ELSEVIER

Journal of Cystic Fibrosis 13 (2014) 653–660

Journal of Cystic Fibrosis

www.elsevier.com/locate/jcf

Original Article

Comparison of two tobramycin nebuliser solutions: Pharmacokinetic, efficacy and safety profiles of T100 and TNS☆

Dorota Sands [a,*], Ewa Sapiejka [b], Grzegorz Gąszczyk [c], Henryk Mazurek [d], for the T100 Study Group

[a] *Instytut Matki i Dziecka (IMiDz), ul. Kasprzaka 17a, 01-211 Warszawa, Poland*
[b] *Specjalistyczny Zespół Opieki Zdrowotnej nad Matką i Dzieckiem w Gdańsku, ul. Polanki 119, 80-308 Gdańsk-Oliwa, Poland*
[c] *Centrum Pulmonologii i Alergologii w Karpaczu S.A., ul. Myśliwska 13, 58-540 Karpacz, Poland*
[d] *Klinika Pneumonologii i Mukowiscydozy IGiChP, ul. Prof. J. Rudnika 3 B, 34-700 Rabka-Zdrój, Poland*

Received 27 November 2013; received in revised form 11 April 2014; accepted 14 April 2014
Available online 15 May 2014

Abstract

Background: Tobramycin inhalation is an accepted treatment of chronic pseudomonal infection in cystic fibrosis (CF) patients. Twice daily inhalation is efficacious, but time-consuming.
Methods: In this randomized, open-label, multicentre, two-period, crossover study, 58 patients with CF and chronic *Pseudomonas aeruginosa* (PA) infection received two tobramycin nebuliser solutions: T100/eFlow or TNS/PARI LC PLUS. The primary objective was to demonstrate the equivalence of both treatments with respect to pharmacokinetics (area under the concentration–time curve and maximum concentration in plasma). Secondary endpoints were tobramycin sputum pharmacokinetics, reduction in PA colony forming units, improvement of lung function, incidence of adverse drug reactions and reduction of inhalation times.
Results: Tobramycin plasma AUC and C_{max} were lower after administration of T100 than after TNS. The study failed to demonstrate systemic bioequivalence of the two treatments. After T100 administration, tobramycin sputum AUC and C_{max} achieved higher values than after TNS. Changes in efficacy parameters from baseline were similar. Safety profiles were not different or unexpected. Inhalation time per inhalation was shorter during treatment with T100.
Conclusion: The lower systemic drug burden and the higher local drug deposition together with a comparable efficacy/safety profile and a shorter inhalation time render T100/eFlow an attractive treatment option for CF patients.
(*www.controlled-trials.com/**ISRCTN85410458***).

Keywords: Tobramycin nebuliser solution; Cystic fibrosis; Chronic *Pseudomonas aeruginosa* infection; Inhalation time; Pharmacokinetics

1. Introduction

For the treatment of CF patients chronically infected with *Pseudomonas aeruginosa* (PA), use of tobramycin solutions for inhalation offers deposition of high local antibiotic drug concentrations at the site of infection, whilst limiting organ toxicities because of minimized systemic exposure. Twice daily inhalation of tobramycin nebuliser solution (TNS) has been established as standard-of-care therapy [1,2]. Nebulisation of large volumes using standard jet nebulisers powered by a table top compressor is time-consuming and one procedure may take 15 min or more. Increase of drug concentration, thus reducing the volume, and use of an efficient nebuliser allow a substantial reduction of the nebulisation time. PARI Pharma GmbH has developed a concentrated tobramycin solution (T100) and a drug-specific nebuliser based on the eFlow technology.

☆ Previous presentation of data. Summaries of the results of this trial have been presented previously as posters at the 36th European Cystic Fibrosis Conference (ECFC), 12–15 June 2013, Lisbon, Portugal and the 23rd Annual Congress of the European Respiratory Society (ERS), 7–11 September 2013, Barcelona, Spain.

* Corresponding author. Tel.: +48 22 32 77 371; fax: +48 22 32 77 043.
E-mail address: dorotasands@rubikon.pl (D. Sands).

http://dx.doi.org/10.1016/j.jcf.2014.04.006
1569-1993/

The intent of the present study was to demonstrate bioequivalence of the efficient drug/device combination T100 to standard TNS regarding tobramycin pharmacokinetics in plasma as well as to compare sputum pharmacokinetics and clinical efficacy and safety.

