

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

201820Orig1s000

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA:	201-820
Submission Date(s):	April 12, 2011
Proposed Brand Name	Bethkis
Generic Name	Tobramycin
Primary Reviewer	Ryan Owen, Ph.D.
Team Leader	Kimberly Bergman, Pharm.D.
OCP Division	DCP4
OND Division	DAIOP
Applicant	Chiesi
Relevant IND(s)	72,068
Submission Type; Code	Original 505(b)(2) ; Type 5 (New Formulation) ; Resubmission
Formulation; Strength(s)	Tobramycin 300 mg/4 mL Inhalation Solution
Indication	For the management of cystic fibrosis patients with <i>Pseudomonas aeruginosa</i> .

BACKGROUND

CHF 1538, a tobramycin solution for nebulization (300 mg/4 mL unit dose ampule) differs from the currently marketed TOBI® (300 mg/5 mL unit dose ampule) in concentration per mL, osmolarity, and pH. CHF1538 has been approved in Europe since 2006, and is marketed as Bramitob® in 15 countries for the long-term management of chronic pulmonary infections caused by *Pseudomonas aeruginosa* in cystic fibrosis (CF) patients six years of age and older.

A 505(b)(2) NDA in support of CHF 1538 for the management of CF patients with *Pseudomonas aeruginosa* was originally submitted on 10/22/10. The original NDA received a complete response letter on 8/25/11 due to concerns about linking the proposed to-be-marketed nebulizer/compressor combination to what was used in the clinical trials, issues with the pulmonary function test data, and several device-related concerns. There were no clinical pharmacology concerns in the complete response letter.

The clinical pharmacology review for the initial NDA submission was written by Dr. Yongheng Zhang (in DARRTS under NDA 201-820, submitted on 6/30/11). This review details all of the clinical pharmacology-related studies that were conducted in support of the initial NDA. Dr. Zhang recommended approval of the original NDA from a clinical pharmacology standpoint. On 4/12/12, the Sponsor re-submitted their NDA. There was no new clinical pharmacology information contained in the resubmission. Therefore, this review is limited to labeling recommendations. The proposed label is included in this review complete with clinical pharmacology recommendations shown as track changes. Please refer to Dr. Zhang's 6/30/11 review for all supporting clinical pharmacology information.

RECOMMENDATION

The Clinical Pharmacology information provided by the Sponsor in the NDA submission is acceptable.

18 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RYAN P OWEN
09/20/2012

KIMBERLY L BERGMAN
09/20/2012

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: 201-820
Submission Date(s): October 22, 2010
Proposed Brand Name: TBD
Generic Name: Tobramycin
Primary Reviewer: Yongheng Zhang, Ph.D.
Team Leader: Kimberly Bergman, Pharm.D.
OCP Division: DCP4
OND Division: DAIOP
Applicant: Chiesi Pharmaceuticals Inc
Relevant IND(s): 72068
Submission Type; Code: Original 505(b)(2); Type 5 (New Formulation)
Formulation; Strength(s): Tobramycin 300 mg/4 mL Inhalation Solution
Indication: For the management of cystic fibrosis patients with *P. aeruginosa*.

TABLE OF CONTENTS

1. EXECUTIVE SUMMARY 2

1.1. RECOMMENDATION 3

1.2. PHASE IV COMMITMENTS 3

1.3. SUMMARY OF IMPORTANT CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FINDINGS 3

2. QUESTION BASED REVIEW 4

2.1. GENERAL ATTRIBUTES OF THE DRUG 4

2.2. GENERAL CLINICAL PHARMACOLOGY 5

2.3. INTRINSIC FACTORS 8

2.4. EXTRINSIC FACTORS 8

2.5. GENERAL BIOPHARMACEUTICS 8

2.6. ANALYTICAL SECTION 8

3. LABELING RECOMMENDATIONS 11

4. APPENDICES..... 12

4.1 INDIVIDUAL STUDY REVIEW..... 12

 4.1.1. *Tobramycin Pharmacokinetics in Plasma and Sputum Following Single Dose Phase 1 Study CPO1 12*

 4.1.2. *Tobramycin Concentrations in Sputum Following Repeated Dosing in Phase 2 Study CT01 ... 18*

1. EXECUTIVE SUMMARY

CHF 1538, a tobramycin solution for nebulization (300 mg/4mL unit dose ampule) differs from the currently marketed TOBI[®] (300 mg/5mL unit dose ampule) in concentration per mL, osmolarity and pH. CHF 1538 has been approved in 2006 in Europe and marketed as Bramitob[®] in 15 countries for the long-term management of chronic pulmonary infections caused by *Pseudomonas aeruginosa* in cystic fibrosis (CF) patients six years of ages and older.

In this 505(b)(2) submission, the Applicant seeks the same indication for CHF 1538 as Bramitob[®] and TOBI[®], and is relying, in part, on the FDA's findings of safety and effectiveness for the approved drug product TOBI[®].

In support of the NDA, the sponsor submitted 4 clinical studies, including:

- One Phase 1 bioavailability and pharmacokinetic study (CP01) to evaluate tobramycin PK in plasma and sputum of CF patients after a single administration by nebulization of CHF 1538 in comparison to TOBI,
- Two double-blind, placebo-controlled studies (CT01 and CT02) to provide evidence for the efficacy and safety of CHF 1538, and
- One open-labelled, active-controlled study (CT03) to provide evidence for the efficacy and safety of CHF 1538.

1.1. Recommendation

The Clinical Pharmacology information provided by the Applicant in the NDA submission is acceptable.

1.2. Phase IV Commitments

None.

1.3. Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

Two clinical pharmacology studies were submitted (**Table 1.3-1**).

The data from the study CP01 following single administration of CHF 1538 and TOBI demonstrated that tobramycin plasma concentration-time profiles were superimposable between two formulations, suggesting that CHF 1538 administration likely leads to similar systemic exposure and thus similar systemic safety profile as TOBI. As expected, tobramycin sputum concentrations were highly variable. The mean tobramycin sputum concentration-time profiles were also similar between two formulations. Three hours after inhalation, sputum tobramycin concentrations declined to approximately 15% of tobramycin concentrations observed at 30 min. PK parameters derived from either plasma or sputum concentration-time profiles are comparable between CHF 1538 and TOBI following single administration.

The data from CT01 PK sub-study demonstrated that the mean sputum concentration of tobramycin at 10 min after dosing on Days 1 and 28 during the four weeks of treatment was not significantly different ($p=0.93$, $\sim 700\mu\text{g/g}$), suggesting tobramycin in sputum did not accumulate following repeated dosing for a 28-day treatment period.

