

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

201688s000

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

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA:	201-688
Submission Date(s):	December 21, 2011
Proposed Brand Name	TOBI Podhaler
Generic Name	Tobramycin
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OND Division	DAIOP
Applicant	Novartis
Relevant IND(s)	64,409
Submission Type; Code	Original 505(b)(1)
Formulation; Strength(s)	Inhalation powder hard capsules: 28 mg
Indication	For the management of cystic fibrosis patients with <i>Pseudomonas aeruginosa</i> .

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1. EXECUTIVE SUMMARY

Novartis submitted a New Drug Application to market TOBI Podhaler, a new formulation of tobramycin for inhalation (dry powder in capsules) to be delivered with the T-326 Inhaler. The tobramycin dry powder used in TOBI Podhaler is referred to throughout this review as TIP (or TPI). The proposed dosing regimen for TIP is the inhalation of four 28 mg capsules (112 mg) twice daily (the label states that the doses should be taken as close to 12 hours apart as possible and that each dose should not be taken less than 6 hours apart) for 28 days. The current standard of care for cystic fibrosis (CF) patients infected with *Pseudomonas aeruginosa* is TOBI® (tobramycin inhalation solution, USP) given as 300 mg q12h via nebulization for 28 days followed by a cycle of 28 days with no drug. As proposed by the Sponsor, the potential benefits of TIP over TOBI include decreased administration time and increased portability, both of which could lead to increased adherence.

The Sponsor conducted one Phase 1 single dose, six-arm, dose-finding trial in CF patients (TPI-001). The trial arms evaluated in TPI-001 were 300 mg TOBI (control), two 14 mg TIP capsules, four 14 mg TIP capsules, two 28 mg TIP capsules, three 28 mg TIP capsules, and four 28 mg TIP capsules. The goal of the study TPI-001 was to determine a dose of TIP that resulted in tobramycin exposures in serum and sputum that were comparable to 300 mg of TOBI. Thus, the four 28 mg capsules (112 mg) dose of TIP was selected for further development.

Additionally, three Phase 3 clinical studies were conducted in support of this NDA:

- Study C2301: Double blind study of TIP vs. placebo (for one cycle, followed by two cycles of open-label TIP treatment) in CF patients aged 6-21 years with no prior exposure to inhaled anti-pseudomonal antibiotics for at least 4 months
- Study C2302: Open-label study of TIP vs. TOBI across three cycles of TIP treatment in CF patients aged ≥ 6 years with no prior exposure to inhaled anti-pseudomonals for one month
- Study C2303: Double-blind study of TIP vs. placebo for one cycle in CF patients aged 6-21 years with no prior exposure to inhaled anti-pseudomonals for at least 4 months.

During late stage development, the Sponsor changed the manufacturing process (but not the formulation) for TIP between conduct of studies C2302 and C2303. Tobramycin serum concentrations between the two manufacturing processes were evaluated through a population pharmacokinetic modeling approach, using data and a model developed from studies TPI-001, C2301, and C2302 to predict observed serum tobramycin concentrations from C2303.

1.1. Recommendation

The Office of Clinical Pharmacology Division 4 has reviewed NDA 201-688 and has determined that it is acceptable from a Clinical Pharmacology perspective.

1.2. Phase IV Commitments

None.

1.3. Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

Tobramycin, the active ingredient in the TOBI Podhaler, has been in routine clinical use for several decades and its pharmacokinetics have been previously characterized. In support of the NDA, the sponsor submitted 4 clinical studies that were relevant for clinical pharmacology:

- Study TPI-001: Single-dose, dose-escalation trial comparing safety, pharmacokinetics, and delivery time of tobramycin powder for inhalation (TPI-Powder) compared to Tobramycin Solution for Inhalation (TOBI)
- Study C2301: Double blind study of TIP vs. placebo (for one cycle, followed by two cycles of open-label TIP treatment) in CF patients aged 6-21 years with no prior exposure to inhaled anti-pseudomonal antibiotics for at least 4 months
- Study C2302: Open-label study of TIP vs. TOBI across three cycles of TIP treatment in CF patients aged ≥ 6 years with no prior exposure to inhaled anti-pseudomonals for one month
- Study C2303: Double-blind study of TIP vs. placebo for one cycle in CF patients aged 6-21 years with no prior exposure to inhaled anti-pseudomonals for at least 4 months.

Initially, there were two key review questions associated with this NDA:

1. Was the chosen dose appropriate?
2. Did the change in manufacturing process result in altered tobramycin pharmacokinetics?

During the review process, additional questions arose from other disciplines. The Microbiology Reviewer (Dr. Peter Coderre) noted that there appeared to be more resistance emerging in the TIP arm compared to the TOBI arm in C2302. The Clinical Reviewer (Dr. Shrimant Mishra) noted that there was an imbalance in ototoxicity between TIP and TOBI. These observations led to the following additional review questions:

3. Was there sufficient pharmacokinetic information collected in the Phase 3 trials to evaluate whether patients who experienced a large increase in baseline MIC were receiving subtherapeutic exposures of TIP?
4. Was there sufficient pharmacokinetic information collected in the Phase 3 trials to evaluate whether patients who experienced ototoxicity had higher TIP exposures compared to patients without ototoxicity?

All four questions are answered in brief below.

Question #1: Was the chosen dose appropriate?

Study TPI-001 was a single dose, six-arm trial in CF patients. The trial arms evaluated in TPI-001 were 300 mg TOBI (control), two 14 mg TIP capsules, four 14 mg TIP capsules, two 28 mg TIP capsules, three 28 mg TIP capsules, and four 28 mg TIP capsules. Pharmacokinetic parameters were calculated in both serum (Table 1.3.1) and sputum (Table 1.3.2) for all trial arms.

Table 1.3.1: Selected Pharmacokinetic Parameters of Tobramycin in Serum after Administration of TOBI (300 mg) and TPI (28 mg, 56 mg, 84 mg, and 112 mg)

Parameter	TOBI 300 mg	TPI 2x14 mg	TPI 4x14 mg	TPI 2x28 mg	TPI 3x28 mg	TPI 4x28 mg
AUC(0,∞) (µg h/mL)	5.3 ± 2.6	1.7 ± 0.6	3.1 ± 0.8	2.9 ± 1.2	4.1 ± 1.5	5.1 ± 2.0
AUC(0,12) (µg h/mL)	4.8 ± 2.5	1.3 ± 0.6	2.8 ± 0.9	2.5 ± 1.2	3.5 ± 1.3	4.6 ± 2.0
C _{max} (µg/mL)	1.04 ± 0.58	0.33 ± 0.09	0.56 ± 0.23	0.50 ± 0.21	0.70 ± 0.33	1.02 ± 0.53
t _{max} ^a (h)	1 (0.5-2)	1 (0.5-2)	1 (0.5-1)	1 (0.5-2)	1 (1-2)	1 (0.5-2)
t _{1/2} (h)	3.0 ± 0.8	2.8 ± 1.1	3.5 ± 0.8	3.3 ± 0.8	3.4 ± 1.0	3.1 ± 0.4
n PK	20	11	13	13	15	12
n total	20	12	13	14	15	13

Source: Table 14.2.1.2.

^a median (range). Except for number of subjects in last 2 rows, other entries are mean ± standard deviation

Table 1.3.2: Selected Pharmacokinetic Parameters of Tobramycin in Sputum after Administration of TOBI (300 mg) and TPI (28 mg, 56 mg, 84 mg, and 112 mg)

Parameter	TOBI 300 mg	TPI 2x14 mg	TPI 4x14 mg	TPI 2x28 mg	TPI 3x28 mg	TPI 4x28 mg
AUC(0,∞) (µg h/g)	1302 ± 1127	390 ± 139	1714 ± 1173	855 ± 469	2044 ± 1334	1740 ± 809
AUC(0,12) (µg h/g)	974 ± 1143	261 ± 168	1195 ± 1224	652 ± 421	1340 ± 1320	1307 ± 978
C _{max} (µg/g)	737 ± 1028	258 ± 194	515 ± 421	574 ± 527	1092 ± 1052	1048 ± 1080
t _{max} ^a (h)	0.5 (0.5-2.0)	0.5 (0.5-0.5)	0.5 (0.5-1.0)	0.5 (0.5-4.0)	0.5 (0.5-2.0)	0.5 (0.5-1.0)
t _{1/2} (h)	1.7 ± 1.6	0.9 ± 0.8	1.8 ± 0.9	1.3 ± 1.5	0.8 ± 0.8	2.2 ± 1.7
n PK ^b	20	11	12	13	15	11
n total	20	12	13	14	15	13

Source: Table 14.2.1.4.

^a median (range). Except for number of subjects in last 2 rows, other entries are mean ± standard deviation

^b n may be different for different parameters. The maximum number of subjects used in any single analysis is listed.

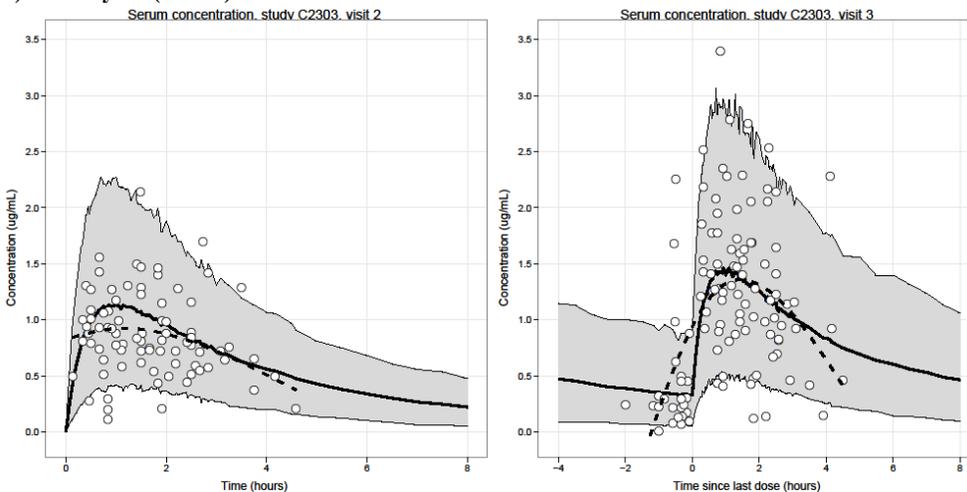
The chosen dose of 4x28 (112) mg TIP resulted in serum tobramycin pharmacokinetic parameters that were very similar to those following the administration of 300 mg of TOBI (mean C_{max} of 1.02 µg/mL vs. 1.04 µg/mL; mean AUC₀₋₁₂ of 4.6 µg*h/mL vs. 4.8 µg*h/mL; and mean AUC_{0-∞} of 5.1 µg*h/mL vs. 5.3 µg*h/mL). The sputum tobramycin pharmacokinetics were more variable, but the 112 mg dose of TIP resulted in mean values of C_{max}, AUC₀₋₁₂ and AUC_{0-∞} that were somewhat higher than those observed following the administration of 300 mg TOBI. Therefore, the Sponsor decided to proceed with the 112 mg dose of TIP. Based on the results of TPI-001, the selection of the 112 mg dose of TIP is appropriate.

Question #2: Did the new manufacturing process change tobramycin pharmacokinetics?

Tobramycin serum concentrations between the two manufacturing processes were evaluated through a population pharmacokinetic modeling approach, using data and a model developed from studies TPI-001, C2301, and C2302 to predict observed serum tobramycin concentrations from C2303.

Simulations using the population PK model of serum concentration profiles for the PK analysis population of C2303 are shown in 1.3.1. These results show that the model captures the central trend and variability of data. The proportion of data points outside of the 90% predictive interval is 13%, close to an expected 10%.

Figure 1.3.1: Comparison of simulated and observed serum concentration time profiles for the PK analysis population of Study C2303 on day 1 (visit 2) and day 28 (visit 3)



The Sponsor's evaluation of differences between the two manufacturing processes is acceptable. The Pharmacometrics Reviewer has evaluated the population pharmacokinetic model and obtained similar results for the visual predictive check as well as confirmed the statistical analyses performed as part of the normalized predictive distribution errors tests. These analyses, as well as the relatively similar tobramycin serum concentrations between C2303 and the earlier studies support the conclusion that the manufacturing process did not result in any significant differences in serum tobramycin concentrations.

Questions 3 and 4: Was sufficient PK information collected to assess imbalances in resistance and ototoxicity between the TIP and TOBI arms?

An imbalance in the number of ototoxicity events and resistance was observed in C2302 between the TOBI and TIP treatment arms (see Medical Officer and Microbiology Reviews by Dr. Mishra and Dr. Coderre). However, the PK data that was collected during C2302, after accounting for storage, was not sufficient to determine whether the imbalance in ototoxicity events observed in the TIP arm versus the TOBI arm were due to increased serum exposures of tobramycin following the use of TIP. Similarly, there was insufficient PK data to assess whether the increase in baseline MIC was due to subtherapeutic exposures of tobramycin (serum or sputum) in the TIP arm.

2. QUESTION BASED REVIEW

Since this application is for a locally delivered and acting drug product that has been previously approved (tobramycin), 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?*

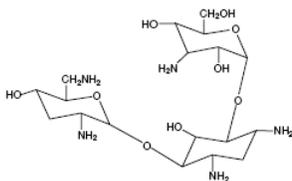
The active pharmaceutical ingredient is tobramycin, an aminoglycoside antibiotic.