2. Methods

2.1. Study subjects

CF patients were eligible for participation if they were ≥4 years of age, had confirmed cystic fibrosis (one or more clinical features and sweat chloride ≥ 60 mEq/l by quantitative pilocarpine iontophoresis test and/or presence of disease-associated CF transmembrane conductance regulator mutations in both allels), FEV_1 % predicted of >25% and ≤85% at screening, confirmed chronic PA lung infection and were able to produce sputum and to perform lung function tests. Besides general criteria excluding patients from study participation, study-specific exclusion criteria were: hypersensitivity to inhaled or systemic aminoglycosides, anti-pseudomonal aminoglycoside therapy within 30 days or other antibiotic therapy within 7 days prior to first study drug administration, haemoptysis, positive *Burkholderia cepacia* culture, presence of allergic bronchopulmonary aspergillosis or other severe respiratory infections and auditory/vestibular dysfunctions. Written informed consent was obtained from all patients or legal representatives.

2.2. Study design

This study was a prospective, multicentre, open-label, randomized, two-period, crossover study comparing the new formulation of T100 with the registered standard TNS.

T100, the new formulation of tobramycin (VANTOBRA, 170 mg tobramycin/1.7 ml; PARI Pharma GmbH, Starnberg, Germany), was delivered via a drug-specific efficient eFlow technology nebuliser handset (Tolero, operated with an eBase controller; PARI Pharma GmbH, Starnberg, Germany). TNS (TOBI; 300 mg tobramycin/5 ml; Novartis, Basle, Switzerland) was administered using the PARI LC PLUS nebuliser in combination with the PARI BOY SX compressor (PARI GmbH, Starnberg, Germany).

After informed consent was obtained, screening tests to establish patient eligibility were performed within one week before first study drug administration. Patient stratification according to age (4–13 or >13 years) and 1:1-randomization were done immediately pre-dose on Day 1 of Treatment Period-1. Study medication was inhaled twice daily as add-on therapy to existing medication for a period of 4 weeks, followed by a 4-week wash-out phase and a crossover to the comparator for another 4-week Treatment Period-2. After completion of the second treatment, patients were observed for 1 week for safety reasons. The study, which was approved by the ethics committees of each participating centre, was conducted according to the ethical principles of the Declaration of Helsinki.

2.3. Determination of FEV_1 % predicted

Lung function tests were standardized and performed according to the recommendations of the American Thoracic Society (ATS)/European Respiratory Society (ERS) [3].

2.4. Evaluation of pharmacokinetics

On the last day of each treatment period blood samples (3–4 ml) for the assessment of tobramycin concentrations were collected in lithium-heparin tubes 30–15 min prior to inhalation, 30, 60, and 90 min and 2, 4, 6, 8 and 12 h after the end of inhalation. For the assessment of tobramycin sputum concentrations, sputum samples were collected in sterile culture dishes 30–15 min prior to inhalation, 10, 30, and 90 min and 2 and 8 h after the end of inhalation on the last treatment day. Tobramycin concentrations were determined using reversed phase HPLC–MS/MS after electrospray ionization. The method was validated with a lower limit of quantification of 30 ng/ml.

2.5. Evaluation of compliance and nebulisation time

Compliance and nebulisation time were determined by diaries completed by the patients for TNS and by electronic recording via chip cards incorporated into the patient monitoring systems for T100. The chip cards recorded date, time and duration of each nebulisation session together with the cause for termination. Compliance was calculated as the ratio of actual to planned inhalations and was depicted graphically per study day and as cumulative compliance from the start until completion of the treatment period.

2.6. Evaluation of safety

The incidence of treatment-emerged adverse events was recorded throughout the complete study period, including abnormal clinical laboratory results with emphasis on voice alterations, signs of tinnitus and bronchospasms. For each event, severity and study drug causality were assessed.

2.7. Statistical analysis

Statistical analysis was performed using SAS (SAS Software Release 9.2, Cary, NC, USA). The primary and secondary pharmacokinetic plasma parameters after logarithmic transformation were subjected to an Analysis of Variance (ANOVA). Consistent with the one-sided tests for bioequivalence, 90%-confidence intervals for the difference between drug formulation least-squares means (LSM) were calculated for the log-transformed parameter plasma AUC_{0-12h} and plasma C_{max}. Plasma t_{max}, sputum pharmacokinetic and clinical parameters were evaluated descriptively. With the assumption of a point estimator of 95–105% and an intra-patient variability of CV of 34% for plasma AUC_{0-12h} (based on the variance observed in a preceding pharmacokinetic study [4]), 50 patients were sufficient to show bioequivalence with a power of 80–90%. Assuming a

drop-out rate of 10%, a total of 60 patients were intended to be randomized.

3. Results

3.1. Patient characteristics

Of the 64 screened patients, 58 patients qualified for study participation were randomized (intent-to-treat population; Fig. 1). Fifty-four patients received both study treatment, 3 patients discontinued participation during the wash-out period and one patient was withdrawn 3 days after start of TNS due to CF-exacerbation. In total, 4 patients (two of each group) were excluded from clinical efficacy analysis (because not starting the crossover treatment) and consequently also excluded from PK analyses. Five further patients were excluded from PK analyses because of insufficient bio-analytical assessments to calculate reliable PK parameters. Patient demographics and baseline characteristics at study entry are summarized in Table 1.