Taken together, these findings provided the supporting evidence for the safety and efficacy of the proposed product from a clinical pharmacology point of view.

Table 1.3-1: Summary of the Clinical Pharmacology Studies

Study	Aim of the Study	Study Design/Population	Study Medications	Primary Endpoints
CP01	To evaluate the PK of tobramycin in plasma and sputum of CF patients after a single administration by nebulization of CHF1538 in comparison to the marketed formulation TOBI®	Single dose, randomized, double-blind, two-way crossover study in CF patients	CHF 1538, 300 mg/4 mL unit-dose ampule TOBI, 300 mg/5 mL unit-dose ampule	CHF 1538 concentration and PK parameters in plasma and sputum
CT01 PK Substudy	To measure the local sputum concentration of tobramycin in a subset of patients treated with CHF 1538	Multiple dose, randomized, double-blind, placebo-controlled, parallel groups, multicenter study in CF patients	CHF 1538, 300 mg/4 mL unit-dose ampule Placebo	CHF 1538 concentration in sputum ten minutes after the first and the last dose (Day 28 of treatment) and after 4-week wash-out (Day 56)

2. QUESTION BASED REVIEW

Since this application is a 505(b)(2) for a locally delivered and acting drug product relying upon conclusions drawn by the agency for a previously approved product, only relevant questions from the OCP Question-Based Review (QBR) format are addressed below.

2.1. General Attributes of the Drug

2.1.1. *What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product?*

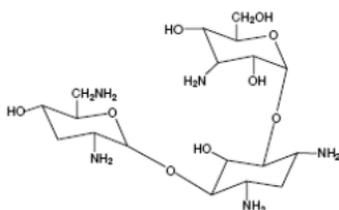
The active pharmaceutical ingredient is tobramycin as the (b) (4). It is an aminoglycoside, broad-spectrum antibiotic produced by *Streptomyces tenebrarius*. Tobramycin occurs as (b) (4), and is freely soluble in water (b) (4).

Structural Formula: C₁₈H₃₇N₅O₉

Molecular Weight: 467.52 Dalton

CAS Index Name: 6 O-3-amino-3-deoxy- α -D-glucopyranosyl-(1 \rightarrow 4)-O-[2,6-diamino- 2,3,6-trideoxy- α -D-ribo-hexopyranosyl-(1 \rightarrow 6)]-2-deoxy-L-streptamine.

Chemical Structure:



Drug Product:

The drug product, CHF 1538, is a (b) (4) weight/volume preservative-free, sterile, nebulized tobramycin solution. As shown in Table 2.1.1-1, each single-use, 4 mL ampule of CHF 1538 contains 300 mg of the active ingredient with (b) (4) sodium chloride in water for injection. Additional inactive ingredients include sulfuric acid and/or sodium hydroxide to adjust the pH to (b) (4) and nitrogen for sparging. It is a sterile, clear, colorless to pale yellow, non-pyrogenic, aqueous solution with the pH and salinity adjusted specifically for administration by a compressed air driven reusable nebulizer.

Table 2.1.1-1: CHF 1538 Composition Per Single-Dose Ampule

Component	Unit Formula per Single-Dose Ampule (per 4 mL) ¹	Function
Tobramycin, USP	300 mg	API
Sodium Chloride, USP	(b) (4)	(b) (4)
2N Sulfuric Acid, NF		
2N Sulfuric Acid, NF		pH Adjustment
1N Sodium Hydroxide, NF		pH Adjustment
Water for Injection, USP		(b) (4)

(b) (4)

2.1.2. *What is the proposed mechanism of drug action and therapeutic indication?*

Tobramycin is an aminoglycoside antibiotic produced by *Streptomyces tenebrarius*. It acts primarily by disrupting protein synthesis, leading to altered cell membrane permeability, progressive disruption of the cell envelope, and eventual cell death. Tobramycin has in-vitro activity against a wide range of gram-negative organisms including *P. aeruginosa*. It is bactericidal at concentrations equal to or slightly greater than inhibitory concentrations.

CHF 1538 is indicated for the management of cystic fibrosis patients with *P. aeruginosa*.

2.1.3. *What are the proposed dosage(s) and route(s) of administration?*

The recommended dosage for both adults and pediatric patients six years of age and older is one single-use ampule (300 mg/4 mL) administered BID for 28 days. Dosage is not adjusted by weight. All patients should be administered 300 mg BID. The doses should be taken as close to 12 hours apart as possible; they should not be taken less than six hours apart. It is administered BID in alternating periods of 28 days. After 28 days of therapy, patients should stop the therapy for the next 28 days, and then resume therapy for the next 28 day on & 28 day off cycle.

2.2. General Clinical Pharmacology

2.2.1. *What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?*

In support of the NDA, the sponsor submitted 4 clinical studies, including:

- One Phase 1 bioavailability and pharmacokinetic study (CP01) to evaluate tobramycin PK in plasma and sputum of CF patients after a single administration by nebulization of CHF 1538 in comparison to TOBI,
- Two double-blind, placebo-controlled studies (CT01 and CT02) to provide the evidence for the efficacy and safety of CHF 1538, and
- One open-labelled, active-controlled study (CT03) to provide the evidence for the efficacy and safety of CHF 1538.

2.2.2. *What is the basis for selecting the response endpoints (i.e., clinical or surrogate endpoints) or biomarkers (collectively called pharmacodynamics [PD]) and how are they measured in clinical pharmacology and clinical studies?*

The primary efficacy endpoint for both Studies CT01 and CT02 was the difference between the CHF 1538 and placebo groups in mean relative change from baseline to last treatment visit in FEV1 % of predicted normal. FEV1 has proven to be a reliable outcome variable in the measurement of pulmonary function in patients with CF who are treated with nebulized tobramycin. Because the study included both adults and children, and lung volume is an age-dependent variable, FEV1 was expressed both as a % of predicted normal and in absolute liters. Pulmonary function is considered the best predictor of morbidity and mortality in this patient population and thus, it is the most widely used endpoint in clinical studies of CF.

2.2.3. *Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?*

Yes, tobramycin concentrations were measured in plasma and sputum samples obtained in the clinical studies CP01 and CT01 (Refer to Section 2.6).

2.2.4. Exposure-response (Not needed? It's not been adequately studied in TOBI)

The characteristics of exposure-response relationships for efficacy and safety of tobramycin for inhalation have been previously described for TOBI®. Refer to the original review for NDA 50-753 dated 12/22/1997.

