ORIGINAL ARTICLE

Population Pharmacokinetics of Inhaled Tobramycin Powder in Cystic Fibrosis Patients

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Tobramycin powder for inhalation (TOBI Podhaler or TIP) is approved for the treatment of *Pseudomonas aeruginosa* airway infection in patients with cystic fibrosis (CF). A population pharmacokinetic model for tobramycin inhalation powder (TIP) in CF patients was developed to characterize the effect of covariates including body mass index (BMI) and lung function (forced expiratory volume in 1 s as percent of the predicted value (FEV$_1$% predicted) at baseline) on the serum exposure parameters. A two-compartment model with first-order elimination and first-order absorption was developed. Across a range of baseline demographic values in the study population, the predicted mean values for the maximum (C_{max}) and trough (C_{trough}) plasma concentrations at steady state were at least 7.5 and 5-fold lower, respectively, than the recommended thresholds for tobramycin toxicity (12 µg/ml for C_{max} and 2 µg/ml for C_{trough}). This model adequately described the tobramycin serum concentration–time course in CF patients following inhalation of TIP. The results indicate that no BMI- or FEV$_1$-based dose adjustment is needed for use of TIP in CF patients.

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The major cause of morbidity and mortality in patients with cystic fibrosis (CF) is progressive deterioration of lung function.[1] By adolescence, the majority of individuals with CF develop an endobronchial infection with *Pseudomonas aeruginosa*.[2] Chronic infection with this pathogen is associated with accelerated progression of obstructive lung disease, increased morbidity, and increased risk of death.[1,3–5]

Tobramycin is an effective antibacterial agent used for the treatment of *P. aeruginosa* infection, but it can cause nephrotoxicity and ototoxicity at high systemic concentrations.[6] The advent of tobramycin inhalation solution (TIS; (TOBI)) provided an effective way of delivering a high concentration of tobramycin to the infected airways while avoiding the toxicity associated with systemic administration. Both US and European treatment guidelines for CF recommend the use of TIS for the treatment of *P. aeruginosa* infections in patients aged ≥6 years.[7,8] TIS is administered b.i.d. via a nebulizer, a process that takes ~15–20 min per dose, including additional time for nebulizer setup and cleaning.[9] This time burden could be one of the major reasons for poor adherence to treatment in patients with CF, which may lead to poor clinical outcomes.[10–13]

Tobramycin powder for inhalation (TOBI Podhaler or TIP) has been developed to enhance the delivery of tobramycin to the lung and shorten administration time. This may lead to improved patient adherence and a better clinical outcome. Tobramycin inhalation powder (TIP) is manufactured using an emulsion-based spray-drying process that yields spherical hollow porous particles designed to be delivered via the TOBI Podhaler (Novartis Pharmaceuticals, San Carlos, CA), a dry powder inhaler that is light, portable, and requires no power source.[14] Furthermore, drug administration time is reduced to 4–6 min for TIP via the Podhaler, compared with 15–20 min for TIS, improving the convenience for patients.[9,15]

Clinical data have shown that 112 mg TIP administered b.i.d. was effective and well tolerated in CF patients with *P. aeruginosa* infection and were consistent with data reported for the currently approved TIS formulation.[15,16] TIP improved lung function, decreased sputum *P. aeruginosa* density, reduced respiratory-tract-related hospitalizations, and reduced the use of other antipseudomonal antibiotics.[16] Additionally, it has been demonstrated that the systemic exposure following 112 mg tobramycin delivered via Podhaler is comparable with that from TIS and is well below known systemic toxicity levels.[16]

Topical delivery of aerosol to the lung is highly variable among individuals and is known to be affected by patient factors such as age, upper and lower airway anatomy, and inspiratory breathing pattern.[17] The aim of this study was to develop a pharmacokinetic model to characterize pharmacokinetic profile for TIP in CF patients, and to characterize the effects of patients' baseline characteristics, including age, body mass index (BMI), creatinine clearance, sex, lung function (as forced expiratory volume in 1 s as percent of the predicted value (FEV$_1$% predicted)) and weight, on the model parameters, if any. Only pharmacokinetic data from TIP were used in this population pharmacokinetic model.