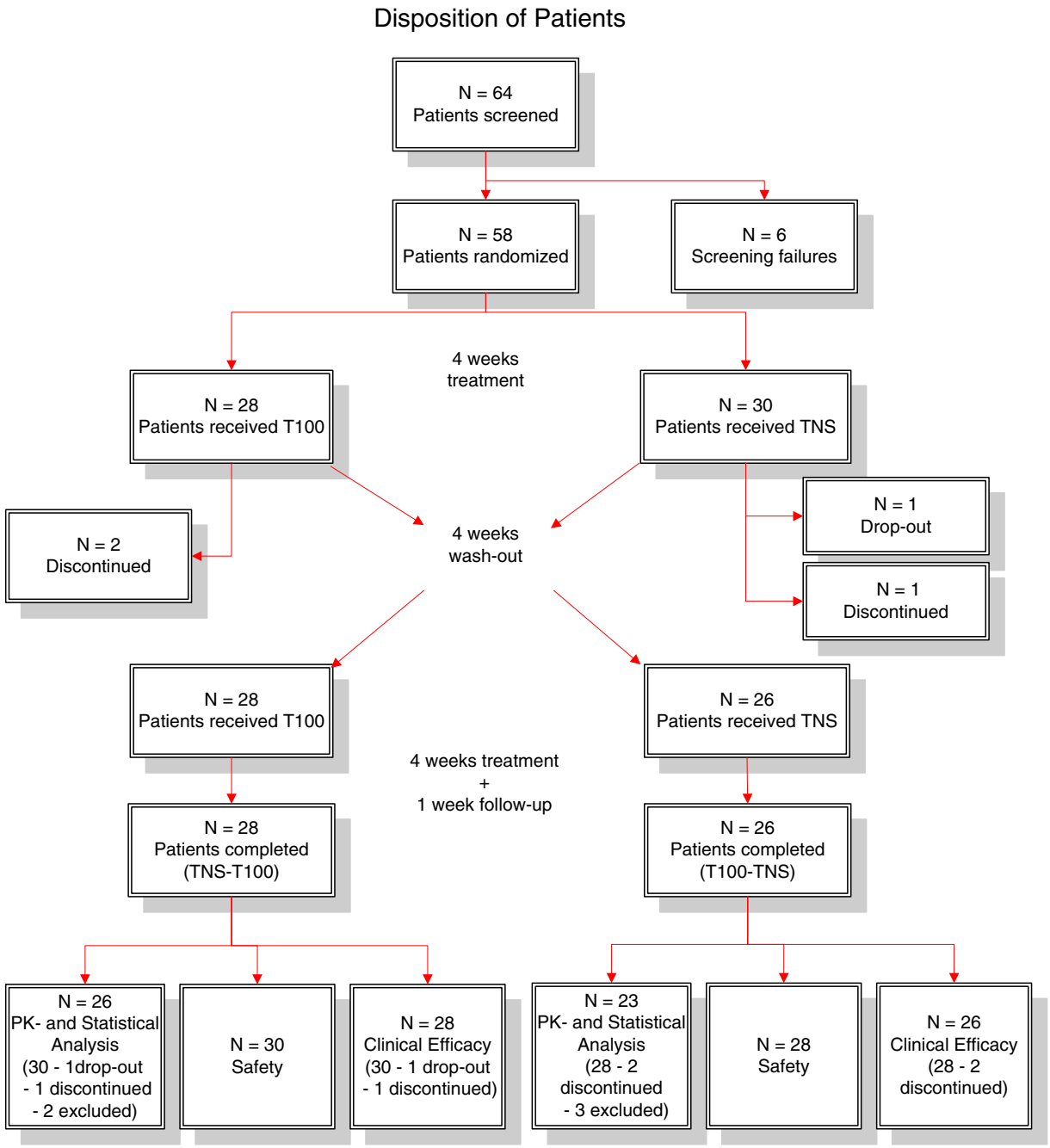

Fig. 1. Disposition of patients and populations for analyses.

Table 1
Demographic and basic characteristics of the intent-to-treat study population.