Structural Formula: $C_{18}H_{37}N_5O_9$

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, TOBI Podhaler, consists of a dry powder formulation of tobramycin for oral inhalation. The inhalation powder is filled into clear, colorless hypromellose capsules. The Podhaler inhaler is a plastic device used to inhale the dry powder contained in the TOBI Podhaler capsule (the Nektar T-326 dry powder inhaler).

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.

TOBI Podhaler 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 of TOBI Podhaler for both adults and pediatric patients 6 years of age and older is the inhalation of four 28 mg TOBI Podhaler capsules twice-daily for 28 days using the Podhaler inhaler. No dose adjustments are recommended on the basis of weight, age, renal

function or concomitant medications. TOBI Podhaler is administered twice-daily in alternating periods of 28 days.

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 that were relevant for clinical pharmacology:

- Study TPI-001: Single-dose, dose-escalation trial comparing safety, pharmacokinetics, and delivery time of tobramycin powder for inhalation (TPI-Powder) compared to Tobramycin Solution for Inhalation (TOBI)
- Study C2301: Double blind study of TIP vs. placebo (for one cycle, followed by two cycles of open-label TIP treatment) in CF patients aged 6-21 years with no prior exposure to inhaled anti-pseudomonal antibiotics for at least 4 months
- Study C2302: Open-label study of TIP vs. TOBI across three cycles of TIP treatment in CF patients aged ≥ 6 years with no prior exposure to inhaled anti-pseudomonals for one month
- Study C2303: Double-blind study of TIP vs. placebo for one cycle in CF patients aged 6-21 years with no prior exposure to inhaled anti-pseudomonals for at least 4 months.

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?*

Primary Efficacy Endpoints for the Phase 3 studies were as follows:

- C2301: To demonstrate efficacy of a 28 day BID dosing regimen of TIP versus placebo as measured by the relative change in FEV₁ percent predicted from baseline (Week 1/Cycle 1, Day 1) to the end of cycle 1 dosing (Week 5/Cycle 1, Day 28)
- C2302: To evaluate the safety of twice daily dosing of TIP delivered with the T-326 inhaler, compared to TOBI delivered with the PARI LC PLUS Jet nebulizer and DeVilbiss PulmoAide compressor or suitable alternatives
- C2303: Evaluate the efficacy of tobramycin inhalation powder after modifications in the manufacturing process for the treatment of infections with *P. aeruginosa* in cystic fibrosis subjects, assessed by relative change from baseline of FEV₁ percent predicted by Day 29 compared to placebo.

Secondary endpoints of C2302 were to evaluate the efficacy of TIP compared to TOBI using a relative change in FEV₁ percent predicted at the end of Cycle 3 compared to baseline, and to assess subject-reported treatment satisfaction through the use of the Treatment Satisfaction Questionnaire for Medication.

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. 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/or sputum samples obtained in Studies TPI-001, C2301, C2302, and C2303 (*Refer to Section 2.6*).

2.2.4. *Exposure-response*

The characteristics of exposure-response relationships for inhaled tobramycin have been well-established for tobramycin solution for inhalation. The exposure-response assessment for the current application focused on the following two review questions:

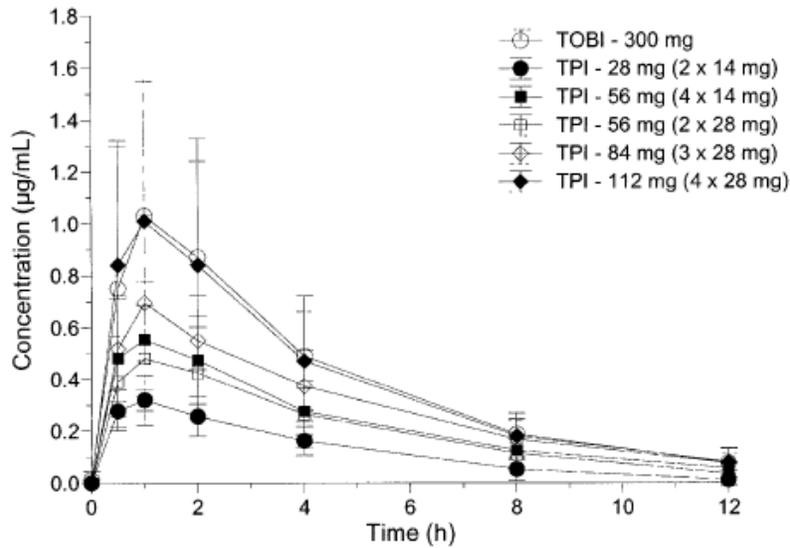
- Was there sufficient pharmacokinetic information collected in the Phase 3 trials to evaluate whether patients who experienced a large increase in baseline MIC were receiving subtherapeutic exposures of TIP?
- Was there sufficient pharmacokinetic information collected in the Phase 3 trials to evaluate whether patients who experienced ototoxicity had higher TIP exposures compared to patients without ototoxicity?

Sparse PK assessments were performed in both the TIP (n=30) and TOBI (n=14) arms in C2302. However, due to storage beyond the validated stability window only a subset of PK samples (TIP: n=13; TOBI: n=6) were acceptable for inclusion in exposure-response analyses. The PK data that was collected during C2302 was not sufficient to determine whether the imbalance in ototoxicity events observed in the TIP arm versus the TOBI arm were due to increased serum exposures of tobramycin following the use of TIP. Similarly, there was insufficient PK data to assess whether the increase in baseline MIC was due to subtherapeutic exposures of tobramycin (serum or sputum) in the TIP arm.

2.2.5. *What are the PK characteristics of the drug?*

Serum and sputum tobramycin pharmacokinetics were evaluated at several doses of TIP in Study TPI-001. Figure 2.2.5.1 shows the mean serum concentration-time profile of tobramycin following administration of different doses of TIP and 300 mg of TOBI.

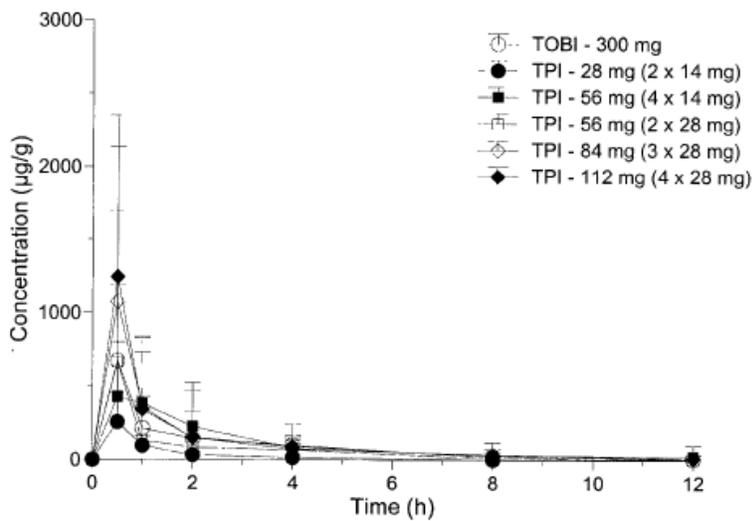
Figure 2.2.5.1: Mean Serum Concentration-Time Profiles of Tobramycin after Administration of TOBI (300 mg) and TPI (various doses).



The mean concentration-time profiles of tobramycin following the administration of 300 mg TOBI and 112 mg of TIP are nearly superimposable. The other doses of TIP clearly result in lower peak concentrations and reduced exposure compared to TOBI.

Figure 2.2.5.2 shows the mean sputum concentration-time profiles of tobramycin following the administration of different doses of TIP and 300 mg of TOBI.

Figure 2.2.5.2: Mean Sputum Concentration-Time Profiles of Tobramycin after Administration of TOBI (300 mg) and TPI (various doses)



The 112 and 84 mg doses of TIP both have higher C_{max} and AUC values than 300 mg TOBI, although the pharmacokinetics are highly variable. Pharmacokinetic parameters of tobramycin in serum and sputum are summarized in Tables 2.2.5.1 and 2.2.5.2, respectively.

Table 2.2.5.1: Selected Pharmacokinetic Parameters of Tobramycin in Serum after Administration of TOBI (300 mg) and TPI (28 mg, 56 mg, 84 mg, 112 mg)

Parameter	TOBI 300 mg	TPI 2x14 mg	TPI 4x14 mg	TPI 2x28 mg	TPI 3x28 mg	TPI 4x28 mg
AUC(0,∞) (µg h/mL)	5.3 ± 2.6	1.7 ± 0.6	3.1 ± 0.8	2.9 ± 1.2	4.1 ± 1.5	5.1 ± 2.0
AUC(0,12) (µg h/mL)	4.8 ± 2.5	1.3 ± 0.6	2.8 ± 0.9	2.5 ± 1.2	3.5 ± 1.3	4.6 ± 2.0
C_{max} (µg/mL)	1.04 ± 0.58	0.33 ± 0.09	0.56 ± 0.23	0.50 ± 0.21	0.70 ± 0.33	1.02 ± 0.53
t_{max}^a (h)	1 (0.5-2)	1 (0.5-2)	1 (0.5-1)	1 (0.5-2)	1 (1-2)	1 (0.5-2)
t1/2 (h)	3.0 ± 0.8	2.8 ± 1.1	3.5 ± 0.8	3.3 ± 0.8	3.4 ± 1.0	3.1 ± 0.4
n PK	20	11	13	13	15	12
n total	20	12	13	14	15	13

Source: Table 14.2.1.2.

^a median (range). Except for number of subjects in last 2 rows, other entries are mean ± standard deviation

Table 2.2.5.2: Selected Pharmacokinetic Parameters of Tobramycin in Sputum after Administration of TOBI (300 mg) and TPI (28 mg, 56 mg, 84 mg, 112 mg)

Parameter	TOBI 300 mg	TPI 2x14 mg	TPI 4x14 mg	TPI 2x28 mg	TPI 3x28 mg	TPI 4x28 mg
AUC(0,∞) (µg h/g)	1302 ± 1127	390 ± 139	1714 ± 1173	855 ± 469	2044 ± 1334	1740 ± 809
AUC(0,12) (µg h/g)	974 ± 1143	261 ± 168	1195 ± 1224	652 ± 421	1340 ± 1320	1307 ± 978
C_{max} (µg/g)	737 ± 1028	258 ± 194	515 ± 421	574 ± 527	1092 ± 1052	1048 ± 1080
t_{max}^a (h)	0.5 (0.5-2.0)	0.5 (0.5-0.5)	0.5 (0.5-1.0)	0.5 (0.5-4.0)	0.5 (0.5-2.0)	0.5 (0.5-1.0)
t1/2 (h)	1.7 ± 1.6	0.9 ± 0.8	1.8 ± 0.9	1.3 ± 1.5	0.8 ± 0.8	2.2 ± 1.7
n PK ^b	20	11	12	13	15	11
n total	20	12	13	14	15	13

Source: Table 14.2.1.4.

^a median (range). Except for number of subjects in last 2 rows, other entries are mean ± standard deviation

^b n may be different for different parameters. The maximum number of subjects used in any single analysis is listed.

Repeat dose administration of TIP was assessed only in the Phase III studies after multiple 112 mg BID administration in CF patients. There was only limited sampling in the Phase 3 trials, and the Sponsor did not make an effort to calculate an AUC for Phase 3 patients. However, approximate peak and trough serum concentrations were reported for C2301 and C2302 (a range is provided because both of those trials went for multiple cycles). Data from C2303 is not

included because the trial was for only one cycle, and the “trough” concentration was collected between 2 and 6 hours after administration so it cannot be directly compared with the others. A summary of tobramycin peak and trough concentration data from the Phase 3 program for TIP is as follows:

C2301

Peak concentration (defined as 60 min post dose): 1.02 – 1.99 µg/mL

Trough Concentration (defined as predose): 0.03 – 0.38 µg/mL

C2302

Peak concentration (defined as 0-2 hours post dose): 0.67 – 1.32 µg/mL

Trough concentration (defined as predose): 0.01 – 0.31 µg/mL

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

This NDA did not include any bioavailability/bioequivalence studies or food effect studies. There were no waiver requests submitted. The to-be-marketed formulation was used in the Phase 3 trials. However, the Sponsor changed the manufacturing process for TIP prior to the initiation of C2303.

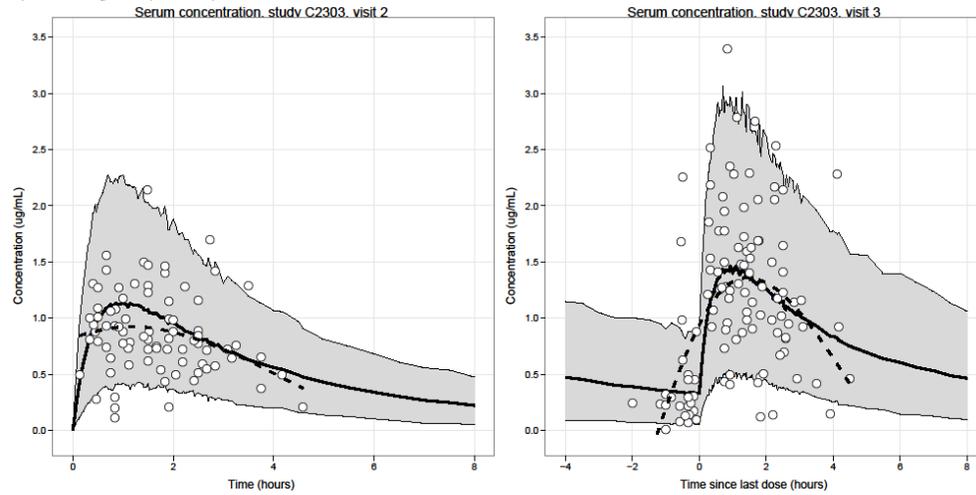
The change in the TIP manufacturing process did not result in statistically different tobramycin serum exposures. Due to sparse sampling within these studies as well as sampling within time windows, a direct comparison of tobramycin serum concentrations between the studies could not be performed. Instead, the Sponsor utilized a population pharmacokinetic modeling approach to evaluate observations between the different TIP manufacturing processes.