2.2.5. What are the PK characteristics of the drug?

Following single dose of CHF 1538 administered via inhalation, the mean plasma concentration-time profile for tobramycin is shown in **Figure 2.2.5-1**. This profile is almost superimposable with that following single administration of TOBI. The mean sputum-concentration-time profile is shown up to the 6 hr time-point in **Figure 2.2.5-2**. Three hours after CHF 1538 administration, sputum tobramycin geomean concentrations declined to approximately 15% of tobramycin levels observed at 30 min. PK parameters derived from either plasma or sputum-time profiles are comparable between CHF 1538 and TOBI® following single administration (**Table 2.2.5-1**).

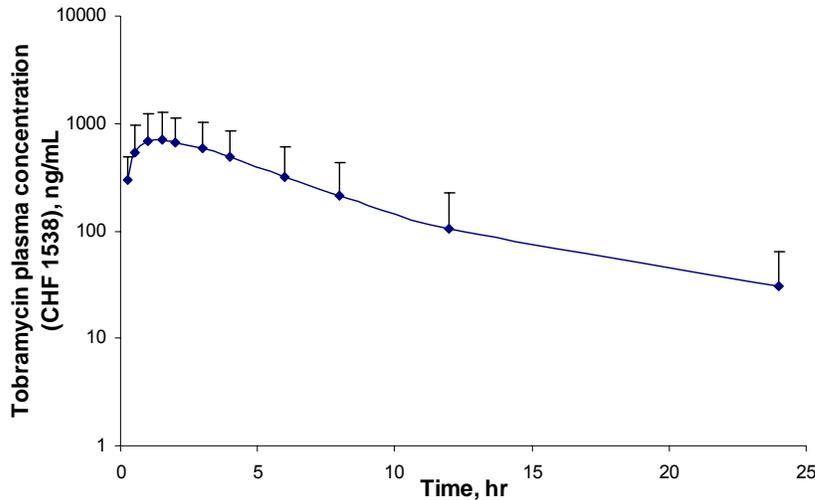


Figure 2.2.5-1: Mean (+SD) Tobramycin Plasma Concentration-Time Profile Observed After Single Inhalation of CHF 1538 (N=9)

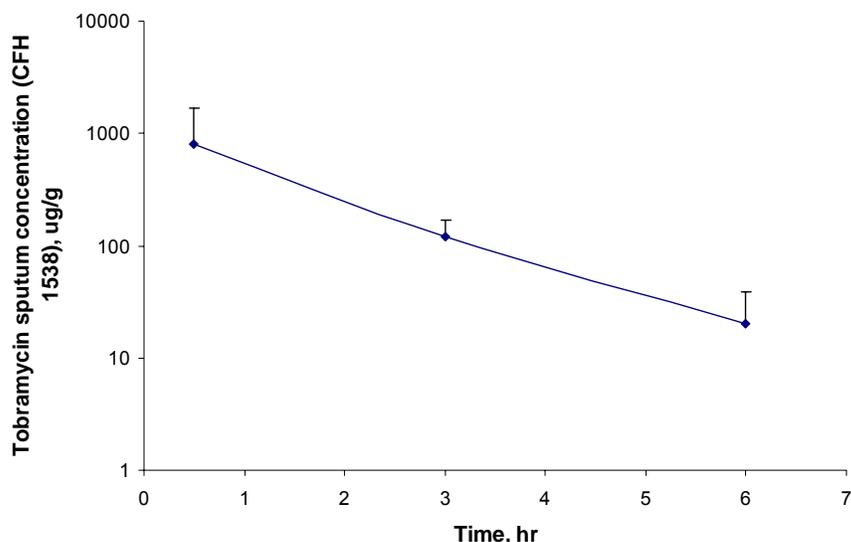


Figure 2.2.5-2: Tobramycin Sputum Concentration (geometric mean + SD) -Time Profile Observed After Single Inhalation of CHF 1538 (N=9)

Table 2.2.5-1: Comparison of Tobramycin Plasma and Sputum PK Parameters After Single Inhalation of CHF 1538 and TOBI (N=9)

PLASMA				
	CHF 1538	TOBI	Point Estimate	Statistical Comparison [90% CI]
C_{max} (ng/mL)	549.10	540.42	1.02	NS (p=0.950) [0.64-1.62]
T_{max} (h)	1.5 (1.0-2.0)	1.0 (0.5-3.0)		NS (p=0.531) [-]
AUC_t (ng×h/mL)	3349.05	3323.88	1.01	NS (p = 0.979)
AUC_{∞} (ng×h/mL)	3470.40	3454.35	1.00 [†]	NS (p=0.987) [0.61-1.66]
$T_{1/2}$ (h)	4.4	4.7	-	- [-]
MRT (h)	5.8	6.1	-	- [-]
SPUTUM				
C_{max} (µg/g)	813.94	543.11	-	NS (p=0.300)
T_{max} (h)	0.5 (0.4-0.6)	0.5 (0.4-0.6)	-	NS (p=0.875)

[†] relative bioavailability

Note: C_{max} shown as geometric means

2.2.5.1. What are the single dose and multiple dose PK parameters?

Plasma PK of tobramycin was only evaluated following single administration of CHF 1538. Results from Study CT01 showed that the mean sputum concentration of tobramycin at 10 min after dosing on Days 1 and 28 during the four weeks of treatment was not significantly different (p=0.93, ~ 700µg/g), suggesting tobramycin in sputum was not accumulated following repeated dosing for a 28-day treatment period.

2.3. Intrinsic Factors

The impact of intrinsic factors on tobramycin exposure following administration via inhalation have been previously described for TOBI[®]. Refer to the approved product labeling for TOBI[®] for information on intrinsic factors.

2.4. Extrinsic Factors

The impact of extrinsic factors on tobramycin exposure following administration via inhalation have been previously described for TOBI[®]. Refer to the approved product labeling for TOBI[®] for information on extrinsic factors.

