

ORIGINAL ARTICLE

Pharmacokinetics and safety of tobramycin nebulization with the I-neb and PARI-LC Plus in children with cystic fibrosis: A randomized, crossover study

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Aims: We aimed to compare the pharmacokinetics (PK) and safety profile of tobramycin inhalation solution (TIS) using the I-neb device to the standard PARI-LC Plus nebulizer in children with cystic fibrosis.

Methods: A randomized, open-label, crossover study was performed. In 2 separate study visits, blood samples from 22 children were collected following TIS nebulization with I-neb (75 mg) and PARI-LC Plus (300 mg). Study visits were separated by 1 month, in which 1 of the study nebulizers was used twice daily. Tobramycin PK for both nebulizers was established using measured tobramycin concentrations and Bayesian PK modelling software. Hearing and renal function tests were performed to test for aminoglycoside associated toxicity. In addition to standard estimated glomerular filtration rate values, biomarkers for tubular injury (KIM-1 and NAG) were measured. Patient and nebulizer satisfaction were assessed.

Results: Inhalations were well tolerated and serum trough concentrations below the predefined toxic limit were reached with no significant differences in PK parameters between nebulizers. Results of audiometry and estimated glomerular filtration rate revealed no abnormalities. However, increased urinary NAG/creatinine ratios at visit 2 for both nebulizers suggest TIS-induced subclinical tubular kidney injury. Nebulization time was 50% shorter and patient satisfaction was significantly higher with the I-neb.

Conclusions: Nebulization of 75 mg TIS with the I-neb in children with cystic fibrosis resulted in comparable systemic exposure to 300 mg TIS with the PARI-LC Plus and was well tolerated and preferred over the PARI-LC Plus. Long-term safety of TIS nebulization should be monitored clinically, especially regarding the effects on tubular kidney injury.

The authors confirm that the PI for this paper is Dr H.M. Janssens, MD, PhD, and that she had direct clinical responsibility for patients. Dutch trial register number NTR4216

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KEYWORDS

children, Cystic fibrosis, inhaled antibiotics, mesh nebulizer, pharmacokinetics

1 | INTRODUCTION

Survival of patients with cystic fibrosis (CF) has improved considerably over recent decades, because of better and new treatments including the use of nebulized antipseudomonal antibiotics.^{1,2} *Pseudomonas aeruginosa* (*Pa*) is the most common pathogen in CF lung disease and *Pa* acquisition is associated with deterioration in lung function.³ A 1 month-on, 1 month-off regimen of twice daily tobramycin inhalation solution (TIS) by nebulization is standard-of-care in the treatment of *Pa* lung infection.³ However, TIS administration with the recommended PARI-LC Plus nebulizer (PARI GmbH, Starnberg, Germany) is time-consuming and requires the use of a noisy and large compressor, for which the presence of an external power source is required. Therefore, treatment compliance and quality of inhalation are often low⁴ and this may impair the beneficial effects of therapy. Moreover, standard nebulizer therapy is very inefficient. A lung deposition of only 5–15% of the initial dose can be achieved and the administered lung dose is highly variable and dependent upon the patient's breathing pattern.^{5,6}

More convenient alternatives have been introduced in recent years, such as tobramycin inhalation powder and mesh or smart nebulizers. The I-neb (Philips Respironics, Chichester, UK) is a small, silent and battery-powered mesh nebulizer that uses adaptive aerosol delivery for a reproducible dosimetric output during inspiration.⁷ A lung deposition of 45–75% of the initial dose can be reached, in a shorter nebulization time compared to conventional nebulization.^{8–11}

Usage of the I-neb can reduce treatment burden and this nebulizer is already widely used in adults and increasingly in children.^{12–15} However, the I-neb has not been tested in children and little is known about pharmacokinetics (PK) and safety of tobramycin delivered with this nebulizer. This lack of knowledge is especially a risk with drugs such as tobramycin, where high trough concentrations and cumulative exposure can lead to nephro- and ototoxicity.^{16,17} Dose recommendations are based on *in vitro* tests and few *in vivo* data in adults.^{9,18}

The I-neb is registered for use with inhaled colistin in the UK, but is increasingly used to deliver TIS off-label in children. Therefore, it is important to investigate whether the recommended dose for tobramycin inhalation using the I-neb is correct in children and if this combination can be used safely in routine paediatric CF care. While the intent of this study is not to recommend that patients use the I-neb as an off-label device to inhale TIS, the authors felt an obligation to generate these data to ensure that the expansion of this practice in the real-world setting is safe for children using TIS. We hypothesized that recommended doses using the I-neb for TIS inhalation might be too high for the younger children, which may give rise to a risk for toxicity. Therefore, we designed a study in children with CF aged 6–18 years with the primary aim to compare PK and systemic

What is already known about this subject

- Tobramycin inhalation solution (TIS) administration with the recommended PARI-LC Plus nebulizer is effective for treatment of *Pseudomonas aeruginosa* infection in children with cystic fibrosis (CF).
- Usage of the I-neb can reduce treatment burden, because this nebulizer is considerably faster, more efficient and more convenient to use.
- The correct dose and safety of TIS inhalation with the I-neb should be investigated before using this off-label combination in routine paediatric CF care.

What this study adds

- Nebulization of 75 mg TIS with the I-neb in children with CF resulted in comparable systemic exposure and safety to 300 mg TIS with the PARI-LC Plus.
- Nebulization time was significantly shortened with the I-neb and the nebulizer was well tolerated and preferred over the PARI-LC Plus.
- Our results suggest that the I-neb nebulizer in combination with 75 mg TIS can be used safely in routine paediatric CF care. Long-term safety, especially renal toxicity, should be monitored clinically, regardless of the nebulizer.

exposure of TIS inhalation between the I-neb and PARI-LC Plus nebulizer including an age subanalysis. As secondary aims we assessed patient satisfaction and short-term safety at 1 month using standard testing and more sensitive biomarkers for aminoglycoside toxicity.