RESULTS

Demographics

The demographic information on the analysis population from the three individual studies and the combined one is summarized in **Table 1**.

Population pharmacokinetic model

The final population pharmacokinetic model developed was a two-compartment disposition model with first-order elimination

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Table 1 Demographic description of the TIP population

	Individual study			
	TPI001	**C2301**	**C2302**	**Combined**
N	64	62	13	139
Age, years: median (SD) [range]	21 (11.1) [7–50]	14 (4.0) [6–21]	31 (13.0) [18–58]	17 (10.8) [6–58]
Age group, *n* (%)				
6–11 years	9 (14.1)	20 (32.3)	0 (0)	29 (20.9)
12–17 years	16 (25)	28 (45.2)	0 (0)	44 (31.7)
≥18 years	39 (60.9)	14 (22.6)	13 (100)	66 (47.5)
Body weight, kg: median (SD) [range]	57.1 (16.4) [18.9–100.9]	37.5 (13.9) [16.2–68.9]	58.8 (11.9) [49.5–91.8]	49.5 (17.7) [16.2–100.9]
BMI, kg/m^2: median (SD) [range]	20.4 (3.6) [13.4–31]	16.2 (3.4) [11.4–25.7]	22.1 (3.5) [16.3–30.7]	18.8 (4.1) [11.4–31]
Creatinine clearance, ml/min: median (SD) [range]	114.9 (32.5) [63.9–222.5]	108.7 (26.9) [69–175.1]	104.8 (22.0) [76.1–150.7]	112.5 (29.5) [63.9–222.5]
FEV$_1$% predicted at baseline: median (SD) [range]	70.0 (20.4) [40.7–119.7]	58.5 (18.2) [24.1–96.2]	50.4 (14.2) [29.7–73.4]	62.1 (20.6) [24.1–119.7]
Sex, *n* (%)				
Female	35 (54.7)	33 (53.2)	6 (46.2)	74 (53.2)
Male	29 (45.3)	29 (46.8)	7 (53.8)	65 (46.8)
Race, *n* (%)				
Black	2 (3.1)	1 (1.6)	0 (0)	3 (2.2)
Caucasian	55 (85.9)	52 (83.9)	13 (100)	120 (86.3)
Hispanic	4 (6.2)	8 (12.9)	0 (0)	12 (8.6)
Other	3 (4.7)	1 (1.6)	0 (0)	4 (2.9)

FEV$_1$% predicted, forced expiratory volume in 1 s as percent of the predicted value; TIP, tobramycin inhalation powder.

and first-order absorption. Interindividual variability (IIV) was estimated on apparent clearance (CL/*F*), apparent central volume of distribution (V_d/*F*), and absorption rate constant (k_a). Interoccasion variability was estimated on CL/*F*. The residual error was modeled to be a combination of proportional and additive errors. The proportional residual variability of study C2301 and study C2302 was more than threefold higher than that in study TPI001, reflecting the many doses and sampling times that were not recorded in the two phase III studies and had to be imputed. The parameter estimates are listed in **Table 2**. The final covariates identified on the model were BMI and FEV$_1$% predicted on V_d/*F*. The relationship between V_d/*F* with FEV$_1$% predicted and BMI was defined as follows:

$$V_d/F = 85.1 \cdot \left(\frac{\text{FEV}_1\%}{62.1}\right)^{-0.303} \cdot \left(\frac{\text{BMI}}{18.8}\right)^{0.624}$$

None of the other investigated variables were found to be statistically significant covariates in the model.