A population pharmacokinetic model was developed based on data from TPI001, C2301, and C2302. This model, as well as the patient characteristics from C2303, was then used to simulate the observed exposures in C2303. The Sponsor used two approaches to determine if the original tobramycin population pharmacokinetic model was capable of describing the tobramycin concentrations from C2303: i) a visual predictive check (see Figure 2.5.1 for Reviewer analysis); and ii) normalized prediction distribution errors (NPDE) tests (see Figure 2.5.2 for Reviewer analysis).

Visual Predictive Check

Simulations using the population PK model of serum concentration profiles for the PK analysis population of C2303 are shown in Figure 2.5.1. These results show that the model captures the central trend and variability of data. The proportion of data points outside of the 90% predictive interval is 13%, close to an expected 10%.

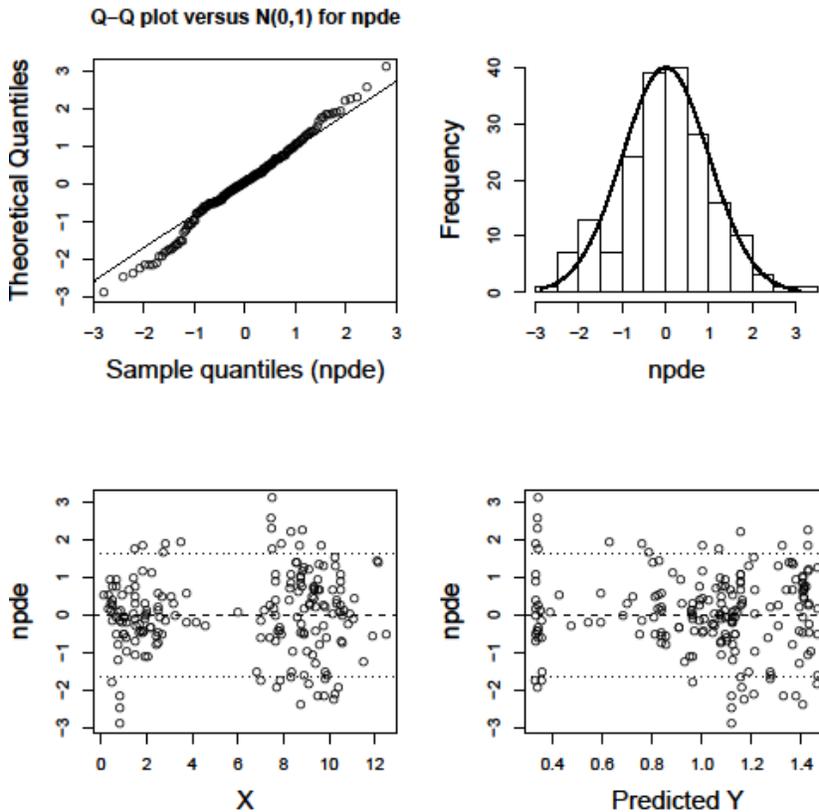
Figure 2.5.1: Comparison of simulated and observed serum concentration time profiles for the PK analysis population of Study C2303 on day 1 (visit 2) and day 28 (visit 3)



Normalized Predictive Distribution Errors Test

P-values of Wilcoxon signed rank test, Fisher variance test and Shapiro-Wilks test for normality are 0.53, 0.27 and 0.27, respectively, signifying that the null hypothesis that the distribution of normalized predictive errors is normal (i.e., the population pharmacokinetic model is capable of describing the data in C2303 and that the TIP manufacturing changes did not significantly change tobramycin systemic exposures). This means that specific tobramycin serum concentrations after inhalation of TIP_{new} are just as likely to be observed as after inhalation of TIP_{old}.

Figure 2.5.2: Diagnostic plots of the NPDE test on data from the PK analysis population of Study C2303



The Sponsor's evaluation of differences between the two manufacturing processes is acceptable. The Reviewer has evaluated the population pharmacokinetic model and obtained similar results for the visual predictive check as well as confirmed the statistical analyses performed as part of the normalized predictive distribution errors tests. These analyses, as well as the relatively similar tobramycin serum concentrations between C2303 and the earlier studies support the conclusion that the manufacturing process did not result in any significant differences in serum tobramycin concentrations.

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 TPI-001, concentrations of tobramycin in serum were analyzed with a modified fluorescence polarization immunoassay (FPIA) method using the Abbot TDx/TDxFLx System. This method was also used for concentrations of tobramycin in C2301 and C2302, but the system

was discontinued prior to the conduct of C2303. An LC-MS/MS method was developed and cross-validated with the FPIA method for C2303.

The concentrations of tobramycin in sputum were analyzed using a validated, reverse-phase, high-performance liquid chromatography (HPLC) method with ultraviolet detection for TPI-001 and C2302. A HPLC method with tandem mass spectrometry (LC-MS/MS) was used for C2303. Sputum concentrations of tobramycin were not assessed in C2301.

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.

2.6.4. What bioanalytical methods are used to assess concentrations?

See Table 2.6.4.1 for the methods used for bioanalysis of tobramycin in serum and Table 2.6.4.2 for the methods used for bioanalysis of tobramycin in sputum.

Table 2.6.4.1: Methods used for bioanalysis of tobramycin in serum

Method ID (assay type)	Study	Site of Bioanalysis	Method validation reports	LLOQ
SE1 (FPIA)	INH-007			(b) (4) 0.05 µg/mL
SE2 (FPIA)	TPI001			0.05 µg/mL
SE3 (FPIA)	C2301			0.05 µg/mL
SE3 (FPIA)	C2302			0.05 µg/mL
SE3 (FPIA)	C2303			0.05 µg/mL
SE4 (LC-MS/MS)	C2303			0.005 µg/mL

* Method development and validation were described in separate reports

Table 2.6.4.2: Methods used for bioanalysis of tobramycin in sputum

Method ID (assay type)	Study	Site of Bioanalysis	Method Validation report	LLOQ
SP1 (HPLC)	TPI001			(b) (4) 20 µg/g
SP2 (HPLC)	C2302			1 µg/g
SP3 (LC-MS/MS)	C2303			0.5 µg/g

* Method development and validation were described in separate reports

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?

The FPIA method assay range is 0.5 to 10 µg/mL and the assay sensitivity is increased ten-fold into the range of 0.05 to 1.0 µg/mL by increasing the volume of sample delivered to the assay cuvette and using a lower range of concentrations. The assay range of the LC-MS/MS method for tobramycin in serum was 0.005 to 2.47 µg/mL. The FPIA method calculates a best-fit curve equation that is used to generate a calibration curve.

For the method used in Study TPI-001, the standard curve ranged from 20 µg/g to 1000 µg/g for sputum samples. The regression curve for sputum tobramycin was weighted 1/x.

The assay ranges for the determination of tobramycin concentrations in both plasma and sputum are adequate.

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

The lower and upper limits of quantitation were 50 ng/mL and 10,000 ng/mL for tobramycin serum samples in TPI-001. For sputum samples, the lower and upper limits of quantitation were 20 µg/g and 1000 µg/g for Study TPI-001.

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

The bioanalytical reports do not provide detailed information about selectivity.

The accuracy of serum tobramycin concentrations ranged from 92% to 106%. The precision of serum tobramycin concentrations ranged from 0 – 10.1 % (%CV).

The accuracy of sputum tobramycin concentrations ranged from 97 to 107%. The precision of sputum tobramycin concentrations ranged from 1.1 – 5.2% (% CV).

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)?

Tobramycin is stable in serum when stored between -20 and -30 degrees Celsius for up to 91.4 weeks (640 days). QC samples ranging between 0.20 µg/mL to 8.00 µg/mL were used in the

long-term stability testing and the mean analytical recovery for these QC samples ranged between 91% and 98% of their nominal concentrations.

Tobramycin is stable in sputum when stored at -20 degrees Celsius for up to 717 days. The % change in low (3.0 µg/g) and high (35.05 µg/g) QC samples assessed during this storage period was 7.35% and 7.64%, respectively.

The freeze/thaw stability was not discussed in the bioanalytical reports. However, the samples did not appear to undergo multiple freeze/thaw cycles, so this omission is not of particular concern.

2.6.4.5. What is the QC sample plan?

Serum

High concentration quality control samples were prepared at equivalent serum concentrations of 0.5, 1, 4, 8, and 9 µg/mL. Low concentration quality control samples were prepared at equivalent serum concentrations of 0.05, 0.10, 0.40, 0.80, and 0.90 µg/mL.

Sputum

Quality controls were prepared at the nominal concentrations of 40.0, 300.0, and 800.0 µg/g.

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Appendix 4.1

Study Title: “A Phase 1, Single-dose, Dose-escalation Trial Comparing Safety, Pharmacokinetics, and Delivery Time of Tobramycin Powder for Inhalation (TPI Powder) Administered by the Nektar T-326 Dry Powder Inhaler Device (T-326 Inhaler) to Tobramycin Solution for Inhalation (TOBI 300 mg/5 mL) Administered by a PARI LC PLUS Jet Nebulizer/De Vilbiss PulmoAide Compressor in Cystic Fibrosis (CF) Patients

Dates: 7/9/03 – 2/23/04

Investigator: Steve Shrewsbury, MD, Chiron Clinical Development, Emeryville, CA

Analysis: (b) (4)

OBJECTIVES:

Primary: To assess the general safety of TPI including the rate of adverse events and the incidence of bronchospasm associated with each dose of TPI and TOBI

Secondary:

- Estimate a comparable dose of TPI to TOBI based on the pharmacokinetics (PK) of tobramycin after single-dose administration
- Assess and compare other safety measures for each treatment regimen
- Assess the administration time for each treatment

BACKGROUND:

TOBI (tobramycin solution for inhalation) is the current standard of care for CF patients; however, compliance with TOBI is an issue for CF patients due to the long administration time required. Dry powder inhalers (DPIs) have become a popular and well-established delivery system for airway diseases in both adults and children as young as four years of age. DPIs require the patient to inspire against the internal resistance of the inhaler, and this in part has accounted for the development and testing of numerous different DPIs in various patient populations.

It has been shown that CF patients with severe lung obstruction (FEV₁ between 32% and 40% of predicted) can generate the necessary inspiratory flow to operate currently available DPIs. Tobramycin inhalation powder (TPI) is a DPI that requires a shorter administration time that is being developed for use in CF patients.

STUDY DESIGN:

This study was a randomized, open-label, sequential-cohort, active-controlled, single-dose, dose-escalation study. Up to 80 subjects were planned to be randomized and treated in a 3:1 ratio, 12 subjects to TPI and 4 subjects to TOBI for a total of 16 subjects per cohort. The five cohorts were as follows:

- Cohort 1: Two capsules of TPI (14 mg dosage strength)
- Cohort 2: Four capsules of TPI (14 mg dosage strength)
- Cohort 3: Two capsules of TPI (28 mg dosage strength)
- Cohort 4: Four capsules of TPI (28 mg dosage strength)
- Cohort 5: Three capsules of TPI (28 mg dosage strength) – dosage regimen was reduced from six capsules as a result of DMC review of cohort 4 data and protocol amendment 2

The control treatment was a single dose of TOBI at 300 mg/5 mL.

Escalation to the next TPI treatment cohort was permitted after review by a Data Monitoring Committee (DMC) of all treatment-emergent adverse events (AEs) experienced by subjects in the completed cohort, and if neither of the following criteria were met:

- Three or more subjects within a cohort treated with TPI experienced a $\geq 20\%$ relative decline in FEV₁ from baseline to 30 minutes after the end of dosing
- Any TPI-dosed subject experienced a study drug-related serious adverse event (SAE)

ASSAY METHODOLOGY:

Concentrations of tobramycin in serum were analyzed with a modified fluorescence polarization immunoassay (FPIA) method using the Abbot TDx/TDxFLx System. Samples were added directly to the dilution well of the sample cartridge. The net polarization was acquired by the TDx/TDxFLx apparatus. A weighted four-parameter logistic equation was used to calculate the concentrations of tobramycin. The concentrations of tobramycin were reported in terms of free base equivalents. Concentrations of tobramycin in sputum were analyzed using a validated, reverse-phase, high-performance liquid chromatography (HPLC) method with ultraviolet detection. See below for validation tables for the respective assays.