2.5. General Biopharmaceutics

The clinical trial material (CTM) used in Studies CP01, CT01 and CT02 had a higher osmolarity (b) (4) vs (b) (4) mOsmol/kg) than the to-be-marked product (TBM). The osmolarity of the CTM was also distinctly different from the European-approved commercial batches ((b) (4) mOsmol/kg), although the formulation and component concentrations were equivalent. An investigation implied that the osmolarity difference between the CTM used in the clinical studies and the European-approved batches was due to the presence of residual ethanol in the drug substance used for the clinical study CTM but not in the European-approved product. Because the osmolarities of the US TBM product (proposed: (b) (4) mOsmol/kg) and the European-approved drug product used in Study CT03 ((b) (4) mOsmol/kg) fall between the osmolarity ranges of TOBI ((b) (4) mOsmol/kg) and the CTM used in Studies CT01, CT02 and CP01 ((b) (4) mOsmol/kg), the Applicant does not believe that the difference in the osmolarity of the two products is clinically relevant. In fact, Study CT03 was provided as a bridging study to support that the efficacy and safety profile of CHF 1538 is not significantly affected by the lower osmolarity of the TBM drug product.

In addition, the compressor and nebulizer used in clinical studies are different from those proposed with the TBM product. Therefore, the Applicant submitted the in vitro performance data to bridge the compressor and nebulizer used in clinical studies with those proposed for use with the TBM product.

The approach of using Clinical trial CT03 and in vitro performance data for compressors and nebulizers to bridge the CTM product with TBM product is acceptable from a clinical pharmacology point of view. Please refer to ONDQA/CMC review and CDRH consult review for more detail.

2.6. Analytical Section

2.6.1. *How are the active moieties identified and measured in the plasma and sputum in the clinical pharmacology and biopharmaceutics studies?*

For Study CP01, plasma samples were prepared using solid-liquid extraction and subsequently analyzed by LC/MS/MS using positive turbo-ionspray ionization mode with sisomicin as the internal standard. The validated concentrations ranged from 5 ng/mL to 2500 ng/mL for plasma samples, and from 10 µg/g to 1000 µg/g for sputum samples.

For Study CT01, the sputum sample preparation involves a cleaning up with chloroform and a pre-column derivatization with 9-Fluorenylmethyl chloroformate (FMOC). Sputum

concentrations were analyzed by a high performance liquid chromatography with fluorimetric detection (HPLC-FD). The method was validated in the range of 1-50 µg/g.

2.6.2. *Which metabolites have been selected for analysis and why?*

No metabolite was selected for analysis. Following parenteral administration, little, if any, metabolic transformation occurs.

2.6.3. *For tobramycin measured, is free, bound, or total measured? What is the basis for that decision, if any, and is it appropriate?*

The reported concentrations represent total concentrations. Free concentrations in the plasma are not considered clinically relevant to the indicated efficacy following inhalation administration.

2.6.4. *What bioanalytical methods are used to assess concentrations?*

Refer to *Section 2.6.1.* for further information.

2.6.4.1. *What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques are used?*

For Study CP01, the standard curve ranged from 5 ng/mL to 2500 ng/mL for plasma samples and from 10 µg/g to 1000 µg/g for sputum samples. For Study CT01, the standard curve ranged from 1 to 50 µg/g for sputum samples. The observed plasma or sputum concentrations of tobramycin in clinical studies did not exceed the upper limit of quantitation for the respective standard curve. The linear regression of the curves for peak area ratios *versus* concentration was weighted $1/x^2$ for the standard curves for both plasma and sputum samples.

2.6.4.2. *What are the lower and upper limits of quantification (LLOQ/ULOQ)?*

The lower and upper limits of quantitation were 5 ng/mL and 2500 ng/mL for tobramycin for plasma samples. For sputum samples, the lower and upper limits of quantitation were 10 µg/g and 1000 µg/g for Study CP01, and 1 µg/g and 50 µg/g for Study CT01, respectively.

2.6.4.3. *What are the accuracy, precision, and selectivity at these limits?*

The between-run accuracy (%RE) and precision (%CV) ranges for tobramycin in plasma samples were -6.2% to 5.16% and -3.48% to 7.44%, respectively.

For Study CP01, the between-run accuracy (%RE) and precision (%CV) ranges for tobramycin in sputum samples were -7.11% to 6.37% and 1.47 to 4.92%, respectively.

For Study CT01, the between-run accuracy (%RE) and precision (%CV) ranges for tobramycin in sputum samples were -5.5% to 8.3% and 1.9 to 4.9%, respectively.

Selectivity was demonstrated by the lack of interference by potential endogenous interfering substances in four batches of human plasma or sputum samples.

2.6.4.4. *What is the sample stability under the conditions used in the study (long-term, freeze-thaw, sample-handling, sample transport, autosampler)?*

For Study CP01, tobramycin was shown to be stable in plasma samples at room temperature up to 4 hours, in extracted samples for 5 days when stored at 4°C, in plasma samples stored at approximately -80°C for about 3 months, and following three freeze/thaw cycles. After extracted from sputum, tobramycin was shown to be stable in the injection solvent when storing injection vials at ~ 4°C up to 2 days.

For Study CT01, tobramycin was shown to be stable in sputum after three freeze/thaw cycles, in sputum stored at room temperature for 24 hours, in final solution up to 12 hours when stored in autosampler vials at 4°C.

2.6.4.5. What is the QC sample plan?

For Study CP01, the concentrations of the QC plasma samples consisted of 5, 10, 500, and 2500 ng/mL tobramycin. Between-run and within-run accuracy and precision were evaluated using replicates (n=6) from each of the four concentrations. The concentrations of the QC sputum samples consisted of 10, 100, and 1000 µg/g tobramycin. Between-run and within-run accuracy and precision were evaluated using replicates (n=4) from each of the three concentrations.

For Study CT01, the concentrations of the QC sputum samples consisted of 1, 3, 6, and 30 µg/g tobramycin. Between-run and within-run accuracy and precision were evaluated using replicates (n=6) from each of the four concentrations.

3. LABELING RECOMMENDATIONS

There has been no internal discussion on labeling; therefore, no labeling recommendations are to be issued during the current review cycle.

APPEARS THIS WAY ON ORIGINAL

4. APPENDICES

4.1 Individual Study Review

4.1.1. Tobramycin Pharmacokinetics in Plasma and Sputum Following Single Dose Phase 1 Study CP01

Study Number: CP01

Comparative Bioavailability Study of Aerosolized Tobramycin in Cystic Fibrosis Patients After Administration of 300 mg CHF 1538 Tobramycin 300mg/4 mL Inhalation Solution or TOBI (Phase 1)

Dates: 11 July, 2001 to 26 April, 2002

Clinical investigator: Hans-Georg Eichler, MD. Vienna University Medical School, Vienna, Austria

Analytical site: [REDACTED] (b) (4) Clinical Pharmacology Research Unit, [REDACTED] (b) (4)

OBJECTIVES:

To evaluate tobramycin PK in plasma and sputum of CF patients after a single administration by nebulization of CHF 1538 in comparison to the marketed formulation TOBI.