Visual predictive checks and goodness-of-fit plots
For single doses, the central trend predicted by the model matched the central trend of observed data in visual predictive check plots (**Figure 1**). The variability observed in the data was adequately captured by the model. In general, observed data at multiple doses were also matched well by the model at the 5th to 95th percentiles (**Figure 1b**), although the median value of the maximum plasma concentration at steady state (C_{max}) was slightly underpredicted. For multiple doses, for the time interval 13–60 h, the 97.5th percentile was underpredicted, which may be explained by the small amount of data (six concentration observations), including one at a significantly higher concentration than the others. Similarly, at the time interval 6–13 h, the observed data at the 97.5th

Table 2 Summary of the final model parameter estimates

Parameter	Estimate (% RSE)	95% Confidence interval[a]
CL/*F* (l/h)	14.5 (5.0)	13.1 to 15.9
V_d/*F* (l)	85.1 (3.6)	79.1 to 91.1
k_a (h^{-1})	2.39 (4.8)	2.17 to 2.61
Q/*F* (l/h)	6.43 (12.9)	4.81 to 8.05
V_2/*F* (l)	210 (29.9)	87.0 to 333
Covariates		
FEV$_1$% on V_d/*F*	–0.303 (36.0)	–0.517 to –0.089
BMI on V_d/*F*	0.624 (24.6)	0.323 to 0.925
IIV		
IIV of CL/*F* (variance)	0.164 (28.2)	0.073 to 0.255
IIV of V_d/*F* (variance)	0.152 (12.3)	0.115 to 0.189
IIV of k_a (variance)	0.129 (23.7)	0.069 to 0.189
COV of CL/*F* and V_d/*F* (variance)	0.123 (20.0)	0.075 to 0.171
IOV of CL/*F* (variance)		
Occasion 1	0.078 (48.0)	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 SD, proportional component		
TPI001	0.073 (10.0)	0.059 to 0.087
C2301 and C2302	0.308 (8.7)	0.256 to 0.36
Residual SD, additive component	0.007 (25.8)	0.004 to 0.011

BMI, body mass index; CL/*F*, apparent clearance; COV, covariance between parameters; FEV$_1$, forced expiratory volume in 1 s; IIV, interindividual variability of parameter as variance; IOV, interoccasion variability; k_a, absorption rate constant; NONMEM, non-linear mixed effects modeling; *Q*/*F*, apparent intercompartmental clearance; RSE, root-mean-square error as percent of the parameter estimate; V_d/*F*, apparent central volume of distribution; V_2, apparent peripheral volume of distribution.
[a]Derived from NONMEM-provided standard errors.

percentile was also not well matched by the model because of observations of high concentrations (in the range of 1–3 µg/ml) compared with the majority (less than 1 µg/ml). Goodness-of-fit plots (see **Supplementary Figures S1 and S2**) also indicate that the model described the data reasonably well. Plots of population and individual predictions against observations showed good agreement between population predictions and data, as indicated by the overlay of unity line and locally weighted scatter plot smoothing (LOESS) line, with a slight underestimation at high concentrations. The residual error model was also found to be appropriate

(comparing individual predictions against individual weighted residuals) and there was no bias in the model predictions against time.

Covariate effect on exposure

The model-predicted mean C_{max} and C_{trough} values at steady state for a typical CF patient either with 62.1% FEV$_1$% predicted at baseline (the population median) and different values of BMI or with 18.8 kg/m^2 BMI (the population median) and different values of FEV$_1$% predicted at baseline are shown in **Figure 2** and **Supplementary Tables S1 and S2**.