Serum:

Criterion	Tobramycin	Comments
Concentration Range	0.05 – 10 µg/mL	Satisfactory
LLOQ	0.05 µg/mL	Satisfactory
Linearity	0.994 – 0.998 (from package insert for assay)	Satisfactory
Accuracy	92 – 106%	Satisfactory
Precision	0– 10.1% (%CV)	Satisfactory

Sputum:

Criterion	Tobramycin	Comments
Concentration Range	20 – 1000 µg/g	Satisfactory
LLOQ	20 µg/g	Satisfactory
Linearity	0.990	Satisfactory
Accuracy	97 – 107%	Satisfactory
Precision	1.1 – 5.2% (%CV)	Satisfactory

PHARMACOKINETIC/PHARMACODYNAMIC ASSESSMENTS AND ANALYSES:

Blood samples were collected at predose and at 0.5, 1, 2, 4, 8, and 12 hours after the start of the first tidal breath during inhalation of study treatment. Sputum samples were expectorated by subjects from a deep cough and collected before day 1 dosing (predose) and at 0.5, 1, 2, 4, 8, and 12 hours after the start of the first tidal breath during inhalation of study treatment.

The concentration versus time data from sputum and serum tobramycin assays were analyzed by model-independent methods to obtain the pharmacokinetic parameters. The maximum concentration (C_{max}) and the time to maximum concentration (t_{max}) were obtained by inspection. The terminal rate constants (λ_z) were determined by log-linear regression of the terminal phase. The half-life was calculated as $t_{1/2} = \ln(2)/\lambda_z$. Concentrations below the lower limit of quantitation were treated as zero for all calculations. The area under the sputum and serum concentration-time curves from time zero (predose) to 12 hours, AUC_{0-12} , was calculated by the trapezoidal rule. The $AUC_{0-\infty}$ was calculated as $AUC_{0-12} + C(12)/\lambda_z$ where $C(12)$ is the concentration 12 h after the start of dosing.

RESULTS:Demographics

Forty-three male and 47 female subjects, 7 to 50 years of age, diagnosed with cystic fibrosis, were enrolled in the study. Mean ages were similar among the treatment groups, ranging from 19.5 years in the TOBI group to 24.1 years in the TPI 2x14 mg group. Fifteen subjects were 7 to 12 years of age, 22 subjects were 13 to 17 years, and 53 subjects were 18 to 50 years of age.

Seventy-nine subjects were Caucasian, five subjects were Hispanic, three subjects were Black, and three subjects were of other origins. Gender and race distributions were similar between TPI and TOBI treatment groups, although a small gender disparity was noted between TPI 4x14 mg and TOBI groups (TPI: 11 female, 3 male subjects; TOBI 8 female, 12 male subjects). The effect of this imbalance on study

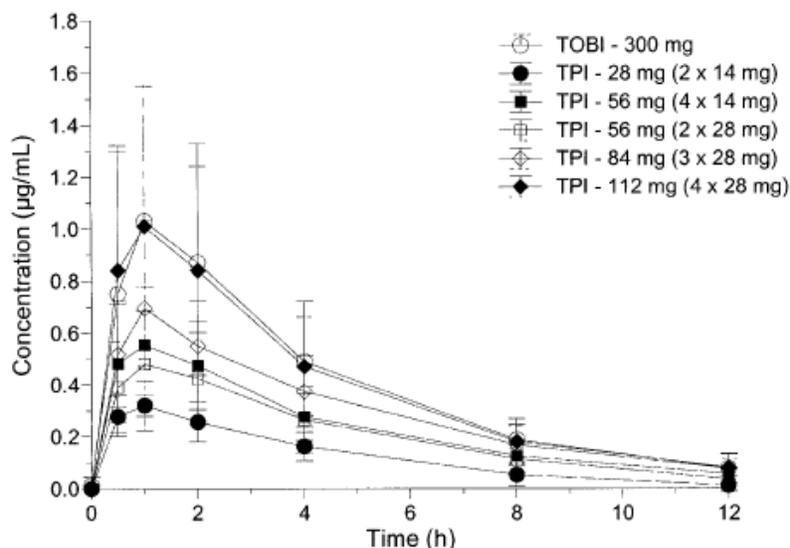
results is uncertain. On average, TPI and TOBI subjects were comparable in height and weight at screening.

Of the ninety subjects enrolled and randomized to one of the cohorts, eighty-six subjects received at least a partial dose of study treatments and were evaluated for safety and administration time objectives; 84 subjects were evaluated for pharmacokinetic and dose comparability objectives.

Plasma Pharmacokinetics

Mean serum concentration-time profiles of tobramycin after administration of TPI and TOBI indicate that the drug is rapidly absorbed (see Figure 1): median t_{max} was 1 h in all treatments. The distribution of the drug appears to be very fast, and the levels declined in a monoexponential fashion, with average terminal half-lives ranging between 2.8 and 3.5 hours. The values of the pharmacokinetic parameters of tobramycin after TOBI administration are consistent with previous studies.

Figure 1: Mean Serum Concentration-Time Profiles of Tobramycin after Administration of TOBI (300 mg) and TPI (28 mg, 56 mg, 84 mg, and 112 mg)



Increases in the dose of TPI led to increases in the exposure to tobramycin, as evidenced by the increasing values of $AUC_{0-\infty}$, AUC_{0-12} , and C_{max} (see Table 1). These increases were slightly less than dose-proportional. Four subjects experienced cough, which caused an interruption in dosing (subjects 06/215, 16/412, 01/518, and 02/507). The interruptions were seen at TPI doses 4x14mg, 3x28 mg, and 4x28 mg. In all evaluated subjects with cough, the values of $AUC_{0-\infty}$, AUC_{0-12} , and C_{max} were within the range of other subjects in their dosing group who completed dosing without interruption. No differences in exposure to tobramycin, as measured by AUC and C_{max} , were detected between subjects receiving 4x14 mg manual-fill capsules vs. 2x28 mg automatic-fill capsules. Therefore, the bioavailability of the hand- and automatic-fill capsules was deemed comparable, and these two groups were consolidated.

In general, there was a weak negative correlation between the percentage of powder left in the device and $AUC_{0-\infty}$ ($r=-0.22$, $P=0.071$), AUC_{0-12} ($r=-0.23$, $P=.0707$), and C_{max} ($r=-0.22$, $P=0.0838$). Lower exposures were associated with higher residual amounts of TPI in the device. One of the subjects in the 4x28 mg TPI dosing group (subject 04/409) had more than 45% residual powder in the device and had exposures of tobramycin that were among the lowest in his treatment group.

Although the study was not powered to assess efficacy, there were no significant correlations between change from baseline in FEV₁ and serum AUC and C_{max} for TPI subjects or for TOBI subjects.

Table 1: Selected Pharmacokinetic Parameters of Tobramycin in Serum after Administration of TOBI (300 mg) and TPI (28 mg, 56 mg, 84 mg, and 112 mg)

Parameter	TOBI 300 mg	TPI 2x14 mg	TPI 4x14 mg	TPI 2x28 mg	TPI 3x28 mg	TPI 4x28 mg
AUC(0,∞) (µg h/mL)	5.3 ± 2.6	1.7 ± 0.6	3.1 ± 0.8	2.9 ± 1.2	4.1 ± 1.5	5.1 ± 2.0
AUC(0,12) (µg h/mL)	4.8 ± 2.5	1.3 ± 0.6	2.8 ± 0.9	2.5 ± 1.2	3.5 ± 1.3	4.6 ± 2.0
C _{max} (µg/mL)	1.04 ± 0.58	0.33 ± 0.09	0.56 ± 0.23	0.50 ± 0.21	0.70 ± 0.33	1.02 ± 0.53
t _{max} ^a (h)	1 (0.5-2)	1 (0.5-2)	1 (0.5-1)	1 (0.5-2)	1 (1-2)	1 (0.5-2)
t _{1/2} (h)	3.0 ± 0.8	2.8 ± 1.1	3.5 ± 0.8	3.3 ± 0.8	3.4 ± 1.0	3.1 ± 0.4
n PK	20	11	13	13	15	12
n total	20	12	13	14	15	13

Source: Table 14.2.1.2.

^a median (range). Except for number of subjects in last 2 rows, other entries are mean ± standard deviation

Comparable Dose Analysis of TPI and TOBI

The exposures achieved after administration of TOBI 300 mg were similar to that seen after administration of 4x28 mg capsules of TPI (see Figures 2 and 3).

Figure 2: Comparable Dose Analysis Based Upon AUC₀₋₁₂

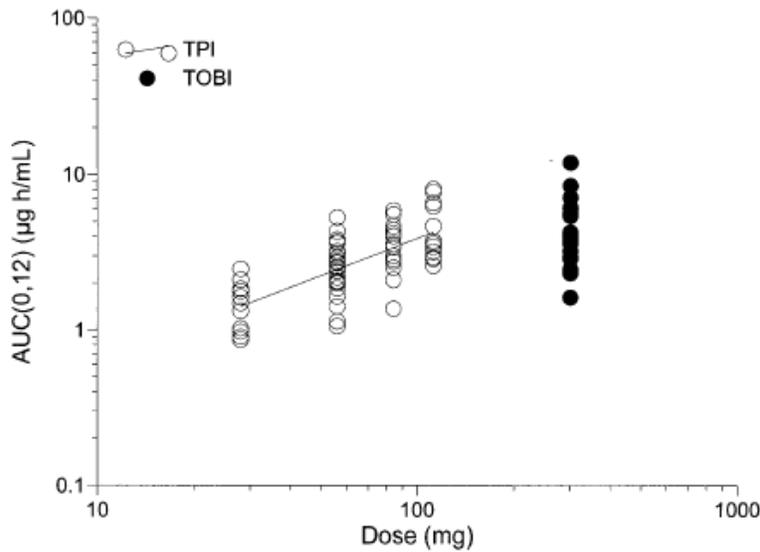
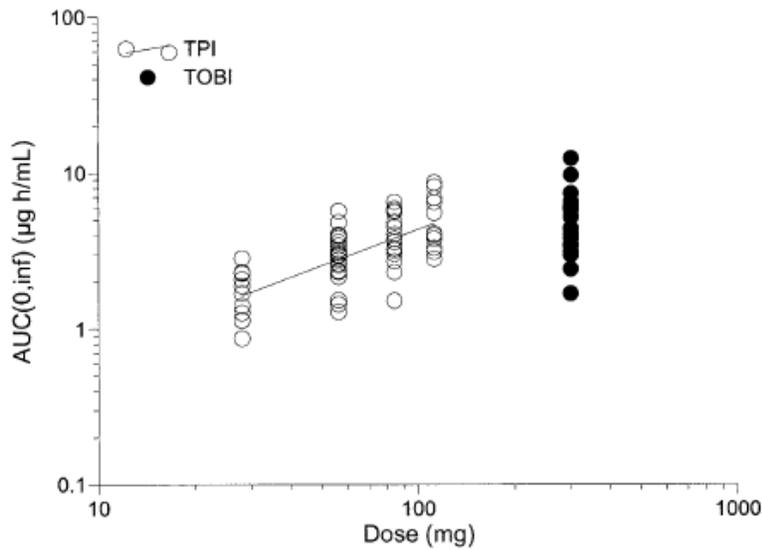


Figure 3: Comparable Dose Analyses Based Upon AUC_{0-∞}



Sputum Pharmacokinetics

After administration of TPI and TOBI, maximum concentrations in sputum were achieved on average at 30 minutes, declining thereafter with an average half-life of 0.8 to 2.2 hours (see Figure 4). In general, these estimates of half-life and t_{max} for TOBI are consistent with previous studies. The variability in pharmacokinetic parameters was higher in sputum as compared to serum. In addition to the inherent variability in sputum-derived pharmacokinetic parameters, some subjects were unable to produce sputum on demand; there were no more than three subjects per group with a missing sputum sample at any one time (see Table 2). As a consequence, while there is a trend of increasing exposure in sputum with increases in dose, dose proportionality based on sputum levels could not be confirmed.

Figure 4: Mean Sputum Concentration-Time Profiles of Tobramycin after Administration of TOBI (300 mg) and TPI (28 mg, 56 mg, 84 mg, and 112 mg)

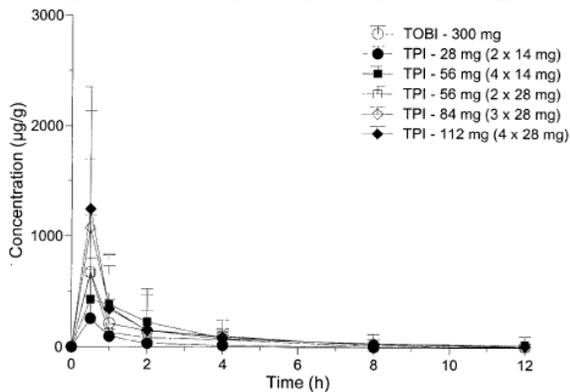


Table 2: Selected Pharmacokinetic Parameters of Tobramycin in Sputum after Administration of TOBI (300 mg) and TPI (28 mg, 56 mg, and 112 mg)

Parameter	TOBI 300 mg	TPI 2x14 mg	TPI 4x14 mg	TPI 2x28 mg	TPI 3x28 mg	TPI 4x28 mg
AUC(0,∞) (µg h/g)	1302 ± 1127	390 ± 139	1714 ± 1173	855 ± 469	2044 ± 1334	1740 ± 809
AUC(0,12) (µg h/g)	974 ± 1143	261 ± 168	1195 ± 1224	652 ± 421	1340 ± 1320	1307 ± 978
C _{max} (µg/g)	737 ± 1028	258 ± 194	515 ± 421	574 ± 527	1092 ± 1052	1048 ± 1080
t _{max} ^a (h)	0.5 (0.5-2.0)	0.5 (0.5-0.5)	0.5 (0.5-1.0)	0.5 (0.5-4.0)	0.5 (0.5-2.0)	0.5 (0.5-1.0)
t _{1/2} (h)	1.7 ± 1.6	0.9 ± 0.8	1.8 ± 0.9	1.3 ± 1.5	0.8 ± 0.8	2.2 ± 1.7
n PK ^b	20	11	12	13	15	11
n total	20	12	13	14	15	13

Source: Table 14.2.1.4.