2 | METHODS

2.1 | Study population

The study was performed at 3 specialized CF centres in The Netherlands: Haga Teaching Hospital-Juliana Children's Hospital in The Hague, Erasmus Medical Center-Sophia Children's Hospital in Rotterdam and University Medical Center Utrecht-Wilhelmina Children's Hospital in Utrecht. Children aged 6–18 years with a genetically confirmed diagnosis of CF and with an early or intermittent *Pa* infection requiring eradication with TIS or with a chronic *Pa* colonization requiring maintenance TIS (month-on, month-off) were eligible for inclusion in this study. Acute exacerbation of pulmonary infection requiring intravenous treatment during study visits, intravenous tobramycin within 1

month prior to or during study visits, start of nephro- or ototoxic drugs (predetermined by the investigators) within 1 month prior to start or during the study, impaired renal function (estimated glomerular filtration rate [eGFR] < 60 mL/min), use of loop diuretics and pregnancy or lactation were exclusion criteria. Patients already on maintenance TIS therapy entered the study following their month-off period.

The study was approved by the local ethics committee (METC Erasmus Medical Center, The Netherlands) and the Central Committee on Research Involving Human Subjects (The Hague, The Netherlands) and was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice. Full informed written consent was obtained from all patients aged 12 years and older and from both parents or legal representatives of all patients.

2.2 | Study design

In a multicentre, randomized, open-label, crossover study, nebulization of TIS with the I-neb was compared to the conventional PARI-LC Plus nebulizer in children with CF. The primary endpoint was systemic bioavailability of inhaled tobramycin, defined as serum tobramycin area under the concentration–time curve from 0 to 24 hours (AUC_{0-24h}) following a supervised inhalation with both nebulizers on separate days. A sample size of 22 patients was required to demonstrate bioequivalence according to the EMA guideline ($\alpha = 0.05$ and 80% power).¹⁹

Study duration for each patient was 1 month and consisted of 2 study visits at the CF centre. Patients were randomly assigned to treatment arm A or B. In treatment arm A, patients performed a supervised single tobramycin inhalation with the I-neb at study visit 1. Blood samples for tobramycin analysis were collected predose and up to 24 hours postnebulization and no second dose was inhaled during this period. Visit 1 was followed by a 28-days home treatment period during which patients inhaled tobramycin twice daily with the I-neb. During the second study visit, these patients performed a supervised inhalation with the PARI-LC Plus. The home treatment period and study visit 2 was separated by a wash-out period of 2 days for complete tobramycin clearance. Patients from treatment arm B started with a PARI-LC Plus inhalation at visit 1, inhaled tobramycin twice daily for 28 days with the PARI-LC Plus and performed a supervised tobramycin inhalation with the I-neb at visit 2. Randomization was stratified for age (6–11 and 12–18 years) and centre (randomized block design).

During the visits blood, urine, and sputum or throat swab samples were collected, spirometry and hearing tests were performed and questionnaires were filled out by the children or their parents. Degree of symptoms regarding cough, sputum production, exercise tolerance, fatigue and disturbed sleep was also scored. Test protocols were equalized as much as possible for the 3 participating CF centres regarding equipment and analysis.

Compliance was determined by counting the number of returned TIS ampoules.

2.2.1 | Protocol amendment

Following inclusion of patient 14, a protocol amendment was written. The investigators noticed that newer nebulizers, such as the I-neb, were increasingly prescribed and preferred by patients, and that the standard nebulizer PARI-LC Plus was less used in daily practice. As patients did not want to run the risk to be assigned to the PARI-LC Plus treatment arm, inclusion rate decreased. From inclusion number 15 onwards patients were assigned to the I-neb during the 28-days treatment period at home. As a consequence, more safety data were collected for the I-neb and relatively fewer for the PARI-LC Plus. Since patients still performed a supervised inhalation with both nebulizers, the primary endpoint of the study did not change.

2.3 | Nebulization

TIS (Bramitob, 300 mg = 4 mL, Chiesi Pharmaceuticals B.V., Rijswijk, The Netherlands) was used as the study medication. Bramitob is licensed for use with the PARI-LC Plus with a recommended dose of twice daily 300 mg. Dose finding studies for tobramycin inhalation with the I-neb are lacking. However, a study in healthy persons investigating deposition of normal saline with the I-neb showed a 4–5 times higher lung deposition compared to what is known for the PARI-LC Plus.⁹ Also, an *in vitro* test showed that inhalation with 75 mg of Bramitob resulted in the same predicted lung dose as 300 mg with the PARI-LC Plus.¹⁸ Therefore, patients in this study inhaled 75 mg TIS with the I-neb and 300 mg with the PARI-LC Plus nebulizer.

The PARI-LC Plus is a breath-enhanced jet nebulizer that was combined with the Portaneb compressor (Philips Respironics, Chichester, UK). The nebulizer was filled with 4 mL Bramitob and patients inhaled until sputtering of the device, according to the manufacturer information. The I-neb is a vibrating mesh nebulizer with adaptive aerosol delivery technology that constantly monitors the patient's breathing pattern and that times the optimal moment for aerosol release during inspiration.⁷ TIS was administered with the I-neb in the target inhalation mode, which guides the patients to inhale slowly and deeply for an optimal lung deposition. Patients inhaled until the device indicated that the full dose was administered. Since there were no medication chambers of 1 mL commercially available, patients inhaled 0.5 mL Bramitob (violet cup) twice per inhalation session in order to inhale a total dose of 75 mg. The remaining 3 mL of each ampoule was thrown away and not used for further administrations.

Nebulizer-naïve patients were trained how to use and clean the nebulizer prior to dosing. No active compounds were inhaled during these training sessions. During the study visits, patients performed a supervised inhalation with the allocated nebulizer. No additional inhalations during this day were performed to allow for PK measurements during 24 hours. The 28-days treatment period at home started the day after visit 1 and patients inhaled TIS twice daily according to standard treatment protocol. The second study visit was scheduled within 1–3 days of the last home inhalation.

2.4 | PK

For tobramycin monitoring, dried blood spots using a finger prick were collected before ($t = 0$) and 15, 45 and 90 minutes after completion of the supervised inhalation. Samples were collected by patients themselves at home 3, 6 and 24 hours after inhalation.²⁰ Careful instruction was given to clean hands and fingers before blood was taken. Tobramycin was measured in the dried blood spots using a validated liquid chromatography–tandem mass spectrometry method and individual PK parameters were calculated and assimilated with patient tobramycin serum concentrations using Bayesian modelling software (MW-Pharm version 3.60, Mediware, Groningen, The Netherlands) equipped with a CF-based 2-compartment open population PK model with elimination from the central compartment.¹¹ Samples from all centres were measured in the same laboratory to minimize interlaboratory error. The following parameters were calculated: area under the concentration–time curve from 0 to 24 hours (AUC_{0-24h}) as measure for exposure, maximum serum concentration (C_{max}), serum concentration 12 and 24 hours after nebulization (C_{trough}) and time to C_{max} (T_{max}). The bioavailability of TIS with the I-neb relative to the PARI-LC Plus (F_{rel}) was calculated with the formula: $F_{rel} = (AUC_{0-24h(I-neb)} / AUC_{0-24h(PARI-LC Plus)}) \times (Dose_{(PARI-LC Plus)} / Dose_{(I-neb)})$.