Simulations showed that when BMI decreases from the 95th percentile (25.1 kg/m^2) to the 5th percentile (13.3 kg/m^2) of the study population distribution, C_{max} increases 21% from 1.3 to 1.57 µg/ml, whereas C_{trough} decreases 16% from 0.38 to 0.32 µg/ml. When FEV$_1$% predicted at baseline increases from the 5th percentile (29.7% predicted) to the 95th percentile (102.5% predicted) of the study population distribution, C_{max} increases 21% from 1.22 to 1.48 µg/ml, whereas C_{trough} decreases 18% from 0.39 to 0.32 µg/ml. Across the range of values of BMI or FEV$_1$% predicted at baseline evaluated, the predicted mean C_{trough} values were at least fivefold lower than the recommended maximum C_{trough} (2 µg/ml) for avoidance of tobramycin-associated toxicity (**Figure 2**).[6] These
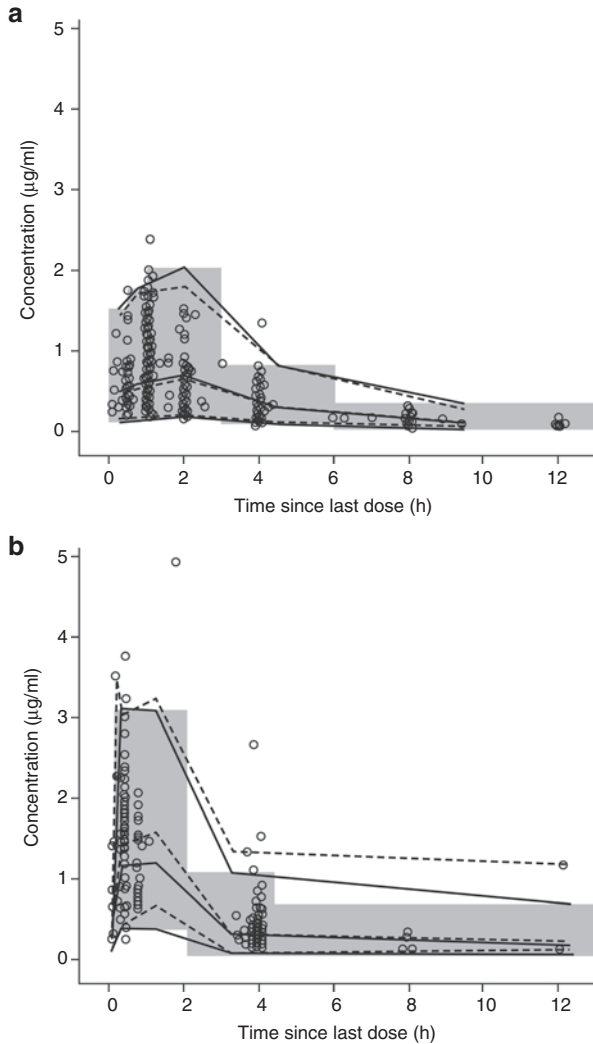
Figure 1 Visual predictive check of the model for tobramycin concentrations. (**a**) Visual predictive check of the model for tobramycin concentrations at first visit of each cycle. The shaded area indicates 2.5th and 97.5th percentiles for bins over time of simulated concentrations. Open circles show observed concentrations. Solid and dashed lines indicate medians and the 2.5th and 97.5th percentiles over simulated and observed concentrations, respectively. (**b**) Visual predictive check of the model for tobramycin concentrations at second visit of each cycle. Open circles show observed concentrations. Dashed lines indicate medians and the 2.5th and 97.5th percentiles over observed concentrations. The solid lines indicate medians and the 2.5th and 97.5th percentiles over simulated concentrations, and the shaded rectangles illustrate binned time intervals over which the percentiles were evaluated.
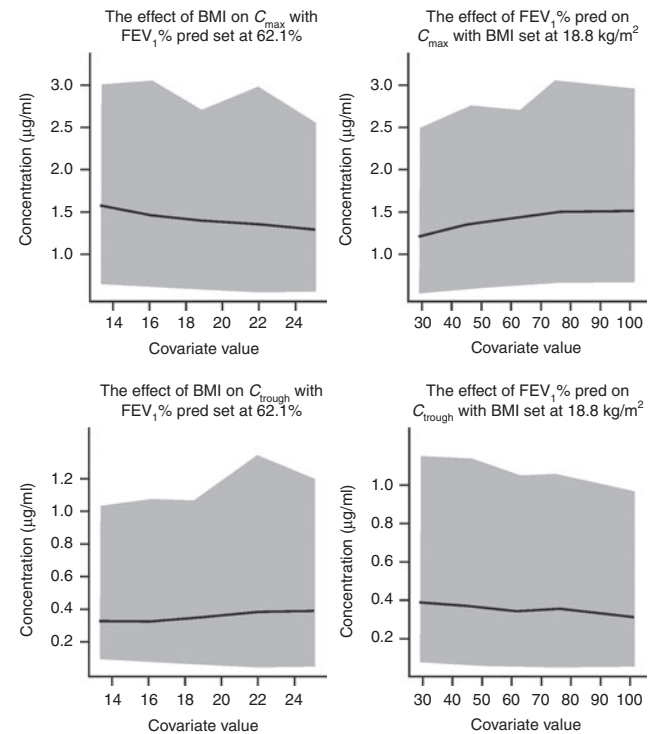
Figure 2 Effect of the covariates body mass index (BMI) and forced expiratory volume in 1 s as percent of the predicted value (FEV$_1$% pred) at baseline on tobramycin serum C_{max} and C_{trough} with 95% predictive interval (PI)*, assuming a typical cystic fibrosis patient with FEV$_1$% predicted of 62.1% and BMI of 18.8 kg/m^2. Gray area represents 95% PI, and solid line represents mean tobramycin concentration. *Obtained by simulation with interindividual variability in pharmacokinetics; PI values are presented for each covariate value, not for the slope of best fit. C_{max}, maximum plasma concentration at steady state; C_{trough}, trough plasma concentration at steady state.