Demographics			
	All	4–13 years	>13 years
Patients (N)	58	28	30
Sex			
Male [n (%)]	25 (43)	15 (54)	10 (33)
Female [n (%)]	33 (57)	13 (46)	20 (67)
Age (years)			
Mean ± SD	15.4 ± 6.81	10.0 ± 1.84	20.6 ± 5.52
Range	7–36	7–13	13–36
Weight (kg)			
Mean ± SD	43.3 ± 13.9	32.1 ± 9.5	53.7 ± 7.8
Range	15.0–72.0	15.0–52.0	38.7–72.0
Height (cm)			
Mean ± SD	152.6 ± 16.4	139.6 ± 13.5	164.6 ± 7.0
Range	113–182	113–164	151–182

Baseline characteristics		
	T100	TNS
Patients (N)	28	30
FEV_1 % predicted		
Mean ± SD	**63.8** ± 17.1	**64.2** ± 17.7
Range (min/max)	30.0/82.8	28.0/83.9
PA colony density (log_{10})		
Mean ± SD	**5.17** ± 3.018	**5.30** ± 3.070
Range (min/max)	0.00/10.10	0.15/10.10

SD, standard deviation; FEV_1, forced expiratory volume in 1 s; PA, *Pseudomonas aeruginosa*.

Table 2
Plasma and sputum tobramycin pharmacokinetics at Day 28 after treatment with T100 or TNS.

Pharmacokinetic parameter	T100	TNS
Serum		
AUC_{0-12h} (μg/ml*h)		
All patients	5.78 ± 3.57	5.81 ± 3.10
4–13years	5.88 ± 3.48	6.13 ± 3.41
>13 years	5.70 ± 3.71	5.55 ± 2.86
C_{max} (μg/ml)		
All patients	1.27 ± 0.81	1.33 ± 0.76
4–13 years	1.35 ± 0.74	1.43 ± 0.84
>13 years	1.21 ± 0.86	1.26 ± 0.89
t_{max} (h)		
All patients	0.80 ± 0.39	0.80 ± 0.31
4–13 years	0.80 ± 0.33	0.90 ± 0.33
>13 years	0.90 ± 0.43	0.80 ± 0.28
Sputum		
AUC_{0-8h} (mg/g*h)		
All patients	1.18 ± 1.15	0.87 ± 0.80
4–13 years	1.25 ± 1.34	0.98 ± 1.00
>13 years	1.12 ± 1.00	0.78 ± 0.60
C_{max} (mg/g)		
All patients	1.95 ± 2.19	1.42 ± 1.51
4–13 years	1.87 ± 2.16	1.23 ± 1.48
>13 years	2.01 ± 2.25	1.57 ± 1.54
t_{max} (h)		
All patients	0.38 ± 1.12	0.39 ± 1.16
4–13 years	0.59 ± 1.66	0.61 ± 1.70
>13 years	0.21 ± 0.12	0.22 ± 0.26

AUC, area under the concentration–time curve; C_{max}, maximum tobramycin concentration; t_{max}, time to C_{max}. Values are arithmetic mean ± standard deviation.

3.2. Plasma tobramycin concentrations

Plasma tobramycin pharmacokinetic parameters after a 4-week treatment period are summarized in Table 2. Areas under the plasma concentration–time curves from the first time point to the time point of the last measured concentration are shown in Fig. 2. Pre-treatment trough plasma tobramycin concentrations (C_0) were low for both drug/device combinations (approx. 0.15 μg/ml). On treatment Day 28, the AUC_{0-12h} was 5.78 ± 3.57 and 5.81 ± 3.10 μg/ml*h for T100 and TNS, respectively (arithmetic means ± SD). The corresponding peak plasma tobramycin concentrations (C_{max}) were 1.27 ± 0.81 and 1.33 ± 0.76 μg/ml. The geometric mean ratios (T100:TNS) for C_{max} and AUC_{0-12h} were 0.83 (90% CI 0.66, 1.04; p = 0.6101) and 0.85 (90% CI 0.68, 1.05; p = 0.1663), respectively. The accepted ranges for the test:reference ratios are 0.75–1.33 for plasma C_{max} and 0.80–1.25 for plasma AUC. The mean t_{max} values were comparable with 0.80 ± 0.39 h (T100) and 0.80 ± 0.31 h (TNS).

3.3. Sputum tobramycin concentrations

Sputum tobramycin pharmacokinetic parameters after a 4-week treatment period are summarized in Table 2. Areas under the sputum concentration–time curves from the first time point to the time point of the last measured concentration are shown in Fig. 2. On treatment Day 28, the AUC_{0-8h} was 1.18 ± 1.15 and 0.87 ± 0.80 mg/g*h for T100 and TNS, respectively (arithmetic mean ± SD). The corresponding peak sputum tobramycin concentrations (C_{max}) were 1.95 ± 2.19 and 1.42 ± 1.51 mg/g. The mean t_{max} values were comparable with 0.38 ± 1.12 h (T100) and 0.39 ± 1.16 h (TNS).