2.5 | Age dependency, safety and patient satisfaction

Secondary endpoints included: differences in AUC_{0-24h} between age groups 6–11 and 12–18 years (*pharmacokinetics*); trough concentrations, change in renal and hearing function after 1 month inhalation and change in forced expiratory volume in the first second (FEV_1) before and after supervised inhalations (*safety*); quality of life, adverse events, tolerability, nebulization time and nebulizer satisfaction (*patient satisfaction*). For an extensive method description about the secondary endpoints, see Appendix S1.

2.5.1 | Renal toxicity

Estimated glomerular filtration rate based on serum creatinine (eGFR) is the standard clinical measure to assess and monitor renal function. However, the eGFR is considered to be an insensitive marker for acute kidney injury (AKI), because changes in serum creatinine are delayed in time and at least 25–50% of the functional nephron capacity has to be lost before this parameter decreases significantly.²¹ Furthermore, serum creatinine is a marker for glomerular filtration and not for tubular function. Although the clinical relevance of kidney injury biomarkers for (long-term) renal damage is yet unknown, urinary KIM-1 (kidney injury molecule-1) and NAG (N-acetyl- β -D-glucosaminidase) were measured as well to determine subclinical tubular kidney injury.

2.6 | Statistical analysis

Statistical analysis was performed with SPSS version 17.0 (PASW Statistics, IBM Corporation, Armonk, NY, USA). P -values $< .05$ were considered to be statistically significant. A mixed linear model with age group and study visit as fixed factors, sex, age, Pa infection (acute/chronic) and nebulizer experience (yes/no) as covariates, patient and CF centre as random factors was used to estimate the effect of the nebulizer on PK parameters and nebulization time. In this model data were first evaluated for the absence of a possible order effect (nebulizer*study visit interaction). Paired t -tests were used to compare differences in patient characteristics baseline values between study visits and to evaluate the effect of 28 days of TIS nebulization with the allocated nebulizer on AKI biomarker/creatinine ratio. Independent t -tests were used to test for differences in PK, safety and patient satisfaction parameters between nebulizers and between age groups. Logarithmic transformation or non-parametric tests (Wilcoxon signed ranks test, Mann–Whitney U test) were used when data were not normally distributed or in case of unequal variances. Possible correlations between PK and, respectively, age, weight, FEV_1 and eGFR and correlations between AKI biomarker/creatinine ratio and, respectively, PK age, sex and eGFR were investigated using the Spearman's correlation and Mann–Whitney U test. The guideline on the investigation of bioequivalence¹⁹ from the committee for medicinal products for human use was used to provide a statement about the bioequivalence of TIS nebulization between the 2 nebulizers. In accordance with this guideline, C_{max} and AUC_{0-24h} were compared using a general linear model in order to assess equivalence.

3 | RESULTS

3.1 | Study population

Twenty-two children with CF with a median age of 11 years were included in the study: 6 patients in The Hague, 5 in Rotterdam and 11 in Utrecht. All patients completed PK data collection for both nebulizers. For the home treatment period, 6 patients used the PARI-LC Plus and 16 patients the I-neb nebulizer. Table 1 reports patient characteristics baseline values (visit 1). There were no significant differences in renal or lung function between study visits. Patient characteristics were comparable for the 2 treatment arms. Patients also had similar degree of symptoms regarding cough, sputum production, exercise tolerance, fatigue and disturbed sleep at visits 1 and 2. Compliance rate was comparable between treatment arms with a median value of 96% (range 55–100%).

Safety data from patients 4 and 8 regarding renal and ototoxicity could not be evaluated, since both patients were unable to complete the 28-days home treatment period with the allocated nebulizer: patient 4 changed from PARI-LC Plus to I-neb on day 21 due to side effects and patient 8 switched to intravenous tobramycin therapy on day 22 for treatment of pulmonary exacerbation. Both patients were

TABLE 1 Patient characteristics baseline values

n = 22	Baseline (visit 1)
Male ^d	11 (50)
Age (group 6–11 years; n = 12) ^e	9 (6–11)
Age (group 12–18 years; n = 10) ^e	13 (13–17)
Height (cm) ^e	149 (121–178)
Weight (kg) ^e	39 (22–64)
BMI ^e	18 (15–21)
eGFR (mL/min) ^e	173 (90–250)
FEV1 (% predicted) ^e	89 (57–109)
Patients on maintenance TIS ^d	9 (41)
Study nebulizer equals own device (I-neb arm) ^d	9 (56)
Study nebulizer equals own device (PARI-LC Plus arm) ^d	2 (33)

Differences between treatment arms were not significant.

^aBMI = body mass index; eGFR = estimated glomerular filtration rate

^b(Schwartz formula); FEV1 = forced expiratory volume in the first second;

^cTIS = tobramycin inhalation solution.

^dData are presented as number (percentage).

^eData are presented as median (range).

included in the PK analysis, as well as in the evaluation of systemic toxicity and bronchospasm following the supervised inhalations and patient satisfaction.

3.2 | Pharmacokinetics

Serum concentration–time profiles are shown in Figure 1 (see Supplementary Table S1 for details). All tobramycin serum concentrations were 0 mg/L predose at both visits. No significant differences were found between I-neb and PARI-LC Plus TIS nebulization in the

administered doses and treatments were considered to be bioequivalent (see Table 2). Mean AUC_{0-24h} , C_{max} , $C_{trough12h}$, $C_{trough24h}$ and T_{max} were 12.27 h*mg/L, 2.07 mg/L, 0.25 mg/L, 0.10 mg/L and 0.57 hours for the I-neb and 11.21 h*mg/L, 1.93 mg/L, 0.25 mg/L, 0.13 mg/L and 0.52 hours for the PARI-LC Plus, respectively. Variability in PK was comparable between nebulizers with parameter coefficients of variance ranging from 65 to 109% for the I-neb and 65 to 133% for the PARI-LC Plus. In general, patients with high systemic exposure for the I-neb also had relatively high systemic exposure with the PARI-LC Plus.