^a median (range). Except for number of subjects in last 2 rows, other entries are mean ± standard deviation

^b n may be different for different parameters. The maximum number of subjects used in any single analysis is listed.

Drug Administration

Drug administration time averaged nearly 16 minutes in TOBI subjects (see Table 3). By comparison, administration time for two capsules of TPI averaged 1.7 and 2.5 minutes for the 2x14 mg and 2x28 mg doses, respectively. Administration times averaged 4.2, 4.5, and 4.9 minutes for TPI 4x14 mg, 3x28 mg, and 4x28 mg doses, but in these cohorts a second device was unpacked and utilized for dosing of the third and fourth capsules, respectively. Thus, TPI administration time increased primarily as the number of capsules increased and, secondarily, as the dosage strength increased.

Table 3: Study Drug Administration Time

Parameter	TOBI 300 mg (N = 20)	TPI 2x14 mg (N = 11)	TPI 4x14 mg (N = 13)	TPI 2x28 mg (N = 14)	TPI 3x28 mg (N = 15)	TPI 4x28 mg (N = 13)
Inhalation Time (min): Mean ± SD	15.8 ± 4.0	1.7 ± 0.6	4.2 ± 1.4	2.5 ± 1.1	4.5 ± 1.1	4.9 ± 1.8

All but two TPI capsules were administered as required (exception: 3rd and 4th capsules for one subject in the TPI 4x28 mg group). Rattling was heard on the second breath in 85% or more of the capsules.

There were no device failures reported by the sites or upon inspection by the Nektar analysts. The sum of the residual tobramycin in the subjects' inhaler(s) and capsules averaged 10.5% of the nominal dose. This analysis includes subject 04/409, who had more than 45% residual powder in the device due to improper dosing, so more than likely, the actual amount of residual powder in the device is less.

Safety

More TPI subjects (60.6%) than TOBI subjects (30.0%) experienced treatment-emergent AEs during or after treatment. The percent of subjects with any AE was similar among the TPI dose levels (45% to 69%); sample sizes were too small to determine whether a trend was present for increasing any AE incidence with increasing TPI dose. All treatment-emergent AEs were mild or moderate in intensity.

One TPI 4x28 mg subject experienced two SAEs (moderate cough and sputum increased indicative of an exacerbation of CF lung disease) that led to hospitalization on the eighth day after the single-dose study

treatment was administered; neither of these SAEs was considered related to TPI treatment. Another TPI 4x28 mg subjects experienced moderate, probably-related cough aggravated, dysgeusia, and lacrimation increased that caused study drug administration to be interrupted and then stopped; the subject then withdrew consent and was withdrawn from the study. Four subjects experienced coughing during inhalation of TPI that led to a modification, interruption, or delay in dosing (one subject each at TPI 4x14 mg and 4x28 mg and two subjects at 3x28 mg); each AE was considered to be probably related to TPI treatment by the investigator. However, in all four cases, dosing was only interrupted briefly, and the subjects resumed and completed dosing without mishap. All subjects in this study reported respiratory baseline symptoms, with ~90% in each cohort reporting cough. Furthermore, the reporting of mild cough is not unexpected from the first administration of a dry powder inhaler, especially when airway irritability is already present.

AEs experienced by the largest number of TPI subjects were cough or cough aggravated (13 of 66 subjects or 19.7%); dysgeusia (11 subjects or 16.7%); pharyngitis, haemoptysis, and rhinorrhea (4 subjects each or 6.1%); sputum increased, crackles lung, lacrimation increased, abdominal pain upper, dizziness, headache NOS, and throat irritation (3 subjects, 4.5% each). The incidence of cough, cough aggravated, and dysgeusia increased slightly with increasing TPI dose. No more than one TOBI subject experienced any AE. TOBI subjects experienced no cough, cough aggravated, or dysgeusia, but 85% of the TOBI recipients were chronic TOBI users.

The investigators considered most instances of cough and cough aggravated, all instances of dysgeusia, and most instances of haemoptysis and throat irritation to be possibly or probably related to TPI treatment. By comparison, single instances of chest tightness, herpes simplex, eosinophil count increased, dry throat, pharyngitis, sputum increased, and sputum viscosity increased were considered related to TOBI treatment.

A single instance of asymptomatic bronchospasm (20.9% reduction in FEV₁) was recorded, similar to an asymptomatic 19.1% reduction in a TOBI subject.

There were no notable changes from baseline in clinical laboratory results, no patterns of increasing change with increasing dose of TPI, no increases in the frequency of above-normal or below-normal results, and no apparent TPI vs. TOBI differences. In a single TOBI subject, an elevated eosinophil count was recorded as an AE.

APPLICANT'S CONCLUSIONS:

Single dose administration of TPI results in a more efficient delivery of tobramycin than TOBI, while maintaining similar tobramycin pharmacokinetics. Systemic exposures achieved after administration of TOBI were very similar to that seen after administration of 4x28 mg capsules of TPI, with an equivalent dose calculation of 115 mg TPI. Hence, four capsules of 28 mg TPI (112 mg total) should produce systemic exposures that are comparable to 300 mg of TOBI.

Minimal dosing interruptions (temporary in all but one case) due to cough were observed and did not appear to alter the single dose pharmacokinetics of tobramycin in serum after administration of TPI.

Approximately 20% of subjects reported cough with TPI, in most cases mild, occasionally causing brief dose interruption, and generally settling quickly. Cough is an expected AE with all inhaled dry powder therapy and was present in the majority of subjects at baseline. While the incidence of AEs was higher in TPI-treated than TOBI-treated subjects, the majority of subjects in most cohorts received chronic cycling TOBI.

In one case, a young subject forgot to take his usual medication (consisting of a long-acting bronchodilator) and experienced moderate cough after dosing, which led to his withdrawal. The loss of usual bronchoprotection is likely the cause of this reaction.

Administration of single doses of TPI in total doses of 28 mg to 112 mg was well-tolerated by CF subjects during the study. One hundred twelve milligrams of TPI powder gives a close systemic exposure to tobramycin to that from TOBI and was taken forward into further clinical studies.

REVIEWER ASSESSMENT:

The Sponsor's conclusions regarding pharmacokinetics are appropriate. The administration of 4x28 mg TPI (112 mg) resulted tobramycin pharmacokinetics (C_{max} , AUC_{0-12} , and $AUC_{0-\infty}$) that were similar to what was observed when 300 mg of TOBI (the reference product) were used. The mean sputum concentrations and exposures resulting from the use of the 4x28 mg TPI regimen were generally higher than what was observed following the administration of 300 mg TOBI. As expected, the sputum pharmacokinetics were more variable than the serum pharmacokinetics.

Even though ~10% of the nominal dose was remaining in the inhaler after administration, this amount should not be clinically relevant. The administration of 4x28 mg TPI resulted in serum and sputum exposures that were either equivalent to or larger than exposures following the administration of 300 mg TOBI despite the loss of the residual dry powder.

There was a significant imbalance in patients who experienced cough with approximately 20% of TPI patients having an AE of cough and no TOBI subjects experiencing cough. The Sponsor states that cough is an expected AE with a dry powder inhaler, and states that most cases of cough were mild.

OFFICE OF CLINICAL PHARMACOLOGY: PHARMACOMETRIC REVIEW

1 SUMMARY OF FINDINGS

1.1 Key Review Questions

The purpose of this review is to address the following key questions.

1.1.1 Does the selected tobramycin inhaled powder (TIP) dose achieve similar serum and sputum concentrations to the approved tobramycin inhalation solution (TOBI) dose?

The Sponsor conducted a single-ascending dose study TPI001 to determine a dose of TIP that would achieve similar tobramycin serum and sputum concentrations to that observed following TOBI 300 mg. The serum (Table 1) and sputum (Table 2) pharmacokinetics of the approved dose of TOBI (300 mg) versus several doses of TIP (or TPI as it is referred to in the table) are shown below. Based on the results of TPI001, the Sponsor selected TIP 4x28 mg (TIP 112 mg) as a dose for further evaluation based on the comparable serum exposure to TOBI and slightly higher though variable sputum exposures.

Table 1: Selected PK Parameters of Tobramycin in Serum After Administration of TOBI (300 mg) and TPI (28 mg, 56 mg, 84 mg, and 112 mg)

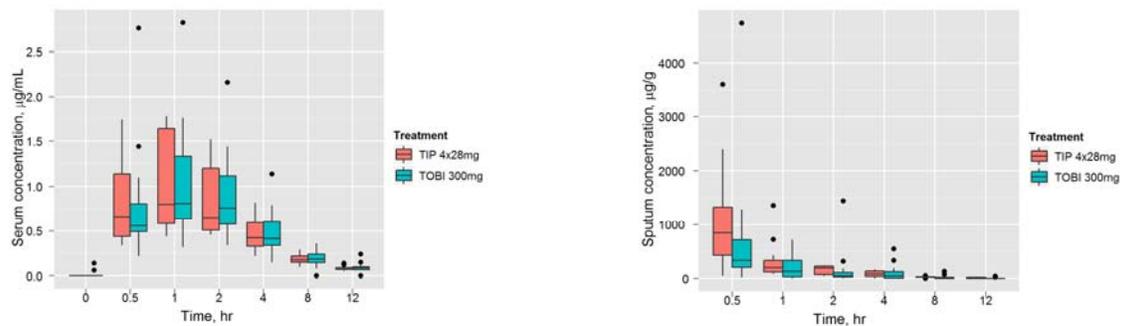
Parameter	TOBI 300 mg	TPI 2x14 mg	TPI 4x14 mg	TPI 2x28 mg	TPI 3x28 mg	TPI 4x28 mg
AUC(0,∞) (µg h/mL)	5.3 ± 2.6	1.7 ± 0.6	3.1 ± 0.8	2.9 ± 1.2	4.1 ± 1.5	5.1 ± 2.0
AUC(0,12) (µg h/mL)	4.8 ± 2.5	1.3 ± 0.6	2.8 ± 0.9	2.5 ± 1.2	3.5 ± 1.3	4.6 ± 2.0
C _{max} (µg/mL)	1.04 ± 0.58	0.33 ± 0.09	0.56 ± 0.23	0.50 ± 0.21	0.70 ± 0.33	1.02 ± 0.53
t _{max} ^a (h)	1 (0.5-2)	1 (0.5-2)	1 (0.5-1)	1 (0.5-2)	1 (1-2)	1 (0.5-2)
t _{1/2} (h)	3.0 ± 0.8	2.8 ± 1.1	3.5 ± 0.8	3.3 ± 0.8	3.4 ± 1.0	3.1 ± 0.4
n PK	20	11	13	13	15	12
n total	20	12	13	14	15	13

Table 2: Selected Pharmacokinetic Parameters in Sputum after Administration of TOBI (300 mg) and TPI (28 mg, 56 mg, 84 mg, and 112 mg)

Parameter	TOBI 300 mg	TPI 2x14 mg	TPI 4x14 mg	TPI 2x28 mg	TPI 3x28 mg	TPI 4x28 mg
AUC(0,∞) (µg h/g)	1302 ± 1127	390 ± 139	1714 ± 1173	855 ± 469	2044 ± 1334	1740 ± 809
AUC(0,12) (µg h/g)	974 ± 1143	261 ± 168	1195 ± 1224	652 ± 421	1340 ± 1320	1307 ± 978
C _{max} (µg/g)	737 ± 1028	258 ± 194	515 ± 421	574 ± 527	1092 ± 1052	1048 ± 1080
t _{max} ^a (h)	0.5 (0.5-2.0)	0.5 (0.5-0.5)	0.5 (0.5-1.0)	0.5 (0.5-4.0)	0.5 (0.5-2.0)	0.5 (0.5-1.0)
t _{1/2} (h)	1.7 ± 1.6	0.9 ± 0.8	1.8 ± 0.9	1.3 ± 1.5	0.8 ± 0.8	2.2 ± 1.7
n PK ^b	20	11	12	13	15	11
n total	20	12	13	14	15	13

In addition to the assessment presented by the sponsor, the reviewer evaluated the time course of tobramycin serum and sputum concentrations (Figure 1) for TOBI 300 mg and the selected TIP regimen (4 x 28 mg; 112 mg). There were no significant differences between exposures from the two regimens at any time point, providing additional supportive evidence for the selected TIP 112 mg dose. There was a numeric trend of higher sputum concentrations for the TIP 112 mg as well as a greater proportion of sputum samples with detectable tobramycin at 2 hrs or more. However, this observation should be interpreted with caution given the high variability in sputum concentrations (CV%: 75–140%).