results illustrate that the effect of BMI and FEV$_1$% predicted on the concentration of tobramycin after administration of TIP 112 mg b.i.d are not expected to be clinically relevant.

The highest value of the upper end point of the 95% predictive interval for C_{max} is 3.08 µg/ml and for C_{trough} is 1.33 µg/ml. The C_{max} and C_{trough} levels are 7.5- and 5-fold lower than the maximum recommended concentrations of serum tobramycin (12 µg/ml for C_{max} and 2 µg/ml for C_{trough}), with 97.5% of patients predicted to have C_{max} and C_{trough} values 4- and 1.5-fold lower than the maximum recommended levels.[6] This inference is applicable to patient populations with baseline values of BMI and FEV$_1$% predicted similar to the values in the study populations.

Influence of excluded data

The final structural model developed was rerun after reintroducing concentrations that were excluded due to lack of FEV$_1$ measurements as described previously, and the difference in the parameter values was examined. There was little change in all the parameter estimates after inclusion of these concentrations, suggesting no influential observations or subjects in these data records. The final model was also rerun with the outliers included, and the difference in the parameter values was not deemed significant (data not shown). There was no pronounced change in the fixed-effects parameter estimates except for the estimate of the apparent peripheral volume of distribution (V_2/F), which increased from 162 to 313 l, resulting in a longer terminal half-life. This increase is probably due to the fact that some of the outliers were measured at more than 20 h after the previous dose but still had detectable concentration levels. However, this change is not considered clinically relevant as the second phase dose not contribute significantly to the overall kinetics or accumulation.

DISCUSSION

Population pharmacokinetic modeling is an established method for identifying the sources of variability in drug exposure in a target population receiving clinically relevant doses of a drug.[18] Some patient or disease characteristics, e.g., weight, renal function, and FEV$_1$, may alter dose–concentration relationships. Modeling approaches have been used to characterize the pharmacokinetics of inhalation solutions for use in nebulizers or aerosols (e.g., (R)-albuterol and (S)-albuterol inhalation solutions in pediatric patients with asthma,[19] levofloxacin inhalation solution for patients with CF).[20]

Systemic C_{max} and C_{trough} of tobramycin above 12 and 2 µg/ml, respectively, are associated with higher risk of nephrotoxicity and ototoxicity in CF patients and should be carefully monitored.[6] A population pharmacokinetic model was therefore developed to describe the tobramycin serum concentration–time course in CF patients following inhalation of TIP, which demonstrates that systemic levels of tobramycin via TIP inhalation are well below the known toxicity levels associated with nephrotoxicity and ototoxicity. Although the systemic C_{max} of 12 µg/ml is a general guidance for intravenous tobramycin, the recommended C_{max} for CF patients are similar (8–12 µg/ml) for t.i.d. tobramycin regimen; no specific recommended C_{max} value is available for q.d. regimen.[21] Therefore,

for conservative estimation of toxicity risk, a 12-µg/ml threshold was used for C_{max} in this study.