3.2.1 | Age dependency and correlations

There were also no significant differences between nebulizers for each age group, except for a higher T_{max} for the I-neb in patients 6–11 years ($P = .043$, see Figure 2). Differences in PK parameters between the 2 age groups were not statistically significant, except for T_{max} for the PARI-LC Plus whereby older patients reached C_{max} significantly later compared to the younger ones ($P = .041$, see Figure 2).

No significant interaction effects between study visit day and nebulizer or between age group and nebulizer were found. Regression analysis revealed no correlations between PK parameters and the child's age, weight, FEV₁ or eGFR values.

3.3 | Safety and patient satisfaction

Results of audiometry and eGFR revealed no abnormalities. Increased urinary NAG/creatinine ratios at visit 2 for both nebulizers suggest, however, that TIS-induced subclinical tubular kidney injury (see Table 3). Nebulization time was 50% shorter and patient satisfaction significantly higher with the I-neb (see Table 4). For full results of the secondary endpoints, see Appendix S2.

FIGURE 1 Mean tobramycin serum concentrations over time following supervised tobramycin inhalation solution nebulization with the I-neb (75 mg) and the PARI-LC Plus (300 mg). Error bars represent the 95% confidence intervals. Tobramycin was measured at $t = 0$, $t = 15$ min, $t = 45$ min, $t = 90$ min, $t = 3$ h, $t = 6$ h and 24 h; serum concentrations at $t = 12$ h were estimated using Bayesian pharmacokinetic modelling

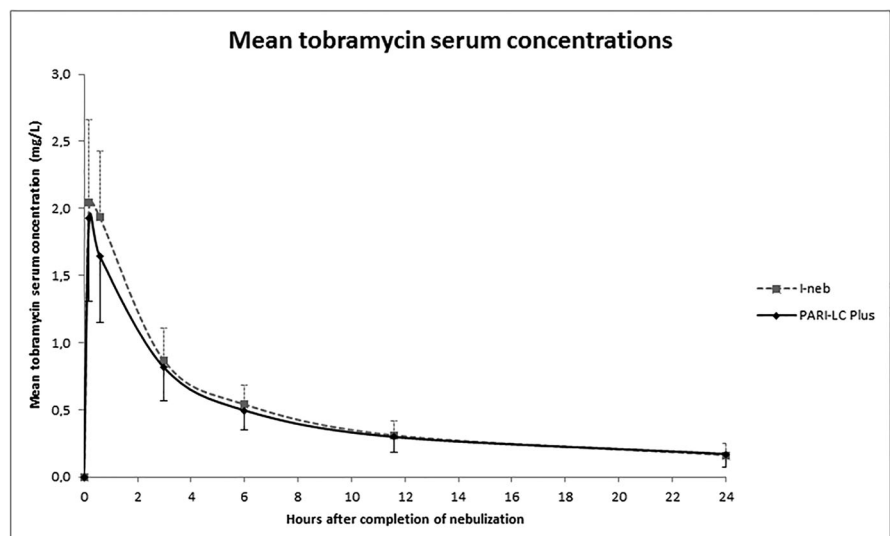


TABLE 2 Bioequivalence

	Geometric mean		Ratio geometric mean (90% CI) I-neb vs PARI-LC Plus	Bioequivalent? ^a
	I-neb	PARI-LC Plus		
Study population <i>n</i> = 22				
Subgroup 6–11 years <i>n</i> = 12				
Subgroup 12–18 years <i>n</i> = 10				
C_{\max} (mg/L) study population	1.70	1.61	1.06 (0.76–1.47)	Yes
6–11 y	1.43	1.60	0.89 (0.52–1.55)	Yes
12–18 y	2.10	1.62	1.29 (0.92–1.82)	Yes
AUC_{0-24} h (h*mg/L) study population	10.19	9.32	1.09 (0.86–1.39)	Yes
6–11 years	9.30	9.37	0.99 (0.66–1.50)	Yes
12–18 years	11.37	9.26	1.23 (0.97–1.56)	Yes

Bioequivalence of TIS nebulization comparing I-neb (75 mg) and PARI-LC Plus (300 mg). CI = confidence interval; C_{\max} = maximum serum concentration; AUC_{0-24h} = area under the concentration–time curve from 0 to 24 h.

^aBioequivalence is accepted when the 90% CI for the geometric mean ratio of a parameter does not fall completely within the acceptance interval of 0.80–1.25.

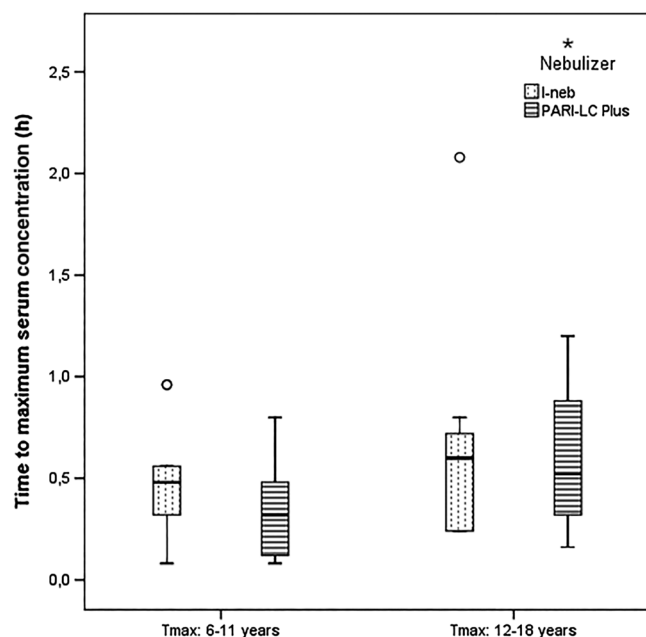


FIGURE 2 Time to maximum serum concentration (T_{\max}) following tobramycin inhalation solution nebulization, reported per age group. In patients 6–11 years: T_{\max} was significantly higher for the I-neb compared to the PARI-LC Plus ($P = .043$); no difference between nebulizers for age group 12–18 years ($P = .764$). When comparing age groups: older patients had a significantly higher T_{\max} compared to younger patients for the PARI-LC Plus nebulizer only ($P = .041$)

4 | DISCUSSION

This is the first study in children comparing the PK for TIS using the I-neb and PARI-LC Plus nebulizer, also taking safety and patient satisfaction into account. We found that nebulization of 75 mg TIS with the I-neb in children with CF resulted in comparable systemic exposure to 300 mg with the PARI-LC Plus. Overall, there were no clear clinical signs of toxicity after 1 month of TIS inhalation with either nebulizer.