Figure 1: Time Course Serum (left) and Sputum (right) Tobramycin Concentrations for TOBI 300 mg and TIP 112 mg



1.1.2 Does the change in TIP manufacturing between studies TPI001, C2301, and C2302 and study C2303 result in different tobramycin serum pharmacokinetics?

The change in the TIP manufacturing process did not result in statistically different tobramycin serum exposures. The sponsor altered the TIP manufacturing process prior to study C2303. Due to sparse sampling within these studies as well as sampling within time windows, a direct comparison of tobramycin serum concentrations between the studies can not be performed. Instead, the sponsor utilized a population pharmacokinetic modeling approach to bridge observations between the different TIP manufacturing processes.

The sponsor developed a population pharmacokinetic model based on data from TPI001, C2301, and C2302. This model, as well as the patient characteristics from C2303, was then used to simulate the observed exposures in C2303. The sponsor used two approaches to determine if the original tobramycin population pharmacokinetic model was capable of describing the tobramycin concentrations from C2303: i) a visual predictive check; and ii) normalized prediction distribution errors (NPDE) tests. Summaries of the methods employed can be found in Section 3.

Results from the visual predictive check showed that the model captures the central trend and variability of data and that the 90% prediction interval includes 87% of the data (ideally, 90% of the data would be included within this interval). The proportion of data points outside of the 90% predictive interval is 13%, close to an expected 10%. The NPDE tests show that the normalized prediction errors followed a standard normal distribution, signifying that the tobramycin serum concentrations observed using the new manufacturing process (C2303) are equally likely to have been observed using the old manufacturing process.

1.1.3 Are there any exposure-response safety or efficacy relationships identifiable based on tobramycin serum pharmacokinetics?

Sparse PK assessments were performed in both the TIP (n=30) and TOBI (n=14) arms in C2302. However, due to storage beyond the validated stability window only a subset of PK samples (TIP: n=13; TOBI: n=6) were appropriate for inclusion in subsequent exposure-response analyses.

An imbalance in the number of ototoxicity events and resistance was observed in C2302 between the TOBI and TIP treatment arms (see Medical Officer and Microbiology Reviews by Dr. Mishra and Dr. Coderre). However, the PK data that was collected during C2302, after accounting for storage, was not sufficient to determine whether the imbalance in ototoxicity events observed in the TIP arm versus the TOBI arm were due to increased serum exposures of tobramycin following the use of TIP. Similarly, there was insufficient PK data to assess whether this increase in baseline MIC was due to subtherapeutic exposures of tobramycin (serum or sputum) in the TIP arm.

1.2 Recommendations

This application is approvable from a clinical pharmacology perspective.

1.3 Label Statements

12.3 Pharmacokinetics

Distribution

A population pharmacokinetic analysis for TOBI Podhaler in cystic fibrosis patients estimated the apparent volume of distribution of tobramycin in the central compartment to be 85.1 L for a typical CF patient. (b) (4)

Elimination

Tobramycin is eliminated from the systemic circulation primarily by glomerular filtration of the unchanged compound. Systemically absorbed tobramycin following TOBI Podhaler administration is also expected to be eliminated principally by glomerular filtration.

The apparent terminal half-life of tobramycin in serum after inhalation of a 112 mg single dose of TOBI Podhaler was approximately 3 hours in cystic fibrosis patients and consistent with the half-life of tobramycin after TOBI inhalation.

A population pharmacokinetic analysis for TOBI Podhaler in cystic fibrosis patients aged 6 to 58 years estimated the apparent serum clearance of tobramycin to be 14.5 L/h. (b) (4)

[-No clinically relevant covariates that were predictive of tobramycin clearance were identified from this analysis.](#)

2 PERTINENT REGULATORY BACKGROUND

Tobramycin solution for inhalation via a nebulizer (TOBI) was first approved in the United States in 1997 for the management of cystic fibrosis (CF) patients 6 years of age and older with *P. aeruginosa* infection. The recommended administration of TOBI is by repeated cycles of 28 days on-drug at a nebulized dose of 300 mg twice daily, followed by 28 days off-drug. Adherence to this regimen is hindered by the time burden for administration which may take several hours per day and the complexity of treatment.

Tobramycin inhalation powder hard capsule (TIP) is a new formulation of tobramycin for inhalation to be delivered with a dry powder inhaler. This system may offer improvement in a reduced administration time, a decrease in the complexity of equipment, increased portability, no need for an external power supply, no need for refrigeration of drug product and reduced maintenance. TIP is intended to offer comparable efficacy and safety as TOBI but with decreased dosing time and simpler administration.

3 RESULTS OF SPONSOR'S ANALYSIS

3.1 Introduction

The primary clinical data in this submission come from three Phase III studies: C2301, C2302, and C2303 and a dose-finding study (TIP001). An additional Phase 3 study (C2303) was included due to a switch in the TIP manufacturing process during late stage development. Studies TIP001, C2301, and C2302 used a similar manufacturing process, but C2303 used a modified manufacturing process for producing TIP.

A direct comparison of serum tobramycin concentrations from the Phase III studies was not possible due to the sparse sampling with the studies and different sampling times (i.e., sampling within a window of time). Tobramycin serum concentrations between the two manufacturing processes were bridged through a population pharmacokinetic modeling approach, using data and a model developed from studies TIP001, C2301, and C2302 to predict observed serum tobramycin concentrations from C2303.

3.2 Population Pharmacokinetic Model Reports

Report 5.3.3.5 Population Pharmacokinetic Report: Pharmacokinetic modeling of tobramycin inhalation powder

Report 5.3.3.5 Population Pharmacokinetic Report: Population pharmacokinetic analysis of inhaled tobramycin in patients with cystic fibrosis using Tobramycin Inhalation Powder (TIP_{new}).

3.2.1 Data

Data from TPI001, C2301, and C2302 was used during model development. Data from C2303 was used in comparing tobramycin serum concentrations between the two manufacturing processes. A summary of the study designs, patient populations, treatments used, and sampling time are provided below in Table 3. Descriptive statistics for the data included in these analyses is presented in Table 4.

Table 3: Study design and PK sampling times for studies contributing to the population PK analysis

Study	Population	Treatment	Sampling times
TPI001	CF patients ≥ 6 years old	Single dose of 28, 58, 84 and 112 mg TIP _{old}	Pre-dose, 0.5, 1, 2, 4, 8, 12 hours after the single dose for 64 subjects with PK data
C2301	CF patients between 6 and 21 years old, FEV1 $\geq 25\%$ to $\leq 80\%$ predicted	Dose 112 mg TIP _{old} b.i.d. for 28 days, then 28 days off treatment (a cycle), for three cycles (those randomized to TIP) and two cycles (those randomized to placebo)	Pre-dose and 1 hour post-dose on day 1 and day 28 of cycles 1 and 2 (those randomized to TIP) and cycle 2 (those randomized to placebo)
C2302	CF patients ≥ 6 years old, FEV1 $\geq 25\%$ to $\leq 75\%$ predicted	Dose 112 mg TIP _{old} b.i.d. for 28 days, then 28 days off treatment (a cycle), for three cycles	Pre-dose, one sample in window 0-2 and two samples in 2-5 hours post-dose on day 1 and day 28 of cycle 1 (visits 2 and 5) and on day 1 and 28 of cycle 3 (visits 9 and 10)
C2303	CF patients between 6 and 21 years old, FEV1 $\geq 25\%$ to $\leq 80\%$ predicted	Dose 112 mg TIP _{new} b.i.d. for 28 days, then 28 days off treatment (a cycle), for a single cycle	Pre-dose, one sample each in windows 0-1, 1-2 and 2-6 hours post-dose on day 1 (visit 2) and day 28 (visit 3) of the cycle

Sponsor's 5.3.3.5 Population Pharmacokinetic Report, pg 12

Table 4: Descriptive statistics of demographic and clinical characteristics of the PK analysis population of TIP studies

	TPI001	C2301	C2302	C2303	Combined
n	64	62	13	30	169
Age (years)	21 (11.1) [7-50]	14 (4) [6-21]	31 (13) [18-58]	12.5 (4.2) [6-21]	16 (10.3) [6-58]
Body weight (kg)	57.1 (16.4) [18.9-100.9]	37.5 (13.9) [16.2-68.9]	58.8 (11.9) [49.5-91.8]	32.2 (13.6) [11-62.5]	47 (17.8) [11-100.9]
Body mass index (kg/m ²)	20.4 (3.6) [13.4-31]	16.2 (3.4) [11.4-25.7]	22.1 (3.5) [16.3-30.7]	15.4 (3.3) [9.1-22.1]	18.5 (4.1) [9.1-31]
Creatinine clearance (mL/min)	114.9 (32.5) [63.9-222.5]	108.7 (26.9) [69-175.1]	104.8 (22) [76.1-150.7]	123.6 (33.6) [55.2-188.4]	113.8 (30.2) [55.2-222.5]
FEV1% predicted at baseline (%)	70 (20.4) [40.7-119.7]	58.5 (18.2) [24.1-96.2]	50.4 (14.2) [29.7-73.4]	66.4 (18.2) [28.9-79.3]	62.3 (20.3) [24.1-119.7]
Sex (Female)	35 (54.7)	33 (53.2)	6 (46.2)	21 (70)	95 (56.2)
Sex (Male)	29 (45.3)	29 (46.8)	7 (53.8)	9 (30)	74 (43.8)
Race (Black)	2 (3.1)	1 (1.6)	0 (0)	0 (0)	3 (1.8)
Race (Caucasian)	55 (85.9)	52 (83.9)	13 (100)	29 (96.7)	149 (88.2)
Race (Hispanic)	4 (6.2)	8 (12.9)	0 (0)	0 (0)	12 (7.1)
Race (Asian)	0 (0)	0 (0)	0 (0)	1 (3.3)	1 (0.6)
Race (Other)	3 (4.7)	1 (1.6)	0 (0)	0 (0)	4 (2.4)

Sponsor's 5.3.3.5 Population Pharmacokinetic Report, pg 18

After exclusion of affected C2302 samples due to excessive storage time and removal of values below the lower limit of quantification and outlying concentrations, there were 662 concentration values from 139 subjects in the population PK analysis data set (studies TPI001, C2301, C2302).

Study C2303 contained a total of 190 concentration values from 30 subjects. (note that 662 concentration values from 139 subjects of studies TPI001, C2301 and C2302 had been used in developing the population PK model.

3.2.2 Methods

3.2.2.1 Population PK Model Development

One- and two-compartment disposition models with first-order absorption and first-order elimination were evaluated based on the prior knowledge of tobramycin pharmacokinetics. Inter-individual variability terms were included on the PK model parameters, where supported by data. Additive, proportional, and a combination of both were tested in the error model development. Furthermore, inclusion of an inter-individual variability term on the error model parameters, as well as different errors for the early and late time concentrations were tested. Model development was carried out using

NONMEM VI Level 1.2, using the first order conditional estimation method with interaction (FOCEI)

The effects of covariates (age, body mass index, creatinine clearance, gender, FEV1% predicted, and weight) on the pharmacokinetic model parameters of tobramycin were investigated. A stepwise forward inclusion and backward elimination process was used for covariate searching. Each covariate was tested individually against the key structural model parameters in a stepwise fashion (forward inclusion). After each step, the strongest covariate relationship was incorporated into the model, and the others sequentially and individually re-tested, until no further covariates could be added with statistical significance. Once all relevant relationships had been tested and a “full” model was obtained, each covariate parameter was sequentially removed in a stepwise fashion (backward elimination).

The final model was evaluated using general goodness of fit graphs, where plots of population predicted values and individual predicted values versus observed concentrations were examined. Residuals versus time and residuals versus predicted concentrations were examined to determine if a model bias existed and the precision of the model parameter estimates was evaluated. Finally, a visual predictive check of expected 95% prediction interval was utilized, based on 500 simulations of the entire data set and comparison with the actual observations.

3.2.2.2 Posterior Predictive Check to Compare Tobramycin PK Between Manufacturing Processes

The Sponsor utilized a posterior predictive check (PPC) to determine if the TIP manufacturing process resulted in any systemic exposure changes between the original TIP (TIP_{old}) and new TIP (TIP_{new}) product. In this approach, the previously developed population pharmacokinetic model and population studied in C2303 is used to simulate the observed tobramycin concentrations from C2303. Compatibility of models and data in statistical analysis is evaluated using a statistic of data and showing that this statistic is large only with a suitably small probability.

To evaluate the magnitude of the probability of such deviation a distribution of the statistic is generated by Monte Carlo simulation under the assumption that the model is true (the null hypothesis). The statistic for PPC is derived from serum concentration of tobramycin $Y_{i,j}$ measured in subject i at time t_j using normalization to decorrelate multiple observations within the same subject. Normalization is performed with respect to Monte Carlo samples from the posterior distribution of concentrations given by the population PK model of TIP, $Y_{k,i,j}^{SIM}$ where index k runs over K simulated subjects. Then prediction errors $pde_{i,j}$ are obtained as percentiles $F_{i,j}$ of $Y_{i,j}^*$ of the corresponding distributions $Y_{k,i,j}^{SIM*}$. Normalized prediction distribution errors (NPDE) are obtained as inverse of the standard normal distribution. The model is compatible with data if the distribution of $npde_{i,j}$ is standard normal.