3.4. Reduction of PA colony forming units

Treatment with tobramycin resulted in an overall reduction in CFU density of *P. aeruginosa*, irrespective of the drug/device combination. In general, the treatment effect was more pronounced in the first compared to the second treatment period (Fig. 3). During Treatment Period-1, a similar log_{10} CFU reduction was achieved with T100 (−1.77 ± 2.74; difference pre- vs. post-treatment: p = 0.0049) and TNS (1.70 ± 2.93; difference pre- vs. post-treatment: p = 0.0020); after Treatment Period-2, the reduction was −1.30 ± 2.55 (p = 0.012) and 0.12 ± 1.78 (p = 0.7341), respectively. There was no treatment difference between T100 and TNS at the end of Treatment Period-1 (p = 0.9245), but a statistically significant difference was reached at the end of Treatment Period-2 (p = 0.0225).

3.5. Lung function (FEV_1 % predicted)

The treatment effects regarding FEV_1 % predicted were similar for both groups, T100 and TNS, during Treatment Period-1. However, a positive treatment effect was also observed for T100 after Treatment Period-2 (Fig. 3). During Treatment Period-1, a

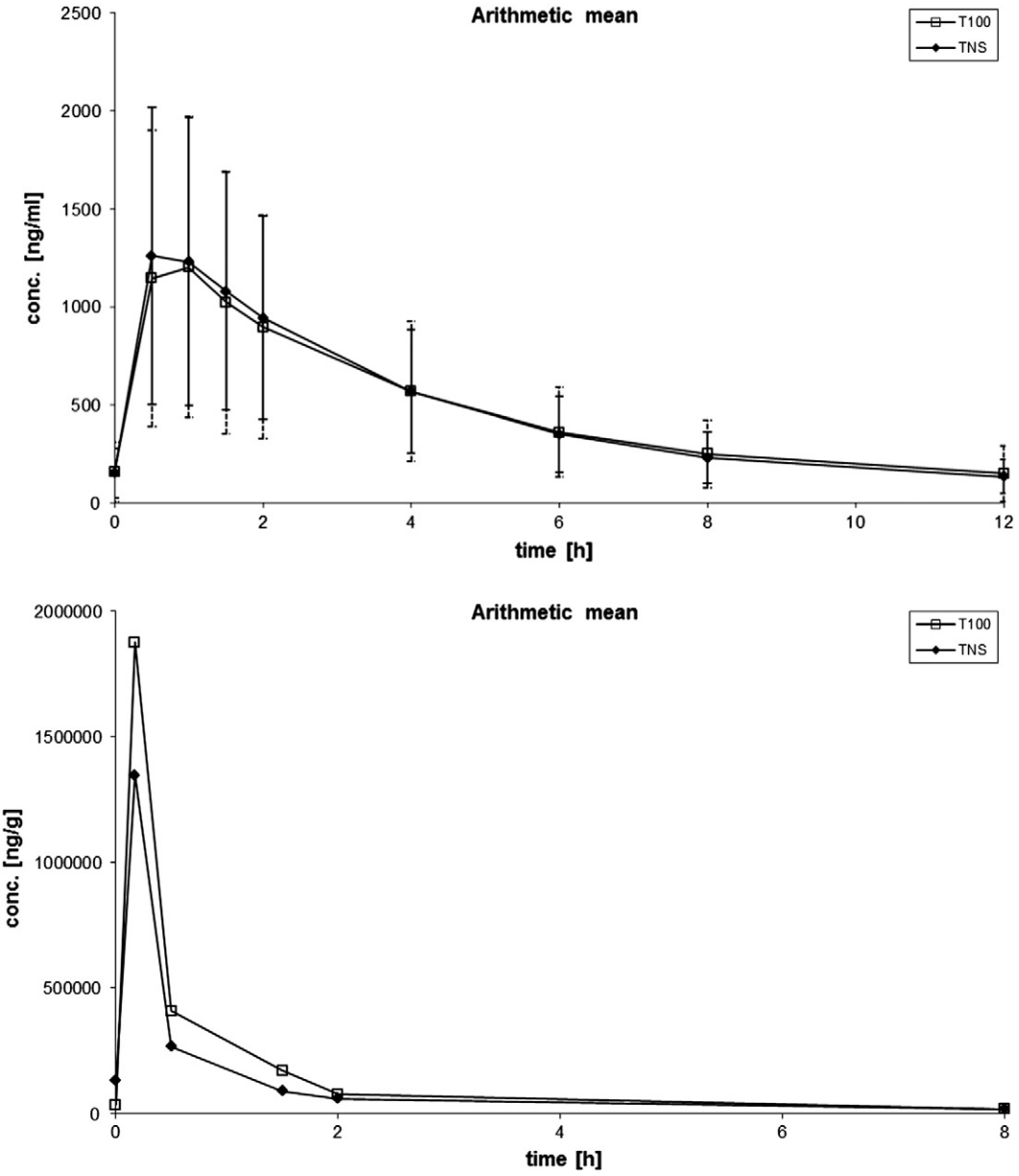

Fig. 2. Mean plasma (*top*) and sputum (*bottom*) tobramycin concentrations over time on Day 28 after administration of T100 (squares) or TNS (rhombi) in the overall study population (PK Analysis Set). Bars represent the 95% confidence intervals.