TABLE 3 AKI biomarkers following 28 days of TIS nebulization

I-neb <i>n</i> = 14 PARI-LC Plus <i>n</i> = 3	Baseline	Day 30	Fold increase (over baseline)
	(visit 1)	(visit 2)	
KIM-1/creatinine ratio ($\mu\text{g/g}$) ^a			
I-neb	0.86 (0.16–3.33)	0.74 (0.17–2.05)	0.9
PARI-LC Plus	0.69 (0.26–2.16)	0.63 (0.24–1.33)	0.9
NAG/creatinine ratio (U/g) ^a			
I-neb	5.10 (1.23–37.08)	18.83 (3.80–106.67)	3.7
PARI-LC Plus	5.17 (1.81–6.02)	12.11 (8.56–39.84)	2.3
eGFR (mL/min)			
I-neb	171.4 (90.5–250.0)	157.7 (97.8–234.7)	0.9
PARI-LC Plus	175.6 (150.8–175.6)	168.6 (154.0–179.3)	1.0

Data are presented as median (range). Differences between nebulizers were not significant. AKI = acute kidney injury; KIM-1 = kidney injury molecule-1; NAG = N-acetyl- β -D-glucosaminidase; eGFR = estimated glomerular filtration rate (Schwartz formula).

^aFor patients with biomarker values below the lower limit of quantitation, a value 50% of this limit was used to calculate the ratio.

I-neb nebulization reduced nebulization time by approximately half and nebulizer satisfaction was significantly better for the I-neb.

4.1 | PK

The primary endpoint was systemic bioavailability of inhaled tobramycin, defined as serum tobramycin AUC_{0-24h} . No significant difference between nebulizers for this endpoint was found, nor for other PK parameters, and serum concentrations were in accordance with previously reported values.^{22–25} The results were found to be independent from age, weight and lung function of the child. Median F_{rel} (bioavailability of TIS with the I-neb relative to the PARI-LC Plus)

TABLE 4 Patient satisfaction

	I-neb (n = 16)	PARI-LC Plus (n = 6)	P-value
Tolerability (scale 0–10) ^a			
Coughing during nebulization	4.2 ± 2.9	4.0 ± 3.6	.860
Coughing after nebulization	3.6 ± 3.0	3.7 ± 3.1	.952
Dyspnoea during nebulization	1.3 ± 1.8	1.6 ± 0.7	.726
Dyspnoea after nebulization	1.1 ± 1.0	1.6 ± 1.4	.341
Dizziness during nebulization	0.8 ± 1.2	0.9 ± 0.8	.822
Dizziness after nebulization	0.5 ± 0.5	0.8 ± 0.7	.300
Nebulization time (min)			
Study visits ^b	13.7 ± 5.4	16.3 ± 8.2	.976
Home treatment period	8.0 ± 4.3	17.6 ± 7.4	.002
Nebulizer satisfaction (scale 0–10) ^c			
Size	9.3 ± 0.8	2.8 ± 2.3	<.001
Noisiness	9.3 ± 0.9	3.6 ± 3.2	<.001
Look	8.5 ± 1.5	5.6 ± 1.8	.001
Nebulization time	6.7 ± 2.8	2.6 ± 1.4	.003
Final grade	8.2 ± 0.9	5.5 ± 1.6	<.001
Cleaning time (min)	9.3 ± 8.2	9.2 ± 10.3	.975

Data are presented as mean ± standard deviation.

^aScale 0–10: 0 = never, 10 = always.

^bn = 22 patients for both nebulizers (supervised inhalations).

^cScale 0–10: 0 = most negative score, 10 = most positive score.

was 4.86, indicating that inhalation of 62 mg TIS with the I-neb is equivalent to standard 300 mg TIS with the PARI-LC Plus. This is in good agreement with previous (in vitro) data^{9,18} and the doses used in daily practice of 60 mg (TOBI) and 75 mg (Bramitob) as recommended by the I-neb manufacturer.

Subgroup analysis revealed no differences in PK parameters between age groups except for T_{max} , for which possible explanations can be appointed. Since subgroups were small and variability was large, clinical relevance of this finding is however uncertain and no firm conclusions can be drawn. First, in patients aged 6–11 years a higher T_{max} was found for the I-neb compared to the PARI-LC Plus. This difference can be explained by a longer nebulization time for the PARI-LC Plus (approximately 19 vs 13 minutes for the I-neb). Because sample collection started immediately *after* completion of the inhalation, sampling started earlier in the I-neb group leading to a mean difference of 6 minutes in time from start of nebulization. From the beginning of nebulization there is absorption and clearance and when 6 minutes is subtracted from the mean T_{max} , there is no significant difference. Secondly, it was found that older children (age 12–18 years) reached C_{max} significantly later compared to the younger ones when inhaling with the PARI-LC Plus. A possible explanation could be delayed absorption due to increased mucus plugging in older children. Children in the older age group using the PARI-LC Plus nebulizer had significantly lower FEV_1 values compared to the younger children using this nebulizer (median 68.8 vs 99.7% predicted,

respectively). Furthermore, there were no differences in lung function between the 2 age groups for inhalation with the I-neb, which might explain similar T_{max} for this nebulizer.

Variability in systemic exposure of inhaled antibiotics is known to be large in CF patients and was also considerable in our study. Heterogeneity in disease severity and renal function, but also age, weight and variable competence in inhalation technique of the child may contribute to this variability. However, no correlations between PK parameters and the child's age, weight, FEV_1 or eGFR values were found. Interestingly, similar coefficients of variation were calculated for the nebulizers. Because of the adaptive aerosol delivery system, a lower variability was expected with I-neb nebulization as was recently shown for another controlled-inhalation device in adults.¹¹

4.2 | Safety

The secondary aim was to assess short-term safety of 1 month of TIS. Tobramycin serum concentrations are often used as proxy for safety since high trough concentrations and cumulative exposure are related to the development of nephro- and ototoxicity. However, no clear toxic limits have been defined yet for tobramycin during chronic inhalation. Based on intravenous administration, a trough concentration below 1 mg/L is considered to be safe.²⁶ Calculated trough serum concentrations 12 hours after completion of the supervised inhalation were below toxic limits for all patients, suggesting that twice daily TIS nebulization is safe with both nebulizers.