FORMULATION & ADMINISTRATION

The study medication was administered via the PARI LC plus nebulizer and the PARI TurboBOY compressor. A bronchodilator (salbutamol 0.2 mg; Sultanol[®]) was taken via a pressurized metered-dose inhaler with a Volumatic[®] spacer one to 23 minutes before study drug nebulization.

TOBI Batch: 05KOA/6; CHF 1538 Batch: 0105012

STUDY DESIGN:

This was a double-blind, single center, randomized, two-way crossover study. All patients were treated with a single dose of 300 mg tobramycin, both as CHF 1538 and as TOBI. A washout of at least five days and not more than nine days separated the two periods of drug administration.

At each study session, patients attended the clinic in a fasting state and blood and sputum samples were taken at the following times to assess tobramycin concentrations:

- Venous blood samples were collected at pre-dose, immediately before nebulization start, immediately after end of nebulization (approximately 0.25 hour), 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12 and 24 hours post-dose;
- Sputum samples (expectorated sputum) were collected at pre-dose, 15 minutes after the end of nebulization (approximately 0.5 hour), 3, 6, 12 and 24 hours post-dose.

Time 0 was defined as the moment when nebulization began. Urine samples were collected in 0-4, 4-8, 8-12 and 12-24 hour intervals on Days 1, 2, 3, and 4, but not analyzed for tobramycin concentrations.

Individual demographic and other baseline data for patients whose data were analyzed are below.

- Five patients were male and four were female;
- All patients were Caucasian;
- The mean age of the patients was 21.9 ± 6.3 years; mean body weight was 58.5 ± 10.9 kg;
- At screening, the mean FEV1 was 2.2 ± 1.1 L, corresponding to $62.7 \pm 32.9\%$ of the predicted normal; and
- Oxyhemoglobin saturation was $94.6 \pm 1.8\%$ at baseline.

ASSAY METHODOLOGY:

Plasma samples were prepared using (b) (4) and subsequently analyzed by LC/MS/MS using (b) (4) as the internal standard. The concentration range was validated from 5 ng/mL to 2500 ng/mL for plasma samples. Sputum samples were extracted by water and then diluted into the mobile phase. The similar analytical method for plasma analysis was adopted for sputum samples and the method was partially validated for the analysis of sputum samples for the concentration range from 10 µg/g to 1000 µg/g.

Criterion	Plasma	Sputum	Comments
Conc. range, LLOQ	5 – 2500 ng/mL 5 ng/mL	10– 1000 µg/g 10 µg/g	satisfactory satisfactory
Linearity, r^2	> 0.99	> 0.99	satisfactory
Accuracy, % RE	-6.2 – 5.16 ^a -5.3 – 4.7 ^b	-7.11 – 6.37 ^c	satisfactory
Precision, % CV	2.27 – 7.44 ^a -3.48 – 3.86 ^b	1.47 – 4.92 ^c	satisfactory
Recovery	Evaluated for analyte at three QC concentrations (10, 500 and 2500 ng/mL) and one IS concentration (100 ng/mL) in plasma samples	Evaluated for analyte at two QC concentrations (10 and 1000 µg/g)	satisfactory
Specificity	Interference by endogenous compounds evaluated		satisfactory
Stability	Stable in plasma at room temperature up to 4 hours, extracted samples for 5 days when stored at 4°C, plasma samples stored at ~ -80°C for about 3 months, and following three freeze/thaw cycles.	Stable in the injection solvent when storing in injection vials at ~ 4°C up to 2 days.	satisfactory

^a, QC samples (5, 10, 500, and 2500 ng/mL) between-run; ^b, calibration standards (5, 10, 50, 200, 500, 1000, 2000, and 5000 ng/mL) between-run; ^c, QC samples (10, 100, and 1000 µg/g) between-run

Based on the Analytical Reports PC40116-1, 2, and 3

DATA ANALYSIS

Plasma and sputum concentrations of tobramycin analyzed according to a non-compartmental kinetic model that was used to determine C_{max} and T_{max} in plasma and sputum, and AUC_t , AUC_{∞} .

%AUC_{extra}, MRT, $t_{1/2e1}$ and F_{rel} (i.e., relative bioavailability, calculated as AUC ratio) in plasma only.

RESULTS:

While 11 patients were randomized, only nine patients completed both crossover phases and were included in the analysis. The inhalation lasted 16 minutes for TOBI (median; range 11 – 20 minutes) and 13 minutes for CHF 1538 (median; range 9 – 22 minutes).

Plasma

The mean plasma concentration profiles overlapped following the administration of the two formulations (**Figure 1**). As shown in **Table 1**, there were no statistically significant differences between formulations for C_{max} ($p=0.950$), AUC_t ($p=0.979$) AUC_{∞} ($p=0.987$), and T_{max} ($p=0.531$). The point estimate calculated for C_{max} , AUC_t and AUC_{∞} was close to 1 indicating a comparable systemic exposure and relative bioavailability. Period of treatment and sequence did not have a statistically relevant effect on C_{max} , AUC_t , and AUC_{∞} . The relative bioavailability, calculated as the ratio $AUC_{\infty CHF 1538} / AUC_{\infty TOBI}$, was 1.20 ± 0.57 , indicating a comparable bioavailability between CHF 1538 and TOBI.

In general, high individual variability was observed in the PK parameters. The CV% for C_{max} was > 80 % and >70 % for TOBI and CHF 1538, respectively. The CV% for AUC_t was > 90 % and >85% for TOBI and CHF 1538, respectively.