similar increase in FEV_1 % predicted was achieved with T100 (8.20 ± 9.49%; difference pre- vs. post-treatment: $p < 0.0001$) and TNS (4.80 ± 9.58%; difference pre- vs. post-treatment: $p = 0.0132$); after Treatment Period-2, the change was 2.40 ± 10.64% ($p = 0.2436$) and −0.44 ± 8.10% ($p = 0.7862$), respectively. In neither Treatment Period, the differences between the T100 and TNS groups reached statistical significance ($p_{[\text{Treatment Period-1}]}$: 0.1881; $p_{[\text{Treatment Period-2}]}$: 0.2789).

3.6. Compliance and nebulisation times

Compliance to therapy of the patients was generally high in both groups with 99% for T100 patients (as recorded by an electronic Monitoring System of the device) and 99% for TNS patients (as recorded in patient diaries). The time per nebulisation was impressively reduced in the new T100 drug/device combination (mean: 4.4 min) as compared to the standard TNS combination (mean: 24.3 min).

3.7. Safety

Overall, 76 adverse events were reported in 29 patients (50% of all patients) of the safety population under investigation (n = 58). Twenty-nine patients experienced no AEs. Three AEs were severe in intensity; all others were classified to be mild to moderate. Thirty-two adverse events (approx. 42% of all AEs) were considered to be related to the study drug, i.e. they were defined as adverse drug reactions (ADRs). All of them were classified as mild to moderate in intensity. In no case study, medication had to be discontinued temporarily or permanently

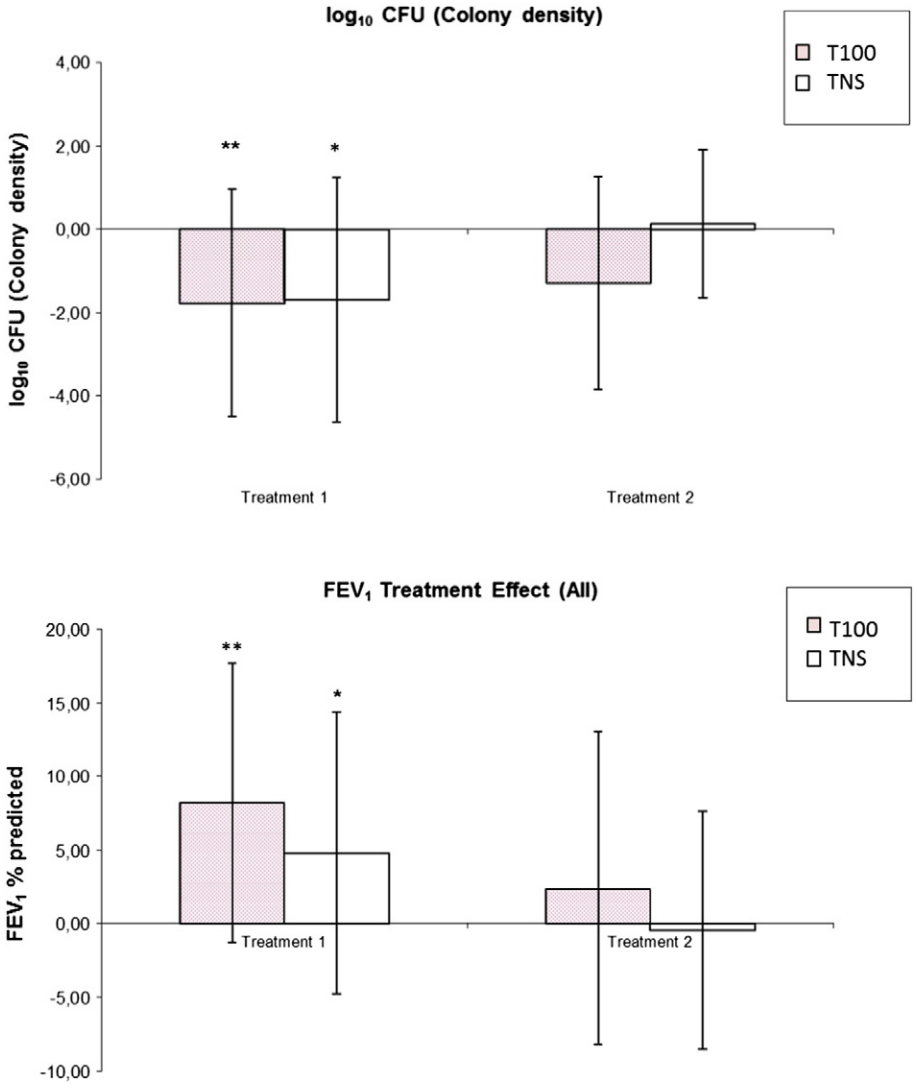

Fig. 3. *Top*: Reduction of *P. aeruginosa* CFU calculated from beginning until end of each treatment cycle (T100: red; TNS: blank); *p < 0.05, and **p < 0.01. *Bottom*: Change of FEV_1 % predicted determined at the beginning and the end of each treatment cycle (T100: red; TNS: blank); *p < 0.01; and **p < 0.001. Bars represent the standard deviations.