Because of the protocol amendment most patients were assigned to the I-neb treatment (n = 14) and only few patients of the PARI-LC Plus treatment arm could be included in the audiometry analysis (n = 4) and AKI biomarker (n = 3), respectively. Consequently, reliable comparison between nebulizers regarding safety could not be made, though results seemed to be similar.

Aminoglycosides have a cochleotoxic effect and can cause irreversible hearing loss. Audiometry results showed no abnormalities for most patients, which is in accordance with results from other studies regarding TIS safety.^{16,27} Tobramycin is also known to damage the kidneys with toxic effects mainly targeted to the proximal tubule epithelial cells. The eGFR values were similar for both study visits and nebulizer groups, indicating no clinical toxic effect on the kidneys. Although the clinical relevance of kidney injury biomarkers for (long-term) renal damage is unknown, urinary KIM-1 and NAG were measured as well to determine subclinical tubular kidney injury. No data exist for KIM-1 and only few data are available in literature regarding NAG (reference) values in children with CF using TIS. One study measured NAG in urinary samples of 10 CF patients aged 2–16 years who received twice daily 300 mg TIS treatment with the eFlow nebulizer²⁸ and 2 other studies reported NAG/creatinine ratios of, respectively, 4 and 14 patients in the age range of 3–22 years receiving 40–80 mg TIS twice daily with a jet nebulizer.^{29,30} Median NAG/creatinine ratios measured in our study were in the same order of magnitude as in the studies mentioned above. However, in all

studies, variability was large and differences in nebulizer and dosing regimens hampers comparison between studies.

Interestingly, no significant differences in KIM-1/creatinine ratios between study visits were found in our study, while a recent review suggests that KIM-1 outperforms other biomarkers in preclinical and clinical studies of aminoglycoside-induced nephrotoxicity.³¹ This can be explained by the relatively high lower limit of quantitation (LLOQ) of 0.6 µg/L of our KIM-1 assay, while the median KIM-1 reference value for healthy children is expected to be around 0.410 µg/L (interquartile range 0.226–0.703 µg/L).^{32,33} Consequently, 44% of the measured KIM-1 values fell below the LLOQ leading to a less reliable calculated KIM-1/creatinine ratio, as 0.3 µg/L (50% of the LLOQ) was used for values below LLOQ.

NAG/creatinine ratios at visit 2 were increased for all patients with a median factor of 3.7 (I-neb) and 2.3 (PARI-LC Plus), suggesting early renal toxicity following 1 month of TIS nebulization for both nebulizers. Unfortunately, no other inhalation studies are available to compare our data with and the clinical relevance of the result cannot be assessed. Also, no correlations between NAG/creatinine ratio and AUC_{0–24h} were detected. As expected, the fold increase in our inhalation study is somewhat lower compared to the reported 3.4–9.2 fold increase over baseline following 2 weeks of intravenous tobramycin therapy in children with CF.^{29,34,35} A limitation of our study is the lack of follow-up data, especially regarding the reversibility of the observed NAG/creatinine ratio increase. Results from previous studies with intravenous aminoglycosides suggest that NAG values effectively return to pretreatment concentrations within 2–8 weeks after the end of therapy.^{29,34–36} Although we do not have follow-up data, we can probably see this reversibility in our study group as well, because almost all children started with a normal concentration of NAG at the start of the study, regardless of whether they were on chronic inhalation or using TIS for *Pa* eradication. However, when comparing baseline NAG/creatinine ratios, median values were twice as high for patients on chronic TIS, indicating that aminoglycoside-induced NAG increase is possibly not fully reversible. The clinical relevance of this finding is currently unknown and requires further investigation, but the findings confirm the need for regularly monitoring of renal function while a child is on chronic inhaled tobramycin. In our study group all patients requiring maintenance TIS were on a month-on, month-off regimen. However, in patients who frequently suffer from acute exacerbations or whose lung function deteriorates rapidly, a regimen of continuously inhaled tobramycin is sometimes used.³ Those patients may be even more at risk for TIS-induced renal toxicity, since there is no recovery time in an off-period.

4.3 | Patient satisfaction

Patients were more satisfied with the I-neb nebulizer. At home, patients had a 2 times shorter nebulization time with the I-neb compared to the PARI-LC Plus. However, nebulization time for the I-neb measured at the study visit was longer than the reported time at home, while no such difference was found for the PARI-LC Plus.

Possibly, more time was spent at the study visit for correct use of the I-neb, especially for I-neb naïve patients. Combined with an expected learning curve in the home treatment period, this could explain the higher nebulization time during the study visit.

4.4 | Limitations

There are several limitations to address. There is a wide degree of variation in our PK results, although this degree of variability is not unusual for inhaled drugs and is inherent to the individual inhalation technique. Furthermore, the study was not powered for the secondary aim: the safety data. Therefore, safety data were obtained in a relatively small number of patients and gathered over a period of 28 days with no follow-up. Also, because of the lack of serum sampling at day 28, possible accumulation following a regular treatment period could not be assessed. Therefore, only statements can be made about short-term safety and further research is necessary to assess long-term safety and reversibility of (subclinical) toxic effects in a larger group of patients.

Moreover, only systemic exposure and no tobramycin airway concentrations or direct lung deposition were measured and clinical efficacy outcomes were not assessed in this study. However, TIS nebulization with the PARI-LC Plus is an effective and approved treatment option for CF patients with *Pa* infection.³ It is also known that serum PK can be used well as surrogate for total lung deposition^{10,22,37–39} and that it is a better measure compared to sputum drug concentrations, which mainly reflects deposition in the large airways. Therefore, for device comparison purposes, one can translate the obtained bioequivalence with the I-neb (75 mg) compared to the PARI-LC Plus (300 mg) in this study, into an expected equivalent deposition and efficacy. We did perform *Pa* culture in sputum or throat swab samples in order to assess the success rate for eradication patients. The success rate was 100% for the PARI-LC Plus users (2 out of 2) and 75% for the patients using the I-neb (6 out of 8). This is comparable to the ELITE study where a success rate of 66% was reached with 28 days of TIS nebulization with the PARI-LC Plus.⁴⁰ Reliable comparison between nebulizers could not be made because of the small numbers (unpowered) and skewed randomization.