In the present study, BMI and FEV$_1$% predicted were found to be statistically significant covariates for V_d/F. Previously, patients with CF and low BMI measurements have been found to be six times more likely to have severely impaired FEV$_1$ values (<40% predicted) than those with a "normal" BMI.[22] In addition, low FEV$_1$% predicted associated with worsening lung disease in CF has been shown to increase total lung deposition of aerosols, mainly to the central airways and areas of obstruction.[17] This would likely account for the increased V_d/F observed with decreasing FEV$_1$% predicted in this population. Despite this effect on V_d/F, however, model-based simulation showed that neither C_{max} nor C_{trough} were substantially affected by change in BMI or FEV$_1$% predicted at baseline. Across the range of baseline BMI or FEV$_1$% predicted values assessed, the predicted mean C_{max} and C_{trough} values were low relative to the maximum systemic concentrations recommended for avoidance of tobramycin-associated toxicity.[6] C_{max} and C_{trough} values were at least 7.5- and 5-fold lower, respectively, than the maximum recommended C_{max} (12 µg/ml) and C_{trough} (2 µg/ml).[6] Hence, the effect of BMI and FEV$_1$% predicted at baseline on the concentration of tobramycin after administration of TIP 112 mg b.i.d. are not expected to be clinically relevant with regard to systemic toxicity.

After adjustment for the effect of BMI, there was no influence of age on the pharmacokinetics of tobramycin. These findings are consistent with the results of previous studies[23,24] or of other inhaled therapies and consistent with the concept that lung dose increases with age but is proportional to body size. Thus, TIP can be dosed at fixed doses (with no dose adjustment necessary) in adults and children above 6 years of age, with an acceptable safety margin due to low systemic exposure. Although tobramycin is known to be eliminated via the renal route and its clearance is dependent on renal function, the current population pharmacokinetic model indicated that creatinine clearance did not affect the pharmacokinetics of tobramycin after TIP administration. This is likely due to the fact that only patients with normal renal function or mild renal impairment were included in the study population (minimum creatinine clearance was 63.9 ml/min in the pharmacokinetic population). Similar to TIS, monitoring of serum tobramycin concentration is recommended if TIP is used in patients with renal dysfunction.

We recognize that different ways of handling concentrations that are below the lower limit of quantification (LLOQ) may influence the final model.[25,26] Common ways of handling data below the limit of quantification (BLOQ) include excluding them from the model, replacing them with a value of LLOQ/2, replacing them with a value of zero, and estimating likelihood of BLOQ and all other observations by maximum likelihood estimation method, to name a few.[25] Although we acknowledge that a potential issue in excluding the BLOQ observations may create bias in the model fit because the lower remaining observations are selectively too high,[25] the extent of such bias is variable and would depend on the structural model and relative proportion of BLOQ data.[27] For example, Xu *et al.*[27] demonstrated that ignoring ≤10% of BLOQ data has minimal impact on the model parameter estimates for one-compartment models, whereas more pronounced impact on the estimation of peripheral compartment parameters (V_p,

Q, and their associated IIV) becomes apparent when the percentage of BLOQ data is >5%, but with limited impact on precision of estimates on the central parameters such as CL, V_d, and k_a. Considering that the assay for tobramycin concentrations is sensitive, with a LLOQ of 0.05 µg/ml, the BLOQ values were low in incidence (6.8%) and observed at times well into the terminal clearance phase, and because the terminal phase contributes minimally to the relevant exposure metrics, excluding the BLOQ concentrations from the model is not expected to affect the final model significantly.