due to an ADR. There were 5 serious adverse events (SAEs) recorded in 4 patients; the reason for seriousness was hospitalisation in all cases. None of the SAEs was drug-related. No fatality was observed. Six events were described as clinically relevant increases in laboratory values (4 in one patient, who discontinued TNS-treatment, and increase of LDH in another two patients, one patient in the T100, one patient in the TNS group, both continued the treatment). All of these abnormal parameters were recorded as AEs, i.e. none of these were drug related. Any other changes of laboratory values outside of the normal range were assessed by the investigators as "not clinically significant". Bronchospasms occurred only in 2 patients under TNS (3.4% of the patients) and were considered by the investigator as adverse drug reactions. Audiology testing revealed two cases of tinnitus in patients under T100 treatment (3.4% of all patients). Both cases were mild in severity, transient and resolving shortly after inhalation. One patient in the T100 group showed pathological signs in pure tone audiometry measured by bone connectivity (highest value for left ear at 2 kHz was 35 dB). Pulmonary exacerbation was observed in one patient only during the wash-out phase after TNS treatment. This patient required treatment with antibiotics which were prohibited as per study protocol and thus was withdrawn from further study participation.

4. Discussion

The intent of this study was to demonstrate equivalence of T100 not only to the standard-of-care treatment using TNS, primarily regarding pharmacokinetics, but also to efficacy and safety. In such case, the reduction of daily nebulisation times of a concentrated tobramycin inhalation solution delivered via an efficient nebuliser based on eFlow technology could be regarded as beneficial for the quality of life of CF patients.

The study failed to demonstrate bioequivalence between the treatments by prospective analysis plan. The point estimates

and the upper confidence levels for both parameters were within the accepted bioequivalence ranges, whereas the lower confidence levels were outside these ranges. Thus, the obtained pharmacokinetic results were indicative for a lower systemic burden of T100 versus TNS, whereas local pulmonary tobramycin concentrations were found to be higher after inhalation of T100. These results have to be interpreted carefully, as plasma concentrations of tobramycin, and even more sputum concentrations, showed very high inter- and intra-individual variability. Not only the T100 was characterised by high coefficients of variation (62%), but also the reference product TNS (53%), an experience already described by others [5–8] who investigated tobramycin pharmacokinetics in CF patients.

Inhaled tobramycin pharmacokinetic investigations in CF patients are challenged mainly by five factors: (1) the CF disease status significantly impacts the physical properties of the mucus and lung morphology; (2) the breathing manoeuvres of the patient exert influence on the drug deposition in the lung; (3) the differences in device design and characteristics used for drug delivery; (4) the high variability of tobramycin pharmacokinetics even when administered intravenously [9,10]; and (5) the patient-individual capability to produce sputum.

Analyses of the investigated clinical parameters (CFU and lung function) were consistent with respect to a concomitant improvement of lung function as a function of decreasing PA density: During the first treatment cycle both drugs provided a similar reduction in density of PA colony forming units. This effect could be repeated when administering T100 as the second treatment whereas in patients receiving TNS as second course such an effect was missing.

Improvement in lung function was observed for all lung function parameters investigated and more pronounced in the first than in the second treatment phase for both products. A continuous decline in clinical efficacy is well known also from the treatment with other antibiotics when administered in an on-treatment/off-treatment schedule [11]. However, under T100 therapy in the second phase patients were able to reverse the decline in lung function during the wash-out phase, whereas this effect could not be observed under TNS therapy, suggesting a carry-over effect of the T100 treatment. Treatment with both products resulted in a comparable overall clinical efficacy, leading to a reduction of PA density and an improvement of lung function. The treatment effects are indicative of therapeutic equivalence.

No significant or unexpected safety problem was associated with the inhalation of tobramycin. All of the ADRs were of mild to moderate intensity. In all cases the reason for seriousness of SAEs was hospitalisation; none of the reported SAEs were related to the study drug. There were no relevant safety findings as indicated by physical examinations, vital sign measurements, number of bronchospasms, audiometry, bronchospasms and clinical laboratory evaluations. All laboratory values numerically outside the reference range were not clinically significant. The study provided no evidence that patients were posed on risk for tobramycin in neither of the two treatment arms. Thus, treatment with T100 and TNS can be regarded as comparable with respect to the products' safety profiles.