5 | CONCLUSION

In conclusion, this study has shown that nebulization of 75 mg TIS with the I-neb in children with CF resulted in similar systemic exposure to 300 mg TIS with the PARI-LC Plus with no clear clinical signs of toxicity after 1 month of inhalation. Therefore, our results suggest that the I-neb nebulizer in combination with 75 mg TIS can be used safely in routine paediatric CF care. No age- or weight-dependent tobramycin serum concentrations were found, hence age- or weight-based dosage adjustments are not necessary. Nebulization time was significantly shortened and a higher degree of satisfaction was

attained with the I-neb nebulizer, which may improve the level of adherence and treatment outcomes.⁴¹

Although long-term, intermittent TIS nebulization is considered to be safe and well tolerated,^{42,43} raised urinary NAG/creatinine ratios with the absence of decreased eGFR in the present study suggest TIS-induced subclinical tubular kidney injury. Therefore, this study stresses the need for carefully monitoring for toxic effects of aminoglycosides in patients on chronic TIS therapy, especially when new nebulizers are used. Also, in future TIS safety studies, the predictive value of novel AKI biomarkers such as NAG and KIM-1 must be assessed, as well as their clinical relevance for CF patients using TIS or other aminoglycosides and especially for those on continuous inhalation regimens.

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COMPETING INTERESTS

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

CONTRIBUTORS

A.J.v.V. contributed to the study design, set-up of the study, data collection, data analysis and writing of the manuscript. J.W.F.U. initiated the study, contributed to the study design and writing of the manuscript. H.G.M.H., G.A.v.Z. and B.P. contributed to the study design and writing of the manuscript. H.G.M.A., M.N. and E.C.v.d.W.

contributed to the data collection and writing of the manuscript. E. M.v.M. and D.J.T. contributed to the study design, data analysis and writing of the manuscript. H.M.J. initiated and facilitated the study, contributed to the study design, set-up of the study, data collection, data analysis and writing of the manuscript.

REFERENCES

- Heijerman H, Westerman E, Conway S, Touw D, Doring G. Inhaled medication and inhalation devices for lung disease in patients with cystic fibrosis: a European consensus. *J Cyst Fibros.* 2009;8(5): 295–315.
- Kulich M, Rosenfeld M, Goss CH, Wilmott R. Improved survival among young patients with cystic fibrosis. *J Pediatr.* 2003;142(6):631–636.
- Doring G, Flume P, Heijerman H, Elborn JS. Treatment of lung infection in patients with cystic fibrosis: current and future strategies. *J Cyst Fibros.* 2012;11(6):461–479.
- Modi AC, Lim CS, Yu N, Geller D, Wagner MH, Quittner AL. A multi-method assessment of treatment adherence for children with cystic fibrosis. *J Cyst Fibros.* 2006;5(3):177–185.
- Fischer A, Stegemann J, Scheuch G, Siekmeier R. Novel devices for individualized controlled inhalation can optimize aerosol therapy in efficacy, patient care and power of clinical trials. *Eur J Med Res.* 2009;14(Suppl 4):71–77.
- Laube BL, Janssens HM, de Jongh FH, et al. What the pulmonary specialist should know about the new inhalation therapies. *Eur Respir J.* 2011;37(6):1308–1331.
- Denyer J, Nikander K, Smith NJ. Adaptive aerosol delivery (AAD) technology. *Expert Opin Drug Deliv.* 2004;1(1):165–176.
- Haussermann S, Winnips C, Edelman J, et al. Lung deposition of alpha-proteinase inhibitor (human) (A-PI[H]) inhalation solution using two inhalation modes of the I-neb adaptive aerosol delivery (AAD) system in healthy subjects and subjects with cystic fibrosis. *J Aerosol Med Pulm Drug Deliv.* 2016;29(3):242–250.
- Nikander K, Prince I, Coughlin S, Warren S, Taylor G. Mode of breathing-tidal or slow and deep-through the I-neb adaptive aerosol delivery (AAD) system affects lung deposition of (99m)Tc-DTPA. *J Aerosol Med Pulm Drug Deliv.* 2010;23(Suppl 1):S37–S43.
- van Velzen AJ, Uges JW, Le Brun PP, Shahbabaï P, Touw DJ, Heijerman HG. The influence of breathing mode on tobramycin serum levels using the I-neb AAD system in adults with cystic fibrosis. *J Cyst Fibros.* 2015;14(6):748–754.
- van Velzen AJ, Bos AC, Touw DJ, Tiddens HA, Heijerman HG, Janssens HM. Pharmacokinetics and tolerability of once daily double dose tobramycin inhalation in cystic fibrosis using controlled and conventional nebulization. *J Aerosol Med Pulm Drug Deliv.* 2016;29(3):273–280.
- Ball R, Southern KW, McCormack P, Duff AJ, Brownlee KG, McNamara PS. Adherence to nebulised therapies in adolescents with cystic fibrosis is best on week-days during school term-time. *J Cyst Fibros.* 2013;12(5):440–444.
- McCormack P, McNamara PS, Southern KW. A randomised controlled trial of breathing modes for adaptive aerosol delivery in children with cystic fibrosis. *J Cyst Fibros.* 2011;10(5):343–349.
- McCormack P, Southern KW, McNamara PS. New nebulizer technology to monitor adherence and nebulizer performance in cystic fibrosis. *J Aerosol Med Pulm Drug Deliv.* 2012;25(6):307–309.
- McNamara PS, McCormack P, McDonald AJ, Heaf L, Southern KW. Open adherence monitoring using routine data download from an adaptive aerosol delivery nebuliser in children with cystic fibrosis. *J Cyst Fibros.* 2009;8(4):258–263.