Three tests were performed to assess normality: (i) Wilcoxon signed rank test, to test whether the mean is significantly different from 0; (ii) Fisher test for variance, to test whether the variance is significantly different from 1; (iii) Shapiro–Wilks test, to test whether the distribution is significantly different from a normal distribution. The sponsor also performed a global test, which consists of considering the three tests above with a Bonferroni correction for multiple hypothesis testing. The p-value for this global test was then reported as the minimum of the three p-values multiplied by 3.

Finally, visual predictive check plots were also constructed to assess the overall agreement between simulated and observed concentration data. A sample mean and the 5th and 95th percentiles of the simulated concentrations at a vector of time points were calculated to represent the predictive distribution of concentrations over time and compared with observed data.

3.2.3 Results

3.2.4 Final Model

The structural model fitted to the serum concentrations was based on a two-compartment disposition model with first-order absorption in the central compartment and first-order elimination. Interindividual variability (IIV) was estimated on apparent clearance (CL/F), apparent central volume of distribution (V_d/F) and absorption rate constant (ka). Interoccasion variability (IOV) was estimated on CL/F. The residual error was modeled to be a combination of proportional and additive.

The final model described the PK profiles well. The final parameters and parameter precisions are listed in Table 5. The goodness-of-fit plots are presented in Figure 2.

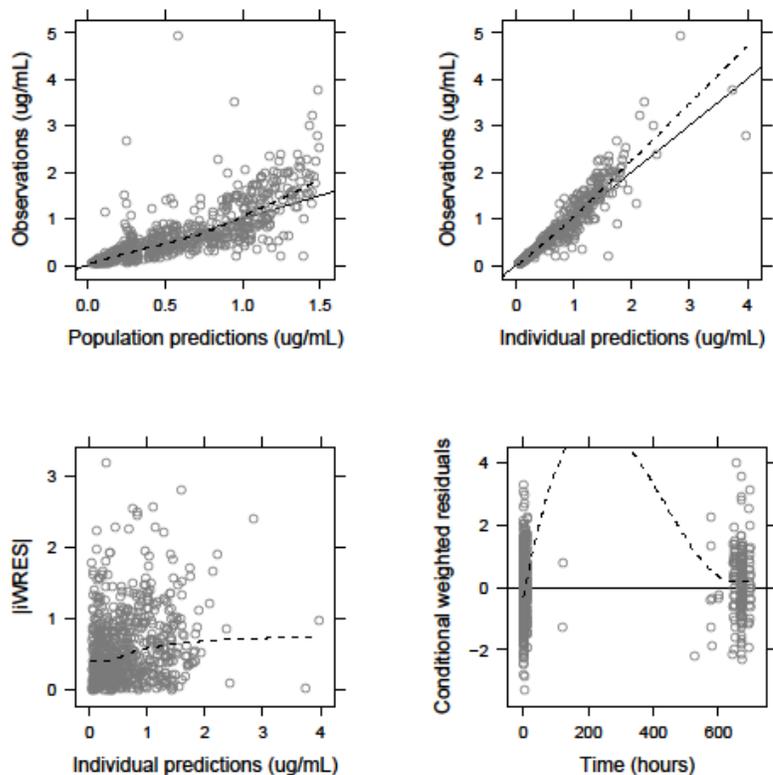
Table 5: Parameters of the final population PK model of tobramycin following inhalation of TIP

Parameters	Estimate (% RMSE)	95% Confidence Interval
CL/F (L/h)	14.5 (5)	[13.089 - 15.911]
V _d /F (L)	85.1 (3.6)	[79.053 - 91.147]
Ka (per h)	2.39 (4.8)	[2.166 - 2.614]
Q/F (L/h)	6.43 (12.9)	[4.808 - 8.052]
V _p /F (L)	210 (29.9)	[86.972 - 333.028]
Covariates		
BMI on V _d /F	0.624 (24.6)	[0.323 - 0.925]
FEV1% on V _d /F	-0.303 (36)	[-0.517 - -0.089]
IIV on CL/F (variance)	0.164 (28.2)	[0.073 - 0.255]
COV of CL/F and V _d /F (variance)	0.123 (20)	[0.075 - 0.171]
IIV on V _d /F (variance)	0.152 (12.3)	[0.115 - 0.189]
IIV on ka (variance)	0.129 (23.7)	[0.069 - 0.189]
IOV on CL/F (variance)		
Occasion 1	0.078 (48)	[0.005 - 0.151]
Occasion 2	Same as above	Same as above
Occasion 3	Same as above	Same as above
Occasion 4	Same as above	Same as above
Residual standard deviation, additive component	0.007 (25.8)	[0.004 - 0.011]
Residual standard deviation, proportional component		
TPI001	0.073 (10)	[0.059 - 0.087]
TBM100C2301 & TBM100C2302	0.308 (8.7)	[0.256 - 0.36]

The model was developed on PK data from Study TPI001, Study C2301 and Study C2302.

Sponsor's 5.3.3.5 Population Pharmacokinetic Report, pg 15

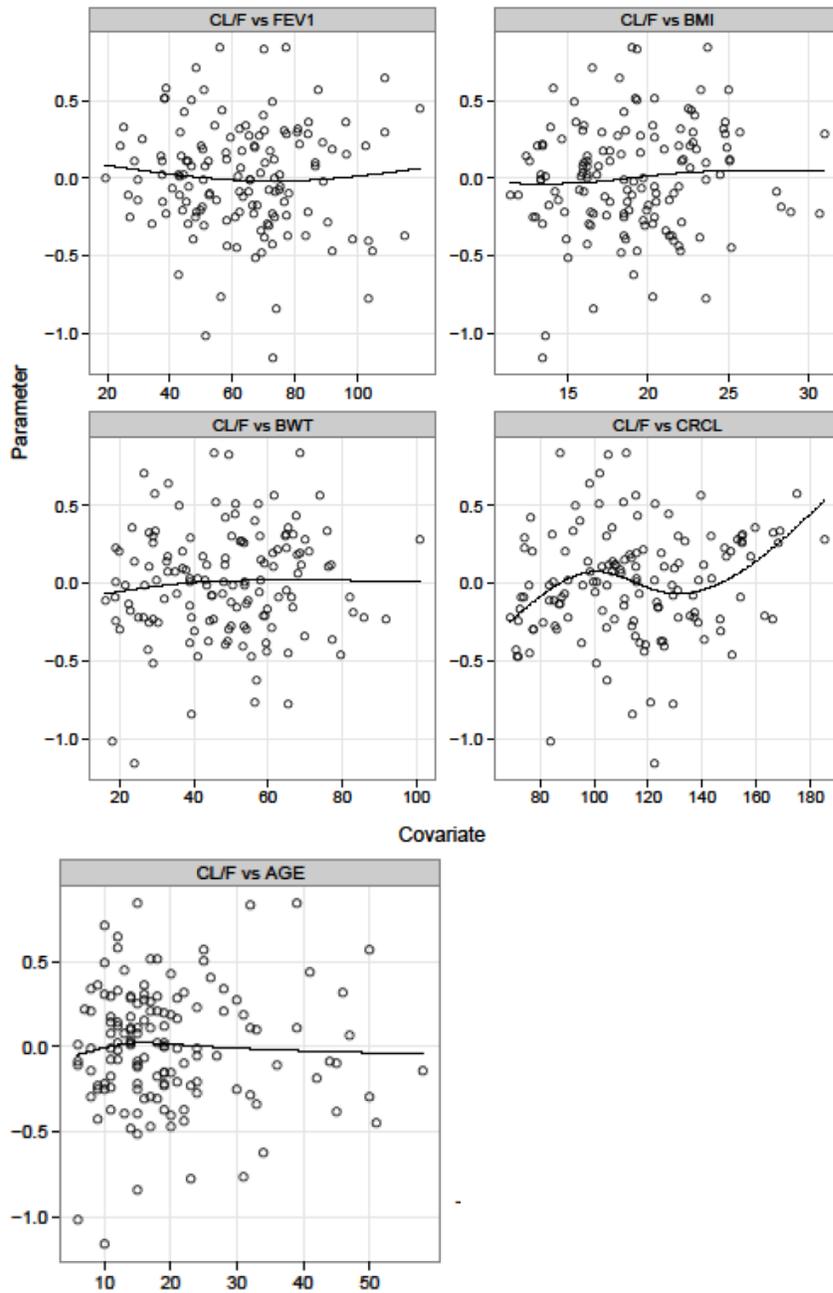
Figure 2: Goodness-of-fit metrics for the final population PK model



Sponsor's 5.3.3.5 Population Pharmacokinetic Report (amendment), pg 17

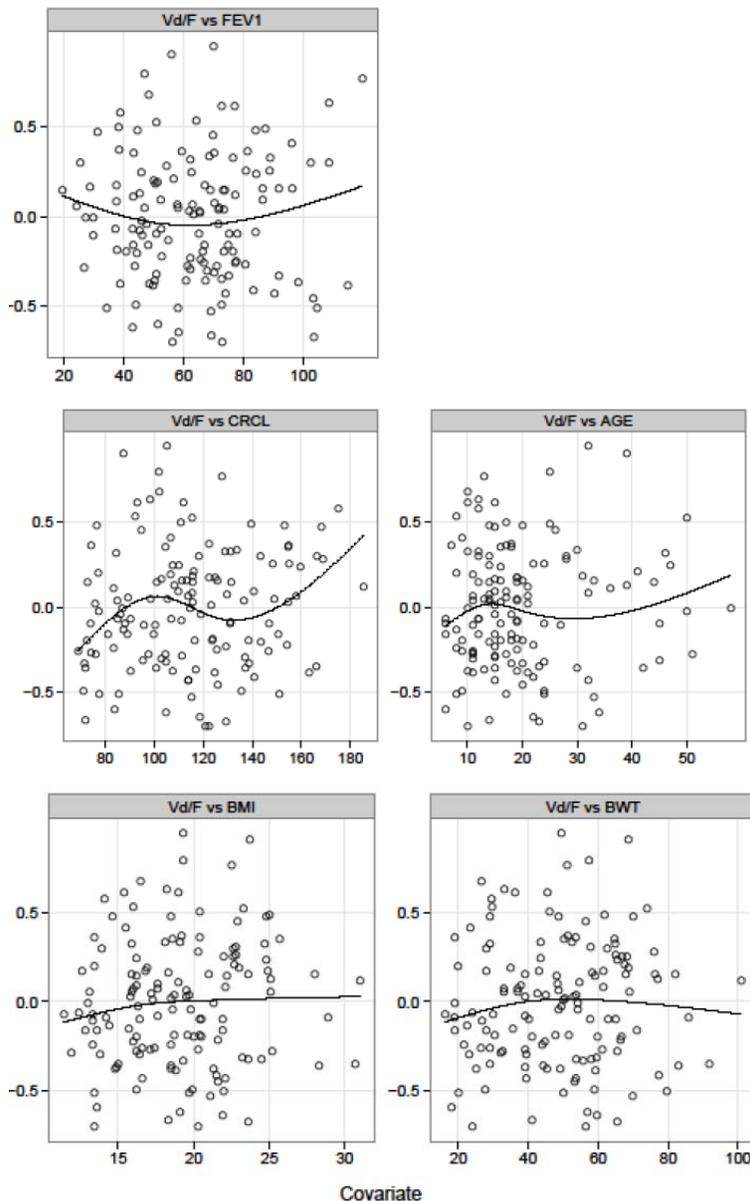
No significant covariate was identified for CL/F (Figure 3), hence no covariate effect on AUC. BMI and FEV1% predicted were found to be statistically significant covariates for V_d/F (Figure 4). Across the range of values of BMI or FEV1% predicted at baseline evaluated, the predicted mean C_{max} and C_{trough} values were at least six-fold 7.6-fold and 5.1-fold lower than the concentration levels associated with tobramycin toxicity, hence, the effect of BMI and FEV1% predicted at baseline on the concentration levels of tobramycin after administration of 112 mg b.i.d. TIP are not expected to be clinically significant.

Figure 3: Empirical Bayesian estimates of interindividual variability parameters for CL/F vs. covariates for the final population PK model



Sponsor's 5.3.3.5 Population Pharmacokinetic Report (amendment), pg 22-23

Figure 4: Empirical Bayesian estimates of interindividual variability parameters for Vd/F vs. covariates for the final population PK model



Sponsor's 5.3.3.5 Population Pharmacokinetic Report (amendment), pg 23-24

Body mass index and FEV₁% were identified as significant covariates during model development. However, the impact on tobramycin exposure was modest and would not alter tobramycin C_{max} or C_{tr} clearance by more than 25% for subjects with covariate values at the 5th to 95th percentile for the studied population. As such, no dose adjustments are recommended based on either covariate.

Reviewer's Comments: The population pharmacokinetic model development by the applicant was sufficient to describe the time course of tobramycin following inhalation.