Beyond that, the study has shown a remarkably shorter nebulisation time with the new T100 tobramycin solution administered via a more efficient nebuliser handset compared to TNS administered via a jet nebuliser. This reduction in nebulisation time of twice 20 min daily may enhance the patients' compliance in routine use and, as a consequence, the therapeutic efficacy and safety of the antibiotic treatment.

In conclusion, the study failed to demonstrate systemic bioequivalence, an accepted surrogate for therapeutic equivalence by regulatory bodies. Despite lower systemic burden, T100 treatment resulted in a similar efficacy and safety profile as TNS. The new drug/device combination T100 (VANTOBRA/Tolero) reduced the inhalation time impressively and thus may contribute to an improvement of the quality of life for CF patients by shortening their daily treatment burden. T100 may also present a viable alternative with short treatment time for those patients who cannot tolerate tobramycin dry powder inhalation.

Conflict of interest

DS, ES, GG and HM were Principal Investigators in the T100 study.

Acknowledgments

The medical devices (Tolero, PARI LC PLUS), the investigational medicinal product (T100, VANTOBRA), and the reference product (TNS, TOBI) were provided by PARI Pharma GmbH (Starnberg, Germany, Grant no. ISRCTN85410458). In addition, the company granted financial support for all analyses. Biological samples were analysed by ACC (Leidersbach, Germany) for tobramycin concentrations. Associated Medical Clinical Science Services Sp. z o.o. (Ruda-Śląska, Poland) was the clinical research organization of this study.

Appendix A

T100 Study Group: Justyna Milczewska, Katarzyna Walicka-Serzysko (IMiDz, Warsaw), Renata Ligarska, Andrzej Pogorzelski, Beata Sochań (IGiChP, Rabka), Ewa Pomarańska (CPiA, Karpacz) and Anna Steinert-Dymecki (Gdansk-Oliwa).

References

[1] Ramsay BW, Pepe MS, Quan JM, Otto KL, Montgomery AB, Williams-Warren J, et al. Intermittent administration of inhaled tobramycin in patients with cystic fibrosis. N Engl J Med 1999;340:23–30.
[2] Hagermann JK, Hancock KE, Klepser ME. Aerosolised antibiotics: a critical appraisal of their use. Expert Opin Drug Deliv 2006;3(1):71–86.
[3] Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of spirometry. Eur Respir J 2005;26:319–38.
[4] Griese M, Eismann C, Börner G, Denk O, Schierholz JM, Keller M, et al. A pharmacokinetics and safety comparison of a highly concentrated tobramycin solution with TOBI. J Aerosol Med Pulm Drug Deliv 2013;26(0):1–8 [Epub ahead of print].
[5] Govoni M, Poli G, Cicerello H, Santoro D, Acerbi D, Ruzicka J. Pharmacokinetics of tobramycin nebulizer solution 300 mg/4ml (Bramitob(r))

administered by Pari eFlow(r) rapid vs. Pari LC(r) Plus nebulizer in cystic fibrosis patients. Respir Drug Deliv 2012:459–64.

[6] Hubert D, Leroy S, Nove-Josserand R, Murris-Espin M, Mely L, Dominique S, et al. Pharmacokinetics and safety of tobramycin administered by the PARI eFlow(r) rapid nebulizer in cystic fibrosis. J Cyst Fibros 2009;8:332–7.

[7] Geller DE, Pitlick WH, Nardella PA, Tracewell WG, Ramsey BW. Pharmacokinetics and bioavailability of aerosolized tobramycin in cystic fibrosis. Chest 2002;122:219–26.

[8] Lenoir G, Antypkin YG, Miano A, Moretti P, Zanda M, Varoli G, et al. Efficacy, safety, and local pharmacokinetics of highly concentrated nebulized tobramycin in patients with cystic fibrosis colonized with *Pseudomonas aeruginosa*. Pediatr Drugs 2007;9(Suppl. 1):11–20.

[9] Kearns GL, Trang JM. Introduction to pharmacokinetics: aminoglycosides in cystic fibrosis as a prototype. J Pediatr 1986;108(2):847–53.

[10] Horrevorts AM, Degener JE, Dzoljic-Danilovic G, Michel MF, Kerrebijn KF, Driessen O, et al. Pharmacokinetics of tobramycin in patients with cystic fibrosis. Implications for the dosing interval. Chest 1985;88:260–4.

[11] Konstan MW, Flume PA, Kappler M, Chiron R, Higgins M, Brockhaus F, et al. Safety, efficacy and convenience of tobramycin inhalation powder in cystic fibrosis patients: the EAGER trial. J Cyst Fibros 2011;10:54–61.