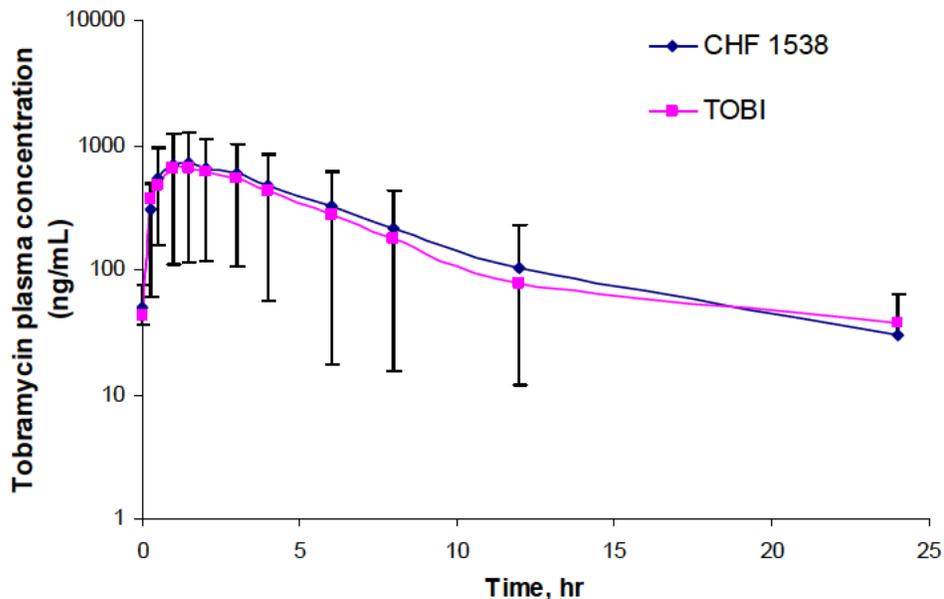


Figure 1: Mean (+SD) Tobramycin Plasma Concentration-Time Profiles Observed After Single Inhalation of TOBI or CHF 1538 (N=9).

Table 1: Tobramycin Plasma Pharmacokinetic Comparison Following TOBI and CHF 1538 Administrations (N=9)

Treatment	C _{max} ¹ (ng/mL)	T _{max} ² (h)	AUC _t ³ (ng×h/mL)	AUC _∞ ⁴ (ng×h/mL)	%AUC _{extra} ⁵ (%)	t _{1/2} ⁶ (h)	MRT ⁷ (h)
TOBI	540.42 ⁸	1.0 (0.5-3.0) ⁹	3323.88 ⁸	3454.35 ⁸	3.3 ⁸	4.7 ⁸	6.1 ⁸
CHF 1538	549.10 ⁸	1.5 (1.0-2.0) ⁹	3349.05 ⁸	3470.40 ⁸	2.5 ⁸	4.4 ⁸	5.8 ⁸
Statistical comparison	NS ¹⁰ (p=0.950)	NS (p=0.531)	NS (p=0.979)	NS (p=0.987)	-	-	-
Point Estimate ¹¹	1.02	-	1.01	1.00	-	-	-
90% CI ¹²	0.64-1.62	-	0.60-1.69	0.61-1.66	-	-	-

¹ maximum plasma concentration

² time to reach C_{max}

³ area under the concentration-time curve from time 0 hours up to time the last measurable time point

⁴ area under the concentration-time curve extrapolated to infinity

⁵ percentage of extrapolated area under the curve with respect to the total area under the curve

⁶ extrapolated terminal half-life

⁷ mean retention time

⁸ geometric mean

⁹ median (range)

¹⁰ not statistically significant

¹¹ Point estimate is calculated as the ratio of the geometric means.

¹² confidence interval

Source: Clinical study report CP01

Sputum concentrations

The sputum concentration profiles following the administration of the two formulations are considered similar as shown in **Figure 2**. Maximum tobramycin concentrations were observed in the first sputum sample taken. Sputum concentrations decreased quickly. After 12 hours they were below the LLOQ in most patients. At 24 hours, tobramycin concentrations could be detected at low levels only in two patients following treatment with CHF 1538.

High individual variability was observed in the sputum concentrations. Due to limited sample points, AUC could not be reliably calculated and compared.

There were no statistically differences for both C_{max} and T_{max} in sputum between formulations. (**Table 2**).

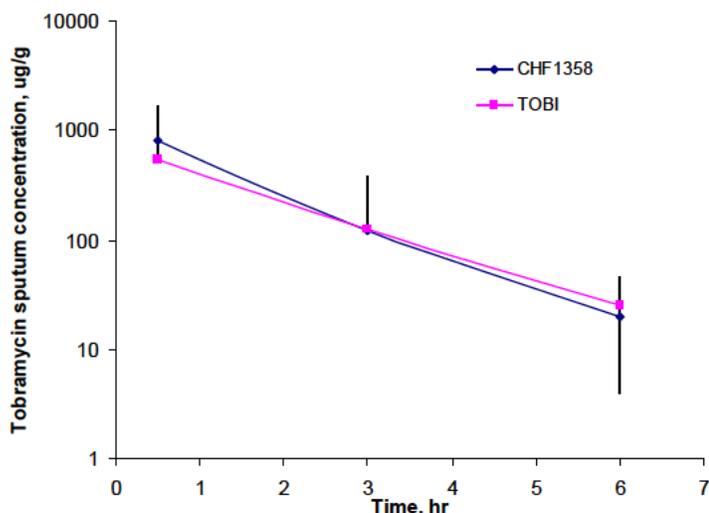


Figure 2: Tobramycin Sputum Concentration (Geometric Mean+SD) -Time Profiles Observed After Single Inhalation of TOBI or CHF 1538 (LLOQ= 10 µg/g, N=9).

Table 2: Tobramycin Sputum Pharmacokinetic Comparison Following TOBI and CHF 1538 Administration, N=9 (Source: Clinical study report CP01)

Treatment	C _{max1} (µg/g)	T _{max} ² (h)
TOBI	543.11 ³	0.5 (0.4-0.6) ⁴
CHF 1538	813.94 ³	0.5 (0.4-0.6) ⁴
Statistical comparison	NS ⁵ (p=0.300)	NS (p=0.875)

¹ maximum sputum concentration

² time to reach C_{max}

³ geometric mean

⁴ median (range)

⁵ not statistically significant

Source: Table 23 and Table 25.

SAFETY RESULTS:

Two female patients (2 out of 11) withdrew from the study, one due to personal reason, and the other due to poor venous access. There were no severe adverse events, and all adverse events, were considered mild in intensity.

SPONSORS CONCLUSIONS:

The systemic tobramycin concentration profiles were similar between formulations and almost superimposable. There were no statistically significant differences between formulations for C_{max}, AUC_t, AUC_∞, and T_{max}.

The sputum concentration-time profiles were also similar between formulations. There were no statistically significant differences between formulations for C_{max} and T_{max}.

Target tobramycin sputum concentration (i.e. 400 µg/g) were reached with the CHF 1538 formulation in the majority of patients (8/9) as compared to TOBI (5/9), without increase in

systemic absorption of tobramycin, supporting comparable systemic exposure for the two drugs. Both study drugs were safe and well-tolerated in the adult CF patients in this study.

