the reference product was inhaling the contents of four capsules twice a day (bis in diem = 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).

Other Adverse Events

	TIP (Tobramycin Inhalation Powder)	Placebo
Total, other (not including serious) adverse events		
# participants affected / at risk	**4/30 (13.33%)**	**6/32 (18.75%)**
Ear and labyrinth disorders		
Hypoacusis † 1		
# participants affected / at risk	**3/30 (10.00%)**	**2/32 (6.25%)**
Infections and infestations		
Respiratory tract infection † 1		
# participants affected / at risk	**0/30 (0.00%)**	**2/32 (6.25%)**
Respiratory tract infection viral † 1		
# participants affected / at risk	**0/30 (0.00%)**	**3/32 (9.38%)**
Respiratory, thoracic and mediastinal disorders		
Cough † 1		
# participants affected / at risk	**3/30 (10.00%)**	**0/32 (0.00%)**

† Events were collected by systematic assessment
1 Term from vocabulary, MedDRA 10.X

Limitations and Caveats

Hide Limitations and Caveats

Limitations of the study, such as early termination leading to small numbers of participants analyzed and technical problems with measurement leading to unreliable or uninterpretable data
No text entered.

More Information

Hide More Information

Certain Agreements:

Principal Investigators are **NOT** employed by the organization sponsoring the study.
There **IS** an agreement between Principal Investigators and the Sponsor (or its agents) that restricts the PI's rights to discuss or publish trial results after the trial is completed.
The agreement is: ☐ The only disclosure restriction on the PI is that the sponsor can review results communications prior to public release and can embargo communications regarding trial results for a period that is **less than or equal to 60 days**. The sponsor cannot require changes to the communication and cannot extend the embargo. ☐ The only disclosure restriction on the PI is that the sponsor can review results communications prior to public release and can embargo communications regarding trial results for a period that is **more than 60 days but less than or equal to 180 days**. The sponsor cannot require changes to the communication and cannot extend the embargo. Other disclosure agreement that restricts the right of the PI to discuss or publish trial results after the trial is completed. ☑ **Restriction Description:** The terms and conditions of Novartis' agreements with its investigators may vary. However, Novartis does not prohibit any investigator from publishing. Any publications from a single-site are postponed until the publication of the pooled data (i.e., data from all sites) in the clinical trial or disclosure of trial results in their entirety.

Results Point of Contact:

Name/Title: Clinical Disclosure Office

Organization: Novartis Pharmaceuticals
phone: 862-778-8300

No publications provided by Novartis

Publications automatically indexed to this study:

Galeva I, Konstan MW, Higgins M, Angyalosi G, Brockhaus F, Piggott S, Thomas K, Chuchalin AG. Tobramycin inhalation powder manufactured by improved process in cystic fibrosis: the randomized EDIT trial. Curr Med Res Opin. 2013 Aug;29(8):947-56. doi: 10.1185/03007995.2013.805122. Epub 2013 Jun 5.

Responsible Party:	Novartis (Novartis Pharmaceuticals)
ClinicalTrials.gov Identifier:	NCT00918957 History of Changes
Other Study ID Numbers:	**CTBM100C2303** 2008-002318-22 (EudraCT Number)
Study First Received:	June 4, 2009
Results First Received:	May 5, 2012
Last Updated:	October 1, 2012
Health Authority:	Bulgaria: Ministry of Health Chile: Instituto de Salud Pública de Chile Egypt: Ministry of Health and Population Estonia: The State Agency of Medicine European Union: European Medicines Agency Ireland: Ministry of Health India: Ministry of Health Latvia: State Agency of Medicines Lithuania: State Medicine Control Agency - Ministry of Health Romania: Ministry of Public Health Russia: Ministry of Health of the Russian Federation South Africa: Department of Health United States: Food and Drug Administration