Population pharmacokinetic modeling plays an important role in drug development, enabling the investigation of factors that may explain some of the variability of the data and leading to a better prediction of clinical response in individual patients,[18,28] even when sampling is minimal. Two previous population pharmacokinetic modeling studies of inhaled products have looked at the variability of pharmacokinetic parameters caused by demographic variables.[20,29] The population pharmacokinetic model of an inhalation solution of levofloxacin for use via a nebulizer in patients with CF showed overlap in pharmacokinetic exposure with each dose of levofloxacin, representing interpatient variability,[20] whereas modeling of an inhaled powder form of zanamivir for patients with influenza showed that demographic variables or levels of infection did not affect the variability of pharmacokinetic parameters.[29] Here we have developed a population pharmacokinetic model to describe the serum concentration–time course of tobramycin in CF patients following inhalation of TIP. Our results demonstrate a statistically significant effect of BMI and FEV$_1$% predicted on V_d/F but no clinically significant impact on tobramycin C_{max} or C_{trough} in CF patients.

METHODS

Included studies

Serum concentration data for TIP from three clinical studies (one phase I (TPI001) and two phase III studies (C2301 and C2302)) were pooled to generate a pharmacokinetic analysis data set for modeling (**Table 3**).[9,15,16] After exclusion of missing data, 662 concentration–time observations from 139 CF patients dosed with 28, 56, 84, or 112 mg single dose, as well as 112 mg b.i.d. multiple doses, were included.

Missing and outlying data

Missing sampling time was imputed from the corresponding dose–time course if the study protocol specified the sampling time schedule. Missing values for FEV$_1$% predicted were replaced with the most recent previous value. In total, 28/1,031 tobramycin concentration observations were omitted from analysis due to missing sampling time or dose information.

In study C2301, 72 tobramycin concentrations from 21 subjects did not have FEV$_1$% assessment information. All 72 concentration records were excluded from the analysis. After the above exclusions, there were a total of 931 concentration records left in the analysis data set, with 6.8% of them (63 concentrations) below LLOQ. After exclusion of concentrations below LLOQ and outlying concentrations identified from the original report, there were 859 concentrations in the analysis data set before exclusion of samples beyond validated stability storage period in study C2302. After exclusion of affected C2302 samples, there were 662 concentration values from 139 subjects in the population pharmacokinetic analysis data set.

Outlying data were identified by visual inspection and excluded from the analysis. Four subjects from study TPI001 were excluded, either because they did not receive the dose or because they received less than a full dose of tobramycin. Three outliers in study C2301 and six outliers in study C2302 (incorrect sample dates/times or discrepancy between elapsed time and visit) were excluded.

Data analysis and modeling methods

The model was developed using the nonlinear mixed-effects modeling (NONMEM) software program NONMEM VI Version 2 (Reagents of the University of California, San Francisco, CA) Standard and the first-order conditional estimation method with interaction (NONMEM coding provided in Supplementary Appendix). The change in the NONMEM objective function

Table 3 Summary of included studies

Study number	Design	TIP doses	PK sampling times	Dose regimen	Number of enrolled patients with PK observation
TPI001, ref. 8	Randomized, open-label, active-controlled, sequential cohort	28 mg (2 × 14 mg) 56 mg (4 × 14 mg) 56 mg (2 × 28 mg) 84 mg (3 × 28 mg) 112 mg (4 × 28 mg)	Predose; 0.5, 1, 2, 4, 8, and 12 h postdose	Single dose	TIP: 64 CF patients Control (TIS): 20 CF patients

C2301, ref. 15	Multicenter, randomized, placebo-controlled, three-cycle, two-arm study	112 mg (4 × 28 mg)	Sparse sampling; predose; and 1 h postdose at weeks 1, 5, 17, and 21	Multiple doses, b.i.d. for 28 days (per cycle)	Cycle 1:
					  TIP: 41 CF patients
					  Control (placebo): 42 CF patients
					Cycles 2 and 3: All patients received TIP. There were 76 patients with TIP PK observations in cycle 2