REVIEWER'S ASSESSMENT & RECOMMENDATION:

Results from Study CP01 adequately described and compared the pharmacokinetics of tobramycin in plasma and sputum following single TOBI or CHF 1538 administration. The data showed that tobramycin plasma concentration-time profiles were almost superimposable between two formulations, supporting that the CHF 1538 should have similar systemic exposure and thus similar systemic safety profile compared to TOBI. As expected, tobramycin sputum concentrations were highly variable following nebulized administration of both formulations. The mean tobramycin sputum concentration-time profiles were similar between two formulations. Three hours after CHF 1538 inhalation, sputum tobramycin concentrations declined to approximately 15% of tobramycin levels observed at 30 min. The sponsor's conclusions are valid.

4.1.2. Tobramycin Concentrations in Sputum Following Repeated Dosing in Phase 2 Study CT01

Study Number: CT01

DOUBLE-BLIND, MULTICENTER, RANDOMIZED, PLACEBO-CONTROLLED, PARALLEL GROUPS, CLINICAL TRIAL OF CHF 1538 TOBRAMYCIN 300 MG/4 ML INHALATION SOLUTION (300 MG BID) IN THE 4-WEEK TREATMENT (PLUS 4 WEEKS OF RUN-OUT) OF PATIENTS WITH CYSTIC FIBROSIS AND A POSITIVE CULTURE FOR PSEUDOMONAS AERUGINOSA

Dates: 12 June, 2002 to 23 April, 2004

Principal investigator: Professor G. Lenoir, M.D. Medicine Interne et Mucoviscidose, Service de Pédiatrie Générale Hôpital Necker des Enfants Malades, Paris Cedex, France

Analytical site: (b) (4)

OBJECTIVES:

Primary: To demonstrate superior efficacy of inhaled aerosolized CHF 1538 (300 mg BID) in comparison with inhaled aerosolized placebo saline solution delivered by a Pari LC Plus[®] nebulizer (Pari, Germany), in a 4-week treatment (plus four weeks of run-out period) of patients with CF and *P. aeruginosa* infection.

Secondary: To measure the local concentrations (in induced sputum) of tobramycin in a subset of at least 24 patients treated with the active substance.

Reviewer's Note: This review only focuses on the PK part of the study.

FORMULATION & ADMINISTRATION:

The study medication was administered via the PARI LC plus nebulizer and the PARI TurboBOY compressor. A bronchodilator (salbutamol 0.2 mg; Sultanol[®]) was taken via a pressurized metered-dose inhaler with a Volumatic[®] spacer one to 23 minutes before study drug nebulization.

Product Description	Form/Strength/Route of Administration	Batch Number	Expiration Date
Tobramycin 300 mg/4 mL Inhalation Solution	Inhalation solution/300 mg per 4 mL/inhalation	0105012	04/2003
		0111035	10/2003
		0303019	02/2005
Placebo Solution	Inhalation solution/NA/inhalation	0105011	04/2004
		0111036	10/2003
		0303020	02/2005

STUDY DESIGN:

This was a double-blind, multinational, multicenter, randomized, placebo-controlled study in patients with CF and *P. aeruginosa* infection to evaluate the efficacy and safety of CHF 1538 compared to placebo administered BID over a 4-week treatment period followed by 4-week

wash-out period. A secondary objective of the study that pertained only to a subset of patients was to measure the local sputum concentration of tobramycin.

Thirty patients (24 patients in CHF 1538 group and six patients in the Placebo group) were planned for PK assessment of tobramycin concentration in the sputum. The sputum sample for PK analysis was collected 10 minutes after the administration of study drug after the first (Day 1) and last dose (Day 28) at the end of the 4-week treatment period, and again at the end of the study after the 4-week wash-out period without treatment (Day 56).

The PK analysis was done only for patients having both baseline and end-of-treatment assessments. Demographic characteristics for these patients are summarized in **Table 1**.

Table 1: Demographic Characteristics - Pharmacokinetic Subgroup

	CHF 1538	Placebo
Number of Patients	21	4
Gender		
Male	9 (42.9%)	2 (50.0%)
Female	12 (57.1%)	2 (50.0%)
p-value		1.000
Age (years)		
Mean	9.5	15.3
SD ²	3.7	10.1
Range	6.0 - 18.0	7.0 - 30.0
N ³	21	4
p-value		0.049
Weight (kg)		
Mean	24.4	43.1
SD	9.4	37.4
Range	15.0 - 47.0	21.4 - 99.0
N	21	4
p-value		0.044
Height (cm)		
Mean	128.2	144.8
SD	19.2	23.2
Range	102.0 - 172.0	122.0 - 177.0
N	21	4
p-value		0.140
BMI (kg/m²)		
Mean	14.4	18.1
SD	2.0	9.0
Range	10.9 - 19.4	12.8 - 31.6
N	21	4
p-value		0.085
Colonization with <i>P. aeruginosa</i>		
N	21	4
Chronic	16 (76.2%)	4 (100%)
First or intermittent	5 (23.8%)	0 (0.0%)
p-value		0.549

ASSAY METHODOLOGY:

The assay was performed using high performance liquid chromatography with (b) (4). The sample preparation involves a (b) (4). The method was validated in the range of 1-50 µg/g.

Criterion	Sputum	Comments
Conc. range,	1– 50 µg/g	satisfactory
LLOQ	1 µg/g	satisfactory
Linearity, r ²	> 0.99	satisfactory
Accuracy, % RE	-5.5 – 8.3 ^a	satisfactory
Precision, % CV	1.9 – 4.9 ^a	satisfactory
Recovery	Not applicable	-
Specificity	Interference by endogenous compounds evaluated	satisfactory
Stability	Stable after three freeze/thaw cycles; in samples stored at room temperature for 24 hours; in final solution up to 12 hours when stored in autosampler vials at 4°C	satisfactory

^a, QC samples (1, 3, 6, 30µg/g) between-run;

Based on the Analytical Report R165-04

DATA ANALYSIS:

The tobramycin concentrations in the sputum samples were summarized by descriptive statistics.

RESULTS:

The PK subset of the study included a total of 25 patients, 21 in the CHF 1538 group and 4 in the Placebo group.

Of these 21 CHF 1538-treated patients in the PK sub-study, 17 patients had detectable tobramycin sputum concentration (i.e., >LLOQ at 1 µg/g) on both Days 1 and 28. Five patients had sputum tobramycin concentrations detectable on Day 56 after the 4-week wash-out. Among the four subjects in the Placebo group, two patients had detectable but low tobramycin concentrations (20 ~ 51 µg/g) at 10 min post mock administration.