16. Hennig S, McKay K, Vidmar S, et al. Safety of inhaled (Tobi(R)) and intravenous tobramycin in young children with cystic fibrosis. *J Cyst Fibros.* 2014;13(4):428–434.
17. Rodman DP, Maxwell AJ, McKnight JT. Extended dosage intervals for aminoglycosides. *Am J Hosp Pharm.* 1994;51(16):2016–2021.
18. Respironics Respiratory Drug Delivery (UK). Technical Note: Delivery of Tobramycin using the I-neb AAD System in Target Inhalation Mode. 2012.
19. European Medicines Agency (EMA) and committee for medicinal products for human use (CHMP). Guideline on the investigation of bio-equivalence. London. Website: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/01/WC500070039.pdf. Accessed 20 January 2010.
20. Wilhelm AJ, den Burger JC, Swart EL. Therapeutic drug monitoring by dried blood spot: progress to date and future directions. *Clin Pharmacokinet.* 2014;53(11):961–973.
21. Askenazi DJ, Ambalavanan N, Goldstein SL. Acute kidney injury in critically ill newborns: what do we know? What do we need to learn? *Pediatr Nephrol.* 2009;24(2):265–274.
22. Geller DE, Konstan MW, Smith J, Noonberg SB, Conrad C. Novel tobramycin inhalation powder in cystic fibrosis subjects: pharmacokinetics and safety. *Pediatr Pulmonol.* 2007;42(4):307–313.
23. Hubert D, Leroy S, Nove-Josserand R, et al. Pharmacokinetics and safety of tobramycin administered by the PARI eFlow rapid nebulizer in cystic fibrosis. *J Cyst Fibros.* 2009;8(5):332–337.
24. Lenney W, Edenborough F, Kho P, Kovarik JM. Lung deposition of inhaled tobramycin with eFlow rapid/LC Plus jet nebuliser in healthy and cystic fibrosis subjects. *J Cyst Fibros.* 2011;10(1):9–14.
25. Poli G, Acerbi D, Pennini R, et al. Clinical pharmacology study of Bramitob, a tobramycin solution for nebulization, in comparison with Tobi. *Paediatr Drugs.* 2007;9(Suppl 1):3–9.
26. Smyth A, Tan KH, Hyman-Taylor P, Mulheran M, Lewis S, Stableforth D. Once versus three-times daily regimens of tobramycin treatment for pulmonary exacerbations of cystic fibrosis--the TOPIC study: a randomised controlled trial. *Lancet.* 2005;365(9459):573–578.
27. Chuchalin A, Amelina E, Bianco F. Tobramycin for inhalation in cystic fibrosis: beyond respiratory improvements. *Pulm Pharmacol Ther.* 2009;22(6):526–532.
28. Guy EL, Bosomworth M, Denton M, Conway SP, Brownlee KG, Lee TW. Serum tobramycin levels following delivery of tobramycin (Tobi) via eFlow advanced nebuliser in children with cystic fibrosis. *J Cyst Fibros.* 2010;9(4):292–295.
29. Steinkamp G, Lutge M, Wurster U, Schulz-Baldes JG, Grone HJ, Ehrlich JH. Renal function in cystic fibrosis: proteinuria and enzymuria before and after tobramycin therapy. *Eur J Pediatr.* 1986;145(6):526–531.
30. Steinkamp G, Tummler B, Gappa M, Albus A, Potel J, Doring G. von der HH. Long-term tobramycin aerosol therapy in cystic fibrosis. *Pediatr Pulmonol.* 1989;6(2):91–98.
31. McWilliam SJ, Antoine DJ, Smyth RL, Pirmohamed M. Aminoglycoside-induced nephrotoxicity in children. *Pediatr Nephrol.* 2016;32(11):2015–2025.
32. Bennett MR, Nehus E, Haffner C, Ma Q, Devarajan P. Pediatric reference ranges for acute kidney injury biomarkers. *Pediatr Nephrol.* 2015;30(4):677–685.
33. Pennemans V, Rigo JM, Faes C, Reynders C, Penders J, Swennen Q. Establishment of reference values for novel urinary biomarkers for renal damage in the healthy population: are age and gender an issue? *Clin Chem Lab Med.* 2013;51(9):1795–1802.
34. Glass S, Plant ND, Spencer DA. The effects of intravenous tobramycin on renal tubular function in children with cystic fibrosis. *J Cyst Fibros.* 2005;4(4):221–225.
35. Riethmueller J, Ballmann M, Schroeter TW, et al. Tobramycin once- vs thrice-daily for elective intravenous antipseudomonal therapy in pediatric cystic fibrosis patients. *Infection.* 2009;37(5):424–431.
36. Etherington C, Bosomworth M, Clifton I, Peckham DG, Conway SP. Measurement of urinary N-acetyl-b-D-glucosaminidase in adult patients with cystic fibrosis: before, during and after treatment with intravenous antibiotics. *J Cyst Fibros.* 2007;6(1):67–73.
37. Geller DE, Rosenfeld M, Waltz DA, Wilmott RW. Efficiency of pulmonary administration of tobramycin solution for inhalation in cystic fibrosis using an improved drug delivery system. *Chest.* 2003;123(1):28–36.
38. Snell NJ, Ganderton D. Assessing lung deposition of inhaled medications. Consensus statement from a workshop of the British Association for Lung Research, held at the Institute of Biology, London, U.K. on 17 April 1998. *Respir Med.* 1999;93(2):123–133.
39. Westerman EM, Boer AH, Touw DJ, et al. Aerosolization of tobramycin (TOBI) with the PARI LC PLUS reusable nebulizer: which compressor to use? Comparison of the CR60 to the PortaNeb compressor. *J Aerosol Med Pulm Drug Deliv.* 2008;21(3):269–280.
40. Ratjen F, Munck A, Kho P, Angyalosi G. Treatment of early *Pseudomonas aeruginosa* infection in patients with cystic fibrosis: the ELITE trial. *Thorax.* 2010;65(4):286–291.
41. Bodnar R, Meszaros A, Olah M, Agh T. Inhaled antibiotics for the treatment of chronic *Pseudomonas aeruginosa* infection in cystic fibrosis patients: challenges to treatment adherence and strategies to improve outcomes. *Patient Prefer Adherence.* 2016;10:183–193.
42. Chuchalin A, Csiszer E, Gyurkovics K, et al. A formulation of aerosolized tobramycin (Bramitob) in the treatment of patients with cystic fibrosis and *Pseudomonas aeruginosa* infection: a double-blind, placebo-controlled, multicenter study. *Paediatr Drugs.* 2007;9(Suppl 1):21–31.
43. Vazquez-Espinosa E, Giron RM, Gomez-Punter RM, et al. Long-term safety and efficacy of tobramycin in the management of cystic fibrosis. *Ther Clin Risk Manag.* 2015;11:407–415.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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