C2302, ref. 14	Multicenter, randomized, open-label, three-cycle, two-arm, active-controlled study	112 mg (4 × 28 mg)	Four serum samples: predose, one sample between 0 and 2 h, and two samples between 2 and 5 h postdose at weeks 1, 5, 17, and 21	Multiple doses, b.i.d. for 28 days (per cycle)	TIP: 13 CF patients with PK observations Control (TIS): 6 CF patients with PK observations

Week 1 corresponds to day 1 (first dose taken at site) of cycle 1, week 5—day 28 of cycle 1, week 17—day 1 of cycle 3, week 21—day 28 of cycle 3.
CF, cystic fibrosis; PK, pharmacokinetics; TIP, tobramycin inhalation powder; TIS, tobramycin inhalation solution.

value and goodness-of-fit plots were used to guide the model development. One- and two-compartment disposition models with first-order absorption and first-order elimination were evaluated based on the previous knowledge of the pharmacokinetic properties of the compound from a single-dose study.[9] IIV was assessed on all structural model parameters, as was interoccasion variability (the occasion variable was derived based on the visit number: it was assumed that concentrations measured at different study visits represented distinct occasions). The pharmacokinetic parameters (k_a, volumes, and clearances) were assumed to be log-normally distributed around the population mean, but the random effects to describe both IIV and interoccasion variability were assumed to be distributed with a mean of zero. The effects of covariates (age, BMI, creatinine clearance, sex, $FEV_1\%$ predicted at baseline, and weight) on the pharmacokinetic model were investigated once an adequate structural and stochastic model had been finalized. Age was categorized into three groups: 6–11, 12–17, and ≥18 years. Each covariate was tested individually against the key structural model parameters k_a, V_d/F, and CL/F in a stepwise fashion (forward inclusion). After each step, the strongest covariate relationship was incorporated into the model, and the others sequentially and individually retested, until no further covariates could be added with statistical significance. The inclusion of a covariate term was considered statistically significant if it produced a difference of 3.84 ($P = 0.05$, given a single degree of freedom) in the NONMEM objective function value during the forward inclusion and if it produced an objective function value difference of 6.64 ($P = 0.01$, given a single degree of freedom) during the backward elimination. A combination of proportional and additive error models was used. The visual predictive check was used to provide an assessment of the model's ability to describe the data and the model's suitability for simulation. For the covariates identified after the stepwise process, 1,000 simulations were performed to evaluate their effect on the drug exposure at steady state using the following metrics: C_{max} and C_{trough}. The sensitivity of each metric to a given covariate was evaluated by simulation using different percentile values of the covariate distribution in the pharmacokinetic population, while keeping values of the other identified covariates in the model fixed at their median values in the pharmacokinetic population. These simulations were undertaken using the population parameter estimates from the final model and the IIV values of pharmacokinetic parameters, and they yielded the metrics of interest and their 95% predictive intervals. Further details of the modeling methods can be found in the **Supplementary Appendix**.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

✓ Studies have shown nebulized tobramycin to be well tolerated and efficacious within certain dose concentrations, but the nebulization process (setup, administration, and cleaning) adds considerably to the burden of treatment for patients with CF. TIP was developed to reduce this burden while maintaining efficacy and tolerability relative to tobramycin delivered via nebulizer.

WHAT QUESTION DID THIS STUDY ADDRESS?

✓ A population pharmacokinetic model was developed to describe the tobramycin serum concentration–time course and evaluate the influence of covariates on systemic exposure following inhalation of TIP in CF patients.

WHAT THIS STUDY ADDS TO OUR KNOWLEDGE

✓ Within a population of CF patients with varied baseline demographics, no dose adjustment of TIP is expected irrespective of BMI, lung function, age, creatinine clearance, sex, or weight of the patient.

HOW THIS MIGHT CHANGE CLINICAL PHARMACOLOGY AND THERAPEUTICS

✓ No covariates were found to have a clinically significant effect on the pharmacokinetic parameters of TIP, suggesting that TIP can be used without the need for dose adjustment by demographics.

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