As shown in **Figures 1 and 2**, sputum concentrations are highly variable. In most cases (13 out of 17), however, for each individual, the sputum concentration on Day 1 was either similar or within 3-fold difference to that on Day 28 (**Figure 1**). For all the subjects (N=5) with detectable sputum concentration on both Days 28 and 56, the individual sputum concentration on Day 28 was much higher (at least 6 fold) than that after a 4-week wash-out period (i.e., Day 56). (**Figure 2**)

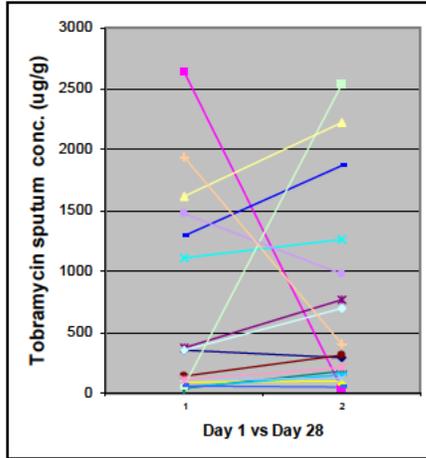


Figure 1: Comparison of tobramycin sputum concentrations for each individual at 10 min post administration on Day 1 and Day 28 (n=17).

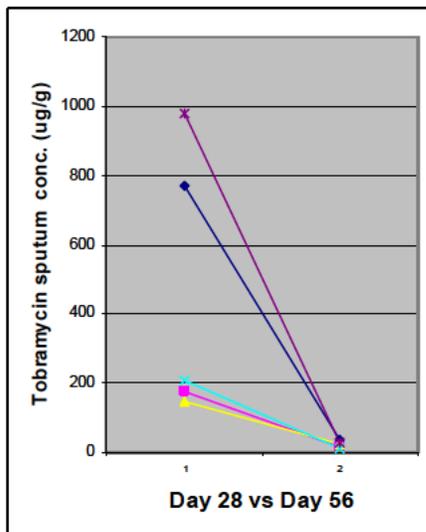


Figure 2: Comparison of tobramycin sputum concentrations for each individual on Day 28 and Day 56 (n=5).

Mean sputum concentrations of tobramycin measured after the first dose were similar to those measured after the last dose despite high variability. Mean concentrations were 695.6 ± 817.0 $\mu\text{g/g}$ (Day 1, after the first dose) and 716.9 ± 799 $\mu\text{g/g}$ (Day 28, after the last dose). – **Table 2.**

Mean sputum concentrations of tobramycin measured at the end of the 4-week wash-out period (Day 56, 22.7 ± 9.5 $\mu\text{g/g}$) were greatly reduced compared with concentrations measured on the last day of treatment (Day 28, 456.0 ± 389.0 $\mu\text{g/g}$) in the five patients with detectable tobramycin concentration in both occasions – **Table 3.** It should be noted that the mean sputum concentration of 22.7 ± 9.5 $\mu\text{g/g}$ on Day 56 is an overestimate, because it was calculated based on the five subjects with detectable tobramycin concentration, while most of the samples (16 out of 21) had tobramycin concentration below LLOQ, i.e. 1 $\mu\text{g/g}$.

In conclusion, after four weeks of treatment, mean sputum concentration of tobramycin was ~ 700 $\mu\text{g/g}$ at 10 min post-administration and tobramycin did not accumulate in sputum after 4

consecutive weeks of treatment. Furthermore, after a 4-week wash-out period, the concentration of tobramycin in sputum becomes relatively insignificant.

Table 2: Summary of Tobramycin Concentration ($\mu\text{g/g}$) in Sputum in the Study CT01 (N=17, subjects with sputum concentration detectable on both Days 1 and 28)

		Visit 2 Baseline	Visit 4 Week 4 Last Dose / End of Treatment Period
	Week of treatment	0	4
Tobramycin ²	mean (SD ³) [$\mu\text{g/g}$]	695.6 (817)	716.9 (799)
(N ⁴ = 17)	mean change (SD) [$\mu\text{g/g}$]		21.33 (1017)
	95% CI ⁵		-499, 541.7
	p-value		0.932

¹ Intent-to-Treat

² Patients with only baseline values were not included. Sputum samples from patients randomized to Placebo group were not analyzed for the tobramycin concentration.

³ standard deviation

⁴ total number of patients

⁵ confidence interval

Source: Appendix 16.2.5.3

Table 3: Summary of Tobramycin Concentration ($\mu\text{g/g}$) in Sputum in the Study CT01 (N=5, including subjects with sputum concentration measured after Weeks 4 and 8)

		Visit 4 Week 4 Last Dose / End of Treatment Period	Visit 5 Week 8 End of Run-Out Period
	Week of treat.	4	
Tobramycin ²	mean (SD ³) [$\mu\text{g/g}$]	456.0 (389)	22.72 (9.5)
(N ⁴ = 5)	mean change (SD) [$\mu\text{g/g}$]		-433 (382)
	95% CI ⁵		-872, 5.45
	Paired t-test; p-value		-2.54;0.064

¹ Intent-to-Treat

² Patients with only baseline values (Visit 2) were not included. Sputum samples from patients randomized to Placebo group were not analyzed for the tobramycin concentration.

³ standard deviation

⁴ total number of patients

⁵ confidence interval

Source: Appendix 16.2.5.3

SPONSORS CONCLUSIONS:

For all patients participating in PK subset analysis, the concentrations of tobramycin measured in the sputum after the first and last doses of CHF 1538 were greater than the respective MICs for *P. aeruginosa* isolated from their sputa, thus indicating that the nebulized dose of CHF 1538 reaches adequate local drug concentrations without evidence of drug accumulation throughout the remainder of the 4-week treatment period.

REVIEWER'S ASSESSMENT & RECOMMENDATION:

Results from Study CT01 described tobramycin concentrations at 10 min on Days 1 and 28 after inhalation following repeated CHF 1538 bid for 28 days and on Day 56 after a 4-week washout period. The reviewer agrees that the mean sputum concentration of tobramycin at 10 min after dosing on Days 1 and 28 during the four weeks of treatment was not significantly different ($p=0.93$, $\sim 700\mu\text{g/g}$), suggesting tobramycin in sputum was not accumulated following repeated dosing for a 28-day treatment period. The sponsor's conclusions are valid.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

YONGHENG ZHANG
06/30/2011

KIMBERLY L BERGMAN
06/30/2011