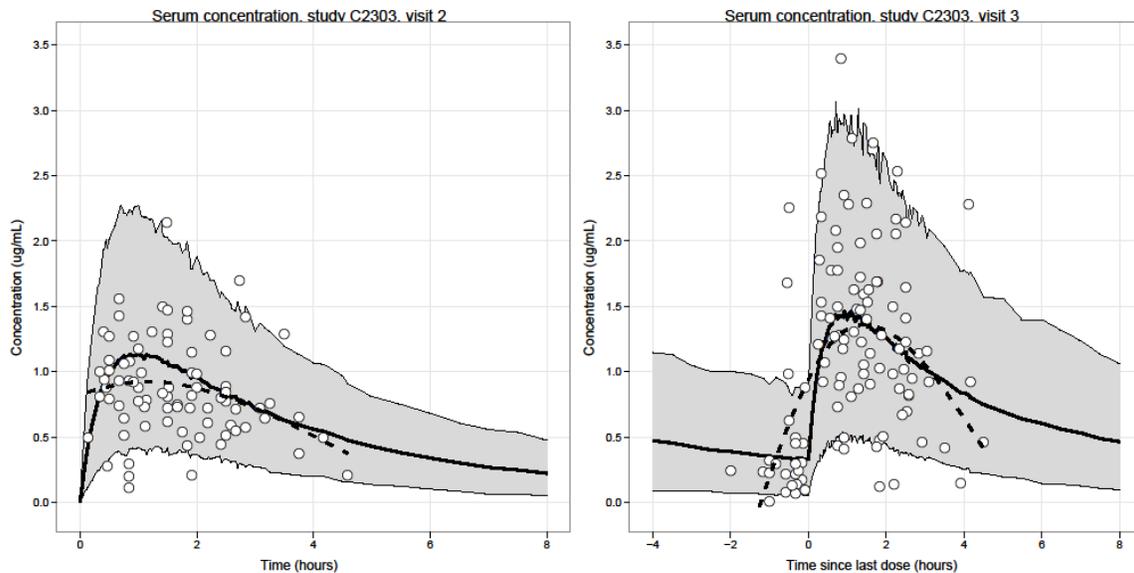
The applicant's label claims of no clinically relevant covariates based on the population pharmacokinetic analysis is supported, however, the available data for pediatrics and for patients with decreased renal function in addition to the limited tobramycin sampling may have limited the ability to identify contribution of these covariates to relevant model parameters (clearance and distribution).

3.2.5 Posterior Predictive Check to Compare Tobramycin PK Between Old and New Manufacturing Processes

3.2.5.1 Visual Predictive Check

Simulations using the population PK model of serum concentration profiles for the PK analysis population of C2303 are shown in Figure 5. These results show that the model captures the central trend and variability of data. The proportion of data points outside of the 90% predictive interval is 13%, close to an expected 10%.

Figure 5: Comparison of simulated and observed serum concentration time profiles for the PK analysis population of Study C2303 on day 1 (visit 2) and day 28 (visit 3)

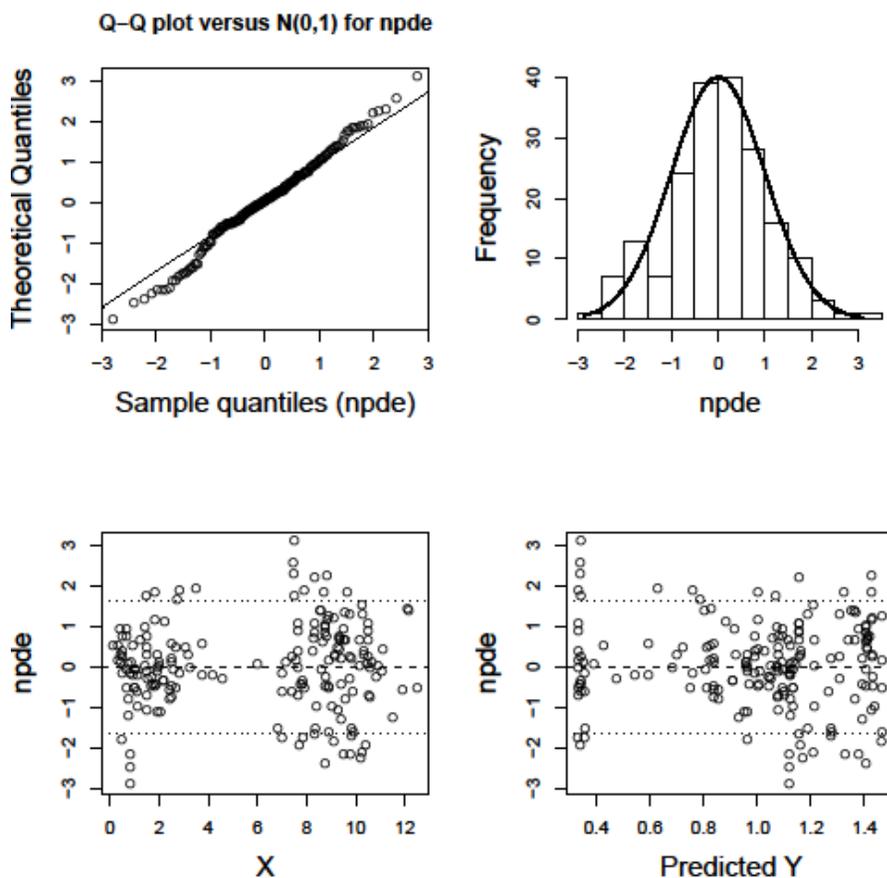


Sponsor's 5.3.3.5 Population Pharmacokinetic Report (C2303), pg 21

3.2.5.2 Normalized Predictive Distribution Errors Test

P-values of Wilcoxon signed rank test, Fisher variance test and Shapiro-Wilks test for normality are 0.53, 0.27 and 0.27, respectively, signifying that the null hypothesis that the distribution of normalized predictive errors is normal (i.e., the population pharmacokinetic model is capable of describing the data in C2303 and that the TIP manufacturing changes did not significantly change tobramycin systemic exposures). This means that specific tobramycin serum concentrations after inhalation of TIP_{new} are just as likely to be observed as after inhalation of TIP_{old}.

Figure 6: Diagnostic plots of the NPDE test on data from the PK analysis population of Study C2303



Sponsor's 5.3.3.5 Population Pharmacokinetic Report (C2303), pg 22

Reviewer's Comment: The sponsor's evaluation of differences between the two manufacturing processes is acceptable. The reviewer has reevaluated the developed population pharmacokinetic model and obtained similar results for the visual predictive check as well as confirmation of the statistical analyses performed as part of the normalized predictive distribution errors tests. These analyses, as well as the relatively similar tobramycin serum concentrations between C2303 and the earlier studies support the conclusion that the manufacturing process did not result in any significant differences in serum tobramycin concentrations.

In addition to the above analysis, the reviewer considered a parameter approach (i.e., evaluating if there were any differences on systemic bioavailability, and to a lesser extent distribution or elimination, between TIP from the two manufacturing processes. Such an approach was performed for thoroughness as the methods already evaluated by the sponsor are more appropriate for identifying whether there are differences in serum tobramycin exposures between the manufacturing processes (i.e., it is unexpected that a

change in the manufacturing process will result in changes to elimination or distribution, which are drug properties, though a different absorption profile may result). This analysis did not identify any significant differences in absorption (or other pharmacokinetic parameters) between the manufacturing processes.

4 REVIEWER'S ANALYSIS

4.1.1 Data Sets

Data sets used are summarized in Table 6.

Table 6. Analysis Data Sets

Study Number	Name	Link to EDR
TPI001	pkcntpil.xpt	\\cdsesub1\EVSPROD\NDA201688\0000\m5\datasets\tbm100ctpi-001\listings
TPI001	pkpmtpil.xpt	\\cdsesub1\EVSPROD\NDA201688\0000\m5\datasets\tbm100ctpi-001\analysis
C2301	pkconc.xpt	\\cdsesub1\EVSPROD\NDA201688\0000\m5\datasets\tbm100c2301\listings
C2301	amic.xpt	\\cdsesub1\EVSPROD\NDA201688\0000\m5\datasets\tbm100c2301\analysis
C2302	pkconc.xpt	\\cdsesub1\EVSPROD\NDA201688\0000\m5\datasets\tbm100c2302\listings
C2302	adarsum.xpt, amic.xpt	\\cdsesub1\EVSPROD\NDA201688\0000\m5\datasets\tbm100c2302\analysis
C2303	phk.xpt	\\cdsesub1\EVSPROD\NDA201688\0000\m5\datasets\tbm100c2303\listings
C2303	amictob.xpt	\\cdsesub1\EVSPROD\NDA201688\0000\m5\datasets\tbm100c2303\analysis

5 LISTING OF ANALYSES CODES AND OUTPUT FILES

File Name	Description	Location in \\cdsnas\pharmacometrics\
TIP_1001_PK_Summary.R	PK summary and plot generation for study TPI001	Tobramycin_NDA201688_JAF\PPK Analyses
TIP_MIC_and_Safety_Analysis.R	Generate MIC plots based on C2302 at various visits. Evaluate exposure-response data for imbalance in ototoxicity events and increased resistance from C2302	Tobramycin_NDA201688_JAF\PPK Analyses

6 APPENDIX

Minimum Inhibitory Concentration Shift Tables

The microbiology reviewer (Dr. Coderre) observed an imbalance in tobramycin resistance development between patients administered TIP compared to patients administered TOBI in C2302. While the pharmacokinetic sampling was insufficient to perform any exposure-response analyses for resistance development, the reviewer performed a separate analysis evaluating the shift in the maximum minimum inhibitory concentration (MIC) from Day 1 of Cycle 1 to Day 28 of Cycle 1 for the treatment arms in C2302. There were a total of 547 subjects with MIC records for C2302 (TIP: n=325; TOBI: n=222). Of these subjects 239 in the TIP treatment arm and 173 in the TOBI treatment arm had both baseline and Day 28 of Cycle 1 MIC assessments available. There were 96 subjects (TIP: n=64; TOBI: n=32) with baseline MIC values available, but no MIC collected at Day 28 of Cycle 1. In addition, there were 31 subjects with no MIC data available and 8 subjects with MIC data available only at Cycle 2 or later.

MIC shift tables from C2302 for TOBI and TIP are shown below (Table 7). The diagonal cells represent no change between MIC at Day 1 of Cycle 1 and Day 28 of Cycle 1. Similarly, cells below the diagonal depict a decrease in MIC between Day 1 of Cycle 1 and Day 28 of Cycle 1 while cells above the diagonal depict an increase in MIC.

Of the subjects with Day 1 of Cycle 1 and Day 28 of Cycle MIC values available, a greater percentage of subjects in the TIP treatment arm experienced an MIC increase to ≥ 32 (15.1%, n=36) or ≥ 128 (10.4%, n=25) compared to 10.4% (n=10) and 3.5% (n=6), respectively, in the TOBI treatment arm.

The reason for the shift towards higher MIC pathogens in the TIP arm is unclear. The pharmacokinetic data from TPI001 indicate that, if taken correctly, 112 mg of TIP should provide comparable exposures to 300 mg of TOBI (see Key Question 1.1.1 above). An exposure-response analysis between TIP or TOBI concentrations and MIC could not be performed on this population due to the limited number of subjects with PK data available (see Key Question 1.1.3 above). In addition, none of the subjects with MIC values exceeding 32 $\mu\text{g}/\text{mL}$ had pharmacokinetic data available for comparison with the TPI001 results. This analysis does not rule out that subjects in the TIP treatment arm may have had lower tobramycin sputum exposures compared to the TOBI patients, which may have contributed to the development of resistance. Such decreased exposure may have resulted from a failure to take capsules properly or a decrease in compliance.

Table 7: MIC Shift Tables Between Day 1 of Cycle 1 and Day 28 of Cycle 1 from C2302 for Subjects on Either TOBI (top) or TIP (bottom)

TIP (n = 239)		MIC at Cycle 1, Day 28				
		0.12≤MIC ≤0.5, % (n/N)	1≤MIC≤4, % (n/N)	8≤MIC≤16, % (n/N)	32≤MIC≤64, % (n/N)	128≤MIC, % (n/N)
MIC at Cycle 1, Day 1	0.12≤MIC≤0.5, (N=63)	40 (25/63)	38 (24/63)	8 (5/63)	5 (3/63)	10 (6/63)
	1≤MIC≤4, (N=97)	15 (15/97)	58 (56/97)	11 (11/97)	4 (4/97)	11 (11/97)
	8≤MIC≤16, (N=39)	10 (4/39)	41 (16/39)	28 (11/39)	10 (4/39)	10 (4/39)
	32≤MIC≤64, (N=19)	11 (2/19)	21 (4/19)	21 (4/19)	26 (5/19)	21 (4/19)
	128≤MIC, (N=21)	0 (0/21)	10 (2/21)	5 (1/21)	19 (4/21)	67 (14/21)

TOBI (n = 173)		MIC at Cycle 1, Day 28				
		0.12≤MIC ≤0.5, % (n/N)	1≤MIC≤4, % (n/N)	8≤MIC≤16, % (n/N)	32≤MIC≤64, % (n/N)	128≤MIC, % (n/N)
MIC at Cycle 1, Day 1	0.12≤MIC≤0.5, (N=43)	51 (22/43)	37 (16/43)	9 (4/43)	0 (0/43)	2 (1/43)
	1≤MIC≤4, (N=68)	16 (11/68)	62 (42/68)	12 (8/68)	4 (3/68)	6 (4/68)
	8≤MIC≤16, (N=34)	3 (1/34)	53 (18/34)	41 (14/34)	3 (1/34)	0 (0/34)
	32≤MIC≤64, (N=9)	0 (0/9)	11 (1/9)	44 (4/9)	33 (3/9)	11 (1/9)
	128≤MIC, (N=19)	0 (0/19)	5 (1/19)	11 (2/19)	26 (5/19)	58 (11/19)

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08/20/2012

KIMBERLY L BERGMAN
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